Statistical Analysis Plan

Clinical Trial Protocol Identification No.	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
Investigational Medicinal Product(s)	MSC 1028703A (rac-PZQ) MSC 2499550A (L-PZQ) Praziquantel (Biltricide® 600 mg)
Clinical Trial Protocol Version	10-Apr-2017/Version 3.0
Statistical Analysis Plan Author	PPD
Statistical Analysis Plan Date and Version	31-January-2018/Version 2.0
Statistical Analysis Plan Reviewers	PPD, Program Statistician PPD, Protocol Lead PPD, Pharmacokineticist PPD, Pharmacokineticist PPD, PP, PPD PPD, Medical Responsible PPD, Program Statistical Programmer

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Statistical Analysis Plan: MS200661-0005

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3 List of Abbreviations and Definition of Terms

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
$AUC_{0-\infty}$	Area under the concentration-time curve (AUC) from time zero to infinity
AUC_{0-t}	Area under the concentration-time curve (AUC) from time zero to the last sampling time at which the concentration is at or above the lower limit of quantification
AUC_{extra}	Extrapolated AUC from time t_{last} to infinity given as percentage from $AUC_{0-\infty}$
CL/f	Apparent total body clearance of drug
Cmax	Maximum observed concentration
CNER	Comité National d'Ethique et de la Recherche
CRF	Case Report Form
CRP	C-reactive Protein
CSR	Clinical Study Report
ERR	Individual Egg Reduction Rates
ERR_A	Group/Collective Egg Reduction Rate (based on arithmetic mean)
ERR_G	Group/Collective Egg Reduction Rate (based on geometric mean)
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
PPD	PPD
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
LSLV	Last subject, last visit
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
NCA	Non-compartmental Analysis

NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
ODT	Oral dispersible tablets
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per Protocol
PT	Preferred term
PZQ	Praziquantel
Q1	First quartile
Q3	Third quartile
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SCI	Schistosomiasis Control Initiative
SD	Standard deviation
SERU	Scientific and Ethics Review Unit
SDTM	Standard Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
t½	Apparent terminal half-life
TEAE	Treatment Emergent Adverse Event
t.i.d.	Three times a day
tlag	Time prior to the first measurable (non-zero) concentration
TLF	Tables, Listings, and Figures
ULN	Upper Limit of Normal
tmax	Time to reach the maximum concentration
Vz/f	Apparent volume of distribution during the terminal phase
λz	Apparent terminal elimination rate constant

4 Modification History

Unique Identifier for SAP Version	Date of SAP Version	Author	Changes from the Previous Version
1.0	01 Aug 2016	PPD	N/A
2.0	xx Oct 2017	PPD	• Removed Part 2b, cohort 10 • Additional site added (Kenya) • 10 infants corrected from 5-10 infants in study design • Abbreviations added • Removed endpoint/analysis regarding in Part 2b • Principal Investigator corrected to Coordinating Investigator • ERR_G (%) was corrected to include log-transformation of all pre- and post-treatment egg counts • Definition of the mITT analysis set was modified, i.e. patients requiring malaria treatment (after taking study drug) were removed from the primary endpoint analysis • Added "Physical Examination" to section 17 • Added list of SOPs to be followed (Appendix C)

5 Purpose of the Statistical Analysis Plan

The purpose of this SAP is to document technical and detailed specifications for the analysis of data collected for both Part 1 and Part 2 of protocol MS200661-0005. Output required by the trial Safety Monitoring Committee (SMC) will be presented in the relevant SMC Charter. Results of the analyses described in this SAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this SAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR, but not identified in this prospective SAP, will be clearly identified in the CSR. The SAP is based upon section 8 (Statistics) of the trial protocol and protocol amendments and is prepared in compliance with ICH E9.

6 Summary of Clinical Trial Features

6.1 Study design and sample size

This is a phase II study consisting of two parts (Part 1 and Part 2). Part 1 will be conducted in a single study site. Part 2 will only start once Part 1 is completed.

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 tablets (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

An 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.

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 randomisation scheme only after SMC approval while randomisation for the other groups can continue to 40 subjects per arm.

Part 2 will run after all subjects in Part 1 (C1-C6/7) have completed and are reviewed by SMC.
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) 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). In addition, a maturation factor will also be included (if applicable) to decide on the dose for these infants.

After 5 to 10 infants age 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.

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)

6.2 Endpoints

Study Objectives	**Primary objective**

	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 6year-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*. **Secondary objectives** **Part 1** • To determine the safety of different doses of rac-PZQ and L-PZQ ODTs in children aged 2 to 6 years infected with *S. mansoni* • 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* • 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 ODTs and L-PZQ ODTs 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-exposure-response relationship for L-PZQ, D-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 I and Part 2Part 2 will only start once Part 1 is completed. The study will be conducted at the district hospital of PPD. An additional site at PPD, may be added depending on patients' recruitment rate.

	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 tablets (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 randomisation scheme only after SMC approval while randomisation for the other groups can continue to 40 subjects per arm. **Part 2** will run after all subjects in Part 1 (C1-C6/7) have completed and are reviewed by the SMC. 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) 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). In addition, a maturation factor will also be included (if applicable) to decide on the dose for these infants. After 10 infants age 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 the 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	Originally, a PK profile of L-PZQ, D-PZQ and rac-PZQ (AUC_{0-t}, C_{max}, t_{max}, t_{lag}, $AUC_{0-\infty}$, AUC_{extra}, $t_{½}$, λ_z, CL/f and V_z/F) was to be produced, followed by assessment in 25% of the subjects of cohorts C1-C7 with a rich sampling scheme and in 75% of the subjects with a sparse sampling scheme. Further, PK would have been assessed in all subjects of Part 2 (cohorts C8 and C9) with a rich sampling scheme. Due to technical challenges in the preparation of the PK samples, it was decided by the Sponsor that no PK variable calculations will be done. The data will only be listed, and not analysed. The planned PK analysis is pending resolution of technical problems with previously validated DBS bioanalytical assay. Depending on the outcome, the PK data may potentially just be listed and not analysed.
Diagnosis	Screening 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.

	Subjects will be tested for *S. haematobium* in order to exclude *S. mansoni/S. haematobium* co-infections. 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). 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. *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 mg eggs per gram of faeces) and heavy (≥ 400 eggs per gram of faeces) 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 screening. 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).

7 Sample Size/Randomisation

7.1 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, considering the stratification factor.

There are limited historical data on the impact of the severity of infection on the observed cure rate. In the recent study by Keiser et al. (unpublished data), the observed cure rate in *S. mansoni* infected children varied between 55% and 60% in moderately infected children and 70% and 85% in light infected children depending on the dose. The table below presents the overall cure rate projections according to different assumptions of true cure rate in mild (low) and moderately infected children.

Overall cure rate (95%CI), (N=50)	**Assumptions of Cure Rate in Light Infections**			
	70%	75%	80%	85%

Assumptions of Cure Rate in Moderate/Heavy Infections	50%	62% (48%, 74%)	65% (52%, 78%)	68% (56%, 80%)	71% (60%, 82%)
	55%	64% (50%, 76%)	67% (54%, 80%)	70% (58%, 82%)	73% (62%, 84%)
	60%	66% (52%, 78%)	69% (56%, 80%)	72% (60%, 84%)	75% (64%, 86%)
	65%	68% (54%, 80%)	71% (58%, 82%)	74% (62%, 86%)	77% (66%, 88%)

A minimum-clinical meaningful cure rate is considered as equal to 70%. With 50 evaluable patients enrolled, stratified as 40% moderate/heavy and 60% light, the corresponding 95% CI lower bound of an observed cure rate of 70% would be above ~58%, depending on potential difference between the strata. This sample size would also provide the minimum number of subjects to estimate the cure rate within strata.

Considering the efficacy criteria for the selection of the dose (observed cure rate >70%), through simulations, the table below 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.

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%

For instance, 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.

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

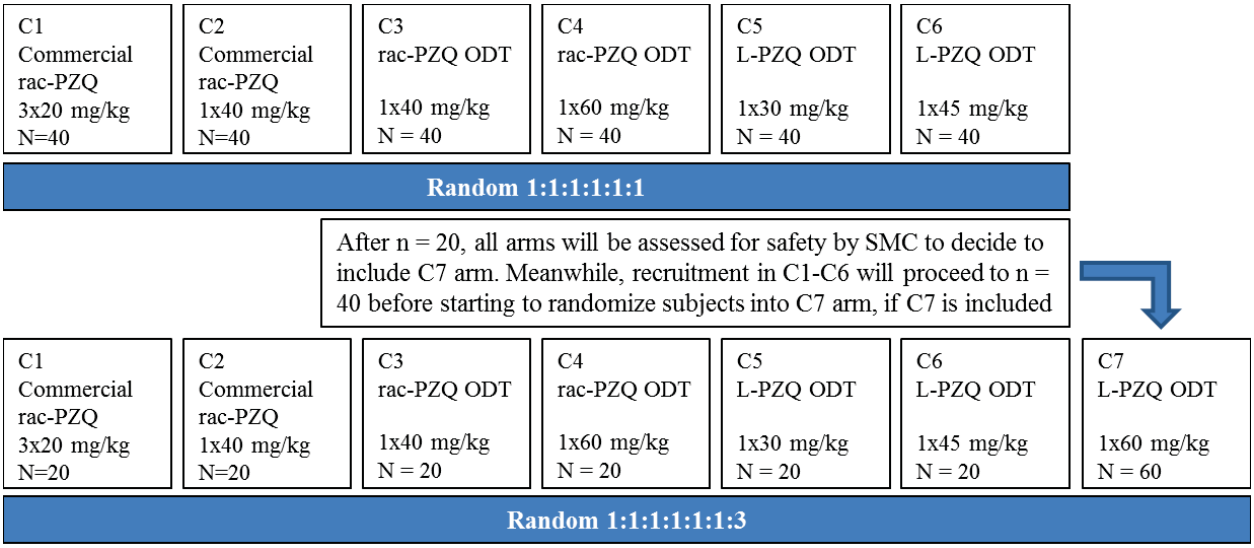
Part 2: 30 subjects infected with *S. mansoni* aged 13 to 24 months (C8) and 10 subjects infected with *S. mansoni* aged 3 to 12 months (C9) will be included to evaluate tolerability and efficacy

7.2 Randomisation

Part 1: Treatment allocation will be random and balanced at a ratio of 1:1:1:1:1:1. Randomisation 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.

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

If the C7 arm is included, randomisation will continue with an allocation ratio of 1:1:1:1:1:1:3 until a total of 60 subjects/arm are randomized in the 7 arms. If C7 arm is not included, the allocation ratio will remain the same (1:1:1:1:1:1) until a total of 60 subjects/arm are randomized in the 6 arms, as shown below.



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 randomisation 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 randomisation in this part.

8 Overview of Planned Analyses

The analyses will take part in a staggered manner for the distinct parts of the study, each part being self-contained. Separate appendices of the SAP will cover interim analyses for periodic safety review by the SMC. An overview of the planned analyses is provided below, in the order in which the analyses would be performed.

8.1 Part 1: Interim Safety Analysis

Cut-off for analysis: 20 enrolled subjects from each of the cohorts C1 to C6 with acute (24-hours post-dose) safety data.

Responsible party: PPD.

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 and the descriptive output evaluated by the SMC, to decide the inclusion of the 7th arm (C7). Output to be included in the SMC data report is detailed in Appendix C of the SMC charter (SMC Decision 1).

No adjustment for multiplicity will be made for any safety analyses. Analysis results will be shared with the SMC prior to the first scheduled SMC meeting.

8.2 Part 1: Final Analysis

Cut-off for analysis: Data for all subjects in Part 1 is available.

Responsible parties: PPD, Merck KGaA.

At the end of Part 1, the final analysis of Part 1 will be conducted on clean safety and efficacy data. The SMC will assess the data (SMC Decision 2 and 3; safety and efficacy) to recommend an optimal ODT dose (L-PZQ or rac-PZQ) for Part 2.

Due to technical challenges in the preparation of the PK samples, PK analysis may be abandoned, in which case the data will only be listed.

All primary, secondary endpoints and safety endpoints will be analysed. No adjustment for multiplicity will be made. Analysis results will be shared with the SMC prior to the next scheduled SMC meeting.

8.3 Part 2: Interim Safety/Efficacy Analysis

Cut-off for analysis: 10 subjects in Part 2 with complete safety and efficacy data.

Responsible parties: PPD, Merck KGaA.

Part 2 of the study will also include a SMC interim safety analysis. After 5 to 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.

All primary, secondary endpoints and safety endpoints will be analysed. The small sample size of this part of the trial limits the applicability of inferential statistics. For this reason and the exploratory nature of this part of the trial, no adjustment for multiplicity will be made. Analysis results will be shared with the SMC prior to the next scheduled SMC meeting. Output to be included in the SMC data report is detailed in Appendix C of the SMC charter (SMC Decision 4).

8.4 Final Analysis of Trial Data

Cut-off for analysis: Final database lock.

Responsible parties: PPD, Merck KGaA.

Following completion of Part 2 of the trial, the final trial analyses identified in this SAP will be performed only after the last subject has completed the treatment phase of the trial with all trial data in-house, all data queries resolved, and the database locked. A data review meeting will be held prior to database lock. In addition, no database can be locked until this SAP has been approved.

All primary, secondary endpoints and safety endpoints will be analysed. The small sample size of this part of the trial limits the applicability of inferential statistics. For this reason and the exploratory nature of this part of the trial, no adjustment for multiplicity will be made.

9 Changes to the Planned Analyses in the Clinical Trial Protocol

The statistical methods as described in the protocol were adopted.

10 Protocol Deviations and Analysis Sets

10.1 Definition of Protocol Deviations and Analysis Sets

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Important protocol deviations include:
- Subjects that are dosed on the study despite not satisfying the eligibility criteria, i.e. any inclusion/exclusion criteria violations
- Subjects that develop withdrawal criteria whilst on the study, but are not withdrawn
- Subjects that receive the incorrect treatment or an incorrect dose
- Deviation from GCP.

The following deviations will be identified and confirmed prior to or at the Data Review Meeting at the latest.
- Important protocol deviations include:
    - Subjects that receive any prohibited medications/foods/fluids as outlined in sections 5.3.1, 5.3.2, 6.5.2 and 6.5.3 of the protocol (see Appendix B for further guidance);
    - Any missed doses of Investigational Medicinal Product (IMP)
    - Vomiting within the first hour of IMP administration
    - Any medical condition that may modify the pharmacokinetic profile of the IMP or compromise the natural immunity of the subject

  - Stool and urine samples required for assessing the any of the study endpoint are missing or collected out-of-window
- Subset(s) of these important protocol deviations are clinically important, if leading to the exclusion of a subject from an analysis set (see section 10.2)

Important protocol deviations should be documented in the SDTM DV dataset whether identified through sites monitoring, medical review or programming. Important protocol deviations will be identified by programming and all clinically-important protocol deviations need to be in listings and described in an appendix of the CSR.

10.2 Definition of Analysis Sets and Subgroups

Screening Analysis Set (SCR)

The screening analysis set includes all subjects who signed the informed consent.

Modified Intention-to-Treat Set (mITT)

Modified intention-to-treat (mITT) population or analysis set includes all randomized subjects who have baseline measurement. In both parts 1 and 2, children who require malaria treatment following IMP administration will not be included in the mITT analysis set.

Safety Analysis Set (SAF)

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

Per Protocol Analysis Set (PP)

Per-protocol analysis set includes all subjects that constitute the mITT population with at least one post-baseline measurement and no clinically-important protocol deviations, including:

- Inclusion/exclusion violations
- Subjects that develop withdrawal criteria whilst on the study, but are not withdrawn
- Subjects that receive the incorrect treatment
- Subjects that receive any prohibited medications/foods/fluids as outlined in sections 5.3, 6.5.2 and 6.5.3 of the protocol;
- Any missed doses of IMP
- Any medical condition that may modify the pharmacokinetic profile of the IMP or compromise the natural immunity of the subject
- End-of-study stool (C1-C9) samples required for assessing the primary endpoint are missing or collected out-of-window (as described in section 11 of this SAP)

PK Analysis

Due to technical challenges in the preparation of the PK samples, PK analysis may be abandoned, in which case the data will only be listed.

10.2.1 Subgroup definition and parameterization

Subgroup analyses will be performed on subgroups as defined below.

The final parameterization will be updated and fixed at the Data Review Meeting at the latest and documented in an amendment to this SAP if different from the following definition.

The following subgroups will be defined:

- Age (some age ranges may not be applicable, depending on certain trial adaptations)
  Part 1:
  - 2 years ≤ age < 4 years
  - 4 years ≤ age ≤ 6 years (Ref)

  Part 2:
  - 3 months ≤ age < 13 months
  - 13 months ≤ age < 24 months (Ref)

- Gender
  - Male (Ref)
  - Female

- Severity of infection (as assessed at Pre-screening [D-28 to D-1])
  - *S. mansoni* infection
    - Light infection: 1 - 99 eggs per gram of faeces (Ref)
    - Moderate/heavy infection: ≥ 100 eggs per gram of feaces

- Treatment group
  - Biltricide® 3x20mg/kg t.i.d
  - Biltricide® 40mg/kg single dose (Ref)
  - rac-PZQ ODT 1x40mg/kg single dose
  - rac-PZQ ODT 1x60mg/kg single dose
  - L-PZQ ODT 1x30mg/kg single dose
  - L-PZQ ODT 1x45mg/kg single dose
  - L-PZQ ODT 1x60mg/kg single dose

- Trial center/country
  - PPD
  - PPD

11 General Specifications for Statistical Analyses

All analyses will be performed using SAS® Software version 9.1 or higher. Unless otherwise indicated all analyses will be presented by treatment group.

Data handling after cut-off date:

Data other than the date of death and the date last known to be alive obtained after the cut-off will not be displayed in any listings or used for summary statistics, e.g. laboratory values of samples taken after data cut-off, AEs with onset date after data cut-off, etc. will not be included in any analysis or listing.

Significance level:

All statistical tests mentioned in this SAP are to be regarded as exploratory. All statistical tests comparing treatment arms will be performed two-sided. If confidence intervals are to be calculated, these will be two-sided with a confidence probability of 95%, unless otherwise specified in this SAP.

Presentation of continuous and qualitative variables:

Continuous variables will be summarized using the following descriptive statistics, i.e.

- number of subjects (N), number of subjects with non-missing values
- mean, standard deviation
- median, 25th Percentile - 75th Percentile (Q1-Q3),
- minimum, and maximum,

Qualitative variables will be summarized by frequency counts and percentages.

Unless otherwise stated the calculation of proportions will be based on the number of subjects of the analysis set of interest. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits percentages will be based on the number of subjects still present in the trial at that visit, unless otherwise specified.

The following conventions are applied for reporting descriptive statistics of all continuous:

Statistic	Reporting convention
Mean	Observed + 1 decimal place
SD, SEM	Observed + 2 decimal place
Minimum	Observed
Median	Observed + 1 decimal place
Maximum	Observed
CV%	Up to 1 decimal place
Point Estimate	Observed + 1 decimal place

95% CI	Observed + 1 decimal place

Definition of baseline:

In general, the last non-missing measurement prior to first IMP administration will serve as the baseline measurement.

Definition of pre-treatment value:

N/A.

Definition of duration:

If required, duration will be calculated by the difference of start and stop date + 1 (if not otherwise specified).

The time since an event will be calculated as reference date minus date of event

Conversion factors:

The following conversion factors will be used to convert days into months or years: *1 month = 30.4375 days, 1 year = 365.25 days.*

Study windows:

Visit	Activity	Trial day	Window period
Visit 1	Pre-screening	Day -28 to Day -1	-28 to -1
Visit 2	Screening / Randomisation / IMP administration / Treatment period	Day 1	1
Visit 3	End of confinement	Day 2	2
Visit 4	Follow-up	Day 3	3+1
Visit 5	Follow-up	Day 8	8
Visit 6	End of study	Day 14 to Day 21	14 to 21 +3

Handling of missing data:

Unless otherwise specified, missing data will not be replaced.

In all subject data listing, imputed values will be presented. In all listings, imputed information will be flagged.

Missing statistics, e.g. when they cannot be calculated, should be presented as “nd”. For example, if n=1, the measure of variability (SD) cannot be computed and should be presented as “nd”.

Where tables are presented over time, the total of missing and non-missing observations at each time-point should reflect the population still in the trial at that time. This does not apply when imputations are made beyond trial withdrawal. For example, if a subject is still in the trial at the time-point but with missing data, it should be counted in the number of missing observations.

Trial day / Treatment day are defined relative to the date of start of treatment. Trial day 1 defines the day of randomisation, the day before is defined as Trial day –1 (no Trial day 0 is defined). Treatment day will be calculated accordingly, i.e. treatment day 1 is defined as the date of first administration of IMP to any one of the study cohorts, C1-C9. Treatment duration will be one day only.

If required for an analysis, incomplete date or date/time fields will be imputed as follows:

- Missing start dates will default to the first day of the month and first month of the year, if month is missing, subject to the following exceptions:
  - If and AE/concomitant medication/procedure start date is missing and month is the same as the month of IMP administration, then the start date will default to the IMP start date. If the month is different, the start date will default to the first day of the month.
  - If start date and month is missing and stop date is not before first IMP administration, then the start date will default to the IMP start date.
  - If start date and month and stop date is missing, then the start date will default to the IMP start date.
  - Missing start dates for medical history and medications stopped prior to IMP administration will not be imputed.
- Missing stop dates will default to the last day of the month and last month of the year, if month is missing, subject to the following exceptions:
  - If stop date is missing for a known medical history/previous medication, then the stop date will default to the IMP start date - 1 day.
  - If stop date and month is missing for a known medical history/prior medication, then the stop date will default to the IMP start date - 1 day.
  - If the stop date and month for a concomitant medication or AE is missing, it will default to the day of last contact with the participant.
- Unknown times will default to 00:00, subject to the following:
  - If an AE/concomitant medication/procedure start time is missing and day and month is the same as the date of IMP administration, then the start time will default to the IMP start time. If the day or month is different, the start time will default to 00:00.
  - If start time, date and month is missing and stop date is not before first IMP administration, then the start date/time will default to the IMP start date/time.
  - If start time, date and month and stop date is missing, then the start date/time will default to the IMP start date/time.
  - Missing start dates for medical history and medications stopped prior to IMP administration will not be imputed.
- Missing years will not be imputed.

12 Trial Subjects

The subsections in this section include specifications for reporting subject disposition and treatment/trial discontinuations. Additionally, procedures for reporting protocol deviations are provided.

12.1 Disposition of Subjects and Discontinuations

Subject disposition will be described in terms of the number and percentage of subjects in each of the following disposition categories:

- Total number of subjects screened (i.e. subjects who gave informed consent).
- Number of subjects who discontinued from the trial prior to randomisation / enrolment, overall and grouped by the main reason (e.g. did not meet eligibility criteria, withdraw of consent, progressive disease, etc.).
- Number of randomised / enrolled subjects, overall and grouped by infection severity (i.e. light, moderate/heavy), cohort as well as analysis set.
- Number of randomised / enrolled subjects who discontinued the trial after randomisation / enrolment, overall and grouped by cohort as well as main reason for discontinuation (e.g. adverse event, lost to follow-up, etc.).
- Number of randomised / enrolled subjects who completed the trial, overall and grouped by cohort. Only those subjects with *End of Study* visits, not due to early withdrawal, will be considered as subjects who completed the trial.

12.2 Protocol Deviations

12.1.1 Important Protocol Deviations

The following summary tables and listings of important protocol deviations will be provided (separately for pre-/post enrolment deviations):

- Frequency table of deviations from each cohort, grouped by reason of important protocol deviations
- Listing of important protocol deviations

12.1.2 Reasons Leading to the Exclusion from an Analysis Set

For subjects excluded from the mITT and PP analysis sets, the reasons for exclusion will be summarized and listed;

- Frequency table of exclusion from each cohort, grouped by analysis set and reason for exclusion
- Listing of reasons of exclusion from analysis sets, grouped by analysis set and cohort

13 Demographics and Other Baseline Characteristics

If not stated otherwise, summaries will be presented for the SAF analysis set.

13.1 Demographics and Baseline Physical Characteristics

Demographic characteristics will be summarized using the following information from the Pre-screening Visit (Day -28 to -1) CRF pages.

- Demographic characteristics
  - Gender: male, female
  - Race/Ethnic: Black or African American, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, White, other, not collected.
  - Age (months and years): summary statistics
  - Age categories:
    - 3 months ≤ age < 13 months
    - 13 months ≤ age < 24 months
    - 2 years ≤ age < 4 years
    - 4 years ≤ age ≤ 6 years
- Height in cm at Baseline: summary statistics
- Weight in kg at Baseline: summary statistics
  - Body-mass index (kg/m^2) at Baseline: summary statistics

Specifications for computation:

- Age [months and years]:
  - For those subjects aged two years and older Age [in years] will be calculated as follows: (date of given informed consent - date of birth + 1) / 365.25
  - For those subjects less than two years old Age [in months] will be calculated as follows: (date of given informed consent - date of birth + 1) / 30.4375
  - In case of missing day for at least one date, but month and year available for both dates: Missing day will default to the first day of the month, i.e. 01
  - In case of missing month for at least one date, but year available for both dates: Missing month will default to the first month of the year, i.e. January or 01

13.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0, preferred term as event category and MedDRA system organ class (SOC) body term as Body System category.

Medical conditions will be summarized by SOC and preferred term, providing the number and percentage of subjects with the condition, as well as the number and percentage of conditions. Summaries will be presented two-fold, first ordered in terms of decreasing percentage for SOC, and PT within SOC, and second, ordered alphabetically for SOC, and PT within SOC.

14 Previous, Concomitant and Prohibited Medications/Procedures

Previous medications are medications, other than trial medications and pre-medications for trial drug, which are taken within four weeks prior to first IMP administration and if the end date of the medication < date of "study day 1".

Previous treatment will be summarized from the "Concomitant Medications" eCRF page. Anatomical Therapeutic Chemical (ATC) term 2nd level and preferred term will be tabulated as given from the WHO Drug Dictionary March 2016 version. In case multiple ATC's are assigned to a drug, all ATC-2nd level will be used for reporting.

Concomitant treatments are medications, other than trial medications, which are taken by subjects any time on-trial (the end date of the medication ≥ date of "study day 1", or medication that is ongoing with a start date ≥ date of "study day 1").

Concomitant treatment will be summarized from the "Concomitant Medications" eCRF. ATC-2nd level and preferred term will be tabulated as given from the WHO Drug Dictionary current version. In case multiple ATC's are assigned to a drug, all ATC-2nd level will be used for reporting.

Prohibited medications are medications, other than trial medications, listed in section 6.5.2 of the trial protocol that are taken by subjects at any time.

- Prohibited prior medications will be summarized from the "Prior Drug History" eCRF page. ATC level 2 and preferred term will be tabulated as given from the WHO Drug Dictionary version of March 2016. In case multiple ATC's are assigned to a drug, all ATC-2nd level will be used for reporting.
- Prohibited concomitant medications, which includes medications that were started prior to dosing but were not stopped prior to dosing, will be summarised and listed separately. Prohibited concomitant medications will be identified from the "Concomitant Medications" eCRF page, using Appendix B as guide. ATC level 2 and preferred term will be tabulated as given from the WHO Drug Dictionary version of March 2016. In case multiple ATC's are assigned to a drug, all ATC-2nd level will be used for reporting.

All **Concomitant Procedures**, which were undertaken any time on trial, will be summarized according to the eCRF page "Concomitant Procedure".

- Concurrent procedures will be listed by verbatim term.
- Number of subjects with concomitant procedures (Prior, on or after the first day of trial treatment or within 28 days after last dose of trial treatment) overall will be presented.

15 Treatment Compliance and Exposure

Compliance and exposure will be reported for the mITT and PP analysis sets.

All dosing calculations and summaries will be based on "Treatment (D1)" CRFs pages.

Compliance will be derived as follows:

- 100 × {Actual number of doses administered / expected number of doses that were to be administered}, rounded to the nearest integer using the ROUND() function.

  Compliance will be categorised as:
  - Compliance = 0% {0 doses administered in C1; 0 doses in C2-C9}
  - Compliance = 33% {1 doses administered in C1}
  - Compliance = 67% {2 doses administered in C1}
  - Compliance = 100% {3 doses administered in C1; 1 dose in C2-C9}

Compliance will be summarised by cohort and compliance level, as well as listed by cohort and subject.

Exposure, in terms of dosing, will be derived as follows:

- Exposure:

  {Cumulative *Actual Dose* [mg]}

  If *Actual Dose* is missing, exposure will be derived as {Cumulative *Planned Dose* [mg]}, which will be flagged in listings

- Exposure with respect to weight:

  {Cumulative *Actual Dose* [mg]} / weight [kg], as calculated using the weight measurement at dosing

  If *Actual Dose* is missing, exposure will be derived as {Cumulative *Planned Dose* [mg/kg]}, which will be flagged in listings

Handling of other missing data:
- In case the start date is missing, it is assumed that the first dose of trial medication is given at the randomisation date. The randomisation date will replace incomplete dates of the first dose of trial medications.

16 Endpoint Evaluation

16.1 Primary Endpoint Analyses

16.1.1 Primary Analyses of Overall Clinical Cure Rate

No hypothesis testing will be performed. Point estimates and corresponding two-sided 95% CIs will be determined.

Analysis set(s):

- Primary analyses will be based on the mITT and PP analysis sets.

Overall clinical cure rate:

Subjects cured of infection during the trial will be labelled as “responders”. Responders will be defined as subjects with no parasite eggs (as determined by Kato-Katz method) in the End of Study

stool samples, 14-21 days after treatment, according to the eCRF page "Follow-up visit on D14-D21". Responders and non-responders will be coded as follows:

- For responders, *response* = 1
- For non-responders, *response* = 0

If the End of Study Kato-Katz egg count is missing, it will be imputed using the Last Observation Carried Forward (LOCF) approach. Subjects with missing data will be considered non-responders.

The proportion of responders in each cohort will be determined based on a binomial distribution. Exact 95% CIs will be calculated based on the Clopper-Pearson method. The PROC FREQ procedure in SAS will be used with the appropriate BINOMIAL and EXACT statements for point estimates and corresponding 95% CIs.

Point estimates and corresponding 95% CIs will be presented for cure rate, in terms of proportion of responders, by cohort. Response will be listed by cohort and subject. Estimates of cure rate will be presented graphically in the form of forest plots presenting means and 95% CIs.

Results will be presented for each analysis set.

16.1.2 Supportive Subgroup Analyses of Primary Endpoint

Analysis set(s):

- Supportive analyses of the primary endpoint will be based on the mITT and PP analysis sets.

Clinical cure rate by subgroup:

Again, analyses will be based on responders, which will be defined as was done in section 16.1.1 of this SAP. If the End of Study Kato-Katz egg count is missing, it will be imputed using the LOCF approach. Subgroup analyses of Part 1 and Part 2 of the study will be performed separately, by the following subgroups:

- Age category
- Gender
- Severity of infection
- Trial site (if applicable, i.e. more than one site)

Descriptive statistics of cure rates for each subgroup, individually and all in combination (four-way), will be estimated for each cohort using PROC FREQ.

Subgroup analysis will be performed utilising logistic regression to model clinical cure, i.e. *response* on gender, age category, severity of infection, day of assessment (e.g., Day 14-21), dose, formulation (ODT or not) and active pharmaceutical ingredient (L-PZQ or not [i.e. rac-PZQ]). The analysis will be repeated and presented separately for planned dose (mg/kg) *vs*. actual dose with respect to body weight (mg/kg) and actual dose in mg. Definitions and reference levels of subgroups are described in section 10.2.1 of this SAP. The PROC LOGISTIC procedure in SAS will be used with appropriate DESCENDING (to model on *response*=1) and PARAM=REF

(dummy coding for parameter estimates) statements to determine odds ratio point estimates and corresponding 95% Wald CIs.

To compliment PROC LOGISTIC results, the diagnostic plots using Pearson residuals will be produced [PLOTS(ONLY LABEL)=(INFLUENCE)].

Cure rate, in terms of proportion of responders, will be summarised by cohort (and by infection severity), and listed by cohort and subject. Estimates of cure rate will be presented graphically in the form of a forest plots presenting means and 95% CIs, by subgroup and cohort. For logistic regression results, odds ratio point estimates of model parameters and corresponding 95% CIs will be presented for each parameter, by cohort. Dose-response curves will be presented for the different active pharmaceutical ingredients (rac-PZQ/L-PZQ), separated by severity of infection, as well as pooled (all infections). Dose response curves will be generated for planned dose (in mg/kg), actual dose with respect to weight (in mg/kg) and actual dose in mg. These summary tables will be followed by the respective diagnostic plots.

Results will be presented for each analysis set.

16.2 Secondary Endpoint Analyses

16.2.1 Cure rate by POC-CCA

Analysis set(s):

- Primary analyses will be based on the mITT and PP analysis sets.

Clinical cure rate by POC-CCA:

CR by POC-CCA will be analysed in the same manner as CR by Kato-Katz as described above. In addition, estimates of cure rate will be presented graphically in the form of forest plots presenting means and 95% CIs of treatment groups and proportion of patients with each POC-CCA response (negative, positive 1+, positive 2+ and positive 3+) for the following time points:

- D-28 to D-1
- D2
- D8
- D14- D21

The proportion of CCA negative, 1+, 2+ and 3+ participants (colour-coded for category) will be plotted over time, for each of the cohorts. The same will be plotted for treatment types (Biltricide®, rac-PZQ and L-PZQ), instead of cohorts.

16.2.2 Egg reduction

Analysis set(s):

- Primary analyses will be based on the mITT and PP analysis sets.

The group/collective egg reduction rate will be determined as follows:

- ERR_A (%) = relative difference expressed in percent between the post-treatment mean egg count and the pre-treatment mean egg count ((pre-treatment egg count - post-treatment egg count) / pre-treatment egg count) including all patients.
- ERR_G (%) = relative difference expressed in percent between the log-transformed post-treatment mean egg count and the log-transformed pre-treatment mean egg count ((log-transformed pre-treatment egg count - log-transformed post-treatment egg count) / log-transformed pre-treatment egg count) including all patients.
    - The following log transformation will be used to calculate the geometric mean: $\boldsymbol{log(x+1)}$

      This log transformation is required, otherwise the ERR_G result would only be calculated on uncured patients only, which would introduce a bias and an important underestimation of the true ERR_G.

All raw egg counts will be multiplied by four prior to use in any derivation. Missing egg counts will be imputed using the LOCF approach.

To prepare the original data for bootstrapping, missing data will be imputed, followed by random sampling of pairs (2-tuples) of baseline and end-of-study egg counts, i.e. $\{Kato\text{-}Katz_{Baseline}; Kato\text{-}Katz_{End\text{-}of\text{-}Study}\}$, using PROC SURVEYSELECT, with unrestricted random sampling, at a sampling rate of 1 and 10 000 replicates. ERR_A and ERR_G will be computed by *replicate*, to establish the bootstrap sample.

The arithmetic mean of the bootstrap sample will constitute the point estimate. Corresponding 95% CIs will be determined using the percentile method, based on the bootstrap sample. Point and interval estimates of ERR_A and ERR_G will be presented by cohort. Mean Kato-Katz egg counts will be listed by cohort and subject and time point. Estimates of ERR_A and ERR_G will be presented graphically in the form of boxplots, by cohort.

The ERR_A or ERR_G slopes by treatment group will be compared to determine which treatment has the fastest egg clearance rate.

Results will be presented for each analysis set.

16.3 Other Endpoint Analyses

16.3.1 Analysis for PK Endpoints

Due to technical challenges in the preparation of the PK samples, the planned PK analysis may be abandoned, in which case the data will only be listed.

16.3.2 PK/PD Correlation/Association

Continuous data:

The Pearson correlation coefficient between individual egg reduction rates (ERR) and the following will be calculated and presented in summary tables and scatterplots:

- Dose exposure (as described in section 15)
- Actual dose

Pearson correlation coefficients and plots will be presented separately for each treatment administered, i.e.:

- Biltiricide®
- rac-PZQ ODT
- L-PZQ ODT

Categorical data:

In terms of clinical cure, the Mantel-Haenszel Chi-Square trend test will be performed between planned dose (in mg/kg) and response frequency, for each treatment administered, i.e.:

- Biltiricide®
- rac-PZQ ODT
- L-PZQ ODT

Similar trend tests will also be applied to actual dose, where actual dose will be categorised as follows:

- Less than 30 mg/kg
- 30 - 40 mg/kg
- 40 – 50 mg/kg
- 50 – 60 mg/kg
- 60 – 70 mg/kg
- More than 70 mg/kg

Again, results will be grouped by:

- Biltiricide®
- rac-PZQ ODT
- L-PZQ ODT

Trend test results will be tabulated. In addition, forest plots of response against planned dose will be presented by treatment administered, as listed above.

17 Safety Evaluation

The safety endpoints are:

- 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

Analysis set(s):

- SAF analysis set.

Safety analyses will be done on the safety analysis set and according to the as-treated principle. The subsections in this section include specifications for summarizing safety endpoints that are common across clinical trials such as AEs, laboratory tests, and vital signs.

17.1 Adverse Events

Details on AEs will be recorded on eCRF page "Adverse Events Details". Treatment-emergent adverse events (TEAEs) will be defined as those events with onset dates occurring after first IMP administration or events that worsen after first IMP administration.

All analyses described in Section 17.1 will be based on TEAEs if not otherwise specified.

Incomplete AE-related dates will be handled as described in section 11 of this SAP. Further information after cut-off (like fatal outcome) might be taken from Safety data base and included separately into CSR.

17.1.1 All Adverse Events

Adverse events will be summarized by worst severity per subject, using MedDRA version 19.0 preferred term as event category and MedDRA 19.0 primary system organ class (SOC) body term as Body System category.

Adverse events summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, as well as alphabetically for SOC, and PT within SOC.

With respect to TEAEs by severity, subjects will be counted only once for multiple events in the same SOC, by worst severity experienced. If a subject experiences more than one TEAE within a PT, he/she will be counted only once in the PT for the greatest severity he/she experienced. If severity is missing for an event, the greatest severity will be assumed.

With respect to TEAEs by severity, subjects will be counted only once for multiple events in the same SOC, by strongest/closest relationship with IP. If the subject experiences more than one TEAE within a PT, he/she will be counted only once in the PT for the strongest relationship to IP he/she experienced. If relationship to study treatment is missing for an event, the strongest relationship will be assumed.

Adverse events related to trial treatment are those events with relationship missing, unknown or yes.

In case a subject had events with missing and non-missing grades, the maximum of the non-missing grades will be displayed.

Treatment refers to the following trial treatments administered, Biltricide®, rac-PZQ ODT, L-PZQ ODT and includes the overall/total group. The following overall frequency tables will be prepared. In addition, the tables will be provided by PT and primary SOC in alphabetical order:

- TEAEs by cohort
- TEAEs by cohort and severity
- TEAEs by cohort and relationship to IMP
- TEAEs by treatment
- TEAEs by treatment and severity
- TEAEs by treatment and relationship to IMP
- TESAEs by treatment
- TESAEs by treatment and severity
- TESAEs by treatment and relationship to IMP

The following listings will be prepared:

- TEAEs
- TESAEs
- TEAEs leading to subject withdrawal
- TEAEs leading to death

Clinical trial.gov and EudraCT -requirements

Summary tables for non-serious adverse events excluding SAEs applying frequency threshold of 5% will be provided.

17.1.2 Adverse Events Leading to Treatment Discontinuation

Only relevant to cohort C1, since all other cohorts will receive a single dose of IMP. All AEs leading to treatment discontinuation will be listed by SOC and PT.

17.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

17.2.1 Deaths

In case a subject dies during the study, “Death” will be recorded as the “Primary reason for not completing” on eCRF page “Study Termination” and a corresponding SAE will to be recorded on the eCRF with outcome “Died”. Date and cause of death will be provided in individual subject data listing together with all dosing information, by cohort.

17.2.2 Serious Adverse Events

Please refer to Section 17.1.1. For these TEAEs, subject listings will be provided in addition.

17.3 Clinical Laboratory Evaluation

Laboratory values (including corresponding normal ranges) will be used for summary statistics and shift tables.

Quantitative data will be examined for trends using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline to each visit over time. The changes computed will be the differences from baseline (Day 1 samples) to end-of-trial (Day 14 / early withdrawal). Qualitative data based on reference ranges will be described according to the categories (i.e. Low, Normal, High). Only the 'high' and 'low' categories will be flagged. The number of subjects with clinical laboratory values below, within, or above normal ranges at baseline compared to endpoint will be tabulated for each test by treatment. Shift tables of baseline versus endpoint (as well as the worst value at any post-baseline visit) will be presented. In case of missing data LOCF will be applied.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will be shown in a data listing.

Baseline (Day 1) is the last measurement prior to the first dose of any trial treatment.

Subjects without post baseline laboratory samples will be excluded from analyses with respect to change from baseline summaries.

Data will also be presented for absolute and change from baseline results using boxplots, by time point/visit.

17.4 Vital Signs

Vital signs including blood pressure (BP), pulse rate (PR) and body temperature will be assessed according to the trial schedule. Vital signs will be considered abnormal as follows:

Parameter	Age	Low	Normal	High
Systolic blood pressure [mmHg]	3 - <12-months	<72	72 - 104	>104
	12-24-months	<86	86 - 106	>106
	2 - <6 years	<89	89 - 115	>115
Diastolic blood pressure [mmHg]	3- <12-month	<37	37 - 56	>56
	12-24-months	<42	42 - 63	>63
	2 - <6 years	<46	46- 76	>76

Parameter	Age	Low	Normal	High
Heart rate [beats/min]	3-<12-months	<100	100-180	>180
	12-24-months	<90	90-160	>160
	2 - <6 years	<80	80 - 140	>140
Oral Temperature [°C]	3-month - <6 years	<35.5	35.5 - 37.5	>37.5

Quantitative data will be examined for trends using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline to each visit over time. Baseline will be defined as the Day 1 pre-dose vital signs measurement.

Subjects data will be listed by cohort, subject and time point. An additional subject data listing will present all changes from baseline reported. Data will also be presented for absolute and change from baseline results using boxplots, by time point/visit.

17.5 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.

17.6 Tolerability Evaluations

The reaction to IMP administration (e.g., spitting, crying), tolerability, will be captured on the "Reactions to IMP/Biltricide® administration" eCRF pages. Data will be summarised through cross-tabulation with reaction category.

Relevant data listings will be presented.

18 Appendices

18.1 Appendix A: Planned analyses for SMC meetings

Refer to the SMC Charter.

18.2 Appendix B: Prohibited concomitant medications

Prohibited medications, by WHO Drug Dictionary ATC classification:

Prohibited medications	ATC Code	ATC level
Praziquantel and other antihelminthics	P02	2
Antimalarials, including chloroquine	P01B	3
Antiepileptics	N03	2
Glucorcorticosteroids (systemic)	H02	2
Anti-infectives for systemic use	J	1
Xanthine-containing drugs	C03BD	4
	N06BC	4
	R03DA	4
	R03DB	4
Anti-retrovirals	J05AB	4
	J05AE	4
	J05AF	4
	J05AG	4
	J05AR	4
	J05AX	4

Specific prohibited medications, listed by preferred term.

- Cimetidine

18.3 Appendix C: List of SOPs to be used

The following biostatistics SOPs will be followed to execute the relevant aspects of the trial:

Number	Version #	Procedural Document Title	Effective Date	Reference legacy number and version
PPD				