STATISTICAL ANALYSIS PLAN

A two-part, Phase 1 study to assess the safety, tolerability, and pharmacokinetic profile of ascending single doses of MMV533, including a pilot food evaluation in healthy participants

Protocol No.: MMV-MMV533_19_01

Product Codes: MMV533

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CHANGES TO SAP

The original SAP was Version 1.0, 9 June 2021 and was approved and signed by MMV and SSR.

The amendments made are:

Details of Amendment	Reason for Amendment
Definition for summary table columns. Change Fasting/ Fed to Fasted/Fed	Label as in protocol
Add time points for visit tabulations: Day 14/ Day 35 and Day 21/ Day 42	Visits are in protocol
Adverse Events starting prior to drug administration are considered Medical History	Definition as per protocol
Added Protocol deviations before Drug administration as occurring during screening period	As per protocol and CRF
Deleted Eligibility listing section	Screening failures not recorded in CRF
Added only IMP related TEAE tables and Procedure related TEAE	As per protocol

SAP APPROVAL

By my signature, I confirm that this SAP has been reviewed and has been approved for use on the MMV-MMV533_19_01 study:

Name	Title / Company	Signature	Date
Denis Gossen	Clinical Science Lead / MMV	Denis Gossen (Signature) Digitally signed by Denis Gossen (Signature) Date: 2022.11.22 09:45:12 +01'00'	
Stephan Chalon	VP - Experimental Med. / MMV	Stephan Chalon	21 Nov 2022
Locadiah Kuwanda	Manager, Statistics / Southern Star Research	Locadiah Kuwanda Electronically signed by: Locadiah Kuwanda Reason: I have authored this document. Date: Nov 23, 2022 12:16 GMT+11	23-Nov-2022

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ABBREVIATIONS

ADaM	Analysis Data Model
ADME	Absorption, distribution, metabolism and excretion
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
β-HCG	β-Human Chorionic Gonadotropin
BDI	Beck Depression Inventory
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CK	Creatine Kinase
CRA	Clinical Research Associate
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DME/T	Drug metabolism enzymes and drug transporters
DTS	Data Transfer Specification
ECG	Electrocardiography
eCRF	Electronic Case Report Form
EDC	Electronic Data capture
EOS	End of Study
FAS	Full Analysis Set
FSH	Follicular Stimulating Hormone
fTBA	Fasting Total Bile Acids
GGT	Gamma Glutamyl Transpeptidase
HBsAg	Hepatitis B Surface Antigen
HDL	High Density Lipoprotein
HEENT	Head, Eyes, Ears, Nose, Throat
HIV	Human Immunodefiniciency Virus
HR	Heart Rate
IMP	Investigational Medicinal Product
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LPLV	Last Participant Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamics
PK	Pharmacokinetics
PN	Preferred Name
PT	Preferred Term
QTcB	Corrected QT interval with Bazett's Formula
QTcF	Corrected QT interval with Fridericia's Formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SBQ	Swiss BioQuant Central
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
SSR	Southern Star Research
TEAE	Treatment Emergent Adverse Event
WHODRL	World Health Organization-Drug Reference List

1 INTRODUCTION

This Statistical Analysis Plan (SAP) provides the outline for the statistical analysis deliverables required for the MMV-MMV533_19_01 study.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. In addition, post hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

Any significant changes from planned analyses will also be described in the final CSR.

A separate pharmacokinetic (PK) analysis plan will be prepared to detail the PK related analyses.

2 PROJECT OVERVIEW

2.1 Study Design

This is a phase 1, single -centre study in 2 parts.

2.1.1 Part 1

Part 1 is a double-blind, randomized, placebo-controlled, sequential ascending single dose study in healthy adult participants, consisting of 7 cohorts. Up to 1 additional cohort may be considered if needed according to the observed safety, tolerability, and pharmacokinetics results.

Up to 64 participants will be enrolled within a 28 day screening period to ensure participants meet all the inclusion criteria and none of the exclusion criteria, with 8 participants per cohort for 7 scheduled cohorts (6 receiving MMV533 and 2 receiving placebo), and up to 1 optional cohort (6 participants receiving MMV533 and 2 receiving placebo). Participants will be admitted to the clinical unit on Day -1 for confinement, and randomised to be administered a single dose of MMV533 or placebo on Day 1. After confinement for at least 96 hours after IMP administration for safety assessments and collection of PK samples, participants will attend subsequent outpatient visits for safety assessments and PK sampling. The End of Study Visit (EOS) will be conducted on Day 28.

A sentinel dosing strategy will be implemented at each dose level to ensure the best conditions of safety. Each cohort will be divided into 2 subgroups. The first group (sentinel cohort) will include 2 participants that will be dosed on the first day, with 1 participant receiving MMV533 and 1 participant receiving placebo. The blinded safety and tolerability data (including, but not limited to: AEs, vital signs, 12-lead ECG, and available clinical laboratory safety tests) from the sentinel cohort up to and including 96 hours post-dose will be reviewed by the Principal Investigator, the study Medical Monitor and the Sponsor's Medical Director. Following a satisfactory safety review, dosing of the remaining participants in the cohort (Rest of Cohort) may proceed.

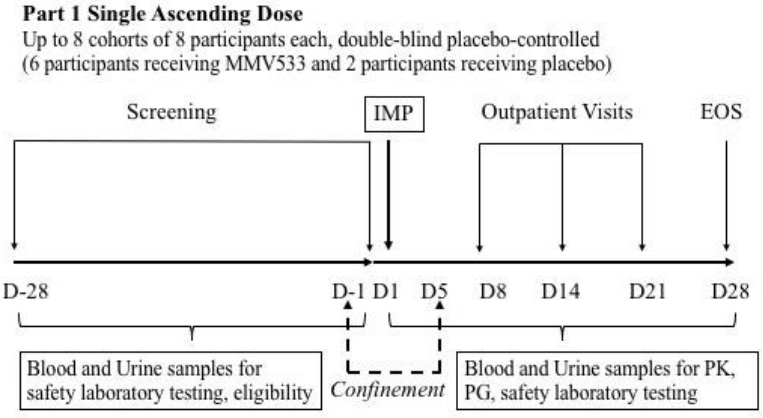

Figure 1: Part 1 Schema

2.1.2 Part 2

Part 2 is an open label, 2-period cross-over, randomised, pilot food effect study to provide preliminary information on the effect of a high-fat meal on the pharmacokinetics of a single-dose oral administration of MMV533 to healthy male and female participants aged between 18-55 years old.

Part 2 may be conducted in parallel to or after completion of Part 1 at the discretion of the Safety Review Committee (SRC). The dose will be selected by the SRC based on PK and safety results obtained in Part 1 and also taking into account the human efficacious dose/exposure predicted from preclinical efficacy studies in rodent malaria models. The dose will be at least 3-fold less than a dose that was determined to be safe in Part 1 in order to cover for a possible increased exposure when the drug is given in a fed state. Part 2 will consist of a single cohort of 8 participants. Participants will be enrolled within a 28 day screening period to ensure participants meet all the inclusion criteria and none of the exclusion criteria. Participants will be admitted to the clinical unit on Day -1 for confinement.

Participants will be randomised to receive initial MMV533 dosing on Day 1 in either a fasted or fed condition in a 1:1 ratio (Period 1). After a wash-out time of 21 days, the participants will cross over to the opposite fed or fasted condition (Period 2). For Period 2, participants will be admitted to the clinical unit 1 day prior to the second MMV533 dose on Day 22. For both periods of the study, participants will be confined within the clinical unit for 96 hours after MMV533 administration for safety assessments and blood sampling for PK analysis. Visits to the clinical unit will then occur on an outpatient basis until the End of Study visit on Day 42. The wash-out time of 21 days between the two periods will be confirmed based on the elimination half-life of MMV533 observed in Part 1 of the study. If the elimination half-life of MMV533 is substantially different than that predicted from the preclinical data, the wash-out period and timing of assessments for Part 2 may be adjusted accordingly by ensuring a minimum of 5 half-lives (5x t½) between the two periods. This will be decided by the SRC before Part 2 commences.

Fasted condition

Participants will be administered a single dose of MMV533 after an overnight fast of at least 10 hours.

Fed condition

Participants will consume a high-fat meal after an overnight fast of at least 10 hours. The high-fat meal will consist of an FDA-type high fat and high calorie breakfast. A single oral dose MMV533 will be administered 30 minutes after the start of the meal; participants will be required to consume the whole meal prior to dosing.

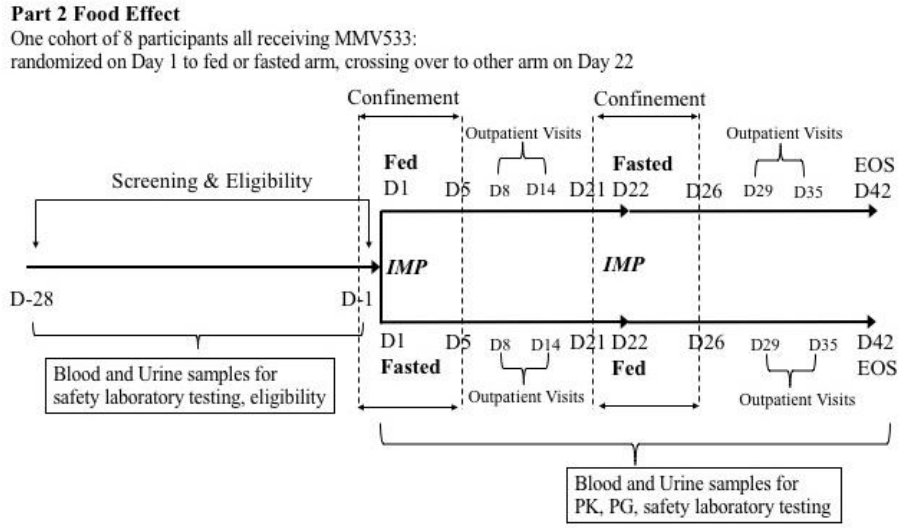

Figure 2: Part 2 Schema

2.2 Sample Size

2.2.1 Part 1 (SAD)

Up to 64 participants: 7 groups (7 incremental doses) with 8 participants each with one additional optional cohort of 8 participants (6 participants receiving MMV533 and 2 participants receiving placebo in each cohort).

2.2.2 Part 2 (Pilot food effect)

1 cohort of 8 participants all receiving MMV533 (same dose for all the participants).

2.3 Treatment Assignment and Randomization

Randomisation procedures for Parts 1 and 2 are described in the Randomisation Plan and Randomisation Procedure. A randomisation number will be allocated to each participants as per the randomisation schedule.

Part 1: Eligible participants in Part 1 will be randomised on Day 1 to be administered either MMV533 or placebo in a ratio of 3:1 overall (a ratio of 1:1 in the sentinel group and 5:1 in the rest of the cohort). Randomisation will be double-blind.

Part 2: This part of the study is open-label, but eligible participants in Part 2 will be randomised on Day 1 to either the fed or fasted arm for Period 1 in a ratio of 1:1. On Day 22, the participants will cross over to the opposite arm.

2.3.1 Replacement of Withdrawn/Discontinued Participants

For each cohort, eligible additional participants may be available as back-up replacements, in the event planned cohort participants withdraw or are withdrawn prior to IMP administration.

2.4 Study Objectives and Endpoints

Primary Objective	Primary Endpoints
• The tolerability and safety of ascending single oral doses of MMV533	• Assessment of adverse events (AEs) /treatment-emergent adverse events (TEAEs) (treatment phase for Part 1 and 2 defined as from IMP administration up to and including EOS). • Clinical laboratory evaluations including hematology, biochemistry, and urinalysis. • Vital signs (blood pressure and heart rate supine and standing, respiratory rate and body temperature), • 12-lead triplicate ECG: triplicate ECGs with central ECG reading from Day 1 pre-dose up to and including 96 hours post-IMP administration, and single ECGs at all subsequent timepoints: RR, heart rate (HR), PR, QRS, QT, QTcB and QTcF. Overall assessment as normal, abnormal not clinically significant, or abnormal clinically significant.
Secondary Objectives	**Secondary Endpoints**
• To characterize the pharmacokinetic (PK) parameters of parent drug and major metabolites after single oral doses of MMV533	Pharmacokinetic of MMV533: • Plasma parameters: at least but not limited to C_{max}, t_{max}, t_{lag}, AUC_{last}, AUC_{inf}, $t_{1/2}$, $C_{L/F}$, V_d/F Pharmacokinetics of major metabolites (if applicable): • Plasma parameters: at least C_{max}, t_{max}, AUC_{last}, AUC
• To obtain preliminary information on the effect of a high-fat meal on the PK of MMV533	Comparison of MMV533 PK parameters (as outlined above) between fed and fasting doses
Exploratory Objectives	**Exploratory Endpoints**
• To explore the excretion of MMV533 in urine	• Exploratory Urine parameters: Ae_{0-t}, fe_{0-t} and CLR_{0-t}.
• To perform genotyping of CYP450 and/or Transporter genes related to drug absorption, distribution, metabolism and excretion in the event of specific circumstances including abnormal or unexpected PK or safety results (to be decided when all data available after last patient last visit [LPLV]).	• Investigation of allelic variants related to drug metabolism enzymes and drug transporters (DME/T) potentially involved in the absorption, distribution, metabolism and excretion (ADME) of MMV533.

3 STATISTICAL CONSIDERATIONS

Data analysis will be performed according to Southern Star Research's Standard Operating Procedures (SOPs).

The general analytical approach for all safety endpoints will be descriptive in nature. Unless otherwise stated, the following statistical approaches will be taken:

Continuous variables:	Descriptive statistics will include the number of non-missing values, mean, standard deviation (SD), median, minimum, and maximum. The minimum and maximum values will be presented to the same number of decimal places as recorded in the raw data; mean, median and SD will be presented to one more decimal place than the raw data.
Categorical variables:	Descriptive statistics will include frequency counts and percentages per category. Percentages will be rounded to one decimal place, with the denominator being the number of participants in the relevant population with non-missing data.
Imputation:	No missing data will be imputed.
Confidence intervals (CIs):	If required, CIs will be two sided and will use 95% confidence levels. Any analyses requiring significance testing will use a two-sided test at the 5% significance level.
Unscheduled assessments:	Unscheduled visits will be excluded from visit-based summary tables.
Early termination visits:	Assessments conducted at Early Termination will be excluded from visit-based summary tables.

3.1 Data Capture

3.1.1 Database

The primary method of data collection is via the study database, developed within the chosen Electronic Data Capture (EDC) platform, IBM Clinical Development. The database has been designed based on the final protocol, the system/core configuration, electronic Case Report Form (eCRF) specifications and/or mock eCRF and consistency check specifications.

Data will be entered directly into the EDC system. Site-collected data will be entered directly from source notes at the site and will be verified by Clinical Research Associates (CRAs) to ensure data integrity.

Refer to the Data Management Plan for further details.

3.1.2 Third Party Data

3.1.2.1 Safety Laboratory (ACL, Australia)

Central safety laboratory data will be received from ACL as specified in the ACL Data Transfer Specification (DTS). An initial transfer will be delivered prior to database lock and reconciled against CRF data. Following successful reconciliation and resolution of any data issues, the data will be incorporated into the End of Study analysis.

No unit conversion of laboratory data will be performed.

3.1.2.2 Central ECG Data (Cardiabase - Banook, France)

Whilst single standard 12-lead ECG results will be recorded directly in the eCRF, triplicate ECG readings will be sent to a central ECG laboratory for assessment. Central ECG data will be transferred to SSR as specified in the relevant DTS.

3.1.2.3 PK Laboratory (SBQ, Switzerland)

PK samples will be analysed by Swiss BioQuant Central (SBQ). Final PK assay data will be transferred to SSR, as specified in the SBQ DTS, for incorporation into the PC SDTM.

3.1.2.4 PK Analysis

PK analysis will be performed by a third party, to be confirmed by MMV. SSR will be required to provide the selected vendor(s) with PK concentration data as well as any CRF datasets required by the vendor ro complete their analyses (e.g. demographics, drug administration data).

3.2 Statistical Programming

3.2.1 Programming Specifications

Programming specifications will be prepared to detail the SAS programming of CDISC (SDTM and ADaM) datasets and listings, tables and figures.

3.2.2 Baseline

Baseline will be defined as the last available assessment prior to the first IMP administration. For part 2, baseline will be assigned separately for the two treatment periods.

3.2.3 Change from Baseline

Change from Baseline will be calculated as:

Part 1: $change\ from\ baseline = (postbaseline\ value) - baseline\ value$

Part 2, Period 1: $change\ from\ baseline = (postbaseline\ value) - period\ 1\ baseline\ value$

Part 2, Period 2: $change\ from\ baseline = (postbaseline\ value) - period\ 2\ baseline\ value$

3.2.4 Study Day

Study Day will be derived as the number of days relative to date of first administration of study drug, where the day of first administration = 1.

3.2.5 Listings, Tables and Figures

Listings, tables and figures will be delivered as individual .rtf files in accordance with the mock listings, tables and figures, with separate sets of outputs for each study part.

Data listings will present all data, with subjects grouped by treatment regimen (part 1) or treatment sequence (part 2).

3.2.6 Treatment Groups – Part 1

Tabulations for part 1 will summarise data by the following treatment groups:

- MMV 533 (5 mg)
- MMV 533 (xx mg)
- MMV 533 (xx mg)
- MMV 533 (xx mg)
- MMV 533 (xx mg)
- MMV 533 (xx mg)
- MMV 533 (xx mg)
- Total Active
- Placebo
- Overall

3.2.7 Treatment Groups – Part 2

Tabulations for part 2 will summarise data as follows:

- Demographics and baseline characteristic data, will be summarised by:
  - MMV533 Fasted/Fed
  - MMV533 Fed/Fasted
  - Total
- Visit based tabulations will be summarised by treatment received (MMV533 Fasted or MMV533 Fed) and total, and timepoint relative to within period dosing. Treatment will be assigned to individual records based on the treatment period. Timepoints will be:
  - Screening (summarised as total only)
  - Day -1 (summarised as total only)
  - Day 1/Day 22 (combination of Day 1 and Day 22, summarised by treatment)
  - Day 2/Day 23 (combination of Day 2 and Day 23, summarised by treatment)
  - Day 3/Day 24 (combination of Day 3 and Day 24, summarised by treatment)
  - Day 4/Day 25 (combination of Day 4 and Day 25, summarised by treatment)
  - Day 5/Day 26 (combination of Day 4 and Day 26, summarised by treatment)
  - Day 8/Day 29 (combination of Day 8 and Day 29, summarised by treatment)
  - Day 14/Day 35 (combination of Day 14 and Day 35, summarised by treatment)
  - Day 21/Day 42 (combination of Day 21 and Day 42, summarised by treatment)

- Event based tabulations (e.g. adverse events, concomitant medications and deviations) will be summarised by treatment and total. Treatment will be assigned to individual records based on the treatment period of the start date of the event.
  - Adverse Events:
    - Events started prior to the Day 1 study drug administration will only be considered as Medical History.
    - If start date is after Day 1 study drug administration, then it will be assigned to the treatment received in Period 1.
    - If start date is after the Day 22 study drug administration, then it will be assigned to the treatment received in Period 2.
  - Protocol Deviations:
    - If date is before Day 1 then it will be assigned to Screening
    - If date of deviation is after Day 1 study drug administration,then it will be assigned to the treatment received in Period 1.
    - If start date is after the Day 22 study drug administration, then it will be assigned to the treatment received Period 2.
  - Prior Medications:
    - Summarised by treatment sequence and total.
  - Concomitant Medications:
    - Based on start and end dates – if subject was on medication within a given period then that medication will be summarised within that period. If subject took medication across both periods then it would be counted in both treatment columns.
- Treatment Exposure will be summarised by sequence and total

4 ANALYSIS SETS

In the first instance, two (2) analysis sets will be used for the analyses: Full Analyses Set (FAS), and Safety Set.

The number of participants in each analysis set will be summarised, with a corresponding listing.

4.1 Analysis Set Descriptions

4.1.1 Full Analysis Set

The Full Analysis Set (FAS) will consist of all enrolled participants. The FAS will be used to assess all participant disposition, baseline, demographic and protocol deviation data.

4.1.2 Safety Set

The Safety Set will include all enrolled participants who received at least one dose (full or partial) of IMP. The Safety Set will be used to assess all safety data.

5 PARTICIPANT DISPOSITION

5.1 Disposition

Analysis Set: FAS

A listing of participant disposition will present:

- Date of informed consent
- Date of randomisation
- Date of first dose of IMP administration
- Did the participant complete the study?
- Date of completion / early withdrawal
- Primary reason for early withdrawal (including instances where early termination was related to COVID-19)

Detailed early withdrawal information will also be listed in a separate listing.

If there are any deaths reported, a separate death listing will be prepared.

The number and percentage of participants entering and discontinuing the study will be summarised along with the reason for discontinuation. The participant disposition summary table will include:

- Number of participants randomised
- Number of participants who received one dose (Part 1) or at least one dose (Part 2) of study medication
- Number of participants who completed the full study
- Number of participants withdrawn from the study early
- Reason for early withdrawal

5.2 Clinical Trial Unit Admission, Confinement and Discharge

All admission, confinement and discharge data will be listed.

6 PROTOCOL DEVIATIONS

Analysis Set: FAS

All protocol deviations will be listed. A protocol deviation summary table will present the total number of protocol deviations as well as the number of participants who reported at least one protocol deviation, broken down by deviation classification and type.

6.1.1 Definition of variables

- Date deviation detected
- Date of deviation
- Deviation classification
    - Minor
    - Major
- Deviation type
    - Informed consent
    - Eligibility
    - Visit not done
    - Visit performed out of window
    - Assessment not done
    - Assessment out of window
    - Safety reporting
    - Investigational Product
    - Privacy and Data Protection
    - Prohibited Medication
    - Standardised meal not completed
    - Blood collected not under fasting condition
    - COVID 19
    - Other
- Deviation description
- Preventative action taken

7 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Analysis Set: FAS

7.1 Demographics

Demographic data will be listed for all enrolled participants and summarised by treatment arm and overall. Data includes:

- Age
- Sex
- Race
- Ethnicity
- Women of Child-bearing potential

7.2 Medical and surgical history

All medical history data will be listed, grouped by participant.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedRA) and summarised by system organ class (SOC) and preferred term (PT).

7.3 Prior Medications

Prior medications will be coded using the World Health Organization-Drug Reference List (WHODRL), the version of which will be included in the footnote of the listing.

Prior medications will be listed for all enrolled participants. Prior medications are defined as any medication that is started before administration of IMP, regardless of when it ended. If a medication has a missing or partial missing start/end date or time and it cannot be determined whether it was taken before IMP or concomitantly, it will be considered as prior and concomitant.

7.4 Eligibility

Eligibility will be listed for all enrolled participants.

7.5 Drug Screen

Drug screen data will be listed for all participants.

7.6 Alcohol Screen

Alcohol screening data will be listed for all participants.

7.7 Beck Depression Inventory

Beck Depression Inventory (BDI-II) data will be listed for all participants, including answers to the individual questions as well as the total scores, which are auto-calculated within the CRF.

8 TREATMENT EXPOSURE

Analysis Set: Safety Set

8.1 Study Drug Administration

Participant exposure to all protocol-specified treatments will be listed and summarised.

8.2 Standardised Breakfast

Meal data for the standardised high fat breakfast provided for the fed treatment during part 2, will be listed for all part 2 participants.

9 PHARMACOKINETICS

PK parameters will be estimated using non-compartmental methods from plasma concentration-time data. Refer to the PK Analysis Plan, Appendix 1, as prepared by SBQ. A formal analysis report will be prepared at the completion of the work and included in the CSR appendices.

Dose-proportionality analyses will also be conducted. Please refer to the Dose Proportionality Analysis Plan. An analysis report will be prepared at the completion of the work and will be included in the CSR appendices.

10 PHARMACODYNAMICS

Not applicable

11 SAFETY

11.1 Safety Endpoints

Safety and tolerability will be assessed by clinical review of the following parameters:

- AEs (including SAEs and AESIs)
- Vital signs
- 12-lead ECG
- Haematology, chemistry (including fasting Total Bile Acids [fTBA]), urinalysis
- Physical examination

All descriptive statistics for safety parameters will be evaluated using the Safety Set.

11.2 Adverse Events

11.2.1 Definitions

- Treatment Emergent Adverse Event (TEAE)
    - A TEAE is defined as an AE that commences on, or after, the first administration of IMP. AEs without an onset date or time will be defined as treatment emergent except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to first administration of IMP, or if the AE stop date indicates that the event started and/or stopped prior to the first administration of IMP.
- Adverse Events of Special Interest (AESI)
    - Adverse Events of Special Interest (AESIs) may be serious or non-serious, and are defined by the Sponsor as being of specific scientific and/or medical concern to the Sponsor's product or programme.

11.2.2 Parameters

- Event Term
- Dates and times of onset and resolution
- Severity (CTCAE Grades 1 to 5)
- Outcome (Recovered/resolved, Recovering/resolving, Not recovered/not resolved, Recovered/resolved with sequelae, Fatal, Unknown)
- Relationship of AE to Investigational medicinal product (Not Related, Related)
- Relationship of AE to Trial Procedures (Not Related, Related)
- Action taken with Investigational medicinal product (Permanently discontinued, No action taken, Not applicable, Unknown)
- Other actions taken (including withdrawal from the study)
- Seriousness (and Serious Adverse Event (SAE) category)
- AESI status (Yes/No)
- Relatedness to COVID-19

Derived parameters:

- Duration in hours
- Time of onset relative to first IMP administration

11.2.3 Biostatistical methods

Adverse events will be coded using MedDRA, and the MedDRA version will be included in the footnote of all AE listings and tables. Their severity will be graded according NCI-CTCAE v5.0.

11.2.3.1 Listings

All AE data will be listed for each participant, including severity, relationship to IMP, relationship to study procedures, outcome and actions taken. In addition, listings of AEs leading to discontinuation of the study, SAEs and deaths, will be provided as applicable.

11.2.3.2 Tables

AE summary tabulations will be restricted to TEAEs only.

All reported TEAEs, including SAEs and AESIs, will be mapped to standard MedDRA coding terms and grouped by SOC and PT.

An **overview summary table** of AEs will be provided by treatment arm including:

- Number of events and number of participants reporting at least one of the following:
    - TEAE
    - IMP related TEAE
    - Procedure related TEAE
    - Serious TEAE
    - IMP related serious TEAE
    - Procedure related serious TEAE
- Number of participants with at least one TEAE by maximum severity
- Number of TEAEs by relationship to IMP
- Number of TEAEs by relationship to procedure
- Number of participants withdrawn from the study due to a TEAE
- Number of deaths

An duplicate overview summary table will also be presented specifically for the AESIs.

The number of events, as well as the number and percentage of participants experiencing a TEAE, will be summarised for each SOC and PT by treatment arm and overall for the following categories of events:

- All TEAEs
- TEAEs by severity
- TEAEs by relationship
- Serious TEAEs
- TEAEs leading to study discontinuation
- TEAEs of Special Interest (AESIs)

For the summaries of TEAEs, participants who experience the same AE (in terms of the MedDRA preferred term) more than once will only be counted once.

11.3 Concomitant Medications

Concomitant medications will be coded using the WHODRL, the version of which will be included in the footnote of all relevant listings and tables

Concomitant medications are defined as medications continued or newly received at or after administration of IMP, through to the End of Study visit. If a medication has a missing or partial missing start/end date or time and it cannot be determined whether it was taken before initial treatment or concomitantly, it will be considered as prior and concomitant.

Concomitant medications will be summarised by Anatomical Therapeutic Class (ATC) level 3 and preferred name (PN). The summary tables will show the number and percentage of participants taking each medication by ATC and PN.

Participants who take the same medication (in terms of the ATC and PN) more than once will only be counted once for that medication.

11.4 Laboratory

11.4.1 Parameters

11.4.1.1 Haematology

- Basophils (absolute)
- Eosinophils (absolute)
- Haematocrit
- Haemoglobin
- Lymphocytes (absolute)
- Monocytes (absolute)
- Neutrophils (absolute)
- Platelet count
- Red cell count
- White cell count

1.1.1.1 *Biochemistry*

- Alanine Aminotransferase (ALT)
- Albumin
- Alkaline phosphatase (ALP)
- Aspartate Aminotransferase (AST)
- Bilirubin (direct)
- Bilirubin (total)
- Chloride
- Cholesterol
- Corrected calcium
- Creatinine
- Creatine Kinase (CK)
- Gamma Glutamyl Transpeptidase (GGT)
- Glucose
- Lactate dehydrogenase (LDH)
- Magnesium
- Potassium
- Protein Total
- Sodium
- Fasting - Total Bile Acids (fTBA)
- Triglyceride
- Urea

Pregnancy Test and FSH

- β-Human Chorionic Gonadotropin (β-HCG) (women of child bearing potential only)
- Follicular Stimulating Hormone (FSH) (post-menopausal women only)

1.1.1.1 *Urinalysis*

Dipstick Testing	***Quantitative Assessments***	***Urine Chemistry***
• Bilirubin • Blood (erythrocytes) • Glucose • Ketone bodies • Leucocyte Esterase • Nitrate • Protein • Urobilinogen • pH	• Red blood cells • White blood cells • Bacteria • Budding yeasts	• Glucose • Protein • Protein:Creatinine Ratio

11.4.1.2 Coagulation

- INR
- Activated partial thromboplastin time (APTT)

11.4.1.3 Serology

- Hepatitis B Surface Antigen (HBsAg)
- Anti-HBc Antibody
- Hepatitis C Antibody (anti-HCV)
- Human Immunodefiniciency Virus (HIV) 1/2 (anti-HIV1 and anti-HIV2 Ab)

11.4.2 Biostatistical methods

1.1.1.2 *Listings*

All laboratory parameters will be listed with flags for values outside the reference ranges and values considered to be clinically significant by the investigator.

Pregnancy test data will be listed only, for all women of child bearing potential.

FSH data will be listed only, for all post-menopausal women.

Coagulation data as well as qualitative and quantitative urinalysis data will be listed only.

1.1.1.3 *Tables*

Haematology, biochemistry and continuous dipstick urinalysis laboratory data will be summarised for each scheduled visit, including observed values, absolute change from each baseline.

Categorical dipstick urinalysis results will be summarised for each scheduled visit using frequency tabulations.

Cross-tabulations (shift tables) may be provided.

11.5 Body Measurements

Body measurement data will be listed for all participants and visits including height, weight and Body Mass Index (BMI) which is auto-calculated within the CRF.

Observed values, as well as absolute changes from each baseline, will be summarised descriptively for weight by visit.

11.6 Vital Signs

11.6.1 Parameters

- Systolic Blood Pressure (SBP) (mmHg)
- Diastolic Blood Pressure (DBP) (mmHg)
- Heart Rate (beats/minute)
- Temperature (°C)
- Respiratory Rate (breaths/minute)

11.6.2 Biostatistical methods

All vital signs data will be listed for all participants. Any values outside of the protocol defined normal ranges (Table 1) will be flagged, with clinical significance status presented for out of range results.

Table 1: Vital Signs Normal Ranges

Parameter	Range
Systolic blood pressure	90-140 mmHg
Diastolic blood pressure	50-90 mmHg
Heart rate	50-100 bpm
Temperature	35.0-37.5°C
Respiratory rate	10-25 breaths/min

Vital sign parameters will be summarised by presenting summary statistics for observed values and change from baseline values for each scheduled visit.

11.7 Physical Examination

11.7.1 Body Systems

- Heart Auscultation
- Respiratory Auscultation
- Peripheral arterial pulse
- Pupil reflexes
- Knee reflexes
- Achilles reflexes
- Plantar reflexes
- Peripheral lymph nodes
- Abdomen
- Other (free text)

11.7.2 Biostatistical methods

Physical examination parameters will be listed for all participants and visits.

11.8 12-Lead ECG

11.8.1 Parameters

- RR interval (msec)
- Heart rate (beats/minute)
- PR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- QTcB interval (msec)
- QTcF interval (msec)
- ECG result (Normal, Abnormal, Not Evaluable)
- ECG abnormality (as appropriate)
- Clinical Significance

11.8.2 Biostatistical methods

ECG parameters will be listed for all participants and visits. Triplicate ECGs will be presented in listings for individual readings as well as the mean for each triplicate. Any values outside of the protocol defined normal ranges (Table 1) will be flagged.

Table 2: ECG Normal Ranges

Parameter	Range
PR interval	≤210 msec
QRS interval	50–120 msec
QTcB/QTcF	≤450 msec

Observed values (or triplicate means where appropriate), as well as absolute changes from each baseline, will be summarised descriptively for all ECG parameters by visit.

An addition table will present the frequencies of participants who fulfill the following criteria, considering all scheduled and non-scheduled visit data:

- QTcF prolongation >30
- QTcB prolongation >30
- QTcF prolongation >60
- QTcB prolongation >60
- QTcF >450 msec
- QTcB >450 msec

12 EXPLORATORY PARAMETERS

12.1 Pharmacogenetics: Drug Metabolism Enzymes and Drug Transporters (DME/T)

Allegic variants related drug metabolism enzymes and drug transporters (DME/T) will be investigated if deemed necessary based on review of observed PK and safety data at study end.

Should an analysis be conducted, genotypes for the following DME/T DNA variables will be analysed:

- 2D6
- CYP1A2
- CYP2C19
- CYP2C9
- CYP3A4
- CYP3A5
- VKORC1

Genotype data will only be presented if relevant to specific analyses.

13 HANDLING OF MISSING DATA

Only recorded data will be analysed/presented and any participants who have missing data will only have observed data reported, with no imputation for missing data.

14 CHANGES AND CLARIFICATIONS TO THE PLANNED ANALYSIS

Not applicable.

15 INTERIM ANALYSES

This trial has no formal interim analyses other than data reviews of safety and tolerability as described in the clinical study protocol.

Analyses for both Parts 1 and 2 will be conducted following the completion of both study parts.

16 SOFTWARE

The following software will be used to perform the statistical analyses: Statistical Analysis System (SAS®) Version 9.4 (SAS Institute, Cary, North Carolina, USA).

17 REFERENCES

1) MMV_MMV533_19_01Clinical Study Protocol, v7.0, 27 October 2021
2) MMV533_19_01_aCRF 2021-05-12

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