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

CONFIDENTIAL

Sponsor code: MMV_OZ439_16_01
PRA code: MMV508EC-165081
EudraCT number: 2016-004923-21

Absolute BA and OZ439 PK effect of different OZ439 dose volumes and cobicistat co-administration study

Investigational product	OZ439
Clinical phase	Phase 1 study
Indication to be studied	Not applicable
SPONSOR	Medicines for Malaria Venture (MMV) Route de Pré-Bois 20 1215 Geneva 15 Switzerland
CONTRACT RESEARCH ORGANIZATION	PRA Health Sciences (PRA) – Early Development Services (EDS) Van Swietenlaan 6 9728 NZ Groningen The Netherlands
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Version 1.0, 26 January 2017

This study will be performed in compliance with the principles of Good Clinical Practice.

AUTHORIZATION OF CLINICAL STUDY PROTOCOL

The Sponsor and the Contract Research Organization agree to conduct the study as outlined in this clinical study protocol. Any modification of the clinical study protocol must be agreed upon by the Sponsor and the Contract Research Organization and must be documented in writing.

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SYNOPSIS

Study 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

Short Study Title

Absolute BA and OZ439 PK effect of different OZ439 dose volumes and cobicistat co-administration study

Study Codes

Sponsor code : MMV_OZ439_16_01
PRA code : MMV508EC-165081
EudraCT number : 2016-004923-21

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Principal Investigator

Jan Jaap van Lier, MD

Objectives

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 pharmacokinetic (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)

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)

Design and Treatments

This is a single-center, 2-part clinical study in healthy subjects.

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)

Study Schedule

Screening : Between Day -28 and Day -1 (admission)
Confinement period : Part 1: the subjects will be admitted to the clinical research center in the afternoon of Day -1. They will be discharged on Day 2 (24 hours post-dose) after completion of the assessments. After discharge, the subjects will return to the clinical research center for ambulatory visits on Days 3, 4, 5 and 8 (at 48, 72, 96 and 168 hours post-dose) for PK and safety assessments
Part 2: subjects will be in the clinic for 3 treatment periods. Each period, the subjects will be admitted to the clinical research center in the afternoon of Day -1. They will be discharged on Day 2 (24 hours post-dose) after completion of the assessments. After discharge, the subjects will return to the clinical research center for ambulatory visits on Days 3, 4, 5 and 8 (at 48, 72, 96 and 168 hours post-dose) of each period for PK and safety assessments. For Treatment D, the subjects will also return to the clinical research center for additional ambulatory visits on Days 10, 12 and 14 for PK and safety assessments (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)
Follow-up : Part 1: subjects will attend a follow-up visit on Day 15 (± 2 days) for a final safety assessment
Part 2: Subjects will attend a follow-up visit between Day 15 and Day 19 of Period 3 (14 to 18 days after last drug administration) for a final safety assessment

Subjects

A total of 26 healthy male subjects and female subjects of non-childbearing potential will be enrolled (excluding any replacement subjects). In Part 1, 8 subjects will be enrolled to ensure data in 6 evaluable subjects for the PK endpoints. In Part 2, 18 subjects will be randomized to ensure data in 15 evaluable subjects for the PK endpoints. In Part 2, 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_{0-168h} and AUC_{0-inf}) for the 3 treatments.

Main Criteria for Inclusion

Gender : healthy male or female of non-childbearing potential
Age : 18-55 years, inclusive, at screening
Weight : >50 kg, at screening
Body mass index : 18.0-30.0 kg/m^2, inclusive, at screening

Study Drug

Active medication

Active substance	: OZ439
Activity	: peroxide anti-malarial agent
Indication	: treatment of uncomplicated malaria
Strength	: 400 mg/64.5 mL, 800 mg/64.5 mL and 800 mg/100 mL
Dosage form	: oral dispersion
Manufacturer	: Novasep (Finorga) (drug substance); PRA pharmacy (oral dispersions)

In the table below the OZ439 doses, the vehicle and volume of vehicle are given for the different treatments.

Treatment	OZ439 Dose	Volume of Vehicle
A	800 mg granules	100 mL of water containing Ora-sweet and polysorbate 80
B	800 mg granules	64.5 mL of solution containing Ora-sweet and polysorbate 80
C	400 mg granules	64.5 mL of solution containing Ora-sweet and polysorbate 80
D	400 mg granules	64.5 mL of solution containing Ora-sweet and polysorbate 80

The exact reconstitution procedure and amounts of Ora-sweet and polysorbate 80 will be described in the pharmacy manual to be provided by MMV.

Active medication

Active substance	: [^{14}C]-OZ439
Activity	: peroxide anti-malarial agent
Indication	: treatment of uncomplicated malaria
Strength	: 10 µg/mL free base containing 4.7 kBq/mL (0.127 µCi/mL) of radioactivity
Dosage form	: iv solution for infusion
Manufacturer	: Almac (drug substance); PRA Pharmacy (iv solution for infusion)

Reference medication

Active substance	: Cobicistat (Tybost®)
Activity	: CYP3A4 inhibitor (PK exposure enhancer)
Indication	: pharmacokinetic enhancer of atazanavir or darunavir as part of anti-retroviral combination therapy in human immunodeficiency virus (HIV)-1 infected adults
Strength	: 150 mg
Dosage form	: oral tablet
Manufacturer	: Gilead Sciences B.V.

Endpoints

Part 1 : Primary Endpoint

- PK: absolute oral bioavailability (F_{po}) of OZ439

Secondary Endpoints

- PK for iv administration of OZ439: V_d, 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

Exploratory Endpoints

- 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 2 : Primary Endpoint

- PK of OZ439: C_{max}, C_{168h}, AUC_{0-168h} and AUC_{0-inf}

Secondary Endpoints
- 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

Exploratory Endpoint
- Future OZ439 metabolites analysis may be performed

Statistical Methods

PK parameters : Descriptive statistics for all relevant PK parameters: n, mean, standard deviation (SD), minimum, median, maximum, geometric mean, and coefficient of variation (CV%); A statistical analysis will be performed on OZ439 PK parameters C_{max}, C_{168h}, AUC_{0-168h}, and AUC_{0-inf}. The PK parameters will undergo a natural logarithmic transformation and will be analyzed using analysis of variance (ANOVA) techniques. The ANOVA model will include treatment as a fixed effect. Adjusted geometric mean ratios (GMRs) and 90% confidence intervals for the adjusted GMRs will be provided for the comparisons between:
- Treatment C versus Treatment D to assess the effect of cobicistat on OZ439
- Treatment A versus Treatment B to explore volume effect (for this no within-subject comparison is possible)
- Treatment B versus Treatment C to explore dosing solution concentration effect (dose normalized)

Safety parameters : Descriptive statistics

Table 1 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					
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	
PK blood samples for [^{14}C]-OZ439										X[7]	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

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

Table 2 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

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LIST OF ABBREVIATIONS

ACPR	Adequate clinical and parasitological response
ACT	Artemisinin-based combination therapy
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
AMS	Accelerator mass spectrometry
ANOVA	Analysis of variance
ART	Artemisinin
AST	Aspartate aminotransferase
BA	Bioavailability
β-hCG	β-human chorionic gonadotropin
BMI	Body mass index
bpm	Beats per minute
CA	Competent authority
CI	Confidence interval
CPMP	Committee for Proprietary Medicinal Products; current name: Committee for Medicinal Products for Human Use (CHMP)
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Clinical Trial Directive
CV	Coefficient of variation
CYP	Cytochrome P450
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early Development Services
eGFR	Estimated glomerular filtration rate
EU	European Union
FQ	Ferroquine
FSH	Follicle stimulating hormone
gamma-GT	Gamma glutamyl transferase
GCP	Good Clinical Practice
GI	Gastrointestinal
GMR	Geometric mean ratio
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation (formerly: International Conference on Harmonisation)
IEC	Independent Ethics Committee
iv	Intravenous
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MEB	Medicine Evaluation Board
MedDRA	Medical Dictionary for Regulatory Activities
MMV	Medicines for Malaria Venture
MPC	Minimum parasiticidal concentration
MQ	Mefloquine
P.	Plasmodium

PCR	Polymerase chain reaction
PI	Principal Investigator
PIB	Powder in bottle
PK	Pharmacokinetic(s)
PQ	Primaquine
PQP	Piperaquine phosphate
PRA	PRA Health Sciences
PRA-EDS	PRA Early Development Services
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TPGS	α-tocopherol polyethylene glycol 1000 succinate
WHO	World Health Organization
WMA	World Medical Association
WMO	Wet medisch-wetenschappelijk onderzoek met mensen (Medical research involving human subjects act)

Note: Definitions of pharmacokinetic (PK) parameters are provided in Section 3.5.3

1. INTRODUCTION

1.1 Background

Malaria is a parasitic disease that threatens half of the world's population. The World Health Organization (WHO) reported that since 2000, the number of malaria cases has fallen from a range of 205 to 316 million to an estimated 214 million new cases in 2013, out of 3.2 billion people at risk. In the same year, malaria caused 438,000 deaths; 90% of the mortality was in the African region. However, even in this region mortality rates have fallen by 66% in all groups and by 71% in children under 5 years and overall, malaria deaths in children under 5 years have decreased to 306,000 in 2015.[1] In 2015 there were approximately 13.8 million cases of *Plasmodium (P.) vivax* malaria globally with most occurring in the WHO Southeast Asia Region.

While global efforts have led to the significant progress in the prevention, diagnosis, and management of malaria, treatment of malarial infections in the face of emerging drug resistance among *Plasmodium* species continues to pose clinical challenges. In particular, the widespread resistance of *P. falciparum* has rendered conventional monotherapies such as chloroquine, amodiaquine, and sulfadoxine/pyrimethamine ineffective. To combat increasing levels of resistance, the WHO recommends artemisinin (ART)-based combination therapy (ACT) as the first-line therapy for the treatment of uncomplicated *P. falciparum* malaria.[1]

ART and its derivatives are currently the most potent and rapidly acting anti-malarial agents available.[2] Their anti-malarial activities are characterized by high parasite kill rates and broad-stage activity that produce a faster clinical and parasitological response than other classes of anti-malarial agents. The peroxidic pharmacophore of ARTs is believed to be the main source of their potent activity. However, ART derivatives have been associated with high recrudescence rates when used as the conventional 3 to 5 days of monotherapy.[3] Combination with other agents has allowed for shorter courses of ACT therapy, improved treatment outcomes, and enhanced patient compliance.

OZ439 is a synthetic trioxolane that has potential value as a peroxide anti-malarial agent.[4] The first synthetic trioxolane, arterolane (RBx11160/OZ277), was identified in a collaborative drug discovery project.[5] Arterolane was launched in India in April 2013. Trioxolanes such as arterolane react with Fe(II) and are partially cleared by blood-mediated degradation. Because of this finding, a program to identify and develop new trioxolanes with increased exposure by reducing blood clearance without compromising activity was initiated by the Medicines for Malaria Venture (MMV). OZ439 is a product of this research, focused on identifying a potential anti-malarial curative treatment which may eventually be able to be administered as part of a single-dose cure in *P. falciparum* malaria.[6,7] Compared to previous compounds in the series, OZ439 shows in *in vitro* and *in vivo* models a high prophylactic potential, longer half-life ($t_{1/2}$), higher oral bioavailability, and better metabolic stability. OZ439 was selected from a large series of trioxolanes because of its high parasite activity and improved stability in blood. It has been found to be effective and safe in animal models

of malaria. The mesylate salt of OZ439 was selected as a development candidate due to its favorable solid state properties and good solubility in water.

1.1.1 Summary of Clinical Studies

At the data cutoff of 11th January 2017, data were available for 15 completed clinical studies (11 Phase Ia studies in healthy volunteers, 1 Phase Ib study in healthy volunteers inoculated with *P. falciparum* [QP12C10], and 2 Phase IIa study [MMV_OZ439_10_002 and MMV_OZ439_12_006] and 1 Phase IIb study [MMV_OZ439_13_003] in malaria patients). In these studies a total of 886 subjects have received at least 1 dose of OZ439. Of them, 337 subjects received OZ439 as a monotherapy (including 87 subjects in Phase IIa and 250 subjects in Phase I) or in combination with either piperaquine phosphate (PQP; 602 subjects), mefloquine (MQ; 13 subjects), ferroquine (FQ; 39 subjects) or primaquine (PQ; 19 subjects).

In addition, 3 clinical studies have recently been completed (3 Phase 1b challenge studies: QPC15C11, QP15C05 and QP14C12) for which reporting is ongoing) and 1 clinical study is ongoing (Phase IIb study DRI12805 FALCI). Validated data from these studies (and MMV_OZ439_12_006) were not available as of the cutoff date of the current valid Investigator's Brochure (IB)[8], i.e. 28th of April 2016, and therefore no results were presented in the IB, however, none of the results changed the risk-benefit ratio of the drug.

In studies in healthy subjects, plasma C_{max} in the fasted state was reached approximately 3 hours after administration of a single dose, and thereafter, OZ439 concentrations decreased in a multiphasic way. Concentrations initially dropped about 100-fold over the first 48 to 60 hours followed by a terminal phase with a $t_{1/2}$ of about 120 hours. Tissue distribution was extensive and plasma clearance (CL/F) was moderate. Following a single dose, the renal excretion of OZ439 and all metabolites was negligible, indicating that renal excretion is a minor pathway in the elimination of oral OZ439. Exposure to OZ439 and its metabolites increased in the presence of piperaquine, but the extent of this effect was limited (<1.7-fold).

In studies in patients with malaria, the PK for OZ439 was not dose-proportional. The apparent CL/F decreased with increasing OZ439 dose: about 50% lower at 800 mg versus 100 mg. In addition, the absorption rate constant decreased with an increase in actual OZ439 dose administered; about 50% lower at 800 mg versus 100 mg. The average exposures after a single dose of 800 mg OZ439 (all patients) were geometric mean (coefficient of variation [CV]%): C_{max} = 869 (78%) ng/mL; $AUC_{0\text{-}inf}$ = 10 (107%) µg*hr/mL, and concentration on Day 7 ($C_{Day\ 7}$) = 3.0 (147%) ng/mL. The overall between subject variability in exposures was considerable.

In vitro metabolism studies have shown that OZ439 is a substrate for CYP3A4; thus, the metabolism of OZ439 could be affected by drugs that either inhibit or induce CYP3A4. Inhibitory studies (up to 30 µM of OZ439) showed that OZ439 is a CYP3A4 inhibitor; thus, there is a potential for PK drug interactions with drugs that are CYP3A4 substrates.

The anti-malarial activity of OZ439 was investigated in a blood stage *P. falciparum* challenge model in healthy subjects who were inoculated with infected erythrocytes (Study QP12C10). Pharmacokinetics/pharmacodynamics modeling of the preliminary study data suggested that the minimum parasiticidal concentration of OZ439 is 3 (1 to 10) ng/mL.

In a Phase IIa study, single oral doses of OZ439 from 200 to 1200 mg demonstrated consistent anti-malarial efficacy, with no tailing off in the effect in the lower dose cohorts. OZ439 cleared more than 97.8% of *P. falciparum* and *P. vivax* parasites by 36 hours, reducing malaria symptomatology and leading to an estimated parasite clearance time of 69 hours or less.

In a Phase IIb study of a single-dose regimen of OZ439 800 mg in combination with 3 doses of PQP (640 mg, 960 mg, and 1440 mg) in adults and children with uncomplicated *P. falciparum* malaria in Africa and Asia, none of the dose arms of the study met the protocol-defined efficacy threshold of 95% efficacy based on the primary endpoint of polymerase chain reaction (PCR)-adjusted adequate clinical and parasitological response (ACPR) outcome on Day 28 in the per protocol analysis set. No clear dose response was observed for crude and PCR-adjusted ACPR on Day 28; however, the PQP 1440 mg dose was overall more efficacious than the lower doses.

To date, OZ439 administered either as a monotherapy or in combination with a partner anti-malarial, has been generally well tolerated in malaria patients and healthy subjects. In a Phase IIa study of OZ439 doses of 200, 400, 800 and 1200 mg in malaria patients, increased blood creatine phosphokinase was the most frequently reported adverse event (AE); a dose relationship was not seen for this AE. Gastrointestinal (GI) AEs, including vomiting, abdominal pain, and diarrhea, and nervous system disorders, including dizziness and headache, were reported more frequently with 1200 mg OZ439 compared to the other dose cohorts. None of these AEs were serious AEs (SAEs).

In a Phase IIb study, where OZ439 was evaluated in combination with PQP, in patients with uncomplicated *P. falciparum* malaria, malaria and electrocardiogram (ECG) QTc prolongation were the most frequently reported AEs. Malaria was reported with a higher incidence in the OZ439 800 mg:PQP 960 mg and in the OZ439 800 mg:PQP 640 mg treatment arms than in the OZ439 800 mg:PQP 1440 mg treatment arm. The ECG QTc prolongation was reported with a higher incidence in the OZ439 800 mg:PQP 1440 mg and the OZ439 800 mg:PQP 960 mg treatment arms than in the OZ439 800 mg:PQP 640 mg treatment arm. Concentration-related QTc prolongation has been widely documented with PQP. Diarrhea and vomiting were the most frequently reported AEs of the GI system in patients treated with both OZ439 and PQP. None of these AEs were SAEs.

The AE profile for OZ439 in healthy subjects was similar to the AE profile in malaria patients. Gastrointestinal AEs, including nausea, vomiting, and diarrhea, were the most frequently reported AEs in healthy subjects treated with OZ439 alone or OZ439 in

combination with either PQP, MQ, or FQ. A tendency for a dose-response relationship was seen for GI events.

No deaths have been reported in any of the clinical studies.

Eight subjects treated with OZ439, including 6 malaria patients and 2 healthy volunteers, have had SAEs, including *P. vivax* relapse, pyelonephritis, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), decreased neutrophil count, anemia, febrile convulsion and decreased hemoglobin in malaria patients; and atrial fibrillation and a gunshot wound in healthy subjects. Five SAEs (increased ALT, increased AST, decreased neutrophil count, anemia and decreased hemoglobin) in malaria patients were assessed as related to study drug by the investigator.

An AE of vomiting led to study drug discontinuation in 1 malaria patient treated with OZ439. Ten healthy subjects treated with OZ439 discontinued a Phase Ia study due to an AE. Vomiting (5 subjects) was the most frequently reported AE leading to study discontinuation in the 10 healthy subjects. Except for a few cases observed with α-tocopherol polyethylene glycol 1000 succinate (TPGS) formulation that will not be used in further studies, vomiting is not reported in healthy subjects at doses < 800 mg OZ439.

No Hy's law cases have been observed. However, mild to severe and reversible increases in ALT and AST were seen in OZ439-treated malaria patients; these increases did not appear to be dose-dependent. Decreases in hemoglobin, neutrophils, and platelets were also seen in OZ439-treated malaria patients; however, these decreases were consistent with those observed in acute malaria. Close monitoring of liver function is required in the clinical studies.

In the clinic, a significant effect on placebo-corrected change from baseline QTcF was not demonstrated for OZ439. In healthy subjects the effect of OZ439 800 mg alone on QTc was minimal, with a maximum mean QTcF increase from baseline and placebo of 8.5 ms (Study MMV_OZ439_12_002). In Study MMV_OZ439_12_003, 1 healthy subject with an undisclosed history of mitral and tricuspid regurgitation was discontinued from the study due to asymptomatic supraventricular/junctional tachycardia after dosing with 120 mg OZ439. QTc prolongations (both QTcB and QTcF) were seen when OZ439 was administered in combination with PQP to malaria patients and healthy subjects. Most of the prolongations were in the range of >30 ms but <60 ms; however, prolongations >60 ms were observed in malaria patients, with QTcF values that exceeded 500 ms in 2 patients (1 hypokalemic patient). Reversible right bundle branch block (3 patients), reversible first degree atrioventricular block (1 patient), and a mild reversible sinus bradycardia (1 patient) were also observed in malaria patients treated with OZ439. Close monitoring of cardiac function is required in the clinical studies.

Additional information on non-clinical and clinical studies conducted with OZ439 is provided in the IB and addendum to the IB.[8,10]

Cobicistat

Cobicistat (Tybost®) is a potent CYP3A4 inhibitor used as "pharmaco-enhancer" for boosting exposures to CYP3A4 substrates and more particularly human immunodeficiency virus (HIV) drugs. The mechanism may involve direct as well as mechanism-based inhibition. Cobicistat was shown to be well tolerated in healthy subjects after both single dose (50-400 mg) and multiple dose (50-300 mg for 14 days) administration.[9] After single dose administration all the AEs observed were of Grade 1. The most frequently reported AEs (in only 2 subjects) were headache, somnolence and abnormal dreams. No notable changes in biology parameters, vital signs or ECGs (QTc) were detected in the first-in-man study. In subsequent studies with multiple dose administration of cobicistat, it was shown that the drug increases serum creatinine concentration by decreasing its elimination, resulting in a decrease in estimated glomerular filtration rate (eGFR). The rise in serum creatinine concentration and decline in eGFR was reversible within 7 days after the discontinuation of cobicistat. This artefactual change in creatinine is not expected after single dose administration.

When midazolam, a reference substrate for CYP3A4, was co-administered with cobicistat at steady-state conditions of the CYP3A4 inhibitor, the lowest dose of cobicistat (50 mg) was associated with a 89% reduction in apparent clearance of oral midazolam. The maximal inhibition of CYP3A4 was achieved with 200 mg (95%) and with marginal gain over the 100 mg dose (93%). These data have demonstrated that a dose ≥100 mg provide near maximal boosting of CYP3A4 substrate and 150 mg was subsequently selected as the boosting dose for HIV drugs.

Detailed information can be found in the Summary of Product Characteristics of cobicistat (Tybost®).

1.2 Risk-Benefit Assessment

There is no expected clinical benefit for the healthy subjects that will participate in this study. The information obtained in this study can be used for the further clinical development of OZ439. Overall, on the basis of the available non-clinical and clinical data, and prior knowledge, the risk-benefit profile of OZ439 and cobicistat are judged acceptable for the proposed clinical study.

1.3 Study Rationale

Work is ongoing to develop a suitable OZ439 formulation to achieve efficacious exposures in patients with malaria, and in addition to meet the target product profile volume criterion: a maximum suspension volume of 15 mL in infants (6 months to 2 years old). It is assumed that 64.5 mL is the equivalent volume in adults (to obtain the similar dose/volume ratio). An intermediate 25 mL volume in infants may be considered and similarly, would translate into approximately 100 mL in adults.

The determination of the absolute bioavailability of the simple dispersible OZ439 granules formulation will allow the estimation of the maximum enhancement of bioavailability achievable through formulation approaches.

The non-linearity of OZ439 PK is addressed by administering the iv microdose at the t_{max} of the oral dose, thus ensuring that the clearance is the same for both iv and oral doses. In order to ensure adequate assay sensitivity for the microdose, OZ439 will be radiolabeled and accelerator mass spectrometry (AMS) will be used to determine the plasma drug concentrations over time.

In vitro evidence has shown that OZ439 is mainly metabolized through cytochrome P450 (CYP) 3A4 in humans. Marketed CYP3A4 inhibitors are indicated to increase systemic exposures of anti-retroviral agents in the treatment of HIV-1 infection, e.g. Tybost® (cobicistat). Further development of OZ439 could include a combination strategy with cobicistat in order to maximize exposures of OZ439 in a single-dose setting. This approach will be tested in the second part of the study, to determine the fractional increase in OZ439 exposure in the presence of the approved 150 mg pharmaco-enhancer dose of cobicistat which is a strong CYP3A4 inhibitor currently used to increase exposure to HIV drugs in patients (Tybost®).

Data collected in previous clinical studies suggested that the total volume of liquid administered with OZ439 may alter the exposure of OZ439 (exposure increasing with increasing volume). The PK and exposures of OZ439 granules formulation when suspended in 2 different target volumes of dosing vehicle will be evaluated under fasted conditions.

Included in the primary PK endpoints evaluating the plasma exposures of OZ439 is the concentration on Day 7 (C_{168h}). This endpoint is considered relevant since concentrations of an effective anti-malarial drug in a combination treatment may be required to exceed the minimum parasiticidal concentration (MPC) for at least 7 days to achieve full clearance of the original parasitaemia. Furthermore, a relationship between C_{168h} and clinical outcome for the combination of OZ439 with PQP has been derived based on Phase IIb data (MMV_OZ439_13_003), allowing direct interpretation of this endpoint.

1.4 Dose Rationale

Table 3 summarises the maximum drug exposures achieved in relevant OZ439 clinical studies, including those studies providing key efficacy and tolerability data supporting the dose rationale for this study. These exposures were generally well tolerated and the exposures in the current study are predicted not to exceed exposure levels investigated in the previous studies. The highest OZ439 exposure ($AUC_{0\text{-}inf}$ of 29,200 ng.h/mL) achieved in healthy subjects to date was in an OZ439 relative bioavailability study (MMV_OZ439_11_001) in which 800 mg OZ439 powder in bottle (PIB) formulation was administered in the fed state.

Table 3 Key Studies - Drug Exposures OZ439

Study	Design	OZ439 Dose (mg)	C_{max} (ng/mL) (CV%)	$AUC_{0\text{-}inf}$ (ng.h/mL) (CV%)	PQP Dose (mg)
MMV_OZ439_09_001	FIH, Part A	400 mg PIB fasted	566 (53.9)	5540 (71.3)	NA
		800 mg PIB fasted	917 (35.6)	9790 (56.7)	NA
	FIH, Part B	800 mg PIB fasted	730 (61.1)	8080 (68.7)	NA
		800 mg PIB fed	2220 (52.6)	23100 (48.9)	NA
MMV_OZ439_11_001	BA OZ439 + TPGS prototype BA	800 mg PIB fasted (Cohort 1)	827 (47.7)	10700 (52.8)	NA
		800 mg PIB fasted (Cohort 2)	538 (33.2)	7460 (34.1)	NA
		800 mg PIB fed (reference)	1910 (32.9)	29200 (31.2)	NA
MMV_OZ439_10_002	Phase IIa efficacy	1200 mg PIB	1500 (90.0)	25100 (85.1)	NA
MMV_OZ439_12_005	3-Day dose escalation (Exposures on Day 3)	700 mg PIB milk	1790 (32.2)	20500 (32.0)*	NA
MMV_OZ439_12_002	OZ439 + PQP safety/DDI	800 mg PIB milk	1650 (26)	20700 (41)	1440 mg milk
		100 mg PIB milk	199 (27)	1520 (26)**	1440 mg milk
MMV_OZ439_13_002	OZ439 + TPGS Phase IIb prototype + PQP BA	800 mg PIB milk (reference)	1610 (37.2)	18600 (45.4)	1440 mg milk
		800 mg + TPGS	1540 (26.0)	17500 (27.9)	1440 mg
MMV_OZ439_13_004	OZ439 + PQP Phase IIb formulation BA	800 mg + TPGS	1260 (35)	14200 (26)	1440 mg
		800 mg + TPGS	1500 (40)	15800 (35.7)	960 mg
		800 mg + TPGS	1270 (29)	14100 (34.7)	960 mg
MMV_OZ439_13_007	PQP + OZ439 PK study in HV	800 mg Prototype 1	877 (41.3)	8780 (43.7)**	960 mg
		800 mg Prototype 2	995 (32.2)	10300 (23.7)**	960 mg
		800 mg Prototype 3	924 (50.5)	9460 (43.0)**	960 mg
MMV_OZ439_15_001	PQP + OZ439 PK study in HV	800 mg TPGS	1600 (36.6)	15300 (26.1)**	960 mg
		800 mg Prototype 1 (110 mL)	824 (38.3)	7920 (26.4)**	960 mg
		800 mg Prototype 3 (110 mL)	616 (49.4)	5610 (38.1)**	960 mg
		800 mg TPGS	1530 (13.2)	14000 (29.6)**	960 mg
		800 mg Prototype 1 (220 mL)	999 (40.8)	9550 (57.5)**	960 mg
		800 mg Prototype 3 (220 mL)	730 (35.7)	7100 (45.7)**	960 mg

Exposures are given as geometric mean

* Day 3 AUC_{τ}; ** AUC_{168h}

BA: bioavailability study; DDI: drug-drug interaction study; FIH: first-in-human study; HV: healthy volunteers; NA: not applicable; PIB: powder in bottle; PK: pharmacokinetic; PQP: piperaquine phosphate; TPGS: α-tocopherol polyethylene glycol 1000 succinate

Single OZ439 doses of up to 800 to 1200 mg giving exposures (C_{max} and AUC_{0-inf}) of up to 2220 ng/mL and 29,200 ng.h/mL, respectively (Table 3) have been shown to be generally well tolerated in patient and in healthy subject studies. Administration of 700 mg OZ439 for 3 days was also well tolerated.

For OZ439, the dose level of 800 mg is close to the upper limit of what can be administered to patients. Even for the best performing, well tolerated but not commercially viable formulations (e.g., TPGS or PIB milk) the exposures for 800 mg may be sufficient but are still considered suboptimal. Therefore, the likely clinical dose level will be 800 mg, and improving the bioavailability is of interest.

Therefore, the bioavailability of OZ439 will be estimated for a basic formulation (granules in dispersion) at the dose level of 800 mg. The anticipated exposures for 800 mg administered as granules in dispersion are about C_{max} 900 ng/mL and AUC_{inf} 10000 ng*hr/mL (studies MMV_OZ439_09_001 and MMV_OZ439_11_001)

Likewise, when evaluating the impact of reducing the administration volumes the most relevant (maximal) dose level is 800 mg. Anticipated exposures are expected to be equal to or lower than what has previously been observed.

For the evaluation of the co-administration of OZ439 and cobicistat, SimCyp simulations are suggesting that a mean 1.20 and 2.55 fold increase in OZ439 exposure for C_{max} and AUC_{inf}, respectively, could be achieved in the presence of an oral 150 mg dose of cobicistat. The simulations assumed that for OZ439 the fraction of CYP3A4 metabolism was 0.9 (from *in vitro* data) and the cobicistat parameters were derived from human PK and interaction with midazolam. The anticipated C_{max} and AUC for a single dose of 400 mg OZ439 (granules in dispersion) when co-administered with a single dose of 150 mg cobicistat are 390 ng/mL and 11,290 ng*hr/mL, respectively (mean value of 10 trials simulations with SimCyp), more than 2-fold lower than the maximal evaluated well tolerated exposures. Therefore, 400 mg was considered a safe dose of OZ439 to be evaluated with cobicistat.

The rationale for the 150 mg cobicistat dose is provided in Section 1.1.1.

2. OBJECTIVES

2.1 Primary

- To determine the absolute bioavailability of OZ439 following a single oral dose of OZ439 dispersion and a simultaneous single 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 CYP3A4 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)

2.2 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)

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Type of Study

This is a single-center, 2-part clinical study in healthy subjects.

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)

3.1.2 Screening Period

Subjects will report to the medical screening facility/clinical site for the eligibility screening (see Section 3.3 for inclusion and exclusion criteria) within 4 weeks prior to (the first) drug administration.

Subjects will sign the study-specific informed consent form (ICF) prior to any study-specific screening procedures being performed. The written informed consent will be obtained for all subjects, regardless of their eligibility for the study; the signed ICFs will be retained and archived at PRA Health Sciences (PRA) and a copy will be provided to the subject.

Eligibility screening will consist of the assessments as presented in the schedules of assessments (Table 1 and Table 2).

3.1.3 Treatment Period

Part 1

The subjects will be admitted to the clinical research center in the afternoon of Day -1. They will be discharged on Day 2 (24 hours post-dose) after completion of the assessments. After discharge, the subjects will return to the clinical research center for ambulatory visits on Days 3, 4, 5 and 8 (at 48, 72, 96 and 168 hours post-dose) for PK and safety assessments.

Part 2

Subjects will be in the clinic for 3 treatment periods. Each period, the subjects will be admitted to the clinical research center in the afternoon of Day -1. They will be discharged on Day 2 (24 hours post-dose) after completion of the assessments. After discharge, the subjects will return to the clinical research center for ambulatory visits on Days 3, 4, 5 and 8 (at 48, 72, 96 and 168 hours post-dose) of each period for PK and safety assessments. For Treatment D, the subjects will also return to the clinical research center for additional ambulatory visits on Days 10, 12 and 14 for PK and safety assessments (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).

Assessments during the treatment period(s) will be performed as presented in the schedules of assessments (Table 1 and Table 2).

3.1.4 Follow-up

Part 1

Subjects will attend a follow-up visit on Day 15 (± 2 days) for a final safety assessment.

Part 2

Subjects will attend a follow-up visit between Day 15 and Day 19 of Period 3 (14 to 18 days after last drug administration) for a final safety assessment.

Assessments during follow-up will be performed as presented in the schedules of assessments (Table 1 and Table 2).

3.2 Discussion of Study Design

In the cross-over design that has been chosen for Part 2 of this study the subjects will be their own control for treatment comparisons. The wash-out period with a minimum of 14 days is considered to be sufficient to avoid a carry-over effect.

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 moderate to high between subject 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.

3.3 Selection of Study Population

A total of 26 healthy male subjects and female subjects of non-childbearing potential will be enrolled (excluding any replacement subjects).

In Part 1, 8 subjects will be enrolled to ensure data in 6 evaluable subjects for the PK endpoints.

In Part 2, 18 subjects will be randomized to ensure data in 15 evaluable subjects for the PK endpoints. In Part 2, 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 $AUC_{0\text{-}inf}$; see Section 3.5.3) for the 3 treatments.

3.3.1 Inclusion Criteria

Note: Restrictions that apply to the period after (the first) admission are described in Section 3.4.8, except when they concern a statement of willingness.

The following inclusion criteria must be met for a subject to be eligible for inclusion in the study:

1. Gender : male or female
2. Age : 18-55 years, inclusive, at screening
3. Body mass index (BMI) : 18.0-30.0 kg/m^2, inclusive, at screening
4. Weight : >50 kg, at screening
5. Status : healthy subjects
6. Female subjects must be of non-childbearing potential (either surgically sterilized or physiologically incapable of becoming pregnant, or post-menopausal [defined as spontaneous amenorrhoea for at least 1 year or spontaneous amenorrhoea for at least 6 months confirmed by a follicle stimulating hormone (FSH) result indicating a post-menopausal status]) and have a negative pregnancy test at screening and at (each) admission to the clinical research center. As all female subjects must be of non-childbearing potential, they are not required to use any contraception during this study.
7. Male subjects must use adequate contraception and not donate sperm from (first) admission to the clinical research center until 90 days after the follow-up visit. Adequate contraception for the male subject (and his female partner) is defined as surgical sterilization (vasectomy), using hormonal contraceptives (implantable, patch, oral, injectable) or an intrauterine device or system combined with at least 1 of the following forms of contraception (barrier method): a diaphragm or cervical cap, or a condom. Also, total abstinence, in accordance with the lifestyle of the subject is acceptable.

8. Must have QTcF ≤450 ms and QTcB ≤450 ms (male subjects); QTcF ≤470 ms and QTcB ≤470 ms (female subjects), and PR-interval ≤200 ms for screening, and Day -1 and pre-dose ECG measurements of the (first) treatment period
9. Ability and willingness to abstain from alcohol and methylxanthine-containing beverages or food (coffee, tea, cola, chocolate, energy drinks) from 48 hours prior to (each) admission to the clinical research center
10. Willing and able to communicate and participate in the whole study
11. Willing and able to sign the ICF

3.3.2 Exclusion Criteria

Note: Restrictions that apply to the period after (the first) admission are described in Section 3.4.8, except when they concern a statement of willingness.

A subject who meets any of the following exclusion criteria will not be eligible for inclusion in the study:

1. Male subjects who have currently pregnant partners or who have partners planning to be pregnant in the 90 days after discharge
2. Evidence or history of clinically significant oncological, pulmonary, chronic respiratory, hepatic, cardiovascular, hematological, metabolic, neurological, immunological, nephrological, endocrine or psychiatric disease, or current infection
3. Clinically relevant (as decided by the Principal Investigator [PI]) abnormalities in the 12-lead ECG, including asymptomatic bundle branch block
4. Family history of sudden death or of congenital prolongation of the QTc-interval or known congenital prolongation of the QTc-interval or any clinical condition known to prolong the QTc-interval
5. History of symptomatic cardiac arrhythmias or with clinically relevant bradycardia, heart rate ≤39 beats per minute (bpm)
6. Electrolyte disturbances, particularly hypokalemia, hypocalcemia or hypomagnesemia
7. Any condition that could possibly affect drug absorption, e.g. gastrectomy or diarrhea
8. History of post-antibiotic colitis
9. History of any drug or alcohol abuse in the past 2 years prior to screening
10. Subjects who regularly smoke more than 5 cigarettes a day
11. Receipt of an investigational drug or participation in another clinical research study within 90 days prior to the first dose of study drug
12. Subjects who are PRA employees, or immediate family members of PRA or Sponsor employees
13. Subjects who have previously been enrolled in this study
14. Use of moderate/strong inhibitors or inducers of CYP cytochromes or transporters within 30 days or 5 half-lives (whichever is longer) prior to the first dose of study drug
15. Consumption of grapefruit, grapefruit juice or grapefruit-related citrus fruits (e.g. Seville oranges, pomelos) within 14 days prior to the first dose of study drug

16. Use of prescription or non-prescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study drug. With the exception of paracetamol (which may be used incidentally or for a short-term treatment at a maximum dose of 2 g per day) and hormone replacement therapy
17. Use of herbal supplements within 30 days prior to the first dose of study drug
18. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody or HIV-1 or HIV-2 antibody results
19. Clinically significant abnormal biochemistry, hematology or urinalysis as judged by the PI. In case of doubt the PI will discuss this with the medical monitor
20. Positive urine drug screen result at screening or admission to the clinical research center
21. Serious adverse reaction or serious hypersensitivity to any drug or the formulation excipients
22. Presence or history of allergy requiring treatment. Hayfever is allowed unless it is active
23. Donation or loss of >100 mL of blood within 90 days prior to drug administration
24. Regular alcohol consumption in males >21 units per week and females >14 units per week (1 unit = 250 mL beer, 25 mL of 40% spirit or 125 mL of wine)
25. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the PI or delegate at screening
26. Failure to satisfy the PI of fitness to participate for any other reason

The Sponsor will not agree to any waiver related to inclusion or exclusion criteria.

Please note that subjects should refrain from consumption of any foods containing poppy seeds within 48 hours (2 days) prior to screening and (first) admission to the clinical research center to avoid false positive drug screen results. In addition, they should refrain from strenuous exercise within 96 hours (4 days) prior to screening and (first) admission as this could result in abnormal clinical laboratory values.

3.3.3 Removal and Replacement of Subjects from the Study

Participation in the study is strictly voluntary. A subject has the right to withdraw from the study at any time for any reason.

The PI has the right to terminate participation of a subject for any of the following reasons: termination of the study, difficulties in obtaining blood samples, major deviation of the protocol, severe AEs or SAEs, or for any other reason relating to the subject's safety or integrity of the study data (eg, concurrent illness or requirement for prohibited medication), at the discretion of the PI.

If a subject is withdrawn from the study, the Sponsor will be informed immediately. If there is a medical reason for withdrawal, the subject will remain under the supervision of the PI until satisfactory health has returned.

If a subject is withdrawn from the study for any reason, whether related to the study drug or not, or if a subject voluntarily withdraws before or after receiving the study drug, such subject will be considered an early-termination subject.

If a subject is withdrawn due to a study drug-related AE or due to termination of the study, the early-termination subject will not be replaced. If a subject does not complete the study for reasons other than safety, the early-termination subject may be replaced after mutual agreement between the Sponsor and PRA. If there are fewer than 6 evaluable subjects for the PK endpoints in Part 1 of the study, replacement subjects may be enrolled to have at least 6 evaluable subjects following discussion between the Sponsor and the PI. If there are fewer than 15 evaluable subjects for the PK endpoints in Part 2 of the study, up to 2 replacement subjects may be enrolled per treatment following discussion between the Sponsor and the PI.

The decision regarding the replacement of subjects will be documented.

PRA will make every effort to ensure that early-termination subjects who have received study drug complete the safety follow-up assessments.

3.4 Treatments

3.4.1 Treatments Administered

The treatments and dose levels for each part are described in detail in Section 3.1.1.

3.4.2 Identity of Investigational Products

Active medication

Active substance	:	OZ439
Activity	:	Peroxide anti-malarial agent
Indication	:	Treatment of uncomplicated malaria
Strength	:	400 mg/64.5 mL, 800 mg/64.5 mL and 800 mg/100 mL
Dosage form	:	Oral dispersion
Manufacturer	:	Novasep (Finorga) (drug substance); PRA pharmacy (oral dispersions)

In the table below the OZ439 doses, the vehicle and volume of vehicle are given for the different treatments.

Treatment	OZ439 Dose	Volume of Vehicle
A	800 mg granules	100 mL of water containing Ora-sweet and polysorbate 80
B	800 mg granules	64.5 mL of solution containing Ora-sweet and polysorbate 80
C	400 mg granules	64.5 mL of solution containing Ora-sweet and polysorbate 80
D	400 mg granules	64.5 mL of solution containing Ora-sweet and polysorbate 80

The exact reconstitution procedure and amounts of Ora-sweet and polysorbate 80 will be described in the pharmacy manual to be provided by MMV.

Active medication

Active substance	:	[^{14}C]-OZ439
Activity	:	Peroxide anti-malarial agent
Indication	:	Treatment of uncomplicated malaria
Strength	:	10 µg/mL free base containing 4.7 kBq/mL (0.127 µCi/mL) of radioactivity
Dosage form	:	iv solution for infusion (10 mL)
Manufacturer	:	Almac (drug substance); PRA Pharmacy (iv solution for infusion)

Reference medication

Active substance	:	Cobicistat
Activity	:	CYP3A4 inhibitor (PK exposure enhancer)
Indication	:	Pharmacokinetic enhancer of atazanavir or darunavir as part of anti-retroviral combination therapy in HIV-1 infected adults
Strength	:	150 mg
Dosage form	:	Oral tablet
Manufacturer	:	Gilead Sciences B.V.

OZ439 and [^{14}C]-OZ439 drug substance will be provided by the Sponsor. The OZ439 oral dispersions and the [^{14}C]-OZ439 iv solution for infusion will be manufactured by the PRA Pharmacy. The reference medication cobicistat will be commercially obtained by the PRA Pharmacy.

For details concerning drug storage and drug accountability see Appendix 9.1.

3.4.3 Method of Assigning Subjects to Treatment Groups

After obtaining informed consent, subjects will be screened according to the inclusion and exclusion criteria. 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.

Subjects who drop out or withdraw for any reason without completing all screening evaluations successfully, will be considered “screening failures“. Such subjects will not receive a subject number, and only applicable data will be entered in the electronic case report forms (eCRFs).

3.4.4 Selection of Doses in the Study

The rationale for dose selection is described in Section 1.4.

3.4.5 Timing of Doses in the Study

Study drug (OZ439 alone or in combination with cobicistat) will be administered to subjects between 08:00 and 11:00 hours in the morning after an overnight fast of at least 10 hours. In Part 1, the iv infusion of 100 µg [^{14}C]-OZ439 (47 kBq [1.27 µCi]) will begin 3 hours after the oral dose administration. Fasting will continue for a period of 6 hours after oral drug administration, ie, until scheduled lunch. During fasting, no fluids are allowed except water; however, water is not allowed from 2 hours pre-dose until 1 hour post-dose (calculated from oral dose administration).

Administration of the study drug will be supervised by the PI or authorized designee. After oral drug administration, a mouth and hand inspection will take place.

3.4.6 Meals During the Study

A fasting period of at least 4 hours is required before obtaining clinical laboratory samples at all time points.

With the exception of the restrictions with respect to methylxanthine- and alcohol containing beverages or food as described in Section 3.4.8 and what has been described in Section 3.4.5, there are no special requirements related to food and beverage intake. When not fasting, meals and snacks (such as decaffeinated coffee, herbal tea, fruit, biscuits) will be provided according to PRA standard operating procedures (SOPs). A light supper will be provided on the evening before those days where fasting is required until lunch time.

3.4.7 Blinding

This is an open-label study.

3.4.8 Concomitant Medication and Other Restrictions During the Study

Note: Restrictions that apply to the period before (the first) admission are described in Section 3.3.1, and Section 3.3.2.

The use of all prescribed medication is not allowed from (first) admission to the clinical research center up to follow-up. The use of all over-the-counter medication, vitamin preparations and other food supplements, herbal medications (e.g. St. John's Wort), grapefruit, grapefruit juice or grapefruit-related citrus fruits (e.g. Seville oranges, pomelos) is not allowed from (first) admission to the clinical research center up to follow-up. An exception is made for paracetamol: from (first) admission onwards, the PI may permit a limited amount of paracetamol for the treatment of headache or any other pain. Other medication to treat AEs may only be prescribed if deemed necessary by the PI. If medication is used, the name of the drug, the dose and dosage regimen will be recorded in the eCRF.

The use of alcohol, methylxanthine-containing beverages or food (coffee, tea, cola, chocolate, energy drinks) and tobacco products is not allowed during the stay(s) in the clinical research center.

Strenuous exercise is not allowed within 96 hours (4 days) prior to (each) admission and during the stay(s) in the clinical research center. Strenuous exercise is also not allowed within 96 hours (4 days) prior to the ambulatory visits on Day 5 (Parts 1 and 2) and Day 10 (after Treatment D in Part 2), and the follow-up visit.

Subjects should not consume any foods containing poppy seeds within 48 hours (2 days) prior to (each) admission to the clinical research center as this could cause a false positive drug screen result.

Contraception, sperm donation and pregnancy

As all female subjects must be of non-childbearing potential, they are not required to use any contraception during this study.

Male subjects are required to use at least 2 adequate methods of contraception (see description below) and not donate sperm from (first) admission to the clinical research center until 90 days after the follow-up visit.

Adequate contraception for male subjects (and his female partner) is defined as surgical sterilization (vasectomy), using hormonal contraceptives (implantable, patch, oral, injectable) or an intrauterine device or system combined with at least 1 of the following forms of contraception (barrier method): a diaphragm or cervical cap, or a condom. Also, total abstinence, in accordance with the lifestyle of the subject is acceptable.

In addition, male subjects who have been sterilized or have partners of non-childbearing potential (including homosexual men) are required to use one barrier method of contraception (condom) from (first) admission to the clinical research center until 90 days after the follow-up visit. This is to prevent unintended exposure of the partner to the study drug via seminal fluid.

Subjects will be instructed that the study drug has known embryotoxicity in rodents and that if they or their partner become pregnant during the study this should be reported to the PI. The PI should also be notified of pregnancy occurring during the study but confirmed after completion of the study. If a subject or subject's partner is subsequently found to be pregnant after the subject is included in the study, then consent will be sought from the partner and, if granted, any pregnancy will be followed and the status of mother and/or child will be reported to the Sponsor after delivery. Any subject reporting a pregnancy during the study will be withdrawn from the study. A pregnancy notification form and follow-up will be completed.

3.4.9 Treatment Compliance

Study drug will be administered in the clinical research center. To ensure treatment compliance, administration of the study drug will be supervised by the PI or authorized designee. Compliance will be further confirmed by bioanalytical assessment of OZ439 in plasma samples (see Section 3.5.4).

The exact times of study drug administration and the number of units administered will be recorded in the eCRF.

3.5 Pharmacokinetic and Safety Measurements and Endpoints

3.5.1 Pharmacokinetic and Safety Measurements Assessed and Schedules of Assessments

The schedules of assessments are presented in Table 1 and Table 2.

3.5.1.1 Pharmacokinetic Measurements

3.5.1.1.1 Blood Sampling

At the time points defined in the schedules of assessments, blood samples of 3 mL and 8 mL each will be taken for the analysis of OZ439 and [^{14}C]-OZ439, respectively, in plasma samples for Part 1. For Part 2, blood samples of 3 mL will be taken for the analysis of OZ439 and cobicistat. Additional blood samples of 3 mL will be collected for future OZ439 metabolites analysis in Part 1 and in Part 2 (Period 1 only). The blood samples will be taken via an indwelling iv catheter or by direct venipuncture.

Samples will be shipped to Swiss BioQuant AG for the analysis of OZ439, OZ439 metabolites and cobicistat, and to Xceleron for the analysis of [^{14}C]-OZ439.

Details on sample collection, handling, storage and shipping will be described in the laboratory manual prepared by PRA.

3.5.1.2 Safety and Tolerability Measurements

Safety and tolerability assessments will consist of AEs, clinical laboratory, vital signs, 12-lead ECG, and physical examination. Assessments will be performed in accordance with the schedules of assessments.

3.5.1.2.1 Adverse Events

Adverse events will be recorded from screening until completion of the follow-up visit. Any clinically significant observations in results of clinical laboratory, 12-lead ECGs, vital signs or physical examinations will be recorded as AEs.

A treatment-emergent AE (TEAE) is defined as any event not present prior to the first administration of the study drug or any event already present that worsens in either severity or frequency following exposure to the study drug.

An AE which occurs prior to the first administration of the study drug will be considered a pre-treatment AE.

At several time points before and after drug administration, subjects will be asked non-leading questions to determine the occurrence of AEs. Subjects will be asked in general terms about any AEs at regular intervals during the study. In addition, all AEs reported spontaneously during the course of the study will be recorded.

All answers will be interpreted by the PI using the Medical Dictionary for Regulatory Activities (MedDRA; most recent version) for AEs and will be recorded in the eCRF.

The severity of the AEs will be rated by the PI as “Grade 1”, “Grade 2”, “Grade 3”, or “Grade 4”, and the relationship between the AEs and the study drug will be assessed by the PI as “certain”, “probable/likely”, “possible”, “unlikely”, “conditional/unclassified” or “unassessable/unclassifiable”. Details on the rating of the severity of the AEs and relationship to the study treatment are given in Appendix 9.2.

Additional details on AEs and information on SAEs and Suspected Unexpected Serious Adverse Reactions (SUSARs) are described in Appendix 9.2.

3.5.1.2.2 Clinical Laboratory

Blood and urine samples for clinical laboratory assessments will be collected according to PRA SOPs.

The following parameters will be measured:

- Clinical chemistry (serum quantitatively):
  total bilirubin, direct bilirubin (only if total is elevated), alkaline phosphatase, gamma glutamyl transferase (gamma-GT), AST, ALT, lactate dehydrogenase (LDH), creatinine, creatine kinase, troponin I (only if creatine kinase is elevated), urea, total protein, glucose, inorganic phosphate, sodium, potassium, calcium, chloride, magnesium, albumin and bicarbonate
- Hematology (blood quantitatively):
  leukocytes, erythrocytes, hemoglobin, hematocrit, thrombocytes, partial automated differentiation: lymphocytes, monocytes, eosinophils, basophils, neutrophils, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC)
- Urinalysis (urine qualitatively):
  hemoglobin, urobilinogen, ketones, glucose, protein, bilirubin, leukocytes, nitrite, pH, specific gravity
- Serology:
  HBsAg, anti-HCV and anti-HIV
- Urine drug and alcohol screen:
  opiates, methadone, cocaine, amphetamines (including ecstasy), cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants, phencyclidine and alcohol
- Pregnancy test (females only):
  β-human chorionic gonadotropin (β-hCG) in serum
- Hormones (serum quantitatively):
  FSH at screening and for females only

In case of unexplained or unexpected clinical laboratory test values, the tests will be repeated as soon as possible and followed up until the results have returned to the normal range and/or an adequate explanation for the abnormality is found. The clinical laboratory will clearly mark all laboratory test values that are outside the normal range and the PI will indicate which of these deviations are clinically significant. These clinically significant deviating laboratory results will then be recorded as AEs and the relationship to the treatment will be indicated (see also Appendix 9.2).

3.5.1.2.3 Vital Signs

Systolic and diastolic blood pressure and pulse will be recorded after the subject has been resting for at least 5 minutes in the supine position. These assessments will be made using an automated device. Tympanic body temperature will be measured subsequently.

If a subject shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality will be followed to resolution if required. Additional measurements may be taken as deemed necessary by the PI. Any clinically significant abnormality, including changes from baseline, must be reported as an AE.

3.5.1.2.4 Electrocardiogram

A standard 12-lead ECG will be recorded after the subject has been resting for at least 5 minutes in the supine position. Triplicate 12-lead ECGs will be recorded at some time points according to the schedules of assessments. Individual ECG measurements as part of a triplicate ECG will be recorded 1 minute (and no more than 2 minutes) apart. The ECG will be recorded using an ECG machine equipped with computer based interval measurements. The following ECG parameters will be recorded: heart rate, PR-interval, QRS-duration, QT-interval, QTc-interval (Bazett's and Fridericia's) and the interpretation of the ECG profile by the PI.

If a subject shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality will be followed to resolution if required. Additional measurements may be taken as deemed necessary by the PI. Any clinically significant abnormality, including changes from baseline, will be reported as an AE.

3.5.1.2.5 Physical Examination

Physical examination will be performed according to PRA SOPs. In addition, body weight and height will be measured according to PRA SOPs.

Any time the protocol indicates that a physical examination will be done, a complete physical examination is performed. The following will be examined: general appearance, skin/subcutaneous tissue, head, ears, nose and throat, neck and thyroid, thorax, lungs, cardiovascular examination, lymph nodes, abdomen, musculoskeletal examination, neurological examination. When a 'targeted' physical examination is required, subject symptoms dictate which systems should be evaluated.

3.5.1.3 Total of Blood Volume

Table 4 and Table 5 present the number and volume of blood samples and the total volume of blood that will be collected throughout the study per subject for Part 1 and Part 2, respectively.

Table 4 Number and Volume of Blood Samples and Total Blood Volume Collected per Subject for Part 1

Assessment	Maximum # samples	Volume of blood per sample (mL)	Total volume of blood (mL)
Pharmacokinetics			
- OZ439 in plasma	18	3	54
- [^{14}C]-OZ439 in plasma	17	8	136
- OZ439 metabolites	4	3	12
Clinical chemistry	5	3.5	17.5
Hematology	5	3	15
Serology	1	5	5
Total volume of blood drawn			**239.5**

Table 5 Number and Volume of Blood Samples and Total Blood Volume Collected per Subject for Part 2

Assessment	Maximum # samples	Volume of blood per sample (mL)	Total volume of blood (mL)
Pharmacokinetics			
- OZ439 in plasma	51	3	153
- Cobicistat in plasma	12	0*	0*
- OZ439 metabolites	4	3	12
Clinical chemistry	15	3.5	52.5
Hematology	15	3	45
Serology	1	5	5
Total volume of blood drawn			**267.5**

* No separate blood samples will be collected for cobicistat analysis. At the corresponding time points, blood collected for OZ439 analysis will also be used for cobicistat analysis. Details on sample collection, handling, storage and shipping will be described in a laboratory manual prepared by PRA.

3.5.2 Appropriateness of Measurements

The assessments, which will be made in this study are standard, and generally recognized as reliable, accurate and relevant.

3.5.2.1 Timing of Assessments

For PK blood sampling

The acceptable deviations from the nominal post-dose blood sampling times are as follows:

- The pre-dose blood sample will be taken ≤1 hour before dosing
- 0 to 1 hour post-dose samples will be taken within ± 2 minutes of the nominal post-dose sampling time
- >1 to 12 hours post-dose samples will be taken within ± 10 minutes of the nominal post-dose sampling time

- >12 hours to 24 hours post-dose samples will be taken within ± 30 minutes of the nominal post-dose sampling time if subjects are resident in the clinical research center
- >24 hours post-dose samples will be taken within ± 2 hours of the nominal post-dose sampling time if subjects are attending an ambulatory visit. Follow-up visits will be within ± 2 days.

Vital signs

The acceptable deviations from the nominal vital signs measurement time points are as follows:

- The pre-dose vital signs measurements will be taken ≤2 hours before dosing
- Post-dose vital signs measurements will be taken ± 15 minutes from the nominal post-dose time points
- For ambulatory visits vital signs measurements will be taken ± 2 hours from the nominal ambulatory visit time point.

ECG

The acceptable deviations from the nominal ECG measurement time points are as follows:

- The pre-dose ECG measurements will be taken ≤2 hours before dosing
- Post-dose ECG measurements will be taken ± 10 minutes from the nominal post-dose time points
- For ambulatory visits ECG measurements will be taken ± 2 hours from the nominal ambulatory visit time point

Clinical laboratory

The acceptable deviations from the nominal blood sampling time points for clinical laboratory assessments are as follows:

- Post-dose blood samples will be taken ± 1 hour from the nominal blood sampling time except when the time point coincides with the PK blood sampling time. In this situation, the time window for the PK blood sample applies.
- Post-dose urine samples will be taken ± 2 hours from the nominal urine sampling time

In the event assessments are planned for the same scheme time, the order of the assessments should be arranged in such a way that PK blood sampling will be done after the ECG and vital signs recordings have been conducted, with PK blood sampling exactly on time.

3.5.3 Pharmacokinetic, Safety and Exploratory Endpoints

3.5.3.1 Endpoints for Part 1

- Primary Endpoint
  - PK: absolute oral bioavailability (F_{po}) of OZ439
- Secondary Endpoints

- PK for iv administration of OZ439: V_d, 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: AEs, clinical laboratory, vital signs, ECG and physical examination

- Exploratory Endpoints
  - 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

3.5.3.2 Endpoints for Part 2

- Primary Endpoint
  - PK of OZ439: C_{max}, C_{168h}, AUC_{0-168h} and AUC_{0-inf}
- Secondary Endpoints
  - 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
- Exploratory Endpoint
  - Future OZ439 metabolites analysis may be performed

3.5.3.3 Pharmacokinetic Parameters

The PK parameters to be determined or calculated using non-compartmental analysis from the plasma concentration-time data for OZ439 and cobicistat include but are not limited to the parameters as given below. A complete list of PK parameters will be provided in the Statistical Analysis Plan (SAP).

Parts 1 and 2

C_{max}	Maximum observed plasma concentration
C_{168h}	Observed plasma concentration at 168 hours post-dose
t_{max}	Time to attain maximum observed plasma concentration
$t_{1/2}$	Terminal elimination half-life, calculated as $0.693/k_{el}$
AUC_{0-t}	Area under the plasma concentration-time curve up to time t, where t is the last point with concentrations above the lower limit of quantitation (LLOQ)
AUC_{0-168h}	Area under the plasma concentration-time curve over a dosing interval of 168 hours
AUC_{0-inf}	Area under the plasma concentration-time curve from time 0 to infinity calculated as: $AUC_{0-inf} = AUC_{0-t} + C_{last}/k_{el}$, where C_{last} is the last measurable plasma concentration
$\%AUC_{extra}$	Percentage of estimated part for the calculation of AUC_{0-inf} $([AUC_{0-inf}-AUC_{0-t}]/AUC_{0-inf})*100\%$
λ_z	Terminal elimination rate constant
CL/F	Apparent clearance

Part 1 only

CL	Total systemic clearance
V_d	Volume of distribution
F_{po}	Oral bioavailability

3.5.4 Drug Concentration Measurements

The analysis of OZ439 in plasma samples will be performed at Swiss BioQuant AG using a validated liquid chromatography with tandem mass spectrometry method (LC-MS/MS). The analysis of [^{14}C]-OZ439 in plasma samples will be performed at Xceleron using a validated LC-AMS method. The analysis of cobicistat in plasma samples will be performed at Swiss BioQuant AG using a validated LC-MS/MS method. The Bioanalytical Reports for the determinations will be included in the clinical study report (CSR).

3.6 Statistical Procedures and Determination of Sample Size

3.6.1 Analysis Sets

3.6.1.1 Safety Set

All subjects who have received at least 1 dose of OZ349.

3.6.1.2 Pharmacokinetic Set

All subjects who have received 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.

3.6.2 Statistical and Analytical Plan for Pharmacokinetic and Safety Evaluation

An SAP will be generated by the Biostatistics Department of PRA; the SAP will be finalized prior to database lock. Full details of the analysis to be performed will be included in the SAP.

Any deviation from the SAP will be reported in the Section “Changes in Planned Analysis” in the CSR.

3.6.2.1 Pharmacokinetic Evaluation

The PK parameters and their statistical evaluation will be included in the CSR of this study.

All data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form.

A statistical analysis will be performed on OZ439 PK parameters C_{max}, C_{168h}, $AUC_{0\text{-}168h}$ and $AUC_{0\text{-}inf}$. The PK parameters will undergo a natural logarithmic transformation and will be analyzed using analysis of variance (ANOVA) techniques. The ANOVA model will include treatment as a fixed effect. Adjusted geometric mean ratios (GMRs) and 90% CIs for the adjusted GMRs will be provided for the comparisons between:

- Treatment C vs Treatment D to assess the effect of cobicistat on OZ439

- Treatment A vs Treatment B to explore volume effect (for this no within-subject comparison is possible)
- Treatment B vs Treatment C to explore dosing solution concentration effect (dose normalized)

3.6.2.2 Evaluation of Safety and Tolerability

Safety and tolerability will be assessed through AEs, clinical laboratory, vital signs, ECGs and physical examination findings, and any other parameter that is relevant for safety assessment.

3.6.2.2.1 Adverse Events

A listing of all individual AEs will be provided. Summary tables of TEAEs will be presented by system organ class based on the MedDRA terminology list (preferred terms): 1 containing the number of TEAEs (frequency of occurrence, number of subjects experiencing the event) by treatment and 1 containing the number of drug-related TEAEs (frequency of occurrence, number of subjects experiencing the event) per treatment. Additional tables of total counts by treatment and relationship and by treatment and severity will be given.

3.6.2.2.2 Clinical Laboratory

Clinical laboratory data will be listed accompanied by an indication if the parameter is outside the reference range. A summary of all data outside the reference range of the clinical laboratory will be provided. Clinical laboratory data will be presented descriptively, where applicable.

3.6.2.2.3 Vital Signs and Electrocardiograms

Vital signs and ECG parameters will be listed and they will be presented descriptively, where applicable.

3.6.2.2.4 Physical Examination

Changes from baseline for physical examination will be described and listed.

3.6.3 Determination of Sample Size

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 all of the primary endpoints (C_{max}, C_{168h}, $AUC_{0\text{-}168h}$, and $AUC_{0\text{-}inf}$) for the 3 treatments.

3.7 Data Quality Assurance

The study may be audited by the Quality Assurance Department at PRA to assess adherence to the clinical study protocol (CSP) and Quality System. During the conduct of the study, process-related audits may be performed. An audit certificate will be provided in the appendices of the final CSR outlining any audits and other related activities performed.

The clinical research site will be monitored by the study monitor to ensure correct performance of the study procedures and assure that the study will be conducted according to the relevant regulatory requirements. The eCRF entries will be verified with the source documentation, if applicable (in some cases there are no source pages, therefore verification is not necessary).

Regulatory authorities, the Independent Ethics Committee (IEC) and/or the Sponsor's clinical quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the PI, who must provide support at all times for these activities.

Quality control principles will be applied throughout the performance of this study. Review procedures will be followed at PRA for all documents that are generated in relation with the study.

An explanation will be given for all missing, unused and spurious data in the relevant sections of the CSR.

4. ETHICS

4.1 Independent Ethics Committee

The CSP and the ICFs will be submitted for review and approval by IEC of the foundation "Beoordeling Ethiek Biomedisch Onderzoek" (English translation: "Evaluation of Ethics in Biomedical Research") (Stationsstraat 9, 9401 KV Assen, The Netherlands) prior to the eligibility screening. The composition of the IEC is in accordance with the recommendations of the WHO, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP)[11], and the European Union (EU) Clinical Trial Directive (CTD) (Directive 2001/20/EC)[12] (see below).

PRA will keep the IEC informed about the progress of the study. All changes in research activities and all unanticipated problems involving risks to human subjects will be immediately reported to the IEC. In accordance with Section 10, Subsection 1, of the Dutch law on Medical Research in Human Subjects (WMO, revised December 2015)[13], PRA will inform the subjects and the IEC if anything occurs on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal, or if further recruitment of subjects in the study has been put on hold for that reason, whichever occurs first. The study may be suspended pending further review by the IEC, except insofar as suspension would jeopardize the subjects' health. PRA will take care that all subjects are kept informed.

No changes will be made in the study without IEC approval, except when required to eliminate apparent immediate hazards to human subjects.

Before the study is initiated, the Sponsor will also obtain approval to conduct the study from the Competent Authority (CA) in The Netherlands.

Notification of the end of the study will be sent by PRA to the CA in The Netherlands and to the IEC within 90 days after completion of follow-up for the last subject. In case a study is temporarily halted, PRA will notify the IEC immediately, including the reason for this. In case a study is ended prematurely, PRA will notify the IEC and the CA in The Netherlands within 15 days, including the reasons for the premature termination. A summary of the results of the study will be sent by PRA to the CA and the IEC within 1 year after the end of the study (last patient last visit).

4.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and subsequent amendments.[14]

This study is also designed to comply with ICH E6 Guideline for GCP (CPMP/ICH/135/95)[11], and the EU CTD Directive 2001/20/EC[12], as incorporated into Dutch Law.[13]

ICH adopted guidelines and other relevant international guidelines, recommendations and requirements will be taken into account as comprehensively as possible, as long as they do not violate Dutch law.

The PI will be responsible for the care of the subjects throughout the study. If the PI is not present at the clinical site, he will leave instructions for the staff and a telephone number where he can be reached.

The PI will be responsible for the medical follow-up of the subjects.

If a subject refuses to follow the instructions of the PI, the latter is released from any legal responsibility.

4.3 Subject Information and Consent

All subjects will be informed verbally and in writing regarding the objectives, procedures and risks of study participation. The subjects will have to sign the Dutch or English version of the ICF before any study-related procedures are started. The ICF contains information about the objectives of the study, about the procedures followed during the study and about the risks and restrictions of the study, with special reference to possible side effects of the medication and potential interactions. In addition, insurance cover provided during the study is explained. The elements addressed in the ICF are according to the ICH E6 Guideline for GCP (CPMP/ICH/135/95).[11]

4.4 Privacy

All personal details will be treated as confidential by the PI and staff at PRA and handling of personal data will be in compliance with the Dutch Data Protection Act. Personal details are stored in databases that have been registered with the Dutch Data Protection Authority.

5. STUDY ADMINISTRATIVE STRUCTURE

5.1 Distribution of Activities

Preparation of study drug

OZ439 and [^{14}C]-OZ439 drug substance will be provided by the Sponsor. The OZ439 oral dispersions and the [^{14}C]-OZ439 iv solution for infusion will be manufactured by the PRA Pharmacy.

Laboratory assessments

The analysis of OZ439 and cobicistat in plasma samples will be performed at Swiss Bioquant AG. The analysis of [^{14}C]-OZ439 in plasma samples will be performed at Xceleron.

The analysis of clinical laboratory samples will be performed at the PRA Clinical Laboratory.

eCRF design

The eCRF design will be performed with the computer program Oracle Clinical (Oracle, Redwood Shores, Redwood City, CA, USA) by the Database Programming Department of PRA.

Data management

Data management will be performed with the computer programs Oracle Clinical (Oracle, Redwood Shores, Redwood City, CA, USA), SAS Enterprise Guide® (SAS Institute Inc., Cary, NC, USA) and EXACT (Kinship EXACT™, Kinship technologies, a technology subsidiary of PRA) by the Data Management Department of PRA.

Statistics

Randomization will be performed by the Biostatistics Department of PRA. An SAP will be provided by the Biostatistics Department of PRA. The safety analysis and the statistical evaluation of PK parameters will be conducted by the Biostatistics Department of PRA. Statistical analysis will be performed with the computer program SAS for Windows® (SAS Institute Inc., Cary, NC, USA).

CSR writing

The CSR, structured in accordance with the guideline 'Structure and Content of Clinical Study Reports - ICH E3'[15], will be written by PRA.

5.2 Documentation

5.2.1 Archiving

All documents concerning the study will be kept on file in the Central Archives of PRA for at least 15 years after conduct of the study. The Sponsor will receive the completed eCRFs (upon request, as PDF file).

5.2.2 Recording of Data in Source Documents and CRFs

Wherever possible, all data will be entered directly into the eCRFs. In some cases source documents will be used.

A Data Management Plan will be written by the Data Management Department of PRA, which will be finalized prior to performing any data validation. An appendix to the Data Management Plan (Source Identification List) will identify any data to be recorded directly in the eCRF (ie, no prior written or electronic record of data), and which data should be considered source data.

6. FINANCE AND INSURANCE

The Sponsor (Medicines for Malaria Venture [MMV]) has funded this study. A no-fault clinical trials insurance has been obtained by the Sponsor. The Sponsor insurance will compensate subjects in accordance with the Dutch law on Medical Research in Human Subjects (WMO, revised December 2015).[13]

7. CONFIDENTIALITY AND PUBLICATION POLICY

By signing this CSP, the PI reaffirms to the Sponsor that he will maintain in confidence all information furnished to him, or resulting from this study. The PI will only divulge such information as may be necessary to the IEC, the members of the staff and the subjects who are involved in this study.

All relevant aspects regarding publication will be part of the contract (or similar document) between the Sponsor and PRA.

8. REFERENCES

1. WHO World Malaria Report 2015a. WHO Global Malaria Programme. http://apps.who.int/iris/bitstream/10665/200018/1/9789241565158_eng.pdf?ua=1, accessed January 2016.
2. Ashley EA, White NJ. Artemisinin-based combinations. Curr Opin Infect Dis 2005; 18 (6): 531-6.
3. Bunnag D, Viravan C, Looareesuwan S, Karbwang J, Harinasuta T. Clinical trial of artesunate and artemether on multidrug resistant falciparum malaria in Thailand. A preliminary report. Southeast Asian J Trop Med Public Health 1991; 22 (3): 380-5.
4. Phyo AP, Jittamala P, Nosten FH et al. Antimalarial activity of artefenomel (OZ439), a novel synthetic antimalarial endoperoxide, in patients with Plasmodium falciparum and Plasmodium vivax malaria: an open-label phase 2 trial. Lancet Infect Dis 2016; 16 (1): 61-9.
5. Vennerstrom JL, Arbe-Barnes S, Brun R et al. Identification of an antimalarial synthetic trioxolane drug development candidate. Nature 2004; 430 (7002): 900-4.
6. Charman SA, Arbe-Barnes S, Bathurst IC et al. Synthetic ozonide drug candidate OZ439 offers new hope for a single-dose cure of uncomplicated malaria. Proc Natl Acad Sci U S A 2011; 108 (11): 4400-5.
7. Wells TN. Discovering and developing new medicines for malaria control and elimination. Infect Disord Drug Targets 2013; 13 (4): 292-302.
8. Investigator's Brochure of OZ439 (artefenomel), Edition 10, July 2016.
9. Mathias AA, German P, Murray BP et al. Pharmacokinetics and pharmacodynamics of GS-9350: a novel pharmacokinetic enhancer without anti-HIV activity. Clin Pharmacol Ther 2010; 87 (3): 322-9.
10. Addendum 1 to Investigator's Brochure of OZ439 (artefenomel), 10 October 2016.
11. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline, E6: Guideline for Good Clinical Practice (CPMP/ICH/135/95), January 1997.
12. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.
13. Medical Research in Human Subjects Act (WMO, Wet Medisch-Wetenschappelijk Onderzoek met mensen), revision December 2015.
14. WMA Declaration of Helsinki (18th WMA General Assembly 1964), revised at 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013.
15. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline, E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95), November 1995.

16. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline, E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Note for Guidance on Clinical Safety Data Management, June 1995.

9. APPENDICES

9.1 Drug Accountability

Upon receipt of the study drug, it will be inspected and counted by the responsible pharmacist. If necessary, all study drug will be re-packed per dosing occasion, and labeled according to PRA SOPs.

The study drug will be kept in the PRA Pharmacy or in a locked and secured storage facility accessible to the pharmacist and the pharmacy assistant only.

The responsible pharmacist will keep an inventory. This will include a description of the formulation and the quantity of study drug received for the study and a record of what is dispensed, to whom and when.

On termination of the study the responsible pharmacist will conduct a final inventory of the study drug supply and will record the results of this inventory in the Drug Accountability Form. Unused study drug will be returned to the Sponsor at the end of the study or will be locally destroyed according to PRA standard procedures.

9.2 Adverse Events and Serious Adverse Events Evaluation and Reporting

9.2.1 Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. AE definitions will be followed as stated in the 'Note for Guidance on clinical safety data management: definitions and standards for expedited reporting' (ICH topic E2A).[16]

All AEs reported by the subjects or apparent from their physical appearance during the clinical study will be reported on the AE eCRF page.

The severity of AEs will be graded using the WHO Recommendations for Grading Acute and Subacute Toxic Effects as given in Section 9.2.1.1.

9.2.1.1 WHO Recommendations for Grading Acute and Subacute Toxic Effects

WHO Recommendations for Grading Acute and Subacute Toxic Effects

Adaptation of *WHO Handbook for Reporting Results of Cancer Treatment*. WHO Offset Publication No. 48.
World Health Organization; Geneva, Switzerland. 1979:16–21.

Adverse Event Severity Table

WHO Recommendations for Grading Acute and Subacute Toxic Effects

Item	Grade 1	Grade 2	Grade 3	Grade 4
Hematology				
Hematocrit	≥28.5 to <31.5%	≥24 to <28.5%	≥19.5 to <24%	<19.5%
Hemoglobin	9.5–10.9 g/dL	8.0–9.4 g/dL	6.5–7.9 g/dL	<6.5 g/dL
Leukocytes	≥2500 to <4000/mm^3	≥1000 to <2500/mm^3	≥800 to <1000/mm^3	<800/mm^3
Absolute neutrophil count	≥1000 to <1500/mm^3	≥750 to <1000/mm^3	≥500 to <750/mm^3	<500/mm^3
Platelets	75,000–99,000/mm^3	50,000–74,999/mm^3	25,000–49,999/mm^3	<25,000/mm^3 or diffuse petechiae
Prothrombin time	1.01–1.25 × ULN	1.26–1.5 × ULN	1.51–3.0 × ULN	>3.0 × ULN
Partial thromboplastin time	1.01–1.66 × ULN	1.67–2.33 × ULN	2.34–3.0 × ULN	>3.0 × ULN
Fibrinogen	0.99–0.75 × LLN	0.74–0.50 × LLN	0.49–0.25 × LLN	<0.25 × LLN
Fibrin split product	20–40 μg/mL	41–50 μg/mL	51–60 μg/mL	>60 μg/mL
Methemoglobin	5.0–9.9%	10.0–14.9%	15.0–19.9%	≥20%
Chemistries				
Hyponatremia	130–132 mEq/L	123–129 mEq/L	116–122 mEq/L	≤115 mEq/L or mental status changes or seizures
Hypernatremia	148–150 mEq/L	151–157 mEq/L	158–165 mEq/L	>165 mEq/L or mental status changes or seizures
Hypokalemia	3.0–3.4 mEq/L	2.5–2.9 mEq/L or requires replacement Rx	2.0–2.4 mEq/L, or requires intensive replacement Rx or hospitalization	<2.0 mEq/L or paresis or ileus or life-threatening arrhythmias
Hyperkalemia	5.6–6.0 mEq/L	6.1–6.5 mEq/L	6.6–7.0 mEq/L	>7.0 mEq/L or paresis or ileus or life-threatening arrhythmias

LLN: lower limit of normal; ULN: upper limit of normal

WHO Recommendations for Grading Acute and Subacute Toxic Effects (cont'd)

Item	Grade 1	Grade 2	Grade 3	Grade 4
Chemistries (cont'd)				
Hypoglycemia	55–64 mg/dL	40–54 mg/dL	30–39 mg/dL	<30 mg/dL or mental status changes or coma
Hyperglycemia	116–160 mg/dL	161–250 mg/dL	251–500 mg/dL	>500 mg/dL or ketoacidosis or seizures
Hypertriglyceridemia	250–400 mg/dL	401–750 mg/dL	751–1250 mg/dL	>1250 mg/dL
Hyperuricemia				
13–18 yrs	9.1–12.0 mg/dL	12.1–14.0 mg/dL	14.1–17.0 mg/dL	>17.0 mg/dL
>18 yrs	9.6–9.9 mg/dL	10.0–12.0 mg/dL	12.1–15.0 mg/dL	>15.0 mg/dL
Hypocalcemia corrected for albumin	8.4–7.8 mg/dL	7.7–7.0 mg/dL	6.9–6.1 mg/dL	<6.1 mg/dL or life-threatening arrhythmias or tetany
Hypercalcemia corrected for albumin	10.6–11.5 mg/dL	11.6–12.5 mg/dL	12.6–13.5 mg/dL	>13.5 mg/dL or coma or cardiac arrhythmias
Hypomagnesemia	0.8–1.0 mEq/L	0.5–0.7 mEq/L or requires replacement Rx	0.3–0.4 mEq/L or requires intensive Rx involving hospitalization	<0.3 mEq/L or life-threatening arrhythmias
Hypophosphatemia	2.0–2.4 mg/dL	1.5–1.9 mg/dL or requires replacement Rx	1.0–1.4 mg/dL or requires intensive Rx involving hospitalization	<1.0 mg/dL or life-threatening arrhythmias or congestive heart failure
BUN	1.25–2.5 × ULN	2.6–4.9 × ULN	5.0–10.0 × ULN	>10 × ULN
Creatinine	1.1–1.5 × ULN	1.6–3.0 × ULN	3.1–6.0 × ULN	>6.0 × ULN or requires dialysis

BUN: blood urea nitrogen; ULN: upper limit of normal

WHO Recommendations for Grading Acute and Subacute Toxic Effects (cont'd)

Item	Grade 1	Grade 2	Grade 3	Grade 4
Chemistries (cont'd)				
Hypocarbia (bicarbonate)	19–21 mEq/L	15–18 mEq/L	10–14 mEq/L	<10 mEq/L
Hypercarbia (bicarbonate)	33–36 mEq/L	37–40 mEq/L	41–45 mEq/L	>45 mEq/L
Hypochloremia	90–93 mEq/L	85–89 mEq/L	80–84 mEq/L	<80 mEq/L
Hyperchloremia	113–116 mEq/L	117–120 mEq/L	121–125 mEq/L	>125 mEq/L
Enzymes				
Bilirubin	1.26–2.5 × ULN	2.6–5.0 × ULN	5.1–10.0 × ULN	>10.0 × ULN
AST/SGOT	1.26–2.5 × ULN	2.6–5.0 × ULN	5.1–10.0 × ULN	>10.0 × ULN
ALT/SGPT	1.26–2.5 × ULN	2.6–5.0 × ULN	5.1–10.0 × ULN	>10.0 × ULN
GGT	1.26–2.5 × ULN	2.6–5.0 × ULN	5.1–10.0 × ULN	>10.0 × ULN
Alkaline phosphatase	1.26–2.5 × ULN	2.6–5.0 × ULN	5.1–10.0 × ULN	>10.0 × ULN
Amylase	1.10–1.39 × ULN	1.40–2.09 × ULN	2.10–5.0 × ULN or mild clinical pancreatitis	>5.0 × ULN or severe clinical pancreatitis
Lipase	1.10–1.39 × ULN	1.40–2.09 × ULN	2.10–5.0 × ULN or mild clinical pancreatitis	>5.0 × ULN or severe clinical pancreatitis
CPK	2.0–3.0 × ULN	3.1–5.0 × ULN; mild myalgia	5.1–10.0 × ULN, or moderate or severe myalgia requiring nonsteroidals	>10.0 × ULN or severe myalgia requiring narcotics
LDH	1.10–1.39 × ULN	1.40–2.09 × ULN	2.10–5.0 × ULN	>5.0 × ULN
Urinalysis				
Proteinuria	≤3 g loss/day	>3–10 g loss/day	>10 g loss/day	Nephrotic syndrome
Hematuria	Microscopic only; ≤10 cells/HPF	Gross; no clots; 11–100 cells/HPF	Gross plus clots; ≥101 cells/HPF	Obstructive or requires catheterization

ALT: alanine aminotransferase; AST: aspartate aminotransferase CPK: creatine phosphokinase; GGT: gamma glutamyl transferase; LDH: lactate dehydrogenase; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; ULN: upper limit of normal

WHO Recommendations for Grading Acute and Subacute Toxic Effects (cont'd)

Item	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac				
Cardiac rhythm	_[a]	Asymptomatic, transient signs; no Rx required	Recurrent or persistent; no Rx required	Requires treatment
Hypertension	Transient; increase >20 mm; no Rx required	Recurrent; chronic >20 mm; Rx required	Requires outpatient care; requires acute Rx	Requires hospitalization
Hypotension	Transient orthostatic hypotension; no Rx required	Symptoms correctable with oral fluid Rx	Requires IV fluids; no hospitalization required	Requires hospitalization
Pericarditis	Asymptomatic effusion	Symptomatic; no tap required	Requires tamponade tap	Requires tamponade or surgery
Hemorrhage, blood loss	Microscopic or occult	Mild; no transfusion required	Gross; 1–2 units transfused	Massive; ≥3 units transfused
Respiratory				
Cough	Transient; no Rx required	Requires local nonnarcotic Rx	Requires narcotic Rx	Uncontrolled
Shortness of breath	Mild; does not interfere with routine activities	Moderate; interferes with routine activities; requires intermittent Rx	Moderate; debilitating; requires nasal oxygen	Severe; requires ventilatory assistance
Bronchospasm (acute)	Transient; FEV_1 or peak flow >70% NL; no Rx required	Normalizes with bronchodilator; FEV_1 or peak flow 49–70% NL; requires Rx	No normalization with bronchodilator; FEV_1 or peak flow 25–50% NL retractions	Cyanosis; FEV_1 or peak flow <25% NL; intubated
Gastrointestinal				
Stomatitis	Mild discomfort; no limits on activity	Some limits on eating or talking	Eating or talking very limited	Cannot drink fluids; requires IV fluids
Nausea	Mild discomfort; maintains reasonable intake	Moderate discomfort; significant decline of intake; some limit of activity	Severe discomfort; no significant food intake; activities limited	Minimal fluid intake

a: no criteria listed for this grade; IV:intravenous

WHO Recommendations for Grading Acute and Subacute Toxic Effects (cont'd)

Item	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal (cont'd)				
Vomiting	Transient emesis	Occasional or moderate vomiting	Orthostatic hypotension or requires IV fluids	Hypotensive shock; hospitalization; requires IV fluids
Constipation	Mild	Moderate; requires Rx	Severe; vomiting; requires Rx	Distension with vomiting
Diarrhea	Transient or nocturnal loose stools, or 3–4 loose stools/day, or both; requires Rx	5–7 loose stools/day or nocturnal loose stools, or both; requires Rx	Orthostatic hypotension of >7 loose stools/day or requiring IV fluids	Hypotensive shock or hospitalization for IV fluids
Abdominal pain	Mild; occasional, transient	Moderate; transient	Severe or requiring analgesic	Severe with guarding; peritoneal signs
Neuropsychological				
Level of consciousness	Mildly inattentive to outside stimuli	Drowsy, but readily responds to verbal or uncomfortable stimuli	Stuporous; can be aroused by vigorous stimuli, but verbal responses are slow or absent; can make some effort to avoid painful stimuli	Comatose; cannot be aroused by vigorous stimuli; makes no purposeful attempt to avoid painful stimuli
Confusion	Oriented to person, place, and time, but has difficulty performing tasks requiring logic, math, or spatial organization	Oriented to person and place, but not time; cannot perform complex tasks requiring logic or math	Oriented to person only; cannot focus attention or care for bodily needs	Delerious; not oriented to person, place, or time; agitated
Neurocerebellar	Slight incoordination; dysdiadokinesia	Intention tremor; dysmetria; slurred speech; nystagmus	Locomotor ataxia	Incapacitated
Mood	Mild anxiety or depression	Moderate anxiety or depression; requires therapy	Severe anxiety, depression, or mania (needs assistance)	Acute psychosis; incapacitated; requires hospitalization

IV: intraevous

WHO Recommendations for Grading Acute and Subacute Toxic Effects (cont'd)

Item	Grade 1	Grade 2	Grade 3	Grade 4
Neuromuscular				
Muscle strength	Subjective weakness; no objective symptoms or signs	Mild objective weakness; no decrease in function	Objective weakness; function limited	Paralysis
Painful neuropathy	Mild discomfort; no therapy required	Moderate discomfort persisting for >72 hours; requires analgesia	Severe discomfort; marked antalgic gait; requires narcotic analgesia with symptomatic improvement	Incapacitating, intolerable discomfort; not improved or cannot walk despite narcotic analgesics
"Pins & needles"	Mild; does not interfere with routine activities	Moderate; interferes with some ADL, but responds to symptomatic therapy	Severe; significantly impairs ability to perform ADL despite symptomatic therapy; interferes with patient's sleep	Very severe; incapacitates patient
Numbness	Mild decrease in sensation reported by patient, but pinprick and vibration exams are normal; does not interfere with ADL	Moderate decrease in sensation reported by patient; reduced pinprick and vibratory sensation on exam; interferes with some ADL, but responds to symptomatic therapy	Severely impaired sensation with inability to perceive pinprick or vibration; significantly impairs ability to perform ADL despite symptomatic therapy	Total lack of sensation on exam; incapacitates patient despite symptomatic therapy
Myalgias	Mild discomfort; no Rx required	Moderate discomfort persisting for >72 hours; requires analgesia	Severe discomfort; requires narcotic analgesia with symptomatic improvement	Severe discomfort not relieved by narcotic analgesia

ADL: activities of daily living

WHO Recommendations for Grading Acute and Subacute Toxic Effects (cont'd)

Item	Grade 1	Grade 2	Grade 3	Grade 4
Neuromuscular (cont'd)				
Myositis	Minimal findings	Patients must have some measures of myositis (positive EMG or muscle biopsy) and one of the following: 1. Mild to moderate myalgias; requires >4 weeks non-steroidal anti-inflammatory agents 2. Difficulty climbing stairs or rising from a sitting position, but can ambulate without assistance	Patients must have some measures of myositis (positive EMG or muscle biopsy) and one of the following: 1. Moderate or severe myalgias or muscle tenderness >4 weeks; requires non-steroidal anti-inflammatory agents 2. Requires some assistance with ambulation or general activities	Patients must have some measures of myositis (positive EMG or muscle biopsy) and one of the following: 1. Severe muscle pain (myalgias) unrelated to exercise; requires narcotics 2. Muscle weakness resulting in inability to ambulate; requires special care and assistance with mobilization 3. Acute rhabdo-myolysis with muscle necrosis and edema; moderate to severe muscle weakness resulting in inability to ambulate or mobilize self without assistance 4. Acute rhabdo-myolysis associated with electrolyte imbalance or renal failure

EMG: electromyography

WHO Recommendations for Grading Acute and Subacute Toxic Effects (cont'd)

Item	Grade 1	Grade 2	Grade 3	Grade 4
Other Parameters				
Fever (oral, without infection, >12 hours)	37.7–38.5 °C or 100.0–101.5 °F	38.6–39.5 °C or 101.6–102.9 °F	39.6–40.5 °C or 103.0–105.0 °F	>40.5 °C or >105.0 °F
Headache	Mild; no Rx required	Transient; requires moderate Rx	Severe; responds to initial narcotic therapy	Intractable; requires repeated narcotic therapy
Fatigue	No decrease in daily activities	Normal activity decreased 25–49%	Normal activity decreased 50%; cannot work	Cannot care for self
Allergic reaction	Pruritus without rash	Localized urticaria; angioedema	Generalized urticaria; angioedema	Anaphylaxis
Local reaction	Tenderness or erythema	Induration <10 cm or phlebitis or inflammation	Induration >10 cm or ulceration	Necrosis
Mucocutaneous	Erythema; pruritis	Diffuse, maculopapular rash; dry desquamation	Vesiculation; moist desquamation; ulceration	Exfoliative dermatitis, with suspected involvement of mucous membrane; Stevens-Johnson syndrome or erythema multiforme; necrosis requiring surgery
Alopecia	Minimal	Patchy	Complete, but reversible	Irreversible

For toxicities not listed above, grade as follows:

Intensity Grades:
1. Mild = does not interfere with routine activity
2. Moderate = interferes with performance of some activities of daily living (ADL), but responds to symptomatic therapy or rest
3. Severe = significantly limits ability to perform ADL despite symptomatic therapy
4. Very severe = incapacitates patient despite symptomatic therapy; requires hospitalization

If an AE has multiple aspects, the aspect with the highest severity will be graded.
It is emphasized that the term severe is a measure of severity; thus, a severe AE is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

In addition, clinically significant changes in physical examination findings and abnormal objective test findings (eg, laboratory, x-ray, ECG) should also be recorded as AEs. Test findings and physical examination findings can result in AEs if they:

- Are associated with accompanying symptoms, and/or
- Require additional diagnostic testing or medical/surgical intervention, and/or
- Lead to a change in study dosing or discontinuation from the study; result in the addition of significant additional concomitant drug treatment or other therapy, and/or
- Lead to any of the outcomes included in the definition of an SAE, and/or
- Are considered to be an AE by the PI or Sponsor.

Reporting as an AE should not be triggered by:

- Merely repeating an abnormal test or
- Any abnormal test result that is determined to be an error.

The relationship of any AE to the study drug will be assessed and graded on a 6-point scale: certain, probable/likely, possible, unlikely, conditional/unclassified, unassessable/unclassifiable.

Causality term	**Assessment criteria**
Certain	a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary
Probable/likely	a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition
Possible	a clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also

	be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear
Unlikely	a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations
Conditional/unclassified	a clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment, or the additional data is under examination
Unassessable/unclassifiable	a report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified

9.2.2 Serious Adverse Events

An SAE is any untoward medical occurrence that, on the basis of medical and scientific judgment:

- Results in death, or
- Is life-threatening (This refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), or
- Requires inpatient hospitalization for a medical reason or prolongation of existing hospitalization (This refers to hospital admission required for treatment of the AE). (Note: this does not include confinement in, for example, a respite unit; a skilled nursing unit; rehabilitation facility; the clinical research center; or confinement due to planned or unplanned reason unrelated to study), or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

SAEs will be collected from admission until the final study visit. SAEs that are related to the investigational drug and continue beyond the normal collection period (ie, are

ongoing at the time a subject exits the study) will be followed until resolution or until stabilized with sequelae. SAEs that begin after the subject's participation in the study is complete, but that the PI considers to be related to study drug, may be reported at any time.

The PI or clinical site personnel must notify the MMV Medical Monitor or his back-up, and to the pharmacovigilance provider (Quintiles LifeCycle Safety) of all SAEs, regardless of relationship to the investigational drug, within 24 hours of clinical site personnel becoming aware of the event. The PI will provide the initial notification by sending a completed "SAE Notification Form", which must include the PI's assessment of the relationship of the event to investigational drug, and must be signed by the PI.

In addition, notification is sent by PRA to the IEC, and the subject's General Practitioner.

Follow-up information, or new information regarding an ongoing SAE, must be provided promptly to the MMV Medical Monitor or his back-up, and to the pharmacovigilance provider (Quintiles LifeCycle Safety). The initial report will be followed up by a full written report within 3 working days or 5 calendar days, whichever comes first, unless no further information is available. A follow-up report and any subsequent reports will be provided as soon as possible when new information becomes available.

All SAE reports should be sent to the contacts provided on Page 3: SAE Contact Information.

All SAEs must be recorded and reported whether or not the PI considers the SAE to be related to the study drug. Photocopies of results, consultant report(s), a summary of the outcome of the reaction and the PI's opinion of study drug relationship to the SAE will accompany the SAE form if and when available.

9.2.3 Suspected Unexpected Serious Adverse Reactions

An SAE that is also an unexpected adverse drug reaction is called a SUSAR. Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (eg, IB for an unapproved investigational medicinal product or the Summary of Product Characteristics for an authorized medicinal product). It is the responsibility of the Sponsor to determine whether a reported SAE fits the classification of a SUSAR and to notify the PI of their decision as soon as possible.

The Sponsor's pharmacovigilance provoider (Quintiles LifeCycle Safety) will report expedited the following SUSARs to the IEC:

- SUSARs that have arisen in the current clinical study that was assessed by the IEC
- SUSARs that have arisen in other clinical studies of the same Sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the current clinical study that was assessed by the IEC

The Sponsor's pharmacovigilance provoider (Quintiles LifeCycle Safety) will report in an expedited manner all SUSARs to the CA and the Medicine Evaluation Board (MEB) of the country where this study is conducted and to the CAs in other Member States, as applicable.

SUSARs that have already been reported to the European Medicines Agency Eudravigilance database do not have to be reported again to the CA and the MEB because they have direct access to the Eudravigilance database.

It is the responsibility of the Sponsor to determine whether an event requires expedited reporting and to notify the PI of their decision as soon as possible. The expedited reporting will occur no later than 15 calendar days after the Sponsor or its representative has first knowledge of the adverse reactions. For fatal or life-threatening cases the term will be maximally 7 calendar days for a preliminary report with another 8 days for completion of the report.

SUSARs must be recorded and reported whether or not the PI considers the SUSAR to be related to the study drug.

9.2.4 Follow-up of Adverse Events

Follow-up of AEs will continue until resolution, stabilization or death. In case of ongoing AEs at the moment of database closure, the data obtained at the moment of database closure will be used in the statistical analysis. The follow-up of the AE will be documented in the source documents and will be described in the final CSR only if considered relevant by the PI.