CLINICAL STUDY PROTOCOL

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 Number:	**MMV-MMV533_19_01**
Investigational Product:	**MMV533 for oral administration**
Principal Investigator:	**Jason Lickliter, Nucleus Network** **Level 5, Burnet Tower, AMREP Precinct,** **89 Commercial Road** **Melbourne, Victoria 3004** **Australia**
Local Sponsor and CRO:	**Southern Star Research Pty Ltd (SSR)** **1 Merriwa St** **Gordon, NSW 2072** **Australia** **Tel: +61 (0)2 9011 6266**
Global Sponsor:	**Medicines for Malaria Venture (MMV)** **ICC-Block G 3rd Floor** **20 route de Pré-Bois** **PO Box 1826** **1215 Geneva 15** **Switzerland**
Trial Medical Monitor:	**Dr Michael Marx, MD** **ICON Clinical Research** **Heinrich-Hertz Str. 26** **63225 Langen** **Germany**
Date and Version:	**Version 7.0 27 October 2021**

Confidentiality Statement

1 PROTOCOL SUMMARY

1.1 PROTOCOL SYNOPSIS

Protocol Title	**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.**
IND Number	Not applicable
Protocol Number	MMV-MMV533_19_01
Local Sponsor/CRO	Southern Star Research Pty Ltd (SSR)
Global Sponsor	Medicines for Malaria Venture (MMV)
Principal Investigator	Jason Lickliter, Nucleus Network (NN)
Phase of Development	Phase 1
Number of Study Sites	A Phase 1 clinical trial unit site will be conducting the study.
Treatment Groups	Part 1: MMV533 or placebo. 8 participants per cohort for 7-8 cohorts (56-64 participants total). Single ascending dose commencing at 5 mg with maximum 400 mg as determined by Safety Review Committee (SRC). Part 2: MMV533. 8 participants in one cohort. Single dose to be determined by SRC after review of Part 1 data.
Participant Population	Healthy adult volunteers. Efforts should be made within each dosing cohort to have a reasonable gender balance.
Investigational Medicinal Product (IMP)	MMV533, single dose taken orally (5mg or 50mg tablets) with 240 mL water under fasting conditions (except as described below for Part 2). **Dose:** Part 1: commencing with 5 mg with single ascending dose per cohort, maximum 400 mg. SRC to determine each dose after review of previous cohort. Part 2: single dose three-fold less than highest dose considered safe by the SRC in Part 1. Participants will consume an FDA-type high fat high calorie breakfast before IMP administration in the fed arm.
Placebo	Part 1 only: Placebo, taken orally as tablets matched to MMV533.
Duration of Study per Participant	Part 1: Screening 28 days (Day -28 to Day -1), Confinement and Treatment period 5 days (Day -1 to Day 5), Follow-up of 23 days until End of Study visit (EOS) (Day 28). Total study duration: up to 8 weeks from Screening until EOS.

	Part 2: Screening 28 days (Day -28 to Day -1), Confinement and Treatment period (in fasted or fed condition) 10 days (Period 1 Day -1 to Day 5 and Period 2 Day 21 to Day 26), follow up of 20 days after last IMP administration until EOS (Day 42). Total study duration: up to 10 weeks from Screening until EOS.
Objectives	**Part 1 and 2 – Single ascending dose (SAD) and food effect:** To assess in healthy adult participants: Primary: • The tolerability and safety of ascending single oral doses of MMV 533 Secondary: • To characterize the pharmacokinetic parameters of parent drug and major metabolites after single oral doses of MMV533 • To obtain preliminary information on the effect of a high-fat meal on the pharmacokinetics of MMV533 Exploratory: • To explore the excretion of MMV533 in urine • To perform genotyping of CYP450 and/or Transporter genes related to drug absorption, distribution, metabolism and excretion of MMV533 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])
Endpoints	**Part 1 and 2:** **Primary endpoints:** **Safety** • 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 haematology, biochemistry, urinalysis. • Vital signs (blood pressure and heart rate supine and standing, respiratory rate and body temperature), • 12-lead electrocardiogram (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 scheduled timepoints: RR, heart rate (HR), PR, QRS, QT, QTcB and QTcF. Overall assessment as normal, abnormal not clinically significant, or abnormal clinically significant. **Secondary endpoints:** **Pharmacokinetics of MMV533** • Plasma parameters: at least but not limited to C_{max}, t_{max}, t_{lag}, AUC_{last}, AUC_{inf}, $t_{1/2}$, CL/F, Vd/F

	Pharmacokinetics of major metabolites (if applicable) • Plasma parameters: at least C_{max}, t_{max}, AUC_{last}, AUC • Comparison of MMV533 PK parameters between fed and fasted dosing **Exploratory endpoints:** • Urine parameters: Ae_{0-t}, fe_{0-t} and CLR_{0-t}. • 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
Study Description	Phase 1, single -centre study in 2 parts. The study designs for each part are well established for first-in-human studies and are appropriate to assess safety, tolerability and preliminary pharmacokinetics. **Part 1:** Double-blind, randomized, placebo-controlled, sequential ascending single dose study in healthy adult participants, 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). Efforts should be made within each dosing cohort to have a reasonable gender balance. 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. **Part 2:** 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. Efforts should be made to have a reasonable gender balance. Part 2 may be conducted in parallel to or after completion of Part 1 at the discretion of the 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 $t_{½}$) between the two periods. This will be decided by the SRC before Part 2 commences. <u>Fasted condition</u> Participants will be administered a single dose of MMV533 after an overnight fast of at least 10 hours. <u>Fed condition</u> 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.
Sample Size	**Part 1 (SAD)** Up to 64 participants: 7 groups with 8 participants each with one additional optional cohort of 8 participants (6 participants receiving MMV533 and 2 participants receiving placebo in each cohort). **Part 2 (Pilot food effect)**

	1 cohort of 8 participants all receiving MMV533 Both Parts: extra eligible participants are permitted to be available per cohort as back-up replacements for any withdrawal of planned participants prior to IMP administration. Efforts should be made within each dosing cohort to have a reasonable gender balance.
Inclusion Criteria	Potential participants must fulfil all of the following inclusion criteria to be eligible to participate in the study: 1. Males and females (of childbearing and non-childbearing potential) , between 18 and 55 years of age, inclusive. Women of childbearing potential (WOCBP) must use highly effective methods of birth control (see Inclusion #3). 2. Females of non-childbearing potential: a) Natural (spontaneous) post-menopausal defined as being amenorrhoeic for at least 12 months without an alternative medical cause with a screening follicle stimulating hormone level (FSH) >25 IU/L (or at the local laboratory levels for post-menopause) b) Premenopausal with irreversible surgical sterilization by hysterectomy and/or bilateral oophorectomy or salpingectomy at least 6 months before screening (as determined by participant medical history) 3. Women of childbearing potential that have or may have male sexual partners during the course of the study must agree to the use of a double method of contraception of a highly effective method of birth control combined with a barrier contraceptive (condom) when appropriate from screening visit to until 60 days after the last dose of IMP (covering a full menstrual cycle of 30 days starting after 5 half-lives of last dose of IMP. This duration is based on the predicted half-life of IMP, and may be amended once the actual half-life is calculated during this study). Note: Highly effective birth control methods include: combined (oestrogen and progestogen containing) oral/intravaginal/transdermal hormonal contraception associated with inhibition of ovulation, progestogen-only oral/injectable/implantable hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, or sexual abstinence or same sex relationship. 4. Male participants who have, or may have female sexual partners during the course of the study must agree to use a double method of contraception including condom plus diaphragm, or condom plus stable insertable (implant or IUD), injectable, transdermal or combination oral contraceptive by the female partner, from the time of informed consent through to 90 days after the last dose of the IMP (covering a full spermatogenesis cycle of 60 days starting after 5 half-lives of last dose of IMP. This duration is based on the predicted half-life of IMP, and may be amended once the actual half-life is calculated during this study).

	Abstinent male participants must agree to start a double method if they begin a sexual relationship with a female during the trial, and through to 90 days after the last dose of the IMP. Male participants with female partners that are surgically sterile or post-menopausal (defined as being amenorrhoeic for at least 12 months without an alternative medical cause), or male participants who have undergone sterilisation and have had testing to confirm the success of the sterilisation, may also be included and will not be required to use above described methods of contraception. Male participants must also agree not to donate sperm up to 3 months after dosing with the IMP. 5. Total body weight greater than or equal to 50 kg, and body mass index (BMI) between 18 and 32 kg/m^2 inclusive. 6. Certified as healthy by a comprehensive clinical assessment (detailed medical history and complete physical examination). 7. Vital signs after 5 minutes resting in supine position: • Systolic blood pressure (SBP) - 90–140 mmHg, • Diastolic blood pressure (DBP) - 40–90 mmHg, • Heart rate (HR) 40–100 bpm. DBP 40-49 mmHg and HR 40-49 bpm are outside the study normal ranges but are acceptable for eligibility (including Screening, Day -1 and Day 1 pre-dose) if considered not clinically significant by the Principal Investigator or delegate. 8. Standard 12-lead electrocardiogram (ECG) parameters after 10 minutes resting in supine position in the following ranges for both males and females, irrespective of clinical significance of out-of-range values: • QRS 50 – 120 msec, • QT ≤ 500 msec, • QTcF ≤450 msec, • QTcB ≤450 msec, and • PR interval ≤210 msec. The ECG tracing must be normal unless the Principal Investigator or delegate considers an ECG tracing abnormality to be not clinically significant. 9. Having given written informed consent prior to undertaking any study-related procedure. 10. Available for the duration of the study and for 2 weeks following the End of Study visit. 11. In the opinion of the Principal Investigator or delegate, the individual has a high probability of adherence with and completion of the study, and willing and able to withdraw and refrain from restricted medications.

	12. Fluent in English and able to understand and comply with written and verbal protocol-related requirements. 13. Willing to defer blood donations to a blood service for a minimum of 6 months after the End of Study visit.
Exclusion Criteria	If any of the following exclusion criteria apply, the potential participant will not be permitted to participate in the study: 1. Haematology, biochemistry or urinalysis results that are abnormal/outside of laboratory normal reference ranges AND are either: • considered clinically significant by the Principal Investigator or delegate; OR • considered not clinically significant by the Principal Investigator or delegate BUT ARE ALSO outside of the Sponsor-approved clinically acceptable laboratory ranges in Appendix 1. NOTE: Participants are not excluded if abnormal/out of laboratory normal reference range results are considered not clinically significant by the Principal Investigator or delegate AND are within the ranges specified in Appendix 1. 2. Positive serum pregnancy test at screening, positive urine pregnancy test upon admission or at other timepoints as specified by schedule of assessments. 3. Male participants with a female partner(s) who is (are) pregnant or lactating from the time of the administration of study medication. 4. Any history or presence of clinically relevant cardiovascular, broncho-pulmonary, gastrointestinal, hepatic/ gallbladder*/ bile duct, renal, metabolic, haematological, neurological, musculoskeletal/rheumatologic, systemic, ocular, gynaecologic (if female), or infectious disease, or signs of acute illness. *including medical history of asymptomatic gallbladder stones. 5. Any gastrointestinal surgery or any condition or disease that could affect drug absorption, distribution or excretion (eg, gastrectomy, cholecystectomy, diarrhoea). 6. Severe recurring headaches (cluster or migrainous headaches) requiring prescription medication/s. History of recurrent nausea and/or vomiting (for vomiting only: more than twice a month). 7. Participation in any research study involving blood sampling (more than 450 mL/unit of blood) or blood donation during the 8 weeks prior to IMP administration (Parts 1 and 2). 8. Any documented evidence of current or past cardiovascular disease including cardiac arrhythmias or family history of congenital long QT syndrome, Brugada syndrome, or unexplained sudden cardiac death. Symptomatic postural hypotension at screening (confirmed on two consecutive

	readings), irrespective of the decrease in blood pressure, or asymptomatic postural hypotension defined as a decrease in systolic blood pressure ≥20 mmHg within 2–3 min when changing from supine to standing position. 9. History or presence of diagnosed (by an allergist/immunologist) or treated (by a physician) food or known drug allergies, or any history of anaphylaxis or other severe allergic reactions including face, mouth, or throat swelling or any difficulty breathing. Participants with seasonal allergies/hay fever or allergy to animals or house dust mite that are untreated and asymptomatic at the time of dosing can be enrolled in the trial. 10. History of convulsion (including drug or vaccine-induced episodes). A medical history of a single febrile convulsion during childhood is not an exclusion criterion. 11. History of substance use disorder(s) within 5 years of screening, including alcohol consumption of more than 40g/4 units/4 standard drinks per day or any prior intravenous use of an illicit substance. 12. Smoked >1 pack of cigarettes per day for >10 years, or who currently (within 14 days prior to IMP administration (Parts 1 and 2) smokes >5 cigarettes per day. 13. Any vitamin supplements within 7 days prior to IMP administration (Parts 1 and 2). 14. Any other medication (including herbal such as St John´s Wort and over the counter [OTC]) within 5 half-lives prior to IMP administration (Parts 1 and 2), except occasional intakes (for acute pain) of ibuprofen at doses up to 1.8g/day, paracetamol at doses up to 4g/day, acetylsalicylic acid (300 to 650 mg orally every 4 to 6 hours as needed, maximum dose: 4g in 24 hours), diclofenac (diclofenac potassium liquid-filled capsules: 25mg orally 4 times a day; diclofenac free acid capsules: 18 or 35 mg orally 3 times a day; diclofenac potassium immediate-release tablets: 50mg orally 3 times a day [initial dose of 100mg orally followed by 50mg oral doses acceptable if required for better relief]) and contraceptives. 15. Any individual who, in the judgement of the Principal Investigator or delegate, is likely to be noncompliant during the study, or unable to cooperate because of a language problem or poor mental development. 16. Any individual in the exclusion period of a previous study according to applicable regulations. 17. Any individual who cannot be contacted in case of emergency. 18. Any individual who is the Investigator, or delegates, research assistant, pharmacist, study coordinator, project manager, or other staff thereof, directly involved in conducting the study. 19. Any individual without a good peripheral venous access.

	20. Participation in any investigational product study within the 12 weeks preceding IMP administration (Parts 1 and 2) or 5 times the half-life of the Investigational product, whichever is longer. 21. Positive serology test for hepatitis B (positive HB sAG or anti-HBc Ab), hepatitis C (anti-HCV) or human immune deficiency virus (HIV) (positive for anti-HIV1 and anti-HIV2 Ab). 22. Positive drug test at screening or prior to IMP dosing. Any drug from the list of drugs tested unless there is an acceptable explanation to the Principal Investigator or delegate (eg, participant has stated in advance that they consumed a prescription of over the counter product which contained the detected drug) and/or the participant has a negative urine drug screen on retest. Any participant tested positive for serum paracetamol at screening may still be eligible for study participation, at the Principal Investigator's or delegate's discretion. 23. Positive alcohol screen at screening or prior to IMP dosing. 24. Any consumption of citrus fruits (grapefruit, Seville oranges) or their juices within 5 days prior to IMP administration. 25. Use of antidepressant medication in the past 12 months prior to IMP administration in Part 1 and 2. 26. Individuals with history of schizophrenia, bipolar disorder psychoses, disorders requiring lithium, attempted or planned suicide, or any other severe (disabling) chronic psychiatric diagnosis including generalised anxiety and obsessive-compulsive disorders. 27. Individuals who have been hospitalised within five years prior to enrolment for either a psychiatric illness or due to danger to self or others. 28. History of an episode of mild/moderate depression lasting more than 6 months that required pharmacological therapy and/or psychotherapy within the last 5 years; or any episode of major depression. The Beck Depression Inventory (BDI-II) will be used as a validated tool for the assessment of depression at screening. In addition to the conditions listed above, individuals with a score of 20 or more on the BDI-II and/or a response of 1, 2 or 3 for item 9 of this inventory (related to suicidal ideation) will not be eligible for participation. These individuals will be referred to a general practitioner or medical specialist as appropriate. Individuals with a BDI-II score of 17 to 19 may be enrolled at the discretion of an Investigator if they do not have a history of the psychiatric conditions mentioned in this criterion and their mental state is not considered to pose additional risk to the health of the individual or to the execution of the trial and interpretation of the data gathered. 29. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in situ* cervical

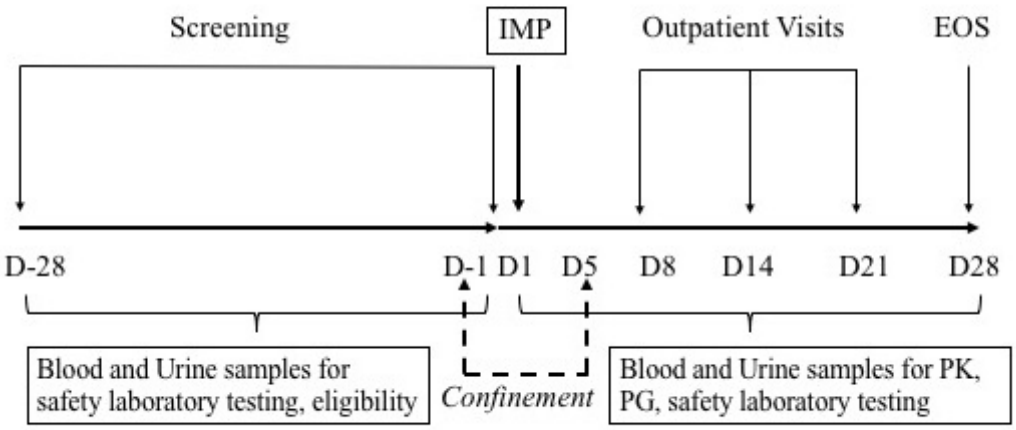
	cancer considered treated and cured), treated or untreated, within 5 years of screening, regardless of whether there is no evidence of local recurrence or metastases. 30. Any COVID-19 vaccine within 14 days of IMP intake, any other vaccination within 28 days of IMP intake, and any vaccination (including COVID-19 initial or second dose) planned up to the final follow-up visit. 31. Any medical condition that in the opinion of the Principal Investigator or delegate would jeopardize the individual's involvement in the study. **Specific to Part 2 only:** 32. Any individual who, in the opinion of the Principal Investigator or delegate, would be unwilling or unable to consume the pre-dose test meal during the fed arm. 33. Individuals with food intolerance or food allergy are excluded. Vegetarian individuals must be excluded, unless they agree to eat a full diet during the study.
Data Analysis	**Safety (all study parts):** Safety analysis (AE, laboratory parameters, vital signs, ECGs) will be based on the review of individual values, and descriptive statistics. The safety analysis will focus on the TEAE period, defined as the time from the first IMP administration up to and including EOS. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Their severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE V5.0 27 Nov 2017). The number (%) of participants experiencing TEAEs will be summarized by dose group. Safety analysis of ECGs will include in particular the number of participants during the study with: • QTcF and/or QTcB prolongation of more than 30 ms and 60 ms; and/or • QTcF and/or QTcB > 450 msec. **Part 1** Concentration-ECG analysis: Exposure-response analysis between the change from baseline in centrally-read ECG intervals and corresponding drug concentrations will be performed using graphical tools and regression methods. Estimate and 90% confidence interval (CI) of change from baseline in ECG parameters (HR, PR, QRS, QTcB and QTcF) at the observed geometric mean of C_{max} will be computed from the final model chosen. This analysis will be supporting further development of MMV533, and results will be presented in a separate companion report after completion of the main study clinical study report (CSR). **Pharmacokinetics**

	For both parts, MMV533 PK profiles will be plotted individually and summarized by dose group and by food intake. For both Parts, MMV533 PK parameters calculated in plasma will be summarized by dose group and by food intake using descriptive statistics. All the statistical analyses described below will be done separately on plasma parameters. The t_{max} values will be represented by histogram plots for each dose level. Dose proportionality will be assessed using a power model on C_{max}, AUC_{last} and AUC. For Part 2 only, impact of food effect on C_{max}, t_{max} AUC_{last} and AUC and $t_{1/2}$ will be assessed. **Exploratory parameters** Exploratory parameters identified for this study (urine excretion of MMV533 and, if analysed, CYP450/Transporter genetic polymorphism) will be summarized by treatment group using descriptive statistics.

1.2 SCHEMAS

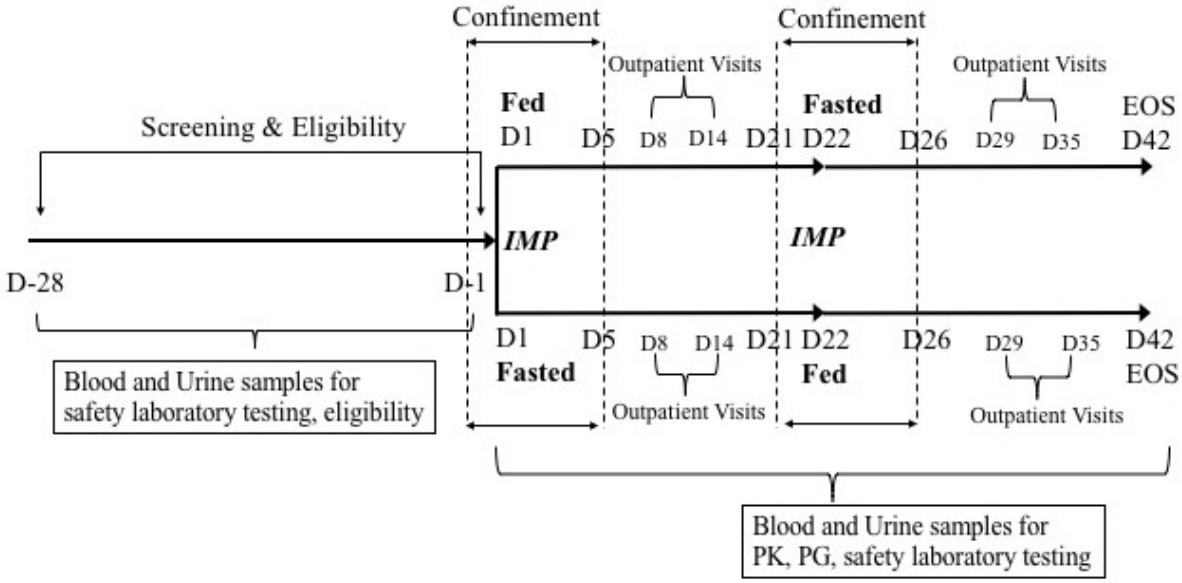
1.2.1 Part 1 Schema

Part 1 Single Ascending Dose
Up to 8 cohorts of 8 participants each, double-blind placebo-controlled
(6 participants receiving MMV533 and 2 participants receiving placebo)



1.2.2 Part 2 Schema

Part 2 Food Effect
One cohort of 8 participants all receiving MMV533:
randomized on Day 1 to fed or fasted arm, crossing over to other arm on Day 22



1.3 SCHEDULE OF ACTIVITIES

Table 1: PART 1 Schedule of Activities

Part 1 Phase	Screening/Eligibility		Treatment and Confinement				Outpatient Monitoring				EOS	Early Termination
Day	**D-28 to D-2**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D8**	**D14**	**D21**	**D28±24h**	
Informed consent	X											
Admission to clinical unit		X										
Confinement at clinical unit			X	X	X	X						
Discharge from clinical unit							X					
Outpatient visit to clinical unit	X							X	X	X	X	X
Inclusion/exclusion criteria – confirm eligibility	X	X										
Medical/surgical history	X	X										
BDI-II	X											
Prior/concomitant medications	<	-	-	-	-	-		-	-	-	>	
Randomization			X									
Study treatment administration												
MMV533 or placebo (IMP)			X									
Safety												
Physical exam - full	X	X									X	X
Physical exam – symptom directed when clinically indicated			X				X	X	X	X		
Height (cm)	X											
Body weight (kg)	X	X										
Serology tests	X											
Drug screen, alcohol test[a]	X	X										
Vital signs (BP, HR & RR: supine and standing at Screening and EOS, all others supine)	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X
Tympanic body temperature (ºCelcius)	X	X	X	X	X	X	X	X	X	X	X	X
Haematology, biochemistry[b], urinalysis	X	X	X	X	X	X	X	X	X	X	X	X

Part 1 Phase	Screening/Eligibility		Treatment and Confinement				Outpatient Monitoring				EOS	Early Termination
Day	**D-28 to D-2**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D8**	**D14**	**D21**	**D28±24h**	
Coagulation	X											
Pregnancy Test/ FSH[c]	X	X									X	X
Adverse event collection[d]	<	-	-	-	-	-		-	-	-	>	
Pharmacokinetics												
MMV533 plasma samples			X	X	X	X	X	X	X	X	X	Xf
MMV533 urine samples[e]			X	X	X							
Pharmacogenetics												
DME/T DNA blood sample[g]			X									

ABBREVIATIONS: BDI-II = Beck Depression Inventory; BP = blood pressure; DME = drug metabolizing enzymes; ECG = Electrocardiogram; exam = examination; EOS = End of study visit; FSH = follicle stimulating hormone; HR = heart rate; IMP= Investigational Medicinal Product; RR = respiratory rate.

a. Drug test will be performed on urine sample, except serum paracetamol which will be assayed using blood sample(s) taken for clinical laboratory testing. Alcohol test will be performed by breathalyser.
b. Blood sampling for safety biochemistry laboratory tests require fasting (at least 10 hours) when taken in the morning: must be fasted for Screening, and fasting blood samples must be collected only in the morning before breakfast when Total Bile Acids (TBA) are tested. TBA will be tested pre-dose, then 24 hours, 48 hours, 72 hours and 96 hours post-IMP administration and on Days 8, 14, 21 and EOS. TBA not required at Screening, Day -1, or at 6 and 12 hours post-IMP administration. Samples taken 6 and 12 hours post-IMP administration are not required to be fasting if not collected in the morning. NOTE: Results of all safety laboratory tests conducted on blood and urine samples collected on Day -1 must be available and reviewed by the Principal Investigator or delegate prior to dosing with IMP on Day 1 and must satisfy relevant inclusion/exclusion criteria.
c. Serum β-human chorionic gonadotropin (hCG) pregnancy test for all female participants and FSH test for post-menopausal female participants at Screening. For women of child bearing potential (WOCBP), urine β-hCG pregnancy test will be performed on Day -1 prior to IMP administration and serum β-hCG pregnancy test conducted at EOS. If urine tests are positive, blood should be collected for serum β-hCG pregnancy test to confirm.
d. Medically untoward events occurring between informed consent and IMP administration will be recorded and considered as medical history; will be recorded as AEs from time of IMP administration.
e. Urine samples for PK analysis: all urine will be collected for defined time intervals as detailed in Table 3.
f. PK sample to be obtained if applicable and in agreement with participant who is withdrawing/having their participation terminated early.
g. Mandatory sample for future analysis of CYP450/Transporter genetic polymorphism.

NOTE: This table is an overview only. See Table 3 for more detailed timepoint and procedural information from Day 1 onwards. Assessment results available prior to dosing must satisfy relevant inclusion/exclusion criteria for first dosing to proceed.

Table 2: PART 2 Schedule of Activities

Part 2 Phase	Screening/ Eligibility		Period 1: Treatment and Confinement				Period 1: Out-patient Monitoring				Period 2: Treatment and Confinement					Period 2: Out-patient Monitoring		EOS	ET
Day	**D-28 to D-2**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D8**	**D 14**	**D21**	**D 22**	**D 23**	**D 24**	**D 25**	**D 26**	**D 29**	**D 35**	**D42**	
Informed consent	X																		
Admission to clinical unit		X								X									
Confinement at clinical unit			X	X	X	X					X	X	X	X					
Discharge from clinical unit							X								X				
Outpatient visit to clinical unit	X							X	X							X	X	X	X
Inclusion/exclusion criteria – confirm eligibility	X	X																	
Medical/surgical history/BDI	X																		
Prior/concomitant medications	<	-	-	-	-	-						-			-	-	-	>	
Randomization			X																
Study treatment administration																			
MMV533			X								X								
High fat breakfast when applicable[a]			X								X								
Safety																			
Physical exam - full	X	X								X								X	X
Physical exam - symptom directed when clinically indicated				X			X	X	X			X			X	X	X		
Height (cm)	X																		
Body weight (kg)	X	X																X	X
Serology tests	X																		
Drug screen, alcohol test[b]	X	X								X									
Vital signs – BP, HR, RR (supine and standing at Screening & EOS; all others supine)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X

Part 2 Phase	**Screening/ Eligibility**		**Period 1: Treatment and Confinement**				**Period 1: Out-patient Monitoring**				**Period 2: Treatment and Confinement**					**Period 2: Out-patient Monitoring**		**EOS**	**ET**
Day	**D-28 to D-2**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D8**	**D 14**	**D21**	**D 22**	**D 23**	**D 24**	**D 25**	**D 26**	**D 29**	**D 35**	**D42**	
Tympanic body temperature (ºCelcius)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haematology, biochemistry[c], urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X																		
Pregnancy Test/ FSH[d]	X	X								X								X	X
Adverse event collection[e]	<	-	-	-	-	-						-			-	-		>	
Pharmacokinetics																			
MMV533 plasma samples			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Xf
Pharmacogenetics																			
DME/T DNA blood sample			Xg																

ABBREVIATIONS: BDI = Beck Depression Inventory; BP = blood pressure; DME = drug metabolizing enzymes; ECG = electrocardiogram; EOS = end of study visit; ET = early termination visit; exam = examination; FSH = follicle stimulating hormone; HR = heart rate; RR = respiratory rate.

a. High fat breakfast (FDA-type high fat and high calorie breakfast) administered in Period 2 only if participant was fasted in Period 1
b. Drug test will be performed on urine sample, except serum paracetamol which will be assayed using blood sample(s) taken for clinical laboratory testing. Alcohol test will be performed by breathalyzer.
c. Safety biochemistry laboratory tests require fasting of at least 10 hours when blood samples collected in the morning. Participants must be fasted for blood sampling at Screening , and fasting blood samples must be collected only in the morning before breakfast in both Periods when Total Bile Acids (TBA) are tested (TBA to be included in testing: pre-dose, then 24 hours, 48 hours, 72 hours and 96 hours post-IMP administration and on Days 8, 14, 21, 29, 35 and EOS Day 42). NOTE: Results of all safety laboratory tests conducted on blood and urine samples collected on Day -1 and Day 21 (except Day 21 TBA results) must be available and reviewed by the Principal Investigator or delegate prior to dosing with IMP on Day 1 and Day 22 respectively. Day -1 results must satisfy relevant inclusion/exclusion criteria.
d. Serum β-human chorionic gonadotropin (hCG) pregnancy test for all female participants and FSH test for post-menopausal female participants at Screening. For WOCBP, urine β-hCG pregnancy test will be performed prior to IMP administration on Days -1 and 21 and serum β-hCG pregnancy test conducted at EOS. If urine tests are positive, blood should be collected for serum β-hCG pregnancy test to confirm.
e. Medically untoward events occurring between informed consent and IMP administration will be recorded and considered as medical history; will be recorded as AEs from time of IMP administration.

f. PK sample to be obtained if applicable and in agreement with participant who is withdrawing/having their participation terminated early.
g. Mandatory sample for future analysis of CYP450/Transporter genetic polymorphism (Period 1 only)

NOTE: This table is an overview only. See Table 4 and Table 5 for more detailed timepoint and procedural information from Day 1 onwards. Assessment results available prior to dosing on Day 1 must satisfy relevant inclusion/exclusion criteria for first dosing to proceed.

Table 3: PART 1 Detailed Schedule of Activities

Part 1 Phase	**Part 1: Treatment and Confinement**																**Part 1: Out-patient Monitoring**			**EOS**
Part 1 Day	**D1**												**D2**	**D3**	**D4**	**D5**	**D8**	**D14**	**D21**	**D28**
Time (hour/minute)[a]	**Pre-dose**	**0H**	**0H 30**	**1H**	**1H 30**	**2H**	**3H**	**4H**	**6H**	**8H**	**10H**	**12H**	**24H**	**48H**	**72H**	**96H**	**168H**	**312H**	**480H**	**648H**
Confinement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Discharge																X				
Outpatient visit at clinical site																	X	X	X	X
Concomitant medications		-	-	-	-	-	-	-	-	-	-	-	-	-	-		-	-	-	>
Randomization	X																			
Study treatment administration																				
MMV533/ placebo (IMP) [b]		X																		
Safety[c]																				
Physical examination									Xd							Xd	Xd	Xd	Xd	X
Tympanic body temperature (ºC)[e]	X								X			X	X	X	X	X	X	X	X	X
Vital signs BP, HR, RR (supine; supine /standing at EOS) [e]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	Xf		Xf	Xf	Xf	Xf	Xf	Xf	Xf	Xf	Xf	Xf	Xf	Xf	Xf	Xf	X	X	X	X
Hematology, biochemistry, urinalysis[g]	Xh								X			X	Xh	Xh	Xh	Xh	Xh	Xh	Xh	Xh
Serum β-hCG (WOCBP only)																				X
Adverse event collection[i]		-	-	-	-	-	-	-	-	-	-	-	-	-	-		-	-	-	>
Pharmacokinetics																				

Part 1 Phase	**Part 1: Treatment and Confinement**																**Part 1: Out-patient Monitoring**			**EOS**
Part 1 Day	**D1**												**D2**	**D3**	**D4**	**D5**	**D8**	**D14**	**D21**	**D28**
Time (hour/minute)[a]	**Pre-dose**	**0H**	**0H 30**	**1H**	**1H 30**	**2H**	**3H**	**4H**	**6H**	**8H**	**10H**	**12H**	**24H**	**48H**	**72H**	**96H**	**168H**	**312H**	**480H**	**648H**
MMV533 PK plasma samples[j]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MMV533 PK urine samples[k]	U00*l*	<	-	-	U01	-	-	><	U02	><	U03	><	U04><	U05><	U06>					
Pharmacogenetics																				
DME/T DNA sample[m]	X																			

ABBREVIATIONS: C = Celcius; DME = drug metabolizing enzymes; ECG = electrocardiogram; EOS = end of study visit; hCG = human chorionic gonadotropin; IMP = investigational medicinal product; PK = pharmacokinetics; WOCBP = woman of child bearing potential.

a. Time (hour/minute) is expressed in reference to the administration of IMP (MMV533/placebo; t = 0). Day 1 is defined as the day of IMP administration. Efforts should be made to ensure all study volunteers are dosed after a minimum of 10 hours fasting and before 10:00AM.
b. A single oral dose of MMV533 or placebo (IMP) will be administered on Day 1 (t = 0). See Section 5.1 for details. Part 1 is double-blinded. Assessment results available prior to dosing must satisfy relevant inclusion/exclusion criteria.
c. Refer to Safety Section 7 for detailed safety investigations.
d. Symptom-directed physical examination: body systems reviewed only if clinically indicated and at discretion of Principal Investigator or delegate. Any results available prior to dosing must satisfy relevant inclusion/exclusion criteria. Prior to participant discharge on Day 5, clinical unit staff must clarify with the Principal Investigator or delegate if a symptom directed physical examination is required. Full physical examination required at EOS.
e. Vital signs (tympanic body temperature [ºCelcius], BP [systolic and diastolic, mmHg], HR [beats per minute], respiratory rate [breaths per minute]. Tympanic body temperature at the timepoints indicated. BP, HR and RR at the timepoints indicated; measured after participant rested supine for at least 5 minutes for all scheduled timepoints except EOS, where BP, HR and RR will be measured after 5 minutes in supine resting position and then after 3 minutes in standing position. Results available prior to dosing must satisfy relevant inclusion/exclusion criteria.Time windows: pre-dose: ≤ 2 hours; post-dose during confinement: ± 15 minutes of nominal timepoints up to and including 12 hours post-dose, and then for all scheduled timepoints as per PK blood sampling time windows in Section 6.3 Table 8.
f. Triplicate 10-second ECGs will be conducted after participant supine for at least 10 minutes: pre-dose on Day 1 (three lots of triplicate baseline ECGs [ie 9 conducted pre-dose] conducted consecutively within one hour prior to dosing with IMP with triplicates performed at least 10 minutes apart from last one to the first one of the next set, prior to any blood sampling) and then at each scheduled timepoint through to Day 5 96H. Results available prior to dosing (using the mean of each triplicate ECG for ECG intervals) must satisfy relevant inclusion/exclusion criteria. All triplicate ECGs will be centrally read. All other scheduled ECGs are single standard 12-lead safety ECGs. From time of IMP dosing to Day 5 inclusive, ECGs will be conducted

within 15 minutes prior to the actual time of PK blood sampling. From Day 8 onwards, ECGs will be conducted +/- 2 hours of the actual PK blood sampling time, except for EOS Day 28 where the time window is as permitted for PK sampling (+/- 24 hours).

g. Safety biochemistry laboratory testing require fasting of at least 10 hours for all scheduled timepoints except for samples collected at 6 and 12 hours post-IMP administration. Time windows for safety blood sampling are as per PK sampling in Section 6.3 Table 8, except ± 15 minutes permitted for the 6 and 12 hour post-dose timepoints. Time windows for urine collection for safety urinalysis are ≤ 2 hours pre-dose, then ± 1 hour post-dose from the nominal timepoint during confinement and then as per PK blood sampling in Section 6.3 Table 8. Day -1 results must be available for review prior to dosing on Day 1 and must satisfy relevant inclusion/exclusion criteria. If available prior to dosing, Day 1 results must also satisfy relevant inclusion/exclusion criteria.
h. Total bile acids (TBA) included in biochemistry laboratory testing (10 hour fasting required for morning sampling before breakfast). TBA not required for safety blood sampling scheduled for 6 and 12 hours post-IMP administration.
i. Medically untoward events occurring between informed consent and IMP administration will be recorded and considered as medical history, and must satisfy relevant inclusion/exclusion criteria for dosing to proceed; will be recorded as AEs from t = 0.
j. Blood samples for PK analysis will be collected at the scheduled timepoints with time windows as per Section 6.3 Table 8.
k. Urine samples for PK analysis will be collected during the following time ranges (hours) post-IMP administration: 0-4 (U01), 4-8 (U02), 8-12 (U03), 12-24 (U04), 24-48 (U05) and 48-72 (U06). All urine will be collected and pooled during these time ranges, except for samples required for safety urinalysis.
l. U00 is a 2-hour pre-dose urine collection. All urine will be collected and pooled from -2h to 0h pre-dose.
m. Mandatory sample for future analysis of CYP450/Transporter genetic polymorphism as per Section 6.2.

NOTE:

- **To respect exact timing of pharmacokinetic samples, the other assessments/activities will be done ahead of the scheduled time from Day 1 to Day 5.** Time windows for PK sampling are defined in Section 6.3 Table 8.
- **When several items take place at the same time, the following order is recommended: urine sampling for PK /urinalysis, vital signs, ECG, blood sampling, drug administration, meal.**
- **Date/time of all assessments/activities must be recorded in source document.**
- **Assessment results available prior to dosing on Day 1 must satisfy relevant inclusion/exclusion criteria before dosing can proceed.**

Table 4: PART 2 Period 1 Detailed Schedule of Activities

Part 2 Phase	**Part 2 Period 1: Treatment and Confinement**															**Part 2 Period 1: Out-patient Monitoring**			
Day	**D1**												**D2**	**D3**	**D4**	**D5**	**D8**	**D14**	**D21**
Time (hour/minute)[a]	**Predose**	**0H**	**0H30**	**1H**	**1H30**	**2H**	**3H**	**4H**	**6H**	**8H**	**10H**	**12H**	**24H**	**48H**	**72H**	**96H**	**168H**	**312H**	**480H**
Confinement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Discharge																X			
Outpatient visit at clinical site																	X	X	
Prior/concomitant medications		-	-	-	-	-							-			-	-	>	
Study treatment administration																			
MMV533[b]		X																	
High fat breakfast when applicable[c]	X																		
Safety[d]																			
Drug screen, alcohol test[e]																			X
Physical Examination[f]	Xf															X	X	X	X
Tympanic body temperature (ºC)[g]	X								X			X	X	X	X	X	X	X	X
Vital signs BP, HR, RR (supine) [g]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	Xh		Xh	Xh	Xh	Xh	Xh	Xh	Xh	Xh	Xh	Xh	Xh	Xh	Xh	Xh	X		X
Hematology, biochemistry, urinalysis	Xi												Xi	Xi	Xi	Xi	Xi	Xi	Xi
Urine β-hCG (WOCBP only)																			Xj

Part 2 Phase	**Part 2 Period 1: Treatment and Confinement**															**Part 2 Period 1: Out-patient Monitoring**			
Day	**D1**												**D2**	**D3**	**D4**	**D5**	**D8**	**D14**	**D21**
Time (hour/minute)[a]	**Predose**	**0H**	**0H30**	**1H**	**1H30**	**2H**	**3H**	**4H**	**6H**	**8H**	**10H**	**12H**	**24H**	**48H**	**72H**	**96H**	**168H**	**312H**	**480H**
Adverse event collection[k]		-	-	-	-	-							-			-	-	>	
Pharmacokinetics																			
MMV533 PK plasma samples[l]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacogenetics																			
DME/T DNA sample	Xm																		

ABBREVIATIONS: BP = blood pressure; C = Celcius; DME = drug metabolizing enzymes; ECG = electrocardiogram; hCG = human chorionic gonadotropin; HR = heart rate; RR = respiratory rate; PK = pharmacokinetics; WOCBP = woman of child bearing potential.

a. Time (hour/minute) is expressed in reference to the administration of MMV533 (t = 0). Day 1 is defined as the day of IMP administration. Efforts should be made to ensure all study volunteers are dosed after a minimum of 10 hours fasting and before 10:00AM.
b. A single oral dose of MMV533 (IMP) will be administered on Day 1 (t = 0) either in the fed or fasted condition as described in Section 5.1.1. Part 2 is open-label; participants will be randomized to the fed or fasted arm for Period 1. Assessment results available prior to dosing on Day 1 must satisfy relevant inclusion/exclusion criteria.
c. If randomized to the fed arm in Period 1, participants will consume a high fat breakfast (FDA-type high fat and high calorie breakfast) after overnight fast of at least 10 hours. Entire breakfast must be consumed within 30 minutes and IMP administered 30 minutes after start of breakfast. See Section 5.3.1.2 for details. If randomized to the fasted arm in Period 1, participants will remain fasted prior to IMP administration.
d. Refer to Safety Section 7 for detailed safety investigations.
e. Drug test will be performed on urine sample except serum paracetamol which will be assayed using blood sample(s) taken for clinical laboratory testing Alcohol test will be performed by breathalyzer.
f. Full physical examination will be conducted on Day 21 (prior to Period 2 IMP administration on Day 22). Symptom directed physical examination may be performed at any time during confinement and at outpatient visits if clinically indicated and at the discretion of the Principal Investigator or delegate. Any results available prior to dosing on Day 1 must satisfy relevant inclusion/exclusion criteria. Prior to participant discharge on Day 5, clinical unit staff must clarify with the Principal Investigator or delegate if a symptom directed physical examination is required.
g. Vital signs (tympanic body temperature [ºCelcius], BP [systolic and diastolic, mmHg], HR [beats per minute], respiratory rate [breaths per minute]. Tympanic body temperature at the timepoints indicated. BP, HR and RR at the timepoints indicated; measured after participant rested supine for at least 5 minutes for all scheduled timepoints. Results available prior to dosing on Day 1 must satisfy relevant inclusion/exclusion criteria. Time windows:

pre-dose: ≤ 2 hours; post-dose during confinement: ± 15 minutes of nominal timepoints up to and including 12 hours post-dose, and then for all scheduled timepoints as per PK blood sampling time windows in Section 6.3 Table 8.

h. Triplicate 10-second ECGs will be conducted pre-dose on Day 1 (three lots of triplicate baseline ECGs [ie 9 conducted pre-dose] conducted consecutively within 90 minutes prior to dosing with IMP with triplicates performed at least 10 minutes apart from last one to the first one of the next set, prior to any blood sampling) and then at each scheduled timepoint through to Day 5 96H. Results available prior to dosing on Day 1 (using the mean of each triplicate ECG for ECG intervals) must satisfy relevant inclusion/exclusion criteria. All triplicate ECGs will be centrally read. All subsequent scheduled ECGs are single standard 12-lead safety ECGs. From time of IMP dosing to Day 5 96H inclusive, ECGs will be conducted within 15 minutes prior to the actual time of PK blood sampling. From Day 8 until Day 21, ECGs will be conducted +/- 2 hours of the PK blood sampling time.
i. Safety biochemistry laboratory tests require fasting for at least 10 hours and to be collected in the morning before breakfast. Total bile acids (TBA) to be included in safety biochemistry laboratory tests. Time windows for safety blood sampling are as per PK sampling in Section 6.3 Table 8. Time windows for urine collection for safety urinalysis are ≤ 2 hours pre-dose, then ± 1 hour post-dose from the nominal timepoint during confinement and then as per PK blood sampling in Section 6.3 Table 8. NOTE: Safety laboratory test results from blood and urine samples collected on Days -1 and 21 (except Day 21 TBA results) must be available and reviewed by the Principal Investigator or delegate prior to dosing with IMP on Days 1 and 22 respectively. Day -1 results (and Day 1 results if available) must satisfy relevant inclusion/exclusion criteria.
j. If urine tests are positive, blood should be collected for serum β-hCG pregnancy test to confirm.
k. Medically untoward events occurring prior to time of IMP administration will be recorded and considered as medical history; will be recorded as AEs from t = 0.
l. Blood samples for PK analysis will be collected at the scheduled timepoints with time windows as per Section 6.3 Table 8.
m. Mandatory sample for future analysis of CYP450/Transporter genetic polymorphism (Period 1 only) as per Section 6.2.

NOTE:

- **To respect exact timing of pharmacokinetic samples, the other assessments/activities will be done ahead of the scheduled time from Day 1 to Day 5.** Time windows for PK sampling are defined in Section 6.3 Table 8.
- **When several items take place at the same time, the following order is recommended: urinalysis, vital signs, ECG, blood sampling, drug administration, meal.**
- **Date/time of all assessments/activities must be recorded in source document.**
- **Available assessment results prior to dosing on Day 1 must satisfy relevant inclusion/exclusion criteria before dosing can proceed.**

Table 5: PART 2 Period 2 Detailed Schedule of Activities

Part 2 Phase	**Part 2 Period 2: Treatment and Confinement**															**Part 2 Period 2: Out-patient Monitoring**			**EOS**
Day	**D22**												**D23**	**D24**	**D25**	**D26**	**D29**	**D35**	**D42**
Time (hour/minute)[a]	**Predose**	**0H**	**0H30**	**1H**	**1H30**	**2H**	**3H**	**4H**	**6H**	**8H**	**10H**	**12H**	**24H**	**48H**	**72H**	**96H**	**168H**	**312H**	**480H**
Confinement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Discharge																X			
Outpatient visit at clinical site																	X	X	X
Prior/concomitant medications		-	-	-	-	-							-			-	-		>
Study treatment administration																			
MMV533[b]		X																	
High fat breakfast when applicable[c]	X																		
Safety[d]																			
Physical Exam[e]	Xe															X	X	X	X
Body weight (kg)																			X
Tympanic body temperature (ºC) [f]	X								X			X	X	X	X	X	X	X	X
Vital signs supine; supine/standing at EOS only [f]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	Xg		Xg	Xg	Xg	Xg	Xg	Xg	Xg	Xg	Xg	Xg	Xg	Xg	Xg	Xg	X		X
Haematology, biochemistry, urinalysis	Xh												Xh	Xh	Xh	Xh	Xh	Xh	Xh

Part 2 Phase	**Part 2 Period 2: Treatment and Confinement**															**Part 2 Period 2: Out-patient Monitoring**			**EOS**
Day	**D22**												**D23**	**D24**	**D25**	**D26**	**D29**	**D35**	**D42**
Time (hour/minute)[a]	**Predose**	**0H**	**0H30**	**1H**	**1H30**	**2H**	**3H**	**4H**	**6H**	**8H**	**10H**	**12H**	**24H**	**48H**	**72H**	**96H**	**168H**	**312H**	**480H**
Serum β-hCG (WOCBP only)																			X
Adverse event collection[i]		-	-	-	-	-							-			-	-		>
Pharmacokinetics																			
MMV533 PK plasma samples[j]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ABBREVIATIONS: C = Celcius; ECG = electrocardiogram; EOS = end of study visit; Exam = examination ; hCG = human chorionic gonadotropin; PK = pharmacokinetics; WOCBP = woman of child bearing potential.

a. Time (hour/minute) is expressed in reference to the administration of MMV533 (t = 0). Day 1 is defined as the day of IMP administration. Efforts should be made to ensure all study volunteers are dosed after a minimum of 10 hours fasting and before 10:00AM.
b. A single oral dose of MMV533 (IMP) will be administered on Day 22 (t = 0) as described in Section 5.1.1. Part 2 is open-label.
c. If randomized to the fasted arm in Period 1, on Day 22 in Period 2 participants will cross over to the fed arm and consume a high fat breakfast (FDA-type high fat and high calorie breakfast) after overnight fast of at least 10 hours. Entire breakfast must be consumed within 30 minutes and IMP administered 30 minutes after start of breakfast. If randomized to the fed arm in Period 1, on Day 22 in Period 2 participants will cross over to the fasted arm and will remain fasted prior to IMP administration.
d. Refer to Safety Section 7 for detailed safety investigations.
e. Full physical examination will be conducted at EOS on Day 42. Symptom directed physical examination may be performed at any time during confinement and at outpatient visits if clinically indicated and at the discretion of the Principal Investigator or delegate. Prior to participant discharge at least 96 hours post-IMP administration, clinical unit staff must clarify with the Principal Investigator or delegate if a symptom directed physical examination is required.
f. Vital signs (tympanic body temperature [ºCelcius], BP [systolic and diastolic, mmHg], HR [beats per minute], respiratory rate [breaths per minute]. Tympanic body temperature at the timepoints indicated. BP, HR and RR at the timepoints indicated; measured after participant rested supine for at least 5 minutes for all scheduled timepoints. Prior to dosing on Day 22, Principal Investigator or delegate must review available results from Days 21 & 22 before confirming dosing can proceed. Time windows: pre-dose: ≤ 2 hours; post-dose during confinement: ± 15 minutes of nominal timepoints up to and including 12 hours post-dose, and then for all scheduled timepoints as per PK blood sampling time windows in Section 6.3 Table 8

g. Triplicate 10-second ECGs will be conducted pre-dose on Day 22 (three lots of triplicate baseline ECGs [ie 9 conducted pre-dose] conducted consecutively within 90 minutes prior to dosing with IMP with triplicates performed at least 10 minutes apart from last one to the first one of the next set, prior to any blood sampling]) and then at each scheduled timepoint through to Day 26 96H. All triplicate ECGs will be reviewed by the Principal Investigator or delegate. Prior to dosing on Day 22, Principal Investigator or delegate must review available results from Days 21 & 22 before confirming dosing can proceed (using the mean of each triplicate ECG for ECG intervals). All other scheduled ECGs are single standard 12-lead safety ECGs. From time of IMP dosing to Day 26 96H inclusive, ECGs will be conducted within 15 minutes prior to the actual time of PK blood sampling. From Day 29 onwards, ECGs will be conducted ± 2 hours of the PK blood sampling time, including EOS.
h. Safety biochemistry laboratory testing requires fasting for at least 10 hours and to be collected in the morning before breakfast. Total bile acids (TBA) to be included in safety biochemistry laboratory tests. Time windows for safety blood sampling are as per PK sampling in Section 6.3 Table 8. Time windows for urine collection for safety urinalysis are ≤ 2 hours pre-dose, then ± 1 hour post-dose from the nominal timepoint during confinement and then as per PK blood sampling in Section 6.3 Table 8. Prior to dosing on Day 22, Principal Investigator or delegate must review results from Day 21 (except TBA) and Day 22 (if available) before confirming dosing can proceed on Day 22 (as per Section 6.1.3).
i. Medically untoward events occurring before time of IMP administration will be recorded and considered as medical history; will be recorded as AEs from t = 0.
j. Blood samples for PK analysis will be collected at the scheduled timepoints with time windows as per Section 6.3 Table 8.

NOTE:

- **To respect exact timing of pharmacokinetic samples, the other assessments/activities will be done ahead of the scheduled time from Day 22 to Day 26.** Time windows for PK sampling are defined in Section 6.3 Table 8.
- **When several items take place at the same time, the following order is recommended: urinalysis, vital signs, ECG, blood sampling, drug administration, meal.**
- **Date/time of all assessments/activities must be recorded in source document.**

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List of Tables

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACT	Artemisinin-based combination therapy
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
Ae0-t	Cumulated amount of drug excreted in urine from time 0 to time t
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the curve
BDI	Beck Depression Inventory
BMI	Body mass index
CLR0-t	Renal clearance of drug estimated from time 0 to time t
CI	Confidence interval
C_{max}	Maximum plasma concentration observed
CSR	Clinical study report
DBP	Diastolic blood pressure
DME/T	Drug metabolism enzymes and drug transporters
ECG	Electrocardiogram
EOS	End of study visit
FDA	Food and Drug Administration (US)
fe0-t	Fraction of dose of drug excreted in urine from time 0 to time t
FSH	Follicle stimulating hormone
GGT	Gamma-glutamyl transferase
GSB	Global Safety Board
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HR	Heart rate
HREC	Human Research Ethics Committee
IC_{50}	Concentration for 50% inhibition
IMP	Investigational medicinal product
INR	International normalised ratio
IUD	Intrauterine device
LDH	Lactate dehydrogenase

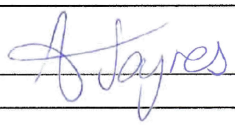
LFT	Liver function tests
LOQ	Limit of quantification
LPLV	Last patient last visit
MMV	Medicines for Malaria Venture
MPC	Minimal parasiticidal concentration
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No observed adverse effect level
OTC	Over the counter
PBPK	Physiologically based pharmacokinetics
PK	Pharmacokinetics
SAD	Single ascending dose
SBP	Systolic blood pressure
SCID	Severe combined immunodeficiency (mouse model)
SRC	Safety Review Committee
SSR	Southern Star Research Pty Ltd
TBA	Total bile acids
$t_{1/2z}$	Terminal half-life
TEAE	Treatment emergent adverse event
t_{lag}	Lag time
t_{max}	Time to reach maximum plasma concentration (C_{max})
ULN	Upper limit of normal
Vss/F	Apparent volume of distribution at the steady state after single dose
Vz/F	Apparent volume of distribution after single dose
WHO	World Health Organisation

PROTOCOL APPROVAL/ SIGNATURES

I herewith approve the following protocol entitled "**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.**", **V7.0 27 October 2021**. Effective Date 27 October 2021

SPONSOR SIGNATURE

Signature:	
Name:	Dr Stephan Chalon MD PhD
Role:	Medical Director, Medicines for Malaria Venture
Date:	27 /OCT /2021

Signature:	
Name:	Dr Andrea Kuemmerle PhD
Role:	Clinical Science Lead, Medicines for Malaria Venture
Date:	27 / Oct /2021

DOCUMENT HISTORY	
Document	**History**
Amendment 5	V7.0 27 October 2021
Amendment 4	V6.0 22 June 2021
Amendment 3	V5.0 16 December 2020
Amendment 2	V4.0 18 September 2020
Amendment 1	V3.0 24 June 2020
Original Protocol	V2.0 25 March 2020

PRINCIPAL INVESTIGATOR SIGNATURE

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.

MMV_MMV533_19_01

Version: **V7.0 27 October 2021**

Issue Date: 27 October 2021

Principal Investigator Agreement

I have read the above-mentioned protocol and am aware of my responsibilities as Principal Investigator for this study. As such, I agree to:

- Personally supervise the conduct of this trial;
- Conduct the trial in accordance with International Conference on Harmonization (ICH) E6 Good Clinical Practice: Consolidated Guidance (GCP), applicable regulatory requirements, and the protocol;
- Comply with the procedures for data recording and reporting as required by the regulatory authorities and the Sponsor;
- Permit monitoring, auditing, and inspection of study records as required by ICH GCP;
- Retain the essential clinical study documents as required by ICH GCP and the Sponsor.

Principal Investigator Signature:	
Principal Investigator Name:	Jason Lickliter
Date:	____/____/2021

2 INTRODUCTION AND RATIONALE

MMV533 is in development as a potential single dose cure, fast acting and long-lasting treatment for malaria.

2.1 DISEASE BACKGROUND

Malaria continues to be a challenge globally. In 2018, some 228 million cases of malaria occurred worldwide, resulting in an estimated 405,000 deaths.[1] Although the incidence rate of malaria globally is declining, the rate of decline has slowed dramatically, remaining at similar levels to that reported in 2014. In 2018, nineteen countries in sub-Saharan Africa and India accounted for almost 85% of global malaria cases, and 94% of all malaria deaths were from the African region.

Malaria is a cyclical parasitic infection of humans and female *Anopheles* mosquitoes.[2] As a brief summary, after a female *Anopheles* mosquito feeds on the blood of a human infected with the malarial parasite it is asymptomatically infected with the parasite. The parasites grow and multiply in the gut of the mosquito before migrating to its salivary glands, and the infected mosquito then injects some of the infected saliva into the next human it feeds on. In the human, the parasites first migrate to the liver before infecting red blood cells, where the cycle continues with successive generations of asexual parasites invading and destroying red blood cells. These blood stage parasites cause the symptoms of malaria. After a period of time, some of the blood stage parasites differentiate into male and female forms (gametocytes) which continue the cycle of infection when ingested by a female *Anopheles* mosquito feeding on the infected human. Worldwide, *Plasmodium falciparum* is the predominant malaria parasite, causing the vast majority of cases in Africa and many cases in South-East Asia, Eastern Mediterranean region and the Western Pacific Region. [1]

The World Health Organisation (WHO) promotes several strategies to help combat malaria, including preventing mosquito bites with use of insecticide-treated mosquito nets while sleeping and insecticide spraying of indoor walls, use of preventative therapies especially for vulnerable groups such as children and pregnant women, and improving institutional structures for accessing care to diagnose and treat malaria. [1] For treatment of malaria, artemisinin-based combination therapy (ACT) has been widely implemented, with an estimated 3 billion courses of ACT procured globally between 2010 and 2018. However, parasite resistance to artemisinin and other therapies are becoming more common especially in Thailand and other South-East Asian countries, while mosquito resistance to insecticide is also widespread.

Therefore, there remains an urgent need to continue the clinical development of novel, effective and well-tolerated anti-malarial drugs, of which MMV533 is a promising candidate.

2.2 INVESTIGATIONAL MEDICINAL PRODUCT - MMV533

MMV533 is a first in class, fast acting, orally bioavailable blood stage inhibitor of *Plasmodium falciparum* with a long half-life. Its mechanism of action is unknown. MMV533 is being developed for the curative treatment of uncomplicated malaria caused by *P. falciparum* in adults and children, and has been evaluated in a range of pharmacological models of malaria.

2.2.1 Clinical Studies

MMV533 has not yet been tested in humans. Part 1 of this study will be the first time MMV533 has been administered to humans.

2.2.2 Non-Clinical Studies

MMV533 has previously been evaluated extensively by Sanofi in nonclinical studies as compound SAR441121. SAR441121 has been acquired by MMV, and renamed as 'MMV533' (short for MMV688533). Refer to the Investigator's Brochure for further details.

MMV533 has been shown to act on malarial parasite Ring/Schizont erythrocytic stages, and has high potency *in vitro* with an IC_{50} of 4-8nM on a panel of sensitive and resistant strains of *Plasmodium falciparum*, 2.5-21nM on a panel of field and mutant strains and 0.8-18 nM on field isolates.

MMV533 has been shown to be highly efficacious with a single oral dose against *Plasmodium falciparum in vivo* in severe combined immunodeficiency (SCID) mouse model. MMV533 also exhibited an outstanding resistance profile after no mutant selection was observed after 6 months of drug pressure.

As observed in animals, a high bioavailability of MMV533 is expected in human based on the good *in vitro* permeability (~ $30.10^{-7}cm^{-1}$ in standard condition). No major food effect is anticipated in human with this compound. *In vitro* investigations in human hepatocytes in primary culture showed MMV533 is very slowly metabolized. Based on this experiment, predicted *in vivo* metabolic clearance values of MMV533 correspond to 0.6, 1.4 and 1.0% of human hepatic blood flow at 0.1, 1 and 10 µM, respectively. Complementary investigation with a model allowing longer incubation time (HepatoPac) suggest involvement of CYP3A4 and possibly CYP2D6 at low concentration (0.1µM) in the metabolic clearance. MMV533 showed *in vitro* competitive inhibition of CYP2B6, 2C8, 2C9, 2C19, 2D6 with apparent Ki values of 12.6, 0.783, 2.39, 8.99 and 4.04 µM, respectively and exhibited time-dependent inhibition of CYP3A with KI and kinact values of 28 µM and 0.036 min-1, respectively. Moreover, there is a risk of increase in exposure of drug sensitive substrates of these CYP isoforms when co-administered with MMV533. This compound was not identified as an inducer of CYP1A1/2, CYP2B6, or CYP3A4. Based on allometric scaling and physiologically based pharmacokinetic (PBPK) modelling, the predicted $t_{1/2z}$ in humans is approximately 100 hours.

MMV533 was found to be a P-glycoprotein (P-gP) inhibitor on Caco-2 cell line with digoxin as PgP substrate (IC_{50}:108 µM). As such, it cannot be ruled out that co-administration of MMV533 will affect the pharmacokinetics of a sensitive substrate such as digoxin.

2.2.3 Safety and Risk/Benefit Assessment

Part 1 of this study will be the first time that MMV533 is administered to humans, and as such there is no existing clinical safety information.

Nonclinical safety testing included genetic toxicity and phototoxicity studies, as well as pivotal Good Laboratory Practice (GLP) safety pharmacology studies and rat and dog repeat dose toxicity studies. All pivotal toxicity and safety pharmacology studies were conducted by the oral route, which is the intended human route.

Potential risks have been identified through review (MMV Global Safety Board) of the nonclinical studies conducted to date with MMV533:

- MMV533 in vitro induced an inhibition of human ether-a-go-go-related gene (hERG) current at 3 µM (average of 22% inhibition, statistically significant) and IC50 value was estimated to be greater than 3 µM. In the Purkinje fiber assay, there was no evidence of torsadogenic potential up to 6.4 µM, while some minimal effects attributable to calcium and sodium channels were noted from 4.9 µM. In the subsequent anesthetized guinea-pig effect (continuous intravenous (IV) infusion at rising doses of 10, 20 and 30 mg/kg), none of the in vitro effects translated into impairment of the cardiovascular function. This was confirmed in the GLP safety pharmacology study in conscious, unrestrained, and telemetered beagle dogs. ECG monitoring (QTc interval including two correction methods used in this study, i.e. QTcF and QTcB) will be performed during single dose escalation in healthy participants and detailed reports will be available for the Safety Review Team to evaluate whether dose-escalation can proceed.
- In the 2-week GLP studies, the dog was the most sensitive species with a no-observed-adverse-effect-level (NOAEL) of 1mg/kg/day above which changes in safety laboratory tests (notably alanine transaminase (ALT)/aspartate transaminase (AST) and bile acids elevations) were detected (3mg/kg/day). These changes appeared after multiple dose administration and are considered reversible based on monitoring in the reversibility group. At 3mg/kg/day, two male dogs also showed minimal bile duct hyperplasia after multiple dose administration which appeared to be reversible based on the analysis of the reversibility group. These findings could possibly suggest an effect of MMV533 or a metabolite on acid bile homeostasis during multiple dose administration. The two dogs with minimal bile duct hyperplasia are not different with respect to exposure or liver enzymes parameters than the other dogs in the same group. Standard liver function parameters AST, ALT, alkaline phosphatases, gamma-glutamyl transferase (GGT), total bilirubin, indirect bilirubin and conjugated bilirubin) will be monitored throughout of the study while Total Bile Acids (TBA) measured in a fasting state will be part of the extended safety monitoring in Part 1 (single dose escalation) and Part 2 (Food effect). Additionally, as serum bile acids are not part of the NCI-CTCAE criteria, a specific toxicity rule is proposed for this First-In-Human study (Part 1). The proposed threshold for clinically relevant elevation in fasted total bile acids in serum is based on published human data.[3,4]
- From these preclinical safety data generated in rodents and dogs with toxicological doses of MMV533 and after a two week administration, it can be concluded that the main safety risk for human volunteers receiving a single dose of MMV533 could possibly consist of an acute or delayed elevation in fasting TBA reflecting a direct drug effect on bile acid secretion and interpreted as a marker for subsequent drug-induced bile duct injury. As the findings in dogs are considered reversible, no major persistent or long-lasting effect would be expected within the proposed dose range (5 to 400 mg). Additionally clinically relevant increase in fasted TBA will be used as a toxicity criteria in Part 1.

Refer to the Investigator's Brochure for more detailed information about the known and expected benefits and risks of MMV533. The risks to the study participants will be managed by frequent safety monitoring, including close monitoring during periods of confinement at the clinical unit when MMV533 as the investigational medicinal product (IMP) will be administered. Safety monitoring will include clinical laboratory safety tests (chemistry, haematology, serology, urinalysis), physical examination, vital signs and frequent ECG analysis. In Part 1, the blinded safety data (including TBA results if

available) of sentinel groups of 2 participants up to and including 96 hours post-dose will be assessed by the Principal Investigator, Sponsor Medical Director and study Medical Monitor prior to commencing the study participation of the rest of the cohort.

There are no known direct benefits to the study participants, as they are healthy volunteers. However, the study has been designed to minimise the risk to participants by appropriate selection of eligibility criteria, and rigorous schedule of clinical monitoring, in-house observation and IMP administration and treatment duration.

2.3 RATIONALE

2.3.1 Rationale for the Study

This is a first-in-human study of MMV533 divided into 2 parts. MMV533 is being developed for the curative treatment of uncomplicated malaria caused by *P. falciparum* in adults and children as a single dose regimen in a fixed-dose combination with another non-artemisinin antimalarial drug. However this study will be performed in healthy adult volunteers with no history of malaria to exclude bias related to previous malarial infection, underlying disease or pathological conditions on the safety and PK parameters. The study designs for each part are well established for first-in-human studies, and are appropriate to assess safety, tolerability and preliminary PK.[5]

Part 1 will be the first safety, tolerability and PK evaluation of single ascending doses (SAD) of MMV533 administered orally to healthy adults under fasting conditions. This part of the study will be double-blind, placebo-controlled and randomised, and is an established SAD design to obtain preliminary safety and tolerability data without bias.

Part 2 will evaluate the effect of food on the PK of MMV533 after being administered orally to healthy adults. This part of the study will be open-label, cross-over and randomised for either the fed or fasted arm, and is an appropriate design to obtain information on the effect of food on oral dosing of MMV533. This evaluation is considered a pilot food effect evaluation and will be conducted with a dose expected to be close to the therapeutic dose. A single dose of MMV533 will be used for Part 2, based on results obtained for Part 1.

2.3.2 Rationale for the Dose

A human dose that could maintain blood concentrations above Minimal Parasiticidal Concentration (MPC) for 100 hours (corresponding to 2 parasite erythrocyte cycles) was identified as a target minimal efficacious dose for the treatment of acute uncomplicated *Plasmodium falciparum* malaria. Using allometry methods and physiologically based pharmacokinetics (PBPK) modelling for predicting human PK profile and a typical human body weight of 70 kg, the predicted efficacious human dose of MMV533 is estimated to be between 50 and 70 mg.

For the Part 1 single ascending dose study, the proposed starting dose is 5 mg, which in humans is predicted to generate mean C_{max} and AUC values of 4.3 ng/ml and 949 ng·h/ml, respectively. These estimates provide a predicted safety margin of 120- and 139-fold-fold when compared to the NOAEL C_{max} (517 ng/ml) and cumulative $AUC_{0\text{-}360}$ (125 µg·h/ml) in the most sensitive species (dog) at 1 mg/kg/day.

After completion of Cohorts 1 to 3 in Part 1, the Safety Review Committee (SRC) will review all available safety data up to and including Day 14 and PK data up to and including Day 8 before the next cohort may progress to the next dose level. For Part 1

cohorts from Cohort 4 onwards, safety and PK data up to and including Day 21 will be reviewed by the SRC.

The highest single dose will be capped at 400 mg, as the safety ratio is 1.7 for AUC and C_{max} and this dose is approximately 5.5 to 8 times above the predicted active dose based on MPC determined from SCID models. See also Section 5.2.1.1.

For Part 2, the dose will be at least 3-fold less than a dose determined to be safe by the SRC in Part 1 as described in Section 5.2.1.2.

3 STUDY OBJECTIVES AND ENDPOINTS

All parts to be assessed in healthy, adult participants.

Part 1 and 2 – Single ascending dose (SAD) and Food Effect	
Objectives	**Endpoints**
Primary:	
• 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:	
• 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

Part 1 and 2 – Single ascending dose (SAD) and Food Effect	
Objectives	**Endpoints**
Exploratory:	
• To explore the excretion of MMV533 in urine	• Exploratory Urine parameters: $Ae_{0\text{-}t}$, $fe_{0\text{-}t}$ and $CLR_{0\text{-}t}$.
• 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.

4 INVESTIGATIONAL PLAN

4.1 DESCRIPTION OF OVERALL STUDY DESIGN AND PLAN

The study is Phase 1 and will be conducted in two parts. Part 1 is first-in-human and will provide information on safety, tolerability and dosing. Part 2 will provide information on the effect of food on the PK of the IMP.

4.1.1 Part 1 Single Ascending Dose (SAD)

Part 1 is a double-blind, randomised, placebo-controlled, sequential ascending single dose study in healthy adult volunteers. Up to 64 participants will be enrolled, with 7 cohorts of 8 participants planned and 1 additional optional cohort of 8 participants if needed according to the observed safety, tolerability and PK results. In each cohort, 6 participants will be randomised to receive MMV533, and 2 to receive placebo. Efforts should be made within each dosing cohort to have a reasonable gender balance.

At each dose level, a sentinel dosing strategy will be implemented to best ensure safety. This strategy will involve dividing each cohort into 2 subgroups, with the first group ('sentinel cohort') composed of 2 participants dosed on the first day. One participant in the sentinel cohort will be administered MMV533, with the other participant administered placebo. The Principal Investigator, Medical Monitor, and the Sponsor's Medical Director will review blinded safety and tolerability data (including, but not limited to, AEs, vital signs, ECG and clinical laboratory safety tests) up to and including 96 hours post-dose. TBA results will be reviewed if available. Only after a satisfactory safety review will the remaining participants in the cohort proceed with dosing. The 96 hour window may be modified by the SRC if the observed IMP half-life is longer than predicted.

Study assessments and procedures are as indicated in Table 1 and Table 3 and as described in Sections 6 and 7. Briefly, potential participants will be screened between Day -28 to Day -1, with written informed consent obtained prior to any study procedures and eligibility to be assessed according to the inclusion and exclusion criteria. Eligibility will be confirmed when participants are admitted to the clinical unit on Day -1 for confinement. Safety laboratory tests will be conducted on Day -1 with results to be reviewed prior to planned dosing with IMP on Day 1 (there is no Day 0). Safety assessment results available prior to dosing must satisfy relevant inclusion/exclusion criteria before dosing. Participants will be dosed with a single oral dose of IMP on Day 1 as described in Section 5.1, with blood sampling for PK analysis and safety assessments at times indicated in Table 3. Participants will be discharged a minimum of 96 hours post-IMP administration, and will attend outpatient visits to the clinical unit for safety monitoring and blood sampling for PK analysis on at least Days 8, 14 and 21, and for the end of study visit (EOS) on Day 28 (648 ± 24 hours post-IMP administration).

4.1.2 Part 2 Effect of Food

Part 2 is an open label, 2-period cross-over, randomised, pilot food effect study, designed to provide preliminary information on the effect of a high-fat meal on the PK of a single dose of IMP to healthy adult volunteers. There will be a single cohort of 8 participants. Part 2 may be conducted in parallel to or after completion of Part 1, at the discretion of the SRC. Efforts should be made to have a reasonable gender balance.

The dose to be used in Part 2 will be selected by the SRC based on the 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 (see Investigator's Brochure for further details). As there may be increased exposure to the IMP when given to participants after food, the dose for Part 2 will be at least 3-fold less than the highest dose determined to be safe in Part 1.

Study assessments and procedures are as indicated in Table 2, Table 4 and Table 5 and as described in Sections 6 and 7. Briefly, potential participants will be screened between Day -28 to Day -1, with written informed consent obtained prior to any study procedures and eligibility to be assessed according to the inclusion and exclusion criteria. Eligibility will be confirmed when participants are admitted to the clinical unit on Day -1 for confinement. Safety laboratory tests will be conducted on Day -1 with results to be reviewed prior to planned dosing with IMP on Day 1 (there is no Day 0). On Day 1, safety assessment results available prior to dosing must satisfy relevant inclusion/exclusion criteria before dosing. On Day 1, participants will be randomised to receive a single oral dose of IMP on Day 1 in either a fasted or fed condition in a 1:1 ratio. The fasted condition is defined as an overnight fast of at least 10 hours. The fed condition is defined as the participant consuming a high-fat meal after an overnight fast of at least 10 hours, with the meal consisting of an FDA-type high fat and high calorie breakfast.[6] The participants will be required to consume the whole meal prior within 30 minutes, and the IMP will be administered as per Section 5.1 30 minutes after the participant has started eating.

After administration of the IMP for both fed and fasted arms, blood samples will be taken for PK and safety analysis at times indicated on Table 4 and as described in Sections 6 and 7. Participants will be discharged from the clinical unit a minimum of 96 hours post-IMP administration, and will attend outpatient visits to the clinical unit for safety monitoring and blood sampling for PK analysis on at least Days 8 and 14.

After a wash-out time of 21 days, participants will be admitted to the clinical unit on Day 21 for Period 2 confinement. Clinical laboratory safety tests will be conducted on Day 21, with results to be reviewed prior to the second dosing with the IMP on Day 22. Other safety assessment results from Days 21 & 22 available prior to dosing will also be reviewed by the Principal Investigator or delegate before confirming dosing can proceed on Day 22. On Day 22, participants will cross over to the opposite arm (either fed or fasted) and will be administered the IMP as per Period 1 and as described in Section 5.1. Blood samples for PK and safety analysis will be taken at times indicated in Table 5 and as described in Sections 6 and 7. Participants will be discharged a minimum of 96 hours post-IMP administration and will attend outpatient visits to the clinical unit for safety monitoring and blood sampling for PK analysis on at least Days 29, 35 and 42. The EOS will be conducted on Day 42.

NOTE: Prior to Part 2 commencing, the wash out period of 21 days will be assessed by the SRC based on the elimination half-life of IMP observed in Part 1. If the elimination half-life of the IMP is substantially different from that predicted from preclinical data, the wash-out period and subsequent timing of assessments for Part 2 may be adjusted accordingly.

4.1.3 Adaptive Design Features

This study incorporates the use of an adaptive design. Study specific adaptive features and their limits are described in Table 6.

Table 6: Adaptive Design Features for the Study

Adaptive Study Design Areas	Features	Limits
Dose	1. All anticipated dosing levels in Part 1 & 2 beyond the initial dose/cohort1 of Part 1 can be adjusted in accordance with PK, safety and tolerability data collected up to the decision-making time-point.	I. The PK derived mean exposure for a dosing regimen will not exceed the defined PK exposure limit (based $AUC_{0\text{-last}}$). Please refer to Section 2.3.2. **PART 1 - SAD:** II. **The starting dose for Part A of the study cannot be changed (5 mg).** III. If the pharmacokinetic analysis with the starting dose demonstrates lower exposure compared with the initial predictions, the **highest revised dose for Part A of the study will not exceed 400 mg** and an amendment will be submitted if doses > 400mg are anticipated. IV. If the pharmacokinetic analysis with the starting dose demonstrates lower exposure compared with the initial predictions, the revised dose increments between the **dose levels 1 to 4 in Part 1** will be **no more than 3-fold.** V. The dose increments between the next dose levels (**from dose level 4 onwards**) in Part 1 will be **no more than 2-fold**. **PART 2 – Food Effect:** VI. The planned dosing regimen anticipated mean exposures will not exceed mean exposures (based on $AUC_{0\text{-last}}$) previously explored in Part 1 with acceptable safety and tolerability, i.e. exposure levels at which no study specific criteria stopping dose progression and/or escalation were met. VII. A potential positive food effect of no less than 3-fold will be assumed when setting the dose for Part 2.
Timing	2. Part 2 can overlap with Part 1	I. Minimum data requirements for initiating each dose level in Parts 1 and 2 apply as outlined in Rules for escalation/progression.

Adaptive Study Design Areas	Features	Limits
Flexible Cohort Sizes	3. Withdrawn participants can be replaced at the discretion of the sponsor and PI. 4. Replacement participants may be enrolled in an ongoing cohort or dosed together as a group or dosed separately. 5. The number of participants in Part 2 can be extended to gather further information on this dose level/impact of food.	I. The maximum extension of Part 2 is 100% of the original cohort size at the selected dosing regimen.
Samples and Assessments	7. The in-house confinement period may be shortened if: a. The evolving PK data demonstrates a shorter half-life than anticipated. b. The Safety Review Team (SRT) considers it appropriate from a safety/tolerability point for an upcoming dose cohort.	**I.** A minimum in-house confinement period of **72 hours post dose.** II. If the in-house confinement period is shortened, the minimum in-house period for study cohorts will be based on evolving safety, tolerability, and PK data.
	8. The in-house confinement period or follow-up period may be prolonged if: a. It is considered clinically necessary by the PI for individuals on a case-by-case basis. b. The Safety Review Team (SRT) considers it necessary from a safety/tolerability point for an upcoming dose cohort. c. The follow-up period for a dose cohort may be prolonged if evolving PK data require a longer follow-up period.	I. A maximum extended in-house confinement period or follow-up period triggered by safety observations **for a given participant** cannot be defined, as the extension will be as long as necessary to ensure the safety of the individual participant(s). II. The maximum extended in-house confinement period or follow-up period **for study cohorts** will be based on evolving safety, tolerability, and PK data and **will not usually exceed 5 half-lives of the IMP** following the last dose.
	9. Additional safety blood and/or urine samples/variables may be taken or analyzed if: a. It is considered clinically necessary by the PI and Medical Monitor for	I. For individuals, a maximum number of safety blood samples will be determined on a case-by-case basis and cannot be pre-defined as investigations will be performed as

Adaptive Study Design Areas	Features	Limits
	individuals on a case-by-case basis. b. The SRT considers it necessary from a safety/tolerability point for an upcoming dose cohort.	necessary to ensure the safety of the individual participants. II. In any case, the study specific **maximum blood volume will not be exceeded**.
	10. Timing of blood and urine PK and/or exploratory assessments may be adjusted in accordance with evolving data and dosing schedule. 11. Additional or less blood and urine PK and/or exploratory assessments may be taken in accordance with evolving data and dosing schedule.	I. Minimum: sufficient PK samples to establish full protocol specific serum PK profile. II. Study specific **maximum blood volume will not be exceeded.**
	12. Timing of safety assessments including but not limited to laboratory safety samples, vital signs and ECGs may be adjusted in accordance with evolving data and dosing schedule. 13. Additional safety assessments including but not limited to laboratory safety samples, vital signs and ECGs may be taken in accordance with evolving data and dosing regimens.	I. Alterations in timing of the safety assessments need to be a reflection of the established PK, safety and tolerability profile up to the decision-making time-point. II. Alterations need to be made in the spirit of the current Clinical Study Protocol (i.e. focus on the capture of essential and useful data) and not affect the risk profile of the study.
	14. Specialist referrals (e.g. to a cardiologist or neurologist) may be made (and may include all relevant assessments and investigations) if it is considered clinically necessary by the PI or Sponsor or SRC for individuals on a case-by-case basis.	I. A maximum for individuals will be determined on a case-by-case basis and cannot be pre-defined as investigations will be performed as necessary to ensure the safety of the individual participants.
	15. Except for those subjects that have been randomized, screening assessments performed on volunteers screened for another study can be used for this study to avoid unnecessary tests.	I. The assessments must meet protocol criteria (e.g. the method to be used). II. The assessments must be performed within the protocol defined screening window.
	16. ECG analysis for the purpose of exploratory QT/QTcF/QTcB analysis / intensive cardiac assessments may be performed on	**I.** For the purpose of exploratory QT/QTcF/QTcB analysis **ECG sampling must match PK sampling time.**

Adaptive Study Design Areas	Features	Limits
	selected or all dose levels in Part 1. Under these circumstances : - If PK sampling times are changed then the ECG sampling times will be changed accordingly, for the purpose of exploratory QT/QTcF/QTcB analysis/ intensive cardiac assessments.	
	17. For Part 2, the washout period may be increased for both periods if IMP half-life calculated from Part 1 PK data is longer than expected.	I. The washout period will be of at least 5 half-lives as recommended by regulatory guidances.

4.2 DISCUSSION OF STUDY DESIGN INCLUDING CHOICE OF CONTROL GROUPS

The study design for Parts 1 and 2 are well established for first-in-human studies and are appropriate to assess safety, tolerability and preliminary PK of the IMP.

Part 1 is the only part to use a placebo-controlled arm in a double-blind, randomised study. This is appropriate for first-in-human study to provide information on the safety and tolerability of the IMP compared to placebo. Part 1 will also use a sentinel group strategy, whereby 2 participants from each cohort form a subgroup that undergoes dosing prior to the rest of the cohort. Dosing of the rest of the cohort with the IMP will only proceed once preliminary blinded safety (including TBA results if available) from the sentinel subgroup up to and including 96 hours post-dose are assessed by the Principal Investigator, study Medical Monitor and the Sponsor's Medical Director.

Parts 2 is open label, to assess the effect of food on the PK of IMP. Control groups are not required or appropriate for this part which will be considered a pilot food effect investigation.

4.3 SELECTION OF STUDY POPULATION

The intended patient population for MMV533 is people infected with *Plasmodium falciparum*, but this first-in-human study will be performed in healthy adult volunteers. Efforts should be made within each dosing cohort to have a reasonable gender balance.

4.3.1 Inclusion Criteria

Potential participants must fulfil all of the following inclusion criteria to be eligible to participate in the study:

1. Males and females (of childbearing and non-childbearing potential) , between 18 and 55 years of age, inclusive. Women of childbearing potential (WOCBP) must use highly effective methods of birth control (see Inclusion #3).
2. Females of non-childbearing potential:

a. Natural (spontaneous) post-menopausal defined as being amenorrhoeic for at least 12 months without an alternative medical cause with a screening follicle stimulating hormone level (FSH) >25 IU/L (or at the local laboratory levels for post-menopause)
b. premenopausal with irreversible surgical sterilization by hysterectomy and/or bilateral oophorectomy or salpingectomy at least 6 months before screening (as determined by participant medical history)

3. Women of childbearing potential that have or may have male sexual partners during the course of the study must agree to the use of a double method of contraception of a highly effective method of birth control combined with a barrier contraceptive (condom) when appropriate from screening visit to until 60 days after the last dose of IMP (covering a full menstrual cycle of 30 days starting after 5 half-lives of last dose of IMP. This duration is based on the predicted half-life of IMP, and may be amended once the actual half-life is calculated during this study).

   Note: Highly effective birth control methods include: combined (estrogen and progestogen containing) oral/intravaginal/transdermal hormonal contraception associated with inhibition of ovulation, progestogen-only oral/injectable/implantable hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, sexual abstinence or same sex relationship.

4. Male participants who have, or may have female sexual partners during the course of the study must agree to use a double method of contraception including condom plus diaphragm, or condom plus stable insertable (implant or IUD), injectable, transdermal or combination oral contraceptive by the female partner, from the time of informed consent through to 90 days after the last dose of the IMP (covering a full spermatogenesis cycle of 60 days starting after 5 half-lives of last dose of IMP. This duration is based on the predicted half-life of IMP, and may be amended once the actual half-life is calculated during this study). Abstinent male participants must agree to start a double method if they begin a sexual relationship with a female during the trial, and through to 90 days after the last dose of the IMP. Male participants with female partners that are surgically sterile or post-menopausal (defined as being amenorrhoeic for at least 12 months without an alternative medical cause), or male participants who have undergone sterilisation and have had testing to confirm the success of the sterilisation, may also be included and will not be required to use above described methods of contraception. Male participants must also agree not to donate sperm up to 3 months after dosing with the IMP.
5. Total body weight greater than or equal to 50 kg, and body mass index (BMI) between 18 and 32 kg/m^2 inclusive.
6. Certified as healthy by a comprehensive clinical assessment (detailed medical history and complete physical examination).
7. Vital signs after 5 minutes resting in supine position:
   - Systolic blood pressure (SBP) – 90-140 mmHg,
   - Diastolic blood pressure (DBP) – 40-90 mmHg,
   - Heart rate (HR) 40-100 bpm.

DBP 40-49 mmHg and HR 40-49 bpm are outside the study normal ranges but are acceptable for eligibility (including Screening, Day -1 and Day 1 pre-dose) if considered not clinically significant by the Principal Investigator or delegate.

8. Standard 12-lead electrocardiogram (ECG) parameters after 10 minutes resting in supine position in the following ranges for both males and females, irrespective of clinical significance of out-of-range value(s):

   - QRS 50 – 120 msec,
   - QT ≤ 500 msec,
   - QTcF ≤ 450 msec,
   - QTcB ≤ 450 msec, and
   - PR interval ≤ 210 msec.

   The ECG tracing must be normal unless the Principal Investigator or delegate considers an ECG tracing abnormality to be not clinically significant.

9. Having given written informed consent prior to undertaking any study-related procedure.
10. Available for the duration of the study and for 2 weeks following the End of Study visit.
11. In the opinion of the Principal Investigator or delegate, the individual has a high probability of adherence with and completion of the study, and willing and able to withdraw and refrain from restricted medications.
12. Fluent in English and able to understand and comply with written and verbal protocol-related requirements.
13. Willing to defer blood donations to a blood service for a minimum of 6 months after the End of Study visit.

4.3.2 Exclusion Criteria

If any of the following exclusion criteria apply, the potential participant will not be permitted to participate in the study:

1. Haematology, biochemistry or urinalysis results that are abnormal/outside of laboratory normal reference ranges AND are either:

   - Considered clinically significant by the Principal Investigator or delegate; OR
   - Considered not clinically significant by the Principal Investigator or delegate BUT ARE ALSO outside of the Sponsor-approved clinically acceptable laboratory ranges in Appendix 1.

   NOTE: Participants are not excluded if abnormal/out of laboratory normal reference range results are considered not clinically significant by the Principal Investigator or delegate AND are within the ranges specified in Appendix 1.

2. Positive serum pregnancy test at screening, positive urine pregnancy test upon admission or at other timepoints as specified by schedule of assessments.
3. Male participants with a female partner(s) who is (are) pregnant or lactating from the time of the administration of study medication.
4. Any history or presence of clinically relevant cardiovascular, broncho-pulmonary, gastrointestinal, hepatic/ gallbladder*/ bile duct, renal, metablic, haematological,

neurological, musculoskeletal/rheumatologic, systemic, ocular, gynaecologic (if female), or infectious disease, or signs of acute illness. *including medical history of asymptomatic gallbladder stones.

5. Any gastrointestinal surgery or any condition or disease that could affect drug absorption, distribution or excretion (eg, gastrectomy, cholecystectomy, diarrhoea).
6. Severe recurring headache (cluster or migrainous headaches) requiring prescription medication/s. History of recurrent nausea and/or vomiting (for vomiting only: more than twice a month).
7. Participation in any research study involving blood sampling (more than 450 mL/unit of blood) or blood donation during the 8 weeks prior to IMP administration (Parts 1 and 2).
8. Any documented evidence of current or past cardiovascular disease including cardiac arrhythmias or family history of congenital long QT syndrome, Brugada syndrome, or unexplained sudden cardiac death. Symptomatic postural hypotension at screening (confirmed on two consecutive readings), irrespective of the decrease in blood pressure, or asymptomatic postural hypotension defined as a decrease in systolic blood pressure ≥ 20 mmHg within 2-3 min when changing from supine to standing position.
9. History or presence of diagnosed (by an allergist/immunologist) or treated (by a physician) food or known drug allergies, or any history of anaphylaxis or other severe allergic reactions including face, mouth, or throat swelling or any difficulty breathing. Participants with seasonal allergies/hay fever or allergy to animal or house dust mite that are untreated and asymptomatic at the time of dosing can be enrolled in the trial.
10. History of convulsion (including drug or vaccine-induced episodes). A medical history of a single febrile convulsion during childhood is not an exclusion criterion.
11. History of substance use disorder(s) within 5 years of screening, including alcohol consumption of more than 40g/4 units/4 standard drinks per day or any prior intravenous use of an illicit substance.
12. Smoked >1 pack of cigarettes per day for >10 years, or who currently (within 14 days prior to IMP administration (Parts 1 and 2) smokes >5 cigarettes per day.
13. Any vitamin supplements within 7 days prior to IMP administration (Parts 1 and 2).
14. Any other medication (including herbal such as St John's Wort and over the counter [OTC]) within 5 half-lives prior to IMP administration (Parts 1 and 2) except occasional intakes (for acute pain) of ibuprofen at doses up to 1.8g/day, paracetamol at doses up to 4g/day, acetyl salicylic acid (300 to 650 mg orally every 4 to 6 hours as needed, maximum dose: 4 g in 24 hours), diclofenac (diclofenac potassium liquid-filled capsules: 25mg orally 4 times a day; diclofenac free acid capsules: 18 or 35 mg orally 3 times a day; diclofenac potassium immediate-release tablets: 50mg orally 3 times a day [initial dose of 100mg orally followed by 50mg oral doses acceptable if required for better relief]) and contraceptives.
15. Any individual who, in the judgement of the Principal Investigator or delegate, is likely to be noncompliant during the study, or unable to cooperate because of a language problem or poor mental development.
16. Any individual in the exclusion period of a previous study according to applicable regulations.

17. Any individual who cannot be contacted in case of emergency.
18. Any individual who is the Investigator, or delegates, research assistant, pharmacist, study coordinator, project manager, or other staff thereof, directly involved in conducting the study.
19. Any individual without a good peripheral venous access.
20. Participation in any investigational product study within the 12 weeks preceding IMP administration (Parts 1 and 2) or 5 times the half-life of the Investigational product, whichever is longer.
21. Positive serology test for hepatitis B (positive HB sAG or anti-HBc Ab), hepatitis C (anti-HCV) or human immune deficiency virus (HIV) (positive for anti-HIV1 and anti-HIV2 Ab).
22. Positive drug test at screening or prior to IMP dosing. Any drug from the list of drugs tested unless there is an acceptable explanation to the Principal Investigator or delegate (eg, participant has stated in advance that they consumed a prescription of over the counter product which contained the detected drug) and/or the participant has a negative urine drug screen on retest. Any participant tested positive for serum paracetamol at screening may still be eligible for study participation, at the Principal Investigator's or delegate's discretion.
23. Positive alcohol screen at screening or prior to IMP dosing.
24. Any consumption of citrus fruits (grapefruit, Seville oranges) or their juices within 5 days prior to IMP administration.
25. Use of antidepressant medication in the past 12 months prior to IMP administration in Part 1 and 2.
26. Individuals with history of schizophrenia, bipolar disorder psychoses, disorders requiring lithium, attempted or planned suicide, or any other severe (disabling) chronic psychiatric diagnosis including generalised anxiety and obsessive-compulsive disorders.
27. Individuals who have been hospitalized within five years prior to enrolment for either a psychiatric illness or due to danger to self or others.
28. History of an episode of mild/moderate depression lasting more than 6 months that required pharmacological therapy and/or psychotherapy within the last 5 years; or any episode of major depression. The Beck Depression Inventory (BDI-II) will be used as a validated tool for the assessment of depression at screening. In addition to the conditions above, individuals with a score of 20 or more on the BDI-II and/or a response of 1, 2 or 3 for item 9 of this inventory (related to suicidal ideation) will not be eligible for participation. These individuals will be referred to a general practitioner or medical specialist as appropriate. Individuals with a BDI-II score of 17-19 may be enrolled at the discretion of an Investigator if they do not have a history of the psychiatric conditions mentioned in this criterion and their mental state is not considered to pose additional risk to the health of the individual or to the execution of the trial and interpretation of the data gathered.
29. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in situ* cervical cancer considered treated and cured), treated or untreated,

within 5 years of screening, regardless of whether there is no evidence of local recurrence or metastases.

30. Any COVID-19 vaccine within 14 days of IMP intake, any other vaccination within 28 days of IMP intake, and any vaccination (including COVID-19 initial or second dose) planned up to the final follow-up visit.
31. Any medical condition that in the opinion of the Principal Investigator or delegate would jeopardize the individual's involvement in the study.

Specific to Part 2 only:

32. Any individual who, in the opinion of the Principal Investigator or delegate, would be unwilling or unable to consume the pre-dose test meal during the fed arm.
33. Individuals with food intolerance or food allergy are excluded. Vegetarian individuals must be excluded, unless they agree to eat a full diet during the study.

4.3.3 Lifestyle Considerations

Participants will be requested to follow a stable lifestyle while participating in the study, with no increased physical activity compared to their usual habits. The participants will also be requested to adhere to the following restrictions, and should be reminded of them throughout the study.

4.3.3.1 Parts 1 and 2

Throughout Parts 1 and 2, the participant should not:

- Consume grapefruit or Seville oranges during the study including 5 days prior to IMP administration;
- Consume poppy seeds in the 24 hours prior to screening and first day of confinement for IMP administration (Part 1 and Part 2 Period 1 Day -1, and Part 2 Period 2 Day 21);
- Consume food or beverages containing alcohol 24 hours prior to each alcohol breath test and for the entire confinement period (Part 1 and Part 2 Period 1 Day -1 to Day 5, and Part 2 Period 2 Day 21 to Day 26).
    - After discharge from the clinical unit (Part 1 and Part 2 Period 1 Day 5 and Part 2 Period 2 Day 26), participants should not drink more than 2 standard drinks per day until the end of the study (Part 1 Day 28±24 hours and Part 2 Day 42)
- Consume beverages containing xanthine bases (eg, Red Bull, coffee) during the entire confinement period (Part 1 and Part 2 Period 1 Day -1 to Day 5, and Part 2 Period 2 Day 21 to Day 26).
    - After discharge from the clinical unit (Part 1 and Part 2 Period 1 Day 5 and Part 2 Period 2 Day 26), participants should not consume more than 400 mg caffeine per day (equivalent to 4 cups of coffee) until the end of the study (Part 1 Day 28±24 hours and Part 2 Day 42)
- Use tobacco during the entire confinement period (Part 1 and Part 2 Period 1 Day -1 to Day 5, and Part 2 Period 2 Day 21 to Day 26).
    - After discharge from the clinical unit (Part 1 and Part 2 Period 1 Day 5 and Part 2 Period 2 Day 26), participants should not smoke more than 5 cigarettes (or equivalent) per day until the end of the study (Part 1 Day 28±24 hours and Part 2 Day 42).

- Abstain from strenuous exercise sessions for 4 days prior to IMP administration until EOS.

4.3.4 Screen Failures

Unscheduled visits may be planned to assess, confirm, and follow-up on out-of-range clinical laboratory test, vital sign, or ECG values that determine a participant's eligibility. One re-test only is permitted if the original results are considered to not represent the expected medical status of the participant (see Section 6.1.1 for further information).

If a participant does not meet all selection criteria (is a screen failure), but at some point in the future is expected to meet the eligibility criteria, the participant may be rescreened on one occasion only. Participants who are to be rescreened will undergo the informed consent process, be assigned a new participant number, and then restart a new screening phase.

4.3.5 Withdrawal of Participants

Participants are free to withdraw from participating in the trial at any time upon request and irrespective of the reason. The Principal Investigator or delegate will endeavour to obtain the reason for withdrawal, and will ask the participant to attend an early termination visit where procedures planned for EOS will be conducted in agreement with the participant (including PK sample if appropriate).

The Sponsor and/or Principal Investigator or delegate may discontinue or withdraw a participant from the trial for one or more of the following reasons:

- Pregnancy in a female participant (must be withdrawn from the study);
- Significant non-compliance or major protocol deviation;
- Any clinical AE, laboratory abnormality or other medical condition or situation occurs that would not be in the best interest of the participant to continue to participate in the study (see also Section 4.3.8 for toxicity rules);
- An exclusion criterion newly develops or was not previously recognized that precludes the participant from continuing to participate in the study;
- Participating in any other investigational product study while enrolled in this study;
- Unblinding of study treatment in Part 1 (on a case by case basis).

The reason for participant discontinuation or withdrawal from the study will be recorded on the eCRF and withdrawn participants will be requested to attend an early termination visit (procedures are the same as for EOS).

The Principal Investigator or delegate will continue to provide medical care for any SAEs with the participant's permission, until symptoms resolve and/or the participant's condition becomes stable.

4.3.5.1 Replacement of Withdrawn/discontinued Participants

Participants who have signed the informed consent form and are randomised but have not been administered IMP may be replaced. Extra eligible participants are permitted per cohort as back-up replacements.

The replacement of participants who have been administered IMP and subsequently withdraw or are withdrawn or discontinued from the trial, must be discussed between the Principal Investigator and the Sponsor.

4.3.6 Lost to Follow-Up

The Principal Investigator or delegate will make every effort to contact participants who fail to return to the clinical site for visits scheduled in the protocol. All efforts must be recorded in source document.

4.3.7 Study Discontinuation

The Sponsor, Principal Investigator, approving HREC, and regulatory authorities independently reserve the right to discontinue the trial at any time for safety or other reasons. Where practical, this will be done in consultation with the Sponsor and all parties notified in writing where applicable. The Sponsor and Principal Investigator will ensure that participants' interest and safety are protected, and the Principal Investigator must review all participants and complete all records as required.

4.3.8 Trial Intervention/Treatment Discontinuation – Toxicity Rules

In addition to the classic assessment of serious adverse events (SAEs) and the occurrence/grading of other AEs including AEs of special interest (AESIs) by the Sponsor and Principal Investigator as described in Sections 7.7 and 7.8, the following toxicity rules are provided as guidance for the SRC in making decisions to suspend or stop dose escalation or suspend or stop IMP administration to additional participants.

4.3.8.1 Toxicity Rules for Part 1 (Single Ascending Dose)

Dose escalation in Part 1 or progression to Part 2 will be suspended pending a detailed safety review by the SRC if any of the following conditions are met within a given cohort:

1. **An SAE in one or more participants which is considered drug-related,**
2. **More than 1 adverse event (AE) in two or more participants within the same cohort (regardless of organ class or body system) of Grade 3 intensity according to NCI-CTCAE V5.0 or as per applied Principal Investigator grading for TBA and other AEs where no CTCAE grading is available (see Section 7.7.3), which are considered drug-related,**
3. **For post-dose fasted Total Bile Acids (TBA) within a full cohort:**
    - **Over 2 consecutive timepoints at least two participants show an elevation of ≥3-fold above upper limit of normal (ULN), or**
    - **Over 2 consecutive timepoints at least two participants show an elevation of ≥2-fold above ULN AND an elevation of ≥5-fold above baseline; if baseline TBA <1 µmol/L, then post-dose TBA must be ≥ 5 µmol/L, or**
    - **At least one participant shows an elevation of ≥5-fold above ULN.**
4. **Any other adverse event (AE) deemed to pose an unacceptable risk to study participants and which is considered drug-related.**
5. **More than fifty percent of participants having at least 1 adverse event (AE) (same organ class or body system) of Grade 2 intensity according to NCI-CTCAE V5.0 or as per applied Principal Investigator grading for TBA and other AEs where no CTCAE grading is available (see Section 7.7.3), which is considered drug-related.**

If any of the above criteria are met, the double-blind (for Part 1) will be broken by the Sponsor for the affected participants and:

- Dose-escalation or progression to rest of cohort dosing from sentinel group in Part 1 will be stopped if one of the criteria 1 to 4 is confirmed. One or more lower dose(s) may be administered in new additional cohorts, only if the SRC agree that it is safe to do so after reviewing all relevant data (PK and safety),
- If criterion 5 is met, IMP administration as per protocol may either continue as planned or be reconsidered as above, depending on the nature of the affected body system, and only if the SRC (and when applicable the HREC) agree that it is safe to do so after reviewing all relevant data.

Local laboratory normal values will be applied for this assessment. In case of suspected technical error or reasonable assumption that test results do not reflect the actual status of the participant (s), measurements should be repeated whenever feasible and or appropriate, prior to grading. Diurnal variations in laboratory variables and other measurements as well as baseline status and conditions will be taken into account when assessing whether abnormalities constitute a drug related AE and when grading, if applicable.

The SRC may decide to break the double-blind for other reasons supported by a clear rationale and/or decide to stop IMP administration based on emerging safety signals not described in the above criteria.

PK exposure criteria

In addition to the above safety-based rules, progression and escalation in Part 1 will also be limited by PK exposure limits.

Two-week GLP toxicology studies conducted in rat and dogs have shown that the dog is the most sensitive species with a NOAEL dose of 1 mg/kg/day.

Based on the toxicity profile above, the NOAEL in the two species and the ability to monitor the observed toxicity, the dog NOAEL is identified as the highest acceptable human exposure for this first-in-human study with single dose administration of MMV533 to healthy volunteers. The corresponding exposure of 125µg.hr/mL is the cumulative $AUC_{0\text{-}360h}$ of the parent drug MMV533 over the 2 weeks of the GLP dog study. As volunteers will receive only a single dose of MMV533, it is considered that the mean exposure in human, $AUC_{0\text{-}last}$, is equivalent to the cumulative $AUC_{0\text{-}t}$ PK derived exposure limit in the 2-week dog toxicology study.

In this first-in-human study, preliminary PK of each dose level in Part 1 will be analyzed after completion of each cohort to ensure that the mean group exposure of the subsequent cohort will not exceed the highest achievable human exposure of 125 µg.hr/mL.

4.3.8.2 Toxicity rules for Part 2 (Food Effect)

Toxicity rules provided for Part 1 will also be used in case of safety events occurring in the single cohort of Part 2.

4.3.9 Emergency Unblinding of Study Participants

Code-break tamper-evident envelopes containing treatment allocation per participant were provided to the study site for emergency unblinding if required. For Part 1, the treatment allocation of a participant should be unblinded by the Principal Investigator or delegate when knowledge of the IMP is required for the treatment of an AE. The SRC may also unblind the treatment allocation of a participant as detailed in Section 4.3.8.1.

Refer to the Safety Plan and/or Randomisation Procedure (if available) for further information on the procedures for code-breaking .

5 TRIAL INTERVENTIONS/TREATMENTS

5.1 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

Both MMV533 (all Parts) and placebo (for Part 1 only) are defined as the IMP for this study. Refer to the Pharmacy Manual for further information on the required handling of the IMP.

Participants will be admitted to the clinical unit for oral dosing of the IMP.

5.1.1 MMV533

For both Parts of the study:

- Participants will fast overnight for at least 10 hours.
- Efforts should be made to ensure all the study volunteers are dosed after a minimum of 10 hours fasting and before 10:00AM.
- Part 2 participants participating in the fed arm will eat breakfast as described below in Section 5.3.1.2.
- Participants will take a single oral dose of IMP with 240 mL of water. The dose of IMP will depend on their cohort (see Section 5.2).
- Participants will then:
    - Be requested to not drink liquids for 1 hour;
    - Remain seated for 10 minutes, then stay in a semi-recumbent position for the next 2 hours (except during assessments that require lying positions);
    - Not be permitted food for at least 4 hours.
- Lunch and dinner will be provided at approximately 5 hours and 12 hours post IMP administration, with snacks available between meals.

5.1.2 Part 1 Placebo

Placebo will be administered in Part 1 as described for MMV533 in Section 5.1.1. Part 2 is open label and does not require a placebo arm.

5.2 SELECTION OF DOSE IN THE STUDY

5.2.1 MMV533

5.2.1.1 Part 1

There will be seven ascending single doses of MMV533, starting at 5 mg under fasting conditions to be taken as per Section 5.1 (with up to 1 optional dose level). See Table 7 below for further information.

A proposed starting dose of 5 mg is predicted to generate in humans mean C_{max} and AUC values of 4.3 ng/ml and 949 ng·h/ml, respectively. These estimates provide a predicted safety margin of 120- and 139-fold when compared to the C_{max} (517 ng/ml) and cumulative $AUC_{0\text{-}360}$ (125 µg·h/ml) in the most sensitive species (dogs) at 1 mg/kg/day.

Table 7: AUCinf and Safety Ratio calculated for the Starting Dose of 5 mg MMV533 and Potential Escalated Doses

Dose (mg)	AUC_{inf} (µg*hr /mL)	Safety Ratio (fold) - Dog NOAEL
5	3.13*	138
10	7.25*	69.1
20	10.06*	34.6
50	28.25#	4.4
100	56.50#	2.2
200	113.0#	1.1
400	226.0#	0.55

*Arithmetic mean AUC_{inf} from observed data available at the time of third SRC meeting.

#Predicted arithmetic mean AUC_{inf} from observed PK data at 5-20mg.

Based on observed human PK data and modeling, and taking into account the AUC cap identified for this First In Human study, the maximum dose is now expected to be 200 mg. These predictions will be refined when PK data at 50 mg and 100 mg will be available.

The proposed doses from 50 mg listed in Table 7 are based on observed human PK at 5-20mg and could be modified based on additional observed human PK data.Increments between doses will be maintained and the highest target human mean exposure at the highest dose will not exceed the AUC_{cap} identified for this project ($AUC_{0\text{-}inf}$=125 µg·h/ml). This AUC cap corresponds to the cumulative $AUC_{0\text{-}360}$ observed at the NOAEL in the most sensitive species (dog).

Currently, the highest single dose is set at 200 mg, the safety ratio is 1.1 and this dose is approximately 4.4 to 10 times above the predictive active dose based on MPC determined from SCID models.

The Safety Review Committee (SRC) will determine whether progression to the next dose cohort is indicated as outlined in Section 7.9. All doses administered will be determined by the SRC in accordance with PK, safety and tolerability data collected up to the decision-making time-point from the preceding cohort/s as outlined above. This will allow dose selection to take into account the predicted safety margins and any unexpected drug exposure levels or safety signals observed in human participants.

5.2.1.2 Part 2

The dose for the food effect cohort will be selected by the SRC based on PK and safety results obtained in Part 1, 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. Choice of the dose to be administered will be also made based on the review of available PK data.

5.3 SELECTION AND TIMING OF DOSE FOR EACH PARTICIPANT

5.3.1 MMV533

5.3.1.1 Part 1

There will be seven ascending single oral doses of IMP (one dose per cohort) to be taken on Day 1, starting at 5 mg. There is an additional one optional dose level, if considered required by the SRC.

Participants will be randomised to receive either MMV533 or placebo on Day 1 (in a cohort, 6 will receive MMV533 and 2 will receive placebo). In the sentinel groups, one participant will receive MMV533 and the other placebo (double-blind, randomised). The procedures for IMP administration will be as described above in Section 5.1.

5.3.1.2 Part 2

In Part 2, the SRC will decide the dose to be used for all participants in the single cohort. The dose will be at least 3-fold less than the highest dose determined to be safe in Part 1.

Part 2 is open label. All participants will receive a single oral dose of MMV533 on Days 1 and 22, with participants randomised on Day 1 to the fed or fasted arm for that day (ratio 1:1). The participants will then cross over to the opposite arm on Day 22.

All participants will be fasted overnight for at least 10 hours.

For the fasted arm, the procedures for IMP administration will be the same as described above in Section 5.1.1.

For the fed arm, the procedures for IMP administration will be the same as described above in Section 5.1.1 except that:

- 30 minutes prior to IMP administration participants will be provided with a standardized 800 kcal high-fat breakfast consisting of:
    - 2 eggs fried in butter, 2 slices of bacon, 2 slices of toast with butter, 100g fried hash brown potatoes and 250 mL whole milk.
- Participants will be required to finish eating the entire breakfast within the timeframe of 30 minutes, and will be monitored by clinical unit staff to ensure this. The start and completion times of eating will be recorded in the eCRF.
- After administration of IMP, the procedures are as described above in Section 5.1.1.

5.4 DOSE INTERRUPTIONS AND REDUCTIONS

Dose interruptions per participant are not applicable to IMP as it will be administered in a single dose. Dose adjustments will be made as outlined above in Section 5.3 and as recommended on an ongoing basis cohort by cohort by the SRC as outlined in Section 7.9.

5.5 SUPPLY, PACKAGING AND LABELLING OF STUDY TREATMENTS

The IMP and other study medications/interventions (non-IMP) will be manufactured and packaged according to Good Manufacturing Practice (GMP), all local regulations and labelled for clinical trial use in accordance with Australian requirements. The IMP will be supplied to the clinical unit with an acknowledgement of receipt form.

5.5.1 MMV533

MMV533 will be supplied by Piramal (Pharmaceutical Development Services, Piramal Enterprises Ltd. Ahmedabad). Two film-coated tablets will be used in the clinical study

at the following strength: 5 mg and 50 mg (identical is shape and size), and a matching placebo. The tablets are white to off-white, round, biconvex, film-coated tablets.

5.5.2 Placebo

Placebo will be supplied by Piramal (Pharmaceutical Development Services, Piramal Enterprises Ltd. Ahmedabad) to exactly match the MMV533 tablets in appearance.

5.6 STORAGE OF STUDY TREATMENTS

Prior to dispensing, the IMP must be stored in a secure and locked storage area with limited access, and under monitored, temperature controlled conditions as appropriate. All storage requirements are detailed in the respective Investigator Brochures or product information/CMI.

The Pharmacist or Designee will be responsible for the correct storage and handling of IMP. Deviations from the storage requirements, including corrective action, must be documented. Refer to the Pharmacy Manual for further information.

5.7 ACCOUNTABILITY, RECONCILIATION AND RETURN OF THE STUDY TREATMENTS

The Principal Investigator or delegate will only dispense the IMP to eligible participants enrolled in this study and will ensure that complete and current dispensing and inventory records are maintained. The site's dispensing logs must record every episode of dispensing of the IMP.

The logs must contain the following information:

- Date of receipt.
- Number of tablets.
- Batch number(s).
- The identification of the participant to whom the tablets was dispensed.
- The date(s), time and quantity dispensed to the participant.
- The cumulative total of IMP at site.
- Tablets damaged, destroyed, or returned.

Supplies of the IMP will be shipped to the clinical unit prior to study start. The study monitor will perform drug accountability during routine monitoring visits.

Once the study has completed or has been discontinued, final accountability and reconciliation will be performed. Any discrepancies will be investigated and the resolution documented. All full, partially full, and empty containers of IMP must be returned to the Pharmacy, Manufacturer or Sponsor for destruction, and the appropriate form sent to the Sponsor. Please refer to the Pharmacy Manual for further details on the storage, handling, and dispensing of IMP.

5.8 PROHIBITED CONCOMITANT THERAPY

Permitted and prohibitied prior and concomitant prescribed medications, over-the-counter medications and supplements are outlined in the exclusion criteria in Section 4.3.2. Before use of any non-study medication during this study, the participant should discuss with the Principal Investigator or delegate.

Ibuprofen may be permitted for use at doses up to 1.8g/day or paracetamol at doses up to 4g/day only after the participants discusses with the Principal Investigator or delegate. Ibuprofen is the preferred treatment, however paracetamol may be used if ibuprofen does

not relieve the participant's symptoms. Acetyl salicylic acid (300 to 650 mg orally every 4 to 6 hours as needed, maximum dose: 4 g in 24 hours), diclofenac (diclofenac potassium liquid-filled capsules: 25mg orally 4 times a day; diclofenac free acid capsules: 18 or 35 mg orally 3 times a day; diclofenac potassium immediate-release tablets: 50mg orally 3 times a day [initial dose of 100mg orally followed by 50mg oral doses may provide better relief in some participants]) may also be permitted after discussion with the Principal Investigator or delegate. Contraceptives are permitted.

Any use of concomitant medication including name of medication, daily dosage and duration of use must be recorded in source documents and in the eCRF.

5.9 TREATMENT COMPLIANCE

Participants will be administered IMP under medical supervision while confined at the clinical unit.

5.10 MEASURES TO MINIMIZE BIAS

5.10.1 Randomisation Procedures

Randomisation procedures for Parts 1 and 2 will be as described in the Randomisation Plan and/or 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.

5.10.2 Blinding

Part 1:

The double blind for Part 1 will be maintained as the placebo will be identical in appearance to the MMV533 tablets. The randomisation list will remain strictly confidential until the time of unblinding and will be accessible only to study personnel authorised to be unblinded.

A participant's treatment allocation should not be unblinded except as described above in Section 4.3.9 or as outlined in Section 4.3.8.1.

Otherwise, blinding of Part 1 will be maintained during the trial until all final clinical data has been entered into the database, all data queries have been resolved and the assignment of participants to analysis sets has been completed.

SRC meetings will be performed blinded, except if unblinding is required as described in Sections 4.3.8.1 and 4.3.9.

Part 2 is open label.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 STUDY CONDUCT SCHEDULE

The schedules for all assessments and study activities are summarised in the Schedule of Activities for each part (Part 1 Table 1 and Part 2 Table 2) and shown in more detail in the Detailed Schedule of Activities for each part (Part 1 Table 3, Part 2 Table 4 and Table 5). All study assessments and procedures are as described below and in Section 7.

Protocol waivers or exemptions are not permitted.

6.1.1 Screening

- The screening period for both parts of the study will be between Day -28 and Day -1. During this time, the participant will sign the patient information consent form (PICF) prior to any study-related procedures or assessments and eligibility will be assessed.
- Any screening visit(s) will be prior to and separate from the safety/eligibility/confinement visit on Day -1 (see Section 6.1.2).
- **Review of screening/eligibility laboratory testing is as follows**:
    - If results are normal/within the laboratory normal reference ranges, the participant may be included (if all inclusion criteria fulfilled and no other exclusion criteria are met).
    - If results are abnormal or outside of the laboratory normal reference ranges, then clinical significance must be assigned by the Principal Investigator or delegate:
        - If clinically significant, the participant is excluded as per Exclusion criterion #1.
        - If not clinically significant, the parameter(s) must be checked against Appendix 1: Sponsor Approved Clinically Acceptable Inclusion Laboratory Ranges:
            - If outside the ranges in Appendix 1, the participant is excluded as per Exclusion criterion #1.
            - If within the ranges in Appendix 1, the participant may be included (if all inclusion criteria fulfilled and no other exclusion criteria are met).
- Retesting of any screening parameters (for example if a lab error is suspected) can be conducted once only.
- A positive urine drug screen should only be re-tested once if there is a strong rationale for doing so (for example, false positive).
- The result of any re-tests must be considered for participant eligibility and must be available prior to IMP administration. Findings made during unscheduled visits should be reported in the source document and electronic case report form (eCRF).

6.1.2 Inclusion/Eligibility/Confinement Visit

- For both Parts, participants will attend the clinical unit on Day -1 prior to IMP administration on Day 1 for completion of screening procedures, to confirm eligibility and for admission to the clinical unit for the confinement period.
- NOTE: Informed consent and initial screening procedures should be completed prior to Day -1, so that the eligibility procedures required on Day -1 are in addition to those conducted for Screening.

- See Section 6.1.1 for review of laboratory test results for eligibility purposes and the use of Appendix 1.
- Part 2 participants will attend the clinical unit on Day 21 for admission to the clinical unit for the Period 2 confinement period, in addition to completing the scheduled assessments for Day 21. Safety laboratory test results from Day 21 sampling (except TBA results) must be available for review prior to IMP administration on Day 22.
- 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.

6.1.3 General Further Information:

- An indwelling cannula may be inserted into a peripheral vein of the participant's forearm either upon admission to the clinical unit for confinement on Day -1 or on Day 1 prior to dosing to obtain blood samples (both Parts) and on Day 21 or Day 22 prior to dosing for Part 2 Period 2. The cannula will be locked with a mandrel between blood samples.
- Only one re-test of any Day 1 pre-dose parameter is permitted, and only if the result can be available for review prior to IMP administration. Assessment results that are available prior to dosing on Day 1 must satisfy the relevant inclusion/exclusion criteria (for ECG intervals, the mean of each triplicate ECG will be used).
- Only participants who meet all of the inclusion criteria and none of the exclusion criteria will be eligible to receive IMP on Day 1 for both Parts.
- For Part 2 Period 2, the Principal Investigator or delegate will review safety assessments from Day 21 and Day 22 pre-IMP administration (except TBA results) before confirming IMP administration on Day 22 can proceed. The Principal Investigator or delegate may discuss clinically significant abnormal findings with the study Medical Monitor and/or Sponsor Medical Director before deciding to proceed.
- Participants will be administered the IMP as described in Section 5.1. Efforts should be made to ensure all the study volunteers are dosed after a minimum of 10 hours fasting and before 10:00AM.
- Participants will only be discharged from the clinical unit a minimum of 96 hours post-IMP administration after the Principal Investigator or delegate has performed a complete review of the available safety data.
- During outpatient periods of the study, participants should immediately contact the Principal Investigator or delegate if they experience any unexpected symptom, effect or event. Participants will be informed that they can contact the clinical unit by telephone 24 hours a day and will be provided with a participant card listing the study number and appropriate clinical unit telephone contact details. The participant must also provide telephone contact details so that they can be contacted in an emergency.

6.2 PHARMACOGENETICS

In Part 1 and Part 2 (Period 1 only), one mandatory blood sample per participant will be collected on Day 1 prior to IMP administration to investigate allelic variants related to drug metabolism enzymes and drug transporters (DME/T) that are potentially involved in the MMV533 ADME. Special procedures for the collection, storage and shipping of the samples are described in a separate laboratory manual.

The objective is to identify genetic factors which may predict response to treatment, and predict susceptibility to drug-drug interactions. No other testing will be conducted and these tests may not diagnose any unknown illness or medical condition. The participant's

confidentiality must be protected, and the sample will be used only for this specific analysis. The blood sample and the extracted DNA will be kept until the end of study and will only be analysed under specific circumstances, including abnormal or unexpected PK or safety results. The decision to conduct the analysis will be taken once all data is available after LPLV. The blood sample and extracted DNA will be destroyed either upon completion of analysis or when it is confirmed they will not be required for analysis.

6.3 PHARMACOKINETICS

Blood and urine sample handling for PK analysis is described in the Laboratory Manual. Plasma samples will be obtained for both Parts of the study and urine samples will be collected for PK analysis in Part 1 only.

Exact timing of PK sampling is to be respected. The actual time of sampling must be recorded in source document and the eCRF. If other assessments or activities are required at the same timepoint, they should be conducted ahead of the scheduled time (see Section 7.3 below for required time windows for ECGs). The following order is recommended if required at the same timepoint: urine sampling for PK/urinalysis, vital signs, ECG, blood sampling, IMP administration, meal (each where applicable).

The following time windows will be permitted for blood sampling for PK assay:

Table 8: Permitted Time Windows for Pharmacokinetic Blood Sampling

Time point	**Tolerance window**
Pharmacokinetic Blood Samples	
In confinement	
Pre-dose (T=0 h)	- 60 min to 0 h, taking into account the pre-dose triplicate ECGs to be conducted prior
0.5-4 hours inclusive after initial IMP administration	± 2 min
6-12 hours inclusive after initial IMP administration	± 5 min
24-96 hours inclusive after initial IMP administration	± 30 min
Outpatient care	
168 hours-480 hours (including EOS Part 2)	± 120 min
EOS (Part 1 only)	± 24 h

6.3.1 Part 1

For Part 1, blood and urine samples will be collected for PK analysis as scheduled on the detailed Part 1 Detailed Schedule of Activities Table 3 with time windows as indicated in Table 8 above.

Blood collection will commence on Day 1 during confinement at the clinical unit pre-dose, then 30, 60, 90 minutes post-IMP administration, and then 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, and 96 hours post-IMP administration. After discharge from the clinical unit, blood samples will be collected on Day 8 (168 hours), Day 14 (312 hours), Day 21 (480 hours) and EOS Day 28 (648 hours).

NOTE: An unscheduled PK blood sample will be taken if ALT or AST values >2x ULN as described in Section 7.4.1.2.

Urine will be collected during the following time ranges (hours) post-IMP administration: -2 to 0 (U00 pre-dose); 0-4 (U01); 4-8 (U02); 8-12 (U03); 12-24 (U04), 24-48 (U05) and 48-72 (U06). During these time ranges, all urine will be collected and pooled, except for samples required for safety urinalysis (Section 7.4.6).

6.3.2 Part 2

For Part 2, blood samples will be collected for PK analysis in Periods 1 and 2 as scheduled on the detailed Part 2 Detailed Schedule of Activities Table 4 (Period 1) and Table 5 (Period 2), with permitted time windows for sampling as indicated above in Table 8. NOTE: An unscheduled PK sample will be taken if ALT or AST values >2x ULN as described in Section 7.4.1.2.

6.3.2.1 Period 1

Blood collection will commence on Day 1 during confinement at the clinical unit pre-dose, then 30, 60, 90 minutes post-IMP administration, and then 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, and 96 hours post-IMP administration. After discharge from the clinical unit, blood samples will be collected on Day 8 (168 hours), Day 14 (312 hours) and Day 21 (480 hours). Day 21 is also the first day of confinement for Period 2.

6.3.2.2 Period 2

Blood collection will commence on Day 22 during confinement at the clinical unit pre-dose, then 30, 60, 90 minutes post-IMP administration, and then 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, and 96 hours post-IMP administration. After discharge from the clinical unit, blood samples will be collected on Day 29 (168 hours), Day 35 (312 hours) and EOS Day 42 (480 hours).

7 SAFETY ASSESSMENTS

- The schedules for all safety assessments/activities are summarised in the Schedule of Activities for each part (general overview in Part 1 Table 1 and Part 2 Table 2, and in more detail in the Detailed Schedule of Activities for each Part (Part 1 Table 3, Part 2 Table 4 and Table 5).
- Protocol waivers or exemptions are not permitted.
- All safety assessments may be conducted at unscheduled visits or timepoints if required for the participant's safety at the discretion of the Principal Investigator or delegate.
- When several assessments/activities are scheduled to take place at the same timepoint, the recommended order is: urine sampling (urinalysis and urine collection for PK), vital signs, ECG, blood sampling, IMP administration, meal (where applicable/appropriate).
- Exact timing for PK blood sampling is to be maintained - see Section 6.3 Table 8 above for permitted PK sampling time windows.
- See Section 7.3 below for required time windows for ECGs.
- Date/time of all assessment/activities must be recorded in source document.
- Clinical significance of any out-of-range or abnormal result or finding must be recorded by the Principal Investigator or delegate. Clinically significant results or findings must be recorded as an AE or indicated as a symptom of a recorded AE.

7.1 PHYSICAL EXAMINATION

Physical examination will include at a minimum: heart and respiratory auscultation; peripheral arterial pulse; pupil, knee, Achilles and plantar reflexes; peripheral lymph nodes and abdomen examination.

Symptom directed physical examination: body systems will be reviewed only if clinically indicated and at the discretion of the Principal Investigator or delegate. Symptom directed physical examination may be performed as required by the Principal Investigator or delegate throughout the study except where a full physical examination is required.

7.1.1 Part 1

In Part 1, full physical examination will be performed at Screening, Day -1 and EOS.

Symptom-directed physical examination may be performed at the discretion of the Principal Investigator or delegate if clinically indicated at any time during confinement. Prior to the discharge of participants from confinement at the clinical unit at least 96 hours post-IMP administration on Day 5, clinical staff will check with the Principal Investigator or delegate to clarify if any participant will require a symptom directed physical examination.

Symptom-directed physical examination may be performed at the discretion of the Principal Investigator or delegate if clinically indicated during outpatient visits to the clinical unit on Days 8, 14 and 21.

7.1.2 Part 2

In Part 2, full physical examination will be performed at Screening, Day -1, Day 21 and EOS Day 42.

Symptom-directed physical examination may be performed at the discretion of the Principal Investigator or delegate if clinically indicated at any time during confinement.

Prior to the discharge of participants from confinement at the clinical unit at least 96 hours post-IMP administration on Day 5 and Day 26, clinical staff will check with the Principal Investigator or delegate to clarify if any participant will require a symptom directed physical examination.

Symptom-directed physical examination may be performed at the discretion of the Principal Investigator or delegate if clinically indicated during outpatient visits to the clinical unit on Days 8, 14, 29, and 35. Similarly, the Principal Investigator or delegate may decide to perform a symptom-directed physical examination at any time during the study.

7.2 VITAL SIGNS AND BODY MEASUREMENTS

7.2.1 Body Measurements

For Parts 1 and 2, Body weight (kg) and height (cm) will be measured at screening, and body weight (kg) will be measured again on Day -1. For Part 2, body weight (kg) will also be measured at EOS Day 42.

7.2.2 Vital signs

- Vital signs: heart rate (beats per minute), systolic and diastolic blood pressure (millimetres of mercury [mmHg]), respiratory rate (breaths per minute), and tympanic body temperature (°Celcius):
    - For Part 1 and Part 2 Screening, Part 1 EOS and Part 2 EOS Day 42, heart rate, systolic and diastolic blood pressure and respiratory rate will be measured after 5 minutes in supine resting position, and after 3 minutes in standing position.
    - At all other timepoints vital signs (heart rate, systolic and diastolic blood pressure and respiratory rate) will be measured only after 5 minutes in the supine resting position.
- Permitted time windows for vital sign measurements:
    - Pre-dose: ≤ 2 hours before IMP administration;
    - Post-dose during confinement (where applicable): ± 15 minutes of the nominal timepoint up to and including 12 hours post-dose, and then as per PK blood sampling time windows in Table 8;
    - Post-dose during outpatient visit period: as per PK blood sampling time windows in Table 8.

In Part 1:

- Vital signs excluding tympanic body temperature (°C) will be measured at Screening, on Day -1 upon admission to the clinical unit for confinement, from Day 1 pre-dose and then at the following hours post-IMP administration: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72 and 96 hours (prior to discharge from the clinical unit). After discharge, vital signs will be measured at outpatient visits to the clinical unit on Days 8, 14, 21 and EOS Day 28 (±24 hours).
- Tympanic body temperature (°C) will be measured at Screening, Day -1 upon admission to the clinical unit for confinement, Day 1 pre-dose and then at the following hours post-IMP administration: 6, 12, 24, 48, 72 and 96 hours (prior to discharge from the clinical unit). After discharge from the clinical unit, tympanic body temperature (°C) will be measured at the same timepoints as the other vital signs.

In Part 2, Period 1:

- Vital signs excluding tympanic body temperature (°C) will be measured at Screening, on Day -1 upon admission to the clinical unit for confinement, from Day 1 pre-dose and then at the following hours post-IMP administration: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72 and 96 hours (prior to discharge from the clinical unit). After discharge, vital signs will be measured at outpatient visits to the clinical unit on Days 8, 14 and 21 (also day of admission to the clinical unit for Period 2 confinement).
- Tympanic body temperature (°C) will be measured at Screening, Day -1 upon admission to the clinical unit for confinement, Day 1 pre-dose and then at the following hours post-IMP administration: 6, 12, 24, 48, 72 and 96 hours (prior to discharge from the clinical unit). After discharge until Day 21, tympanic body temperature (°C) will be measured at the same timepoints as the other vital signs.

In Part 2, Period 2:

- Vital signs excluding tympanic body temperature (°C) will be measured from Day 22 pre-dose and then at the following hours post-IMP administration: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72 and 96 hours (prior to discharge from the clinical unit). After discharge, vital signs will be measured at outpatient visits to the clinical unit on Days 29, 35, and EOS Day 42.
- Tympanic body temperature (°C) will be measured at Day 21 upon admission to the clinical unit for confinement, Day 22 pre-dose and then at the following hours post-IMP administration: 6, 12, 24, 48, 72 and 96 hours (prior to discharge from the clinical unit). After discharge, tympanic body temperature (°C) will be measured at the same timepoints as the other vital signs.

For both Parts, assessment results available prior to dosing on Day 1 must satisfy relevant inclusion/exclusion criteria.

For both Parts, the study normal ranges for supine and standing vital signs are:

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

If results are out of these ranges, the Principal Investigator or delegate must assess, assign and document clinical significance.

Please note for Inclusion critierion #7: vital signs in supine position for eligibility prior to IMP dosing (including at screening, Day -1 and Day 1 pre-dose), an out of range value of 40-49 bpm for heart rate and/or 40-49 mmHg for diastolic blood pressure will be acceptable if considered not clinically significant (NCS) by the Principal Investigator or delegate.

7.3 12-LEAD ELECTROCARDIOGRAM (ECG)

Standard 12-lead ECGs (safety ECGs) will be recorded after at least 10 minutes in supine position using a validated electrocardiographic device. The electrodes will be positioned

at the same place for each ECG recording throughout the study (attachment sites of the leads will be marked with an indelible pen). See also manual supplied by the central ECG reading Vendor.

When triplicate ECGs are required, 3 ECGs will be recorded within 5 minutes with at least 1 minute between 2 replicates. Each ECG consists of a 10-second recording of the 12 leads simultaneously, leading to:

- A single 12-lead ECG (25 mm/s, 10mm/mV) printout with heart rate, PR, QRS, QT, QTcB and QTcF automatic correction evaluation (by the ECG device) and at least 3 complexes for each lead. The Principal Investigator's or delegate's medical opinion and automatic values will be recorded in the eCRF. This printout will be retained at the site,
- A digital storage that enables eventual further reading by an ECG central laboratory: each digital file will be identified by theoretical time, real date and real time (recorder time), Sponsor study code, participant number (i.e., 3 digits), and site and country numbers, if relevant. The digital recording, data storage, and transmission (whenever requested) need to comply with all applicable regulatory requirements (i.e., FDA 21 CFR, part 11).

Part 1:

- Single standard 12-lead ECGs will be recorded at Screening and on Day -1 upon admission to the clinical unit for confinement.
- From Day 1, standard 12-lead ECGs will be performed in triplicate as described above:
    - pre-dose: three lots of triplicate baseline ECGs [ie 9 conducted pre-dose] within one hour prior to dosing with IMP, with triplicates performed at least 10 minutes apart from last one to the first one of the next set, and all to be completed prior to blood sampling;
    - then at the following hours post-IMP administration: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72 and 96 hours [triplicates will be performed within 15 minutes prior to the actual time of PK blood sampling];
    - The triplicate ECGs will be centrally read.
- After discharge from the clinical unit, single standard 12-lead ECGs will be recorded at outpatient visits to the clinical unit on Days 8, 14, 21 (all ± 2 hours of the actual PK blood sampling time) and EOS Day 28 as permitted for PK blood sampling (±24 hours – see Table 8).

Part 2:

- Single standard 12-lead ECGs will be recorded at Screening, Day -1 and Day 21 upon admission to the clinical unit for confinement.
- From Period 1 Day 1 and Period 2 Day 22, standard 12-lead ECGs will be performed in triplicate as described above:
    - pre-dose: three lots of triplicate baseline ECGs [ie 9 conducted pre-dose] within 90 minutes prior to dosing with IMP, with triplicates performed at least 10 minutes apart from last one to the first one of the next set, and all to be completed prior to blood sampling;
    - then at the following hours post-IMP administration: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72 and 96 hours [triplicates performed within 15 minutes prior to the actual time of PK blood sampling];

- The triplicate ECGs will be centrally read.

- After discharge from the clinical unit, single standard 12-lead ECGs will be recorded at outpatient visits to the clinical unit on Days 8, 21, 29 and EOS Day 42 (all ± 2 hours of the actual PK blood sampling time).

For both Parts, results available prior to dosing on Day 1 must satisfy relevant inclusion/exclusion criteria. For ECG intervals, the mean of each triplicate ECG will be used.

For both Parts, the study normal ranges for ECG parameters are:

ECG Parameter	Range
PR interval	≤210 msec
QRS	50–120 msec
QTcB/QTcF	≤450 msec for males and females
QT	≤500 msec for males and females

For study eligibility as per Inclusion criterion #8 (including at Screening, Day -1 and Day 1 pre-dose), results out of these ranges are exclusionary irrespective of the clinical significance of any out-of-range value.

If results are out of these ranges post-IMP dosing, the Principal Investigator or delegate must assess, assign and document clinical significance. See also Section 7.7.5.2.

7.4 CLINICAL LABORATORY TESTS

- Blood and urine will be collected for clinical laboratory safety tests. Handling of samples is described in the Pathology Vendor Laboratory Manual.
- See Section 6.1.1 for information on the review of results of all screening and eligibility clinical laboratory tests.
- Results of all safety laboratory tests (except TBA results from Part 2 Day 21) on samples collected on Day -1 Part 1, Day -1 Part 2 Period 1, and Day 21 Part 2 Period 2, must be available and reviewed by the Principal Investigator or delegate prior to dosing with IMP on Day 1 Part 1, Day 1 Part 2 Period 1, and Day 22 in Part 2 respectively. NOTE: Day -1 test results (and any Day 1 results available prior to dosing) must satisfy relevant inclusion/exclusion criteria.
- NOTE: Participants must have fasted for at least 10 hours prior to collecting safety blood samples when scheduled in the morning. Participants must have fasted for Screening and for all biochemistry safety blood tests that include TBA (must be collected in the morning before breakfast).

7.4.1 Safety Blood Tests

- Permitted time windows for collecting safety blood samples:
  - Pre-dose: as per PK blood sampling in Table 8;
  - Post-dose during confinement (where applicable): ± 15 minutes for the 6-12 hour post-IMP timepoints; then as per PK blood sampling in Table 8;
  - Post-dose during outpatient visit period: as per PK blood sampling in Table 8.
- Blood for standard safety blood tests will be collected:

Part 1: Screening, Day -1, Day 1 prior to IMP administration, and then at the following hours post-IMP administration: 6, 12, 24, 48, 72 and 96 hours prior to discharge from the clinical unit. After discharge from the clinical unit, blood will be collected on Days 8, 14, 21 and EOS Day 28.

- Fasting total bile acids (TBA) will also be part of the safety blood tests in Part 1 at the following time-points: Day 1 pre-dose, then at the following hours post-dose: 24, 48, 72, 96, then on Days 8, 14, 21 and EOS.
- Blood samples collected at 6 and 12 hours post-IMP administration on Day 1 are not required to be fasting (TBA not required for these samples).

Part 2 Period 1: Screening, Day -1, Day 1 prior to IMP administration, Day 2 (24 hours), Day 3 (48 hours), Day 4 (72 hours), Day 5 (96 hours), Day 8, Day 14 and Day 21.

- Fasting TBA will be part of the safety blood tests in Part 2 Period 1 at the following time points: pre-dose Day 1, then at the following hours post-dose: 24, 48, 72, 96, and then on Days 8, 14 and 21.

Part 2 Period 2: Day 22 prior to IMP administration, Day 23 (24 hours), Day 24 (48 hours), Day 25 (72 hours), Day 26 (96 hours), Day 29, Day 35 and EOS Day 42.

- Fasting TBA will be part of the safety blood tests in Part 2 Period 2 at the following time points: pre-dose Day 22, and then at the following hours post-dose: 24, 48 72, 96, and then on Days 29, 35 and EOS Day 42.

7.4.1.1 Haematology

Red blood cell count, haematocrit, haemoglobin, white blood cell count with differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes), platelets.

NOTE: blood will also be collected for an unscheduled haematology assessment if ALT or AST >2x ULN as described in Section 7.4.1.2.

7.4.1.2 Biochemistry

- Plasma/serum electrolytes (sodium, potassium, chloride, calcium (corrected), magnesium);
- Liver function tests (AST, ALT, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), total and direct bilirubin; TBA to be included at timepoints detailed in Section 7.4.1)
- Renal function (urea, creatinine)
- Metabolism (glucose, albumin, total proteins, cholesterol, triglycerides)
- Potential muscle toxicity (creatine kinase)

NOTE: If ALT or AST values >2 xULN at any time post-IMP administration (see Section 7.7.5.1 and, if applicable, Section 4.3.8), then:

- blood must be collected for the following tests within 24-48 hours:
    - Coagulation (see Section 7.4.2; see also Section 7.7.5.1)
    - Liver panel (ALT, AST, LDH, ALP, GGT, total and direct bilirubin)
    - CK
    - Haematology (see Section 7.4.1.1)
    - Unscheduled PK sample (see Section 6.3).
- Collect additional recent history of potentially hepatoxic concomitant medications/substances (including paracetamol and alcohol) and exercise.

7.4.2 Coagulation

Blood will be collected for coagulation studies only at Screening for both Parts, and will include international normalized ratio (INR) and activated partial thromboplastin time (APTT). Additional coagulation tests (including INR) may be requested for safety at the

discretion of the Principal Investigator or delegate, and must be requested if ALT or AST > 2x ULN as described in Section 7.7.5.1 and Section 7.4.1.2.

7.4.3 Serology

Blood will be collected for serology tests at Screening for both Parts, and will include: hepatitis B surface antigen (HB sAG), anti-hepatitis B core antibodies (anti-HBc Ab), hepatitis C antibodies, anti-HIV1 and anti-HIV2 antibodies.

7.4.4 Pregnancy Testing

Blood will be collected from all female participants for serum β-human chorionic gonadotropin (β-hCG) testing at Screening for both Parts of the study. Blood will be collected from WOCBP for serum β-hCG testing at EOS both Parts of the study.

Urine will be collected from WOCBP for β-hCG testing: for Part 1 Day -1 prior to IMP administration; Part 2 Day -1 and Day 21 prior to IMP administration.

Blood will also be collected from a female participant for unscheduled serum β-hCG testing if their urine β-hCG test returns a positive result.

7.4.5 Confirming Menopause

Blood will be collected from post-menopausal female participants for follicle stimulating hormone (FSH) testing at Screening for both Parts of the study.

7.4.6 Urinalysis

Urine will be collected as part of the clinical laboratory safety testing at the same timepoints as for safety blood tests above in Section 7.4.1.

- Permitted time windows for collecting safety urinalysis samples:
    - Pre-dose: ≤ 2 hours before IMP administration;
    - Post-dose during confinement (where applicable): ± 1 hour of the nominal urine sampling timepoint.
    - Post-dose during outpatient visit period: as per PK blood sampling time windows in Table 8.

Qualitative: a dipstick test will be performed on a freshly voided urine sample including tests for proteins, glucose, blood (erythrocytes), leucocytes, ketone bodies, nitrate, bilirubin, urobilinogen, and pH.

Quantitative: any urine dip stick result of more than traces (pH will not trigger quantitative analysis) will trigger a quantitative analysis for all of the following parameters: protein, protein/creatinine ratio, glucose, red blood cells, white blood cells, and organism. If available, the quantitative result will be the leading one over the dip stick results for decision making e.g. for study inclusion/exclusion or clinical assessment.

7.5 ALCOHOL AND DRUG SCREENING

Alcohol will be measured by breath test at the clinical unit.

Drug screening will be conducted both in urine and in serum as per below specifications.

Urine will be collected, using suitable dipstick test for: amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, tetrahydrocannabinol, tricyclic antidepressants.

Drug screening will also include testing for serum paracetamol using blood sample(s) collected at the timepoints below for clinical laboratory tests (see Section 7.4) (NOTE: paracetamol is not exclusionary. A subject may still be eligible for study participation, at the Principal Investigator's or delegate's discretion). Based on the quantitative results of the serum paracetamol assay, the following binary classification will be used:

- Negative test: serum levels < 20 µmol/L
- Positive test: serum levels ≥ 20 µmol/L

Alcohol and drug screening will be conducted:

Part 1: Screening and Day -1.

Part 2: Screening, Day -1 and Day 21.

If considered necessary to confirm lifestyle considerations are being adhered to during the study (Section 4.3.3), alcohol and drug screening may also be conducted at other unscheduled timepoints at the discretion of the Principal Investigator or delegate.

7.6 BECK DEPRESSION INVENTORY

Originally described by Beck et al (1961), the Beck Depression Inventory (BDI) is a validated objective tool for the assessment of depression.[7] Updated in 1996, the BDI II is 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression, and participants will be required to complete the BDI-II at Screening for both parts of the study.[8] The BDI II takes approximately 10 minutes to complete, although clients require a fifth – sixth grade reading level to adequately understand the questions. A score of ≥20 at screening and/or a response of 1, 2 or 3 for item 9 indicating current suicidal ideation is exclusionary. A BDI score of 17 to 19 may be enrolled at the discretion of the Principal Investigator if they do not have a history of the psychiatric conditions mentioned in exclusion criterion 26 and their mental state is not considered to pose additional risk to the health of the volunteer or the execution of the study and interpretation of the data gathered.

7.7 ADVERSE EVENTS (AEs)

The Principal Investigator or delegate and clinical unit staff are responsible for detecting recording and reporting events that meet the criteria and definition of adverse events as described below. Adverse events may be reported by the participant or observed by the Principal Investigator, delegate or other clinical site staff.

All AEs will be followed until the event has resolved, no further medically relevant information from the event can be expected and it is acceptable to discontinue follow-up of the event in the assessment of the Principal Investigator. The Principal Investigator should continue to follow up AEs that were unresolved at the participant's EOS as long as medically required or until the participant has been satisfactorily referred to a general practitioner or medical specialist as appropriate.

Medically untoward events occurring in participants between the time of consent (Screening) and the time of IMP administration (for Part 1 and Part 2 Period 1) will be considered medical history and not recorded as AEs.

7.7.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a clinical trial participant administered a medicinal product, and that does not necessarily have a causal relationship with this treatment.

AEs include, but are not limited to:

- A new symptom, sign or medical condition.
- A disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.
- An exacerbation of a pre-existing medical condition/disease.
- An increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Continuous persistent disease or symptoms present at study start that worsen following the start of the study.
- An abnormal assessment (e.g., change on physical examination, ECG finding) if it represents a clinically significant finding that was not present at study start or worsened during the course of the study.
- An abnormal laboratory test result if it represents a clinically significant finding (e.g., CTCAE grade 2 or above), symptomatic or not, which was not present at study start or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment.

Abnormal laboratory findings and other objective assessments should NOT be routinely captured and reported as AEs. However, abnormal laboratory findings or other objective measurements that meet the following criteria should be captured and reported in the AE Section of the eCRF:

- The result meets the criteria for reporting as an SAE
- The test result is associated with accompanying symptoms, and/or
- It requires additional diagnostic testing or medical/surgical intervention, and/or
- It leads to a change in IMP dosing, or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- It is considered by the Principal Investigator (or delegate) or Sponsor to be clinically significant or represent a clinically significant change from baseline.

AEs will not include:

- A medical or surgical procedure such as surgery, endoscopy, tooth extraction, or transfusion (although the condition that leads to the procedure may be an AE).
- A pre-existing disease or condition present at the start of the study that does not worsen during the study.
- Any situation where an untoward medical occurrence has not occurred (for example, hospitalizations for cosmetic elective surgery or social admissions).

7.7.2 Causal Relationship to Investigational Medicinal Product and Other Study Treatments

The Investigator or delegate is required to assess the causality for all AEs, and must indicate this in the source document and eCRF. An adverse event with reasonable causal relationship to the IMP means there is evidence or argument to suggest a causal relationship.

If considered related:

- The temporal relationship between the event and the administration of the IMP is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the participant’s medical condition, other therapies or accident.

If considered not related:

- The event can be readily explained by other factors such as the participant's underlying medical condition, concomitant therapy or accident and no plausible temporal or biologic relationship exists between the IMP and the event.

7.7.3 Severity Grading of Adverse Events

The severity of AEs (except for elevated fasting TBA) will be recorded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, published 27 November 2017 where available. A severity grading system has been developed specifically for elevated fasting TBA to be implemented for this study from 14 April 2021. See Appendix 2: Severity Grading for Fasting TBA in Phase 1 Volunteers. The Principal Investigator will provide severity assessment as per below should there be no CTCAE grading available for a specific AE. This guidance provides a common language to describe levels of severity, to analyse and interpret data, to scale the aggregate AE score, and to articulate the clinical significance of AEs.

The severity of AEs will be graded as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

An AE that is assessed as severe is not the same as a serious AE. Severity is a category utilized for rating the intensity of an event and both AEs and SAEs can be assessed as severe. An AE is defined as 'serious' when it meets one of the pre-defined serious outcomes as described below in Section 7.8.1.

7.7.4 Documentation of Adverse Events

The Principal Investigator or delegate is responsible for reviewing all documentation related to each AE, and for recording all relevant AE/SAE information in source document and in the CRF. The Principal Investigator or delegate will attempt to establish a diagnosis of the AE based on signs, symptoms and/or other clinical information, and where possible the diagnosis will be documented as the AE/SAE (and not individual signs or symptoms).

The following information should be recorded for all AEs:

- Description
- Dates and times of onset and resolution
- Duration in hours
- Time of onset relative to IMP administration
- Seriousness
- Severity
    - In the source data, the description of the AE will report the various severities observed over time. If the severity of an AE increases, separate AEs per severity grading will be recorded into the eCRF.

  - If the AE resolves and then reoccurs, then two AEs will be reported.
- Action taken in response to the AE regarding IMP:
  - Permanently discontinued, or
  - No action taken, or
  - Unknown/not applicable.
- Outcome of AE:
  - Recovered/resolved, or
  - Recovering/resolving, or
  - Not recovered/not resolved, or
  - Recovered with sequelae/resolved with sequelae
  - Fatal
  - Unknown
- Relationship to the IMP or procedures conducted during the trial (causality assessment of related or not related.

7.7.5 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. Documentation and reporting of AESIs are applicable only post-first dose of IMP and will be required to be monitored and reported promptly to the Sponsor by the Principal Investigator or delegate. Such an event may require further investigation in order to characterise and understand it.

All AESIs (both serious and non-serious) must be notified to the pharmacovigilance provider (Prime Vigilance) within 24 hours of the clinical study staff becoming aware of the event (see Section 7.8.3 below). Reporting should be via a Serious Adverse Event Report Form marked as 'AE of special interest'. Follow-up information will be submitted in a timely fashion as it becomes available.

7.7.5.1 Hepatic AEs of Special Interest

- Any ALT or AST above 5×ULN,
- An elevation in bilirubin of 2×ULN or more,
- An elevation in fasting total bile acids (TBA) of >1 x ULN
- Any AST or ALT above 2×ULN (see Section 7.4.1.2) and:
  - Total Bilirubin Level (TBL) >1.5×ULN OR
  - INR >1.4 (see Section 7.4.2)
- Any AST or ALT above 2×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (eosinophil percent or count above the ULN).

7.7.5.2 Cardiac AEs of Special Interest

- QTcB or QTcF at any time >480 msec,
- Bundle branch block (except right bundle branch block that was present prior to IMP administration),
- Any arrhythmia, except:
  - Sinus bradycardia that is clinically asymptomatic, and not associated with any other relevant ECG abnormalities,
  - sinus tachycardia that is clinically asymptomatic, and associated with a body temperature >38.0°C, and not associated with any other relevant ECG abnormalities,

- Respiratory sinus arrhythmia,
- Wandering atrial pacemaker,
- Isolated, single premature atrial/ventricular complex (i.e., no bigeminy, trigeminy, couplets, triplets or salvos) that does not occur more than once in a particular ECG tracing.

7.7.5.3 Haematological AEs of Special Interest

- Absolute neutrophil count $<0.5 \times 10^9$/L,
- Platelet count $<75 \times 10^9$/L.

7.7.5.4 Dermatological AEs of Special Interest

Clinical signs of possible cutaneous adverse reactions such as:

- Dermatitis,
- Rash, including erythematous, macular, papular, maculopapular, pruritic, pustular, and vesicular.

If one of these cutaneous reaction is observed and when feasible, pictures of the lesions should be obtained.

Dermatological AEs do not need to be reported as AESIs if clearly unrelated to study drug (e.g. rash from cannula dressing or ECG dots).

7.7.6 Treatment of Overdose

Overdose of IMP is considered unlikely as it is a single dose administered under supervision at the clinical unit. However symptomatic overdose of IMP is an event suspected by the Principal Investigator or delegate, or notified by the participant, and defined as at least twice the intended dose within the intended therapeutic interval adjusted according to the tested drug. Such an event should be reported promptly to the Sponsor as for AESIs. Asymptomatic overdose will be reported as a standard AE.

7.8 SERIOUS ADVERSE EVENTS (SAES)

7.8.1 Definitions of Serious Adverse Events (SAEs)

A serious adverse event (SAE) is any AE that:

- Results in death, or
- Is life-threatening, and/or
- Requires inpatient hospitalisation or prolongs existing hospitalisation, and/or
- Results in persistent or significant disability or incapacity, and/or
- Is a congenital anomaly or birth defect, and/or
- Constitutes a possible Hy's Law case:
    - Hy's Law case is defined as a participant with any value of alanine or aspartate aminotransferase greater than 3×ULN together with an increase in total bilirubin to a value greater than 2×ULN and not associated to an alkaline phosphatase value greater than 2×ULN (FDA Guidance on Drug Induced Liver Injury: Premarketing Clinical Evaluation [2009]).

Note: Life-threatening in the definition of an SAE refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Note: Medical and scientific judgement should be exercised in deciding whether an AE should be classified as serious in other situations. Important medical events that are not

immediately life-threatening or do not result in death or hospitalization, but may jeopardise the participant or may require intervention to prevent one of the other outcomes above should also be considered serious.

Planned procedures that require admission to hospital for this study, or any planned elective procedure that requires hospitalization are not considered SAEs unless the underlying condition has worsened or the participant's condition worsens after the procedure.

7.8.2 Pregnancy

Pregnancy itself is not defined as an AE/SAE. Any complication or termination of pregnancy for medical reasons are to be reported as an AE/SAE. Spontaneous abortion, still birth or congenital anomaly must be reported as an SAE.

Any WOCBP (Woman of Child-Bearing Potential) enrolled in the study who becomes pregnant during the study and the following 60 days after the dosing should be followed through delivery or termination of the pregnancy. The Investigator will collect pregnancy information and report as for an SAE (see Section 7.8.3) within 24 hours of becoming aware of a participant's pregnancy. Follow-up will generally not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Once pregnancy is confirmed, pregnant female participants will be immediately withdrawn from the study as outlined in Section 4.3.5.

Where possible, the Investigator will also attempt to collect and report information regarding pregnancy outcomes of female partners of any male participants who were administered IMP in this study and the following 60 days after the last dosing. Appropriate signed informed consent will be required directly from the pregnant female partner to obtain and report this information. Any participant's female partner who becomes pregnant during the study should be followed through delivery or termination of the pregnancy.

7.8.3 Reporting for Serious Adverse Events (24 hours)

If any SAE occurs, the Investigator will take immediate appropriate action and strive to identify the causes of the event/s. The Investigator must notify the SAE to the pharmacovigilance provider (Prime Vigilance) by email within 24 hours of becoming aware of the event.

All reports must be signed by the Principal Investigator or delegate and notified to Prime Vigilance preferably by email or fax to:

Email: MMV@primevigilance.com

Back-up fax number: +44 800 471 5694

Prime Vigilance Contact:
Andreja Baricevic
e-mail: andreja.baricevic@primevigilance.com
Phone: +44 385 1 46 28 183
Mobile: +44 385 99 2680 787

Head Office: +44 1483 307920

Any copies of participant's medical records provided for SAE reporting must have all participant identifiers redacted before submission.

The SAE report form will always be completed as thoroughly as possible with all available details of the event and signed by the Principal Investigator or delegate. If the Principal Investigator or delegate does not have all information regarding an SAE, he/she will not wait to receive additional information before reporting the event. A follow-up SAE report should be completed within 14 days, or if there is no new information the SAE report form should be updated when additional information is received.

The Principal Investigator or delegate will always provide an assessment of causality at the time of the initial report.

Email transmission of the SAE report form is the preferred method to transmit this information to Prime Vigilance. In rare circumstances notification by telephone is acceptable, with a copy of the SAE report form sent by overnight mail.

The Principal Investigator or delegate, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the HREC.

7.9 SAFETY REVIEW COMMITTEE (SRC)

The SRC will be responsible for decisions related to the safety of participants and to inform decision making on trial progression and details will be outlined in the SRC Charter. The required data (blinded for Part 1) to be reviewed will be detailed in the SRC Charter and will be sent to the SRC prior to all scheduled and any ad hoc SRC meetings associated with the trial.

The Safety Review Committee (SRC) will be composed at a minimum of the Sponsor's Medical Director, the Principal Investigator, an Independent Clinical Pharmacology Physician and the study Medical Monitor. Representative/s for PK analysis will also be included. The study will proceed cohort by cohort with SRC review in between each cohort, with some parallel overlap for the subsequent Parts if deemed safe to do so by the SRC. In the event of an incomplete cohort, a minimum number of 7 participants in a

cohort is required for SRC review and decision to dose-escalate. The SRC may decide to discontinue a Part or the study after any of the cohort reviews.

Part 1:

The SRC will evaluate all available blinded safety data up to and including Day 14 and PK data up to and including Day 8 for Cohorts 1 to 3. The SRC will then decide if the subsequent dose cohort should proceed. For Cohorts 4 onwards, the SRC will review safety and PK data up to and including Day 21 before deciding to proceed with the next cohort. The SRC may unblind treatment allocation if an AE or AEs occur that stop dose escalation as per Section 4.3.8.

All doses administered in Part 1 will be determined by the SRC in this manner, and each cohort will not proceed until the SRC has reviewed the previous cohort's data as described above. This will ensure that the selected doses take into account the predicted pre-clinical safety margins and any unexpected drug exposure levels or safety signals observed in the participants of this study.

The minutes of each SRC meeting will be shared with the GSB (Global Safety Board [MMV Safety Board]) for their information. Initial study HREC approval required that after completion of the cohort dosed with 200 mg, a comprehensive preliminary data report with observed safety/tolerability and PK data was to be provided to the HREC before progressing to the next dose level. As 200 mg is now likely to be the final dose level, the report will instead be provided to the HREC before progressing to the 200 mg cohort and after completion of the previous cohort. Before proceeding with the last planned dose at 200 mg, all available safety data up to and including Day 14 and PK data up to and including Day 21 will be shared with the GSB for their approval to test the dose of 200 mg.

Part 2:

The dose for Part 2 will be decided by the SRC based on data from Part 1. Wash-out periods may be adjusted by the SRC if required. Safety and PK data from Part 2 will be reviewed by the SRC after completion of the second period of the food effect study.

8 STATISTICAL ANALYSES

8.1 GENERAL APPROACH

The following sections describe the statistical analysis as it is foreseen during the planning phase of trial. A detailed Statistical Analysis Plan (SAP) will be finalised and approved prior to database lock and will provide details of all analyses to be performed as well as the format of listings and tables to be provided for completion of the clinical study report (CSR). Any deviations from the SAP will be described and justified in the final CSR. A separate Analysis Plan will be provided for PK analysis. The study Sponsor may decide to conduct an MMV533 concentration – QTcB and/or QTcF analysis after completion/review of the study (see Section 8.9.2). This analysis, if to be conducted, will be described in a separate companion SAP and reported in a dedicated companion CSR.

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 cohort 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.

8.2 SAMPLE SIZE AND JUSTIFICATION

Sample size for this study was based upon empirical considerations. No sample size calculation was performed. The food effect evaluation is a pilot one and will be followed by a definitive powered food effect study in the future if this NCE moves into further development.

Part 1 (SAD)

Up to 64 participants including up to one optional cohort: up to 8 cohorts with 8 participants each (6 participants receiving MMV533 and 2 participants receiving placebo in each cohort).

Part 2 (Pilot food effect)

1 cohort of 8 participants all receiving MMV533.

8.3 ANALYSIS SETS AND SUB-SETS

8.3.1 Analysis Sets

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

Additional analysis populations may be defined in the SAP or the PK Analysis Plan.

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

8.3.1.1 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.

8.3.1.2 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.

8.4 PARTICIPANT DISPOSITION

A listing of participant disposition will present participant dates of informed consent, enrolment, randomisation, key visits as well as study completion details. Early termination data, including the reason for early termination will be listed in an additional listing.

A participant disposition summary table will present, at a minimum, the number of participants who completed the study and the number of participants who discontinued classified by reason for early termination.

8.5 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

8.5.1 Demographics

Demographic data will be listed for all enrolled participants and summarised by cohort and overall.

8.5.2 Medical History

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

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

8.5.3 Prior Medications

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.

8.5.4 Eligibility

Eligibility will be listed for all enrolled participants.

8.6 PROTOCOL DEVIATIONS

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 type including (but not limited to):

- Informed consent
- Eligibility
- Visit not done
- Visit performed out of window
- Study procedure not done
- Study procedure done out of window
- Safety reporting
- Investigational Product
- Privacy and Data Protection
- Concomitant Medication
- COVID 19
- Other

8.7 TREATMENT EXPOSURE

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

8.8 SAFETY (PRIMARY ENDPOINT)

8.8.1 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, urinalysis
- Physical examination

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

8.8.2 Adverse Events

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

All AE summaries will be restricted to TEAEs only, where a TEAE is defined as an AE that commences on, or after, the first administration of IMP up to EOS (inclusive). TEAEs 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.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class (SOC) and preferred terms (PT). Their severity will be graded according NCI-CTCAE v5.0.

At a minimum, the following AE summary tables will be provided:

- Overall summary of TEAEs
- All TEAEs
- TEAEs by severity
- TEAEs by relationship
- Serious TEAEs
- TEAEs leading to study withdrawal

8.8.3 Concomitant Medications

Medications used in this study will be coded using WHO-DDE.

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) and preferred name (PN). The summary tables will show the number and percentage of participants taking each medication by ATC and PN.

For the summaries of prior and concomitant medications, participants who take the same medication (in terms of the ATC and PN) more than once will only be counted once for that medication.

8.8.4 Laboratory Findings

Laboratory parameters will be listed by participant and visit, including:

- haematology,
- biochemistry,
- urinalysis,
- serology,
- drug screening,
- alcohol screening
- FSH, and
- pregnancy test.

Haematology, biochemistry and continuous urinalysis laboratory data will be summarised for each scheduled visit, including observed values, absolute change from each baseline. Categorical urinalysis results will be summarised for each scheduled visit using frequency tabulations. Shift tables may be provided.

8.8.5 Physical Examination

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

8.8.6 Body Measurements

Height and weight will be listed for all participants and visits.

For Part 2, observed values (including changes from each baseline) will be summarised for weight.

8.8.7 Vital Signs

Vital sign parameters will be listed for all participants and visits.

Observed values, as well as absolute changes from each baseline, will be summarised descriptively for all vital sign parameters by visit.

8.8.8 12-lead ECG

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. The triplicate means will be used for the summary table.

Observed values, as well as absolute changes from each baseline, will be summarised descriptively for all ECG parameters by visit. Safety analysis of ECGs will include in particular the number of participants during the study with:

- QTcF or QTcB prolongation of more than 30 msec and 60 msec, and/or
- QTcB and/or QTcF > 450 msec.

8.9 PHARMACOKINETIC ENDPOINTS

8.9.1 Pharmacokinetic Parameters

For both Parts, MMV533 PK profiles will be plotted individually and summarized by dose group and by food intake.

For both Parts, MMV533 PK parameters calculated in plasma will be summarized by dose group and by food intake using descriptive statistics. All the statistical analyses described below will be done on plasma parameters.

The t_{max} values will be represented by histogram plots for each dose level. Dose proportionality will be assessed using a power model on C_{max}, AUC_{last} and AUC.

For Part 2 only, impact of food effect on C_{max}, t_{max} AUC_{last} and AUC and $t_{1/2}$ will be assessed.

8.9.2 Concentration-ECG Analysis

This pharmacokinetic-pharmacodynamic (PK-PD) analysis will be performed after finalization of the study CSR and reported in a separate report.

Exposure-response analysis between the change from baseline in centrally-read ECG intervals and corresponding drug concentrations will be performed using graphical tools and regression methods. Estimate and 90% CI of change from baseline in ECG parameters (HR, PR, QRS, QTcB and QTcF) at the observed geometric mean of C_{max} will be computed from the final model chosen.

8.10 EXPLORATORY PARAMETERS

If applicable, exploratory parameters will be summarized by treatment group using descriptive statistics and may be reported separately.

8.11 INTERIM ANALYSIS

This trial has no formal interim analysis.

9 STUDY ADMINISTRATION

9.1 ETHICAL CONSIDERATIONS

9.1.1 Ethical Principles

This clinical study was designed and shall be implemented and reported in accordance with the Declaration of Helsinki, the Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) dated 09 November 2016 and the National Statement on Ethical Conduct in Human Research, (2007 – updated 2018).

9.1.2 Informed Consent

Eligible participants may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the participant source documents and a copy of the signed patient information and consent form provided to the participant.

9.1.3 Investigator and Human Research Ethics Committee (HREC) Responsibilities

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Human Research Ethics Committee (HREC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants.

Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the Sponsor appointed monitors, auditors, Quality Assurance representatives, HREC representatives, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the Sponsor immediately that this request has been made.

9.2 PROTOCOL ADHERENCE

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. In this instance the Sponsor medical monitor must be advised before or as soon as possible after such assessments are conducted.

Under no circumstances should an Investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs. Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study, this must be considered a protocol amendment and cannot be implemented unless such an amendment is agreed upon by the Sponsor and approved by the HREC. All significant protocol deviations will be recorded and reported in the clinical study report (CSR).

9.3 PROTOCOL AMENDMENTS

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Sponsor and the HREC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to participants

may be implemented immediately provided the Sponsors medical monitor is notified as soon as possible after the event and the reviewing HREC is subsequently notified. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, the Medical Monitor and Sponsor must be notified immediately.

9.4 DATA HANDLING AND RECORD KEEPING

Participants will be assigned a unique identifier when participating in the study, and any participant datasets or records that are transferred to the Sponsor or CRO will only contain this identifier. Any other identifiable information about the participant will not be transferred. The Principal Investigator will ensure procedures are in place to appropriately protect the confidentiality of the participant records and data, including adequate safe guards for digital/computer access. The participants will be informed that their personal study-related data will be used by the Sponsor and that their medical records may be examined by auditors and regulatory agencies.

Study-related participant data will be entered into printed or electronic case report forms (eCRFs), except for data that may be transmitted to the Sponsor or CRO electronically (such as laboratory data). The Principal Investigator is responsible for ensuring that accurate source documents for all data entered into the CRF are maintained at the study site.

All study documents including source documents and signed PICFs must be retained by the Principal Investigator for at least 15 years and according to local regulatory requirements. No study documents may be destroyed or transferred during the retention period without the Sponsor being directly notified in writing.

9.5 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor or CRO maintains responsibility for quality assurance of the data and for data management, and retains accountability for actions delegated to other parties (including CRO). Study monitors appointed by the Sponsor or CRO will conduct ongoing visits to the study sites to confirm the CRF data is accurate according to source documents and complete, and that the study is being appropriately conducted according to the protocol, ICH GCP and local regulatory requirements. Details will be provided in the Monitoring Plan.

9.6 PUBLICATION POLICY

Neither the complete nor partial results of the study achieved under this protocol, nor any of the information provided by the Sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study Sponsor. Any Investigator involved with this study is obligated to provide the Sponsor with complete study results and all data derived from the study.

Results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10 REFERENCES

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11 APPENDICES

APPENDIX 1: SPONSOR APPROVED CLINICALLY ACCEPTABLE INCLUSION LABORATORY RANGES

V3.0 24 JUNE 2020

Test	Acceptable Inclusion Range	
	Low	High
Sodium	130 mmol/L	150 mmol/L
Potassium	3.0 mmol/L	5.5 mmol/L
Chloride	0.95 x LLN	1.05 x ULN
Magnesium	0.95 x LLN	1.05 x ULN
Calcium (Corrected)	0.95 x LLN	1.05 x ULN
Glucose Fasted	N/A	1.0 x ULN
Urea	N/A	1.75 x ULN
Creatinine	N/A	1.0 x ULN
Creatine kinase	N/A	< 2.5 x ULN
Total Protein	≥ 0.85 x LLN	≤ 1.25 x ULN
Albumin	≥ 0.85 x LLN	≤ 1.25 x ULN
Total Bilirubin	N/A	1.25 x ULN
Direct Bilirubin	N/A	1.25 x ULN
ALP	N/A	1.5 x ULN
AST	N/A	1 x ULN
ALT	N/A	1 x ULN
GGT	N/A	1.5 x ULN
Lactate Dehydrogenase	0.9 x LLN	1.1 x ULN
Cholesterol	N/A	1.2 x ULN
Triglycerides	N/A	1.2 x ULN
Prothrombin time INR and APTT	1.0 x LLN	1.0 x ULN
Haemoglobin	0.9 x LLN	1.1.x ULN

Test	Acceptable Inclusion Range	
	Low	**High**
Red blood count	0.9 x LLN	1.1 x ULN
Platelets	0.9 x LLN	1.1 x ULN
White Blood Cells	0.9 x LLN	1.1 x ULN
Neutrophils	1.0 x LLN	1.0x ULN
Lymphocytes	1.0 x LLN	1.0 x ULN
Monocytes	N/A	1.2 x ULN
Eosinophils	N/A	1.0 x ULN
Basophils	N/A	2.0 x ULN
Urinalysis		
Glucose (quantitative)	N/A	< 3 mmol/L
Protein (quantitative)	N/A	< 0.16 g/L
Protein/creatinine ratio (quantitative)	N/A	< 21 mg/mmol
Red Blood Cells (quantitative)	N/A	<20 x 10^6/L*
White Blood Cells (quantitative)	N/A	<10 x 10^6/L
Organism (quantitative)	NA	< 1+
Ketones (dipstick)	N/A	< 1+
Nitrate (dipstick)	NA	Negative
Bilirubin (dipstick)	N/A	< 1+
Urobilinogen (dipstick)	N/A	< 1+

ABBREVIATIONS: ALP = alkaline phosphatase; ALT = alanine transaminase; APTT = activated partial thromboplastin time; AST = aspartate transaminase; GGT = gamma-glutamyl transferase; INR = international normalised ratio; LLN = lower limit of normal; N/A = not applicable; ULN = upper limit of normal.

*A result ≥ 20 x 10^6/L is acceptable for female participants currently menstruating.

APPENDIX 2: SEVERITY GRADING FOR FASTING TBA IN PHASE 1 VOLUNTEERS

Fasting-TBA in Phase1 Volunteers

Proposed severity grading

	CTCAE – General Definitions	Fasting TBA Change	Lab Range
Grade 1 (Mild)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	**>ULN - 2.5 x ULN**	> 9 - 22.5
Grade 2 (Moderate)	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.	**>2.5 - 5.0 x ULN**	> 22.5 - 45
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.	**>5.0 - 15.0 x ULN**	> 45 - 135
Grade 4	Life-threatening consequences; urgent intervention indicated.	**>15.0 x ULN**	>135

Activities of Daily Living (ADL)

**Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

***Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*