Integrated Analysis Plan

Clinical Trial Protocol Identification No.	MS200585_0004
Title	A Phase I, open-label, randomized, four-period, crossover, fully replicated, reference-scaled, single center study to assess the bioequivalence of a single oral dose of 1200 mg of the coated Cesol tablet formulation versus comparator Biltricide® in healthy male volunteers
Trial Phase	1
Investigational Medicinal Product(s)	MSC1028703A (Praziquantel)
Clinical Trial Protocol Version	09 Jan 2020 / Version 1.0
Integrated Analysis Plan Author	**Coordinating Author** On behalf of PPD Merck — PPD **Function** — **Author / Biostatistician** PPD, Nuvisan — PPD
Integrated Analysis Plan Date and Version	09 Jul 2020 / Final Version 1.0
Integrated Analysis Plan Reviewers	**Function** — **Name** Medical Responsible, Merck — PPD Clinical Trial Lead, Merck PPD Merck PPD Merck PPD, Merck PPD Merck PPD Merck PPD, Merck Biostatistician, Merck

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Signature Page

Integrated Analysis Plan: MS200585-0004

A Phase I, open-label, randomized, four-period, crossover, fully replicated, reference-scaled, single center study to assess the bioequivalence of a single oral dose of 1200 mg of the coated Cesol tablet formulation versus comparator Biltricide® in healthy male volunteers

Approval of the IAP by all Merck Data Analysis Responsible is documented within ELDORADO. With the approval within Eldorado, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

Merck responsible	Date	Signature
PPD , PPD	Via ELDORADO approval process	
PPD , PPD	Via ELDORADO approval process	

1 Table of Contents

2 List of Abbreviations and Definition of Terms

AE	Adverse Event
ANOVA	Analysis of variance
BMI	Body Mass Index
CI	Confidence Interval
eCRF	Electronic Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of variation
CV_{WR}	Within-subject coefficient of variation for the reference treatment
ECG	Electrocardiogram
GeoCV%	Geometric Coefficient of Variation
GeoMean	Geometric Mean
GMR	Geometric Mean Ratio
IAP	Integrated Analysis Plan
ICH	International Conference on Harmonization
I.e.	That is
LCI	Lower Confidence Interval Bound
LLOQ	Lower Limit of Quantification
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
N.R.	No result
Max	Maximum
Min	Minimum
PT	Preferred Term
PK	Pharmacokinetics
PZQ	Praziquantel
Q1	First Quartile

Q3	Third Quartile
QTcF	Corrected QT interval per Fridericia's formula
SAE	Serious Adverse Event
SEM	Standard Error of the Mean
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
UCI	Upper Confidence Interval Bound
ULOQ	Upper Limit of Quantification

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
Final 1.0	09-Jul-2020	PPD	Original Document

4 Purpose of the Integrated Analysis Plan

The purpose of this integrated analysis plan (IAP) is to document technical and detailed specifications for the final analysis of data collected for protocol MS200585_0004. 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 clinical study protocol (CSP) and is prepared in compliance with ICH E9.

5 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	IAP section
Primary		
To assess the BE of the 600 mg coated Cesol tablet versus the comparator 600 mg tablet of Biltricide at a dose of 1200 mg with regard to rac-PZQ	PK parameters C_{max} and area under the plasma concentration-time curve from time zero to last measurable concentration (AUC_{0-t}) of rac-PZQ after single dose administration	Section 16.1
Secondary		
To evaluate the safety and tolerability of the 600 mg coated Cesol tablet versus the comparator 600 mg tablet of Biltricide at a dose of 1200 mg	Occurrence of TEAEs and treatment related AEs per Qualitative Toxicity Scale Standard laboratory hematology and biochemical parameters, vital signs (body temperature, systolic and diastolic blood pressure, and pulse rate) and ECG parameters.	Section 15
To assess the BE of the 600 mg coated Cesol tablet versus the comparator 600 mg tablet of Biltricide at a dose of 1200 mg with regard to PZQ enantiomers	PK parameters Cmax and area under the plasma concentration-time curve from time zero to last measurable concentration (AUC_{0-t}) of R-(-)-PZQ and S-(+)-PZQ after single dose administration	Section 16.1
To further characterize the PK profile of the 600 mg coated Cesol tablet versus the comparator 600 mg tablet of Biltricide at a dose of 1200 mg	PK parameters of rac-PZQ, R-(-)-PZQ and S-(+)-PZQ after single dosing: $AUC_{0-\infty}$, time to reach maximum plasma concentration (t_{max}), t_{lag}, $t_{½}$, λ_z, $CL/_f$ and $V_{Z/f}$	Section 16.1

6 Overview of Planned Analyses

6.1 Interim Analysis

No interim analysis is planned for this study.

6.2 Final Analysis

The final, planned analyses identified in the CSP and in this IAP will be performed after the last participant has completed the last visit, i.e. end of treatment/safety follow-up visit 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 for the final analysis. In addition, no database can be locked until this IAP has been approved.

7 Changes to the Planned Analyses in the Clinical Study Protocol

There are no changes to the planned analyses in the CSP.

8 Protocol Deviations and Analysis Sets

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

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

Important protocol deviations include

- Deviations from the inclusion and exclusion criteria
- Concomitant medication violations (see Section 6.5.2 of the protocol)
- Use of prohibited medicines (see Section 6.5.3 of the protocol)
- Participants who receive incorrect treatment or dose
- Sample processing errors that may lead to inaccurate bioanalytical results
- Vomiting or diarrhea following oral dosing (these instances will be discussed on a case-by-case basis)
- Deviation from Good Clinical Practice

- Non-compliance to study procedures or deviations from study procedures likely to affect the primary endpoints (e.g. participant develops withdrawal criteria whilst in the study but is not withdrawn)

- Deviation from study medication compliance in terms of medical conditions and/or AEs that may have interfered with drug disposition or with respect to factors likely to affect the primary endpoints

All important protocol deviations will be documented in Clinical Data Interchange Standard Consortium (CDISC) Study Data Tabulation Model (SDTM) datasets whether identified through sites monitoring or medical review.

8.2 Definition of Analysis Sets

Analysis Set	Description
Screening (SCR)	The Screening Analysis Set will include all participants, who provided informed consent, regardless of the participant's randomization and study intervention status in the study.
Safety (SAF)	The Safety Analysis Set will include all participants who were administered any dose of any study intervention. Analyses will consider participants as treated. All safety analyses will be based on this analysis set.
PK	The PK Analysis Set will include all participants, who receive at least one dose of study intervention, have no clinically important protocol deviations or important events affecting PK, and provide at least one measurable postdose concentration. Participants will be analyzed per the actual study intervention they received. The PK population will include all participants: • Who have completed at least one study period without any relevant protocol deviations and factors likely to affect the comparability of PK results • With adequate study intervention compliance • With evaluable PK data, i.e., nonmissing values for primary endpoints in each completed study period. If participants received prohibited concomitant therapy or medicines, as specified in Section 6.5 of the CSP, they will be excluded from the PK population. Relevant decisions will be made before database lock. All PK analyses will be based on this analysis.

9 General Specifications for Data Analyses

Statistical analyses will be performed using the computer program package SAS® System for Windows™ (Version 9.4 or later; SAS Institute, Cary, North Carolina, USA).

The results of this trial will be reported using summary tables, figures, and data listings, as appropriate. All data will be summarized by treatment sequence, period, treatment and/or scheduled time point, as appropriate. All individual data will be listed as measured in the individual participant data listing. Repeated and unscheduled measurements will be included in the listings.

For demographic, baseline and safety assessments, continuous measurements will be summarized by means of descriptive statistics (i.e. number and percentage of observations, number and percentage of missing observations, mean, standard deviation [SD], median, the first and third quartile [Q1 and Q3], minimum [Min], and maximum [Max]) and categorical data will be summarized by means of frequency tables (i.e., count and percentages), if not stated otherwise.

Percentages are based on the number of subjects dosed with each treatment in summary tables by treatment T1, T2, R1, R2, or the number of subjects in the respective analysis population for summary tables by total treatment T and R [N]. A respective footnote will be provided in the summary tables.

Mean, Median, Q1, Q3, Min, Max will have the same precision as the SDTM data (decimal places). SD will be presented with one decimal place more than the mean. For participant disposition and demographic tables the denominator will be the number of participants in the analysis set. Counts of missing observations will be included as a separate category.

If not otherwise specified, ‘baseline’ refers to the last scheduled measurement before administration of the first drug in each period.

If no baseline or previous to baseline evaluations per period exist then the baseline value will be treated as missing.

The following calculations and derivations, as applicable, will be used:

- Change from baseline: post-baseline visit value - baseline value
- Duration of AE (in days hh:mm) = end date and time - start date and time of the AE, if missing time for either the beginning or end then = end date – start date + 1; in case of multiple records for the same AE, the duration will be calculated over all these records
- Days hh:mm from dosing = start date and time of the event - date and time dose administration (for TEAEs), if missing time for either the dosing or event then days hh:mm from dosing = event start date – date of dose administration + 1

- Rel. Day in period of AE = start date of the event – date of First Admin in period + 1 (for AEs on or after the day of dosing)

- Rel. Day in study of AE = start date of the event – date of First Admin (for AEs before the day of dosing of the study only)

Repeated and unscheduled measurements will be included in the listings, but not used for statistical analysis or summary tables, unless the repeated measurement was performed due to unreliable values/technical reasons, e.g., clotted samples.

In this phase 1 PK study, missing observations will be assumed to be missing completely at random (MCAR). No action will be taken to handle missing data. A participant who withdraws prior to the last planned observation in a trial period will be included in the analyses up to the time of discontinuation.

The following treatment labels will be used:

Treatment Tx: x. administration of coated Cesol tablet, 2 tablets of praziquantel 600 mg per period,

Treatment Rx: x. administration of Biltricide®, 2 tablets of praziquantel 600 mg per period

where x=1 or x=2 defines the first and second administration of test or reference product, respectively. These labels will be used in listings and summaries by first treatment and second treatment.

Treatment Total T: coated Cesol tablet, 2 tablets of praziquantel 600 mg per period,

Treatment Total R: Biltricide®, 2 tablets of praziquantel 600 mg per period,

whereby these treatment labels will be used in summaries by total treatment.

10 Trial Participants

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

Considering the study objectives, it is planned to enroll 36 participants in the study to ensure inclusion of at least 32 evaluable participants for the treatment comparisons.

The participants will be randomized to one of the two treatment sequences: T1-R1-T2-R2 or R1-T1-R2-T2, where T is Test product and R is Reference product, with a washout period of at least 1 week in between.

	Period 1		Period 2		Period 3		Period 4
Sequence 1 (18 participants)	Test 1	Washout at least 7 days	Reference 1	Washout at least 7 days	Test 2	Washout at least 7 days	Reference 2
Sequence 2 (18 participants)	Reference 1		Test 1		Reference 2		Test 2

Test = coated Cesol tablet, 2 tablets of praziquantel 600 mg;
Reference = Biltricide, 2 tablets of praziquantel 600 mg.

10.1 Disposition of Participants and Discontinuations

This following will be presented in a summary table:

- Total number of participants screened (i.e., participants who gave informed consent)
- Number of screened participants who discontinued from the trial prior to treatment overall and grouped by the main reason for discontinuation:
    - Participant did not meet all eligibility criteria
    - Withdrew consent
    - Other (COVID-19-related and COVID-19-non-related)
- Number of randomized participants
- Number of randomized participants who did not receive treatment (as applicable)
- Number of treated participants by treatment T1, T2, R1, R2 and overall
- Number and percentage of treated participants who completed study by treatment T1, T2, R1, R2 and overall
- Number and percentage of treated participants who discontinued the study overall and number of subjects who discontinued treatment by treatment T1, T2, R1, R2, with the primary reason of discontinuation: :
    - Adverse event
    - Lost to follow-up
    - Protocol non-compliance
    - Death
    - Withdrew consent

- Other (COVID-19-related and COVID-19-non-related)

A listing of discontinued participants will be provided.

A listing of participants affected by the COVID-19 related study disruption by unique subject number identifier will also be provided.

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

Listings of important protocol deviations will be provided including the date and relative day in relation to dosing in the relevant period.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

All criteria/reasons leading to the exclusion of a participant from an analysis set will be listed based on the safety set.

Reasons for excluding individual PK concentrations will also be listed separately and flagged in the main listing based on the Safety Analysis Set.

11 Demographics and Other Baseline Characteristics

11.1 Demographics

Summaries will be given for both the safety and the PK set, if different.

Demographic characteristics will be listed by participant and treatment sequence and summarized by treatment sequence and overall using the following information from the Screening/Baseline Visit eCRF pages.

Demographic characteristics:

- Sex: male, female, undifferentiated
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Pacific Islander, White, Other
- Ethnic origin - Hispanic or Latino: yes, no
- Ethnic origin - Japanese: yes, no
- Age (years): summary statistics
- Height (cm) at Screening : summary statistics

- Weight (kg) at Screening : summary statistics
- BMI (kg/m²) at Screening: summary statistics

Age will be taken from the eCRF and cannot be derived from the data because only the year of birth is collected in the eCRF.

BMI will be re-derived (ie, not taken directly from the database) according to the following formula:

- BMI (kg/m²) = weight (kg) / (height (m) * height (m))

11.2 Medical History

The medical history will be listed by participant including the preferred term (PT) and MedDRA system organ class (SOC) body using MedDRA, current version.

11.3 Other Baseline Characteristics

Other baseline characteristics will be listed by participant and summarized by treatment sequence and overall using the following information from the Screening/Baseline Visit eCRF pages.

Other baseline characteristics may include:

- Smoking status
- Alcohol consumption

12 Previous or Concomitant Medications/Procedures

Previous medications are medications, other than trial medications and pre-medications for trial drug, which started and stopped before first administration of trial drug.

Concomitant treatments are medications, other than trial medications, which are taken by participants any time on-trial (on or after the first day of trial drug treatment for each participant).

In case the date values will not allow to unequivocally allocate a medication to previous or concomitant medication the medication will be considered as concomitant medication.

Any previous and concomitant medication will be encoded with WHO-DD, latest version. Prior and concomitant medications will be listed by participant (safety set).

The following information will be displayed in a listing: generic or trade name (as reported in CRF), WHO drug name, dose/unit, route, frequency, reason for use, start/end date and time.

Concomitant procedures will be presented in a data listing.

13 Treatment Compliance and Exposure

The dosing of each participant is monitored by the study nurse or investigator. A listing of date and time of each drug administration and each blood sampling, including time deviations as well as measured rac-PZQ, R-(-)-PZQ and S-(+)-PZQ concentration, will be provided sorted by participant.

14 Efficacy Analyses

Not applicable.

15 Safety Analyses

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical trials such as adverse events, laboratory tests and vital signs.

Safety data analysis will be conducted on the Safety Analysis Set.

15.1 Adverse Events

Adverse Events will be listed by treatment T1, T2, R1, R2.

Generally, the number and percentage of participants experiencing at least one TEAE will be summarized by treatment T1, T2, R1, R2, by total T, total R and overall as well as the number of events.

A TEAE is an AE with onset after start of treatment or with onset date before the treatment start date but worsening after the treatment start date. Tables by relationship to trial drug and by severity will be generated. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology, latest version.

If an event was reported more than once, the worst severity will be tabulated.

Incomplete TEAE-related dates will be handled as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of trial treatment then the onset date will be replaced by the minimum of start of trial treatment and TEAE resolution date.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of the participant's death. In the latter case, the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed.

15.1.1 All Adverse Events

All AEs recorded during the course of the trial (i.e. assessed from signature of informed consent until the end of treatment/safety follow-up visit) will be coded according to MedDRA latest version and assigned to a SOC and PT.

TEAEs will be summarized by worst severity, using MedDRA latest version PT as event category and MedDRA primary SOC body term as Body System category. The severity of AEs will be assessed by the investigator per the Qualitative Toxicity Scale as detailed in the study protocol: mild, moderate, severe.

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

The following will be summarized in an overview table with the number and percentage of participants (and the number of events) by treatment and overall:

- Any TEAEs
- Any trial treatment-related TEAEs
- Any serious TEAEs
- Any trial treatment-related serious TEAEs
- Any severe TEAE
- Any trial treatment-related severe TEAEs
- Any TEAEs leading to death
- Any trial treatment-related TEAEs leading to death

TEAEs will be summarized by treatment and total T, total R and overall in tables with:

- The number and percentage of participants by treatment with at least one TEAE and the number of events overall and by SOC and PT. SOC terms will be sorted alphabetically and PTs within each SOC term will be sorted by descending overall frequency.
- The number and percentage of participants by treatment with at least one non-serious TEAE and the number of non-serious TEAE applying frequency threshold of 5% according to SOC (i.e. SOCs events with frequency > 5% in any arm). SOC terms will be sorted alphabetically and PTs within each SOC term will be sorted by descending overall frequency.

In addition the following tables will be provided. SOC terms will be sorted alphabetically and PTs within each SOC term will be sorted by descending frequency (based on all treatment groups combined):

- A table by severity of TEAEs with the number and percentage of participants by treatment with at least one TEAE and the number of events by SOC and PT.

- A table by relationship to trial treatment with the number and percentage of participants by treatment with at least one TEAE and the number of events by SOC and PT.

Pre-treatment AEs (AEs with onset after informed consent but before start of treatment) and TEAEs will be listed separately.

15.1.2 Adverse Events Leading to Treatment Discontinuation

TEAEs leading to permanent discontinuation of trial treatment will be summarized by treatment and overall including number of participants, percentage and number of events.

A listing of TEAEs leading to permanent discontinuation of a trial treatment will additionally be provided.

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

15.2.1 Deaths

All deaths as well as reason for death will be based on information from the "Report of Participant Death" CRFs.

Listing of deaths, if any, will be provided displaying date and cause of death (including TEAE leading to death and relatedness to trial treatment, when applicable), and date and time of treatment administration.

15.2.2 Serious Adverse Events

A summary table of serious adverse events (SAEs), if any, by treatment and overall will be provided displaying the number and percentage of participants by treatment with at least one SAE and the number of SAEs overall and by SOC and PT. SOC terms and PTs within each SOC term will be sorted alphabetically.

Listing of SAEs, if any, will be provided in addition.

15.3 Clinical Laboratory Evaluation

All laboratory data will be reported with SI units. Laboratory parameters will be listed by participant and treatment T1, T2, R1, R2 and time-point and summarized indicating the treatment

T and R at the respective time-point using descriptive statistics for absolute values and change from baseline (period-baseline) over time.

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 will additionally be listed separately.

See Appendix 5 of the CSP for a table of the safety laboratory evaluations.

Safety laboratory values are separated into:

- Hematology
- Biochemistry
- Urinalysis
- Other tests

Summary tables will be produced for the groups Hematology and Biochemistry.

15.4 Vital Signs

Vital signs will be listed by participant and time-point and summarized for absolute values and changes-from-baseline (period-baseline) by time point and treatment T1, T2, R1 and R2 using descriptive statistics. Descriptive statistics tables will start at baseline.

15.5 ECG Evaluation

ECG data will be listed by participant and time-point and summarized by absolute values and changes-from-baseline (period-baseline) by treatment T1, T2, R1 and R2 using descriptive statistics. Descriptive statistics tables will start at baseline. Clinically significant ECG findings for individual participants will be listed and summarized.

The time intervals (PR, QRS, RR, QT and corrected QT intervals [based on Fridericia's formula, QTcF]) will be summarized descriptively by treatment.

The Fridericia's Correction (QTcF) is derived as follows:

Fridericia's Correction (QTcF) $$QTc_f = \frac{QT}{\sqrt[3]{RR}}$$

where: RR = RR-interval measured in seconds.

Observed QTcF values will be categorized according to their absolute values into the categories

- ≤ 430 ms,
- > 430 and ≤ 450 ms,
- > 450 and ≤ 480 ms,
- > 480 and ≤ 500 ms, and
- > 500 ms,

and categorized according to their absolute change from period baseline into the categories

- ≤ 30 ms,
- > 30 and ≤ 60 ms, and
- > 60 ms.

The number and percentage of participants by these categories at any post-dose assessment will be tabulated by treatment T1, T2, R1 and R2. All ECG measurements and changes from period baseline will be listed, with abnormalities (as reported of the investigator on the ECG eCRF page) indicated.

Investigator reported interpretation results will also be tabulated by treatment T1, T2, R1 and R2 using the number and percentage of participants for each interpretation category (Normal, Abnormal Not Clinically Significant [NCS], Abnormal Clinically Significant [CS]).

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

General Specifications for Plasma Concentration Data

PK evaluation will be performed by the Clinical PK/PD Group, Merck Healthcare KGaA, Darmstadt, Germany, or by a CRO selected by the Sponsor.

Concentrations of rac-PZQ, R-(-)-PZQ and S-(+)-PZQ in plasma will be presented in tables and descriptively summarized by treatment T1, T2, R1, R2 and nominal time point using number of observations (n), Mean, SD, standard error of the mean (SEM), median, Min, Max, and CV%. Descriptive statistics of 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, SEM:	4 significant digits
CV%:	1 decimal place

Values below the lower limit of quantification of the assay (LLOQ) will be taken as zero for summary statistics of PK concentration data. Missing concentrations (e.g., no sample, insufficient sample volume for analysis, no result, or result not valid) will be reported and used generally as “no result” (“N.R.”). Pre-dose samples that occur before the first drug

administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study drug administration.

All available concentration data will be listed. Data of participants not in the PK analysis set or invalid data will be flagged accordingly. Any flags will be included in SDTM and ADaM, respectively.

General Specifications for PK Parameter Data

PK parameter data will be descriptively summarized: n, Mean, SEM, SD, CV%, Min, median, Max, geometric mean (GeoMean), the geometric coefficient of variation (GeoCV%) and the 95% confidence interval (CI) for the GeoMean (LCI 95% GM, UCI 95% GM).

PK parameter 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/inferential statistics of PK parameter data:

Mean, Min, Median, Max, GeoMean, 95% CI:	3 significant digits
SD, SEM:	4 significant digits
CV%, GeoCV%:	1 decimal place
Ratio of GeoMean (in %) and 95% CI	2 decimal places

To ensure a reliable estimate of the extent of exposure, AUC_{extra} should be less than or equal to 20%. If AUC_{extra} is greater than 20%, all parameters derived using λ_z (i.e. λ_z, $t_{1/2}$, $AUC_{0-\infty}$, AUC_{extra}, V_z/f, CL/F) will be listed, but set to missing for the calculation of descriptive statistics.

All statistical analyses and descriptive summaries of pharmacokinetic data will be performed on the PK Analysis Set. All available data will be listed. Data of participants not in the PK analysis set or invalid data will be flagged accordingly. Any flags will be included in SDTM and ADaM, respectively.

16.1.1 Planned Analyses of PK Parameter Data

The following PK parameter tables will be produced:

- Summary of PK parameters by treatment T1, T2, R1 and R2 of all analytes.

The following listing will be produced:

- Individual PK parameters listed by treatment T1, T2, R1, R2. Excluded PK parameters will be flagged.

The following figures will be produced for PK parameters:

- Boxplots for the C_{max} and AUC_{0-t} by treatment T1, T2, R1, R2 of all analytes.

The analysis of the primary endpoints AUC_{0-t} and C_{max} of rac-PZQ will be performed using the PK population. The analysis of the secondary endpoints AUC_{0-t} and C_{max} of R-(-)-PZQ and S-(+)-PZQ will use a similar approach.

For the analysis of AUC_{0-t} and C_{max}, a reference-scaled BE approach will be applied as follows:

The within-subject variability of the reference product will be calculated from a linear model fitted to the log-transformed PK parameters C_{max} and AUC_{0-t}, obtained under reference treatment only, with sequence, subject within sequence, period included as fixed effects, described in Section 3.4 of Question 8 in EMA/618604/2008 Rev. 13: Questions & Answers: positions on specific questions addressed to the Pharmacokinetics Working Party (PKWP). In this analysis, only participants with evaluable data from both administrations of the reference product will be included. If the within-subject coefficient of variation for the reference treatment (CV_{WR}) ≤ 30% for C_{max} or AUC_{0-t} (i.e. the within-subject CV for the reference drug is ≤ 30%), then the common acceptance range (80.00% to 125.00%) for BE will apply for the respective PK parameter. For 30% < CV_{WR} ≤ 50% the acceptance interval will be widened according to $[L, U] = exp(\mp k\, s_{WR})$, where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and s_{WR} is the intrasubject standard deviation of the log-transformed values of C_{max} or AUC_{0-t} of the reference product, and $CV_{WR} = \sqrt{\exp(s_{WR}^2) - 1}$. s_{WR} will be calculated using the data under reference treatment only. For all values of CV_{WR} greater than 50% the acceptance range is fixed to [69.84% to 143.19%].

An analysis of variance (ANOVA) with treatment, period, sequence and subject within sequence as fixed effects, will be fitted to log-transformed PK parameters AUC_{0-t} and C_{max} according to Method A in Question 8 in EMA/618604/2008 Rev. 13. Only participants with at least one valid PK parameter under both reference and test treatment will be included in this model. Least-squares mean differences between treatments will be derived on the log-scale together with 90% confidence intervals.

Estimates and confidence intervals will be back-transformed to the natural scale. Bioequivalence will be accepted if, firstly, the back-transformed 90% confidence intervals are included in the acceptance range, and, secondly, the geometric mean ratios are contained in the conventional acceptance range 80.00% to 125.00%.

The estimated within-subject variability CV_{WR} may be inflated in the presence of outliers. In order to exclude such inflation, sensitivity analyses will be performed. In these analyses, outliers will be identified using graphical methods by plotting the PK parameter after the first administration (R1) against the corresponding value after the second administration (R2), and/or statistical methods (such as identifying subjects whose studentized residuals fall outside the

interquartile range and/or outside the whiskers), and the acceptance range will be based on CV_{WR} calculated with outliers removed from the dataset.

16.1.2 Plasma Concentration Data

The following tables will be produced for all analytes:

- Summary of plasma concentrations by treatment T1, T2, R1, and R2 and nominal time.

The following figures will be produced for plasma concentrations of all analytes:

- Arithmetic mean plasma concentration-time profiles overlaying all treatments on linear and semi-logarithmic scale
- Arithmetic mean plasma concentration-time profiles overlaying all treatments on linear scale including SD error bars
- Individual plasma concentration-time profiles overlaying participants, for each treatment T1, T2, R1 and R2 separately on linear and semi-logarithmic scale
- Individual plasma concentration-time profiles overlaying all treatments identified as T1, T2, R1, R2, separately for each participant on linear and semi-logarithmic scale

The following listing will be produced:

- Plasma concentrations will be listed by nominal time and treatment T1, T2, R1, R2. Excluded plasma concentrations will be flagged.
- PK sampling date, actual time, nominal time, deviation from scheduled time and concentration by nominal time and treatment T1, T2, R1, and R2.

16.1.3 Estimation of Individual PK Parameters

The following non-compartmental PK parameters will be calculated from the individual plasma rac-PZQ, R-(-)-PZQ and S-(+)-PZQ concentration-time data using commercial software Phoenix®/WinNonlin® (Version 6.3 or higher) at PPD. C_{max} and AUC_{0-t} are the main parameters for further statistical analysis.

Symbol	Definition
AUC_{0-t}	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) 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).

Symbol	Definition
$AUC_{0-\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last} , as estimated using the linear regression from λ_z determination. $AUC_{0-\infty} = AUC_{0-t} + C_{last\ pred}/\lambda_z$.
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. $AUC_{extra\%}$ = (extrapolated area/$AUC_{0-\infty}$)*100. The predicted $AUC_{0-\infty}$ should be used.
CL/f	The apparent oral clearance. CL/f = Dose $_{p.o.}$ /$AUC_{0-\infty}$. The predicted $AUC_{0-\infty}$ should be used.
C_{max}	Maximum observed concentration.
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$.
t_{lag}	The time prior to the first measurable (non zero) concentration.
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (i.e., 1st occurrence in case of multiple/identical C_{max} values).
V_Z/f	The apparent volume of distribution during the terminal phase following extravascular administration. V_z/f = Dose/($AUC_{0-\infty}*\lambda_z$) following single dose.
λ_z	Terminal first order (elimination) rate constant. Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve.

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- First ($\lambda_{z\ low}$) and last ($\lambda_{z\ upp}$) time point of the time interval of the log-linear regression to determine λ_z.
- Number of data points (N_λ) included in the log-linear regression analysis to determine λ_z.
- Goodness of fit statistic (adjusted Rsq) for calculation of λ_z.

The predose sample will be considered as if it had been taken simultaneously with the administration of study intervention.

Plasma concentrations below lower limit of quantification (LLOQ) before the last quantifiable data point will be taken as zero for calculating the AUC (i.e., embedded below the limit of

quantitation values set to zero). Plasma concentrations below LLOQ after the last quantifiable data point will not be considered for the determination of λ_z.

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. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data.The regression analysis should contain data from at least 3 different time points in the terminal phase consistent with the assessment of a straight line on the log-transformed scale. Phoenix WinNonlin best fit methodology will be used as standard. However, in some cases, further adjustment may be made by the pharmacokineticist, if warranted, after agreement with the Sponsor. The last quantifiable concentration should always be included in the regression analysis, while the concentration at t_{max} and any <LLOQ concentrations that occur after the last quantifiable data point should not be used.

The coefficient of correlation (R^2) should be ≥ 0.8 and the observation period over which the regression line is estimated should be at least twofold the resulting $t_{1/2}$ itself. If these criteria are not met, then the corresponding values should be flagged in the listing displaying Individual Plasma Pharmacokinetic Diagnostic Parameters for Each Treatment. Any flags should be included in the study specific SDTM/ADaM. Then the rate constants and all derived parameters (e.g. $AUC_{0-\infty}$, $\%AUC_{extra}$, CL/f, $t_{1/2}$, and V_Z/f) will be included in the parameter listings and will be discussed appropriately in alignment with the protocol lead and quantitative pharmacology representative.

The Phoenix WinNonlin NCA Core Output will be provided in a separate listing.

17 References

EMA/618604/2008 Rev. 13: https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-positions-specific-questions-addressed-pharmacokinetics-working-party_en.pdf

18 Appendices

None.