Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS200661-0003
Title	An open-label, Phase III efficacy and safety study of L-praziquantel orodispersible tablets (L-PZQ ODT) in Schistosoma-infected children 3 months to 6 years of age, including a 2:1 randomized, controlled cohort of Schistosoma mansoni-infected children 4 to 6 years of age treated with L-PZQ ODT or commercial PZQ (Biltricide®)
Study Phase	III
Investigational Medicinal Product(s)	MSC 2499550A (L-PZQ)
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Integrated Analysis Plan Author	PPD
Integrated Analysis Plan Date and Version	16-Aug-2021/Version 3.0
Integrated Analysis Plan Reviewers	Merck: PPD, PPD PPD, PPD PPD, Medical Responsible PPD, Safety Representative PPD, PPD PPD, Pharmacokineticist PPD, PPD PPD PPD PPD, Biostatistician

Approval Page

Integrated Analysis Plan: MS200661-0003

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PPD

PPD

Phone: PPD
E-mail:

PPD

Digitally signed by PP
PPD
DN: cn=PPD
o=PPD
PPD
ou=PPD
email=PPD
PPD c=IN
Reason: I am the author of this document
Date: 2021.08.17 10:52:52 +05'30'

PPD

PPD , EMD Serono Inc.
45 Middlesex Turnpike, Billerica, MA 01821
USA
Phone : PPD
Email :

PPD

1 Table of Contents

2 List of Abbreviations and Definition of Terms

ADaM	Analysis Data Model
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical (ATC) Classification System
AUC_{0-t}	Area Under the Plasma Concentration-Time Curve from Dosing to Timepoint *t*
BP	Blood pressure
C_{max}	Maximum Observed Plasma Concentration
CCA	Circulating Cathodic Antigen
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CV%	Percentage coefficient of variation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ERR	Egg Reduction Rate
GM/GeoMean	Geometric Mean
ICH	International Council for Harmonization
IDMC	Independent data monitoring committee
iERR	Individual Egg Reduction Rate
IMP	Investigational Medicinal Product
L-PZQ	Levorotatory enantiomer of praziquantel
LOCF	Last Observation Carried Forward
LCI	Lower Limit of the Confidence Interval
LLOQ	Lower Limit of Quantitation
mg	Milligram
Kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
ODT	Orodispersible Tablet
PK	Pharmacokinetics

PKP	Pharmacokinetic Analysis Population
POC-CCA	Point-of-Care Circulating Cathodic Antigen
PP	Per Protocol
PR	Pulse Rate
PZQ	Praziquantel
PT	Preferred Term
SAE	Serious Adverse Event
Q1	First Quartile
Q3	Third Quartile
SAF	Safety Analysis Population
SCR	Screening Analysis Population
SD	Standard deviation
SDTM	Standard Data Tabulation Model
SOC	System Organ Class
TEAEs	Treatment-Emergent Adverse Events
TESAEs	Treatment-Emergent Serious Adverse Events
t_{max}	Time when C_{max} is Observed
t_{lag}	Time Prior to the First Measurable Plasma Concentration
UCI	Upper Limit of the Confidence Interval
VAS	Visual Analogue Scale
WHO	World Health Organization

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	08-Nov-2019	PPD	Initial document
2.0	18-Nov-2020	PPD	• Updated name of Sponsor medical responsible in reviewer list. • Text was added regarding the additional assessment visit (Extended Follow-up visit, Day 35 to 40) for cohort 4, and regarding additional PK sampling in cohort 1b (Biltricide arm) and in cohort 4 treated with 60 mg/kg in the Objectives and the Endpoints Table and wherever applicable. • Addition of an interim analysis without pausing the study to be performed after 30 participants in Cohort 4 were treated at 60 mg/kg in Interim efficacy and safety analysis section 6.2. • Note added for classification and presentation of S. haematobium infection in definition of analysis populations and subgroups section 8.2. Specifically, participants in cohort 4 treated with L-PZQ 50 mg/kg was named as treatment group 4a, and those treated with 60 mg/kg was named as treatment group 4b • Added note for decimal place presentation and baseline definition update in general specifications for data analyses section 9. • Updated date presentation in summary tables in Demographics section 11.1.

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
			• ERR Derivation method updated in efficacy analysis section 14 • Added the number of additional subjects with PK sampling: up to 15 in the haematobium arm treated at 60 mg/kg (4b) and up to 15 subjects in Biltricide arm (1b) in Pharmacokinetics section 16. • Imputation strategy revised for incomplete dates for medical history, Adverse event and previous or concomitant medication section 11.2,12,15 respectively.
3.0	16AUG2021	PPD	• Updated the determination of systemic concentrations of R-Praziquantel, S-Praziquantel, R-4-OH-Trans Praziquantel and S-4-OH-Trans Praziquantel R-(-)-PZQ after treatment in Section 16.

4 Purpose of the Integrated Analysis Plan

The purpose of this IAP is to document technical and detailed specifications for the final analysis of data collected for protocol MS200661-0003. Output required by the trial independent data monitoring committee (IDMC) for reviewing the safety and efficacy data of the Phase III. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP will 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 IAP will be clearly identified in the CSR. The IAP is based upon Section 9 (Statistical Considerations) of the study protocol and protocol amendments and is prepared in compliance with ICH E9.

5 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe	IAP section
Primary			
To assess the efficacy of a single dose (50 mg/Kg) of L-PZQ ODT as assessed by cure rate 17 to 21 days after treatment, in children 4 to 6 years of age infected with S. mansoni (Treatment group 1a). The efficacy of a single dose (40 mg/kg) of commercial PZQ tablets (Biltricide®) in the same patient population (Treatment group 1b) will be considered as an internal control.	Clinical cure is defined as no parasite eggs in the stool 17 to 21 days after treatment. Egg counts will be determined by the Kato-Katz method: One stool sample will be collected during the pre screening period (Day -28 to Day -1) and the second one within a maximum of 5 days thereafter as baseline. Two additional stool samples will be collected between Day 17 to 21 after dosing to determine efficacy: the first one will be collected within the 17 to 21 day window and the second one within a maximum of 5 days following collection of the 1st sample. Three Kato-Katz thick smears (41.7 mg) will be prepared from each stool sample.	End-of-Study visit (17 to 21 days after treatment).	14.1
Secondary			
To assess the safety of a single dose (50 mg/Kg) of L-PZQ ODT in children 4 to 6 years of age infected with S. mansoni (Treatment group 1a)	Safety and tolerability assessments: - Occurrence, nature, severity and outcome of adverse events (AEs), - Occurrence of treatment-related AEs - Changes in laboratory safety parameters (hematology, biochemistry, urinalysis) and vital signs (body temperature, blood pressure and pulse rate)	First treatment to planned End-of-Study visit	15
To assess the efficacy of a single dose (50 mg/Kg) of L-PZQ ODT as assessed by cure rate 17 to 21 days after treatment, in children 2 to 3 years of age and in infants/toddlers 3 to <24 months of age infected with S. mansoni (Cohorts 2 and 3, respectively)	Same as Cohort 1.	End-of-Study visit	14.2
To assess the safety of a single dose (50 mg/Kg) of L-PZQ ODT in children 2 to 3 years of age and in infants/toddlers 3 months to < 24 months of age infected with S. mansoni (Cohort 2 and 3, respectively)	Same as Cohort 1.	First treatment to planned End-of-Study visit	15

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe	IAP section
To assess the efficacy of a single dose (50 mg/kg, 60 mg/kg based on IDMC) of L-PZQ ODT as assessed by cure rate 17 to 21 days and 35 to 40 days after treatment, in children 3 months to 6 years of age infected with S. haematobium (Cohort 4)	At each assessment visit after treatment clinical cure is defined as no parasite eggs in the urine samples. Egg counts will be determined by urine examination using the urine filtration technique: The first sample will be collected during the pre screening period (Day -28 to Day -1) and the second and the third one within a maximum of 5 days thereafter as baseline. At the End-of-Study visit (between Day 17 and 21) Cohort 4 participants will be asked to provide three urine samples (about 10 mL each: the first one will be collected within the 17 to 21-day window and the other two within a maximum of 5 days following collection of the 1st sample, for analysis by the filtration method. Similarly, at the Extended Follow-up visit, Cohort 4 participants will be asked to provide three additional urine samples (about 10 mL each) on different days between Day 35 and Day 40, for efficacy assessment by the filtration method. The urine samples will be filtered through a filter mesh. This mesh is then examined under the microscope for S. haematobium egg count.	End-of-Study visit and Extended Follow-up visit	14.2
To assess the safety of a single dose (50 mg/Kg,60 mg/kg based on IDMC) of L-PZQ ODT in children 3 months to 6 years of age infected with S. haematobium (Cohort 4)	Same as Cohort 1.	First treatment to planned End-of-Study visit	15
To assess the efficacy of a single dose (50 mg/Kg) of the L-PZQ ODT as assessed by egg reduction rate (ERR) 17 to 21 days after treatment, in children 4 to 6 years of age infected with S. mansoni (Treatment group 1a). The efficacy (ERR) of a single dose (40 mg/Kg) of commercial PZQ tablets (Biltricide®) in the same patient population (Treatment group 1b) will be considered as an internal control.	ERR from pre treatment to 17 to 21 days after treatment, using parasite egg counts as determined by the Kato-Katz method for Cohort 1.	Pre screening visit to End-of-Study visit	14.2
To assess the efficacy of a single dose (50 mg/Kg) of L-PZQ ODT as determined by ERR in children 2 to 3 years of age and in infants and toddlers 3 months to < 24 months of age infected with S.mansoni (Cohorts 2 and 3, respectively) and in children 3 months to 6 years of age infected with S. haematobium (Cohort 4).	ERR from pre treatment to 17 to 21 days after treatment, using parasite egg counts as determined by the Kato-Katz method for Cohorts 2 and 3 and the urine filtration method for Cohort 4. Additionally, for Cohort 4 participants treated with 60 mg/kg, ERR from baseline to 35 to 40 days after treatment, using parasite egg counts as determined by the urine filtration method.	Pre screening visit to End-of-Study visit and Extended Follow-up visit	14.2

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe	IAP section
To assess the cure rate as demonstrated with use of the commercially available point-of-care circulating cathodic antigen (POC-CCA®) test (Cohorts 1, 2, and 3).	One urine sample will be collected 17 to 21 days after treatment. Cure is defined as absence of test line in the POC-CCA® test cassette (i.e., no Schistosoma antigens detected).	End-of-Study visit	14.2
To assess acceptability in terms of ease of administration of the selected ODT (Treatment group 1a, Cohorts 2, 3, and 4) and commercial PZQ tablet (Treatment group 1b)	Reaction to Study Intervention administration (e.g., spitting, crying) to describe tolerability as assessed by nurse/site staff for all children enrolled in the study. Palatability assessment using a human gustatory sensation test (100-mm visual analogue scale [VAS]) scoring modified by the incorporation of a 3-point facial hedonic scale for all children 5 and 6 years of age enrolled in the study.	At Study Intervention administration	15.6
To assess the concentration-time profile of the L-PZQ ODT and Biltricide formulation in a subset of children	Concentrations of R-(-)-PZQ and rac-PZQ and, if appropriate, pharmacokinetics (PK) parameters (eg, C_{max}, t_{max}, AUC_{0-t})	Pre dose to 12 hours afterwards	16.1

6 Overview of Planned Analyses

6.1 Study Design and Sample Size

This is an open-label study in which participants in 4 cohorts based on age and Schistosoma species of infection will receive a single treatment dose of the new L-PZQ ODT at Day 1. The study includes 2:1 randomization of children 4 to 6 years of age infected with S. mansoni to the PZQ ODT treatment (Treatment group 1a) or the control treatment (40 mg/Kg racemic PZQ crushed tablets, Treatment group 1b). Specifically,

- Cohort 1: S. mansoni-infected children 4 to 6 years of age (n=150) will be randomized in a 2:1 ratio. Treatment group 1a, n=100, will be treated with a single dose of 50 mg/Kg of L-PZQ ODT (as the test treatment); Treatment group 1b, n=50, will be treated with the reference PZQ commercial product (Biltricide® 600 mg) crushed tablets at a single dose of 40 mg/Kg (as the internal control treatment).

- Cohort 2: S. mansoni-infected children 2 to 3 years of age (n=30) will be treated with a single dose of 50 mg/Kg of L-PZQ ODT. The primary aim of the descriptive efficacy analysis in this cohort is to explore whether the treatment effect is consistent with the treatment effect in older children (not an independent proof of efficacy in this subgroup).

- Cohort 3: S. mansoni-infected infants and toddlers 3 to 24 months of age (n=25 to 65) will be treated with a single dose of 50 mg/Kg of L-PZQ ODT. The primary aim of the descriptive efficacy analysis in this cohort is to explore whether the treatment effect is

consistent with the treatment effect in older children (not an independent proof of efficacy in this subgroup).

- Cohort 4: S. haematobium-infected children 3 months to 6 years of age (n=60) will be treated with a single dose of 50 mg/Kg of L-PZQ ODT, to assess the safety and efficacy in this group (not an independent proof of efficacy in this subgroup). After 30 children are enrolled and treated in Cohort 4, the efficacy and safety data will be summarized and evaluated by the IDMC to decide whether there is a need to increase the dose to 60 mg/Kg. [1] If a dose increase is needed, 30 additional patients will be added to this cohort (i.e., total sample size of 90 for Cohort 4, n=60 receiving the final dose) and treated with the 60 mg/Kg dose of L-PZQ ODT.

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

6.2 Interim Efficacy and Safety Analysis

Independent Data Monitoring Committee (IDMC):

Cut-off for analysis: 30 participants are enrolled, treated, completed follow-up visit (17 to 21 days after treatment) and their data entered to the database, in Cohort 4.

Responsible party: Triclinium Clinical Development, Merck Healthcare KGaA.

An IDMC will evaluate the interim efficacy and safety results after 30 participants are enrolled and treated in Cohort 4, in order to determine whether there is a need to increase the dose of L-PZQ ODT to 60 mg/Kg in this Cohort. The IDMC will also review the safety data for all patients who have been treated with L-PZQ ODTs that are available at that time. The evaluation will be based on an extract from the on-going database as clean as possible. No database lock or soft lock is planned for this purpose.

Analysis results will be shared with the IDMC.

Interim Analysis:

Cut-off for analysis: The first 30 subjects in Cohort 4 treated with 60 mg/kg of L-PZQ ODT have completed all assessments.

Responsible party: Triclinium Clinical Development, Merck Healthcare KGaA.

An interim analysis for efficacy based on ongoing database without pausing the study is planned when the first 30 subjects in Cohort 4 treated with 60 mg/kg of L-PZQ ODT have completed all assessments. The results will be available only to the internal clinical team to inform other studies in the PZQ clinical program, e.g. whether another clinical trial is necessary to evaluate the efficacy of L-PZQ ODT on S. haematobium infected children. No action to this ongoing study is planned subsequent to the interim analysis. The evaluation will be based on an extract from the on-going database as clean as possible. No database lock or soft lock is planned for this purpose.

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

6.3 Final Analysis

Cut-off for analysis: Final database lock.

Responsible party: Triclinium Clinical Development, Merck Healthcare KGaA.

Following completion of the trial, the final trial analyses identified in this IAP will be performed only after the last subject has completed the scheduled assessments of the trial with all trial data in-house, all data queries resolved, and the database locked.

All primary, secondary endpoints and safety endpoints will be analysed.

A data review meeting will be held prior to database lock. In addition, no database can be locked until this IAP has been approved.

7 Changes to the Planned Analyses in the Clinical Study Protocol

The statistical methods as described in the protocol and protocol amendments were adopted. There are no changes to the planned analyses.

Impact of COVID-19 considerations:

This is a single dose study with lean design. Efficacy assessments are taken at home based follow up visits. The impact of COVID-19 on efficacy assessment was deemed low. Missing data and increase in protocol deviations due to COVID-19 are not anticipated, hence no sample size re-estimation is planned, and no change in this IAP is made for COVID-19.

If in rare scenarios COVID-19 is diagnosed for any subjects, the occurrence of this disease will be summarized in the AE tables. If protocol deviation was determined with COVID-19 as the reason, the scenario will be also summarized in protocol deviation table(s).

8 Protocol Deviations and Analysis Populations

8.1 Definition of Protocol Deviations and Analysis Populations

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 participant's rights, safety, or well-being.

Important protocol deviations include:

- Participants that are dosed on the study despite not satisfying the inclusion or meeting the exclusion criteria, i.e. any inclusion/exclusion criteria violations

- Participants that develop withdrawal criteria whilst on the study but are not withdrawn
- Participants that receive the wrong study intervention or an incorrect dose
- Deviation from Good Clinical Practice

The following deviations will be identified and confirmed prior to or at the Data Review Meeting at the latest:

- 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 any of the study endpoint are missing or collected out-of-window. Some of these important protocol deviations are clinically important, if leading to the exclusion of a participant from an analysis population (see Section 10.2)

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

8.2 Definition of Analysis Populations and Subgroups

Screening Analysis Population (SCR)

The Screening analysis population includes all participants who signed the informed consent.

Intention-to-Treat (ITT)

For the purposes of this trial the ITT analysis set described in the protocol and the safety analysis set described below are considered equivalent. For this reason, the safety analysis set will be utilized for ITT and safety analysis purposes.

Modified ITT Analysis Population (mITT)

The modified ITT (mITT) analysis population will includes all enrolled participants who receive one dose of treatment and have baseline measurement. Children who require malaria treatment after enrollment in the study will not be included in the mITT population. The primary analysis of this study will be performed on the mITT population.

Per Protocol Analysis Population (PP)

Per-protocol (PP) Analysis population includes all participants who are in the mITT population and have one post baseline measurement for Cohorts 1, 2, 3 and 4a, and two post baseline measurements for Cohort 4b, without any clinically important protocol deviations. Details of the

criteria for exclusion from the PP population are provided below. An additional determination will be made prior to database lock, based on a review of data accrued during the conduct of the study.

Participants who meet any one of the following criteria will be excluded from the PP:

- 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-C3) samples or urine samples (C4) required for assessing the primary endpoint are missing or collected out-of-window

Safety Analysis Population (SAF)

The Safety analysis population will include all participants who receive a dose of study treatment. Participants will be analyzed according to the actual treatment they receive.

Pharmacokinetic Analysis Population (PKP)

The PK Analysis Population is a subset of the SAF population and will consist of all participants who receive at least one dose of active IMP and provide at least one measurable post-dose concentration. A measurement below lower limit of quantification (BLQ) is considered a valid measurement. Participants will be analyzed according to the actual treatment they received. Subjects in this analysis population may not have taken prohibited medications/foods/fluids, and may not have experienced any diarrhea or vomiting after IMP administration.

Additional Subgroup Analysis Populations

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 IAP if different from the following definition.

The following subgroups will be defined:

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

- Male
- 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
    - Moderate/heavy infection: ≥ 100 eggs per gram of faeces
  - *S. haematobium* infection
    - Light infection: < 50 eggs/10 mL of urine
    - Heavy infection: ≥ 50 eggs/10 mL of urine

  Note: In summary tables, S. haematobium heavy infection will be classified as Moderate /Heavy when being presented side-to-side with other cohorts.
- Trial center/country
  - PPD
  -

9 General Specifications for Data Analyses

Study intervention groups

Study intervention groups are defined and labelled as Biltricide® and L-PZQ ODT.

Unless otherwise indicated all analyses will be presented separately for treatment groups. Specifically, Cohorts 1a and 1b will be presented separately in all tables. In general, in this IAP the term "cohorts" represents Cohorts 1, 2, 3 and 4, whereas the term "treatment groups" stands for Cohorts 1a, 1b, 2, 3, 4a and 4b with 4a and 4b representing Cohort 4 participants treated with 50 mg/kg and 60 mg/kg, respectively.

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 cutoff, etc. will not be included in any analysis or listing.

Significance level

No formal comparisons were planned for the primary objective. CCI

Presentation of continuous and qualitative variables

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

- number of participants, number of participants with missing values,
- mean, standard deviation,
- median, 25th percentile, 75th percentile (Q1, Q3),
- minimum and maximum.

Qualitative variables will be summarized by counts and percentages.

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

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
Q1	Observed + 1 decimal place
Q3	Observed + 1 decimal place

Note: At rare situations, there might be deviations from the above convention.

Definition of baseline

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

Definition of change from baseline

Change from baseline = visit value – baseline value

Percent Change from Baseline = 100 * (visit value – baseline value) / baseline value

Note: If baseline observation is missing then respective subject summary will not be calculated for Change from Baseline or Percent Change from Baseline.

Definition of pre-treatment value

In general, the last non-missing measurement prior to the first study intervention will be used as the pre-treatment baseline measurement.

Definition of duration

If required, duration in days 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.

Handling of missing data

Unless otherwise specified (Sections 13, 15, 16 and 17), missing data will not be imputed.

In all participant data listings, 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".

Time window

Day 1 is the day of the study intervention, the day before is Day -1 (no Day 0 is defined).

Study day is defined relative to Day 1.

Software(s)

The statistical software SAS® (windows version 9.1 or higher) may be used to perform statistical analyses, produce tables, listings and figures and calculate summary statistics of PK Parameters if appropriate. WinNonlin (version 6.4 or higher) will be used for estimating PK parameters.

10 Study Participants

This section includes specifications for reporting participant disposition and study intervention/study discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Participants and Discontinuations

- Total number of participants screened (i.e. participants who gave informed consent)
- Number of subjects who excluded from the trial prior to randomisation / enrolment, overall and grouped by the main reason (e.g. did not meet eligibility criteria, withdrawal of consent, 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 completed the trial.
- Number of subjects in the mITT, PP, SCR, SAF analysis populations

The number and percentage of participants in each of the above disposition categories will be presented by group (cohort/treatment) and overall. Percentages will be presented with respect to the number of enrolled/randomized participants.

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

The following summary tables and listings of important protocol deviations will be provided:

- Frequency table per reason of important protocol deviations by treatment group.
- Listing of important protocol deviations

10.2.2 Reasons Leading to the Exclusion from an Analysis Population

For participants excluded from the mITT and PP, the reasons for exclusion will be summarized and listed:

- Frequency table of deviations from each cohort, grouped by reason of important protocol deviations, including COVID-19 as a reason, if applicable
- Listing of reasons of exclusion

11 Demographics and Other Baseline Characteristics

If not stated otherwise, summaries will be presented on the SAF and on the mITT analysis population, by treatment group and overall.

11.1 Demographics

Demographic characteristics will be summarized using the following information from the Screening/Baseline Visit 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 at site.
- Age (months and years): summary statistics
- Age categories:
    - 4 to 6 years of age
    - 2 to 3 years of age
    - 3 to < 24 months of age

- Height in cm at Baseline: summary statistics
- Weight in kg at Baseline: summary statistics
- Body-mass index (kg/m2) at Baseline: summary statistics

Specifications for computation:

- Age [months and years]:
    - Age [in years] will be calculated as follows:
      (date of given informed consent - date of birth + 1) / 365.25
    - 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

In all tables, age will be summarized in years.

11.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using MedDRA, version 22.0 (or above), preferred term as event category and 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, ordered alphabetically for SOC, and PT within SOC.

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

- Missing start day and month will default to the first day of the month and first month of the year, subject to the following exceptions:
    - Missing start day and month for medical history stopped prior to IMP administration will not be imputed.
- Missing stop day and month will default to the last day of the month and last month of the year, subject to the following exceptions:

- If stop day is missing for a known medical history, then the stop day will default to 1 day prior the IMP start day.
- If stop day and month is missing for a known medical history, then the stop month and day will default to 1 day prior to IMP start date.

- Missing years will not be imputed.

12 Previous or Concomitant 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 for which 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 WHODrug Global Version is March 2019 (or above) and format is B3. 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 WHODrug Global Version is March 2019 (or above) and format is B3. 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 6.5.3 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 WHODrug Global Version is March 2019 (or above) and format is B3. 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 WHODrug Global Version is March 2019 (or above) and format is B3. 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 listed according to the eCRF page "Concomitant Procedure".

- Concurrent procedures will be listed by verbatim term.

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

- Missing start day and month will default to the first day of the month and first month of the year, subject to the following exceptions:

- If concomitant medication start day is missing and month and year is the same as the month and year of IMP administration, then the start day will default to the IMP start day. If the month or year are different, the start day will default to the first day of the month.
- If start day and month is missing and year is the same as the year of IMP administration and stop date is not missing stop date, then the start day and month will default to the IMP start day and month. If the year is different, then the start day=01 and month=Jan.

- Missing stop dates will default to the last day of the month and last month of the year, subject to the following exceptions:
  - If stop day is missing for a known previous medication, then the stop day will default to 1 day prior the IMP start day.
  - If stop day and month is missing for a known prior medication, then the stop month and day will default to 1 day prior to IMP start date.
  - If the stop day and month for a concomitant medication is missing, it will default to the day and month of last contact with the participant.
- Missing years will not be imputed.

Note: ATC coding will not be indication/other differentiators (namely route) based, but all ATC available for a drug in the dictionary will be provided.

13 Treatment Compliance and Exposure

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

All dosing calculations and summaries will be based on "Dosing Preparation" 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 dose administered in C1-C4}
  - Compliance = 100% {1 dose administered in C1-C4}

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:

  {*Actual Dose* [mg]}

  If *Actual Dose* is missing, exposure will be kept as missing.

- Exposure with respect to baseline weight:

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

If Actual Dose is missing, exposure will be kept as missing.

14 Efficacy Analyses

14.1 Primary Endpoint Analyses

14.1.1 Primary Analyses of Clinical Cure Rate

Analysis (Analysis Population)	Derivation	Statistical Analysis Methods	Missing data handling
Primary endpoint: Cure rate 17 to 21 days after treatment, in children 4 to 6 years of age infected with S. mansoni (Treatment group 1a and 1b)			
Primary (mITT)	Clinical cure is defined as no parasite eggs in the stool 17 to 21 days after treatment. Egg counts will be determined by the Kato-Katz method: One stool sample will be collected during the pre screening period (Day -28 to Day -1) and the second one within a maximum of 5 days thereafter as baseline. Two additional stool samples will be collected between Day 17 to 21 after dosing to determine efficacy: the first one will be collected within the 17 to 21 day window and the second one within a maximum of 5 days following collection of the 1st sample. Three Kato-Katz thick smears (41.7 mg) will be prepared from each stool sample	No hypothesis testing will be performed. Point estimates and corresponding two-sided 95% CIs will be determined. 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, 17 to 21 days after treatment, according to the eCRF page "End of Study (Day 17 to Day 21)". Responders and non-responders will be coded as follows: • For responders, *response* = 1 • For non-responders, *response* = 0 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 BINOMIAL and EXACT option 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 point estimates and 95% CIs. For mITT analysis tables will be presented with imputation and without imputation. Results will be presented for each analysis set.	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.
Sensitive (PP)			No imputation will be done
Sensitive (SAF)			No imputation will be done

14.2 Secondary Endpoint Analyses

Analysis (Analysis Population)	Derivation	Statistical Analysis Methods	Missing data handling

Secondary endpoint: Cure rate 17 to 21 days after treatment, in children 2 to 3 years of age and in infants/toddlers 3 to < 24 months of age infected with S. mansoni (Cohorts 2 and 3, respectively)			
Primary (mITT) See 14.2.1 for details about analysis for participant 3 to 24 months of age (Cohort 3).	Same as Cohort 1 (primary analysis).	Same as Cohort 1 (primary analysis).	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.
Primary (PP)			No Imputation will be done.
Secondary endpoint: Cure rate 17 to 21 days and 35 to 40 days after treatment, in children 3 months to 6 years of age infected with S. haematobium (Cohort 4)			
Primary (mITT)	At each assessment visit after treatment, clinical cure is defined as no parasite eggs in the urine samples. Egg counts will be determined by urine examination using the urine filtration technique: The first sample will be collected during the pre screening period (Day -28 to Day -1) and the second and the third one within a maximum of 5 days thereafter as baseline. At the End-of-Study visit (between Day 17 and 21) Cohort 4 participants will be asked to provide three urine samples (about 10 mL each): the first one will be collected within the 17 to 21-day window and the other two within a maximum of 5 days following collection of the 1st sample, for analysis by the filtration method. Similarly, at the Extended Follow-up	No hypothesis testing will be performed. Point estimates and corresponding two-sided 95% CIs will be determined. Subjects cured of infection during the trial will be labelled as "responders". At each of the End of Study visit (17 to 21 days after treatment, according to the eCRF page "End of Study (Day 17 to Day 21)") and the Extended Follow-up visit (35 to 40 days after treatment, according to the eCRF page "Extended Follow-up (Day 35 to Day 40)"), responders will be defined as subjects with no parasite eggs urine samples, (as determined by urine filtration method) Responders and non-responders will be coded as follows: • For responders, *response* = 1 • For non-responders, *response* = 0 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 point estimates and 95% CIs. Results will be presented for each analysis set.	If the End of Study or Extended Follow-up visit egg count is missing, carried forward for imputation. According to this rule subjects with missing egg count data at post-treatment assessment will be considered as non-responders at the End-of-study visit. For cohort 4b, if the assessment at Extended Follow-up visit is missing, the assessment result at End-of-study visit will be carried forward.

	visit, Cohort 4 participants will be asked to provide three additional urine samples (about 10 mL each) on different days between Day 35 and Day 40. Each urine samples will be filtered through a filter mesh. This mesh is then examined under the microscope for S. haematobium egg count.		
Secondary endpoint: Egg Reduction Rate (ERR) 17 to 21 days after treatment, in children 4 to 6 years of age infected with S. mansoni (Treatment group 1a and 1b)			
Primary (mITT)	ERR from pre treatment to 17 to 21 days after treatment, using parasite egg counts as determined by the Kato-Katz method for Cohort 1.	The group/collective egg reduction rate will be determined for cohort 1a and 1b as follows: Step 1: Calculate the arithmetic group mean and geometric group mean egg counts (egp) at each visit. The geometric mean is defined as: $GM(x_1, \dots, x_n) = e^{(1/n \sum_{i=1}^{n} log(x_i+1))} - 1$ Where x_i is the egg count for subject *i*. Step 2: Calculate group ERR for each treatment group and individual ERR • ERR_A (%) = relative difference expressed in percent between the post-treatment mean egg count and the pre-treatment mean egg count ((pre-treatment mean egg count - post-treatment mean egg count) / pre-treatment egg count). • ERR_G (%) = relative difference expressed in percent between the geometric mean post-treatment egg count and geometric mean pre-treatment egg count ((geometric mean pre-treatment egg count - log-transformed post-treatment egg count) / geometric mean pre-treatment egg count). In addition: individual ERR (iERR) will be calculated for each patient: • iERR (%) = relative difference expressed in percent between the post-treatment egg count and the pre-treatment egg count ((pre-treatment egg count - post-treatment egg count) / pre-treatment egg count). All raw egg counts will be multiplied by 4 in background of EDC system generating egg counts as eggs/gram (mansoni) and eggs/10ml (haematobium) respectively.	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.
Primary (PP)			No Imputation will be done.

		Point and interval estimates of ERR_A, ERR_G and proportion of individuals with iERR≥90% will be presented by treatment group. 95% CIs of these 3 parameters will be calculated by bootstrapping (using SAS procedure SURVEYSELECT). Mean Kato-Katz egg counts will be listed by cohort and subject and time point. Estimates of ERR_A, ERR_G and iERR will be presented graphically in the form of boxplots, by cohort. Results will be presented for each analysis set.	
Secondary endpoint: Egg Reduction Rate (ERR) in children 2 to 3 years of age and in infants and toddlers 3 months to < 24 months of age infected with S. mansoni (Cohorts 2 and 3, respectively) and in children 3 months to 6 years of age infected with S. haematobium (Cohort 4).			
Primary (mITT) See 14.1.2 for details about analysis for participant 3 to 24 months of age (Cohort 3).	ERR from pre treatment to 17 to 21 days after treatment, using parasite egg counts as determined by the Kato-Katz method for Cohorts 2 and 3 and the urine filtration method for Cohort 4. Additionally, for Cohort 4b participants ERR from baseline to 35 to 40 days after treatment, using parasite egg counts as determined by the urine filtration method,	Same as Cohort 1 (Secondary analysis).	If the End of Study egg count is missing, it will be imputed using the Last Observation Carried Forward (LOCF) approach. Subjects with all post-baseline egg counts missing will be considered non-responders. For cohort 4b, if egg counts is missing only at Extended Follow-up visit, it will be imputed by taking the value from End-of-study visit.
Secondary endpoint: cure rate as demonstrated with use of the commercially available point-of-care circulating cathodic antigen (POC-CCA®) test (Cohorts 1, 2, and 3).			
Primary (mITT) See 14.2.1 for details about analysis for participant 3 to 24 months of age (Cohort 3).	One urine sample will be collected 17 to 21 days after treatment. Cure is defined as absence of test line in the POC-CCA® test cassette (i.e., no Schistosoma antigens detected).	Cure rate by POC-CCA® (Cohorts 1, 2, and 3) will be analyzed in the same manner as the primary endpoint, with proportion cured and its 95% CI. In addition, estimates of cure rate will be presented graphically in the form of forest plots presenting point estimates 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 • D17 to 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® and L-PZQ), instead of cohorts.	If the End of by POC-CCA 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.
Primary (PP)			No Imputation will be done.
Note: • Pooled analysis of Cohort 3 mITT population from this study and the mITT population for participants 3 to 24 months of age in the Phase II study MS200661-0005 (Cohorts 8 and 9) is detailed in Section 14.2.1.			

- For mITT analysis tables will be presented with imputation and without imputation.

14.2.1 Pooled analysis of 3 to 24-month-old participants:

A total of 65 participants 3 to 24 months of age infected with *S. mansoni* is planned for analysis. Since the sample size in either the Phase II or Phase III study alone is too small to have adequate precision on the cure rate, the results in this Phase III study (MS200661-0003, Cohort 3) will be pooled with Cohorts 8 and 9 of the Phase II study (MS200661-0005, Cohorts 8 and 9). Data that will be pooled for analysis purposes comprises efficacy data, as well as demographics, other baseline characteristics and compliance & drug accountability . Relevant participants' data from the subject-level (ADSL) and efficacy ADaM datasets of the Phase II study (ADLBPARA) will be pooled with the applicable ADaM datasets from the Phase III study (to be prepared). Derived variables will be pooled, directly given that the relevant derivation rules are the same across the two studies. Imputations will be handled in the same way. Efficacy endpoint data that will be pooled from the ADLBPARA dataset from MS200661-0005 include the following:

- Infection intensity data
- Egg counts
- POC-CCA data

For presentation purposes, results from the MS200661-0003 trial will be presented in one table, and then additional tables will be prepared, specifically for participants aged 3 to 24 months, i.e. Cohort 3 from MS200661-0003, and Cohort 8 and 9 from MS200661-0005. These additional tables will be prepared for demographics, other relevant baseline characteristics and all primary and secondary efficacy results.

To align the data from MS200661-0003 the following visits from MS200661-0005 will be used in efficacy analyses:

- Baseline: DAYS -28 TO -1
- FOLLOW UP DAYS 14 to 21 (for analysis purposes this visit will be considered the same as the "DAYS 17 to 21" visit from MS200661-0003)

The definitions of analysis sets including SAF, mITT and PP are the same across the two studies, so the flag for them will not be redrived for the MS200661-0005 participants. The pooled analysis will only apply at the final analysis of the trial data.

14.3 Supportive Subgroup Analyses for Efficacy Analysis

Analysis set(s):

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

Clinical cure rate by subgroup:

If the End of Study Kato-Katz egg count is missing, it will be imputed using the LOCF approach. Subgroup analyses the study will be performed, by the following subgroups:

- Age category (Cohort 4 only)

- Gender
- Severity of infection
- Country

Descriptive statistics of cure rates for each subgroup will be estimated for each cohort.

Cure rate, in terms of proportion of responders, will be summarised by cohort and by infection severity, gender and country and listed by cohort and subject. Estimates of cure rate will be presented graphically in the form of a forest plots presenting point estimates and 95% CIs, by treatment group and subgroup. Forest plot by age group is needed for Cohort 4 only. Cure rates will be presented as percentages, not proportions, i.e. $cure\ rate \times 100$.

For mITT analysis tables will be presented with imputation and without imputation.

15 Safety Analyses

Safety and tolerability assessments:

- Occurrence, nature, severity and outcome of adverse events (AEs),
- Occurrence of treatment-related AEs
- Changes in laboratory safety parameters (hematology, biochemistry, urinalysis) and vital signs (body temperature, blood pressure and pulse rate)

Analysis set(s):

- SAF analysis set.

Safety analyses will be done on the SAF analysis set and according to the as-treated principle. This section includes specifications for summarizing safety endpoints that are common across clinical trials such as AEs, laboratory tests, reactions to the IMP and vital signs.

15.1 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/time occurring after first IMP administration or events that worsen after first IMP administration.

All analyses described in Section 15.1 will be based on TEAEs if not otherwise specified.

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, subject to the following exceptions:
    - If an AE start day is missing and month and year is the same as the month and year of IMP administration, then the start day will default to the IMP start day. If the month or year is different, the start day will default to the first day of the month.
    - If start day and month are missing and year is equal to IMP administration year, then the start day and month will be the minimum of IMP administration start date and AE resolution date (AE end date).

- Missing stop dates imputation:
    - If only the day is missing then the last day of the month is used if this does not result in a date after the subject's death in which case the death date will be used;
    - In all other cases the AE end date will not be imputed.
- Unknown times will default to 00:00, subject to the following exceptions:
    - If an AE 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 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 years will not be imputed.

Further information after cut-off (like fatal outcome) might be taken from Safety data base and included separately into CSR.

15.1.1 All Adverse Events

Adverse events will be summarized by worst severity per subject, using MedDRA version 22.0 (or above) preferred term as event category and MedDRA 22.0 (or above) primary system organ class (SOC) body term as Body System category.

Adverse events summaries will be ordered alphabetically for SOC, and PT within SOC unless otherwise specified.

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 relationship to IMP, subjects will be counted only once for multiple events in the same SOC, by strongest/closest relationship with IP. If a 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® or 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, unless otherwise specified:

- TEAEs by treatment group
- TEAEs by treatment group and severity
- Related TEAEs by treatment group
- Related TEAEs by treatment group and severity
- TESAEs by treatment group
- TESAEs by treatment group and severity
- Related TESAEs by treatment group
- Related TESAEs by treatment group and severity
- Most commonly reported AEs by PT, sorted by overall frequency

The following listings will be also be prepared:

- TEAEs leading to subject withdrawal
- TEAEs leading to death

Clinical trial.gov and EudraCT -requirements

The following summary tables for non-serious adverse events (excluding SAEs) applying frequency threshold of 5% will be provided.

- TEAEs by treatment group
- Related TEAEs by treatment group

In all adverse events tables Treatment groups 1a and 1b will be presented as separate columns.

15.1.2 Adverse Events Leading to Study Intervention Discontinuation

All AEs leading to treatment discontinuation will be listed by SOC and PT.

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

15.2.1 Deaths

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

15.2.2 Serious Adverse Events

Tables will be provided by PT and primary SOC in alphabetical order:

- TESAEs by treatment group
- TESAEs by treatment group and severity
- Related TESAEs by treatment group
- Related TESAEs by treatment group and severity

In addition, listings will be provided of all SAEs.

15.3 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 -7 to Day 1 samples(screening)) to end-of-treatment (Day 1 12hrs sample / 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 will be tabulated for each test by treatment group. Shift tables of baseline versus end-of-treatment will be presented.

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 -7 to Day 1 samples(screening)) is the last measurement prior to the 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.

Note: In order for summarization, quantitative clinical laboratory measurements reported as "<X", i.e. below limit of quantitation, will be converted to X/2, i.e. half value of the lower limit of quantitation; quantitative clinical laboratory measurements reported as ">X" i.e. above the upper limit of quantification, will be converted by as 1.5X, i.e. 1.5 folds of upper limit of quantification.

15.4 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]s	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 summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline to each visit over time.

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.

15.5 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. Any abnormal physical examination findings will be presented as adverse events.

15.6 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.

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

Quantitative data will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum, frequency and percentage) of palatability assessment.

Relevant data listings will be presented.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

To get information on systemic plasma concentrations after administration of L-PZQ ODT formulation in the targeted pediatric age groups, a subgroup of 20 participants 4 to 6 years of age (Treatment group 1a), 15 participants 2 to 3 years of age (Cohort 2), between 5 and 10 participants 3 to <24 months of age (Cohort 3), and 15 participants infected with S. haematobium (Cohort 4) are planned to supply blood samples for determination of systemic concentrations of R-Praziquantel, S-Praziquantel, R-4-OH-Trans Praziquantel and S-4-OH-Trans Praziquantel after treatment of L-PZQ 50 mg/kg. PK sampling from up to 15 participants in Treatment Group 1b will provide information on the systemic plasma concentrations

observed after Biltricide administration. An additional up to 15 participants will be collected for the 60 mg/kg dose group in Cohort 4b to study the systemic concentration of R-Praziquantel, S-Praziquantel, R-4-OH-Trans Praziquantel and S-4-OH-Trans Praziquantel after treatment of L-PZQ 60 mg/kg. A separate written informed consent will be obtained for PK sampling. Only participants with minimum hemoglobin of 10 g/dL will be asked to take part in the PK sub-study.

Blood samples of approximately 1 mL per time point will be collected for measurement of plasma concentrations of R-Praziquantel, S-Praziquantel, R-4-OH-Trans Praziquantel and S-4-OH-Trans Praziquantel, immediately prior to dosing (pre dose) and thereafter (post-dose), multiple times till 12 hours after dosing, as specified in the Schedule of Activities (Section 1.3 in protocol) and below. Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of drug administration and each sample will be recorded in the eCRF.

Note: Analyses that took place prior to 01-Mar-2021 will only include R-Praziquantel and S-Praziquantel. All analyses taking place from 01-Mar-2021 will include 4 analytes R-Praziquantel, S-Praziquantel, R-4-OH-Trans Praziquantel and S-4-OH-Trans Praziquantel.

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

Table 1 PK sampling times per body weight group

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

Note: the tolerance window of ±10% for the collections of timepoints.

Plasma concentrations will be tabulated and summarized using descriptive statistics. PK parameters will be calculated if possible as appropriate for the respective sampling schemes. All PK parameters will be calculated using standard non compartmental methods and the actual administered dose. Calculations will be performed using a validated software tool as described below.

The following PK parameters will be calculated, when appropriate:

Table 2 PK parameters

Symbol	Definition
C_{max}	Maximum observed concentration in plasma
AUC_{0-t}	Area under the plasma concentration-time curve (AUC) from time zero to the last sampling time at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log linear trapezoidal rule (linear up, log down).
t_{max}	Time to reach the maximum plasma concentration
t_{lag}	Time prior to the first measurable (non-zero) concentration

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

Estimation of Individual PK Parameters:

- Pharmacokinetic parameters will be calculated by the Clinical PK/PD Group of Translational Medicine, Merck, Darmstadt, Germany, or by a Contract Research Organization (CRO) selected by the Sponsor, using standard non-compartmental methods and the actual administered dose. PK parameters will be calculated using the actual elapsed time since dosing, given with a precision of 14 significant digits or the SAS format Best12. When the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data.

- Non-compartmental computation of pharmacokinetic parameters will be performed using the computer program Phoenix® WinNonlin® version 6.3, or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA).

- The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows version 9.1 or higher) may be used to produce tables, listings and figures, if appropriate (see below). No other analyses are planned.

16.1.1 Presentation of PK Concentration and PK Parameter Data

16.1.1.1 Listings and Tables (PK Analysis Population)

Statistical analyses and descriptive summaries of pharmacokinetic data will be performed on the PK Analysis Population (PKP, as defined in Section 8.2). The following PK tables and listings will be produced:

a) Descriptive Statistics of PK Concentration Data:

- PK measurements will be descriptively summarized using: number of non-missing observations (N), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max).

- Descriptive statistics will only be calculated for N>2 in which a measurement of <LLOQ represents a valid measurement

- Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data and rounded for reporting purposes only.

- The following conventions will be applied when reporting descriptive statistics of PK concentration data:
    - Mean, Min, Median, Max: 3 significant digits
    - SD 4 significant digits
    - CV%: 1 decimal place

b) Descriptive Statistics of PK Parameter Data

- PK parameter data will be descriptively summarized using: number of non-missing observations (as N), arithmetic mean, standard deviation (SD), coefficient of variation (CV%), minimum, median, maximum, geometric mean (GeoMean), the geometric coefficient of variation (GeoCV) and the 95% confidence interval for the GeoMean (LCI 95% GM, UCI 95% GM). For time to reach maximum observed concentration (t_{max}), only n, minimum, median, and maximum will be reported.

- Descriptive statistics will only be calculated for a PK parameter when N>2.

- PK parameters read directly from the measurements (i.e. C_{max}) will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures. In export datasets, as well as in the SDTM PP domain, PK parameters will be provided with full precision and will not be rounded. Descriptive statistics of PK parameter data will be calculated using full precision values and rounded for reporting purposes only.

- The following conventions will be applied when reporting descriptive statistics of PK parameter data:
    - Mean, Min, Median, Max, GeoMean, 95% CI: 3 significant digits
    - SD: 4 significant digits
    - CV%, GeoCV%: 1 decimal place

16.1.1.2 Graphical Summaries and Individual plots (PK Analysis Population)

- Individual concentration versus time plots; linear and semi-log; using the actual time points by participants, day, analyte, matrix and group; if any post-dose concentrations is <LLOQ the line representing LLOQ will be added to the semi-log plots.

- Overlaid individual concentration versus time plots; linear and semi-log; by analyte, matrix and group; if any post-dose concentrations is <LLOQ the line representing LLOQ will be added to the semi-log plots.

- Mean concentration time plots; linear with standard deviation and semi-log; using scheduled (nominal) time points by day, analyte, matrix and group; if any post-dose

concentration is <LLOQ the line representing LLOQ will be added to the semi-log plots. Error bars should be included only in the linear plots.

17 References

Clinical protocol number **MS200661-0003**

19 Mar 2019 /V1.1 Côte D'Ivoire
20 Feb 2019 /V1.1 Kenya,
11 August 2020/V1.2

18 Appendices

18.1 Appendix A: Planned analyses for IDMC meetings

Refer to the IDMC 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