Statistical Analysis Plan

Sponsor:	Medicines for Malaria Venture (MMV)
Protocol No:	MMV_OZ439_16_01
Protocol Title:	AN OPEN-LABEL, TWO-PART STUDY TO DETERMINE THE ABSOLUTE BIOAVAILABILITY (BA) OF OZ439 USING SIMULTANEOUS INTRAVENOUS [^{14}C] OZ439 MICRODOSE/800 MG ORAL DOSING AND TO INVESTIGATE THE PHARMACOKINETICS (PK) OF OZ439 GRANULES ADMINISTERED AS SINGLE DOSES SUSPENDED IN DIFFERENT VOLUMES AND WHEN CO-ADMINISTERED WITH A SINGLE DOSE OF COBICISTAT, A STRONG CYP3A4 INHIBITOR, TO HEALTHY SUBJECTS IN FASTED STATE
PRA Project ID:	MMV508EC-165081
Version Date:	14-Jun-2017

1.0 Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

Name of Sponsor Representative / Title:	Fiona Macintyre / Clinical Lead
Signature of Sponsor Representative / Date:	F. Macintyre 15/06/17
Name of Sponsor Representative / Title:	Stephan Chalon / Medical Director
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2.0 Table of Contents

3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under Medicines for Malaria Venture (MMV) Protocol MMV_OZ439_16_01.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the SAP has been developed using the protocol version 2.0 dated 16-Mar-2017 (including all amendments up to this protocol date) and the final CRF(s) dated 24-Mar-2017.

An approved and signed SAP is a requirement for database hard lock.

This SAP only covers the results that will be processed by the PRA Early Development Services (EDS) Biostatistics Department.

PRA EDS will perform the pharmacokinetic (PK) (except the exploratory endpoint), safety and tolerability evaluation. Estimation of fraction absorbed, extraction ratio, liver first pass and deconvolution of absorption profile over time for OZ439 will be performed by BEL Pharm Consulting and reported in the clinical study report (CSR). Future OZ439 metabolites analysis that may be performed will not be reported in the CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the CSR but not included in this SAP, will be clearly identified in Section 9.8.2 of the CSR. Changes to planned analyses do not require an updated SAP but should be included in the CSR if significant.

4.0 Changes from Previous Version of Approved SAP

This is the first version of the SAP.

5.0 Study Objectives

5.1 Primary

- To determine the absolute bioavailability of OZ439 following a single oral dose of OZ439 dispersion and a simultaneous single intravenous (iv) microdose (100 µg) infusion of [^{14}C]-OZ439 under fasted conditions (Part 1)
- To evaluate the effects of a single oral dose of cobicistat, a strong cytochrome P450 (CYP) 3A4 inhibitor, on the PK profile of a single oral dose of a dispersion of OZ439 simple granules under fasted conditions (Part 2)
- To evaluate the PK of single doses of OZ439 granules when restricting the target dosing volumes to 64.5 or 100 mL (Parts 1 and 2)

5.1.1 Primary Endpoints

- Part 1: PK: absolute oral bioavailability (F_{po}) of OZ439
- Part 2: PK of OZ439: C_{max}, C_{168h}, $AUC_{0\text{-}168h}$ and $AUC_{0\text{-}inf}$

5.2 Secondary

- To assess the safety and tolerability of OZ439 when administered alone, and to assess the safety and tolerability of OZ439 and cobicistat when co-administered as single doses to healthy subjects (Parts 1 and 2)
- To determine the PK parameters of OZ439 single iv microdose (100 µg) infusion of [^{14}C]-OZ439 (Part 1)

- To assess the effects of the total dosing volume and of dose to volume ratio on OZ439 PK under fasted conditions (Parts 1 and 2)
- To determine the PK parameters and exposures of cobicistat (Part 2)

5.2.1 Secondary Endpoints

Part 1:

- PK for iv administration of OZ439: Vd, CL, $t_{1/2}$, AUC_{0-t}, AUC_{0-inf} and λ_z
- PK for oral administration of OZ439: C_{max}, t_{max}, $t_{1/2}$, C_{168h}, AUC_{0-168h}, AUC_{0-t}, AUC_{0-inf}, CL/F and λ_z
- Safety: adverse events (AE), clinical laboratory, vital signs, electrocardiogram (ECG) and physical examination

Part 2:

- PK of OZ439: t_{max}, $t_{1/2}$, AUC_{0-t} and λ_z
- PK of cobicistat: C_{max}, t_{max}, $t_{1/2}$, AUC_{0-t}, AUC_{0-inf}, CL/F and λ_z
- Safety: AEs, clinical laboratory, vital signs, ECG and physical examination

5.2.2 Exploratory Endpoints

- Part 1: Estimation of fraction absorbed, extraction ratio, liver first pass and deconvolution of absorption profile over time for OZ439
- Future OZ439 metabolites analysis may be performed (Part 1 and Part 2)

6.0 Study Design

Part 1

This is an open-label study in 8 healthy subjects to determine the absolute bioavailability of OZ439 following a single oral dose of OZ439 and a simultaneous single iv infusion of [^{14}C]-OZ439 radiolabeled microdose administered at the anticipated t_{max} of the oral dose. Subjects will receive the following treatment:

Treatment A: a single oral dose of 800 mg OZ439 simple granules administered as a 100-mL dispersion followed by a 15-minute 10-mL iv infusion of 100 µg [^{14}C]-OZ439 (47 kBq [1.27 µCi]) beginning 3 hours after the oral dose administration.

Part 2

This is an open-label, randomized, single-dose, 3-way cross-over study in 18 healthy subjects. Each subject will participate in 3 treatment periods and each subject will receive a single dose of each of the following 3 treatments in a randomized order with a 14-day wash-out period between each treatment:

Treatment B: a single oral dose of 800 mg OZ439 simple granules administered as a 64.5-mL dispersion

Treatment C: a single oral dose of 400 mg OZ439 simple granules administered as a 64.5-mL dispersion

Treatment D: a single oral dose of 400 mg OZ439 simple granules administered as a 64.5-mL dispersion and co-administered with a 150 mg cobicistat tablet (CYP3A4 inhibitor)

6.1 Sample Size Considerations

The study is exploratory and no formal sample size calculation has been made. Based on experience from previous similar studies and taking into account OZ439 large variability, a total of 8 subjects enrolled in Part 1 of the study to achieve a minimum of 6 evaluable subjects is considered sufficient. A total of 8 subjects is also considered sufficient to assess the effects of the total dosing volume and of dose to volume ratio on OZ439 PK under fasted conditions (in combination with Part 2). In Part 2 of the study a sample size of 18 subjects is considered appropriate to estimate the increase in OZ439 exposure in the

presence of a single dose of 150 mg cobicistat with sufficient precision, assuming a mean ratio of 2. Based on the assumptions of a point estimate (mean ratio) of 2.0 and a CV of 23%, a sample size of 18 subjects would give a 90% confidence interval (CI) of 1.75 - 2.28 and this number of subjects is therefore considered sufficient. In Part 2, 18 subjects will be randomized to ensure data in 15 evaluable subjects for the PK endpoints. A subject will be considered evaluable for the primary analysis if they have sufficient PK data to estimate the primary endpoints C_{max} and $AUC_{0\text{-}inf}$ for the 3 treatments. Note: the primary analysis refers to the statistical analysis of the treatment comparisons defined in Section 16.3.1.

6.2 Randomization

Subjects who have met all eligibility criteria will receive a subject number upon inclusion in the study (for Part 1: subject numbers 101-108; for Part 2: subject numbers 201-218). They will receive the subject number according to the order of enrolment in Part 1 of the study, and according to the randomization code generated by the Biostatistics Department of PRA in Part 2 of the study. The subject number will ensure identification throughout the study. Replacement subjects will receive the number of the subject to be replaced, increased by 1000 (e.g. 1101 replacement number for subject number 101), and will be administered the same or remaining treatments in the same order.

In Part 2, subjects were randomized to 1 of 6 treatment sequences (BCD, BDC, CBD, CDB, DBC, or DCB), with 3 subjects per sequence (balanced randomization).

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

In the protocol it was stated that a subject will be considered evaluable for the primary analysis if they have sufficient PK data to estimate all of the primary endpoints (C_{max}, C_{168h}, $AUC_{0\text{-}168h}$, and $AUC_{0\text{-}inf}$) for the 3 treatments. This was changed in the SAP to: 'a subject will be considered evaluable for the primary analysis if they have sufficient PK data to estimate the primary endpoints C_{max} and $AUC_{0\text{-}inf}$ for the 3 treatments'.

7.2 Interim Analysis and Key Results

Interim PK results of Part 1 will be provided to the Sponsor. The interim Tables, Figures and Listings (TFLs) will include a PK concentration table (Table 15.2.1), individual values and descriptive statistics of PK parameters (Table 15.2.2), a summary of the statistical analysis of bioavailability (Table 15.2.3), plots of combined individual PK profiles (Figure 15.2.6), and plots of geometric mean PK profiles (Figure 15.2.5).

7.3 Final Analysis

Draft TFLs will be provided with the draft CSR. After Sponsor comments have been incorporated, the TFLs will be finalized and incorporated in the final CSR.

8.0 Data Review

8.1 Data Management

Data handling and transfer will take place under the PRA Data Management Plan for the study.

8.2 Acceptance of Data for Summarization

Programming of analysis datasets and TFLs may be ongoing during the data management of the study. However, programming of analysis datasets and TFLs will be completed and quality controlled (QC'd) after database lock. Only quality assured (QA'd) results released by the Safety Laboratory, Bioanalytical Laboratory, or other external data source will be used for the programming of analysis datasets and TFLs for the final report. Any data values requiring investigation or corrections that are identified while programming the analysis datasets and TFLs will be sent to the project Data Manager. Database will not

be locked until the identified issues are resolved. If the issue affects the TFLs the Programmer or Statistician who identified the issue will follow it to resolution.

9.0 Definitions and General Analysis Methods

9.1 Analysis Data Presentation

9.1.1 Rounding

In listings, data will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes.

For all non-PK summaries, mean, Standard Deviation (SD), median, minimum and maximum will be presented with the same precision as the original data (i.e., the same number of decimals). The derived PK parameters, except t_{max}, will be listed and summarized with a precision of 3 significant digits or as integers when the value is >1000; t_{max} values will be presented with 2 decimals, %AUC extra will be presented with 1 decimal.

CV% will be presented with 1 decimal and frequency percentages will be presented as whole numbers.

P-values will be reported to 4 decimal places; p-value less than 0.0001 will be reported as p <0.0001.

9.1.2 Imputation

Unless otherwise noted data will not be imputed. Exceptions are missing start and end times of AEs, see Section 17.1.1 and PK concentrations under lower limit of quantification (LLOQ), see Section 16.2.

9.1.3 Descriptive Statistics

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics: n (number of observations), (arithmetic) mean, SD, minimum (min) value, median, and maximum (max) value. For PK parameters the geometric mean (except for t_{max}) and the coefficient of variation (CV%) will also be presented.

Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of subjects exposed within a treatment.

9.1.4 Pooling

Summary statistics will be calculated by treatment (and time point, if applicable).

9.1.5 Unscheduled Measurements

Unscheduled measurements will be included in the listings. With the exception of unscheduled measurements used for baseline, unscheduled measurements will be excluded from the descriptive statistics and statistical analysis.

9.2 Analysis Data Definitions

9.2.1 Baseline Definition

Unless otherwise stated, baseline for post-dose evaluations within each period is defined as the last observation recorded before the first study drug administration in each period. The last observation can be an unscheduled / repeated measurement.

9.2.2 Treatment/Subject Grouping Definition

Throughout this SAP treatment refers to Treatment A, B, C, and D (see Section 6.0).

9.2.3 Other Definitions

Variable	Data Type	Definition/Calculation
Change from Baseline	All	Post-dose Observation minus Baseline Observation
Study Day (Prior to Dose)	All	Date of Measurement minus first Dose Date for each period
Study Day (Post-Dose)	All	Date of Measurement minus first Dose Date +1 for each period
TEAE	Adverse Events	AE is a TEAE if the AE Date/Time is greater than the first OZ439 or cobicistat Dose Date/Time
Time post dose	PK	Time relative to drug adminstration. For the iv treatment time post dose will be relative to the iv drug administration (3 hours after the oral administration)

9.2.4 Critical Data

As the primary objective of this study is to determine bioavailability and to characterize the PK, the datasets considered critical are Pharmacokinetic Parameters Analysis Dataset (ADPP) and Subject Level Analysis Dataset (ADSL).

The analysis datasets that will be created are ADSL, ADAE, ADLB, ADVS, ADEG, ADPC and ADPP. The analysis datasets will be generated in accordance with Clinical Data Interchange Standard Consortium (CDISC) Analysis Data Model (ADaM) Version 2.1 (ADaM Implementation Guide v1.1). ADaM compliant datasets will be delivered to the Sponsor, including a define.xml (not including analysis results metadata).

9.2.5 QC

The analysis datasets and the TFLs will be QC'd according to the general PRA EDS QC plan.

9.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ Version 9.4 or higher (SAS Institute, Inc.).

PK parameter calculations will be done using Phoenix® WinNonlin® Version 6.3 or higher (Pharsight, Inc.).

9.4 Statistical Methods

9.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

9.4.2 Predetermined Covariates and Prognostic Factors

There are no predetermined covariates or prognostic factors.

9.5 TFL Layout

Report layout will be according to the PRA EDS – ICH E3 compliant – CSR Template. The layout of TFLs will be according to the PRA EDS standards.

No table shells will be provided. The TFLs will be provided in Adobe PDF format (in A4 Format).

Format:

- Data in listings will be sorted by subject number, period and time point.

- Data in tables will be sorted by treatment and time point.
- Column titles will be in title case letters.
- All tables and listings will be in landscape format. For figures, the portrait format may be used as well.
- The treatment labels A, B, C, and D will be used in the TFLs, with footnotes explaining the abbreviations.

10.0 Analysis Sets

Analyses	Randomized Set	Safety Set	Pharmacokinetic Set
Disposition Summaries	✓		
Safety Assessments		✓	
Baseline Characteristics		✓	
Primary Analysis			✓
PK Concentrations		✓	
PK Parameters			✓

10.1 Randomized

The randomized set will consist of subjects who are assigned a randomization number in the study. This set will be used for disposition summaries.

10.2 Safety

The safety set will consist of subjects who receive at least 1 dose of OZ439. This set will be used for the safety data summaries, baseline characteristic summaries, and PK concentration summaries.

10.3 Pharmacokinetic

The PK set will consist of all subjects who receive at least 1 dose of OZ439 and provided sufficient bioanalytical assessment results to calculate reliable estimates of at least one of the primary endpoints PK parameters or secondary endpoint parameters. This set will be used for descriptive statistics of PK parameters.

10.4 Pharmacokinetic Summary

The PK summary set will consist of all subjects who are considered evaluable for the primary statistical analysis, defined as follows:

For Part 2, a subject will be considered evaluable for the primary statistical analysis if they have sufficient PK data to estimate the primary endpoints C_{max} and $AUC_{0\text{-}inf}$ for the 3 treatments.

For Part 1, a subject will be considered evaluable for the primary statistical analysis (bioavailability) if they have sufficient PK data to estimate the primary endpoint F_{po}.

This set will be used for the statistical analysis of the treatment comparisons defined in Section 16.3.1.

11.0 Subject Disposition

A listing containing the information for each subject with regard to completing the study and study withdrawal will be presented.

The number and percentage of subjects randomized, dosed, and members of each analysis set will be presented. The number and percentage of subjects who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal will also be presented.

A listing containing study dates by subject will be presented, containing the following dates: informed consent, screening, dose administration in each period, follow-up and last assessment.

12.0 Protocol Deviations and Violations

Protocol deviations/violations will be included in the CSR.

13.0 Demographic and Baseline Characteristics

13.1 Demographics

Individual demographic data will be listed.

Subject demographics will be summarized descriptively for all subjects by study part. The summary will include the subjects' age at informed consent (in years), gender, race, ethnicity, weight (in kg), height (in cm), and body mass index (BMI) (in kg/m2). Demographics will be summarized for the safety and PK sets.

13.2 Medical History

Medical history will be listed.

13.3 Other Baseline Characteristics

The results of drug and alcohol screen at screening and admission will be listed.

The results of serology at screening will be listed.

The results of pregnancy tests at screening and admission will be listed (females only).

The results of hormone tests (follicle stimulating hormone [FSH]) at screening for females only will be listed.

14.0 Prior/Concomitant Medications

Concomitant medication will be listed. Medications with an end date prior to the first dose of study drug will be considered prior medications and will be listed separately. If a partial date allows a medication to be considered concomitant it will be categorized as such.

15.0 Treatment Compliance and Exposure

Study drug administration data will be listed by subject.

16.0 Pharmacokinetic Analyses

The plasma samples for OZ439 and Cobicistat will be analyzed by Swiss Bioquant AG and concentration data will be transferred to PRA.

The plasma samples for [^{14}C]-OZ439 will be analyzed by transferred Xceleron Inc and concentration data will be transferred to PRA.

16.1 Pharmacokinetic Variables

- Plasma concentrations of OZ439 (Part 1 and Part 2)
- Plasma concentrations of [^{14}C]-OZ439 (Part 1)
- Plasma concentrations of cobicistat (part 2)
- Plasma concentrations of total radioactivity (Part 1)
- PK parameters for OZ439 in plasma (Part 1 and Part 2)
- PK parameters for [^{14}C]-OZ439 in plasma (Part 1)
- PK parameters for total radioactivity in plasma (Part 1)
- PK parameters for cobicistat (Part 2)

Parameter	Description	SAS Programming Notes	Part 1 OZ439 iv/ oral	Part 2 OZ439/ cobicistat
Cmax	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units	Cmax from WNL	iv and oral	OZ439 and cobicistat
C_{168h}	Observed plasma concentration at 168 hours post-dose		oral	OZ439
Tmax	Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	Tmax from WNL	iv and oral	OZ439 and cobicistat
AUCs	Calculated using linear up / log down, expressed in units of concentration x time.			
AUC_{0-t}	Area under the concentration-time curve (time 0 to time of last quantifiable concentration).	AUClast from WNL	iv and oral	OZ439 and cobicistat
AUC_{0-inf}	Area under the plasma concentration-time curve (time 0 to infinity). Percent extrapolation less than or equal to 20% is required to retain AUCinf.	AUCINF_obs from WNL If AUC_%Extrap_obs >20% then parameter is flagged	iv and oral	OZ439 and cobicistat
$\%AUC_{extra}$	Percentage of estimated part for the calculation of AUC. $\%AUC_{extra} = ((AUC_{0-inf}-AUC_{0-t})/AUC_{0-inf})*100\%$.	AUC_%Extrap_obs from WNL	iv and oral	OZ439 and cobicistat
AUC_{0-168}	Area under the serum concentration-time curve from time 0 to 168 hours post-dose.	AUC0-168 from WNL where partial time =168	oral	OZ439
λ_z	Terminal phase rate constant	Lambda_z from WNL	iv and oral	OZ439 and

Parameter	Description	SAS Programming Notes	Part 1 OZ439 iv/ oral	Part 2 OZ439/ cobicistat
	calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve. Linear regression of at least three is required (regression of two points will be flagged).	If adjusted Rsq ≤ .80 then parameter is flagged		cobicistat
$t_{1/2}$	Terminal phase half-life expressed in time units.	HL_Lambda_z from WNL If adjusted Rsq ≤ .80 then parameter is flagged	iv and oral	OZ439 and cobicistat
CL/F	Apparent oral clearance, calculated	Cl_F_obs from WNL	oral	cobicistat
CL	Clearance, calculated as dose/AUC_{0-inf}	Cl_obs from WNL	iv	OZ439
V_d	Volume of distribution at terminal phase, calculated as CL/λ_z	Vz_F_obs from WNL	iv	OZ439
F_{po}	Absolute bioavailability, calculated as: $F=(AUC_{oral}*D_{iv})/(AUC_{iv}*D_{oral})$, where AUC_{oral} is the AUC_{0-inf} of OZ439 and AUC_{iv} is the AUC_{0-inf} of [^{14}C]-OZ439; D_{oral} is the oral dose and D_{iv} is the iv microdose			OZ439

16.2 Pharmacokinetic Concentrations

Plasma concentrations for total radioactivity, [^{14}C]-OZ439, OZ439 or cobicistat below the quantifiable limit (BQL) will be set to ½ LLOQ in the computation of mean concentration values. Descriptive statistics (number of subjects, arithmetic mean, geometric mean, SD, CV%, median, minimum, and maximum) will be used to summarize the plasma concentrations by treatment at each scheduled time point. If over ½ the subjects in a given cell have values BQL then the descriptive statistics will not be presented except for the minimum and maximum and the mean will be displayed as BQL.

Linear and semi-logarithmic plots of the geometric mean total radioactivity, OZ439 and cobicistat plasma concentration by scheduled sampling time will be provided by treatment. These plots will show time in hours. The plots will match the summary table results and will not have an observation at a given time point if more than half of the subjects have values BQL. The following mean plots will be provided:

- Geometric mean oral OZ439 concentration, iv total radioactivity and OZ439 specific radioactivity versus time plot (in the same plot). A linear plot including SD bars, and a semi-logarithmic plot will be provided [treatment A, Part 1].
- Geometric mean oral OZ439 concentration vs time plot for treatments C and D in the same plot. A linear plot including SD bars, and a semi-logarithmic plot will be provided [Part 2].
- Geometric mean oral OZ439 concentration vs time plot for treatments A, B and C (with C dose-normalized to 800mg) in the same plot. A linear plot including SD bars, and a semi-logarithmic plot will be provided [Part 1 and 2].
- Mean plot of oral cobicistat concentration vs time (linear) [treatment D, Part 2].

Linear and semi-logarithmic plots of the combined individual plasma concentration by actual sampling time will be provided in a single plot by treatment and analyte (total radioactivity, OZ439, [^{14}C]-OZ439 and cobicistat).

Linear and semi-logarithmic plots of the individual plasma concentration by actual sampling time will be provided by subject (1 subject per page). For Part 1, total radioactivity, OZ439 and [^{14}C]-OZ439 concentration-time profiles will be shown in the same plot; For Part 2, OZ439 concentration-time profiles for Treatments B, C and D will be shown in the same plot. The cobicistat concentration-time profiles (Part 2, Treatment D only) will be presented separately. In all plots, colours will be used to distinguish between treatments.

All individual subject plasma concentration data will be listed.

16.3 Pharmacokinetic Parameters

PK parameters for total radioactivity, OZ439 and cobicistat will be estimated using non-compartmental methods with Phoenix WinNonlin® Version 6.3.

The plasma PK parameters will be estimated from the concentration-time profiles for all subjects in the safety population. In estimating the PK parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Values that are embedded between BQLs, or quantifiable values occurring after 2 or more BQLs, will be set to missing at the discretion of the pharmacokineticist.

Actual blood sampling times will be used in the PK parameter calculations. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameter.

The terminal elimination rate constant (λ_z) will be determined by plotting the concentration data versus time on a semi-logarithmic scale. The time interval of the terminal elimination phase will be determined by visual inspection. Linear regression on log-transformed concentrations within this interval will be used to calculate the terminal elimination rate constant. At least 3 data points are required to obtain a reliable λ_z and associated parameters. Points prior to and including Cmax will not be used to estimate λ_z. Terminal half-life and λ_z values (and derived parameters) will be flagged if λ_z cannot be accurately estimated (adjusted r2 < 0.8). In calculations of AUC parameters, the linear up / log down trapezoidal method will be used. For $AUC_{0\text{-}inf}$, if the %extrapolation from last quantifiable concentration to infinity >20%, then the data will be flagged.

Descriptive statistics (number of subjects, mean, geometric mean, SD, CV%, median, minimum, and maximum) will be used to summarize the calculated PK parameters by treatment. For t_{max}, the geometric mean will not be presented.

16.3.1 Calculation Exploratory Endpoints

Assuming little or no extra-hepatic clearance of OZ439 and under the assumptions of the well-stirred model, the following exploratory endpoints will be calculated [Yang et al, 2007]:

- Extraction ratio (ER) = CLiv/(Qh*BPratio), where
    - CLiv is the average IV plasma clearance (ml/min) estimated in Part 1 of the study
    - Qh is an estimation of the liver blood flow: Qh= 1450 [Davis & Morris, 1993] * (mean BW/70kg)^0.75 ml/min; mean BW is the mean bodyweight of the subjects in Part 1.
    - BPratio is the Blood:Plasma ratio=1.2 as reported in the CIB [CIB v3.0 2011]
- Liver First Pass (Fh) = 1-ER
- Fraction absorbed (Fa = Ftot/Fh), where
    - Ftot is the average total bio-availability estimated in Part 1 of the study

The deconvolution of absorption profile over time for OZ439 will be performed using appropriate software.

16.3.2 Statistical Analysis

Part 1:

To determine the absolute bioavailability, an analysis of variance (ANOVA) will be performed on OZ439 PK parameter $AUC_{0\text{-}inf}$ using the SAS procedure for mixed effect models (PROC MIXED). The PK parameter will be natural logarithm transformed prior to analysis. The model will include a fixed effect for treatment (i.e. OZ439 oral or OZ439 iv), and a random effect for subject.

From the ANOVA model the back-transformed least-squares means (LSMeans) for test (OZ439 oral) and reference (OZ439 iv) treatments will be presented. The ratio of the LSMeans for the comparison of oral and iv OZ439 (i.e. the absolute bioavailability) will be obtained by exponentiating the difference of the LSMeans on the log scale. The absolute bioavailability and the corresponding 90% CI will be presented.

The individual bioavailability values will also be reported for each subject.

Part 2:

An analysis of variance (ANOVA) will be performed on OZ439 PK parameters C_{max}, C_{168h}, $AUC_{0\text{-}168}$ and $AUC_{0\text{-}inf}$ using the SAS procedure for mixed effect models (PROC MIXED). The PK parameters will be natural logarithm transformed prior to analysis. The model will include fixed effects for treatment, period, and sequence, and a random effect for subject within sequence (comparisons D vs C and B vs C; for comparison B vs A only a fixed effect for treatment will be included).

From the ANOVA model the back-transformed least-squares means (LSMeans) for test and reference treatments will be presented. The ratios of the LSMeans for the comparison of the treatments D vs C, B vs A and B vs C will be obtained by exponentiating the difference of the LSMeans on the log scale. This ratio and the corresponding 90% CI will be presented for the comparisons between:

- Treatment D vs Treatment C to assess the effect of cobicistat on OZ439
- Treatment B vs Treatment A to explore volume effect (for this no within-subject comparison is possible)
- Treatment B vs Treatment C to explore dosing solution concentration effect (Treatment C will be dose normalized to 800 mg (only for this comparison))

17.0 Safety Analyses

17.1 Safety Variables

The following safety variables will be summarized:

- AEs
- Vital Signs
  - Supine Blood Pressure
    - Systolic Blood Pressure
    - Diastolic Blood Pressure
  - Pulse rate
  - Tympanic body temperature
- Electrocardiograms (ECG)
  - Heart Rate
  - PR Interval
  - QRS Duration
  - QT Interval
  - QTc (Bazett and Fridericia) Interval
  - Interpretation of the ECG profile by the PI
- Clinical Laboratory Evaluations
  - Clinical Chemistry
  - Hematology

- Urinalysis

17.1.1 Adverse Events

All AEs reported during the study will be reported and coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0 or higher.

A treatment-emergent AE (TEAE) is defined as an event not present prior to the first administration of the study drug (first administration of OZ439 or cobicistat) or an event already present that worsens in either severity or frequency following exposure to the study drug (first administration of OZ439 or cobicistat). An AE which occurs prior to the first administration of the study drug will be considered a pre-treatment AE.

All AEs (including non-treatment-emergent events) and all AEs leading to study discontinuation will be listed, including the AE description (verbatim term), MedDRA system organ class (SOC) and preferred term (PT), start date and time, end date and time, severity, intervention, relation to study drug, seriousness, action taken, and outcome.

All AE summaries will include only TEAEs. The incidence of TEAEs will be summarized (number of TEAEs, number and percentage of subjects) by SOC and PT by treatment, for all causalities and for only related events. An overview of TEAEs will be presented by treatment, relationship and severity (number of TEAEs, number and percentage of subjects).

TEAEs of which the relationship of the test drug was classified as “possible”, “probable/likely” or ‘’certain” will be assessed as related, whereas AEs that will be assessed as “unlikely” will be considered not to be related. Missing AE severity or relationship will be assumed to be severe or related, respectively.

TEAEs occurring following dosing in a specific period but before dosing in the next period will be attributed to that specific period. If the time is missing for an AE on a dosing day then the AE will be attributed to the treatment given on that day.

The following missing data will be imputed as defined:

- Missing AE start and / or end times for the calculation of onset and duration will be assumed to be at 00:01 for a start time and 23:59 for end times
- Missing AE severity or relationship will be assumed to be severe or related, respectively
- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment
- Missing AE start times for the determination of treatment assignment will be assumed to occur after treatment on the recorded date
- Missing AE start date will be assumed to be after treatment for the determination of TEAE and on treatment for single treatment studies but will not be attributed to treatment in studies with multiple treatments

17.1.2 Deaths and Serious Adverse Events

A listing of deaths and other serious adverse events will be provided (if applicable).

17.1.3 Laboratory Data

Clinical laboratory data will be presented using Système International (SI) units (also used in the Study Data Tabulation Model (SDTM) Controlled Terminology).

All laboratory data will be listed. Listings will be split into clinical chemistry, hematology and urinalysis. In addition, a summary listing of all data outside the reference range(s) will be presented.

Descriptive statistics of clinical chemistry and hematology parameters (original values and change from baseline) will be provided to summarize continuous laboratory results by treatment and scheduled time.

17.1.4 Vital Signs

Vital signs parameters will be listed and descriptive statistics of original values and change from baseline will be provided to summarize vital signs by treatment and scheduled time.

17.1.5 Electrocardiograms

ECG parameters will be listed and descriptive statistics of original values and change from baseline will be provided to summarize ECG parameters by treatment and scheduled time. At some time points triplicate 12-lead ECGs will be recorded. The average of these triplicate values will be used in the calculation of descriptive statistics and change from baseline, and the average of the triplicate values at pre-dose will be used as baseline. The individual triplicate values will be listed.

A frequency table of QTc (Bazett and Fridericia) values will be presented by treatment and scheduled time. The number of incidences (number of subjects) and percentage of subjects will be presented. The following categories will be used:

- < 450 ms
- >= 450 - 480 ms
- >= 480 - 500 ms
- >= 500 ms

A frequency table of QTc (Bazett and Fridericia) change from baseline values will be presented by treatment and scheduled time. The number of incidences (number of subjects) and percentage of subjects will be presented. The following categories will be used:

- < 30 ms
- >= 30 - 60 ms
- >= 60 ms

17.1.6 Physical Examination

Abnormalities and changes from baseline will be listed.

18.0 References

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Clinical Study Protocol. AN OPEN-LABEL, TWO-PART STUDY TO DETERMINE THE ABSOLUTE BIOAVAILABILITY (BA) OF OZ439 USING SIMULTANEOUS INTRAVENOUS [^{14}C] OZ439 MICRODOSE/800 MG ORAL DOSING AND TO INVESTIGATE THE PHARMACOKINETICS (PK) OF OZ439 GRANULES ADMINISTERED AS SINGLE DOSES SUSPENDED IN DIFFERENT VOLUMES AND WHEN CO-ADMINISTERED WITH A SINGLE DOSE OF COBICISTAT, A STRONG CYP3A4 INHIBITOR, TO HEALTHY SUBJECTS IN FASTED STATE. Version 2.0, 16 Mar 2017.

Davis & Morris, Physiological parameters in laboratory animals and humans. Pharmaceutical Res 10, 1093, 1993.

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Appendix 1: Glossary of Abbreviations

Glossary of Abbreviations:	
ADaM	Analysis Data Model
AE	Adverse Event
ANOVA	Analysis of Variance
BMI	Body Mass Index
BQL	Below the Quantifiable Limit
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CV	Coefficient of Variation
CRF	Case Report Form
CSR	Clinical Study Report
CYP	Cytochrome P450
ECG	Electrocardiogram
EDS	Early Development Services
FSH	Follicle Stimulating Hormone
ICH	International Conference on Harmonization
IV	Intravenous
LLOQ	Lower Limit of Quantification
LSMeans	Least Squares Means
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PT	Preferred Term
QA'd	Quality Assured
QC'd	Quality Controlled
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SI	Système International
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TFL(s)	Tables, Figures and Listings
WNL	WinNonlin

Appendix 2: Schedule of Assessments – Part 1

		Assessment Period[1]																			
	Screening	Pre-Treatment		Treatment																	Follow-up
Study Day	-28 to -2	-1	1													2	3	4	5	8	15 (± 2)
Hours			Pre-dose	0	0.25	0.5	0.75	1	2	3	4	5	6	8	12	16	24	48	72	96	168	
Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Ambulatory visit																	X	X	X	X	X
Admission		X																			
Discharge																X					
Informed consent	X																				
Medical history	X																				
Demographics	X																				
Prior and concomitant medication check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height (including BMI calculation)	X																				
Physical examination	X	X[2]	X[2]													X[2]					X
Serology (HBsAg, anti-HCV, anti-HIV 1 and 2)	X																				
Drug and alcohol screen	X	X																			
Pregnancy test (females only)	X	X[3]																			
FSH (females only)	X																				
Clinical laboratory[4]	X[4]	X[4]														X			X		X
12-lead ECG[5]	X	X	X						X		X			X	X	X					X
Vital signs[6]	X	X	X						X		X			X	X	X					X
Eligibility check	X	X	X																		
OZ439 oral administration				X																	
[^{14}C]-OZ439 iv administration										X											
PK blood samples for OZ439			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK blood samples for [^{14}C]-OZ439										X[7]	X	X	X	X	X	X	X	X	X	X	X	

Blood samples for OZ439 metabolites											X			X	X		X					
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1 Subjects will be in the clinic from Day -1 until 24 hours post-dose (Day 2). Subjects will return for ambulatory visits on Days 3, 4, 5 and 8 (at 48, 72, 96 and 168 hours post-dose)

2 A targeted physical examination of applicable body systems will be performed if needed as per the judgment of the PI (eg, if the subject reports AEs) at pre-dose, on Day -1 and at discharge

3 Confirmation of negative pregnancy test result required before dosing

4 Clinical laboratory tests (including clinical chemistry, hematology and urinalysis): all results must be available before dosing; out-of-range results judged to be possibly relevant by the PI are to be discussed with the medical monitor before dosing

5 Triplicate 12-lead ECG only required at pre-dose on Day 1 and at 2 and 4 hours post-dose on Day 1. Individual ECG measurements as part of a triplicate ECG will be recorded 1 minute (and no more than 2 minutes) apart. Single 12-lead ECGs will be done at the rest of the time points indicated in the schedule of assessments.

6 Vital signs will consist of supine systolic and diastolic blood pressure, pulse and body temperature

7 PK blood samples for [^{14}C]-OZ439 will be collected at the start of iv infusion and at 10, 15 (just prior to end of iv infusion), 20, 30 and 45 minutes after start of iv infusion

AE: adverse event; BMI: body mass index; ECG: electrocardiogram; FSH: follicle stimulating hormone; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; iv: intravenous; PK: pharmacokinetic(s); PI: Principal Investigator

Appendix 3: Schedule of Assessments – Part 2

		Assessment Period 1, 2 or 3[1]																				
	Screening	Pre-Treatment		Treatment																		Follow-up
Study Day	-28 to -2	-1	1											2	3	4	5	8	10[2]	12[2]	14[2]	15-19 of Period 3
Hours			Pre-dose	0	0.5	1	2	3	4	5	6	8	12	16	24	48	72	96	168	216	264	312	
Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X								
Ambulatory visit																X	X	X	X	X	X	X	X
Admission		X																					
Discharge															X								
Informed consent	X																						
Medical history	X																						
Demographics	X																						
Prior and concomitant medication check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height (including BMI calculation)	X																						
Physical examination	X	X[3]	X[3]												X[3]								X[3]
Serology (HBsAg, anti-HCV, anti-HIV 1 and 2)	X																						
Drug and alcohol screen	X	X																					
Pregnancy test (females only)	X	X[4]																					
FSH (females only)	X																						
Clinical laboratory[5]	X[5]	X[5]					X								X			X		X			X
12-lead ECG[6]	X	X	X				X		X			X	X		X			X		X			X
Vital signs[7]	X	X	X				X		X			X	X		X			X		X			X
Eligibility check	X	X	X																				
Drug administration				X																			
PK blood samples for OZ439			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK blood samples for cobicistat[8]			X		X	X	X	X	X	X	X	X	X		X	X							
Blood samples for OZ439 metabolites[9]									X			X	X		X								
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1 Subjects will be in the clinic for 3 periods, each period from Day -1 until 24 hours post-dose (Day 2). Subjects will return for ambulatory visits on Days 3, 4, 5 and 8 (at 48, 72, 96 and 168 hours post-dose) of each period
2 Additional ambulatory visits on Days 10, 12 and 14 for Treatment D only (a single oral dose of 400 mg OZ439 simple granules administered as a 60-mL dispersion and co-administered with a 150 mg cobicistat tablet [CYP3A4 inhibitor]). Day 14 will coincide with Day -1 of the next period when a subject is randomized to Treatment D in Period 1 or Period 2.
3 A targeted physical examination of applicable body systems will be performed if needed as per the judgment of the PI (eg, if the subject reports AEs) at pre-dose, on Day -1 and at discharge
4 Confirmation of negative pregnancy test result required before dosing
5 Clinical laboratory tests (including clinical chemistry, hematology and urinalysis): all results must be available before dosing; out-of-range results judged to be possibly relevant by the PI are to be discussed with the medical monitor before dosing
6 Triplicate 12-lead ECG only required at pre-dose on Day 1 and at 2 and 4 hours post-dose on Day 1. Individual ECG measurements as part of a triplicate ECG will be recorded 1 minute (and no more than 2 minutes) apart. Single 12-lead ECGs will be done at the rest of the time points indicated in the schedule of assessments.
7 Vital signs will consist of supine systolic and diastolic blood pressure, pulse and body temperature
8 Only applicable for Treatment D (a single oral dose of 400 mg OZ439 simple granules administered as a 60-mL dispersion and co-administered with a 150 mg cobicistat tablet [CYP3A4 inhibitor])
9 Blood samples for future OZ439 metabolites analysis will be collected in Period 1 only

AE: adverse event; BMI: body mass index; ECG: electrocardiogram; FSH: follicle stimulating hormone; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; PK: pharmacokinetic(s); PI: Principal Investigator

Appendix 4: List of In-Text Outputs

The planned tables, figures and subject data listings for the CSR are listed below. The placement and numbering presented is for tracking / development purpose and may deviate from the placement order and numbering listed in the CSR.

This list defines the tables to be produced by programming. The MW can decide to insert any of the figures or create more tables for the CSR text independently of this SAP.

List of CSR In-Text Outputs:		
Output	**Title**	**Population Set**
10.1 Subject Disposition and Data Sets Analyzed		
Table 1	Summary with Number of Subjects Included and the Number of Subjects Evaluated	All Subjects
10.3 Demographic and Other Baseline Characteristics		
Table 2	Summary of Demographics	Safety
11 Pharmacokinetic Results		
Figure 1	Mean OZ439 Concentration vs Time Plot – iv, oral and total radioactivity in the same plot (linear with SD and semi-log) [Part 1]	PK
Figure 2	Mean Oral OZ439 Concentration vs Time Plot - treatments C and D in the same plot (linear with SD and semi-log) [Part 2]	PK
Figure 3	Mean Oral OZ439 Concentration vs Time Plot - treatments A, B and C (with C dose-normalized to 800mg) in the same plot (linear with SD and semi-log) [Part 1 and 2]	PK
Table 3	Summary of OZ439 and Cobicistat PK Parameters	PK
Table 4	Statistical Analysis of Absolute Bioavailability (Part 1)	PK
Table 5	Statistical Analysis of OZ439 PK Parameters (Part 2)	PK
12 Safety Results		
Table 6	Summary of all TEAEs by System Organ Class and Preferred Term	Safety
Table 7	Summary of TEAEs by Relationship and Severity	Safety

Appendix 5: List of End of Text Tables and Figures

List of End of Text Tables and Figures:		
Output	**Title**	**Population Set**
15.1 Demographic Data		
Table 15.1.1	Summary of Subject Disposition	Safety
Table 15.1.2	Summary of Demographics	Safety
Table 15.1.3	Summary of Dosing	Safety
15.2 Pharmacokinetic Data		
Table 15.2.1	Summary and Listing of OZ439 and Cobicistat Plasma Concentrations	PK
Table 15.2.2	Summary and Listing of OZ439 and Cobicistat PK Parameters	PK
Table 15.2.3	Statistical Analysis of Absolute Bioavailability (Part 1)	PK
Table 15.2.4	Statistical Analysis of OZ439 PK Parameters (Part 2)	PK
Figure 15.2.5	Mean Plot of Oral OZ439 Concentration, IV Total Radioactivity and OZ439 Radioactivity versus Time (Linear and Semi-logarithmic)	PK
Figure 15.2.6	Mean Plot of Oral Cobicistat Concentration vs Time (Linear)	PK
Figure 15.2.7	Plot of Combined Individual OZ439 and Cobicistat Plasma Concentrations versus Time (Linear and Semi-Logarithmic)	PK
Figure 15.2.8	Plot of Individual OZ439 and Cobicistat Plasma Concentrations versus Time (Linear and Semi-Logarithmic)	PK
15.3 Safety Data		
15.3.1 Adverse Events		
Table 15.3.1.1	Summary of TEAEs by System Organ Class and Preferred Term	Safety
Table 15.3.1.2	Summary of Related TEAEs by System Organ Class and Preferred Term	Safety
Table 15.3.1.3	Summary of TEAEs by Relationship and Severity	Safety
15.3.2 Lists of Deaths, Other Serious and Significant Adverse Events		
Table 15.3.2	Listing of Deaths and Other Serious Adverse Events	Safety
15.3.3 Clinical Laboratory		

Table 15.3.3.1	Listing of Abnormal Laboratory Values	Safety
Table 15.3.3.2	Summary of Clinical Laboratory Data - Clinical Chemistry	Safety
Table 15.3.3.3	Summary of Clinical Laboratory Data - Hematology	Safety
15.3.4 Other Safety Parameters		
Table 15.3.4.1	Summary of Vital Signs	Safety
Table 15.3.4.2	Summary of 12-Lead Electrocardiogram	Safety
Table 15.3.4.3	Frequency Table of QTc Values	Safety
Table 15.3.4.4	Frequency Table of QTc Change from Baseline Values	Safety

Appendix 6: List of End of Text Listings

List of End-of-Text Listings:	
Output	**Title**
16.1.7 Randomization Scheme and Codes	
Appendix 16.1.7	Randomization
16.2.1 Discontinued Subjects	
Listing 16.2.1.1	Subject Disposition
16.2.2 Protocol Deviations	
Listing 16.2.2.1	Protocol Deviations (*reference to Clinical Study Report only)*
16.2.3 Subjects Excluded from the Analysis	
Listing 16.2.3.1	Overview of Analysis Sets
16.2.4 Demographics Data and Other Baseline Characteristics	
Listing 16.2.4.1	Demographic Data
Listing 16.2.4.2	Medical History
Listing 16.2.4.3	Previous Medication
Listing 16.2.4.4	Alcohol and Drug Screen Results
Listing 16.2.4.5	Serology Results
Listing 16.2.4.6	Pregnancy Test and FSH (Females Only)
16.2.5 Compliance and Drug Concentration Data	
Listing 16.2.5.1	Study Dates
Listing 16.2.5.2	Study Drug Administration
Listing 16.2.5.3	PK Blood Sampling Time Deviations and Comments
16.2.6 Adverse Events and Concomitant Medication	
Listing 16.2.6.1	Adverse Events
Listing 16.2.6.2	Concomitant Medication
16.2.7 Clinical Laboratory Data	
Listing 16.2.7.1	Clinical Laboratory Results – Clinical Chemistry
Listing 16.2.7.2	Clinical Laboratory Results – Hematology
Listing 16.2.7.3	Clinical Laboratory Results – Urinalysis
Listing 16.2.7.4	Clinical Laboratory Results – Comments (depending on amount of data, comments may be listed together with the results)
16.2.8 Other Safety Parameters	
Listing 16.2.8.1	Vital Signs
Listing 16.2.8.2	12-Lead Electrocardiogram Results
Listing 16.2.8.3	Physical Examinations

Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes (if created from a template, include template code)
15-May-2017	Gerk Rozema	First Draft
01-Jun-2017	Gerk Rozema	Sponsor comments incorporated
14-Jun-2017	Gerk Rozema	Sponsor comments incorporated