Clinical Trial Protocol

Clinical Trial Protocol Number	MS200661-0005
Title	Open-label, dose-finding, 2-parts, efficacy phase II study with three formulations (racemate praziquantel commercial oral tablets, new oral disintegrating tablets of racemate praziquantel and L-praziquantel) in schistosomiasis (*S. mansoni*) infected children aged 2-6 years (Part 1), followed by an assessment of efficacy and safety with the selected formulation and dosage in *S. mansoni* infected infants aged 3-24 months (Part 2)
Phase	II
IND Number	Not Applicable
EudraCT Number	Not Applicable
Coordinating Investigator (PPD PPD	PPD PPD
Sponsor	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany
Medical Responsible	PPD Merck KGaA, Frankfurter Strasse 250, Darmstadt, Germany Phone: PPD Fax: PPD E-mail: PPD
Clinical Trial Protocol Version	3.1 / 28 February 2018
Replaces Version	3.0 / 10 April 2017

[redacted]

Summary of changes from Version 3.0 / 10 Apr 2017 to 3.1 / 28.Feb 2018

	Text in protocol Version 3.0 / 10 Apr 2017	Text in protocol Version 3.1 / 28 Feb 2018
1	**Principal Investigator**	
	Coordinating Investigator (PPD**)** PPD PPD **Coordinating Investigator** PPD PPD PPD	**Coordinating Investigator (**PPD**)** PPD PPD ~~**Coordinating Investigator**~~ PPD PPD PPD
2	**Tables of in text figures**	
	Table 7. PK rich sampling scheme Table 8. PK sparse sampling scheme Table 9. Overall cure rate projections according to assumptions of cure rate in light and moderate/heavy infections Table 10. Probability of observing an overall cure rate ≥70% based on different scenarios of true cure rates based on different strata	~~Table 7. PK rich sampling scheme~~ ~~Table 8. PK sparse sampling scheme~~ ~~Table 9~~ Table 7. Overall cure rate projections according to assumptions of cure rate in light and moderate/heavy infections ~~Table 10~~ Table 8. Probability of observing an overall cure rate ≥70% based on different scenarios of true cure rates based on different strata
3	**Abbreviations**	
	PPD	PPD
4	**Synopsis - Coordinating investigator**	
	Coordinating Investigator (PPD**)** PPD PPD **Coordinating Investigator (**PPD PPD PPD P PPD P D	**Coordinating Investigator (**PPD**)** PPD PPD ~~**Coordinating Investigator**~~ PPD PPD PPD PPD
5	**Synopsis - Trial centres/countries**	
	PPD	PPD
6	**Synopsis - Planned trial period**	
	Enrolment start date (FPI): Jun 2016 (Part 1) Jan 2018 (Part 2) Enrolment finish date (LPI): Sep 2017 (Part 1) Apr 2018 (Part 2) Treatment period end date (LP off treatment): Sep 2017 (Part 1)	Enrolment start date (FPI): Jun 2016 (Part 1) Apr 2018 (Part 2) Enrolment finish date (LPI): Dec 2017 (Part 1) Aug 2018 (Part 2) Treatment period end date (LP off treatment): Dec 2017 (Part 1)

	Apr 2018 (Part 2) Follow-up period end date (LP off study): Oct 2017 (Part 1) May 2018 (Part 2) Planned date for primary analysis: Nov 2017 Planned date for final analysis: Jun 2018	Aug 2018 (Part 2) Follow-up period end date (LP off study): Dec 2017 (Part 1) Sep 2018 (Part 2) Planned date for primary analysis: Feb 2018 Planned date for final analysis: Oct 2018
7	**Synopsis - Secondary objectives /**	
	Part 1 • To explore the dose-exposure-response relationship for L-PZQ, D-PZQ and rac-PZQ in children aged 2 to 6 years infected with *S. mansoni* **Part2** • To explore the dose-exposure -response relationship for L-PZQ, D-PZQ and rac-PZQ in 3- to 24-month infants infected with *S. mansoni*	**Part 1** • To explore the dose-~~exposure~~ response relationship for L-PZQ~~, D-PZQ~~ and rac-PZQ in children aged 2 to 6 years infected with *S. mansoni* **Part2** • To explore the dose-~~exposure~~ response relationship for L-PZQ~~, D-PZQ~~ and rac-PZQ in 3- to 24-month infants infected with *S. mansoni*
8	**Synopsis - Study design and plan**	
	This is a phase II study consisting of two parts (Part 1 and Part 2). Part 2 will only start once Part 1 is completed. The study will be conducted at the PPD An additional site at PPD may be added depending on patients' recruitment rate. […] C7 will be included in the randomization scheme only after SMC approval while randomization for the other groups can continue to 40 subjects per arm. In addition, in case of safety concerns raised by SMC on the L-PZQ ODTs treated cohorts, PK drug exposure in a minimum of 10 subjects from cohorts C5 and C6 will be assessed before deciding to escalate to the higher L-PZQ ODT dose in C7. […] Infants in cohort C8 will be treated with rac-PZQ ODT or L-PZQ ODT at the optimal dose level selected by SMC from Part 1 (based on benefits-risks evaluation), corrected by standard allometric scaling of the PK available data. In addition, a maturation factor will also be included (if applicable) to decide on the dose for these infants.	This is a phase II study consisting of two parts (Part 1 and Part 2). Part 2 will only start once Part 1 is completed. The study will be conducted at the PPD ~~An additional site at~~ PPD ~~may be added depending on patients' recruitment rate.~~ […] C7 will be included in the randomization scheme only after SMC approval while randomization for the other groups can continue to 40 subjects per arm. In case of safety concerns observed with the L-PZQ ODTs treated cohorts, the SMC can decide to assess the exposure in a minimum of 10 subjects in the L-PZQ ODTs cohorts C5 and C6 before deciding to escalate to a higher dose of L-PZQ. […] Infants in cohort C8 will be treated with rac-PZQ ODT or L-PZQ ODT at the optimal dose level selected by SMC from Part 1 (based on benefits-risks evaluation)~~ corrected by standard allometric scaling of the PK available data. In addition, a maturation factor will also be included (if applicable) to decide on the dose for these infant~~.
9	**Synopsis - Pharmacokinetics**	
	PK profile of L-PZQ, D-PZQ and rac-PZQ (AUC_{0-t}, C_{max}, t_{max}, t_{lag}, $AUC_{0-\infty}$, AUC_{extra}, $t_{½}$, λz, CL/f and V_z/F). PK will be assessed in 25% of the subjects of cohorts C1-C7 with a rich sampling scheme and in	Not applicable

	75% of the subjects with a sparse sampling scheme. PK will be assessed in all subjects of Part 2 (cohorts C8 and C9) with a rich sampling scheme.	
10	**Synopsis - Diagnosis**	
	Screening diagnosis of *S. mansoni* infection will be done using a single POC-CCA urine cassette test. […] Kato-Katz diagnosis of *S. mansoni* infection: two stool samples will be collected from each subject on different days within a maximum of five days, at screening as baseline and 14-21 days after dosing (for treatment efficacy assessment). […] One urine sample will be collected from each subject at screening.	Diagnosis of *S. mansoni* infection will be done using a single POC-CCA urine cassette test. […] Kato-Katz diagnosis of *S. mansoni* infection: two stool samples will be collected from each subject on different days within a maximum of five days, at ~~screening~~ day -28 to day -1 as baseline and 14-21 days after dosing (for treatment efficacy assessment). […] One urine sample will be collected from each subject at ~~screening~~ day -28 to day -1.
11	**Synopsis – Eligibility criteria / 5.3.1 Inclusion Criteria**	
	• To provide stool and urine samples at screening, 24 h and 8 days after treatment, as well as 14-21 days after treatment • To provide venous blood samples for safety assessments.	• To provide stool and urine samples at ~~screening~~ day -28 to day -1 ,24 h and 8 days after treatment, as well as 14-21 days after treatment • To provide venous blood samples for safety assessments.
12	**Synopsis - Investigational Medicinal Product**	
	Part 2: Rac-PZQ ODTs or L-PZQ ODTs dose selected from Part 1 and including a dose correction (maturation factor).	Part 2: Rac-PZQ ODTs or L-PZQ ODTs dose selected from Part 1 ~~and including a dose correction (maturation factor)~~.
13	**Synopsis – Planned trial and treatment duration per subject**	
	Maximum 28 days of screening period, followed by 1 day treatment and 14-21 days of follow-up period.	Maximum 28 days of pre-screening and screening period, followed by 1 day treatment and 14-21 days of follow-up period.
14	**Synopsis – Statistical methods**	
	All efficacy safety and pharmacokinetic endpoints will be analysed descriptively.	All efficacy and safety ~~and pharmacokinetic~~ endpoints will be analysed descriptively.
15	**2 Sponsor, Investigators and Trial Administrative Structure**	
	The trial will be conducted at the PPD PPD PPD An additional site at PPD may be added depending on patients' recruitment rate. The Coordinating Investigators PPD represent all Investigators for decisions and discussions regarding this trial, consistent with the	The trial will be conducted at the PPD PPD PPD . ~~An additional site at~~ PPD ~~may be added depending on patients' recruitment rate.~~ The Coordinating Investigators~~s~~ PPD represents all Investigators for decisions and discussions regarding this trial, consistent with the

	International Conference on Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigators will provide expert medical input and advice relating to trial design and execution and are responsible for the review and signoff of the clinical trial report. Signature pages for the Protocol Lead and the Coordinating Investigators as well as a list of Sponsor responsible persons are in Appendix I.	International Conference on Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigator will provide expert medical input and advice relating to trial design and execution and ~~are~~ is responsible for the review and signoff of the clinical trial report. Signature pages for the Protocol Lead and the Coordinating Investigator~~s~~ as well as a list of Sponsor responsible persons are in Appendix I.
16	**3.2 Study rationale**	
	Younger children (13 to 24 months) infected with *S. mansoni* will subsequently be treated with the selected ODT dose from Part 1 corrected due to allometric scaling of PK data as well as a maturation factor (to compensate for the immature metabolic system in infants). Only when this corrected dose has been assessed as safe, lower aged children 3 to 12 months will be included.	Younger children (13 to 24 months) infected with *S. mansoni* will subsequently be treated with the selected ODT dose from Part 1 ~~corrected due to allometric scaling of PK data as well as a maturation factor (to compensate for the immature metabolic system in infants)~~. Only when this ~~corrected~~ dose has been assessed as safe, lower aged children 3 to 12 months will be included.
17	**4.2 Secondary objectives**	
	Part 1 • To explore the dose-exposure-response relationship for L-PZQ, D-PZQ ODT and rac-PZQ ODT in children aged 2 to 6 years infected with *S. mansoni* Part 2 • To explore the dose-exposure-response relationship for LPZQ, D-PZQ and rac-PZQ in 3- to 24-month infants infected with *S. mansoni*	Part 1 • To explore the dose-~~exposure~~-response relationship for L-PZQ~~, D-PZQ~~ ODT and rac-PZQ ODT in children aged 2 to 6 years infected with *S. mansoni* Part 2 • To explore the dose-~~exposure~~-response relationship for LPZQ, ~~D-PZQ~~ and rac-PZQ in 3- to 24-month infants infected with *S. mansoni*
18	**5.1 Overall Trial Design and Plan**	
	Part 1 is an open-label, randomized, controlled, exploratory dose-finding study conducted in two study sites with three formulations of PZQ (commercial rac-PZQ tablets, L-PZQ ODTs and rac-PZQ ODTs) in children aged between 2 and 6 years infected with *S. mansoni*. […] In case of safety concerns observed with the L-PZQ ODTs treated cohorts, the SMC can decide to assess the exposure in a minimum of 10 subjects in the L-PZQ ODTs cohorts C5 and C6 before deciding to escalate to a higher dose of L-PZQ. In addition, the SMC may propose a change in the sampling times (but not an increase in the total blood volume) and may decide to skip further sparse PK sampling in case erratic PK profiles are observed (see also Section 7.5). **Part 2** includes a cohort with infants of 13-24 months infected with *S. mansoni* (C8) and a cohort	**Part 1** is an open-label, randomized, controlled, exploratory dose-finding study conducted in one ~~two~~ study site~~s~~ with three formulations of PZQ (commercial rac-PZQ tablets, L-PZQ ODTs and rac-PZQ ODTs) in children aged between 2 and 6 years infected with *S. mansoni*. […] In case of safety concerns observed with the L-PZQ ODTs treated cohorts, the SMC can decide to assess the exposure in a minimum of 10 subjects in the L-PZQ ODTs cohorts C5 and C6 before deciding to escalate to a higher dose of L-PZQ. ~~In addition, the SMC may propose a change in the sampling times (but not an increase in the total blood volume) and may decide to skip further sparse PK sampling in case erratic PK profiles are observed (see also Section 7.5).~~ **Part 2** includes a cohort with infants of 13-24 months infected with *S. mansoni* (C8) and a cohort

	with infants of 3-12 months infected with *S. mansoni* (C9) which will be enrolled in an age-staggered approach. This part of the study will be conducted at one or two study sites, depending on recruitment […] Infants in cohort C8 will be treated with rac-PZQ or L-PZQ ODTs at the optimal dose level selected by SMC from Part 1 (based on benefits-risks evaluation), corrected by a maturation factor which takes into account all the known enzymes involved in the metabolism of PZQ, as well as the immature status of these enzymes in the lower aged children. In addition standard allometric scaling will also be included (if applicable) to decide on the dose for these children. After 10 infants of 13 to 24 months have been enrolled, the overall safety and efficacy data in these children will be evaluated by the SMC for the decision to include the lower age group (cohort C9). Due to the low number of subjects and the expected high variability in the PK, the PK data from these infants are not mandatory for the decision to include C9. SMC will also decide whether dose level adaptations are needed before starting to enrol C9.	with infants of 3-12 months infected with *S. mansoni* (C9) which will be enrolled in an age-staggered approach. ~~This part of the study will be conducted at one or two study sites, depending on recruitment~~ […] Infants in cohort C8 will be treated with rac-PZQ or L-PZQ ODTs at the optimal dose level selected by SMC from Part 1 (based on benefits-risks evaluation)~~, corrected by a maturation factor which takes into account all the known enzymes involved in the metabolism of PZQ, as well as the immature status of these enzymes in the lower aged children. In addition standard allometric scaling will also be included (if applicable) to decide on the dose for these children~~. After 10 infants of 13 to 24 months have been enrolled, the overall safety and efficacy data in these children will be evaluated by the SMC for the decision to include the lower age group (cohort C9). ~~Due to the low number of subjects and the expected high variability in the PK, the PK data from these infants are not mandatory for the decision to include C9.~~ SMC will also decide whether dose level adaptations are needed before starting to enrol C9.
19	**5.2.** Discussion of Trial Design	
	[…] In summary, due to the uncertainties about the available exposure-response or concentration-response relationship and the predicted efficacy response, combined with the PK variability observed for PZQ, as well as the uncertainty in the translation of adult data of PZQ to children, a PK only approach is not deemed appropriate and therefore a partial extrapolation PK/PD dose ranging approach has to be considered instead. The design of this study therefore considers cure rate and egg reduction rate as clinical efficacy endpoints with additional PK analysis, in order to analyse the exposure response relationship in the targeted population.	[…] In summary, due to the uncertainties about the available exposure-response or concentration-response relationship and the predicted efficacy response, combined with the high PK variability observed for PZQ, as well as the uncertainty in the translation of adult data of PZQ to children, a PK only approach is not deemed appropriate and therefore a partial extrapolation PK/PD dose ranging approach has to be considered instead. Due to inconclusive PK data from the first subset of study participants, PK sampling is abandoned. The design of this study therefore considers cure rate and egg reduction rate as clinical efficacy endpoints with no additional PK analysis, and evaluates the dose-response relationship instead of the exposure response relationship in the targeted population.
20	**5.3.1 Inclusion criteria**	
	○ To provide stool and urine samples at screening, 24 h and 8 days after treatment, as well as 14-21 days after treatment • To provide finger prick blood samples for PK studies and venous blood samples for safety	○ To provide stool and urine samples at ~~screening~~ day -28 to day -1, 24 h and 8 days after treatment, as well as 14-21 days after treatment • To provide ~~finger prick blood samples for PK studies~~ venous blood samples for safety

	assessments	assessments

21	**6.1 Description of the Investigational Medicinal Product**	
	Praziquantel (Biltricide® 600 mg) […] In Kenya, the German commercial product will be used. The tablet contains 600 mg of praziquantel and the following inactive ingredients: corn starch, magnesium stearate, microcrystalline cellulose, povidone 25, dodécylsulfate de sodium, Macrogol 4000, titan dioxide (E171) and hypromellose.	**Praziquantel (Biltricide® 600 mg)** […] ~~In Kenya, the German commercial product will be used. The tablet contains 600 mg of praziquantel and the following inactive ingredients: corn starch, magnesium stearate, microcrystalline cellulose, povidone 25, dodécylsulfate de sodium, Macrogol 4000, titan dioxide (E171) and hypromellose.~~
22	**6.5 Concomitant Medications and Procedures**	
	[…] All subjects will undergo a diagnostic test for malaria at pre screening or at screening.	[…] All subjects will undergo a diagnostic test for malaria at ~~pre screening or at~~ screening.
23	**6.5.2 Prohibited medicines**	
	[…] Also, any medication from screening until last PK sampling is not allowed without prior approval from the Investigator (except for occasional use of paracetamol or ibuprofen).	[…] Also, any medication from screening until ~~last PK~~ end of confinement is not allowed without prior approval from the Investigator (except for occasional use of paracetamol or ibuprofen).
24	**6.10 Blinding**	
	The study is open label. For Part 1, PK/PD laboratory testing and evaluation of primary endpoint (i.e. number of eggs per gram of faeces) will be evaluated without laboratory staff being aware of the actual treatment received by subjects.	The study is open label. For Part 1, ~~PK/PD laboratory testing and~~ evaluation of primary endpoint (i.e. number of eggs per gram of faeces) will be evaluated without laboratory staff being aware of the actual treatment received by subjects.
25	**7.1.1 Screening**	**7.1.1~~Screening~~ Pre-screening**
		Study participants will be selected from communities living in the region of PPD Prior to study onset, a list of all children aged 2-6 years (Part 1) and 3-24 months (Part 2) living in the selected areas will be prepared using records obtained from the latest census. At study beginning, all households in the villages will be informed about the study. Prior to performing any trial assessments that are not part of routine medical care for the subject, the Investigator or an appropriate designee (if local regulations permit) will obtain written pre-screening consent from one of the parents or a legal representative of the subject to allow the diagnosis activities and the identification of infected children as described in Section 9.2.

		Parents/legal representatives of participating subjects will be provided with plastic containers labelled with unique identification numbers (IDs) at the first day of pre-screening. 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 will be processed on the same day. Pre-screening diagnosis of *S. mansoni* infection will be done using a single POC-CCA urine cassette test. Subjects who are positive for POC-CCA test will provide: • One urine sample to assess *S. haematobium* co-infection using the filtration technique. One urine sample will be collected from each subject .10 ml of urine samples will be filtered through a filter mesh which will be then examined under the microscope for *S. haematobium* egg count.*S. haematobium* positive diagnosis is defined as positive egg counts of *S. haematobium* in urine (> 1 egg/10 ml of urine) according to WHO classification: light (<50 eggs/10 ml of urine) and heavy (≥50 eggs/10 ml of urine) infections. • Two stool samples to assess infection intensity using the Kato-Katz method. Two stool samples will be collected from each subject on different days within a maximum of 5 days, at day -28 to day -1 as baseline and 14-21 days after dosing. Infection intensity (expressed as egg count per gram of stool (epg)) will be calculated for each individual. *S. mansoni* positive diagnosis is defined as positive egg counts of *S. mansoni* in stool (>1 egg/1 occasion) according to the WHO classification: light (1-99 eggs per gram of faeces), moderate (100-399 eggs per gram of faeces) and heavy (≥ 400 eggs per gram of faeces) infections.
26	**7.1.1 Screening**	~~**7.1.2**~~ **7.1.2 Screening**
	Study participants will be selected from communities living in the PPD Prior to study onset, a list of all children aged 2-6 years (Part 1) and 3-24 months (Part 2) living in the selected areas will be prepared using records obtained from the latest census. At study beginning, all households in the villages will be informed about the study. Prior to performing any trial assessments that are not part of routine medical care for the subject, the Investigator	~~Study participants will be selected from communities living in the~~PPD ~~Prior to study onset, a list of all children aged 2-6 years (Part 1) and 3-24 months (Part 2) living in the selected areas will be prepared using records obtained from the latest census.~~ ~~At study beginning, all households in the villages will be informed about the study. Prior to performing any trial assessments that are not part of routine medical care for the subject, the Investigator~~

	or an appropriate designee (if local regulations permit) will obtain written informed consent from one of the parents or a legal representative of the subject as described in Section 9.2.	~~or an appropriate designee (if local regulations permit) will obtain written informed consent from one of the parents or a legal representative of the subject as described in Section 9.2.~~
	Parents/legal representatives of participating subjects will be provided with plastic containers labelled with unique identification numbers (IDs) at the first day of screening. 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 will be processed on the same day.	~~Parents/legal representatives of participating subjects will be provided with plastic containers labelled with unique identification numbers (IDs) at the first day of screening. 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 will be processed on the same day.~~
	Screening diagnosis of *S. mansoni* infection will be done using a single POC-CCA urine cassette test. Subjects who are positive for POC-CCA test will provide: • One blood sample collected by finger puncture to detect malaria infection using a Rapid Diagnostic Test (RDT). Treatment of concomitant diseases such as malaria will be done according to the country national guidelines. Subjects who require malaria treatment before receiving the study drug will be withdrawn from the study. • One urine sample to assess *S. haematobium* co-infection using the filtration technique. *S. haematobium* positive diagnosis is defined as positive egg counts of *S. haematobium* in urine (> 1 egg/10 ml of urine) according to WHO classification: light (<50 eggs/10 ml of urine) and heavy (≥50 eggs/10 ml of urine) infections. • Two stool samples to assess infection intensity using the Kato-Katz method. Two stool samples will be collected from each subject on different days within a maximum of 5 days, at screening as baseline and 14-21 days after dosing. Infection intensity (expressed as egg count per gram of stool (epg)) will be calculated for each individual. *S. mansoni* positive diagnosis is defined as positive egg counts of *S. mansoni* in stool (>1 egg/1 occasion) according to the WHO classification: light (1-99 eggs per gram of faeces), moderate (100-399 eggs per gram of faeces) and heavy (≥ 400 eggs per gram of faeces) infections.	~~Screening diagnosis of *S. mansoni* infection will be done using a single POC-CCA urine cassette test. Subjects who are positive for POC-CCA test will provide:~~ • ~~One blood sample collected by finger puncture to detect malaria infection using a Rapid Diagnostic Test (RDT). Treatment of concomitant diseases such as malaria will be done according to the country national guidelines. Subjects who require malaria treatment before receiving the study drug will be withdrawn from the study.~~ • ~~One urine sample to assess *S. haematobium* co-infection using the filtration technique. *S. haematobium* positive diagnosis is defined as positive egg counts of *S. haematobium* in urine (> 1 egg/10 ml of urine) according to WHO classification: light (<50 eggs/10 ml of urine) and heavy (≥50 eggs/10 ml of urine) infections.~~ • ~~Two stool samples to assess infection intensity using the Kato-Katz method. Two stool samples will be collected from each subject on different days within a maximum of 5 days, at screening as baseline and 14-21 days after dosing. Infection intensity (expressed as egg count per gram of stool (epg)) will be calculated for each individual. *S. mansoni* positive diagnosis is defined as positive egg counts of *S. mansoni* in stool (>1 egg/1 occasion) according to the WHO classification: light (1-99 eggs per gram of faeces), moderate (100-399 eggs per gram of faeces) and heavy (≥ 400 eggs per gram of faeces) infections.~~
	Schistosome-positive subjects together with one of their parents/legal representatives will be transferred to the study hospital, where the following tests/information gathering will be performed within maximum four weeks prior to treatment initiation:	Schistosome-positive subjects after assessment by the Kato Katz method together with one of their parents/legal representatives will be invited to the study hospital ~~where the following tests/information gathering will be performed within maximum four weeks prior to treatment initiation:~~. The Investigator

	[…] Malaria rapid diagnostic test , if not done at pre-screening	or an appropriate designee (if local regulations permit) will obtain written informed consent to allow the participation in the study and the completion of the study procedures, from one of the parents or a legal representative of the subject as described in Section 9.2. In the hospital, the following tests/information gathering will be performed within maximum ~~four weeks~~ one week prior to treatment initiation: […] ~~Malaria rapid diagnostic test , if not done at pre-screening~~ A Rapid Diagnostic Test (RDT) to detect malaria infection (one blood sample collected by finger puncture). Treatment of concomitant diseases such as malaria will be done according to the country national guidelines. Subjects who require malaria treatment before receiving the study drug will be withdrawn from the study.
27	**7.1.2 Treatment period**	**7.1.3 Treatment period**
	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** Subjects 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 sample will be taken within maximum 1 hour prior to dosing. **Post-dose assessments** PK samples will be taken according to the sampling scheme (see Section 0). 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. In cohort C1, vital signs will be recorded 8 hours after first dosing, before PK samples are taken. Physical examination will be performed 8 and 24 hours (± 10% in hours) after first dosing, before PK samples are taken. PK sampling after the first dose should be taken before the second dose is administered. In cohorts C2-C9, vital signs will be recorded 8 hours after dosing, before PK samples are taken. Physical examination will be performed 8 and 24 hours (± 10% in hours) after dosing, before PK samples are taken.	~~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** Subjects 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 sample will be taken within maximum 1 hour prior to dosing.~~ **Post-dose assessments** ~~PK samples will be taken according to the sampling scheme (see Section 0). 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.~~ ~~In cohort C1~~ Vital signs will be recorded 8 hours after first dosing~~, before PK samples are taken~~. Physical examination will be performed 8 and 24 hours (± 10% in hours) after first dosing~~, before PK samples are taken. PK sampling after the first dose should be taken before the second dose is administered.~~ ~~In cohorts C2-C9, vital signs will be recorded 8 hours after dosing, before PK samples are taken. Physical examination will be performed 8 and 24 hours (± 10% in hours) after dosing, before PK samples are taken.~~

	Clinical safety laboratory evaluations (i.e. hematology, biochemistry and urinalysis) and urine collection for POC-CCA test will be performed 24 hours (± 10% in hours) after dosing. All biological assessments will be performed in fasting condition, if possible.	Clinical safety laboratory evaluations (i.e. hematology, biochemistry and urinalysis) and urine collection for POC-CCA test will be performed 24 hours (± 10% in hours) after dosing. All biological assessments will be performed in fasting condition, if possible. 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 after the specified 18/24 Hours and the additional night will not be considered as part of confinement. As such, it will not qualify as SAE, as described in section 7.4.1.1.
28	**7.4.1.2 Safety Reporting to Health Authorities, Independent Ethics Committees/Institutional Review Boards and Investigators**	
	At each trial visit, the subject and the parents/representatives will be queried on changes in his or her condition..	~~At each trial visit,~~ From screening visit to end of study, the subject and the parents/representatives will be queried on changes in his or her condition.
29	**7.4.1.3 Definition of the Adverse Event Reporting Period**	
	The AE reporting period for safety surveillance begins when the subject is initially included in the trial (date of first signature of informed consent) and continues through the trial's post treatment follow-up period until the End of Trial Visit.	The AE reporting period for safety surveillance begins ~~when the subject is initially included in the trial~~ at screening visit, (date of signature of informed screening consent) and continues through the trial's post treatment follow-up period until the End of Trial Visit.
30	**7.5. Pharmacokynetics**	
	[…]	Not applicable
31	**8.4 Analysis sets**	
	[…] PK analysis sets: There will be two analysis sets, one for non-compartmental PK analysis (NCA) and one for Population PK. The NCA Analysis Set will consist of all subjects who receive at least one dose of any formulation of PZQ, have been allocated to rich PK sampling, have no protocol deviations affecting PK and provide at least three measurable post-dose concentrations. The Population PK Analysis Set will consist of all subjects who receive at least one dose of any formulation of PZQ, have no protocol deviations affecting PK and provide at least one measurable post-dose concentration. Subjects will be analyzed according to the actual treatment they received. All concentrations measured will be included in the descriptive statistics for concentration data.	[…] ~~PK analysis sets:~~ ~~There will be two analysis sets, one for non-compartmental PK analysis (NCA) and one for Population PK. The NCA Analysis Set will consist of all subjects who receive at least one dose of any formulation of PZQ, have been allocated to rich PK sampling, have no protocol deviations affecting PK and provide at least three measurable post-dose concentrations. The Population PK Analysis Set will consist of all subjects who receive at least one dose of any formulation of PZQ, have no protocol deviations affecting PK and provide at least one measurable post-dose concentration.~~ ~~Subjects will be analyzed according to the actual treatment they received. All concentrations measured will be included in the descriptive statistics for concentration data.~~
32	**8.5 Analysis sets**	

	All efficacy, safety and pharmacokinetic endpoints will be analysed descriptively. Graphs will be produced as appropriate. Point estimation and 95% confidence interval (CI) will be calculated for primary and key secondary endpoints for each treatment arm.	All efficacy and safety ~~and pharmacokinetic~~ endpoints will be analysed descriptively. Graphs will be produced as appropriate. Point estimation and 95% confidence interval (CI) will be calculated for primary and key secondary endpoints for each treatment arm.
33	**8.5.1 General considerations**	
	Pharmacokinetic calculations See Section 7.5.2	**Pharmacokinetic calculations** Not applicable.
34	**8.6 Interim and Additional Planned Analyses**	
	[…] At the end of Part 1, the final analysis will be conducted on data as clean as possible. The Safety Monitoring Committee will assess the data (safety, efficacy and PK) in order to recommend an optimal ODT dose (L-PZQ or rac-PZQ) for Part 2. This optimal ODT dose (L-PZQ or rac-PZQ) will be corrected by using allometric scaling of the PK data available from Part 1 as well as a maturation factor (to compensate for the immature metabolic system in infants), in order to identify the appropriate dose(s) to treat cohorts 8 and 9.	[…] At the end of Part 1, the final analysis will be conducted on data as clean as possible. The Safety Monitoring Committee will assess the data (safety and efficacy) in order to recommend an optimal ODT dose (L-PZQ or rac-PZQ) for Part 2. ~~This optimal ODT dose (L-PZQ or rac-PZQ) will be corrected by using allometric scaling of the PK data available from Part 1 as well as a maturation factor (to compensate for the immature metabolic system in infants), in order to identify the appropriate dose(s) to treat cohorts 8 and 9.~~
35	**9.2 Subject Information and Informed Consent**	
	[…] A subject information sheet must be prepared in the local language PPD) in accordance with ICH GCP and will be provided by the Sponsor for the purpose of obtaining informed consent/assent.	[…] A subject information sheet must be prepared in the local language, PPD in accordance with ICH GCP and will be provided by the Sponsor for the purpose of obtaining informed consent/assent.
36	**9.6 Independent Ethics Committee or Institutional Review Board**	
	Prior to commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents (e.g., informed consent form, documents of subjects data collection, certificate of insurance, etc.) to the responsible IECs/IRBs (PPD) for their favourable opinion or approval, which will be filed in the Investigator Site File. Contact details of the PPD are as follows: PPD PPD	Prior to commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents (e.g., informed consent form, documents of subjects data collection, certificate of insurance, etc.) to the responsible IECs/IRBs PPD) for their favourable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Trial Master File at PPD ~~Contact details of the~~ PPD ~~are as follows:~~ PPD PPD

	Tel: PPD E-mail: PPD	~~Tel:~~ PPD ~~E-mail:~~ PPD
37	**9.7 Health Authorities**	
	The clinical trial protocol and any applicable documentation (e.g., Investigational Medicinal Product Dossier, Subject Information and Informed Consent Form) will be submitted or notified to the Ivory Coast and Kenyan Health Authorities in accordance with their national regulations and requirements.	The clinical trial protocol and any applicable documentation (e.g., Investigational Medicinal Product Dossier, Subject Information and Informed Consent Form) will be submitted or notified to the Ivory Coast ~~and Kenyan Health~~ Health Authorities in accordance with its national regulations and requirements.
38	**10.4 Monitoring, Quality Assurance and Inspection by Health Authorities**	
	This trial will be monitored in accordance with the ICH GCP guidelines and any other applicable regulations. The site Monitor will perform visits to the trial site at regular intervals according to the monitoring plan.	This trial will be monitored in accordance with the ICH GCP guidelines and any other applicable regulations. The site Monitor will perform off-site and on-site visits at regular intervals according to the monitoring plan.
39		**Signature Page – Sponsor Medical Responsible**
		Name, academic degree: PPD Function/Title: Medical Responsible Institution: Merck KGaA Address: Frankfurter Strasse 250 64293 Darmstadt, Germany Telephone number: PPD Fax number: PPD E-mail address: PPD
40	**Signature Page – Coordinating Investigator**	
	Name, academic degree: PPD Function/Title: Coordinating Investigator Institution: PPD Telephone number: PPD E-mail address: PPD	~~Name, academic degree:~~ PPD ~~Function/Title: Coordinating Investigator~~ ~~Institution:~~ PPD ~~Telephone number:~~ PPD ~~E-mail address:~~ PPD
41	**Appendix II:Table of study procedures and assessment – Cohort C1**	
	PK sampling	~~PK sampling~~

<table>
<tr><td>42</td><td colspan="2">Appendix II: Table of study procedures and assessments - Cohort C2-C7</td></tr>
<tr><td></td><td>PK sampling</td><td>~~PK sampling~~</td></tr>
<tr><td>43</td><td colspan="2">Appendix II: Table of study procedures and assessments - Cohort C8-C9</td></tr>
<tr><td></td><td>•
• ICF signature at pre-screening (D-28 to D-1)
• Malaria rapid diagnostic test at pre-screening (D-28 to D-1) or at screening if not done at pre-screening
• PK sampling</td><td>• Pre-screening consent at D-28 to D-1
• ICF signature at ~~pre-~~screening (D-7 to D1)
• Malaria rapid diagnostic test at screening (D-7 to D1
• ~~PK sampling~~</td></tr>
<tr><td>44</td><td colspan="2">Appendix III: Volume of biological fluid collected at each assessment time point (Cohorts C1-C7)</td></tr>
<tr><td></td><td>Treatment (D1)
<table>
<tr><th>Body Fluid</th><th>Type of Test</th><th>Specific Test</th><th>Number of Sampling</th><th>Volume per Sampling (approx.)</th><th>Total Volume</th></tr>
<tr><td>Blood</td><td>PK</td><td>NA</td><td>4-11</td><td>100 µl</td><td>400-1100 µl</td></tr>
</table>
End of Confinement Visit (D2)
<table>
<tr><th>Body Fluid</th><th>Type of Test</th><th>Specific Test</th><th>Number of Sampling</th><th>Volume per Sampling (approx.)</th><th>Total Volume</th></tr>
<tr><td rowspan="2">Urine</td><td>Parasitology</td><td>POC-CCA test</td><td>1</td><td>100 µl</td><td rowspan="2">5-10 ml</td></tr>
<tr><td>Urinalysis</td><td>NA</td><td>1</td><td>5-10 ml</td></tr>
<tr><td rowspan="3">Blood</td><td>PK</td><td>NA</td><td>1</td><td>100 µl</td><td rowspan="3">5-10 ml</td></tr>
<tr><td>Haematology</td><td>NA</td><td>1</td><td>5-10 ml</td></tr>
<tr><td>Biochemistry</td><td>NA</td><td>1</td><td>5-10 ml</td></tr>
</table></td><td>~~Treatment (D1)~~
End of Confinement Visit (D2)
<table>
<tr><th>Body Fluid</th><th>Type of Test</th><th>Specific Test</th><th>Number of Sampling</th><th>Volume per Sampling (approx.)</th><th>Total Volume</th></tr>
<tr><td rowspan="2">Urine</td><td>Parasitology</td><td>POC-CCA test</td><td>1</td><td>100 µl</td><td rowspan="2">5-10 ml</td></tr>
<tr><td>Urinalysis</td><td>NA</td><td>1</td><td>5-10 ml</td></tr>
<tr><td rowspan="3">Blood</td><td>~~PK~~</td><td>~~NA~~</td><td>~~1~~</td><td>~~100 µl~~</td><td rowspan="3">5-10 ml</td></tr>
<tr><td>Haematology</td><td>NA</td><td>1</td><td>5-10 ml</td></tr>
<tr><td>Biochemistry</td><td>NA</td><td>1</td><td>5-10 ml</td></tr>
</table></td></tr>
<tr><td>45</td><td colspan="2">Appendix III: Volume of biological fluid collected at each assessment time point (Cohorts C8-C9)</td></tr>
<tr><td></td><td></td><td>Pre-screening (D-28 to D-1)
<table>
<tr><th>Body Fluid</th><th>Type of Test</th><th>Specific Test</th><th>Number of Sampling</th><th>Volume/weight per Sampling (approx.)</th><th>Total Volume</th></tr>
<tr><td>Stool</td><td>Parasitology</td><td>Kato-Katz</td><td>2</td><td>2 g</td><td>4 g</td></tr>
<tr><td rowspan="2">Urine</td><td rowspan="2">Parasitology</td><td>POC-CCA test</td><td>1</td><td>100 µl</td><td rowspan="2">10 ml</td></tr>
<tr><td>Filtration</td><td>1</td><td>10 ml</td></tr>
</table>
Screening (D-7 to D1)
<table>
<tr><th>Body Fluid</th><th>Type of Test</th><th>Specific Test</th><th>Number of Sampling</th><th>Volume per Sampling (approx.)</th><th>Total Volume</th></tr>
<tr><td>Urine</td><td>Urinalysis</td><td>NA</td><td>1</td><td>5-10 ml</td><td>5-10 ml</td></tr>
<tr><td rowspan="3">Blood</td><td>Parasitology</td><td>Malaria RDT</td><td>1</td><td>20-50 µl</td><td>20-50 µl</td></tr>
<tr><td>Haematology</td><td>NA</td><td>1</td><td>5-10 ml</td><td rowspan="2">5-10 ml</td></tr>
<tr><td>Biochemistry</td><td>NA</td><td>1</td><td>5-10 ml</td></tr>
</table>
End of Confinement Visit (D2)
<table>
<tr><th>Body Fluid</th><th>Type of Test</th><th>Specific Test</th><th>Number of Sampling</th><th>Volume per Sampling (approx.)</th><th>Total Volume</th></tr>
<tr><td rowspan="2">Urine</td><td>Parasitology</td><td>POC-CCA test</td><td>1</td><td>100 µl</td><td rowspan="2">5-10 ml</td></tr>
<tr><td>Urinalysis</td><td>NA</td><td>1</td><td>5-10 ml</td></tr>
<tr><td rowspan="2">Blood</td><td>Haematology</td><td>NA</td><td>1</td><td>5-10 ml</td><td rowspan="2">5-10 ml</td></tr>
<tr><td>Biochemistry</td><td>NA</td><td>1</td><td>5-10 ml</td></tr>
</table>
Follow up Visit (D8)
<table>
<tr><th>Body Fluid</th><th>Type of Test</th><th>Specific Test</th><th>Number of Sampling</th><th>Volume per Sampling (approx.)</th><th>Total Volume</th></tr>
<tr><td>Urine</td><td>Parasitology</td><td>POC-CCA test</td><td>1</td><td>100 µl</td><td>100 µl</td></tr>
</table>
End of Study Visit (D14-D21)</td></tr>
</table>

Body Fluid	Type of Test	Specific Test	Number of Sampling	Volume per Sampling (approx.)	Total Volume
Stool	Parasitology	Kato-Katz	2	2 g	4 g
Urine	Parasitology	POC-CCA test	1	100 µl	100 µl

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List of Abbreviations

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{extra}	Extrapolated AUC from time t_{last} to infinity given as percentage from $AUC_{0-\infty}$
$AUC_{0-\infty}$	AUC from time zero to infinity
AUC_{0-t}	AUC from time zero to the last sampling time at which the concentration is at or above the lower limit of quantification
BA	Bioavailability
BP	Blood pressure
CI	Confidence Interval
CL/f	Apparent total body clearance of drug from plasma
C_{max}	Maximum observed concentration in plasma
CMO	Contract Manufacturing Organization
CCI	[redacted]
CR	Cure Rate
CRF	Case Report Form
CRP	C-reactive Protein
CV	Coefficient of Variability
DBS	Dried Blood Sample
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
CCI	[redacted]
ERR	Egg Reduction Rate
EU	European Union
FDA	Food and Drug Administration
FPI	First Patient In
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification number

IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IST	Investigator Sponsored Trial
LLOQ	Lower Limit of Quantification
LP	Last Patient
LPI	Last Patient In
L-PZQ	Levorotatory enantiomer of praziquantel
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention to Treat
NCA	Non-Compartmental Analysis
NTDs	Neglected Tropical Diseases
ODT	Oral Dispersible Tablet
PACTR	Pan African Clinical Trials Registry
PD	Pharmacodynamics
PGx	Pharmacogenetics/Pharmacogenomics
PK	Pharmacokinetics
POC-CCA	Point-of-Care Circulating Cathodic Antigen
PP	Per Protocol
PQP	Prequalification of Medicines Programme
PR	Pulse Rate
Pre-SAC	Pre-school aged children
PSUR	Period Safety Update Report
PZQ	Praziquantel
Rac	Racemate
RDT	Rapid Diagnostic Test
rINN	Recommended International Nonproprietary name
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCI	Schistosomiasis Control Initiative
SERU	Scientific and Ethics Review Unit
SMC	Safety Monitoring Committee
SPC	Summary of Product Characteristics
STH	Soil Transmitted Helminthes
SUSAR	Suspected unexpected serious adverse reactions
CCI	[redacted]

$t_{1/2}$	Apparent terminal half-life
t_{lag}	Time prior to the first measurable (non-zero) concentration
t_{max}	Time to reach the maximum plasma concentration
ULN	Upper Limit of Normal
Vz/f	Apparent volume of distribution during the terminal phase
WHA	World Health Assembly
WHO	World Health Organization
λ_z	Apparent terminal elimination rate constant

1 Synopsis

Clinical Trial Protocol Number	MS200661-0005
Title	Open-label, dose-finding, 2-parts, efficacy phase II study with three formulations (racemate praziquantel commercial oral tablets, new oral disintegrating tablets of racemate praziquantel and L-praziquantel) in schistosomiasis (*S. mansoni*) infected children aged 2-6 years (Part 1), followed by an assessment of efficacy and safety with the selected formulation and dosage in *S. mansoni* infected infants aged 3-24 months (Part 2)
Trial Phase	II
IND Number	Not Applicable
FDA covered trial	No
EudraCT Number	Not Applicable
Coordinating Investigator (PPD)	PPD PPD
Sponsor	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany
Trial centers/countries	PPD
Planned trial period	Enrolment start date (FPI): Jun 2016 (Part 1) Apr 2018 (Part 2) Enrolment finish date (LPI): Dec 2017 (Part 1) Aug 2018 (Part 2) Treatment period end date (LP off treatment): Dec 2017 (Part 1) Aug 2018 (Part 2) Follow-up period end date (LP off study): Dec2017 (Part 1) Sep 2018 (Part 2) Planned date for primary analysis: Feb 2018 Planned date for final analysis: Oct 2018
Trial Registry	Clinicaltrials.gov, PACTR

Study Objectives	**Primary objective** **<u>Part 1</u>** • To identify the optimal single dose of rac-PZQ ODT or L-PZQ ODT formulation which has a clinically meaningful cure rate (as assessed by Kato-Katz method) and an acceptable safety profile in 2- to 6-year-old children infected with *S. mansoni*. **<u>Part 2</u>** • To evaluate the efficacy and safety of the selected ODT formulation (L-PZQ or rac-PZQ) from Part 1 at the appropriate adjusted dose(s) in infants aged 3 to 24 months infected with *S. mansoni*. **Secondary objectives** **<u>Part 1</u>** • To determine the safety of different doses of rac-PZQ ODT and L-PZQ ODT in children aged 2 to 6 years infected with *S. mansoni* • To explore the dose-response relationship for L-PZQ ODT and rac-PZQ ODT in children aged 2 to 6 years infected with *S. mansoni* • To assess the efficacy and safety of rac-PZQ commercial tablet at 20 mg/kg t.i.d. dose administration and at 40 mg/kg single dose administration in children aged 2 to 6 years infected with *S. mansoni* • To assess the acceptability in terms of ease of administration of the rac-PZQ ODT and L-PZQ ODT in children aged 2 to 6 years infected with *S. mansoni* **<u>Part 2</u>** • To assess the acceptability in terms of ease of administration of the selected ODTs (rac-PZQ or L-PZQ) in 3- to 24-month infants infected with *S. mansoni* • To explore the dose-response relationship for L-PZQ and rac-PZQ in 3- to 24-month infants infected with *S. mansoni*
Study design and plan	This is a phase II study consisting of two parts (Part 1 and Part 2). Part 2 will only start once Part 1 is completed. The study will be conducted at the PPD **Part 1** is an open-label, randomized, controlled, dose-finding study with three formulations of PZQ (commercial rac-PZQ tablets, oral disintegrating tablets of rac-PZQ and L-PZQ) in children aged 2-6 years infected with *S. mansoni*. Subjects will be randomized to one

	of the following arms: C1: commercial rac-PZQ (Biltricide®) at 20 mg/kg dose t.i.d. (three times a day) C2: commercial rac-PZQ tablets (Biltricide®) at 40 mg/kg single dose C3: rac-PZQ ODTs at 40 mg/kg single dose C4: rac-PZQ ODTs at 60 mg/kg single dose C5: L-PZQ ODTs at 30 mg/kg single dose C6: L-PZQ ODTs at 45 mg/kg single dose C7: L-PZQ ODTs at 60 mg/kg single dose After 20 patients from each of the cohorts C1 to C6 are treated, the acute (24-hour) safety data of all groups will be summarized and evaluated by the SMC, to decide on inclusion of the 7th arm (C7). C7 will be included in the randomization scheme only after SMC approval while randomization for the other groups can continue to 40 subjects per arm. In case of safety concerns observed with the L-PZQ ODTs treated cohorts, the SMC can decide to assess the exposure in a minimum of 10 subjects in the L-PZQ ODTs cohorts C5 and C6 before deciding to escalate to a higher dose of L-PZQ. **Part 2** includes a cohort with infants of 13-24 months infected with *S. mansoni* (C8) and a cohort with infants of 3-12 months infected with *S. mansoni* (C9) which will be enrolled in an age-staggered approach. Infants in cohort C8 will be treated with rac-PZQ ODT or L-PZQ ODT at the optimal dose level selected by SMC from Part 1 (based on benefits-risks evaluation). After 10 infants aged 13 to 24 months have been enrolled, the overall safety and efficacy data in these patients will be evaluated by the SMC for the decision to include the lower age group of infants (cohort C9). SMC will also decide whether dose level adaptations are needed before starting enrolling C9.
Planned number of subjects	Total number of subjects: 360-420 (if C7 is included) enrolled subjects in Part 1 and 40 enrolled subjects in Part 2. Number of subjects per treatment arm: Part 1: 60 enrolled subjects in each cohort (C1 to C7) Part 2: 30 enrolled subjects in the 13-24 months cohort (C8) 10 enrolled subjects in the 3-12 months cohort (C9)
Primary endpoint	Clinical cure defined as no parasite eggs in the stools (*S. mansoni* infections) 14-21 days after treatment. Egg counts will be determined by the Kato-Katz method.

Secondary endpoints	**Efficacy endpoints** • Egg Reduction Rate (ERR, %) calculated based on the arithmetic (and geometric) mean egg count per gram of stool (epg) before and 14-21 days after treatment (as determined by Kato-Katz method). • Cure defined as absence of parasite antigens in urine as assessed by the commercially available POC-CCA test for *S. mansoni* • **Safety and tolerability endpoints** • Changes in laboratory safety parameters and vital signs (body temperature, blood pressure and pulse rate) • Occurrence, nature, severity and outcome of adverse events • Occurrence of Adverse Drug Reactions per treatment group
Pharmacokinetics	Not applicable
Diagnosis	Diagnosis of *S. mansoni* infection will be done using a single POC-CCA urine cassette test. Briefly, one urine sample will be collected from each subject and evaluated with a commercially available POC-CCA cassette test. Subjects who are positive for POC-CCA test will provide stool samples to assess infection intensity using the Kato-Katz method. Kato-Katz diagnosis of *S. mansoni* infection: two stool samples will be collected from each subject on different days within a maximum of five days, at day -28 to day -1 as baseline and 14-21 days after dosing (for treatment efficacy assessment). Three Kato-Katz thick smears (41.7 mg) will be prepared from each stool sample and read under a microscope following the instructions of the Kato-Katz manual from the World Health Organization. Infection intensity (expressed as egg count per gram of stool (epg)) will be calculated for each individual. *S. mansoni* positive diagnosis is defined as positive egg counts of *S. mansoni* in stool (>1 egg/1 occasion) according to the WHO classification: light (1-99 eggs per gram of faeces), moderate (100-399 eggs per gram of faeces) and heavy (≥ 400 eggs per gram of faeces) infections. Subjects will be tested for *S. haematobium* in order to exclude *S. mansoni/S. haematobium* co-infections. Diagnosis of *S. haematobium* infection will be made by urine examination using the filtration technique. One urine sample will be collected from each subject at day -28 to day -1 .10 ml of urine samples will be filtered through a filter mesh which will be then examined under the microscope for *S. haematobium* egg count. *S. haematobium* positive diagnosis is defined as positive egg counts of *S. haematobium* in urine (>1 egg/10 ml of urine).

Eligibility criteria	To be eligible for the study, subjects must meet all of the inclusion criteria and none of the exclusion criteria. **Inclusion criteria** • Written informed consent from one of the parents/legal representatives prior to any trial related procedure • Male and female children aged 2 to 6 years (Part 1) and 3 to 24 months (Part 2) • *S. mansoni* positive diagnosis defined as positive egg counts in stool (>1 egg/1 occasion) according to WHO classification [1]: light (1-99 eggs per gram of faeces), moderate (100-399 eggs per gram of faeces) and heavy (≥400 eggs per gram of faeces) infections • Minimum weight of 8.0 kg in 2- to 6-year-old children and of 4.0 kg in 3- to 24-month infants • Parent/legal representative's ability to communicate well with the Investigator, to understand the protocol requirements and restrictions, and willing their children to comply with the requirements of the entire trial, i.e.: - To be examined by a study physician at screening and 14-21 days after treatment - To provide stool and urine samples at day -28 to day -1 ,24 h and 8 days after treatment, as well as 14-21 days after treatment - To provide venous blood samples for safety assessments. **Exclusion criteria** • Treatment in the 4 weeks prior to study screening with PZQ, other anti-helminthic, anti-malarial or anti-retroviral compounds or any other medication that might affect the PK of PZQ such as certain antiepileptics (e.g., carbamazepine or phenytoin), glucocorticosteroids (e.g., dexamethasone), chloroquine, rifampicin or cimetidine (see Section 6.5.2 and Biltricide® SPC) • For children being breast fed, treatment of the mothers/wet nurses with PZQ in the 3 days prior to administration of IMP • Previous history of adverse reactions associated with PZQ treatment • History of acute or severe chronic disease including hepato-splenic schistosomiasis • Marked increases of the liver transaminases (alanine aminotransferase and/or aspartate aminotransferase) above 3x

	ULN • Fever defined as temperature above 38.0°C • Debilitating illnesses such as tuberculosis, malnutrition, etc. as well as a medical history of seizures • Mixed *S. haematobium and S. mansoni* infections • Findings in the clinical examination of schistosome-infected children participating in the study as performed by the study clinician on the treatment day, that in the opinion of the Investigator constitutes a risk or a contraindication for the participation of the subject in the study or that could interfere with the study objectives, conduct or evaluation • Unlikelihood to comply with the protocol requirements, instructions and trial-related restrictions, e.g., uncooperative attitude, inability to return for follow-up visits, and improbability of completing the trial
Investigational Medicinal Product	• Rac-PZQ 150 mg orally disintegrating tablets (ODTs) • L- PZQ 150 mg orally disintegrating tablets (ODTs) **Mode of administration:** tablets will be dispersed in water and the solution will be swallowed after a meal. **Doses** Part 1**:** • Rac-PZQ ODTs at 40 mg/kg (cohort C3) and 60 mg/kg (cohort C4), single doses • L-PZQ ODTs at 30 mg/kg (cohort C5), 45 mg/kg (cohort C6) and 60 mg/kg (cohort C7, optional), single doses Part 2: • Rac-PZQ ODTs or L-PZQ ODTs dose selected from Part 1
Reference therapy	Rac-PZQ oral tablets (Biltricide® 600 mg) in crushed form **Mode of administration:** the tablets (scored) will be divided into 150 mg parts, crushed, suspended in water and the solution will be swallowed after a meal. **Doses:** 20 mg/kg t.i.d. dose given every 4 hours (cohort C1) and 40 mg/kg single dose (cohort C2)
Planned trial and treatment duration per subject	Maximum 28 days of pre-screening and screening period, followed by 1 day treatment and 14-21 days of follow-up period. Total duration per subject: up to 7 weeks.
Statistical methods	All efficacy and safety endpoints will be analysed descriptively. Point estimation and 95% confidence interval (CI) will be calculated for primary and secondary efficacy endpoints for each treatment

	arm. The calculation of 95% CIs for proportions will rely on the Clopper-Pearson (exact) method. The primary efficacy endpoint will be presented as cure rate (Kato-Katz method). For each treatment arm, the cure rate will correspond to the percentage of subjects becoming egg-negative 14-21 days after treatment with the study drug. Criteria for dose selection will be described in a SAP prior to first patient first dose. Secondary endpoints will be described by treatment arms: • Mean Egg Reduction Rate (ERR, %) 14-21 days after treatment (Kato-Katz method) • Cure rate (POC-CCA method) as assessed by the absence of parasite antigens as determined in urine with the commercially available POC-CCA assay for *S. mansoni* **Sample size estimation** This study is exploratory. There is no null hypothesis tested. Part 1: the sample size is based on the precision of the 95% CI of the cure rate (Kato-Katz method) in each arm. A cure rate of 70% is considered as the minimum-clinically meaningful threshold. A sample size of 50 evaluable subjects provides a probability of around 85% to observe a cure rate of ≥70%, if the overall true cure rate is 75% (assuming 40% of moderate/heavy and 60% of light infections). Assuming an approximately 17% dropout rate, 60 subjects per arm will be randomized to ensure at least 50 evaluable subjects per arm. Part 2: 30 subjects aged 13 to 24 months infected with *S. mansoni* (C8) and 10 subjects aged 3 to 12 months infected with *S. mansoni* (C9) will be included to evaluate drug tolerability and efficacy.

2 Sponsor, Investigators and Trial Administrative Structure

This clinical trial will be sponsored by:

Merck KGaA

Frankfurter Strasse 250

64293 Darmstadt, Germany.

The trial will be conducted at the PPD

The Coordinating Investigator PPD represents all Investigators for decisions and discussions regarding this trial, consistent with the International Conference on Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigator will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical trial report.

Signature pages for the Protocol Lead and the Coordinating Investigator as well as a list of Sponsor responsible persons are in Appendix I.

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

The trial will be outsourced, including monitoring, to the PPD as well as to PPD

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.

3 Background and rationale

3.1 Background on schistosomiasis

Schistosomiasis, also called bilharzia, belongs to one of the most neglected tropical diseases (NTDs) caused by flatworms and remains one of the most prevalent parasitic diseases in developing countries. After malaria, leishmaniasis and other helminth diseases, schistosomiasis is the most important tropical disease in terms of human morbidity with significant economic and public health consequences. The disease is a severe chronic inflammatory disease and is endemic in about 75 developing countries, infecting more than 220 million people, with more than 90% of them living in Africa. They live in rural agricultural and peri-urban areas, and place more than 700 million people at risk. Of the infected patients, 20 million suffer severe morbidities from the disease and some estimate that there are approximately 11,700 deaths related to schistosomiasis yearly. In many areas, schistosomiasis infects a large proportion of children under the age of 14 years [2-4].

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 are *Schistosoma mansoni* (intestinal schistosomiasis) and *Schistosoma haematobium* (causing urogenital schistosomiasis). Urogenital schistosomiasis is also considered to be a risk factor for HIV infection, especially in women.

The WHO recommended control strategy of schistosomiasis is based on preventive chemotherapy interventions targeting the majority of the at-risk population. The current gold standard treatment employs annual single oral dose of the drug Praziquantel (PZQ) 600 mg tablets for adults and children over 4 years at 40 mg/kg. For individual treatment, a 3 times 20 mg/kg bodyweight dose given every 4 to 6 hours [5] has also been registered. The product has been jointly developed by Bayer-Merck in the 1970's, and commercialized as Biltricide® (Bayer), and Cesol®/Cysticide® 500/600 mg (Merck KGaA) for human use, as well as other generic products. In Brazil a single dose of 60 mg/kg bodyweight is the recommended dose to treat children.

The prevalence of schistosomiasis in children is very high, accounting for about 50% of the total infected population of 220 million and many more are at risk from the disease. At the World Health Assembly (WHA) 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-aged children who are at risk of morbidity from schistosomiasis and STH by the year 2010. However, pre-school aged children (pre-SAC), which are a high-risk group for schistosome infections accounting for 10-20 million of the global prevalence, are currently not included in the schistosomiasis control programs due to the lack of a suitable PZQ pediatric formulation. WHA passed Resolution 66.20 (2013) where the Member States essentially confirmed their commitment to fulfil the 2020 Roadmap for Neglected Tropical Diseases (NTDs).

In order to tackle this important public health problem, a pediatric schistosomiasis consortium was formed in July 2012 under the leadership of Merck with the goal of developing a suitable pediatric formulation of PZQ for pre-school-aged children and register its use in schistosomiasis. The consortium currently consists of seven partners: Merck KGaA (Germany), Top Institute Pharma currently called Lygature (Netherlands), Astellas Pharma Inc. (Japan), Swiss Tropical and Public Health Institute (Switzerland), Farmanguinhos (Fiocruz Foundation, Brazil), Simcyp (UK) and Schistosomiasis Control Initiative (SCI) (UK). This Consortium addresses the WHO recommendation (2010 September Meeting Geneva, Switzerland) to develop a water-dispersible formulation for appropriate treatment of pre-school aged children.

3.2 Study rationale

The ultimate goal of this phase II study is to identify the optimal dose of a water-dispersible PZQ formulation (either L-PZQ or rac-PZQ) for further confirmation of safety and efficacy in a phase III trial in pre-school aged children infected with *S. mansoni*. First, the optimal ODT dose (dose that delivers a clinically meaningful efficacy with an acceptable safety profile) to treat children aged 2-6 years infected with *S. mansoni* will be identified. Younger children (13 to 24 months) infected with *S. mansoni* will subsequently be treated with the selected ODT dose from Part 1

Only when this dose has been assessed as safe, lower aged children 3 to 12 months will be included.

3.3 Investigational drug and pre-clinical data

PZQ is a racemic mixture composed of the L-PZQ and D-PZQ enantiomers in a 1:1 ratio. The cidal activity on *S. mansoni* worms resides in the L-PZQ enantiomer (as shown *in vitro* and in animal experiments [6]) whereas the D-PZQ enantiomer was suggested to be largely responsible for the bitterness of the oral formulation [7]. Cidal effects of L-PZQ on *S. japonica* in mice have also been reported [8] and confirmed by efficacy data in humans [9]. So far, the activity of L-PZQ on *S. haematobium* worms has not been studied due to the difficulty of breeding this *Schistosoma* species under laboratory conditions.

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3.4 Clinical evidence to date

3.4.1 Clinical data in adults

Over 40 years of treatment with PZQ racemate tablets showed a good safety and tolerability profile in previous trials, in the recent meta-analysis in children and adults conducted by the WHO [11] and according to the current Periodic Safety Update Reports (PSURs). The recent phase I studies (EMR200661-001 and EMR200585-001) confirmed the good safety profile for rac-PZQ ODTs and L-PZQ ODTs in adults.

The most common and known side effects of PZQ treatment are associated with gastrointestinal effects: diarrhea, nausea, vomiting and abdominal pain. Although also transient neurological effects have been recorded (headache and dizziness), dizziness was not observed after L-PZQ ODTs administration in the phase I study. Regarding the general disorders the following adverse events have been reported: weakness, fatigue and increased body temperature. All these symptoms are usually transient, and spontaneously resolve. Adverse reactions, including hypersensitivity reactions, may partly represent endogenous reactions to the killing off of the parasites by PZQ, and were not observed in the phase I study with L-PZQ or rac-PZQ ODTs in healthy volunteers.

For patients suffering schistosomiasis, this underlying parasitosis could also mask the adverse events 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 [10].

It is frequently not clear whether the complaints reported by patients or adverse effects determined by the doctor have been caused directly by PZQ (I, direct relationship), whether these are to be regarded as an endogenous reaction to the killing off of the parasites by PZQ (II, indirect relationship) or else represent signs and symptoms of the parasitic infection (III, no relationship). It is often difficult to reliably differentiate between possibilities I, II and III (Master SPC for PZQ, dated 22 Feb 2013).

PZQ is contraindicated in proven hypersensitivity to PZQ or any of the excipients as well as in intraocular cysticercosis or in combination with rifampicin. Caution is warranted in decompensated hepatic insufficiency or in patients with hepatosplenic schistosomiasis. Patients 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.

3.4.2 Clinical data in children

3.4.2.1 Efficacy data

A meta-analysis in children combining data from thirty-five studies identified through a systematic literature search was recently conducted [11]. In total 12,562 preschool and school-aged children and adolescents were enrolled, of whom 91% were assessed within 8 weeks of treatment with PZQ at 40 mg/kg dose (54%) or comparators (46%). The meta-analysis showed that the overall cure rate (CR) with PZQ at 40 mg/kg dose was 75.0% (95% CI, 70.2% - 79.6%) and 76.6% (95% CI, 67.4% - 84.7%) for children infected with *S. mansoni* and *S. haematobium*, respectively (Table 1). The mean egg reduction rate (ERR) was 95% for children infected with *S. japonicum*, 94.1% for *S. haematobium* and 86.3% for *S. mansoni*. No significant relationship between dose and ERR was detected. However, the number of pre-school aged children infected with *S. mansoni* in this analysis was limited (n = 988) and this age group received only PZQ doses of 40 mg/kg.

Children age group	Species	Efficacy indicator	Number of groups	Number of children	Mean	Bootstrap 95%CI Lower	Upper
Pre-school	S. Mansoni	CR	12	988	79.4%	71.7%	87.1%
		ERR	9	988	76.1%	59.1%	89.4%
	S. Haematobium	CR	5	179	87.0%	81.9%	93.2%
		ERR	5	179	63.9%	35.3%	89.7%
School-aged	S. Mansoni	CR	25	3169	74.4%	68.4%	80.0%
		ERR	18	2245	85.5%	79.2%	90.9%
	S. Haematobium	CR	22	2876	73.3%	64.3%	81.3%
		ERR	19	2168	91.6%	86.3%	96.0%
Total	S. Mansoni	CR	37	4157	76.0%	71.4%	80.2%
		ERR	27	3233	82.4%	75.2%	88.5%
	S. Haematobium	CR	27	3055	75.9%	67.9%	82.7%
		ERR	24	2347	85.9%	77.7%	92.9%

Legend: CI, confidence interval; CR, cure rate; ERR, egg reduction rate

Table 1. Meta analysis results of cure rates and egg reduction rates after administration of single dose of 40 mg/kg rac-PZQ by age group (courtesy of J. Zwang - personal communication).

PZQ at a single dose of 60 mg/kg was safely administered in a study recently performed in Brazil, including only few pre-school aged children. The results showed that there was no evidence of difference in effectiveness between the different age groups (Table 2).

Age (years)	N	Cure rate	95% CI
4-6	24	91.7%	67.6% - 99.1%
7-8	97	89.7%	80.1% - 95.3%
9-10	119	89.1%	80.5% - 94.4%
11-15	299	91.6%	87.2% - 94.8%

Table 2. Cure rates after administration of rac-PZQ 60 mg/kg single dose, observed in Brazilian children of different age groups infected with *S. mansoni* (courtesy of O. Pieri, Fiocruz Brazil - personal communication)

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3.4.2.2 Safety and tolerability data

A recent meta-analysis on comparative clinical trials where PZQ had been given to pre-school children showed no major safety findings in 1167 pre-school and school-aged children treated with PZQ at 40 mg/kg [11]. A study conducted in Niger in pre-school aged children reported that 34.2% (95% CI, 28.2% - 40.2%) of the pre-school children had experienced an adverse event within 24 hours from PZQ dosing but most of the adverse events occurred within 4 hours after drug administration [13] (Table 4). The most frequent adverse events in pre-school children were drowsiness (29.1%; 95% CI, 28.0% - 30.1%), dizziness (22.4%; 95% CI, 1.3% - 33.9%), fatigue (13.3%; 95% CI, 0.9% - 20.9%) and abdominal pain (13.1%; 95% CI, 3.0% - 30.6%). School aged children had higher frequency of treatment-emergent adverse events, i.e. drowsiness, nausea, abdominal pain, headache and diarrhoea, compared to pre-school children while pre-school had higher frequency in dizziness compared to school-aged children (Table 4).

	Pre-school aged					School-aged				
			Incidence (bootstrap 95% CI)					Incidence (bootstrap 95%CI)		
Adverse event	Number of study arms	Number of subjects	%	Lower bound	Upper bound	Number of study arms	Number of subjects	%	Lower bound	Upper bound
Any adverse event	1	243	34.2	28.2	40.2	9	1342	57.8	44.7	72.0
Drowsiness	2	503	29.1	28.0	30.1	2	285	42.4	35.8	49.0
Dizziness	3	737	22.4	1.3	33.9	13	2812	9.1	4.6	13.8
Fatigue	3	737	13.3	0.9	20.9	3	781	13.2	0.4	28.9
Abdominal pain	4	980	13.1	3.0	30.6	18	3175	33.3	22.5	45.6
Itching/rash	2	503	8.6	8.0	9.1	8	1504	5.5	2.3	9.3
Nausea	3	737	7.8	2.1	12.6	12	2738	13.1	5.9	21.7
Diarrhoea	4	980	7.3	2.6	16.2	15	2786	11.8	5.2	19.5
Vomiting	4	980	6.9	1.7	9.6	14	2591	8.2	3.6	14.5
Headache	3	737	4.4	0.4	6.7	16	2994	16.6	9.8	24.0

Table 4. Adverse event incidence within 24 hours by children age group, PZQ 40 mg/kg (courtesy of J. Zwang - personal communication).

In another study conducted in Uganda, PZQ tablets proved to be safe with only mild, transient reported side effects [14]. As the cohort study progressed (6-month and 12-month follow-ups), the number of cases of dizziness, sleepiness, fatigue, cramps, nausea, sweating and night fevers post-treatment decreased significantly compared to baseline. No symptom became more prevalent with time. Keiser et al. [15] reported no life-threatening adverse events following treatment. Only mild adverse events were observed, with the exception of abdominal pain at moderate severity in few children. In another study [16], three quarter of the adverse events were observed within the first 4 hours after treatment, including abdominal pain, diarrhoea, nausea,

vomiting, dizziness, fever, fatigue, face and body inflammation, and headache. Twenty-four hours post-treatment, none of the children reported multiple adverse events.

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3.4.2.3 Palatability data

The palatability of L-PZQ and rac-PZQ ODTs was assessed in a taste study in African 6 to 11 year-old children (EMR200661-002). Better palatability of L- and rac-PZQ ODTs as compared to the rac-PZQ commercial product (Cesol® 600 mg) was confirmed.

3.5 Dose rationale

Rac-PZQ ODTs dose

The relative BA study in adult healthy volunteers (EMR 200585-001) showed that the rac-PZQ ODT formulation (150 mg tablet) is bioequivalent at 40 mg/kg to the commercial PZQ (Cysticide® 500 mg tablets) in term of overall AUC of L-PZQ (the study results meet the FDA's current bioequivalence criteria). However, C_{max} for the rac-PZQ ODTs was higher as compared to Cysticide® C_{max}. The overall mean time-concentration profile was also different in the two formulations, with rac-PZQ ODT formulation having later t_{max} compared to Cysticide®.

The rac-PZQ ODT doses selected for this trial are 40 mg/kg and 60 mg/kg bodyweight as single dose administration. The dose choice is based on the following considerations:

The 40 mg/kg dose is the recommended dose by WHO in adults and school-aged children [1, 5, 17].

The 60 mg/kg single dose is the recommended dose by the Ministry of Health in Brazil for the treatment of 2- to 15-year-old children infected with *S. mansoni* whereas a 50 mg/kg single dose is recommended for older children and adults [18].

In one of its reports [19], WHO recommends the use of rac-PZQ for schistosomiasis in adults and children over 4 years at 40-60 mg/kg as a single dose or alternatively 3 doses of 20 mg/kg on one day at intervals of 4-6 hours.

No data are available on the safety of administration of a 80 mg/kg single dose of rac-PZQ.

Over the past years, many studies with rac-PZQ have been conducted in different populations (i.e. different ethnicities, species of *Schistosoma* infections, age of subjects and gender) and it is generally agreed that the 60 mg/kg dose does not offer an advantage over the 40 mg/kg dose in adults and school-aged children [20].

L-PZQ ODTs dose

For the L-PZQ ODTs dose to be used in this study, the following considerations have been taken into account:

a. Underlying assumptions of expected cure rates after different doses of PZQ (commercial formulations) are administered to children (see Section 3.4.2.1)

b. Data on drug exposures to L-PZQ (L-PZQ ODT vs. rac-PZQ commercial formulation) in healthy adults (data from the relative bioavailability study EMR200661-001)

c. Available PK data of PZQ in children

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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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3.6 Explanation for choice of comparator

According to the EU Guidance Ethical considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population [21], use of placebo in children is more restricted than in adults because children cannot consent. The Guidance also states that placebo should not be used when it means withholding effective treatment. Furthermore, the use of placebo may be warranted in children only when evidence for any particular treatment is lacking or when the

placebo effect is known to be very variable. Since it is known that PZQ is an effective treatment in schistosomiasis, the ethical justification for placebo use cannot be warranted.

Therefore, the current commercial rac-PZQ tablet formulation (Biltricide® 600 mg), which is the recommended PZQ comparator by the WHO Prequalification of Medicines Programme (PQP), will be used in crushed form at the following doses:

20 mg/kg bodyweight three times a day (t.i.d) as a one day treatment, at intervals of not less than 4 hours. Biltricide® is approved for treatment of schistosomiasis infected children over 4 years of age but can be used to treat children below this age under medical supervision.

Single dose of 40 mg/kg bodyweight, which is the recommended dose by WHO to treat adults and school-aged children and is widely used for WHO mass drug administration PZQ programs in Sub-Saharan Africa. Currently, the PZQ commercial products registered in Mexico by Merck for the treatment of schistosomiasis (Cisticid® 600 mg) and also made available to WHO by the Merck donation program (under the tradename of Cesol® 600 mg) have a label including both a single dose administration of 40 mg/kg bodyweight and a 3 times 20 mg/kg bodyweight administration regimen (in one day). There is a large safety database available on Merck's donated drug Cesol® 600 mg showing that PZQ administered as a single dose of 40 mg/kg bodyweight is a safe compound in adults and school-aged children and has mostly mild and transient AEs.

These reference treatments aim at providing information on the susceptibility of the study population to treatment with the rac-PZQ commercial formulations. Indeed, it is documented that different areas can show differences in susceptibility to treatment effects [22].

The Bilitricide® tablets will be crushed since they are too big for children to swallow. In the EMR200585-001 phase I study, the relative bioavailability of crushed tablets (Cysticide®) was compared to the one of non-crushed tablets and mean exposure to L-PZQ and rac-PZQ was shown to be ~20% and 14% lower respectively (ratio of 82.1; 95% CI 68.5% - 98.3% and 86.1; 95% CI 75.4% -98.4%).

Refer to the Investigator's Brochure (IB) for further information about the nonclinical and clinical programs and Guidance for the Investigator.

Based on the available nonclinical and clinical data on rac- and L-PZQ ODTs to date, the conduct of the trial specified in this protocol is considered justifiable.

4 Trial Objectives

4.1 Primary Objectives

Part 1

To identify the optimal single dose of rac-PZQ ODT or L-PZQ ODT formulation which has a clinically meaningful cure rate (as assessed by Kato-Katz method) and an acceptable safety profile in 2- to 6-year-old children infected with *S. mansoni*.

Part 2

To evaluate the efficacy and safety of the selected ODT formulation (L-PZQ or rac-PZQ) from Part 1 at the appropriate adjusted dose(s) in infants aged 3 to 24 months infected with *S. mansoni*.

4.2 Secondary Objectives

Part 1

To determine the safety of different doses of rac-PZQ ODT and L-PZQ ODT in children aged 2 to 6 years infected with *S. mansoni*

To explore the dose-response relationship for L-PZQ ODT and rac-PZQ ODT in children aged 2 to 6 years infected with *S. mansoni*

To assess the efficacy and safety of rac-PZQ commercial tablet at 20 mg/kg t.i.d. dose administration and at 40 mg/kg single dose administration in children aged 2 to 6 years infected with *S. mansoni*

To assess the acceptability in terms of ease of administration of the rac-PZQ ODT and L-PZQ ODT in children aged 2 to 6 years infected with *S. mansoni*

Part 2

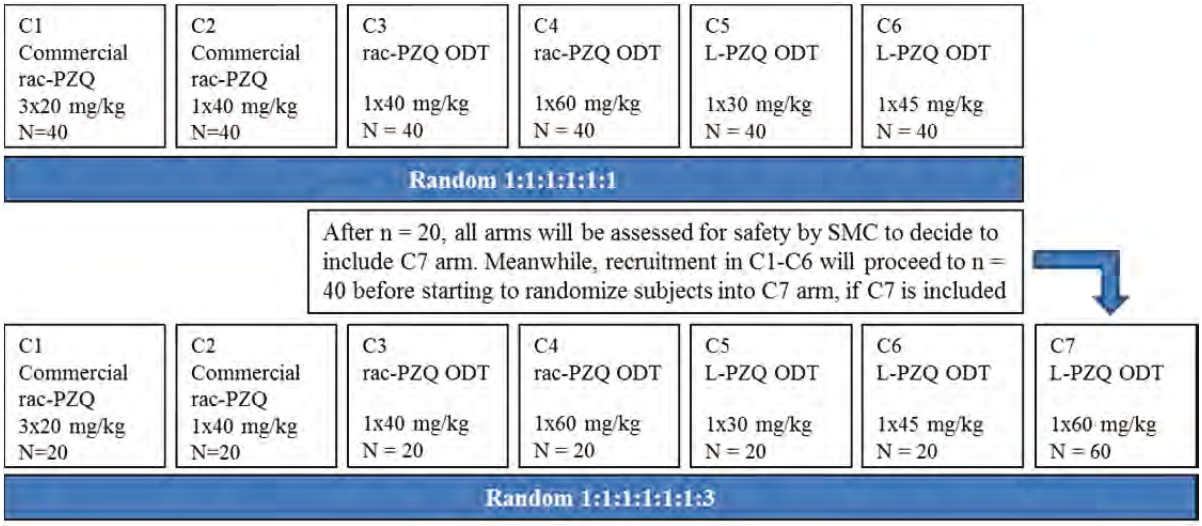
To assess the acceptability in terms of ease of administration of the selected ODTs (rac-PZQ or L-PZQ) in 3- to 24-month infants infected with *S. mansoni*

To explore the dose -response relationship for L-PZQ and rac-PZQ in 3- to 24-month infants infected with *S. mansoni*

5 Investigational Plan

5.1 Overall Trial Design and Plan

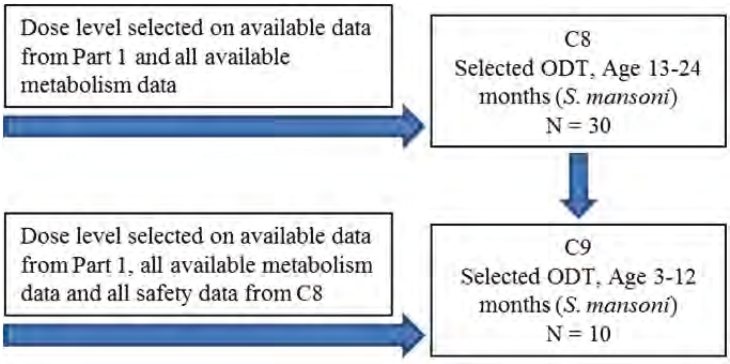
This is a phase II study consisting of two parts. The second part will only start once the first part is completed.



Part 1 is an open-label, randomized, controlled, exploratory dose-finding study conducted in one study site with three formulations of PZQ (commercial rac-PZQ tablets, L-PZQ ODTs and rac-PZQ ODTs) in children aged between 2 and 6 years infected with *S. mansoni*.

The main objective of Part 1 is to identify the optimal (i.e. dose with a clinically meaningful cure rate and an acceptable safety profile) single dose of rac-PZQ or L-PZQ ODT formulation to treat 2- to 6-year-old children infected with *S. mansoni*.

After 20 patients from each of cohorts C1 to C6 are treated, all the acute (24-hour) safety data available (from all cohorts) will be summarized and evaluated by the SMC to decide on the inclusion of the 7th arm. C7 will be included in the randomization scheme only after SMC approval while randomization for the other groups can continue enrolling a total of 40 subjects per group/cohort. In case of safety concerns observed with the L-PZQ ODTs treated cohorts, the SMC can decide to assess the exposure in a minimum of 10 subjects in the L-PZQ ODTs cohorts C5 and C6 before deciding to escalate to a higher dose of L-PZQ.



Part 2 includes a cohort with infants of 13-24 months infected with *S. mansoni* (C8) and a cohort with infants of 3-12 months infected with *S. mansoni* (C9) which will be enrolled in an age-staggered approach..

Infants in cohort C8 will be treated with rac-PZQ or L-PZQ ODTs at the optimal dose level selected by SMC from Part 1 (based on benefits-risks evaluation).

After 10 infants of 13 to 24 months have been enrolled, the overall safety and efficacy data in these children will be evaluated by the SMC for the decision to include the lower age group (cohort C9). SMC will also decide whether dose level adaptations are needed before starting to enrol C9.

5.2 Discussion of Trial Design

In the FDA Guidance of 2014 for pediatric development [11] it is mentioned that a PK approach can be followed when it is reasonable to assume that children, when compared to adults, have (1) a similar progression of disease; (2) a similar response of the disease to treatment; (3) a similar exposure-response or concentration-response relationship; and (4) the drug (or active metabolite) concentration is measureable and predictive of the clinical response. In that case a phase II design focused on reaching similar exposure in children as in adults is the first choice for a pediatric development. Although the requirement number 1 (similar progression) and 2 (similar treatment response) are certainly fulfilled for PZQ, there are uncertainties regarding the requirements 3 and 4, as further discussed below.

Currently, there are no data available showing a correlation between the dose, the AUC or C_{max} and the efficacy of PZQ, neither in adults nor in children. This could be related to the fact that the product was registered in the 80ies and adequately designed dose-finding studies were not performed at that time. Most data regarding efficacious doses are obtained from investigator sponsored trials (ISTs), often small studies with only one or two doses.

The translation of a dose in adults to a comparable dose in children should take scaling of the clearance into account. This is related to the assumption that clearance scales with body size to the ¾ power. Adjusting the dose by a simple mg/kg factor would result in lower exposures in children who weigh the least. By contrast, scaling the dose in the same manner as clearance is scaled would result in a consistent exposure across the entire weight range. However, preliminary data indicate that the allometric scaling approach for pediatric dose prediction from adult data is not applicable to PZQ. First, recent data from the relative BA studies (EMR200585-001 and EMR200661-001) showed that the time versus concentration profile in adults is highly variable in regard to shape and cannot be described with one model. When limiting it to AUC and C_{max}, a model that describes the data can be developed. However, when applying allometric scaling of the data, the predicted doses in children needed to achieve a comparable exposure are too high, i.e. the model under-predicts the exposure. This result was observed when comparing the predicted doses and their exposures with the observed exposures following non-scaled doses of 20, 40 and 60 mg/kg in pre-school aged children obtained from a recent IST study conducted by Keiser et al. in Ivory Coast. These results could be explained by the very high absolute dose administered to adults (around 3000 mg) compared to children (around 600 mg). Also, the dose might not completely be absorbed in adults whereas children receiving a much lower absolute dose might absorb it completely. In conclusion, the relation between dose and exposure may be different between adults and children, explaining why the predicted doses based on adult exposure data may be off and dose-finding needs to be done in the intended population.

In summary, due to the uncertainties about the available exposure-response or concentration-response relationship and the predicted efficacy response, combined with the high PK variability observed for PZQ, as well as the uncertainty in the translation of adult data of PZQ to children, a PK only approach is not deemed appropriate and therefore a partial extrapolation PK/PD dose ranging approach has to be considered instead. Due to inconclusive PK data from the first subset of study participants, PK sampling is abandoned. The design of this study therefore considers cure rate and egg reduction rate as clinical efficacy endpoints with no additional PK analysis, and evaluates the dose-response relationship instead of the exposure response relationship in the targeted population.

5.2.1 Inclusion of Special Populations

Children and infants of 3 months to 6 years of age will be included in this study. These pre-school aged children (pre-SAC), which are a high-risk group for schistosome infections accounting for 10-20 million of the global prevalence, are currently not treated in the schistosomiasis control programs as the current formulation is not suitable for administration to young children.

Children are viewed as vulnerable subjects who should be protected from the risks of research. In this trial, no risk is anticipated to its participants at the tested dosages of 40 and 60 mg/kg for the rac-PZQ ODTs and for the 30, 45 and 60 mg/kg dosage of the L-PZQ ODTs. Biltricide® is approved for treatment of schistosomiasis infected children over 4 years of age but can be used to treat children below this age under medical supervision. Subjects will remain in the facility for 24 hours after dosing and will be closely monitored. Laboratory safety tests are included to show that subjects participating in the study are not getting worse and these tests will be repeated at the end of hospitalization.

Subjects will require the written informed consent of one of their parents or their legal representatives. Whenever possible, child's assent should be also provided. According to the EU guidance for clinical trials on pediatric populations, it is not possible to obtain assent in children aged 3 months to 3 years. Children between 3 and 6 years of age should participate in the (informed) consent process together with the parents/legal representatives, whenever appropriate and give an oral assent that will be recorded on the informed consent form.

After the trial, commercial PZQ will be made available to study participants through the mass drug administration program according to National Guidelines. In that way, subjects who received a sub-optimal PZQ dose and did not benefit from the treatment could be treated accordingly.

5.3 Selection of Trial Population

Only children meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as subjects. Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject's legal representative has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled:

- Written informed consent from one of the parents/legal representatives prior to any trial related procedure
- Male and female children aged 2 to 6 years (Part 1) and 3 to 24 months (Part 2)
- *S. mansoni* positive diagnosis, defined as positive egg counts in stool (>1 egg/1 occasion) according to WHO classification [1]: light (1-99 eggs per gram of faeces), moderate (100-399 eggs per gram of faeces) and heavy (≥400 eggs per gram of faeces) infections
- Minimum weight of 8.0 kg in 2- to 6-year-old children and of 4.0 kg in 3- to 24-month infants
- Parent/legal representative ability to communicate well with the Investigator, to understand the protocol requirements and restrictions, and willing their children to comply with the requirements of the entire trial, i.e.:
  - To be examined by a study physician at screening and 14-21 days after treatment
  - To provide stool and urine samples at day -28 to day -1, 24 h and 8 days after treatment, as well as 14-21 days after treatment
  - To provide venous blood samples for safety assessments

5.3.2 Exclusion Criteria

Subjects are not eligible for this study if they fulfil one or more of the following exclusion criteria:

- Treatment in the 4 weeks prior to study screening with PZQ, other anti-helminthic, anti-malarial or anti-retroviral compounds or any other medication that might affect the PK of PZQ such as certain antiepileptics (e.g., carbamazepine or phenytoin), glucocorticosteroids (e.g., dexamethasone), chloroquine, rifampicin or cimetidine (see Section 6.5.2 and Biltricide® SPC)For children being breast fed, treatment of the mothers/wet nurses with PZQ in the 3 days prior to administration of IMP
- Previous history of adverse reactions associated with PZQ treatment
- History of acute or severe chronic disease, including hepato-splenic schistosomiasis
- Marked increases of the liver transaminases (alanine aminotransferase and/or aspartate aminotransferase) above 3x ULN
- Fever defined as temperature above 38.0°C
- Debilitating illnesses such as tuberculosis, malnutrition, etc. as well as a medical history of seizures
- Mixed *S. haematobium* and *S. mansoni* infections
- Findings in the clinical examination of schistosome-infected children participating in the study as performed by the study clinician on the treatment day, that in the opinion of the

Investigator constitutes a risk or a contraindication for the participation of the subject in the study or that could interfere with the study objectives, conduct or evaluation

- Unlikelihood to comply with the protocol requirements, instructions and trial-related restrictions, e.g., uncooperative attitude, inability to return for follow-up visits, and improbability of completing the trial

5.4 Criteria for Initiation of Trial Treatment

Not applicable

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from the Trial Treatment

A subject in cohort C1 who does not receive the full course of treatment (20 mg/kg t.i.d. in one day treatment) must be withdrawn from the trial. If a subject withdraws from the study treatment, 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. Subjects withdrawn from the trial treatment will not be replaced.

5.5.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the trial.

A subject must be withdrawn if any of the following occur during the trial:

- Subject's parents or his/her legal representatives withdrew consent
- Subject lost to follow up
- Subject's participation in another clinical trial
- Any events that unacceptably endanger the safety of the subject.

Children who require malaria treatment after receiving trial treatment will not be withdrawn from the study, but because some anti-malarial agents (artemisinin derivatives) have activity against *S. mansoni*, they will be removed from the primary efficacy analysis.

If a subject 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.

If a subject withdraws from the study, if possible, the reason must be reported in the CRF.

If a subject is withdrawn from the study because of treatment limiting adverse event, thorough efforts should be made to clearly document the outcome.

Data obtained prior to subject's withdrawal will still be included in the efficacy and safety analysis.

Subjects withdrawn from the study will not be replaced.

If a subject does not return for a scheduled visit, all necessary measures should be taken to contact him/her. In any case, all necessary measures should be taken to document the subject's outcome, if possible.

5.6 Premature Termination of the Trial

The clinical trial may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavourable risk benefit judgment for any IMP. The Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons, for poor enrolment, or because of discontinuation of clinical development of an IMP or withdrawal of an IMP or comparator from the market for safety reasons.

Health Authorities and Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

All study data will be archived according to the description in Chapter 10.3.

5.7 Definition of End of Trial

A clinical trial protocol may not be considered closed as long as:

- Any subject is still receiving any IMP
- Visits specified by the protocol are still taking place
- Procedures or interventions according to the protocol are still being undertaken in any subject
- The post-treatment follow-up period, defined in the clinical trial protocol as being part of the trial, has not yet been completed for any subject.

The end of Part 1 and 2 dates will be the Last Subject Last Visit date of Part 1 and 2, respectively. The trial will end when all treated subjects in the trial have completed/discontinued the trial as per protocol.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term "Investigational Medicinal Product" refers to an active substance or a placebo being tested or used as a reference therapy in a clinical trial, including products that have a marketing authorization but are formulated, packaged, or administered differently from the authorized form,

used for an unauthorized indication, or used to gain further information about the authorized form.

6.1 Description of the Investigational Medicinal Product

MSC 1028703A (referred to as rac-PZQ)

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
Company or Laboratory Code:	MSC1028703A
Molecular Formula:	C19H24N2O2
Relative Molecular Mass:	312.4 g/mol

White or almost white, crystalline powder.

MSC1028703A is presented as 150 mg strength ODT.

CCI [redacted]

CCI [redacted]

MSC 2499550A (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 ODT.

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:	$C_{19}H_{24}N_2O_2$
Relative Molecular Mass:	312.4 g/mol

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

CCI [redacted] The tablet contains 600 mg of praziquantel and the following inactive ingredients: corn starch, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulphate, polyethylene glycol, titanium dioxide and hypromellose.

6.2 Dosage and Administration

The dosages to be administered in the Part 1 of this trial are either a three times a day (t.i.d.) dose as a one day treatment of commercial rac-PZQ (Biltricide® 600 mg) at 20 mg/kg or a single dose of commercial rac-PZQ (Biltricide® 600 mg) at 40 mg/kg or a single dose of rac-PZQ ODT (150 mg tablet) at 40 or 60 mg/kg or a single dose of L-PZQ ODT (150 mg tablet) at 30, 45 or 60 mg/kg.

In Part 2 of this trial, rac- or L-PZQ ODTs will be administered at the optimal dose(s) from Part 1 adjusted to the lower age group of 13-24 months and 3-12 months.

The actual doses will be based on measured bodyweight and rounded to the next/closest 150 mg. A table with the number of tablets for each bodyweight group will be included in the Pharmacy Manual.

The rac- and L-PZQ ODT tablets will be dispersed in water and ingested. Commercial rac-PZQ (Biltricide® 600 mg) tablets will be split in 4 if necessary to adjust the dose and then crushed, suspended in water and ingested. A mouth check should be performed after the IMP/Biltricide® ingestion to ensure all particles have been cleared off the mouth. If any IMP/Biltricide® particle is visible, the subject should be asked to rinse his/her mouth with water and swallow it.

A detailed description of the medication preparation and administration will be included in the Pharmacy Manual.

Dosing will be done after a meal. The type of meal will be dictated by local customs and should be kept the same for all subjects in the 2- to 6-year age group. Deviations of eating times and leftover foods should be recorded. Standardized meals will be given throughout the day. Children in the cohort C1 will receive a meal before each dosing.

6.2.1 Dose adaptation

Dosages in Part 2 will be adapted as described in Section 5.1.

If the subject vomits or spits the IMP/Biltricide® after dosing, he/she will not receive a new dose of IMP/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 study.

6.3 Assignment to Treatment Groups

Subjects will receive their subject identification number after one of the parents/legal representatives has signed the informed consent and children have given their assent, when applicable. Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized after recheck of eligibility on Day 1.

The Investigator or his/her designee will allocate a randomization number to each subject in each stratification group following a sequential order before first dosing of IMP (see also Section 8.2).

6.4 Noninvestigational Medicinal Products to be Used

Not Applicable.

6.5 Concomitant Medications and Procedures

All concomitant medications taken by the subject during the trial, from the date of signature of informed consent are to be recorded in the appropriate section of the CRF, noting the name, dose, start and end date and indication of each drug. Non-drug interventions, concomitant procedures/therapy and any changes to a concomitant medication or other intervention should also be recorded in the CRF.

All subjects will undergo a diagnostic test for malaria at screening. All subjects with positive Rapid Diagnostic Test (RDT) will be treated according to the country national guidelines.

6.5.1 Permitted Medicines

Any medications that are considered necessary to protect subject welfare and that do not interfere with the trial medication (see Section 6.5.2) may be given at the Investigator's discretion.

Rescue medications may be administered to address ineffective treatment, anticipated adverse reactions or anticipated emergency situations.

6.5.2 Prohibited Medicines

As referred in the exclusion criteria, administration of any investigational product or use of any investigational device within four weeks prior to first administration of IMP and during the entire clinical trial is not permitted. For children being breast fed, administration of praziquantel to nursing mothers is not allowed.

Also, any medication from screening until end of confinement is not allowed without prior approval from the Investigator (except for occasional use of paracetamol or ibuprofen).

The concomitant administration of agents that induce the drug metabolising enzyme system in the liver (cytochrome P 450), such as certain antiepileptics (e.g., carbamazepine or phenytoin), glucocorticosteroids (e.g., dexamethasone) or chloroquine, may lead to reduced plasma levels of praziquantel.

The concomitant administration of rifampicin which is a strong inducer of cytochrome P 450 is contraindicated as no therapeutic effective plasma levels of praziquantel can be expected.

The concomitant administration of agents that inhibit the drug metabolising enzyme system in the liver (cytochrome P 450), e.g., cimetidine, may lead to increased plasma levels and a prolonged retention period of praziquantel.

Similarly, simultaneous consumption of grapefruit juice may lead to increased praziquantel levels.

If the administration of a non-permitted concomitant drug becomes necessary during the trial, e.g., because of AEs, the subject should be discontinued from the trial but only after consultation with the Sponsor.

6.5.3 Other Interventions

Any unplanned diagnostic, therapeutic, or surgical procedure performed during the trial period must be recorded in the concomitant procedure section in the CRF, 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.

Standardization of diet

Subjects aged 2 to 6 years will eat a standardized meal before dosing. After dosing, subjects will fast for 4 hours (except for an occasional sweet) and then receive a standardised meal. Subjects in the cohort C1 will receive a standardized meal before each dosing. Water will be allowed 1 hour after dosing. If water is needed earlier this will be documented.

Subjects aged 3 to 24 months will be breastfed or receive a meal before IMP administration.

Subjects will be instructed not to consume caffeine, grapefruit juice and xanthine-containing products (chocolate, tea, coffee, cola, etc.) from 48 hours prior to IMP administration until 24 hours after IMP administration.

6.5.4 Special Precautions

The medication administration part of the trial 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 trial site in case of severe allergic reactions.

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

No risk is anticipated to subjects at the tested doses of 40 and 60 mg/kg for the rac-PZQ ODTs and for the 30, 45 and 60 mg/kg dose of the L-PZQ ODTs. Subjects remain in the facility for 24

hours after dosing and will be closely observed. Safety laboratory evaluations will be conducted at the end of the confinement visit just before discharge from the hospital (i.e. at ~24 hours after dosing). In case of an AE related to liver function, the subject will be further monitored by the study team in the villages and an additional blood sample will be collected at Day 8 for liver function evaluation.

Most AEs are reported to occur directly after dosing. In addition, regular AE assessments are performed and the subjects are visited by study staff at scheduled times in the first week after dosing.

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

6.6 Packaging and Labelling of the Investigational Medicinal Product

All IMPs will be packaged and labelled in accordance with all applicable regulatory requirements and Good Manufacturing Practice (GMP) Guidelines.

MSC1028703A (rac-PZQ ODT) will be packed in bottles containing 50 tablets of IMP each. Each bottle will be numbered and used for multiple subjects.

MSC2499550A (L-PZQ ODT) will be packed in bottles containing 60 tablets of IMP each. Each bottle will be numbered and used for multiple subjects.

Current rac-PZQ (Biltricide® 600 mg) is packed at 6 tablets per bottle. Each bottle will be numbered and used for multiple subjects.

Other accessories (e.g., syringes, disposable beakers, etc.) for dispensing study drug will be provided as bulk supply.

6.7 Preparation, Handling, and Storage of the Investigational Medicinal Product

The preparation of the dispersed and reconstituted solutions for the individual subject in each arm will be done by a competent person (e.g., a pharmacist) under the responsibility of the Investigator. The pharmacy will prepare all IMPs for all subjects according to the treatment randomization list, the measured body weight and in accordance with the Pharmacy Manual.

[redacted], in a secure, locked location with adequate storage conditions. IMP/Biltricide should not be frozen. Any deviation from the recommended storage conditions should be immediately reported to the Sponsor and the IMPs should not be used until authorization has been received from the Sponsor.

6.8 Investigational Medicinal Product Accountability

The Investigator (or specify designee) is responsible for ensuring IMP accountability of the Investigator site, including reconciliation of drugs and maintenance of records.

- Upon receipt of IMP, the Investigator (or designee) will check for accurate delivery and acknowledge receipt by signing or initialling and dating the appropriate documentation provided by the Sponsor/CMO and returning it to the Sponsor/CMO. A copy will be archived for the Investigator Site File.
- IMP dispensing will be carefully recorded on the appropriate drug accountability forms so that accurate records will be available for verification by the Sponsor Monitor at each monitoring visit.
- Trial site IMP accountability records will include the following:
  - Confirmation of IMP receipt, in good condition and in the defined temperature range
  - The inventory of IMP provided by the Sponsor/CMO and prepared at the site
  - The use of each dose by each subject
  - The disposition (including return, if applicable) of any unused IMP
  - Dates, quantities, batch numbers, vial numbers, expiry dates, formulation (for IMP prepared at the site) and the individual subject trial numbers

The Investigator site should maintain records which adequately document that subjects were provided the doses specified in this protocol and all IMPs provided by the Sponsor/CMO were fully reconciled.

Unused IMP must not be discarded or used for any purpose other than the present trial. No IMP that is dispensed to a subject may be re-dispensed to a different subject.

A Trial Monitor will periodically collect the IMP accountability forms.

6.9 Assessment of Investigational Medicinal Product Compliance

All IMPs will be administered as oral tablets dispersed in water under the supervision of the Investigator or designee. The IMP administration will be recorded in the CRF.

Drug administration records will be used to assess compliance.

The Investigator is responsible for the control of drugs under investigation; adequate record of receipt (e.g., Drug Receipt Record) and disposition (e.g., Drug Accountability Record, Drug Destruction Record) of the investigational drug including dates, quantities and use by subject must be maintained.

All records and drug supplies must be available for inspection at every monitoring visit. When the study is terminated and drug 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 clinical trial site after written

approval by Sponsor. The completed Drug Accountability and Drug Destruction Records will be sent to the monitor or its designee.

The site pharmacist or study drug preparer must maintain records of the IMP delivery to the trial site, the inventory at the site, the use by each subject and its destruction or returning after drug accountability has been performed by the responsible monitor. The drug-dispensing log must be kept updated, listing the identification of the subject 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 drug supply is not used for any purpose other than this trial.

6.10 Blinding

The study is open label. For Part 1, evaluation of primary endpoint (i.e. number of eggs per gram of faeces) will be evaluated without laboratory staff being aware of the actual treatment received by subjects.

6.11 Emergency Unblinding

Not Applicable.

6.12 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in a clinical trial protocol or planned for an individual subject enrolled in the trial. Even if it does not meet other criteria for an SAE, any overdose must be recorded in the trial medication section of the CRF and reported to the Drug Safety of the Sponsor in an expedited manner using the SAE Report Form, and following the procedure in Section 7.4.

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.

6.13 Medical Care of Subjects after End of Trial

After the trial, commercial PZQ will be made available to study participants through the mass drug administration program according to the country national guidelines. In that way, subjects who received a sub-optimal PZQ dose and did not benefit from the treatment could be treated accordingly.

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

The list of study procedures and assessment is given in Appendix II: Table of study procedures and assessments.

7.1.1 Pre-screening

Study participants will be selected from communities living in the PPD
Prior to study onset, a list of all children aged 2-6 years (Part 1) and 3-24 months (Part 2) living in the selected areas will be prepared using records obtained from the latest census. At study beginning, all households in the villages will be informed about the study. Prior to performing any trial assessments that are not part of routine medical care for the subject, the Investigator or an appropriate designee (if local regulations permit) will obtain written pre-screening consent from one of the parents or a legal representative of the subject to allow the diagnosis activities and the identification of infected children, as described in Section 9.2.

Parents/legal representatives of participating subjects will be provided with plastic containers labelled with unique identification numbers (IDs) at the first day of pre-screening. 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 will be processed on the same day.

Pre-screening diagnosis of *S. mansoni* infection will be done using a single POC-CCA urine cassette test. Subjects who are positive for POC-CCA test will provide:

- One urine sample to assess *S. haematobium* co-infection using the filtration technique. One urine sample will be collected from each subject. 10 ml of urine samples will be filtered through a filter mesh which will be then examined under the microscope for *S. haematobium* egg count.*S. haematobium* positive diagnosis is defined as positive egg counts of *S. haematobium* in urine (> 1 egg/10 ml of urine) according to WHO classification: light (<50 eggs/10 ml of urine) and heavy (≥50 eggs/10 ml of urine) infections.
- Two stool samples to assess infection intensity using the Kato-Katz method. Two stool samples will be collected from each subject on different days within a maximum of 5 days, at day -28 to day -1 as baseline and 14-21 days after dosing. Infection intensity (expressed as egg count per gram of stool (epg)) will be calculated for each individual. *S. mansoni* positive diagnosis is defined as positive egg counts of *S. mansoni* in stool (>1 egg/1 occasion) according to the WHO classification: light (1-99 eggs per gram of faeces), moderate (100-399 eggs per gram of faeces) and heavy (≥ 400 eggs per gram of faeces) infections.

7.1.2 Screening

Schistosome-positive subjects after assessment by the Kato Katz method together with one of their parents/legal representatives will be invited to the study hospital. The Investigator or an appropriate designee (if local regulations permit) will obtain written informed consent to allow the participation in the study and the completion of the study procedures, from one of the parents or a legal representative of the subject as described in Section 9.2.

In the hospital, the following tests/information gathering will be performed within maximum one week prior to treatment initiation:

- Clinical safety laboratory evaluations: haematology, biochemistry and urinalysis. All biological assessments will be performed in fasting condition, if possible.

- A Rapid Diagnostic Test (RDT) to detect malaria infection (one blood sample collected by finger puncture). Treatment of concomitant diseases such as malaria will be done according to the country national guidelines. Subjects who require malaria treatment before receiving the study drug will be withdrawn from the study.
- Demographic data, consisting of date of birth, gender and height
- Medical history including occurrence of seizures consisting of all previous diseases as considered relevant (relevant defined as needing medical treatment for at least 1 week) by the Investigator
- Previous medication consisting of all previous medications within the last 6 months as considered relevant by the Investigator and all regular medications within the last 6 months.
- Complete physical examination including body weight
- Vital signs in supine position including:
  - Blood pressure (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

Subjects who fail to meet the protocol specified criteria before first dosing or withdraw their consent in the screening period before first dosing are considered screening failures. Data to be collected from these subjects are: date of informed consent, demographics, laboratory parameters (if available), AEs and reasons for non-inclusion.

7.1.3 Treatment period

Treatment period will last 1 day. Subjects will be hospitalized from the morning of dosing until at least 24 hours after IMP administration. During this time, subjects will be monitored for AEs.

Pre-dose assessments

Subjects 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.

Post-dose assessments

Vital signs will be recorded 8 hours after first dosing. Physical examination will be performed 8 and 24 hours (± 10% IN HOURS) after first dosing.

Clinical safety laboratory evaluations (i.e. hematology, biochemistry and urinalysis) and urine collection for POC-CCA test will be performed 24 hours (± 10% in hours) after dosing. All biological assessments will be performed in fasting condition, if possible.

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 after the specified 18/24 Hours and the

additional night will not be considered as part of confinement. As such, it will not qualify as SAE, as described in section 7.4.1.1.

7.1.4 Follow-up visit

Follow-up visits will take place as specified in APPENDIX II.

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

At day 8 (+/- 1 day), urine samples will be collected for the POC-CCA test. If an AE related to liver function occurs before hospital discharge (within 24 hours after dosing), the subject will be further monitored by the study team in the villages and an additional blood sample will be collected at Day 8 for biochemistry evaluation.

At the End of Study visit (between day 14 and 21), subjects will be asked to provide stool and urine samples for Kato-Katz method and POC-CCA test. The following tests and information gathering will be also performed:

Vital signs in supine position including:

- Blood pressure (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

Complete physical examination

If a subject withdraws prematurely from the trial, 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.

Any ongoing medically relevant abnormal findings at the End of Study visit, including safety laboratory tests, will be followed up until resolution or stabilization (according to Section 7.4.1.6)

7.2 Demographic and Other Baseline Characteristics

At screening, the following demographic data will be collected: date of birth, date of informed consent signature, gender and height.

Medical history within the last year, consisting of all previous diseases as considered relevant by the Investigator and all hospital stays, will be recorded.

Previous medication consisting of all previous medications within the last 6 months as considered relevant by the Investigator and all regularly taken medications within the last 6 months will be recorded.

Use of caffeine or xanthine-containing beverages and concomitant medication will be assessed at screening.

7.3 Efficacy Assessments

7.3.1 Assessment of primary efficacy endpoint

Egg counts in the stools (expressed as egg count per gram of stool (epg) 14-21 days after treatment as determined by Kato-Katz method. Two stool samples will be collected from each subject on different days within a maximum of 5 days, at screening and 14-21 days after treatment. Three Kato-Katz thick smears will be prepared from each stool sample and read under the microscope.

7.3.2 Assessment of secondary efficacy endpoints

Frequency of POC-CCA test scores using the commercially available POC-CCA cassette.

7.4 Safety Assessments

The safety profile of the IMP will be assessed through the recording, reporting and analysis of baseline medical conditions, adverse events (AEs), physical examination findings including vital signs and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent and throughout the trial. The Investigator will report any AEs, whether observed by the Investigator or reported by the subject (see Section 7.4.1.2). The reporting period for AEs is described in Section 7.4.1.3.

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, regardless of causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not 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 according to the Qualitative Toxicity Scale, as follows:

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

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

Severe: Significant impairment of functioning: the subject 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 IMP(s)/study treatment (including any other non-IMPs, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMP include, but may not be limited to, temporal relationship between the AE and the IMP, known side effects of IMP, medical history, concomitant medication, course of the underlying disease, trial procedures.

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

Related: Reasonably related to the IMP/study treatment. AE could medically (pharmacologically/clinically) be attributed to the IMP/study treatment under study in this clinical trial 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 treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfils these criteria, the identified medical condition (e.g., anaemia, 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. (Note: The term “life-threatening” refers to an event in which the subject 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

Note: 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 subject 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 an IMP is also considered an SAE, as described in Section 7.4.1.4.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial 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 (e.g., 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 trial visit that do not worsen in severity or frequency during the trial 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 subjects might experience diarrhoea, 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.

7.4.1.2 Methods of Recording and Assessing Adverse Events

From screening visit to end of study, the subject and the parents/representatives will be queried on changes in his or her condition. During the reporting period, any unfavourable changes in the subject's condition will be recorded as AEs, whether reported by the subject 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 Section 7.4.1.4.

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

Specific guidance can be found in the CRF Completion and Monitoring Conventions provided by the Sponsor.

7.4.1.3 Definition of the Adverse Event Reporting Period

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

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

7.4.1.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities

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 and the Safety Monitoring Committee 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, telephone and fax numbers for SAE reporting will be included in the trial specific- SAE Report Form.

Relevant pages from the CRF may be provided in parallel (e.g., medical history, concomitant medications). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, and 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 Global Drug Safety department may contact the Investigator directly to obtain further information or to discuss the event.

7.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/Institutional 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 trial subjects to the IEC/IRB that approved the trial.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IEC's/IRB's approval/favourable 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 trials 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.

7.4.1.6 Monitoring of Subjects with Adverse Events

AEs are recorded and assessed continuously throughout the trial (see Section 7.4.1.3) and are assessed for final outcome at the End of Trial Visit. All SAEs ongoing at the End of Trial Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject 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.

7.4.2 Pregnancy and In Utero Drug Exposure

Not Applicable.

7.4.3 Clinical Laboratory Assessments

Stool, urine and blood samples will be collected according to the schedule given in Appendix II. The volumes of biological fluids collected at each assessment time point are presented in Appendix III. All samples should be clearly identified. Detailed description of the procedures and methods as well as the safety laboratory parameters (haematology, biochemistry and urinalysis) analysed at screening and at the End of Study visit will be given in a separate laboratory manual.

For screening diagnosis of *S. mansoni* infections urine samples will be subjected to a commercially available POC-CCA cassette test.

For diagnosis of *S. mansoni* infections, stool samples will be analysed by Kato-Katz method. Briefly, three Kato-Katz thick smears (41.7 mg) will be prepared from each stool sample (2 stools samples, 3 Kato-Katz smears per stool, i.e. total of 6 smears per subject) and read under a microscope following the instructions of the Kato-Katz manual from the World Health Organization. Infection levels will be determined as described in Section 7.1.1.

For diagnosis of *S. haematobium* co-infections, urine samples will be analysed by the filtration technique. Briefly, urine samples will be strained through filter paper and examined under the microscope for presence of *Schistosoma* eggs.

The Sponsor should receive a list of laboratory normal ranges before shipment of trial drug. Any change in laboratory normal ranges during the trial should be forwarded to Sponsor.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

7.4.4.1 Vital Signs

Vital signs including blood pressure (BP), pulse rate (PR) and body temperature will be assessed according to the trial schedule in Appendix II. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) will be measured on the same arm after the subject has been in resting supine position for about 5 minutes. Pulse rate will be recorded simultaneously with the BP measurements. BP and pulse rate measurements should be obtained with the subject's arm unconstrained by clothing or other material. The measurements will be obtained with the appropriate cuff size from the opposite arm from that used for blood sampling, where possible.

Body temperature will be measured using a digital thermometer. Body temperature will be taken together with measurements of blood pressure and pulse rate.

7.4.4.2 Physical examination

Physical examination will be done according to local procedures. Body weight will be recorded during the physical examination, i.e. at screening (before dosing) and 24 hours after dosing.

7.4.4.3 Tolerability of IMP

The reaction to IMP administration (e.g., spitting, crying) will be recorded directly after dosing.

7.5 Pharmacokinetics

Not applicable

7.6 Biomarkers/Pharmacogenetics (PGx)

Not Applicable.

8 Statistics

8.1 Sample Size

Part 1: this study is exploratory. There is no hypothesis testing.

The sample size is based on the minimum number of subjects to reach a meaningful precision of the primary efficacy endpoint estimate (cure rate) in each arm, taking into account the stratification factor.

CCI [redacted]

Taking into account the efficacy criteria for the selection of the dose (observed cure rate >70%), through simulations, Table 8 presents the probability of observing an overall cure rate ≥70% based on different scenarios of true cure rates based on different strata, assuming a stratification of 40% moderate/heavy infections and 60% light infections. For example, a sample size of 50 evaluable subjects provides a probability of around 85% to observe a cure rate of ≥70% if the overall true cure rate is 75% with 40% of moderate/heavy and 60% of light infections.

Probability of observing a cure rate ≥ 70%, N=50,		**Assumptions of Cure Rate in Light Infections**			
		70%	75%	80%	85%
Assumptions of Cure Rate in Moderate/Heavy Infections	50%	15%	27%	45%	64%
	55%	23%	38%	57%	76%
	60%	33%	51%	70%	85%
	65%	45%	63%	80%	92%

Table 8. Probability of observing an overall cure rate ≥70% based on different scenarios of true cure rates based on different strata

Assuming an approximately 17% dropout rate, 60 subjects per arm will be randomized to ensure at least 50 evaluable subjects per arm.

Part 2: 30 subjects infected with *S. mansoni* aged 13 to 24 months (C8) and 10 subjects infected with *S. mansoni* aged 3 to 12 months (C9) will be included to evaluate tolerability and efficacy.

8.2 Randomization

Part 1: Treatment allocation will be random and balanced at a ratio of 1:1:1:1:1:1. Randomization will be stratified by the infection severity (40% moderate/heavy and 60% light infections). After 20 subjects/arm are randomized, the SMC will decide on the inclusion of the 7th arm.

Randomization will continue for arms C1-C6 at a ratio of 1:1:1:1:1:1 until a total of 40 subjects/arm are randomized.

If the C7 arm is included, randomization will continue with an allocation ratio of 1:1:1:1:1:1:3. If C7 arm is not included, the allocation ratio will remain the same (1:1:1:1:1:1).

Randomisation lists indicating a randomisation number and which treatment is to be given, will be produced prior to the start of the trial by the statistician at the PPD. Based on the randomisation lists sequentially numbered sealed envelopes which contain a randomisation number and the treatment allocation will be prepared. The sealed randomization envelopes will look identical and will be kept in a locked cupboard to which only the study pharmacist will have access.

Part 2: There is no randomization in this part.

8.3 Endpoints

8.3.1 Primary Endpoints

Clinical cure defined as no parasite eggs in the stools 14-21 days after treatment. Egg counts will be determined by Kato-Katz method. Cure rate will be calculated for each treatment arm as the percentage of subjects becoming egg-negative 14-21 days after treatment.

8.3.2 Secondary Endpoints

Egg Reduction Rate (ERR, %), calculated based on the arithmetic (and geometric) mean egg count per gram of stool (epg) before and 14-21 days after treatment as determined by Kato-Katz method

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

8.3.3 Other Endpoints

Changes in laboratory safety parameters and vital signs (body temperature, blood pressure and pulse rate)

Occurrence, nature, severity and outcome of adverse events

Occurrence of Adverse Drug Reactions per treatment group

8.4 Analysis sets

Part 1:

Modified intention-to-treat (mITT) population or analysis set includes all randomized subjects who have baseline measurement. Children who require malaria treatment after enrolment in the study will not be included in the mITT analysis set.

Per-protocol (PP) analysis set includes all subjects 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 SAP prior to first patient first dose.

Safety analysis set includes all subjects who have received at least one dose of treatment.

Part 2:

Modified intent-to-treat (mITT) population or analysis set includes all subjects (single arm, no randomization) who have baseline measurements. Children who require malaria treatment after enrolment in the study will not be included in the mITT analysis set.

Per-protocol (PP) analysis set includes all subjects who are in the mITT population and have at least one post-baseline measurement without any clinically important protocol deviation. Details of the criteria for exclusion from the PP population will be provided in the SAP prior to first patient first dose.

Safety analysis set includes all subjects who have received at least one dose of treatment.

8.5 Description of Statistical Analyses

All efficacy and safety endpoints will be analysed descriptively. Graphs will be produced as appropriate. Point estimation and 95% confidence interval (CI) will be calculated for primary and key secondary endpoints for each treatment arm.

Descriptive statistics for qualitative variables will include frequency counts and percentages. For proportion endpoints, the calculation of 95% CIs will be relied on the Clopper-Pearson (exact) method.

For continuous endpoints, the 95% CIs around the mean will be calculated where applicable. Descriptive statistics for quantitative variables will include: number of available observations, mean, median, lower quartile (Q1), upper quartile (Q3), minimum, maximum, and standard deviation.

8.5.1 General Considerations

Handling of subjects who drop out from the trial and missing data

For continuous endpoints, the imputation method of last observation carried forward will be used for the missing at the post-baseline measurement.

For binary endpoints, the imputation method of worst case will be used for the missing data at the post-baseline measurement.

The primary analysis will be based on mITT analysis population with missing imputations. All the observed cases will be analysed as sensitivity analysis.

Pharmacokinetic calculations

Not applicable..

8.5.2 Analysis of Primary Endpoints

Clinical cure rate (point estimation and 95% CI) will be calculated for each treatment arm on mITT and PP populations. 95% CI will be calculated on the Clopper-Pearson (exact) method. Subgroup analyses will be also conducted by severity of infections (stratification factor), gender and specific age groups.

8.5.3 Analysis of Secondary Endpoints

Egg reduction rate (ERR, %), calculated based on the arithmetic (and geometric) mean egg count per gram of stool (egp) will be calculated for each treatment arm after 14-21 days.

According to WHO guidelines, the group based egg reduction rates (ERR) after 14-21 days of PZQ drug administration is defined as:

ERR (%) = 100×(1-arithmetic mean egg counts at post-baseline/arithmetic mean egg counts at baseline)

To assess the corresponding ERRs for each treatment arm, Bootstrap resampling method with 10,000 replicates will be used to calculate 95% CIs for ERRs in each treatment arm.

Clinical cure rate assessed by POC-CCA assay for *S. mansoni* will be calculated (point estimation and 95% CIs) for each treatment arm.

8.5.4 Analysis of Safety and Other Endpoints

Values for all safety variables will be listed by subject and time point. Where appropriate, safety variables will be summarized using descriptive statistics.

Adverse events (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 treatment emergent AE within each system organ class and preferred term, separated by treatment group. Treatment-emergent AEs will also be summarized by relationship to treatment and by severity within each treatment group.

By-patient listings of clinical laboratory data and vital signs will include indications of value 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.

8.6 Interim and Additional Planned Analyses

The analyses will take part in a staggered manner for the different parts of the study, each part being self-contained.

A Safety Monitoring Committee (SMC) will be formed to evaluate the interim safety analysis, and will continue to monitor the safety data on a regular basis in both Part 1 and 2, including recommendations about additional monitoring measures that may be deemed necessary. The SMC will consist of internal Sponsor members and Coordinating Investigators. Details regarding SMC roles, responsibilities, activities, procedures to reduce potential bias and possible SMC recommendations will be provided in a separate SMC charter.

A safety (acute AE only) analysis is planned in Part 1 after 20 subjects from each of the treatment arms C1 to C6 are treated. The acute (24 hour) safety data of all six treatment arms will be summarized per each treatment arm by a Biostatistician, and evaluated by the Safety Monitoring Committee, to decide on the inclusion of the 7th arm (C7).

At the end of Part 1, the final analysis will be conducted on data as clean as possible. The Safety Monitoring Committee will assess the data (safety and efficacy) in order to recommend an optimal ODT dose (L-PZQ or rac-PZQ) for Part 2.

Details will be outlined in the SMC charter and dose selection criteria described in a SAP prior to first subject first dose.

9 Ethical and Regulatory Aspects

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP, and any other applicable regulatory requirements.

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at the site and will ensure that the trial is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, ICH GCP, and any other applicable regulations. The Investigator must ensure that

only subjects whose parent/legal representative has given informed consent are included in the trial.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for each subject prior to participation in the trial is written informed consent, which must be given before any trial-related activities are carried out. Adequate information must therefore be given to the subject by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

Written informed consent will be provided by either one of the subject's parents or one of his/her legal representatives. In addition to the parental consent, children who are older than three and capable of assenting will provide oral assent. This will be recorded on the informed consent form.

A subject information sheet must be prepared in the local language, French, in accordance with ICH GCP and will be provided by the Sponsor for the purpose of obtaining informed consent/assent. In addition to providing this written information to a potential subject's parent or legal representative, the Investigator or a designate will inform them verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The subject's parent or legal representative will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

If permitted by national regulations, a person other than the Investigator (designee) may inform the subject's parent or legal representative about the trial and sign the Informed Consent Form, as above.

If the subject's parent or his/her legal representative is illiterate, an impartial witness must be present during the information session. The witness will explain to the parent/legal representative the information contained in the written document and ask to give consent to have his/her child participating in the study. Consent of the subject's parent/legal representative will be confirmed by his/her fingerprint on the form whereas the witness will sign and date the form.

After the information is provided by the Investigator or an appropriate designee, the Informed Consent Form must be signed and dated by one of the subject's parents or his/her legal representatives and the Investigator or his designee.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and Informed Consent Form should be provided to one of the subject's parents or his/her legal representatives prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the subject information sheet and any other written information to be provided to the subjects' parents or his/her legal representatives and submit

them to the IRB for review and opinion. Using the approved revised subject information sheet and other written information, the Investigator or an appropriate designee will explain the changes to the previous version to each trial subject' parent or his/her legal representative and obtain new written consent for continued participation in the trial. The subject' parent or his/her legal representative will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

9.3 Subject Identification and Privacy

The obtained data will be handled strictly confidentially. For each subject, 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 subjects. Confidentiality and anonymity will be ensured throughout the entire research project.

A unique number will be assigned to each subject, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database. All subject data collected in the trial will be stored under the appropriate subject number. Only the Investigator or designee will be able to link trial data to an individual subject via an identification list kept at the site.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

9.4 Emergency Medical Support and Subject Card

Subjects will be provided with Emergency Medical Support cards supplied by the Sponsor for use during trial participation in order to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial and to give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the subject.

The first point of contact for all emergencies will be the clinical trial Investigator or designee caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, he/she will answer any questions. Any subsequent action will follow the standard process established for Investigators.

In cases where the Investigator or designee is not available, the Sponsor provides the appropriate means to contact a Sponsor physician. This includes the provision of a 24-hour contact number at a call centre, 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 subject concerned.

9.5 Clinical Trial Insurance and Compensation to Subjects

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

One of the parents/legal representatives of the subjects 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.

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents (e.g., informed consent form, documents of subjects data collection, certificate of insurance, etc.) to the responsible IECs/IRBs (PPD) for their favourable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Trial Master File at PPD .

Contact details of the PPD) are as follows:
PPD

The trial will not start at a site before the Sponsor has obtained written favourable opinion/approval from the concerned IEC/IRB. The IEC/IRB will be asked to document the date of the meeting at which the favourable opinion or approval was given and the members and voting members present. Written evidence of favourable opinion or approval that clearly identifies the trial, the clinical trial protocol version and date and the Subject Information and Informed Consent Form version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to this clinical trial protocol will also be submitted to the concerned IEC or IRB, before implementation of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC or IRB during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (e.g., Investigational Medicinal Product Dossier, Subject Information and Informed Consent Form) will be submitted or notified to the Ivory Coast Health Authorities in accordance with its national regulations and requirements.

10 Trial Management

10.1 Case Report Form Handling

Study specific information will be entered into an electronic Case Report Form (eCRF). The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible and timely. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this trial is accurate and documented appropriately on all applicable forms. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator or designee must ensure that the eCRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any subject names.

The data will be entered into a validated database. PPD will be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control and quality assurance procedures have been completed.

10.2 Source Data and Subject Files

The Investigator or designee must keep a file (medical file, original medical records) on paper for every subject in the trial. It must be possible to identify each subject by using this subject file. This file will contain the demographic and medical information for the subject listed below and should be as complete as possible.

- Subject's full name, date of birth, sex, height, weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification, that is, the Sponsor trial number for this clinical trial, and subject number
- Dates of entry into the trial (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs
- Date that the subject left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

All documents containing source data must be filed, including, but not limited to ECG recordings, laboratory results and special assessment reports. Such documents must bear the subject number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

10.3 Investigator Site File and Archiving

Upon initiation of the trial, the Investigator or designee will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject Informed Consent Forms. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH GCP guidelines and any other applicable regulations. The site Monitor will perform off-site and on-site visits at regular intervals according to the monitoring plan.

The clinical trial protocol, each step of the data capture procedure and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial 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 trial documents and other materials at the site, including the Investigator Site File, the completed CRFs, all IMP and IMP accountability records, and the original medical records or files for each subject.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favourable opinion. In such cases, the amendment will be implemented only after approval or favourable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the subject's agreement to participate in the trial requires additional informed consent prior to implementation following the process as described in Section 9.2.

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the trial, a clinical trial report will be written by the Sponsor in consultation with the Coordinating Investigators following the guidance in ICH Topic E3.

10.6.2 Publication

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 trial. 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.

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12 Appendices

Appendix I: Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title	Open-label, dose-finding, 2-parts, efficacy phase II study with three formulations (racemate praziquantel commercial oral tablets, new oral disintegrating tablets of racemate praziquantel and L-praziquantel) in schistosomiasis (*S. mansoni*) infected children aged 2-6 years (Part 1), followed by an assessment of efficacy and safety with the selected formulation and dosage in *S. mansoni* infected infants aged 3-24 months (Part 2)
Clinical Trial Protocol Date / Version	3.1 / 28 February 2018

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial:

PPD

Signature

PPD

Date of Signature

Name, academic degree: PPD

Function/Title: PPD

Institution: Institution EMD Serono R&D Institute
A subsidiary of Merck KGaA, Darmstadt, Germany

Address: 45A Middlesex Turnpike, Billerica, MA 01821, USA

Telephone number: Phone: PPD
Mobile: PPD

Fax number: PPD

E-mail address: PPD

Signature Page - Sponsor Medical Responsible

Trial Title	Open-label, dose-finding, 2-parts, efficacy phase II study with three formulations (racemate praziquantel commercial oral tablets, new oral disintegrating tablets of racemate praziquantel and L-praziquantel) in schistosomiasis (*S. mansoni*) infected children aged 2-6 years (Part 1), followed by an assessment of efficacy and safety with the selected formulation and dosage in *S. mansoni* infected infants aged 3-24 months (Part 2)
Clinical Trial Protocol Date / Version	3.1 / 28.February 2018

Sponsor Medical Responsible:

I approve the design of the clinical trial:

PPD

PPD

Signature

Date of Signature

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

Signature Page – Coordinating Investigator

Trial Title	Open-label, dose-finding, 2-parts, efficacy phase II study with three formulations (racemate praziquantel commercial oral tablets, new oral disintegrating tablets of racemate praziquantel and L-praziquantel) in schistosomiasis (*S. mansoni*) infected children aged 2-6 years (Part 1), followed by an assessment of efficacy and safety with the selected formulation and dosage in *S. mansoni* infected infants aged 3-24 months (Part 2)
Clinical Trial Protocol Date / Version	3.1 / 28.February 2018
Center Number	1
Coordinating Investigator	PPD

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Conference on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD _____ PPD _____

Signature Date of Signature

Name, academic degree: PPD

Function/Title: Coordinating Investigator

Institution: PPD

Address:

Telephone number: PPD

E-mail address:

Sponsor Responsible Person

Name, academic degree:	PPD
Function/Title:	PPD
Institution:	EMD Serono Inc. ¦ One Technology Place A subsidiary of Merck KGaA, Darmstadt, Germany
Address:	Rockland, MA 02370, USA
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Appendix II: Table of study procedures and assessments - Cohort C1

		Pre-screening[1]	Screen-ing	Treatment												End of Confinement visit	Follow-up visits		End of Study visit
	Day/Time of the Assessment	**D-28 to D-1**	**D1**	**D1**												**D2**	**D3-D4**	**D8**	**D14-D21**
					Post 1st dose						Post 3rd dose					Post 3rd dose			
	Time of the Assessment		Pre-dose	H0	H0.5	H1	H2	H3	H4	H8	H0.5	H1	H2	H3	H4	D1H16			
	ICF signature	X																	
Diagnosis	POC-CCA test	X														X		X	X
	Kato-Katz method	X																	X
	Filtration method	X																	
Screening	Malaria rapid diagnostic test	X	X[2]																
	Safety laboratory tests (haematology, biochemistry, urinalysis)		X													X		X[3]	
	Demographics, medical history and history of medication		X																
	Vital signs (BP, HR, Temperature)		X							X									X
	Physical examination		X							X						X			X
	Inclusion/exclusion criteria checked		X																
Treatment	Confinement[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
	Food administration		X						X	X									
	Administration of IMP			X					X	X									
	Reaction to IMP administration			X					X	X									
	AE and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Pre-screening will be conducted in the villages. Only children who are positive for *S. mansoni* and negative for *S. haematobium* will be transferred to the hospital for further screening
[2] If not done at pre-screening only
[3] Safety laboratory tests, if required for AE follow up
[4] Confinement from the morning of the first dosing until at least 16 hours after the last IMP administration

Table of study procedures and assessments - Cohorts C2-C7

		Pre-screening[1]	Screening	Treatment									End of Confinement visit	Follow-up visits		End of Study visit
	Day/Time of the Assessment	**D-28 to D-1**	**D1**	**D1**									**D2**	**D3-D4**	**D8**	**D14-D21**
	Time of the Assessment		Pre-dose	H0	H0.5	H1	H2	H3	H4	H4.5	H6	H8	D1H24			
	ICF signature	X														
Diagnosis	POC-CCA test	X											X		X	X
	Kato-Katz method	X														X
	Filtration method	X														
Screening	Malaria rapid diagnostic test	X	X[2]													
	Safety laboratory tests (haematology, biochemistry, urinalysis)		X										X		X[3]	
	Demographics, medical history and history of medication		X													
	Vital signs (BP, HR, Temperature)		X									X				X
	Physical examination		X									X	X			X
	Inclusion/exclusion criteria checked		X													
Treatment	Confinement[4]		X	X	X	X	X	X	X	X	X	X	X			
	Food administration		X						X			X				
	Administration of IMP			X												
	Reaction to IMP administration			X												
	AE and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Pre-screening will be conducted in the villages. Only children who are positive for *S. mansoni* and negative for *S. haematobium* will be transferred to the hospital for further screening
[2] If not done at pre-screening only
[3] Safety laboratory tests, if required for AE follow up
[4] Confinement from the morning of the first dosing until at least 24 hours after the IMP administration

Table of study procedures and assessments - Cohorts C8-C9

		Pre-screening[1]	Screening	Treatment									End of Confinement visit	Follow-up visits		End of Study visit
	Day/Time of the Assessment	**D-28 to D-1**	**D-7 to D1**	**D1**									**D2**	**D3-D4**	**D8**	**D14-D21**
	Time of the Assessment		Pre-dose	H0	H0.5	H1	H2	H3	H4	H4.5	H6	H8	D1H24			
Pre-screening	Pre-Screening CF signature	X														
	POC-CCA test	X											X		X	X
	Kato-Katz method	X														X
	Filtration method	X														
Screening	ICF signature		X													
	Malaria rapid diagnostic test		X													
	Safety laboratory tests (haematology, biochemistry, urinalysis)		X										X		X[2]	
	Demographics, medical history and history of medication		X													
	Vital signs (BP, HR, Temperature)		X									X	X			X
	Physical examination		X									X	X			X
	Inclusion/exclusion criteria checked		X													
Treatment	Confinement[3]		X	X	X	X	X	X	X	X	X	X	X			
	Food administration		X						X			X				
	Administration of IMP			X												
	Reaction to IMP administration			X												
	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. Only children who are positive for *S. mansoni* and negative for *S. haematobium* will be transferred to the hospital for further screening
[2] Safety laboratory tests, if required for AE follow up
[3] Confinement from the morning of the first dosing until at least 24 hours after the IMP administration

Appendix III: Volume of biological fluid collected at each assessment time point (Cohorts C1-C7)

Pre-screening (D-28 to D-1)

Body Fluid	Type of Test	Specific Test	Number of Sampling	Volume/weight per Sampling (approx.)	Total Volume
Blood	Parasitology	Malaria RDT	1	20-50 µl	20-50 µl
Stool	Parasitology	Kato-Katz	2	2 g	4 g
Urine	Parasitology	POC-CCA test	1	100 µl	10 ml
		Filtration	1	10 ml	

Screening (D1)

Body Fluid	Type of Test	Specific Test	Number of Sampling	Volume per Sampling (approx.)	Total Volume
Urine	Urinalysis	NA	1	5-10 ml	5-10 ml
Blood	Parasitology	Malaria RDT[1]	1	20-50 µl	20-50 µl
	Haematology	NA	1	5-10 ml	5-10 ml
	Biochemistry	NA	1	5-10 ml	

End of Confinement Visit (D2)

Body Fluid	Type of Test	Specific Test	Number of Sampling	Volume per Sampling (approx.)	Total Volume
Urine	Parasitology	POC-CCA test	1	100 µl	5-10 ml
	Urinalysis	NA	1	5-10 ml	
Blood					5-10 ml
	Haematology	NA	1	5-10 ml	
	Biochemistry	NA	1	5-10 ml	

Follow up Visit (D8)

Body Fluid	Type of Test	Specific Test	Number of Sampling	Volume per Sampling (approx.)	Total Volume
Urine	Parasitology	POC-CCA test	1	100 µl	100 µl

End of Study Visit (D14-D21)

Body Fluid	Type of Test	Specific Test	Number of Sampling	Volume per Sampling (approx.)	Total Volume
Stool	Parasitology	Kato-Katz	2	2 g	4 g
Urine	Parasitology	POC-CCA test	1	100 µl	100 µl

[1] If not done at pre-screening only

Volume of biological fluid collected at each assessment time point (Cohorts C8-C9)

Pre-Screening (D-28 to D-1)

Body Fluid	Type of Test	Specific Test	Number of Sampling	Volume/weight per Sampling (approx.)	Total Volume
Stool	Parasitology	Kato-Katz	2	2 g	4 g
Urine	Parasitology	POC-CCA test	1	100 µl	10 ml
		Filtration	1	10 ml	

Screening (D-7 to D1)

Body Fluid	Type of Test	Specific Test	Number of Sampling	Volume per Sampling (approx.)	Total Volume
Urine	Urinalysis	NA	1	5-10 ml	5-10 ml
Blood	Parasitology	Malaria RDT	1	20-50 µl	20-50 µl
	Haematology	NA	1	5-10 ml	5-10 ml
	Biochemistry	NA	1	5-10 ml	

End of Confinement Visit (D2)

Body Fluid	Type of Test	Specific Test	Number of Sampling	Volume per Sampling (approx.)	Total Volume
Urine	Parasitology	POC-CCA test	1	100 µl	5-10 ml
	Urinalysis	NA	1	5-10 ml	
Blood	Haematology	NA	1	5-10 ml	5-10 ml
	Biochemistry	NA	1	5-10 ml	

Follow up Visit (D8)

Body Fluid	Type of Test	Specific Test	Number of Sampling	Volume per Sampling (approx.)	Total Volume
Urine	Parasitology	POC-CCA test	1	100 µl	100 µl

End of Study Visit (D14-D21)

Body Fluid	Type of Test	Specific Test	Number of Sampling	Volume per Sampling (approx.)	Total Volume
Stool	Parasitology	Kato-Katz	2	2 g	4 g
Urine	Parasitology	POC-CCA test	1	100 µl	100 µl

Annexe IV: Biological analyses

Biochemistry:

- CRP
- Urea
- Creatinin
- Glycemia
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Total Protein

Haematology:

Complete blood count

Urinalysis:

Standard Urinalysis