nature metabolism

Supplementary information

https://doi.org/10.1038/s42255-025-01311-z

A nitroalkene derivative of salicylate, SANA, induces creatine-dependent thermogenesis and promotes weight loss

In the format provided by the authors and unedited

CLINICAL STUDY REPORT

A Phase 1, Randomised, Double-blind, Placebo-controlled, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Doses of MVD1 in Normal Weight or Overweight Healthy Adults Volunteers and Multiple Doses of MVD1 in Overweight or Obese Healthy Adult Volunteers.

Protocol No.: MVD1-AU-001

08 Nov 2024

Version 1.0

CONFIDENTIAL

1. TITLE PAGE

Study Title:	A Phase 1, Randomised, Double-blind, Placebo-controlled, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Doses of MVD1 in Normal Weight or Overweight Healthy Adult Volunteers and Multiple Doses of MVD1 in Overweight or Obese Healthy Adult Volunteers
Protocol No.:	MVD1-AU-001
Study Treatment:	MVD1 capsules
Placebo:	Placebo capsules containing microcrystalline cellulose
Indication:	Healthy and Healthy Obese Adults
Study Design:	This was a Phase 1, First-in Human, single and multiple dose escalation clinical study conducted in normal weight or overweight healthy adult and healthy overweight or obese adult volunteers. The safety, tolerability, pharmacokinetics and pharmacodynamics of MVD1 following single and multiple dose administrations was evaluated using a randomised, double-blind, placebo-controlled study design.
Development Phase:	Phase 1
Sponsor:	Eolo Pharma Pty Ltd
Sponsor Signatory:	Carlos Batthyany
Principal Investigator:	Professor Sepehr Shakib
Study Dates:	First Participant Screened: 21 Feb 2023 First Participant Dosed: 10 Mar 2023 Last Participant Visit Completed:12 Apr 2024
Report Date:	Version 1.0, 08Nov2024

This study was conducted in accordance with the World Medical Association Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP) E6 (R2), the applicable regulatory requirements, and the Australian National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research incorporating all updates.

2. SYNOPSIS

<table>
<tr><td>Name of Sponsor:
Eolo Pharma Pty Ltd</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For national Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
MVD1</td></tr>
<tr><td>Name of Active Ingredient:
MVD1 (2-hydroxy-5-[(E)-2-nitroethenyl] benzoic acid)</td></tr>
<tr><td colspan="3">Title of Study:
A Phase 1, Randomised, Double-blind, Placebo-controlled, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Doses of MVD1 in Normal Weight or Overweight Healthy Adult Volunteers and Multiple Doses of MVD1 in Overweight or Obese Healthy Adult Volunteers</td></tr>
<tr><td colspan="3">Investigator: Professor Sepehr Shakib</td></tr>
<tr><td colspan="3">Investigational site:
CMAX
Ground Floor, 21-24 North Terrace
Adelaide SA 5000 Australia</td></tr>
<tr><td colspan="3">Publication (reference): There have been no publications at the time of writing this report.</td></tr>
<tr><td colspan="2">Study Period (years):
Date of first participant screened: 21 Feb 2023
Date of last participant visit completed: 12 Apr 2024</td><td>Phase of Development: 1</td></tr>
<tr><td colspan="3">Objectives:
<u>Primary:</u>
To investigate the safety and tolerability of single and 15-day repeat oral doses of MVD1 in healthy adult volunteers and healthy obese adult volunteers respectively.
<u>Secondary:</u>
To assess the pharmacokinetics (PK) of MVD1 and metabolites in plasma and urine following administration of single and 15-day repeat oral doses in healthy volunteers and healthy obese adult volunteers.
<u>Exploratory (Part B only):</u>
To investigate biomarker changes following administration of multiple doses of MVD1 in healthy obese adult volunteers.
To investigate MVD1 exposure in white adipose tissue.
To evaluate the participant’s impression of change following study treatment.</td></tr>
</table>

Methodology:

This was a Phase 1, first-in-human (FIH) randomised, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK and PD of single doses of MVD1 in normal weight or overweight healthy adult volunteers and multiple ascending doses of MVD1 in overweight or obese healthy adult volunteers.

The study was conducted in 2 parts:

Part A: Single ascending dose (SAD) in normal weight or overweight healthy adult volunteers.

Part B: Multiple ascending dose (MAD) in overweight or obese healthy adult volunteers.

A total of up to 42 healthy and healthy obese adult volunteers were planned to be enrolled across the two study parts (Part A and Part B).

Part A (SAD) consisted of 3 cohorts (S1-S3) with 6 participants planned per cohort, randomised at a ratio of 2:1 (MVD1: placebo) within each cohort. Participants were dosed once a day via oral route of administration.

Part B (MAD) consisted of 3 cohorts (M1-M3) with 8 participants planned per cohort, randomised at a ratio of 3:1 (MVD1: placebo) within each cohort. Participants were dosed twice a day (administered approximately 12 hours apart, one in the morning and one in the evening) for 14 days, with a single dose administered on Day 15 via oral route of administration.

Dose escalation was planned for Part A (SAD) and Part B (MAD), as described in Table S-A.

Table S-A Planned Administration of Study Drug

Cohort	MVD1 Dose (mg)	Number of Participants	
		MVD1	Placebo
Part A (SAD): Single Oral Administration			
S1	200 mg	4	2
S2	400 mg	4	2
S3	800 mg	4	2
Part B (MAD): Twice Daily Oral Administration			
M1	200 mg (2 x 100 mg)	6	2
M2	300 mg (2 x 150 mg)	6	2
M3	400 mg (2 x 200 mg)	6	2

Abbreviations: MAD = multiple ascending dose; SAD = single ascending dose.

The decision to escalate between dose levels in Part A (SAD) and proceed from Part A to Part B (MAD) was based on review of the safety and available PK data by the safety review committee (SRC). A dose level was only evaluated in Part B, if it was determined to be safe in Part A.

In Part A (SAD), normal weight or overweight healthy adult volunteers were screened between Day -28 and Day -2, inclusive. Participants eligible to be included in the study were admitted to the investigational site on Day -1. Following confirmation of eligibility on Day 1, participants were enrolled and randomised to receive either MVD1 or placebo. Dosing occurred on Day 1 with MVD1 or placebo in a double-blind manner. Participants were discharged from the clinical facility on Day 4 following completion of study assessments and were required to attend the clinic for a final follow-up visit on Day 8 ± 1 day.

For each Part A cohort, dosing was initiated in 2 sentinel participants with 1 participant randomised to receive MVD1 and the other randomised to receive placebo. The remainder of the participants within each cohort only commenced dosing following satisfactory review of sentinel Day 2 data by the Principal Investigator (PI)/Independent Medical Monitor (IMM).

Escalation to the next dose level occurred following satisfactory Safety Review Committee (SRC) review of available safety data up to Day 4 and available PK data from all participants at that dose

level. In Part B (MAD), healthy obese adult volunteers were screened between Day -35 and Day -2, inclusive. Participants eligible to be included in the study were admitted to the investigational site on Day -1. Following confirmation of eligibility on Day 1, participants were enrolled and randomised to receive either MVD1 or placebo. Dosing occurred on Days 1 to15 with MVD1 or placebo (two daily oral doses of study drug taken 12 hours apart [morning and evening] on Days 1-14 with a final single dose administration on the morning of Day 15) in a double-blind manner. Participants were discharged from the clinical facility on Day 18 following completion of study assessments and were required to attend the clinic for a final follow-up visit on Day 22 ± 1 day. Sentinels were not included in Part B.

Escalation to the next dose level occurred following satisfactory SRC review of available safety data up to Day 18 and available PK data from all participants at that dose level. Body weight was measured at Day 1, 15 and 22. Blood samples for PK and PD analysis were to be collected pre-dose and at several timepoints post-dose.

Diagnosis and Main Criteria for Inclusion – Part A (SAD):

Healthy volunteers were included in Part A (SAD) of the study if they satisfied all the following criteria (assessed at the screening visit and prior to administration on study Day 1, unless otherwise specified):

1. Must have given written informed consent before any study-related activities were carried out and must have been able to understand the full nature and purpose of the trial, including possible risks and adverse effects.
2. Male or female, 18-60 years of age inclusive at the time of screening.
3. Body mass index (BMI) ≥ 20 and < 30 kg/m^2 at the time of screening.
4. Female participants:
    a. Must have been of non-childbearing potential i.e., surgically sterilized (hysterectomy, bilateral salpingectomy, bilateral oophorectomy or bilateral tube ligation/occlusion at least 6 weeks before the Screening visit) or postmenopausal where menopause is defined as 12 months of amenorrhea without an alternative medical cause (females must have had a documented serum follicle stimulating hormone level consistent with postmenopausal status, per local laboratory guidelines) OR
    b. If of childbearing potential (defined as any female who has experienced menarche and who has not undergone surgical sterilization and is not postmenopausal), must have agreed to not attempt to become pregnant, to not donate ova and must have agreed to use an acceptable form of contraception (protocol Appendix 8) from signing the consent form until at least 30 days after the last dose of study drug.
5. Male participants:
    a. Must have been biologically or surgically sterile (i.e., have had a vasectomy at least 3 months prior to screening) OR
    b. If not biologically or surgically sterile, must have agreed not to donate sperm and agreed to use an acceptable contraceptive method (protocol Appendix 8) in addition to having the female partner use an acceptable contraceptive method from signing the consent form until at least 90 days after the last dose of study drug.
6. Participant was willing and able to comply with all scheduled visits, treatment plans, laboratory tests and other study procedures.

Diagnosis and Main Criteria for Exclusion – Part A (SAD):

Normal weight or overweight healthy volunteers were excluded from Part A (SAD) of the study if there was evidence of any of the following (assessed at the screening visit or prior to administration of the first dose on study Day 1):

1. History or presence of significant cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic or neurological disease, including any acute illness or major surgery within the past 3 months determined by the PI to be clinically significant (CS).
2. Current infection that required systemically absorbed antibiotic, antifungal, antiparasitic or antiviral medications.
3. Any history of malignant disease in the last 10 years (excluded surgically resected skin squamous cell or in situ cervical squamous cell or basal cell carcinoma).
4. Screening 12-lead ECG outside the normal range for the triplicate mean (QT interval corrected using the Fridericia method (QTcF) males > 450 msec; females > 470 msec) or with abnormalities, which were hazardous to the participant according to the opinion of the Investigator.
5. Presence of clinically relevant immunosuppression from, but not limited to, immunodeficiency conditions such as common variable hypogammaglobulinemia.
6. Use of or planned to use systemic immunosuppressive (e.g., corticosteroids, methotrexate, azathioprine, cyclosporine) or immunomodulating medications (e.g., interferon) during the study or within 3 months prior to the first study drug administration.
7. History of risk factors for torsade de pointes (including a family history of long QT syndrome or sudden cardiac death) or a known arrythmia.
8. Change in body weight of ≥ 5% within 6 months prior to screening visit.
9. Liver function test results elevated more than 1.5-fold above the upper limit of normal (ULN) for gamma glutamyl transferase (GGT), bilirubin (total or unconjugated), alkaline phosphatase (ALP), aspartate transferase (AST) or alanine aminotransferase (ALT).
10. Positive test results for active human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibodies at the screening visit.
11. Presence or having sequelae of gastrointestinal, liver (including Gilbert's syndrome), kidney, or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs.
12. Estimated glomerular filtration rate (eGFR) < 60 mL/min/ 1.73 m^2 or serum creatinine more than 1.5-fold above the ULN.
13. History of substance abuse or alcohol abuse (defined as more than 10 standard drinks per week or regularly consumed more than 4 standard drinks on any one day; where 1 standard drink is 10 g of pure alcohol and is equivalent to 285 mL beer [4.9% Alc./Vol], 100 mL wine [12% Alc./Vol], 30 mL spirit [40% Alc./Vol]) within 12 weeks prior to the screening visit.
14. Positive urine cotinine test, drugs of abuse or alcohol breath test results at the screening visit or at check-in (Day -1).
15. Use of any prescription or over-the-counter medication (including herbal products, diet aids, hormone supplements, topical ointments, vitamins and dietary supplements) within 10 days or 5 half-lives of the medication (whichever is longer) prior to the first study drug administration, with the exception of hormonal contraceptives, medications used to manage adverse events (AEs) including the occasional use of paracetamol (doses of 500 mg up to every 6 hours or 2 g per day maximum for no more than 3 consecutive days).

16. Demonstrated CS (required intervention, e.g., emergency room visit, epinephrine administration) allergic reactions (e.g., food, drug, or atopic reactions, asthmatic episodes) which, in the opinion of the Investigator, would have interfered with the volunteer's ability to participate in the trial.
17. Known hypersensitivity to any of the study drug ingredients.
18. Use of any vaccinations within 14 days prior to the first study drug administration.
19. For women of childbearing potential (WOCBP), a positive serum pregnancy test at the screening visit or a positive urine pregnancy test (with confirmatory serum pregnancy test) at check-in (Day -1).
20. Females who were lactating at any time during the study.
21. Donation of blood or plasma within 30 days prior to first study drug administration, or loss of whole blood of more than 500 mL within 30 days prior to first study drug administration, or receipt of a blood transfusion within 1 year of first study drug administration.
22. Participation in another clinical trial of an investigational drug within 60 days or 5 half-lives of the investigational agent (whichever was longer) prior to the first study drug administration.
23. Difficulty in swallowing the study medication.
24. Any other condition or prior therapy that in the opinion of the Investigator would have made the volunteer unsuitable for this study, including inability to cooperate fully with the requirements of the study protocol or likelihood of noncompliance with any study requirements.

Diagnosis and Main Criteria for Inclusion – Part B (MAD):

Overweight or obese healthy volunteers were included in Part B (MAD) of the study if they satisfied all the following criteria (assessed at the screening visit and prior to administration on study Day 1):

1. Must have given written informed consent before any study-related activities were carried out and must have been able to understand the full nature and purpose of the trial, including possible risks and adverse effects.
2. Male or female, 25-60 years of age inclusive at the time of screening.
3. In good health as determined by the outcome of medical history, physical examination, and clinical judgement by the Investigator. Chronic stable non-inflammatory conditions such as, hypertension, hyperlipidemia, osteoarthritis, gout, Chronic Pain Disorders, Thyroid Disease, controlled psychiatric conditions such as anxiety or depression, were permitted, as determined by the Investigator.
4. Body mass index (BMI) between 28 and 35 kg/m^2 at the time of screening.
5. Female participants:
    a. Must have been of non-childbearing potential i.e., surgically sterilized (hysterectomy, bilateral salpingectomy, bilateral oophorectomy or bilateral tube ligation/occlusion at least 6 weeks before the Screening visit) or postmenopausal where menopause is defined as 12 months of amenorrhea without an alternative medical cause (females must have had a documented serum follicle stimulating hormone level consistent with postmenopausal status, per local laboratory guidelines) OR
    b. If of childbearing potential (defined as any female who has experienced menarche and who has not undergone surgical sterilization and was not postmenopausal), had to agree not to attempt to become pregnant, and not donate ova and agreed to use an acceptable form of contraception (protocol Appendix 8) from signing the

consent form until at least 30 days after the last dose of study drug.

6. Male participants:
    a. Must have been biologically or surgically sterile (i.e., have had a vasectomy at least 3 months prior to screening) OR
    b. If not biologically or surgically sterile, must have agreed not to donate sperm and agreed to use an acceptable contraceptive method (protocol Appendix 8) in addition to having the female partner use an acceptable contraceptive method from signing the consent form until at least 90 days after the last dose of study drug.
7. Willing and able to comply with all scheduled visits, treatment plans, laboratory tests and other study procedures.

Diagnosis and Main Criteria for Exclusion – Part B (MAD):

Overweight or obese healthy volunteers were excluded from this study if there was evidence of any of the following at the screening visit or prior to administration of the first dose on study Day 1:

1. History or presence of significant cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic or neurological disease, including any acute illness or major surgery within the past 3 months determined by the PI to be CS.
2. Current infection that required systemically absorbed antibiotic, antifungal, antiparasitic or antiviral medications.
3. Any history of malignant disease in the last 10 years (excluded surgically resected skin squamous cell or in situ cervical squamous cell or basal cell carcinoma).
4. Screening 12-lead ECG outside the normal range for the triplicate mean (QT interval corrected using the Fridericia method (QTcF) males > 450 msec; females > 470 msec) or with abnormalities, which were hazardous to the participant according to the opinion of the Investigator.
5. Presence of clinically relevant immunosuppression from, but not limited to, immunodeficiency conditions such as common variable hypogammaglobulinemia.
6. Use of or planned to use systemic immunosuppressive (e.g., corticosteroids, methotrexate, azathioprine, cyclosporine) or immunomodulating medications (e.g., interferon) during the study or within 3 months prior to the first study drug administration.
7. History of risk factors for torsade de pointes (including a family history of long QT syndrome or sudden cardiac death) or a known arrythmia.
8. Change in body weight of ≥ 5% within 6 months prior to screening visit.
9. Liver function test results elevated more than 1.5-fold above the ULN for GGT, bilirubin (total or unconjugated), ALP, AST or ALT.
10. Positive test results for active HIV, HBsAg or HCV antibodies at the screening visit.
11. Presence or having sequelae of gastrointestinal, liver, kidney, or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs.
12. eGFR < 60 mL/min/ 1.73 m^2 or serum creatinine more than 1.5-fold above the ULN.
13. History of substance abuse or alcohol abuse (defined as regularly consuming more than 4 standard drinks on any one day; where 1 standard drink is 10 g of pure alcohol and is equivalent to 285 mL beer [4.9% Alc./Vol], 100 mL wine [12% Alc./Vol], 30 mL spirit [40% Alc./Vol]) within 12 weeks prior to the screening visit.
14. Positive urine cotinine test, drugs of abuse or alcohol breath test results at the screening visit or at check-in (Day -1).
15. Use of any prescription or over-the-counter medication (including herbal products, diet

aids, hormone supplements, topical ointments, vitamins and dietary supplements) within 10 days or 5 half-lives of the medication (whichever is longer) prior to the first study drug administration, with the exception of hormonal contraceptives, medications used to manage AEs including the occasional use of paracetamol (doses of 500 mg up to every 6 hours or 2 g per day maximum for no more than 3 consecutive days), stable use (4 weeks or longer prior to screening) of medications used to treat hypertension and high cholesterol and medications for hay fever.

16. Demonstrated CS (required intervention, e.g., emergency room visit, epinephrine administration) allergic reactions (e.g., food, drug, or atopic reactions, asthmatic episodes) which, in the opinion of the Investigator, would have interfered with the volunteer's ability to participate in the trial.
17. Known hypersensitivity to any of the study drug ingredients.
18. Use of any vaccinations within 14 days prior to the first study drug administration.
19. For WOCBP, a positive serum pregnancy test at the screening visit or a positive urine pregnancy test (with confirmatory serum pregnancy test) at check-in (Day -1).
20. Females who were lactating at any time during the study.
21. Donation of blood or plasma within 30 days prior to first study drug administration, or loss of whole blood of more than 500 mL within 30 days prior to first study drug administration, or receipt of a blood transfusion within 1 year of first study drug administration.
22. Participation in another clinical trial of an investigational drug within 60 days or 5 half-lives of the investigational agent (whichever was longer) prior to the first study drug administration.
23. Difficulty in swallowing the study medication.
24. Any other condition or prior therapy that in the opinion of the Investigator would have made the volunteer unsuitable for this study, including inability to cooperate fully with the requirements of the study protocol or likelihood of noncompliance with any study requirements.
25. A screening urinalysis result, or first morning urine protein dipstick result on Day 1 prior to first dose of study drug showing more than a trace of protein. Test may have been repeated to confirm.
26. Body weight > 120 kg at screening.

Test Product, Dose, and Mode of Administration, Batch Number:

MVD1 drug substance (batch # CM-BPR-N4661-02-001-20-RPK1) was manufactured by Eurofins Advinus India. The drug product consisted of MVD1 drug substance packed into opaque hard gelatine capsules for oral administration and were prepared and labelled by Syntro Health.

Duration of Study Participation:

Part A (SAD): The maximum duration for each participant in Cohorts S1-S3 was up to 37 days, inclusive of visit windows. Participants underwent a Screening Period of up to 27 days, a 5-day confinement period, and an end of study follow-up visit on Day 8 (± 1 day).

Part B (MAD): The maximum duration for each participant in Cohorts M1-M3 was up to 58 days, inclusive of visit windows. Participants underwent a Screening Period of up to 34 days, a 19-day confinement period, and an end of study follow-up visit on Day 22 (± 1 day).

Reference Therapy, Dose, and Mode of Administration, Batch Number:

The placebo was prepared as the same amount of microcrystalline cellulose (manufactured by Accent Microcell Ltd. India) as the dose level for that cohort, in opaque hard gelatine capsules for oral administration.

Criteria for Evaluation:

Primary Endpoints

Safety endpoints included the evaluation of the following:

- Safety endpoints as change from baseline and where appropriate over time and versus placebo, included:
  - Incidence, severity, and relationship of AEs or serious adverse events (SAEs) (including withdrawals due to AEs)
  - Change in vital signs
  - Change in ECG parameters
  - Change in clinical laboratory parameters (hematology, serum chemistry, coagulation, and urinalysis)
  - Stool diary
  - Nutritional appetite questionnaire (Part B only)

Secondary Endpoints

Plasma MVD1 and metabolite M1 PK endpoints included:

- Maximum observed plasma concentration (C_{max})
- Time to C_{max} (T_{max})
- Area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration ($AUC_{0\text{-}last}$)
- Area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$), following single dose only
- Apparent terminal elimination half-life ($\tau_{1/2}$)
- Terminal elimination rate constant (λz)
- Apparent clearance (CL/F)
- Apparent volume of distribution (Vz/F) (Part A only)
- Minimum observed concentration (C_{min}) (Day 15) (Part B only)
- Area under the plasma concentration-time curve from time 0 to 12 hours ($AUC_{0\text{-}12}$)

Urine MVD1 PK endpoints included (but were not limited to):

- Cumulative amount of unchanged drug excreted (Ae) in urine
- Renal clearance (CLr)

Exploratory Endpoints (Part B only)

MVD1 PD endpoints included (but were not limited to) a change from baseline in the following serum biomarkers:

- Glucose
- Oral glucose tolerance test (OGTT)
- Insulin
- C peptide
- High sensitivity C reactive protein (hsCRP)
- Fructosamine
- Glycohemoglobin (MAD cohorts M1 and M2 only)
- Free fatty acids
- Triglycerides
- Leptin levels

Additional exploratory endpoints included:

- MVD1 target engagement in white adipose tissue sampled using a single needle biopsy on Day -1 and Day 7.
- Body Weight (Day -1, Day 15 and Day 22)
- Patient general impression of change (PGIC) questionnaire completed by study participants at the end of the study treatment period.

Statistical Methods:

Adverse Events

AE verbatim terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.1. All AE summaries were restricted to treatment-emergent adverse events (TEAEs) only and summarised by system organ class (SOC), preferred term (PT), causality and severity.

These were presented using summary tables which included the number of participants and percentage (%) of participants experiencing an event followed by the number of events.

All AEs were listed and included the verbatim term, SOC, PT, SAE, TEAE, start/end date/time, severity, relationship to study treatment, outcome, action taken, and study withdrawal.

Safety Laboratory Assessments

For haematology, coagulation and serum chemistry continuous data summary statistics were presented for observed values and change from baseline values at each visit and timepoint. Where applicable, clinical assessment results (normal, abnormal not clinically significant [NCS], and abnormal CS) were summarised by counts and percentages for baseline and each scheduled visit.

For urinalysis, clinical assessment of abnormality (normal/abnormal NCS/abnormal CS) was presented at each visit and timepoint.

The listings of laboratory parameters were presented by treatment group and included all the information collected. The change from baseline values (where applicable) at each post-baseline (scheduled and unscheduled) visit were presented.

Vital Sign Measurements

Observed values and changes from baseline for vital signs (systolic and diastolic BP, HR and body temperature) were summarised at each baseline and scheduled post-baseline visit using descriptive statistics and tabulated for each dose group. In addition, overall clinical interpretation (normal, abnormal NCS, abnormal CS) was summarised. A shift table from baseline to worst outcome on treatment for clinical interpretation was also presented by treatment group.

For Part B, a summary of change between post-dose and pre-dose values was also presented for each dose and time point.

All available vital signs results were displayed in a data listing and included all information collected.

Electrocardiograms

The following ECG parameters were analysed; PR interval, QT interval, QRS duration, QTcF and ventricular HR. Observed values and changes from baseline for ECG parameters were summarised at each scheduled timepoint using descriptive statistics and tabulated for each dose group. In addition, clinical results of ECG interpretations (Normal, Abnormal NCS, and Abnormal CS) were summarised by counts and percentages for baseline and for each scheduled post baseline visit. A shift table from baseline to worst outcome on treatment for clinical interpretation was also presented by treatment group for the SS. For Part B, a summary of change between post-dose and pre-dose values was also presented for each dose and time point.

Physical Examinations

All physical examination data was listed. The listing is presented by the treatment groups sorted by participant ID and visit, along with age, sex, race and baseline weight of the participant.

Stool Diary

All available stool diary results were listed. The listing is presented by the treatment groups sorted by participant ID and visit for the Safety Analysis Set, along with age, sex, race and baseline weight of the participant.

Simplified Nutritional Appetite Questionnaire

All available results were listed, presented by the treatment groups sorted by participant ID and visit, along with age, sex, race and baseline weight of the participant.

Pharmacokinetics

Plasma and Urine Concentration Data

Individual plasma and urine concentrations of MVD1 and metabolites were used for analyses as supplied by the laboratory (including units). Actual sampling date and time, if available, were listed for plasma, by participant and nominal sampling time, with time deviation (difference in hours between nominal and actual sampling times) calculated. Individual plasma concentrations of MVD1 and metabolites over actual time were plotted by cohort with the concentration result (y-axis) displayed on linear and semi-logarithmic scales.

Pharmacokinetic Parameter Calculation

A non-compartmental analysis was conducted in plasma using Phoenix WinNonlin software version 8.3. Following oral (capsule) route of administration, MVD1 and metabolites were analysed using the extravascular model. Parameters were generated following single dosing on Day 1 (Parts A and B) and Day 15 (Part B), using actual sampling times and doses, if available. For the purposes of the PK parameter calculations, concentrations that were below the limit of quantification (BLQ) were treated as zero.

Statistical Analysis of Plasma Concentration and Pharmacokinetic Parameters

Plasma and urine concentrations and PK parameters were summarised using descriptive statistics (number of non-missing observations [n], arithmetic mean, standard deviation, coefficient of variation [CV%], geometric mean, median, minimum and maximum, and geometric CV%) for each time point and by treatment group. Urine Concentrations were summarised by interval rather than timepoint. Concentrations < BLQ were treated as zero in the calculation of summary statistics, except geometric mean. BLQ values were excluded from the calculation of geometric mean.

Mean plasma concentrations over scheduled time were plotted with the concentration result (y-axis) displayed on linear and semi-logarithmic scales.

Dose proportionality was assessed using the Power Model for all dosed cohorts. Natural log-transformed PK parameter overall C_{max}, total AUC_{last} and AUC_{inf} and natural log-transformed dose was used to estimate the slope parameter and the 90% CI for the slope. Plasma PK parameters were assessed by fitting the following power model and testing the null hypothesis of linearity, that $\beta = 1$, by a generalised linear model (GLM) approach using the GLM procedure in SAS:

$$\ln(\text{Parameter}) = \alpha + \beta \times \ln(\text{Dose}) + \text{random error}$$

Dose proportionality was generally concluded if the 90% CI around the slope estimate (β) included the value of 1. R square was also computed.

The relationship between PK parameters and dose was also presented graphically. All tables and figures were produced using SAS.

Pharmacodynamics (Part B only)

Pharmacodynamic data was analysed using the Pharmacodynamic Analysis Set (PDS) and presented for Part B only.

Serum Biomarkers

The following biomarkers assessed were taken at timepoints specified in the SoA:

- Glucose, Insulin, C peptide, hsCRP, Fructosamine, Glycohemoglobin (Cohort MAD 1 and MAD 2 only), Free fatty acids, Triglycerides, Leptin levels and body weight. Continuous data summary statistics were presented for values and change from baseline value at baseline and each scheduled post baseline visit. A figure is presented showing mean values over time for each parameter.
- All serum biomarker results are presented in a data listing and include all information collected. In addition, observations that were used as the baseline record (value) for each parameter were flagged, and the change from baseline values (where applicable) at each scheduled post baseline (scheduled and unscheduled) visit are presented.

Oral Glucose Tolerance Test

An Oral Glucose Tolerance Teats (OGTT) was conducted on Day -1 and on Day 16. The OGTT was conducted following an overnight fast of at least 8 hours. After an initial blood sample had

been collected to establish baseline fasting glucose, participants were required to consume ~75 grams of glucose administered in 250 mL water. Blood samples were obtained at 1 hour and 2 hours post glucose challenge to determine glucose tolerance.

Continuous data summary statistics are presented for values and change from baseline value at baseline and each scheduled post baseline visit. A figure is also presented showing mean values at each visit and time point with all treatment groups presented on the same page.

All OGTT results are presented in a data listing and include all information collected. In addition, the observations that are used as the baseline record (value) for each parameter were flagged, and the change from baseline values (where applicable) at each scheduled post baseline (scheduled and unscheduled) visit are presented.

Exploratory Analyses

White adipose tissue sampling

A single sample of white adipose tissue was obtained by punch biopsy approximately 2 hours following the morning dose of study drug on Day 7 (Part B) which was analysed for the presence of MVD1.

All white adipose tissue sampling results are displayed in a data listing and include all information collected, including presence of MVD1. This listing is presented by the treatment groups, sorted by participant ID and visit, along with age, sex, race, and baseline weight of the participant.

Patient General Impression of Change

The PGIC is a scale that asks the participant to rate how much their disease has improved or worsened relative to a baseline state after starting an intervention. PGIC was assessed at the time points specified in the study procedure schedule.

Since the start of the study, my general health is:

1 = Very Much Improved
2 = Much Improved
3 = Slightly Improved
4 = No Change
5 = Slightly Worse
6 = Much Worse
7 = Very Much Worse

All PGIC results are displayed in a data listing and include all information collected. This listing is presented by the treatment groups, sorted by participant ID and visit, along with age, sex, race, and baseline weight of the participant.

Results:

Safety:

Across study Part A (SAD), 18 TEAEs were reported in 6 (35.3%) of 17 participants, the incidence of which was similar in participants administered MVD1 (12 events in 4 [36.4%] of 11 participants) and placebo (6 events in 2 [33.3%] of 6 participants). There was a higher incidence of TEAEs in the MVD1 800 mg group (5 TEAEs reported in 2 [66.7%] of 3 participants) compared to the 200 mg and 400 mg groups (5 TEAEs reported in 1 [25.0%] of 4 participants and 2 TEAEs reported in 1 [25.0%] of 4 participants, respectively). There were no serious TEAEs or TEAEs resulting in study drug discontinuation, withdrawal from the study or death. The majority of TEAEs were mild in severity (13 TEAEs in 3 [17.6%] of 17 participants) and 5 TEAEs were of moderate severity reported in 3 [17.6%] of 17 participants (2 administered MVD1 and 1 administered placebo). There were no severe or life threatening TEAEs reported. There were 8 TEAEs in 5 [29.4%] of 17 participants considered related to study drug. The majority of the related TEAEs were mild in severity (6 related TEAEs in 3 (17.6%) of 17 participants) with 2 related TEAEs in 2 (11.8%) participants of moderate severity.

Across study Part B (MAD), 107 TEAEs were reported in 24 (100%) of 24 participants, the incidence of which was the same in participants administered MVD1 (76 events in 18 [100%] of 18 participants) and placebo (31 events in 6 [100%] of 6 participants). There appeared to be an increase in the number of TEAEs with increasing dose of MVD1 although the incidence of events in each group was the same (200 mg had 16 TEAEs reported in 6 [100%] of 6 participants, 300 mg had 26 TEAEs reported in 6 [100%] of 6 participants, and 400 mg MVD1 had 34 TEAEs reported in 6 [100%] of 6 participants). There were no serious TEAEs or TEAEs resulting in death. There was one TEAE in 1 (16.7%) of 6 participants leading to study drug discontinuation and study withdrawal in the 200 mg MVD1 group. The majority of TEAEs were mild in severity (102 TEAEs in 19 [79.2%] of 24 participants) and 5 TEAEs of moderate severity reported in 5 [20.8%] of 24 participants. Four moderate TEAEs were reported in 4 (22.2%) of 18 participants administered MVD1, 2 (33.3%) of each of the 6 participants in the 300 mg MVD1 and 400 mg MVD1 treatment groups. One moderate TEAE was reported for 1 (16.7%) of 6 participants in the placebo group. There were no severe or life threatening TEAEs reported. There were 18 TEAEs for 13 [54.2%] of 24 participants considered related to study drug. The majority of the related TEAEs were mild in severity (17 related TEAEs in 12 (50.0%) of 24 participants) with 1 related TEAE in 1 (4.2%) participant of moderate severity. The majority of TAEs observed in the study were not related to study drug and were due to biopsy or blood extraction procedures. Across Parts A and B, there were no abnormalities in hematology, serum chemistry or coagulation parameters which were deemed by the PI to be CS or met the criteria of an AE. No CS changes were seen for vital signs or physical examinations.

Pharmacokinetic:

Single dose PK characteristics of MVD1 were assessed in 11 participants, for ascending dose levels of 200, 400 and 800 mg. Multiple dose PK characteristics of MVD1 were assessed in 18 participants, for ascending total daily dose levels of 200, 300, and 400 mg.

The average elimination half-life of MVD1 was approximately 1.5-2.0 hours. There was minimal accumulation over the 15 days of multiple dosing BID, with pre-dose trough levels of MVD1 from Day 2 onwards generally quantifiable but quite low.

For the metabolite M1, the average elimination half-life was 1.5-2.5 hours. There was minimal accumulation for the metabolite, with pre-dose trough levels of M1 generally quantifiable but quite low. The ratio of metabolite M1 to MVD1 remained constant at approximately 30-40% as the dose of MVD1 increased.

For single dose, the mean exposure parameters increased monotonically by dose level in an approximately dose proportional manner, however the power model analyses did not meet criteria for dose proportionality for MVD1. For multiple dosing, the power model accounted for less than 50% of the variability in exposure versus dose except for MVD1 AUC_{0-12} on Day 1 and also dose dependence was noted to be non-monotonic on Day 15.

Median T_{max} varied across dose levels with no dose related trend.

There was little MVD1 excreted unchanged in urine (< 10%). It is noted that there was no noticeable increase in amount excreted at the highest dose level for single and multiple dosing. More of the drug was excreted in urine as metabolite M1 than as unchanged MVD1.

Pharmacodynamic:

Pharmacodynamic data from Part B suggest no significant changes in the PD biomarkers assessed (i.e., glucose, insulin, C-peptide, fructosamine, free fatty acids, triglycerides, leptin levels, OGTT and cytokines) when participants were given multiple doses of MVD1. Following multiple administrations of MVD1 (400 mg, 200 mg/12 hrs) after 15 days of treatment significant body weight reduction was observed, demonstrating encouraging efficacy of MVD1.

Conclusions:

This was a Phase 1, First-in Human, single and multiple dose escalation clinical study conducted in normal weight or overweight healthy adults and healthy overweight or obese adults. The safety, tolerability, pharmacokinetics and pharmacodynamics of MVD1 following single and multiple dose administrations was evaluated using a randomised, double-blind, placebo-controlled study design.

There were no clear differences in safety as assessed by AE monitoring, clinical laboratory tests, vital signs, physical examinations, ECG assessments and PD biomarkers between MVD1 and placebo following administration of single or multiple doses, and no dose related trends were noted. MVD1 demonstrated body weight reduction efficacy following multiple doses at 400 mg. MVD1 was generally well tolerated when delivered as single and multiple doses in the range of 200 mg to 800 mg. There were no deaths or other SAEs reported in this study.

3. TABLE OF CONTENTS

3.1 LIST OF IN-TEXT FIGURES

Figure 10-A *Enrolment, Disposition, and Analysis Populations (Part A – SAD)..... 93*

3.2 LIST OF IN-TEXT TABLES

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ACR	Albumin:creatinine ratio
ADL	Activities of daily living
Alc	Alcohol
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ARS	All randomised analysis set
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical classification
BID	Twice a day
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
cGMP	Current good manufacturing practice
COVID-19	Coronavirus disease 2019
COX	Cyclooxygenase
CS	Clinically significant
CSR	Clinical Study Report
DIO	Diet induced obesity
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EIU	Exposure in utero
EoS	End of study
ETV	Early termination visit
FDA	Food and Drug Administration
FIH	First in human
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GGT	Gamma-glutamyl transpeptidase
GMP	Good manufacturing practice
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotrophin
HCV	Hepatitis C virus
HED	Human equivalent dose
HIV	Human immunodeficiency virus
HR	Heart rate
HREC	Human research ethics committee
hsCRP	High sensitivity C reactive protein
IB	Investigators Brochure

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMM	Independent medical monitor
IP	Investigational product
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	Not clinically significant
NF-KB	Nuclear factor kappa B
NOAEL	No observed adverse event level
NSAID	Non-steroidal anti-inflammatory drugs
OGTT	Oral glucose tolerance test
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PDS	Pharmacodynamic analysis set
PGIC	Patient's global impression of change
PI	Principal investigator
PICF	Participant information and informed consent form
PK	Pharmacokinetic
PKS	Pharmacokinetic analysis set
PT	Preferred term
RAT	Rapid antigen test
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SMR	Sponsor medical representative
SNAQ	Simplified nutritional appetite questionnaire
SoA	Schedule of assessments
SOC	System organ class
SRC	Safety review committee
SS	Safet analysis set
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
TMF	Trial Master File
TNF	Tumor necrosis factor
ULN	Upper limit of normal
Vol	Volume
WAT	White adipose tissue
WHO-DD	World Health Organisation Drug Dictionary
WOCBP	Women of childbearing potential

Pharmacokinetic abbreviations are defined in Section 9.7.1.8 (plasma and urine).

5. ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE OR INSTITUTIONAL REVIEW BOARD

The protocol, protocol amendment, and any material provided to the participant were reviewed and approved by an appropriate human research ethics committee (HREC) before the study was initiated. Documentation of this approval was provided to the Sponsor or the Sponsor's designee.

The HREC was appropriately constituted and operated in accordance with the Integrated Addendum to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6(R1): Guideline for Good Clinical Practice (GCP) ICH E6(R2), annotated with comments by the NHMRC National Statement on Ethical Conduct in Human Research (2007).

Initial HREC approval for the study was granted on 20 Dec 2022. The study was initiated after the Sponsor and Clinical Research Organisation had obtained written approval from the HREC.

Information about the HREC, including the chairperson, is provided in Appendix 16.1.3.

MVD1 protocol Versions 2.0, 3.0 and 4.0 and associated Protocol Clarification Letters are provided in Appendix 16.1.1.

5.2 ETHICAL CONDUCT OF THE STUDY

The requirements for the conduct of clinical trials in accordance with the applicable regulations of the Australian Therapeutic Goods Administration (TGA) under the Clinical Trial Notification scheme were met before commencement of this study.

This study was carried out according to the principles of the Declaration of Helsinki, the ICH Guideline for GCP E6(R2) (2016) (as adopted in Australia) and the NHMRC National Statement on Ethical Conduct in Human Research.

The Principal Investigator (PI) notified the HREC of the completion of the study on 24 July 2024. The acknowledgement of study completion was received from the HREC on 31 Jul 2024.

5.3 PARTICIPANT INFORMATION AND CONSENT

Informed consent was obtained before a participant could participate in the study. The contents and process of obtaining informed consent were to be in accordance with all applicable regulatory requirements and to adhere to ICH GCP guidelines and the principles of the Declaration of Helsinki. Study participation included all screening and training procedures, as well as any wash-out of excluded medications.

It was the responsibility of the PI or person delegated to conduct the informed consent procedure to obtain a voluntary signed and dated informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study, as well as the right to withdraw from the study at any time without prejudice.

The Participant Information and Informed Consent Form (PICF) was compliant with ICH GCP (E6) as well as state, local, and institutional policies.

Following an amendment to the protocol, if the PICF needed to be revised to reflect the changes to the protocol, it was the responsibility of the Sponsor (or designee) to ensure that an amended PICF was reviewed and had received favourable opinion from HREC, and the Investigator ensured that the amended PICF was signed by all participants subsequently entered in the study and those currently in the study, if affected by the amendment.

The PI (or delegate) was to advise the participant's general practitioner of their participation in the study which was to be noted in their medical record.

Details of written informed consent are presented by participant in Listing 16.2.1.1.a (Part A, single ascending dose [SAD]) and Listing 16.2.1.1.b (Part B, multiple ascending dose [MAD]).

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 STUDY INVESTIGATORS AND ADMINISTRATIVE STRUCTURE

The study's administrative structure is described in Table 6-A. The Clinical Study Report (CSR) was reviewed and signed by a Sponsor representative and the PI. These signatures are provided in Appendix 16.1.5.

Table 6-A Administrative Structure

ROLE	NAME
Sponsor	Eolo Pharma Pty Ltd Level 5, 63 Pirie Street, Adelaide SA 5000, Australia
Local Sponsor	Avance Clinical Pty Ltd 213 Glynburn Road, Firle SA 5070, Australia
Principal Investigator	Professor Sepher Shakib
Clinical Research Unit	CMAX Ground Floor, 21-24 North Terrace, Adelaide SA 5000, Australia
Study Management	Avance Clinical Pty Ltd 213 Glynburn Road, Firle SA 5070, Australia
Clinical Laboratory Safety Sample Analysis and Pharmacodynamic Blood Chemistry	• Australian Clinical Labs (ACL) 1 Bulter Road, Adelaide SA 5095, Australia • Ashford Hospital Laboratory ACL (Out of Hours) 55 Anzac Highway, Ashford SA 5035, Australia
Oral Glucose Tolerance Test	Australian Clinical Labs 1 Bulter Road, Adelaide SA 5095, Australia
Bioanalysis of Pharmacokinetic Samples (Blood and Urine)	Agilex Biolabs 31 Dalgleish Street, Thebarton SA 5031, Australia
Adipose Tissue Biopsy Processing and Analysis	Institut Pasteur de Montevideo Mataojo 2020 CP 11400 Montevideo, Uruguay
Data Management	Avance Clinical Pty Ltd 213 Glynburn Road, Firle SA 5070, Australia
Statistician	Avance Clinical Pty Ltd 213 Glynburn Road, Firle SA 5070, Australia
Pharmacometrician	Avance Clinical Pty Ltd 213 Glynburn Road, Firle SA 5070, Australia
Clinical Study Report Author	Avance Clinical Pty Ltd 213 Glynburn Road, Firle SA 5070, Australia

6.2 SAFETY MONITORING GROUP

A Safety Review Committee (SRC) was established to provide safety oversight for the study participants including providing advice on decisions regarding dose escalation, repeat of a dose level, change in the dose level of subsequent cohorts, or stopping the study. The role and responsibility of the SRC was outlined in an SRC Charter which was finalised prior to the study commencing.

The SRC consisted of the PI, an Independent Medical Monitor (IMM), and a Sponsor Medical Representative (SMR). Other individuals (e.g., medical experts) may have been invited to participate at the discretion of the SRC to provide additional input into the review process.

The decision to escalate between dose levels and proceed from Part A (SAD) to Part B (MAD) of the study was based upon review by the SRC of blinded safety and pharmacokinetic (PK) data. The clinical facility provided the SRC with blinded safety data, and the bioanalytical laboratory and pharmacokineticist provided the SRC with blinded PK data as it became available.

The SRC reviewed all available safety, PK data and recommended if dosing would continue at that dose, or de-escalate to a lower dose level, or if the cohort, the dose level or the entire study would be terminated.

In Part A, there were 5 SRC meetings which were held following the completion of dosing for each cohort (S1-S3). Additional ad-hoc meetings were also held during S3:

- SAD Cohort S1: 27 Mar 2023;
- SAD Cohort S2: 27 Apr 2023;
- SAD Cohort S3 (AdHoc): 16 May 2023;
- SAD Cohort S3: 08 Jun 2023;
- SAD Cohort S3 (Ad hoc post SAD Cohort S3): 11 Jul 2023.

Following review cohorts S1-S3, the SRC confirmed that MAD Cohort 1 (M1) twice daily dosing of 50 mg MVD1 (total daily dose of 100 mg) (or placebo) could commence.

There were 4 SRC meetings which were held following the completion of dosing for each cohort (M1-M3). An additional ad-hoc meeting was also held during Cohort M1:

- MAD Cohort M1: 01 Dec 2023;
- MAD Cohort M1(AdHoc post MAD Cohort M1): 09 Nov 2023;
- MAD Cohort M2: 08 Jan 2024;
- MAD Cohort M3: 17 Apr 2024.

7. INTRODUCTION

MVD1 is a novel oral small molecule salicylic acid derivative which is being developed by Eolo Pharma for the prevention and treatment of obesity and its metabolic complications (CVD, type 2 diabetes, NALD, etc.). Obesity is a chronic disease that affects > 13% of adults worldwide and is the primary mediator of metabolic syndrome, the principal risk factor for Type II diabetes and cardiovascular diseases (1).

Weight gain and obesity are accompanied by the activation of JunK and nuclear factor kappa B (NF-κB) inflammatory pathways in white adipose tissue (WAT) and liver (2) which induces a localised restructuring of metabolic pathways and impaired insulin signaling in both adipose tissue and liver as well as later systemic effects in muscle tissue (3, 4). Adipose Tissue-mediated inflammation thus presents a potential therapeutic target for the prevention of obesity related metabolic disorders.

Salicylates, which are a class of non-steroidal anti-inflammatory drugs (NSAIDs) commonly used in the treatment of rheumatoid arthritis, have been known to reduce blood glucose levels in diabetics when used at high doses. One of the most well-known salicylates is aspirin (acetyl salicylic acid) which mediates its anti-inflammatory effects through non-selective inhibition of cyclooxygenase (COX) enzymes COX1 and COX2 and through inhibition of the tumor necrosis factor (TNF)-α driven NF-κB pathway. Inhibitory effects on COX1 and COX2 are mediated by irreversible acetylation by aspirin which leads to an inhibition of prostaglandin synthesis and platelet aggregation which in addition to being used as an anti-thrombotic agent, carries the risk of increased bleeding. Aspirin is also associated with gastrointestinal irritation and erosion and as such, limits the utility of chronic high-dose aspirin for diabetes management. Non-acetylated salicylates such as salsalate, a dimer of salicylate, which lack the COX inhibition and bleeding risk associated with aspirin but still inhibit NF-κB and activates AMP-activated protein kinase, have also demonstrated clinical efficacy at improving basal glycemia, glycosylated hemoglobin and C reactive protein levels in prediabetic, diabetic and obese individuals however the excessive dose levels required (up to 4g/day) and modest effects observed have halted ongoing clinical development (5, 6, 7).

Recently, it was shown that the nitroalkene group of unsaturated nitro-fatty acids can be attached to different molecular scaffolds to confer beneficial drug actions (8, 9, 10) including in models of obesity (8). Similar to salicylate, nitroalkenes have demonstrated significant anti-inflammatory properties (11, 12, 13, 14) and there is some evidence that they may have beneficial metabolic effects during obesity (13, 14, 15). In combination, these observations suggest that the addition of a nitroalkene to salicylate may have the dual benefit of increasing the efficacy of salicylates and contributing independent beneficial metabolic effects of nitroalkenes.

MVD1 was therefore rationally designed as a synthetic nitroalkene derivative of salicylic acid. As hypothesised, non-clinical studies indicate that MVD1 exhibits anti-inflammatory activity mediated through NF-κB pathway inhibition. In addition, orally administered MVD1 was found to confer beneficial metabolic effects in a mouse model of diet induced obesity (DIO) which in part was due to increasing creatine-dependent energy expenditure in WAT. Importantly, the data indicate greater potency of MVD1 when compared to salicylic acid.

With the incidence of obesity and related metabolic dysfunction increasing to pandemic proportions there is a great unmet need to develop a pharmacological intervention that can

reduce excess adipose tissue accumulation and reverse metabolic defects that lead to the development of type 2 diabetes, cardiovascular disease and other comorbidities in addition to the modest effects of lifestyle changes. Historical and recent clinical data have provided a precedent for the safety and utility of salicylates in improving basal glycemia in prediabetic and obese individuals, but the modest effects and high doses required make this impractical.

MVD1 represents a next generation salicylate derivative with improved potency demonstrated in DIO mice and an acceptable safety profile that warrants clinical investigation for the prevention and treatment of obesity and its associated metabolic complications.

8. STUDY OBJECTIVES AND ENDPOINTS

8.1 OBJECTIVES

8.1.1 Primary Objective

The primary objective of the study was to investigate the safety and tolerability of single and 15-day repeat oral doses of MVD1 in healthy adult volunteers and healthy obese adult volunteers respectively.

8.1.2 Secondary Objective

The secondary objective of the study was to assess the PK of MVD1 and metabolites in plasma and urine following administration of single and 15-day repeat oral doses in healthy volunteers and healthy obese adult volunteers.

8.1.3 Exploratory Objective (Part B only)

The exploratory objectives of the study were:

- To investigate biomarker changes following administration of multiple doses of MVD1 in healthy obese adult volunteers.
- To investigate MVD1 exposure in WAT.
- To evaluate the participants impression of change following study treatment.

8.2 ENDPOINTS

8.2.1 Primary Endpoints

Safety endpoints included the evaluation of the change from baseline and where appropriate overtime and versus placebo, including:

- Incidence, severity, and relationship of Adverse events (AEs) or Serious adverse events (SAEs) (including withdrawals due to AEs)
- Change in vital signs
- Change in electrocardiogram (ECG) parameters
- Change in clinical laboratory parameters (haematology, serum chemistry, coagulation, and urinalysis)
- Stool Diary
- Nutritional appetite questionnaire (Part B only)

8.2.2 Secondary Endpoints

Plasma MVD1 and metabolite M1 PK endpoints included:

- Maximum observed plasma concentration (C_{max})
- Time to C_{max} (T_{max})
- Area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration ($AUC_{0\text{-}last}$)
- Area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$) following single dose only
- Apparent terminal elimination half-life ($t_{1/2}$)
- Terminal elimination rate constant (λz)
- Apparent clearance (CL/F)
- Apparent volume of distribution (Vz/F) (Part A only)
- Minimum observed concentration C_{min} (Day 15) (Part B only)

- Area under the plasma concentration-time curve from time 0 to 12 hours (AUC_{0-12}).

Urine MVD1 PK endpoints included (but were not limited to):

- Cumulative amount of unchanged drug excreted (Ae) in urine
- Renal clearance (CLr)

8.2.3 Exploratory Endpoints (Part B only)

MVD1 pharmacodynamic (PD) endpoints included (but were not limited to) a change from baseline in the following serum biomarkers:

- Glucose
- Oral glucose tolerance test (OGGT)
- Insulin
- C peptide
- High sensitivity C reactive protein (hsCRP)
- Glycohemoglobin (MAD cohorts M1 and M2 only)
- Fructosamine
- Free fatty acids
- Triglycerides
- Leptin levels

Additional exploratory endpoints included:

- MVD1 target engagement in white adipose tissue sampled using a single needle biopsy on Day -1 and Day 7.
- Body Weight (Day -1, Day 15 and Day 22)
- Patient general impression of change (PGIC) questionnaire completed by study participants at the end of the study treatment period.

9. INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN

This was a Phase 1, first in human (FIH), randomised, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK and PD of single and multiple ascending doses of MVD1 in normal weight and overweight healthy adult volunteers and multiple doses of MVD1 in overweight or obese healthy adult volunteers. The study was conducted in two parts: Part A (SAD) in normal weight or overweight healthy adults and Part B (MAD) in overweight or obese healthy adults.

A total of up to 42 normal weight/overweight healthy adult volunteers and overweight/obese healthy adult volunteers were planned to be enrolled across the two study parts (Part A and Part B).

Part A (SAD) consisted of 3 cohorts (S1-S3) with 6 participants planned per cohort, randomised at a ratio of 2:1 (MVD1: placebo) within each cohort. Participants were dosed once a day via oral route of administration.

Part B (MAD) consisted of 3 cohorts (M1-M3) with 8 participants planned per cohort, randomised at a ratio of 3:1 (MVD1: placebo) within each cohort. Participants were dosed twice a day (administered approximately 12 hours apart, one in the morning and one in the evening) for 14 days, with a single dose administered on Day 15 via oral route of administration.

All cohorts were planned to be dosed in sequential order, as described in Table 9-A. A dose level was only evaluated in Part B, if it was determined to be safe based on a review by the SRC of safety, tolerability and PK data in Part A, as described in Section 6.2.

Table 9-A Planned Administration of Study Drug

Cohort	MVD1 Dose (mg)	Number of Participants	
		MVD1	Placebo
Part A (SAD): Single Oral Administration			
S1	200 mg	4	2
S2	400 mg	4	2
S3	800 mg	4	2
Part B (MAD): Twice Daily Oral Administration			
M1	200 mg (2 x 100 mg)	6	2
M2	300 mg (2 x 150 mg)	6	2
M3	400 (2 x 200 mg)	6	2

Abbreviations: MAD = multiple ascending dose; SAD = single ascending dose.

For each Part A cohort, dosing was initiated in 2 sentinel participants with 1 participant randomised to receive MVD1 and the other randomised to receive placebo. The remainder of participants within each cohort commenced dosing following a satisfactory review of sentinel Day 2 safety data by the PI/IMM.

Normal weight or overweight healthy adult volunteers were screened between Day -28 and Day -2, inclusive. Participants eligible to be included in the study were admitted to the investigational site on Day -1. Following confirmation of eligibility on Day 1, participants were randomised to receive either MVD1 or placebo. In Part A, the

confinement period commenced on Day -1, followed by dosing on Day 1 with MVD1 or placebo in a double-blinded manner. Participants were discharged from the clinical facility on Day 4 following completion of study assessments and were required to attend the clinical facility for a final follow-up visit on Day 8 ±1 day.

For Part B (MAD), MVD1 multiple dose escalation was conducted in 3 cohorts (M1 to M3) of overweight or obese healthy adult volunteers. Screening for study eligibility in Part B occurred between Day -35 and Day -2 inclusive, with eligible participants administered to the clinical facility on Day -1. Following confirmation of eligibility on Day 1, participants were randomised to receive either MVD1 or placebo. The confinement period in Part B, commenced on Day -1, followed by dosing on Days 1-15 with MVD1 or placebo (two daily oral doses of study drug taken 12 hours apart [morning and evening] on Days 1-14 with a final single dose administration on the morning of Day 15) in a double-blinded manner. Participants were discharged from the clinical facility on Day 18 following completion of study assessments and were required to attend the clinic for a final follow-up visit on Day 22 ± 1 day. Sentinels were not included in Part B.

Blood and urine samples were collected pre-dose and at several timepoints post-dose for PK in both Parts A and B, for assessment of MVD1 and main metabolite M1 concentrations and PK parameters.

Blood samples for assessment of PD biomarkers were collected for Part B only.

The maximum overall study duration of each participant in Part A was up to 37 days, inclusive of visit windows. Key study dates are listed below:

- First participant screened: 21 Feb 2023
- First participant dosed Cohort S1: 10 Mar 2023
- First participant dosed Cohort S2: 04 Apr 2023
- First participant dosed Cohort S3: 04 May 2023
- Last participant completed: 21 Jun 2023

The maximum overall study duration of each participant in Part B was up to 58 days, inclusive of visit windows. Key study dates are listed below:

- First participant screened: 12 Sep 2023
- First participant dosed Cohort M1: 04 Oct 2023
- First participant dosed Cohort M2: 06 Dec 2023
- First participant dosed Cohort M3: 31 Jan 2024
- Last participant completed: 12 Apr 2024

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

A randomised, double-blind, placebo-controlled, single and multiple ascending dose design is typical for a FIH study with safety and tolerability as the primary objective. This design allowed for the escalation to higher dose levels only after lower dose levels were determined to be safe and well-tolerated. Treatment assignment to active or placebo was randomised and double-blinded to minimize bias when evaluating severity and causality of AEs and abnormal safety assessments. The placebo control was used to account for effects not related to the study drug. Sentinel participants were utilized for each new dose cohort (Part A only), to monitor the tolerability of investigational product (IP) in one participant before dosing the remainder of participants allocated to each dose level.

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria – Part A

Normal weight or overweight healthy volunteers were included in this study if they satisfied all the following criteria (assessed at the screening visit and prior to administration on study Day 1, unless otherwise specified):

1. Must have given written informed consent before any study-related activities were carried out and must have been able to understand the full nature and purpose of the trial, including possible risks and adverse effects.
2. Male or female, 18-60 years of age inclusive at the time of screening.
3. Body mass index (BMI) ≥ 20 and < 30 kg/m^2 at the time of screening.
4. Female participants:
    a. Must have been of non-childbearing potential i.e., surgically sterilized (hysterectomy, bilateral salpingectomy, bilateral oophorectomy or bilateral tube ligation/occlusion at least 6 weeks before the Screening visit) or postmenopausal where menopause was defined as 12 months of amenorrhea without an alternative medical cause (females must have a documented serum follicle stimulating hormone (FSH) level consistent with postmenopausal status, per local laboratory guidelines) OR
    b. If of childbearing potential (defined as any female who has experienced menarche and who had not undergone surgical sterilization and is not postmenopausal), had to agree not to attempt to become pregnant, and to not donate ova and agreed to use an acceptable form of contraception (protocol Appendix 8) from signing the consent form until at least 30 days after the last dose of study drug.
5. Male participants:
    a. Must have been biologically or surgically sterile (i.e., had had a vasectomy at least 3 months prior to screening) OR
    b. If not biologically or surgically sterile, must have agreed not to donate sperm and agreed to use an acceptable contraceptive method (protocol Appendix 8) in addition to having the female partner use an acceptable contraceptive method from signing the consent form until at least 90 days after the last dose of study drug.
6. Willing and able to comply with all scheduled visits, treatment plans, laboratory tests and other study procedures.

9.3.2 Exclusion Criteria – Part A

Normal weight or overweight healthy volunteers were excluded from this study if there was evidence of any of the following (assessed at the screening visit or prior to administration of the first dose on study Day 1):

1. History or presence of significant cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic or neurological disease, including any acute illness or major surgery within the past 3 months determined by the PI to be clinically significant (CS).
2. Current infection that required systemically absorbed antibiotic, antifungal, antiparasitic or antiviral medications.
3. Any history of malignant disease in the last 10 years (excluded surgically resected skin squamous cell or in situ cervical squamous cell or basal cell carcinoma).

4. Screening 12-lead ECG outside the normal range for the triplicate mean (QT interval corrected using the Fridericia method (QTcF) males > 450 msec; females > 470 msec) or with abnormalities, which were hazardous to the participant according to the opinion of the Investigator.
5. Presence of clinically relevant immunosuppression from, but not limited to, immunodeficiency conditions such as common variable hypogammaglobulinemia.
6. Use of or planned to use systemic immunosuppressive (e.g., corticosteroids, methotrexate, azathioprine, cyclosporine) or immunomodulating medications (e.g., interferon) during the study or within 3 months prior to the first study drug administration.
7. History of risk factors for torsade de pointes (including a family history of long QT syndrome or sudden cardiac death) or a known arrythmia.
8. Change in body weight of ≥ 5% within 6 months prior to screening visit.
9. Liver function test results elevated more than 1.5-fold above the upper limit of normal (ULN) for gamma glutamyl transferase (GGT), bilirubin (total or unconjugated), alkaline phosphatase (ALP), aspartate transferase (AST) or alanine aminotransferase (ALT).
10. Positive test results for active human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibodies at the screening visit.
11. Presence or having sequelae of gastrointestinal, liver (including Gilbert's syndrome), kidney, or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs.
12. Estimated glomerular filtration rate (eGFR) < 60 mL/min/ 1.73 m^2 or serum creatinine more than 1.5-fold above the ULN.
13. History of substance abuse or alcohol abuse (defined as more than 10 standard drinks per week or regularly consumed more than 4 standard drinks on any one day; where 1 standard drink is 10 g of pure alcohol and is equivalent to 285 mL beer [4.9% Alc./Vol], 100 mL wine [12% Alc./Vol], 30 mL spirit [40% Alc./Vol]) within 12 weeks prior to the screening visit.
14. Positive urine cotinine test, drugs of abuse or alcohol breath test results at the screening visit or at check-in (Day -1).
15. Use of any prescription or over-the-counter medication (including herbal products, diet aids, hormone supplements, topical ointments, vitamins and dietary supplements) within 10 days or 5 half-lives of the medication (whichever is longer) prior to the first study drug administration, with the exception of hormonal contraceptives, medications used to manage AEs including the occasional use of paracetamol (doses of 500 mg up to every 6 hours or 2 g per day maximum for no more than 3 consecutive days).
16. Demonstrated CS (required intervention, e.g., emergency room visit, epinephrine administration) allergic reactions (e.g., food, drug, or atopic reactions, asthmatic episodes) which, in the opinion of the Investigator, would have interfered with the volunteer's ability to participate in the trial.
17. Known hypersensitivity to any of the study drug ingredients.
18. Use of any vaccinations within 14 days prior to the first study drug administration.
19. For women of childbearing potential (WOCBP), a positive serum pregnancy test at the screening visit or a positive urine pregnancy test (with confirmatory serum pregnancy test) at check-in (Day -1).
20. Females who were lactating at any time during the study.

21. Donation of blood or plasma within 30 days prior to first study drug administration, or loss of whole blood of more than 500 mL within 30 days prior to first study drug administration, or receipt of a blood transfusion within 1 year of first study drug administration.
22. Participation in another clinical trial of an investigational drug within 60 days or 5 half-lives of the investigational agent (whichever was longer) prior to the first study drug administration.
23. Difficulty in swallowing the study medication.
24. Any other condition or prior therapy that in the opinion of the Investigator would have made the volunteer unsuitable for this study, including inability to cooperate fully with the requirements of the study protocol or likelihood of noncompliance with any study requirements.

9.3.3 Inclusion Criteria – Part B

Overweight or obese healthy volunteers were included in this study if they satisfied all of the following criteria as assessed at the screening visit or prior to administration of the first dose on study Day 1:

1. Must have given written informed consent before any study-related activities were carried out and must be able to understand the full nature and purpose of the trial, including possible risks and adverse effects.
2. Male or female, 25-60 years of age inclusive at the time of screening.
3. In good health as determined by the outcome of medical history, physical examination, and clinical judgement by the Investigator. Chronic stable non-inflammatory conditions such as, hypertension, hyperlipidemia, osteoarthritis, gout, Chronic Pain Disorders, Thyroid Disease, controlled psychiatric conditions such as anxiety or depression, were permitted, as determined by the Investigator.
4. Body mass index (BMI) between 28 and 35 kg/m^2 at the time of screening.
5. Female participants:
    a. Must have been of non-childbearing potential i.e., surgically sterilized (hysterectomy, bilateral salpingectomy, bilateral oophorectomy or bilateral tube ligation/occlusion at least 6 weeks before the Screening visit) or postmenopausal where menopause is defined as 12 months of amenorrhea without an alternative medical cause (females must have had a documented serum FSH level consistent with postmenopausal status, per local laboratory guidelines) OR
    b. If of childbearing potential (defined as any female who has experienced menarche and who had not undergone surgical sterilization and was not postmenopausal), agreed not to attempt to become pregnant, not to donate ova and agreed to use an acceptable form of contraception (protocol Appendix 8) from signing the consent form until at least 30 days after the last dose of study drug.
6. Male participants:
    a. Must have been biologically or surgically sterile (i.e., have had a vasectomy at least 3 months prior to screening) OR
    b. If not biologically or surgically sterile, must have agreed not to donate sperm and agreed to use an acceptable contraceptive method (protocol Appendix 8) in addition to having the female partner use an acceptable contraceptive method from signing the consent form until at least 90 days after the last dose of study drug.

7. Willing and able to comply with all scheduled visits, treatment plans, laboratory tests and other study procedures.

9.3.4 Exclusion Criteria – Part B

Overweight or obese healthy volunteers were excluded from this study if there was evidence of any of the following at the screening visit or prior to administration of the first dose on study Day 1:

1. History or presence of significant cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic or neurological disease, including any acute illness or major surgery within the past 3 months determined by the PI to be CS.
2. Current infection that required systemically absorbed antibiotic, antifungal, antiparasitic or antiviral medications.
3. Any history of malignant disease in the last 10 years (excluded surgically resected skin squamous cell or in situ cervical squamous cell or basal cell carcinoma).
4. Screening 12-lead ECG outside the normal range for the triplicate mean (QTcF: males > 450 msec; females > 470 msec) or with abnormalities, which were hazardous to the participant according to the opinion of the Investigator.
5. Presence of clinically relevant immunosuppression from, but not limited to, immunodeficiency conditions such as common variable hypogammaglobulinemia.
6. Use of or planned to use systemic immunosuppressive (e.g., corticosteroids, methotrexate, azathioprine, cyclosporine) or immunomodulating medications (e.g., interferon) during the study or within 3 months prior to the first study drug administration.
7. History of risk factors for torsade de pointes (including a family history of long QT syndrome or sudden cardiac death) or a known arrythmia.
8. Change in body weight of ≥ 5% within 6 months prior to screening visit.
9. Liver function test results elevated more than 1.5-fold above the ULN for GGT bilirubin (total or unconjugated), ALP, AST or ALT.
10. Positive test results for active HIV, HBsAg or HCV antibodies at the screening visit.
11. Presence or having sequelae of gastrointestinal, liver, kidney, or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs
12. eGFR < 60 mL/min/ 1.73 m^2 or serum creatinine more than 1.5-fold above the ULN.
13. History of substance abuse or alcohol abuse (defined as regularly consuming more than 4 standard drinks on any one day; where 1 standard drink is 10 g of pure alcohol and is equivalent to 285 mL beer [4.9% Alc./Vol], 100 mL wine [12% Alc./Vol], 30 mL spirit [40% Alc./Vol]) within 12 weeks prior to the screening visit.
14. Positive urine cotinine test, drugs of abuse or alcohol breath test results at the screening visit or at check-in (Day -1).
15. Use of any prescription or over-the-counter medication (including herbal products, diet aids, hormone supplements, topical ointments, vitamins and dietary supplements) within 10 days or 5 half-lives of the medication (whichever is longer) prior to the first study drug administration, with the exception of hormonal contraceptives, medications used to manage AEs including the occasional use of paracetamol (doses of 500 mg up to every 6 hours or 2 g per day maximum for no

more than 3 consecutive days), stable use (4 weeks or longer prior to screening) of medications used to treat hypertension and high cholesterol and medications for hay fever.

16. Demonstrated CS (required intervention, e.g., emergency room visit, epinephrine administration) allergic reactions (e.g., food, drug, or atopic reactions, asthmatic episodes) which, in the opinion of the Investigator, would have interfered with the volunteer's ability to participate in the trial.
17. Known hypersensitivity to any of the study drug ingredients.
18. Use of any vaccinations within 14 days prior to the first study drug administration.
19. For WOCBP, a positive serum pregnancy test at the screening visit or a positive urine pregnancy test (with confirmatory serum pregnancy test) at check-in (Day -1).
20. Females who were lactating at any time during the study.
21. Donation of blood or plasma within 30 days prior to first study drug administration, or loss of whole blood of more than 500 mL within 30 days prior to first study drug administration, or receipt of a blood transfusion within 1 year of first study drug administration.
22. Participation in another clinical trial of an investigational drug within 60 days or 5 half-lives of the investigational agent (whichever was longer) prior to the first study drug administration.
23. Difficulty in swallowing the study medication.
24. Any other condition or prior therapy that in the opinion of the Investigator would have made the volunteer unsuitable for this study, including inability to cooperate fully with the requirements of the study protocol or likelihood of noncompliance with any study requirements.
25. A screening urinalysis result, or first morning urine protein dipstick result on Day 1 prior to first dose of study drug showing more than a trace of protein. Test may have been repeated to confirm.
26. Body weight > 120 kg at screening.

9.3.5 Participant Withdrawal Criteria

Participants were advised that they were free to withdraw from the study at any time for any reason or, if necessary, the Investigator (or medically trained nominee) could discontinue a participant from the study if medically indicated. A participant could voluntarily withdraw or be withdrawn from the study for reasons including, but not limited to, the following:

- The need to take medication which could have interfered with study measurements
- Intolerable/unacceptable AEs
- Noncompliance of the participant with the protocol
- Withdrawal of consent
- If, in the Investigator's judgement, continued participation affected the data integrity or
- If, in the Investigator's judgement, it was in the participant's best interest

The Sponsor was to be notified as soon as possible if any participant withdrew. The date and reasons for withdrawal were to be recorded in the electronic case report form (eCRF) and included in the final CSR, along with any AEs and necessary medical treatment.

If a participant prematurely discontinued study drug, all scheduled safety, PK and PD assessments were to be performed, including all follow-up visit assessments as scheduled. If a participant withdrew from the study, an attempt was to be made to collect all remaining safety, PK and PD samples scheduled for that day.

In the event that a participant was discontinued from the study due to an SAE, the Investigator, or medically trained nominee, was to evaluate the urgency of the event. If the situation warranted, the Investigator, or medically trained nominee, were to take appropriate diagnostic and therapeutic measures and make an attempt to notify the SMR. If the situation was not an immediate emergency, the Investigator, or medically trained nominee, at the clinical study facility were to attempt to contact the IMM and the SMR for consultation. No medical help, diagnosis, or advice was to be withheld from the participant due to an inability to contact the IMM or SMR. The participant was to be encouraged to remain available for follow-up medical monitoring.

9.3.6 Dose Escalation and Stopping Rules

The decision to escalate between dose levels and proceed from Part A to Part B was based on a review of available safety and PK data by the SRC. The SRC may have recommended repeat of a cohort, a change in the dose levels of subsequent cohorts, addition of a cohort or that no further dose escalation cohorts occur and may have recommended the final sample size of the MAD cohorts based upon consensus and emerging safety and PK data.

Dose escalation in Part A and Part B proceeded to the next dose level until evaluation of the highest dose level was completed or the trial was stopped by the SRC. Escalation to the next dose level occurred following satisfactory review of available safety data (up to Day 4 for Part A and Day 18 for Part B) and available PK data from all participants at the current dose level.

If any of the below occurred, the SRC would be convened and may have decided to stop dosing within a cohort or dose escalation between cohorts:

- One occurrence of an SAE in Part A or Part B assessed to be probably related to dosing with the study drug and that in the opinion of the SRC has a high likelihood to be repeated in additional dose levels and would mean a significant risk to study participants.
- One occurrence of Hy's law criteria are met and confirmed by an immediate repeat blood draw: this is defined by at least 3-fold elevations of serum ALT or AST above the ULN, **plus** an elevation of serum total bilirubin > 2 times ULN without elevated serum ALP, and no other disease or condition can be found to explain the liver test abnormalities, and no other potential explanation in the opinion of the SRC can be a probable cause for this event, and in the opinion of the SRC study continuation would mean a significant risk to study participants.
- One or more participants with a QTcF of $\geqslant$ 500 msec which is confirmed on repeat (the mean of the triplicates should be used).
- Two or more participants with $\geqslant$ 60 msec increase over baseline (pre-dose Day 1) in QTcF (the mean of the triplicates should be used).
- If 4 or more participants experience the same or similar Grade III or higher AE which is possibly or probably related to the study drug, and according to SRC opinion study continuation would mean a significant risk to study participants.
- Presence of any AEs that are assessed as probably related to study drug that are,

in the opinion of the SRC, medically relevant and may potentially endanger the welfare of study participants.

- If, based on the observed data, the group mean C_{max} or Area under the concentration-time curve (AUC) (based on total plasma concentration) of the next planned dose is projected to exceed the exposure observed at the no observed adverse event limit (NOAEL) in rats after 4 weeks of dosing, that dose will not be explored. Modified doses may be explored if they are not expected to exceed this PK stopping criterion.

For any of the scenarios described above, the SRC was to review all available safety and PK data, and recommend if dosing should continue at that dose, or de-escalate to a lower dose level, or if the cohort, the dose level, or the entire study should be terminated. No more healthy volunteers were to be enrolled (or participants dosed) until this safety review was completed. Details were outlined in a formal SRC charter.

In addition, dosing was to be stopped for an individual participant in MAD cohorts (M1 to M3) if their pre-dose dipstick urinary protein was more than trace and confirmed upon repeat test, or if urine albumin:creatine ratio (ACR) was abnormal, or had increased by more than 50% from baseline, if the baseline on the morning of dosing was abnormal.

9.3.7 Suspension or Termination of the Study at the Investigational Site

The Sponsor reserved the right to:

- Suspend or terminate the execution of the clinical study at any time
- Suspend or terminate participation of an investigational site of this clinical study at any time

9.3.8 Study Restrictions

Prior and Concomitant Medications

Part A and Part B: The use of concomitant medication during the study was prohibited with the exception of the medications used to manage AEs. If the need for concomitant medication arose to treat an AE, the Investigator was to make decisions based on the participant and clinical factors. Any concomitant medication that was taken by or administered to a participant during the course of the study was recorded in the eCRF. The entry had to include medication name, dose, regimen, route, indication and dates of use.

Participants were instructed not to take any prescription or over-the-counter medication (including herbal products, diet aids, hormone supplements, topical ointments, vitamins and dietary supplements) within 10 days or at least 5 half-lives of the medication (whichever was longer) prior to the first study drug administration and for the duration of the study.

The use of hormonal contraceptives by women of childbearing potential was permitted if the participant had used the medication for at least 3 months prior to screening visit.

Participants were also instructed not to have any vaccinations (including Corona virus disease 2019 [COVID-19]) within 14 days prior to the first study drug administration and during the study. In addition, participants were not permitted to take systemic immunosuppressive (e.g., corticosteroids, methotrexate, azathioprine, cyclosporine) or immunomodulating medications (e.g., interferon) within 3 months prior to the first study

drug administration and during the study (the use of medications for hay fever may have been permitted at the discretion of the PI).

Medication used to manage AEs throughout the study were permitted at the discretion of the PI including occasional use of paracetamol (doses of 500 mg up to every 6 hours or 2 g per day maximum for no more than 3 consecutive days).

Part B only: The use of medications for the treatment of hypertension and high cholesterol was permitted by participants in Part B as long as these medications were being used by participants for a period of at least 4 weeks prior to screening visit.

Caffeine, Tobacco, and Alcohol

Participants were instructed to abstain from consuming caffeine and/or xanthene products (i.e., coffee, tea, chocolate, and caffeine-containing sodas, colas) or alcohol for at least 24 hours prior to Day -1, and while confined to the clinical facility.

Participants must have passed the urine cotinine test at Screening and Day -1 and were to refrain from smoking within 14 days prior to screening and for the duration of the study.

Participants must have had a negative result in a urine drugs of abuse test and alcohol breath test at screening and check-in (Day -1) and were required to abstain from recreational drug use throughout the study.

Compliance to the above restrictions were assessed prior to checking in for the study on Day -1.

Dietary Requirements

Fasting:

In Part A, participants in Cohort S1 to S3 were required to fast overnight for at least 8 hours prior to admission to the clinical facility on Day -1. Participants were also required to fast overnight for at least 8 hours prior to drug administration and until at least 4 hours post-dose on Day 1.

In Part B, participants were required to fast overnight for at least 8 hours prior to the screening visit and prior to admission to the clinical facility on Day -1. On all dosing days (Day 1 to Day 15), participants were required to fast for at least 2 hours prior to administration of each dose of study drug and until at least 2 hours post-dose. A final overnight fast of at least 8 hours was required on Day 15 prior to final PD measurements on Day 16.

During all fasting periods in Part A and Part B, no food or beverages were to be consumed by the study participants except for water.

Diet:

Participants in Part B were required to consume a carbohydrate rich diet (250-300 g carbohydrate per day) for the duration of the study.

Contraception

Female participants of childbearing potential agreed not to donate ova, not to attempt to become pregnant and, if engaging in sexual intercourse with a male partner, to use adequate contraception from signing the consent form until at least 30 days after the last dose of study drug.

From signing the consent form until at least 90 days after the last dose of study drug, male participants, who were not surgically sterilized, agreed not to donate sperm and if engaging in sexual intercourse with a female partner who could become pregnant, must have agreed to use an acceptable form of contraception (as described in Appendix 8 of the protocol provided in Appendix 16.1.1).

Male and female participants of childbearing potential for whom heterosexual relationships were not their usual lifestyle were exempt from contraceptive requirements. However, all female participants of childbearing potential were to undergo pregnancy testing.

Physical Activity

Participants were instructed to abstain from strenuous exercise for 3 days prior to admission to the clinical facility. Participants were not permitted to exercise while confined to the clinical facility.

9.4 TREATMENTS

9.4.1 Treatments Administered

Test Product: MVD1 drug substance in size 0 or 000 opaque hard gelatine capsules.

Placebo: Microcrystalline cellulose in size 0 or size 000 capsule.

Detailed instructions for the preparation and administration of MVD1 and placebo for this study are provided in the study Pharmacy Manual, which is provided in the Trial Master File (TMF).

Part A: Participants in SAD Cohorts S1 to S3 received a single dose of either MVD1 or placebo on Day 1 following an overnight fast of at least 8 hours. Participants were required to fast for at least an additional 4 hours post-dose after which they were provided with a standard meal. No food or beverages were permitted to be consumed for Part A participants during fasting periods except for water.

Part B: Participants in MAD Cohorts M1 to M3 received two doses of MVD1 or placebo (administered approximately 12 hours apart with one dose administered in the morning and the other dose administered in the evening) daily from Day 1 to Day 14. A final dose of MVD1 or placebo was administered in the morning of Day 15. All doses of study drug were to be administered following a fast of at least 2 hours. Participants were required to fast for at least an additional 2 hours after each dose. No food or beverages were permitted to be consumed by participants during fasting periods except for water.

Participants in Part A and Part B were required to drink 250 mL water when swallowing study drug. An additional 100 mL of water was permitted to be consumed if required.

Delegated study site personnel supervised and instructed the participants on the administration of the study drug. Table 9-B summarizes the allocation of participants to receive MVD1 or placebo.

Table 9-B Administration of Study Drug

Cohort	MVD1 Dose (mg)	Number of Participants	
		MVD1	Placebo
Part A (SAD): Single Oral Administration			
S1	200 mg	4	2
S2	400 mg	4	2
S3	800 mg	3	2
Part B (MAD): Twice Daily Oral Administration			
M1	200 mg (2 x 100 mg)	6	2
M2	300 mg (2 x 150 mg)	6	2
M3	400 mg (2 x 200 mg)	6	2

Abbreviations: MAD = multiple ascending dose; SAD = single ascending dose.

9.4.2 Identity of Investigational Product and Placebo

MVD1 and Placebo

Investigational product (MVD1) and placebo (microcrystalline cellulose) were packed into opaque hard gelatine capsules for oral administration. MVD1 drug product was manufactured at dose strengths of 50, 100, 150, 200 and 400 mg MVD1/capsule in size 0 capsules (for 50, 100, 150 and 200 mg dose strengths) or size 000 capsules (400 mg dose strength). Placebo capsules contained the same amount of microcrystalline cellulose to the corresponding cohort's planned dosage in size 0 or 000 capsule. The placebo capsule was identical in appearance and size to the MVD1 capsule so as not to break the blind.

MVD1 drug substance was manufactured by Eurofins Advinus India, a Good Manufacturing Practice (GMP) licensed facility under Current Good Manufacturing Practice (cGMP) conditions:

Batch No.: CM-BPR-N4661-02-001-20-RPK1
Date of Manufacture: 25 Aug 2020
Re-test Date: 24 Aug 2024

Microcrystalline cellulose was manufactured by Accent Microcell Ltd. India, a GMP licensed facility:

Batch No.: D104210348
Date of Manufacture: April 2021
Re-test Date: March 2026

The final products (MVD1 or placebo capsules) were prepared by Syntro Health (558-562 Swan Street, Richmond VIC 3121, Australia) a GMP-accredited manufacturing facility, and consisted of the MVD1 drug substance packed into opaque hard gelatine capsules for oral administration (

Table 9-C).

Table 9-C Investigational Product Batch Numbers

	Batch/Lot Number	Date of Labelling/Manufacture	Expiry Date
SAD Cohort 1 – MVD1	SYN.23.0052/0053	27 Feb 2023	24 Aug 2023
SAD Cohort 1 – Placebo			
SAD Cohort 2 – MVD1	SYN.23.0082/0083	28 Mar 2023	24 Aug 2023
SAD Cohort 2 – Placebo			
SAD Cohort 3 – MVD1	SYN.23.0118/0119	28 Apr 2023	24 Aug 2023
SAD Cohort 3 – Placebo			
MAD Cohort 1 – MVD1	SYN.23.0345/0346	25-26 Sep 2023	24 Aug 2024
MAD Cohort 1 – Placebo	SYN.23.0345/0346	22-25 Sep 2023	24 Aug 2024
MAD Cohort 2 – MVD1	SYN.23.0396/0397	29-30 Nov 2023	24 Aug 2024
MAD Cohort 2 – Placebo	SYN.23.0396/0397	28 Nov 2023	24 Aug 2024
MAD Cohort 3 – MVD1	SYN.24.0035/0036	18-19 Dec 2023	24 Aug 2024
MAD Cohort 3 – Placebo	SYN.24.0035/0036	17 Jan 2024	24 Aug 2024

Supply, Handling and Storage

MVD1 and placebo capsules were supplied by a designated GMP manufacturer/distributor of the Sponsor (Syntro Health) directly to the clinical study site pharmacy. The clinical study site pharmacy was provided with a sufficient quantity of MVD1 and placebo capsules for the conduct of the study.

The study drugs (MVD1 and placebo) were stored in a secure area at the site pharmacy with access limited to the PI and authorized staff at 15-25 °C ± 2°C and in accordance with State and Commonwealth laws. The PI (or delegate) ensured that deliveries of study drug from the Sponsor (or designated supplier) were correctly received by a responsible person, that all receipts of shipments were recorded on the appropriate drug accountability forms prepared by the site pharmacy and that the study drugs were stored in a secure area under the recommended storage conditions.

An authorized, trained staff member from the site pharmacy, dispensed the study drugs according to pre-defined drug dispensing requirements. The site staff member was responsible for dispensing study drug in accordance with the randomization schedule. Individual doses were dispensed by the site pharmacy staff member on the morning of dosing and recorded in the appropriate dispensing and drug accountability records. The dispensing was verified by a second member of the site pharmacy staff.

The site pharmacy dispensed the study drug to the clinical facility and the clinical facility staff administered the study drug only to participants included in the study. Administration of study drugs was recorded in the appropriate drug accountability records and the eCRF. Administration of study drug was verified by a second staff member. Each participant was given only the study drug preparation carrying his/her study number.

For more information relating to the preparation, handling, and recommended storage conditions of the MVD1 and placebo, please refer to the study Pharmacy Manual, which is provided in the TMF.

Accountability of Study Drug Supplies

The PI was responsible for study drug accountability, reconciliation, and record maintenance at the clinical facility. In accordance with all applicable regulatory requirements, the PI or designated trained site staff were to maintain study drug accountability records throughout the course of the study. The amount of MVD1 and placebo materials received by the site pharmacy and the amount dispensed and administered to participants was to be documented.

A blinded Study Monitor performed initial and ongoing study drug accountability checks. Used containers of the study drug were retained and made available to the unblinded Study Monitor during MVD1 and placebo reconciliation.

As requested in writing by the Sponsor and following drug accountability and reconciliation, all unused study drug was returned to the Sponsor no study drug and placebo supplies were destroyed by the Investigator (or delegate). Records were to be maintained of the return or destruction of the study drug materials. These records were to show the identification and quantity of each unit returned or disposed, the method of destruction (taking into account the requirements of local law), and the person who returned or disposed of the study drug materials. Such records were to be submitted to the Sponsor.

9.4.3 Method of Assigning Participants to Treatment Groups

All study participants who signed an informed consent form at screening received a unique sequential number (i.e., Screening Number). Participants who met eligibility criteria were assigned a randomization number on Day 1, which corresponded to a study treatment (MVD1 or placebo), in accordance with the randomization schedule.

The randomization schedule was prepared by unblinded statisticians at Avance Clinical using SAS version 9.4 statistical software package and was maintained under controlled access. A copy of the randomization schedule was provided to unblinded site pharmacy staff for the purposes of dispensing the study drugs.

Copies of the master randomization schedules are provided in Appendix 16.1.7.

Participant randomization is presented in Listing 16.2.5.1.A (Part A) and Listing 16.2.5.1.B (Part B).

9.4.4 Selection of Doses in the Study

The dose levels of MVD1 investigated in this FIH study ranged from 200 mg to 800 mg daily, administered as single or multiple oral doses.

The starting dose of 200 mg MVD1 was approximately 10-fold lower than the human equivalent dose (HED) of the NOAEL in the most sensitive species (Sprague-Dawley rat),

(32.26 mg/kg; 1938 mg in a 60 kg person). The starting dose selected, and the dose range to be evaluated (200 to 800 mg) was therefore consistent with the US Food and Drug Administration (FDA) Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers.

Dose escalation decisions were undertaken by the SRC after review of the blinded safety data and available PK from all participants in the current cohort.

9.4.5 Selection and Timing of Doses

Part A: On Day 1 all participants were administered a single oral dose of MVD1 or placebo.

Part B: On Days 1 to 14, participants were administered two doses of MVD1 or placebo, one in the morning and the evening. On Day 15 participants were administered a single oral dose of MVD1 or placebo in the morning.

The exact date and time of study drug administration was recorded in the eCRF for each participant.

9.4.6 Blinding and Breaking Code

This was a double-blinded study. Those blinded to study drug assignment included the Sponsor, PI, clinical study personnel participating in participants' care or clinical evaluations, and the study participants.

Those unblinded to study drug assignment included the statisticians preparing the randomization and code break envelopes, pharmacy personnel dispensing the study drugs, the unblinded Study Monitor, the bioanalytical laboratory, and the unblinded Pharmacokineticist performing interim PK analysis for the SRC.

In the event of a medical emergency in which knowledge of an individual participant's assignment was considered critical to the participant's wellbeing and management, the PI (or documented designee treating physician) could unblind the treatment assignment for the participant using the participant's code break envelope. Unless the clinical situation warranted emergency unblinding, the PI was advised to discuss options with the Sponsor or Medical Monitor prior to any unblinding. The PI was to contact the Sponsor and Medical Monitor to discuss the participant and circumstances requiring the unblinding. The blind was to be broken only for the specific participant under consideration. If the blind was broken for any reason and the PI was unable to contact the Sponsor and Medical Monitor before unblinding, the PI was to notify the Sponsor as soon as possible, without revealing the participant's study drug treatment assignment (unless important to the safety of participants remaining in the study). The Sponsor (and any Sponsor nominee, e.g., blinded Study Monitor/s) were to remain blinded to the participant assignment. Every effort was to be made to restrict knowledge of the participant assignment to study treatment to the Investigator only in the event of an emergency unblinding. A record, including date, time, name, and signature of person opening the envelope and reason for unblinding, were to be made both on the opened envelope and in the participant's medical records. The Sponsor designated Study Monitor was to be informed promptly by the PI (or a designated site staff member).

There was no intentional or accidental unblinding of any participant in the study prior to database lock.

9.4.7 Prior and Concomitant Medication

Prior medications were defined as any medication where the use was started prior to the start date/time of first study drug administration.

A concomitant medication was defined as any non-study medication taken at least once after the start of first study drug administration. The medication/therapy name as well as indication, dose, frequency, route of administration, indication and dates and times of use were recorded in the eCRF, as applicable.

9.4.8 Treatment Compliance

Administration of study drugs took place at the investigational site. Compliance was assured by site staff supervising and instructing participants on the administration of study drug. Only authorized and trained site staff were permitted to dispense and administer study drug. The date and time of administration and the treatment and dose administered were recorded in the eCRF. Compliance with the fasting requirements in the protocol was also recorded in the eCRF.

9.5 DEMOGRAPHIC, BASELINE, SAFETY, PHARMACOKINETIC, PHARMACODYNAMIC AND EXPLORATORY VARIABLES

9.5.1 Measurements Assessed and Overall Schedule of Activities

The Schedule of Assessments (SoA) for Part A (SAD) and Part B (MAD) is presented in Table 9-D and Table 9-E. Clinical staff were to perform assessments at the nominated timepoints within the time windows indicated in the SoA. Actual times of procedures for each participant were to be recorded in the eCRF. An example of the unique pages of the eCRF is provided in Appendix 16.1.2.

In the event of multiple procedures scheduled at the same time, the order, where possible, was to be 12-lead ECG, measurement of vital signs, PK and PD sampling, and safety laboratory assessment sampling.

Table 9-D Schedule of Assessments Part A (SAD Cohorts S1 to S3)

STUDY TIME SCHEDULE																		
STUDY PERIODS►	**Screen**	**Confinement**																**EoS/ETV**
STUDY DAY►	**-28 to -2**	**-1**	**1**												**2**	**3**	**4**	**8 (± 1 day)**
STUDY HOUR			**Pre**	**0**	**0.25**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**24**	**48**	**72**	**1**
VISIT & FOLLOW UP SCHEDULE																		
CLINIC VISIT	X	X																X
Informed Consent	X																	
Eligibility Criteria [1]	X	X	X															
Randomisation [2]			X															
Demographics	X																	
Medical History	X																	
Height [3]	X																	
Body Weight [3]	X	X																
Concomitant Medication Assessment [4]	X	X	X												X	X	X	X
Alcohol breath test	X	X																
Urine drugs of abuse and cotinine	X	X																
Serology (HIV/Hepatitis)	X																	
COVID-19 test [5]	X	X																
12 Lead ECG[6]	X	X	X			X		X			X			X	X	X	X	X
Physical Examination (Full) [7]	X																	X
Physical Examination (Symptom directed) [8]		X	X	X														
Vital Signs (BP, HR, temp) [9]	X	X	X			X		X			X			X	X	X	X	X
Pregnancy Test (Serum) [10]	X																	X
Pregnancy Test (Urine)[10]		X																
Serum FSH test[11]	X																	
Clinical Laboratory Blood and Urine Tests [12]	X	X													X		X	
PK Blood sampling[13]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
PK Urine sampling[14]		X			X					X								
AEs [15]		X																
Stool Diary[16]			X															
Dose administration [17]				X														

Abbreviations: AE = adverse events; BL = baseline; BP = blood pressure; COVID-19 = Corona virus disease; ECG = electrocardiogram; EoS = End of Study; ETV = Early Termination Visit; FSH = follicle stimulating hormone; HIV = Human immunodseficiency virus; HR = heart rate; PK = pharmacokinetic; SAD = single ascending dose; SOA = Schedule of Assessmenrs; temp = temperature.

Notes: Schedule of Assessments Part A, (SAD Cohorts S1 to S3)

1 Eligibility was confirmed on Day 1 prior to dosing after completion of all eligibility assessments.

2 Randomization was performed after eligibility confirmation on Day 1.

3 Body mass index was calculated using the height and body weight values recorded at screening.

4 Evaluated throughout the study as indicated

5 A COVID-19 polymerase chain reaction or rapid antigen test was performed at screening and again on admission to the clinical facility on Day -1 as required by clinical study site and state health policy. A COVID-19 test may also have been required at other times throughout the study if clinically indicated.

6 All ECGs were done in triplicate, conducted within 5 minutes with each recording separated by at least 1 minute. ECGs were taken after participants had been resting quietly in a supine position for at least 5 minutes. Predose ECGs were to be performed within 1.5 hours prior to dosing. All post-dose ECGs were to be performed within a ± 20-minute window of the scheduled timepoint except for assessments performed at EoS/ETV where this time window did not apply.

7 Full physical examinations included, at a minimum, assessment of the following: general appearance, head, ears, eyes, nose and throat, neck (including thyroid and lymph nodes), respiratory system, cardiovascular system, gastrointestinal system, renal system, neurological condition, musculoskeletal system, skin and any other focused assessments suggested by the presence of specific symptoms.

8 Symptom directed physical examination (focused assessments suggested by the presence of specific symptoms) were performed if clinically indicated, as determined by the Investigator. A symptom-directed physical examination assessment was performed on Day -1 (Check-in) and within 1.5 hours prior to dosing on Day 1.

9 Participants were resting in a supine position for at least 5 minutes prior to and during vital signs measurements. Pre-dose vital signs assessments were performed within 1.5 hours prior to dosing. All post-dose vital signs assessments were to be performed within a ± 20-minute window of the scheduled timepoint except for assessments performed at the EoS/ETV where this time window did not apply.

10 For women of childbearing potential only. If the urine test was positive it was to be confirmed by a serum pregnancy test.

11 Follicle- stimulating hormone (FSH) levels were measured in female participants who reported as postmenopausal. If serum FSH levels were below the cut-off limit as defined by the local testing laboratory, participants would be considered to be of childbearing potential and would be required to use appropriate contraception for the duration of the study.

12 Conducted at screening and on Day -1 to determine study eligibility. Laboratory test results were assessed by the Investigator, or medically qualified nominee, before confirmation of eligibility on Day 1. Any deviation in laboratory values that were confirmed on re-examination to be CS by the investigator, or medically qualified nominee (i.e. would jeopardize the safety of the participant or impact on the validity of the study results), would have resulted in exclusion of that participant. A blood and urine test was also conducted post-dose on Day 2 and Day 4 as part of the drug safety assessment.

13 Blood PK sampling was conducted throughout the study as indicated in the SOA. The following windows applied: Day 1 pre-dose (within 15 minutes prior to dosing), Day 1, 0.25 hours – 2

hours post-dose (± 5 min), Day 1, 3 hours – 12 hours post-dose (± 15 minutes), Day 2, 24 hours post-dose (± 15 minutes), Day 3, 48 hours post-dose (± 30 minutes); Day 4, 72 hours post-dose (± 30 minutes).

14 Pooled urine was collected overnight (from approximately 10 pm) on Day -1 up to pre-dose on Day 1 for pre-dose PK assessment and for up to 24 hours post-dose for post-dose PK assessment.

15 Assessment performed throughout the study as indicated.

16 Stool diary was to be completed starting on Day 1 until discharge on Day 4.

17 Single oral dose administered following an overnight fast of at least 8 hours. Fasting was required for at least a further 4 hours post-dose. During this time no food or beverages were to be consumed by the participant except for water.

Table 9-E Schedule of Assessments Part B (MAD Cohorts M1 to M3)

STUDY TIME SCHEDULE																							
STUDY PERIODS►	**Screen**	**Confinement**																					**EoS/ETV**
STUDY DAY►	**-35 to -2**	**-1**	**1**		**2,4**		**7**			**10**		**3, 5, 11**		**6, 8, 9, 12, 13,14**		**15**			**16**	**17**	**18**	**22 (± 1 day)**
STUDY HOUR[1]			**Pre**	**4**	**Pre**	**4**	**Pre**	**2**	**4**	**Pre**	**4**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**2**	**4**	**24**	**48**	**72**	
VISIT & FOLLOW UP SCHEDULE																							
CLINIC VISIT	X	X																					X
Informed Consent	X																						
Eligibility Criteria [2]	X	X	X																				
Randomisation [3]			X																				
Demographics	X																						
Medical History	X																						
Height [4]	X																						
Body Weight [4]	X	X																					
Concomitant Medication Assessment [5]	X	X	X		X		X			X		X		X		X			X	X	X	X	X
Alcohol breath test	X	X																					
Urine drugs of abuse and cotinine	X	X																					
Serology (HIV/Hepatitis)	X																						
COVID-19 test [6]	X	X																					
12 Lead ECG [7]	X	X	X	X	X	X	X		X	X	X					X		X			X	X	X
Physical Examination (Full) [8]	X																						X
Physical Examination (symptom directed) [9]		X	X									X											
Vital Signs (BP, HR, temp) [10]	X	X	X	X	X	X	X		X	X	X					X		X	X	X	X	X	X
Pregnancy Test (Serum) [11]	X																						X
Pregnancy Test (Urine) [11]		X																					
Serum FSH test [12]	X																						
Urine protein dipstick test [13]			X		X		X			X		X		X		X							
Urine albumin:creatinine ratio test [14]			X		X		X			X		X		X		X							
Clinical Laboratory Blood and Urine Tests [15]	X	X										X							X		X		
PK Blood sampling [16]			X													X							
PK Urine sampling [17]		X														X							

STUDY TIME SCHEDULE																							
STUDY PERIODS►	**Screen**	**Confinement**																					**EoS/ETV**
STUDY DAY►	**-28 to -2**	**-1**	**1**		**2,4**		**7**			**10**		**3, 5, 11**		**6, 8, 9, 12, 13,14**		**15**			**16**	**17**	**18**		**22 (± 1 day)**
STUDY HOUR			**Pre**	**4**	**Pre**	**4**	**Pre**	**2**	**4**	**Pre**	**4**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**2**	**4**	**24**	**48**	**72**		
VISIT & FOLLOW UP SCHEDULE																							
CLINIC VISIT	**X**	**X**																					**X**
PD Blood chemistry sampling [18]			**X**					**X**									**X**		**X**				
PD OGTT [19]		**X**																	**X**				
Adipose tissue Biopsy [20]								**X**															
PGIC questionnaire [21]																			**X**				
AEs [22]		**X**																					
SNAQ [23]		**X**														**X**							
Stool Diary [24]			**X**																				
Dose administration [25]			**X**		**X**		**X**			**X**		**X**		**X**		**X**							

Abbreviations: ACR = urine albumin to creatinine ratio; AE = adverse event; BP = blood pressure; COVID-19 = Coronavirus disease; ECG = electrocardiogram; EoS = end of study; ETV = early termination visit; HIV = human immunodeficiency virus; HR = heart rate; hs-CRP = high-sensitivity C-reactive protein; MAD = multiple ascending dose; OGTT = oral glucose tolerance test; PD = pharmacodynamic; PGIC = patient general impression of change; PK = pharmacokinetic; post = post-dose administration; pre = pre-dose administration; SNAQ = simplified nutritional appetite questionnaire; SOA = Schedule of Assessments; study hour = number of hours post-dose; temp = temperature; WAT = white adipose tissue.

Notes: Schedule of Assessments Part B, (MAD Cohorts M1 to M3)

1 Pre and post assessments on dosing Days 1 to 15 applied to both the morning and evening dose of study drug on Day 1. On all other days pre and post dose assessments refer to the morning dose only.

2 Eligibility was confirmed on Day 1 prior to dosing after completion of all eligibility assessments.

3 Randomization was performed after eligibility confirmation on Day 1.

4 Body mass index was calculated using the height and body weight values recorded at screening.

5 Evaluated throughout the study as indicated.

6 A COVID-19 polymerase chain reaction or rapid antigen test was performed at screening and again on admission to the clinical facility on Day -1 as required by clinical study site and state health policy. A COVID-19 test may also have been required at other times throughout the study if clinically indicated.

7 All ECGs were in triplicate, conducted within 5 minutes with each recording separated by at least 1 minute. ECGs were taken after participants had been resting quietly in a supine position for at least 5 minutes. Pre-dose ECGs were to be performed within 1.5 hours prior to dosing. All post-dose ECGs were to be performed within a ± 30-minute window of the scheduled timepoint except for assessments performed at EoS/ETV where this time window did not apply. 4-hour post-dose ECG assessments were only required after both morning and evening dose on Day 1 and following the morning dose only on all other dosing days.

8 Full physical examinations included, at a minimum, assessment of the following: general appearance, head, ears, eyes, nose and throat, neck (including thyroid and lymph nodes), respiratory system, cardiovascular system, gastrointestinal system, renal system, neurological condition, musculoskeletal system, skin and any other focused assessments suggested by the presence of specific symptoms.

9 Symptom directed physical examination (focused assessments suggested by the presence of specific symptoms) were performed if clinically indicated, as determined by the Investigator. A symptom-directed physical examination assessment was performed on Day -1 (Check-in) and within 1.5 hours prior to first (morning) dose administration on Day 1 to Day 15. Post-dose assessments were also performed if required.

10 Participants were to be resting in a supine position for at least 5 minutes prior to and during vital signs measurements. Pre-dose vital signs assessments were to be performed within 1.5 hours prior to dosing. All post-dose vital signs assessments were to be performed within a ± 30-minute window of the scheduled timepoint except for assessments performed at the EoS/ETV where this time window did not apply. 4-hour post-dose vital signs assessment only required after both morning and evening dose on Day 1 and following the morning dose only on all other dosing days.

11 For women of childbearing potential only. If the urine test was positive, it was confirmed by a serum pregnancy test.

12 Follicle- stimulating hormone (FSH) levels were measured in female participants who reported as postmenopausal. If serum FSH levels were below the cut-off limit as defined by the local testing laboratory, participants would be considered to be of childbearing

potential and would be required to use appropriate contraception for the duration of the study.

13 Test administered on first morning urine sample within 6 hours prior to first dose administration on Day 1. A urine dipstick protein test showing more than a trace of protein prior to first dose on Day 1 was to result in participant exclusion. A first morning urine protein dipstick test was also conducted prior to administration of the first daily dose of study drug on Days 2 to 15. Urine dipstick protein testing was required on Days 1 to 14 prior to administration of the second (evening) dose of study drug. First morning urine dipstick testing was required following the dosing period on Days 16 to 18. Detection of more than a trace of protein pre-dose on Day 1, pre-dose 2 and prior to any dose administered on Days 2 to Day 15 was to result in suspension of dosing for the participant. All urine dipstick tests showing a trace of protein or less were sent for urine ACR assessment.

14 Urine ACR to be assessed at the time points specified for all urine dipstick protein tests where dipstick test showed a trace of protein or less. This test was to be in addition to urinalysis conducted as part of standard clinical safety laboratory assessments.

15 Conducted at screening and on Day -1 to determine study eligibility. Clinical laboratory test results were assessed by the Investigator, or medically qualified nominee, before confirmation of eligibility on Day 1. Any deviation in laboratory values that were confirmed on re-examination to be CS by the investigator, or medically qualified nominee (i.e. would jeopardize the safety of the participant or impact on the validity of the study results), would result in exclusion of that participant. A clinical laboratory blood and urine test was also conducted prior to the first (morning) dose only on Days 3, 5 and 11 and at 24 hours and 72 hours post final (Day 15) dose on Day 16 and Day 18 respectively as part of the drug safety assessment.

16 Blood PK sampling was conducted throughout the study as indicated in the SoA. All pre-dose samples were to be collected within 15 minutes prior to dosing. The following time windows applied for all other samples: ± 5 min for samples collected 0.25 – 2 hours post-dose; ± 15 min for samples collected 3 – 24 hours post-dose; ± 30 min for samples collected 48 – 72 hours post-dose.

17 Pooled Urine was collected overnight (from approximately 10 pm) on Day -1 up to pre-dose 1 on Day 1 for pre-dose urine PK assessment and on Day 15 for up to 24 hours post -dose for post-dose urine PK assessment.

18 Blood chemistry PD sampling was conducted pre-dose 1 on Day 1, at approximately 2 hours post-dose 1 on Day 7, at approximately 2 hours post final dose on Day 15, and 24 hours post final dose (Day 16). Blood PD markers included: Leptin, C peptide, hsCRP, glycohaemoglobin, fructomsaine, triglycerides, free fatty acids, fasting glucose, insulin in accordance with the sampling timepoints shown in Protocol Appendix 11.

19 Oral glucose tolerance test was conducted in a fasted state on Day -1 and on Day 16 (day after final dose) as indicated in Protocol Appendix 11.

20 Single needle biopsy (aspiration) of subcutaneous white adipose tissue sampling was obtained approximately 2 hours (± 1 hour) after first (morning) dose of study drug on Day 7.

21 PGIC questionnaire was evaluated on Day 16 only (the day after the last dose of study drug).

22 AEs were monitored throughout the study as indicated.

23 Simplified nutritional appetite questionnaire (SNAQ) based on appetite assessments at Day -1 after dinner, and again on Day 15 after dinner.

24 Stool diary was completed starting on Day 1 until discharge on Day 18.

25 Two daily oral doses of study drug taken 12 hours apart (morning and evening) were administered on Days 1 to 14. Final single dose administration was on the morning of Day 15. All doses were to be administered following a fasting for at least 2 hours. Fasting was required for at least a further 2 hours after each dose on each dosing day. During this time no food or beverages were to be consumed by the participant except for water.

9.5.2 Baseline and Demographic Assessments

9.5.2.1 Demographics

Demographic information, including sex, age, race, and ethnicity were recorded at screening.

9.5.2.2 Medical History

Medical history including pre-existing conditions, allergies, prior significant illnesses, surgical history, alcohol consumption, and smoking history were recorded at screening and following check-in on Day -1.

9.5.2.3 Body Height and Weight

Body height (centimeters) and weight (kilograms) without shoes were measured. Height was measured according to site standard procedure. Body mass index was calculated using the height recorded at screening and body weight recorded at screening using the formula:

$$\text{BMI} = \text{weight (kg)}/\text{height (m)}^2$$

9.5.2.4 Prior Medication

Prior medications were defined as any medication where the use was started prior to the start date/time of the first study drug administration.

9.5.2.5 Urinary Proteinuria (Part B only)

In addition to standard urinalysis, urine dipstick protein was performed in house for all Part B MAD cohorts (M1 to M3) pre-dose on Day 1 to determine study eligibility. The presence of more than a trace of protein in urine was to result in exclusion from the study. Urine dipstick protein was also performed throughout the study as an early indicator of kidney toxicity at the timepoints specified in the SoA. At all timepoints, urine samples were also sent for ACR for a more sensitive assessment of proteinuria.

9.5.2.6 Serology

Serology (HIV-1, HIV-2, HBsAg, and HCV antibody testing) was performed at the screening visit. Participants were to be counselled if any tests returned a positive result. Participants who returned a positive test result for HBsAg, HCV, or HIV at the screening visit were not eligible to participate in the study.

9.5.2.7 COVID-19 Test

A COVID-19 Rapid Antigen Test (RAT) or polymerase chain reaction (PCR) test may have been performed at screening and at check-in to the clinical facility on Day -1 as required in accordance with the clinical site and state health policy.

9.5.2.8 Drugs of Abuse, Cotinine, and Alcohol

An alcohol breath test, urine cotinine test and urine drugs of abuse screen was performed at screening and upon admission on Day -1. A positive test in any of these parameters resulted in exclusion from participation in the study.

9.5.2.9 Pregnancy and Follicle Stimulating Hormone Testing

Women of childbearing potential had a serum human chorionic gonadotropin (hCG) pregnancy test at screening to determine their eligibility for participation in this study and at the end of study (EoS) or early termination visit (ETV) to confirm no study drug exposure-in-utero (EIU). A urine hCG pregnancy test was also to be conducted on Day -1. If a urine test was positive, pregnancy was to be confirmed with a serum pregnancy test. During their participation in the study, participants were instructed to notify the investigational site if they or their partner became pregnant during the study.

Follicle-stimulating hormone (FSH) levels were measured in female participants who reported as postmenopausal to have their postmenopausal status confirmed. If serum FSH levels were below the cut-off limit as defined by the local testing laboratory, participants were considered to be of childbearing potential and were required to use appropriate contraception for the duration of the study.

9.5.3 Safety and Tolerability Assessments

9.5.3.1 Adverse Events

Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a study participant administered a pharmaceutical product and-which does not necessarily have to have a causal relationship with the treatment.

An AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

An adverse drug reaction is any AE where there is a reasonable possibility that there is a causal relationship to IP (i.e., possibly, probably, or definitely related).

Definition of Serious Adverse Event

An SAE is defined as any AE that:

- Resulted in death;
- Was life-threatening (i.e., an event in which the participant was at risk of death at the time of the event; not an event which hypothetically might have caused death if it were more severe);
- Required inpatient hospitalization or prolongation of existing hospitalization (note only hospitalizations that were longer than expected based on Investigator judgement, were considered prolonged hospitalizations);
- Resulted in persistent or significant disability/incapacity (i.e., resulted in a substantial

disruption of a person's ability to conduct normal life functions); or
- Was a congenital anomaly/birth defect (i.e., a congenital anomaly/birth defect that occurred in the offspring of a participant exposed to the IP).

Medical and scientific judgement was to be exercised in deciding whether other situations, should be considered serious, such as important medical events that were not immediately life-threatening or resulted in death or hospitalization but may have jeopardized the participant or required medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These were also to be considered serious.

Examples of such events were intensive treatment in an ER or at home for allergic bronchospasm, blood dyscrasias or convulsions that did not result in hospitalization, or development of drug dependency or drug abuse.

The Investigator or designee was responsible for detection, recording, and reporting of events that met the criteria and definition of AEs.

Abnormal laboratory findings (e.g., serum chemistry, haematology, and urinalysis) or other abnormal assessments (e.g., vital signs, and physical examination findings) that were judged by the Investigator as CS were to be recorded as AEs or SAEs if they met the definitions as stated above. Clinically significant abnormal laboratory findings or other abnormal assessments that were detected after the first administration of the study drug or were present at baseline and significantly worsened following administration of the study drug were to be reported as AEs or SAEs. The Investigator was to exercise their medical and scientific judgement in deciding whether an abnormal laboratory finding, or other abnormal assessment, was CS.

Definition of a Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is an AE that met all the following criteria:

- Was serious.
- There was at least a reasonable possibility of a causal relationship between the event and the IP.
- Was considered unexpected (i.e., the event was not listed in the Investigator's Brochure (IB) or not listed at the specificity or severity that had been observed). "Unexpected" as used in this definition, also refers to AEs that were mentioned in the IB as occurring with a class of drugs or were anticipated from the pharmacological properties of the drug but were not specifically mentioned as occurring with the particular drug under investigation.

Time Period for Detecting and Recording Adverse Events

As a consistent method of detecting AEs, the participants were to be asked a nonleading question such as: "How do you feel?".

Detection and recording of study-related AEs was to occur from check in to the clinical facility on Day -1 until completion of the last study-related procedure (including follow-up for safety assessments). Any AE reported or observed after the start of dosing with the study drug was recorded as a treatment-emergent AE (TEAE).

Any change in health status that was reported or observed after informed consent but prior to starting study treatment and deemed by the PI to be "not related" to study procedures, was documented as medical history.

Any pre-existing conditions or signs and/or symptoms present in a volunteer prior to any involvement in the study (i.e., before informed consent) was recorded as medical history. In addition, any change in health status, reported after informed consent but started prior to informed consent by the volunteer, was documented as medical history. Any worsening of a pre-existing condition that occurred following check-in to the clinical facility on Day -1, was recorded as an AE.

A post-study AE/SAE is defined as any event that occurred outside of the nominal AE/SAE study detection period. The Investigator was not obligated to actively seek AEs in former study participants. However, if the Investigator learned of any SAE, including a death, up to 30 days after a participant had completed the study and they considered the event reasonably related to the study drug, the PI was to promptly notify the local Sponsor.

All AEs, regardless of seriousness, severity, or relationship to study treatment, were required to be recorded using medical terminology in the eCRF and/or other sources. Whenever possible, diagnoses were to be given when signs and symptoms were due to a common aetiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion may be reported as "upper respiratory infection"). Investigators were required to record in the eCRF the date of onset of the event, their opinion concerning the relationship of the event to study drug, severity of the event, whether the event was serious or nonserious, actions taken to manage the event, the outcome of the event, and date of resolution where applicable.

Severity of Adverse Events

The Investigator made an assessment based on clinical judgement of the severity of each AE reported during the study. Severity was graded using the most current version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (Version 5.0) 5-point scale:

- **Mild (Grade I)**: Asymptomatic or mild symptoms: clinical or diagnostic observations only; intervention not indicated
- **Moderate (Grade II)**: Minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- **Severe (Grade III)**: Severe or medically significant but not immediately life-threatening: hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL
- **Life-threatening (Grade IV)**: Life-threatening consequences; urgent intervention indicated, and
- **Death (Grade V)**: Death related to AE.

If an AE had multiple aspects (symptoms), the aspect with the highest severity was graded.

Assessment of Causality

The Investigator was to make an assessment as to the relationship between study drug and the occurrence of each AE using clinical judgement. Alternative causes, such as natural history

of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug were to be considered and investigated. The Investigator was to also consult the IB in the determination of their assessment.

The causal relationship of the study drug to an AE was rated according to the following 5-point scale:

- **Unrelated:** Clearly and incontrovertibly due only to extraneous causes, and did not meet criteria listed under unlikely, possible, or probable
- **Unlikely:** Did not follow a reasonable temporal sequence from administration of study drug; might have been produced by the participant's clinical state or by environmental factors or other therapies administered
- **Possibly:** Followed a reasonable temporal sequence from administration of study drug; might have been produced by the participant's clinical state or by environmental factors or other therapies administered
- **Probably:** Clear temporal association to administration of study drug with improvement on cessation of study drug or reduction in dose. Reappeared upon rechallenge (if rechallenge occurred) or followed a known pattern of response to the study drug
- **Definitely:** Could not be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time to study drug administration was very suggestive.

The causality assessment was one of the criteria used when determining regulatory reporting requirements, therefore, the Investigator was required to make an assessment of causality based on all available information for every event and prior to transmission of an SAE form to the Sponsor (if applicable). The Investigator may have changed their opinion regarding causality in light of follow-up information and was to amend the eCRF and SAE form (if applicable) accordingly.

Management, Action Taken, and Outcome

Actions taken could include any of the following:

- Dose note changed
- Dose reduced
- Study drug withdrawn temporarily (= interruption and resumption)
- Study permanently withdrawn (= discontinuation)
- Not applicable
- Unknown
- No action
- Medication required
- Termination of a concomitant medication
- Change of the dose of a concomitant medication
- Hospitalisation or prolongation of hospitalisation
- Initiation/termination of a non-drug therapy
- Other

The following terms and definitions were used in assessing the final outcome of an AE:

- **Recovered–**The participant had fully recovered, or by medical or surgical treatment the condition had returned to the level observed at the first study-related activity after the participant signed the informed consent.
- **Recovering–**The condition was improving, and the participant was expected to recover from the event.
- **Recovered with sequelae–**The participant had recovered from the condition, but with lasting effect due to a disease, injury, treatment, or procedure. If a sequela met an SAE criterion, the AE was required to be reported as an SAE.
- **Not recovered–**The condition of the participant had not improved, and the symptoms were unchanged, or the outcome was not known at the time of reporting.
- **Fatal–**This term was only applicable if the participant died from a condition related to the reported AE. Outcomes of other reported AEs in a participant before they died should be assessed as "recovered", "recovering", "recovered with sequelae" or "not recovered". An AE with fatal outcome was required to be reported as an SAE.
- **Unknown–**This term was only applicable if the participant was lost to follow-up.

Follow-up of Adverse Events

Following initial observation of an AE/SAE, the Investigator was required to proactively follow progress of the participant. Any information obtained in relation to the status of the AE and the condition of the participant was required to be appropriately documented in the eCRF and in a follow-up SAE form (if applicable).

All AEs/SAEs documented at a previous visit/contact that were designated as ongoing, were to be reviewed at subsequent visits/contacts. Adverse events that had not resolved by the end of the study, or that had not resolved upon discontinuation of the participant's involvement in the study, were required to be followed until any of the following occurred:

- The event resolved
- The event stabilised
- The event returned to baseline, if a baseline value was available
- The event could be attributed to agents other than the study drug or to factors unrelated to study conduct, or
- It became unlikely that any additional information could be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

The Investigator ensured that AE/SAE follow-up included any supplemental investigations as may have been indicated to elucidate the nature and/or causality of the event. This may have included additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. The Sponsor may also have requested that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations.

If a participant died during participation in the study or during a recognised follow-up period, the Sponsor would be provided with a copy of any post-mortem findings, including histopathology.

Reporting of Serious Adverse Events

In the event of an SAE, the Investigator was required to notify the Sponsor (and the Sponsor designated study Safety Officer) within 24 hours of becoming aware of the occurrence of an SAE. Information regarding SAEs was transmitted to the Sponsor (and designated study Safety Officer) using an SAE form as described in the study SAE Report Form Completion Guidelines. The SAE form was required to be completed and signed by a member of the investigational staff and the Investigator.

Any new or updated clinical information on the SAE was to be recorded on a new SAE form and sent to the Sponsor (and designated study Safety Officer) within 24 hours of the information being available.

The Investigator was also required to report SAEs to the appropriate HREC that approved the protocol according to their requirements.

Serious AEs and SUSARs were reported to regulatory authorities in accordance with national requirements. The Sponsor assumed responsibility for appropriate reporting of SAEs and SUSARs to the regulatory authorities.

Exposure*-in-Utero *Management and Reporting

Planned dosing of the study drug was required to be discontinued immediately in event of a reported (or suspected) pregnancy in a female participant (including a positive pregnancy test regardless of age).

The Investigator was required to notify the Sponsor and designated study Safety Officer of this event and document the pregnancy on the EIU form as described in the study Pregnancy/EIU Report Form Completion Guidelines. The pregnant participant (or the male participant's pregnant partner) was required to be advised to call her Healthcare Provider.

The Investigator was required to obtain informed consent from the pregnant female participant (or male participant's pregnant partner) in order to allow them to access and review relevant medical records to conduct follow-up throughout the gestational period and on the infant following delivery. The Investigator was required to follow-up newborn infants that had been exposed to IP *in utero* for a minimum of 12 months. Upon discovery of any congenital anomalies (or neonatal deaths) the Investigator was required to submit a follow-up report to the Sponsor (and Sponsor designated study Safety Officer) using an SAE form (as per the SAE Report Form Completion Guidelines) including information regarding the status of the newborn. A miscarriage or abortion was required to also be reported by the Investigator to the Sponsor (and Sponsor designated study Safety Officer) using an SAE form.

There were no reported pregnancies throughout the study.

9.5.3.2 Concomitant Medication

Any non-study medication or therapy that was taken by or administered to a participant during the study was recorded.

A concomitant medication was defined as any non-study medication taken at least once after the start of first administration of study drug.

Medications stopped prior to the day of first study drug administration were not considered concomitant medications. If a clear determination could not be made as to whether the medication was concomitant or not due to missing or incomplete data, the medication was treated as concomitant medication taken during the study.

Refer to Section 9.5.2.4 for the definition of prior medication for this study.

9.5.3.3 Clinical Laboratory Evaluation

Blood samples for haematology, serum chemistry, and coagulation as well as urine samples for urinalysis were to be collected at selected time points throughout the study as defined in the SoA (Table 9-D [Part A] and Table 9-E [Part B]). A full list of clinical laboratory tests performed for this study are listed in Table 9-F, below.

All clinical laboratory safety assessments were assessed by a certified local laboratory, using that laboratory's normal ranges. The Investigator was to review the laboratory report and document this review. All out of range (abnormal) laboratory values were to be evaluated and commented on by the Investigator for clinical significance. Laboratory safety test results were classified as normal, abnormal not clinically significant (NCS), or abnormal CS. All CS findings were to be recorded as AEs.

In addition to standard urinalysis, urine dipstick protein was performed in house for all Part B MAD cohorts (M1 to M3) pre-dose on Day 1 to determine study eligibility as described in Section 9.5.2.5.

Table 9-F Haematology, Coagulation, Serum Chemistry, and Urinalysis Parameters

Haematology	Biochemistry	Coagulation	Urinalysis [1]
Hematocrit Hemoglobin Mean Cell Hemoglobin (MCH) Mean cell volume (MCV) Mean corpuscular haemoglobin Concentration (MCH) Monocytes Platelet count Mean Platelet Volume (MPV) Red cell count Red cell distribution width **WBC count with differential:** • Neutrophil count • Eosinophil count • Basophil count • Lymphocyte count	**Electrolytes:** Anion Gap Bicarbonate Calcium (adjusted) Calcium Chloride Ionised calcium Phosphorous Potassium Sodium **Liver function:** ALP ALT AST Bilirubin (total, direct and indirect) GGT **Other:** Albumin Cholesterol Creatinine eGFR Globulin Glucose Lactate dehydrogenase Protein Urea Uric acid	aPTT INR PT **Urine Drug Screen, Alcohol Breath Test and Cotinine Test** Methamphetamines Opiates Cocaine THC Benzodiazepines Barbiturates Methadone Tricyclic Antidepressants Amphetamines Alcohol Cotinine **Pregnancy Test** Urine hCG Serum hCG [3] **Confirmation of postmenopausal status** FSH [4]	Bilirubin Blood Glucose Ketones Protein ACR Specific Gravity Leukocyte esterase. pH Nitrite Urobilinogen
Viral serology HIV-1/-2 HBsAg HCV SARS-COV-2 [2]			

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial prothrombin time; AST = aspartate aminotransferase; CrCl = creatinine clearance; FSH = follicle stimulating hormone; GGT = gamma glutamyl transferase; HBsAg = Hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HDL = high density lipoprotein; HIV = Human Immunodeficiency Virus; INR = international normalised ratio; LDH = lactate dehydrogenase; LDL = low density lipoprotein; PT = prothrombin time; RBC = red blood cell; SARS-COV-2 = severe acute respiratory corona virus 2; THC = tetrahydrocannabinol; WBC = white blood cell.
1 Urine sediment microscopy will be conducted in the instance of abnormal blood or leukocyte esterase urinalysis findings.
2 To be performed before inclusion to the study and if clinically indicated, as determined by the Investigator as per site and state policy
3 If the urine hCG is positive, pregnancy will be confirmed by a serum hCG test
4 To be conducted for females of nonchildbearing potential to confirm postmenopausal status

9.5.3.4 Vital Signs

Vital signs assessments included systolic and diastolic blood pressure (BP), heart rate (HR), and body temperature (tympanic). Participants were to be resting in a supine position for at least 5 minutes prior to and during vital signs measurements. Pre-dose vital signs assessments were to be performed within 1.5 hours prior to dosing. For MAD cohorts M1 to M3, vital signs assessments were to be performed within 1.5 hours prior to the first dose of study drug and within 20 minutes prior to the second (evening) dose. All post-dose vital signs assessments were to be performed within the windows specified in the SoA (Table 9-D [Part A] and Table 9-E [Part B]).

Abnormal vital signs assessments that were NCS may have been repeated at the Investigator's discretion. Abnormal vital signs assessments that were CS would be repeated. All CS findings were recorded as AEs.

9.5.3.5 Physical Examination

Full physical examinations included, at a minimum, assessment of general appearance, head, ears, eyes, nose and throat, neck (including thyroid and lymph nodes), respiratory system, cardiovascular system, GI system, renal system, neurological system, musculoskeletal system, skin, and any other focused assessments suggested by the presence of specific symptoms.

Symptom directed physical examinations included focused assessments as indicated by the presence of specific symptoms, and were performed if clinically indicated, as determined by the Investigator.

All physical examinations were to be conducted by a licensed physician within the time windows specified in the SoA (Table 9-D [Part A] and Table 9-E [Part B]). Physical examinations could be performed at various unscheduled timepoints if deemed necessary by the Investigator. All CS findings post-dose were to be recorded as AEs.

9.5.3.6 Electrocardiograms

Twelve-lead ECG measurements (including but not limited to the measurements of ventricular HR, PR interval, QRS duration, QT interval and QTcF) were to be performed at the timepoints and windows indicated in the SoA (Table 9-D [Part A] and Table 9-E [Part B]). Twelve-lead ECGs were to be performed in triplicate with each replicate separated by at least 1 minute and the full set of triplicates completed within 5 minutes. The mean value for the triplicate was to be recorded. If any of the mean values were out of the acceptable range, a repeat triplicate ECG was to be performed. Each ECG was to be conducted in a supine (or semi-supine) position after the participant had been resting for at least 5 minutes in a quiet setting without distractions (e.g., television, phones).

Electrocardiograms were to be interpreted, signed, and dated by the Investigator, or qualified designee. The ECGs were to be classified as normal, abnormal NCS, or abnormal CS. In addition, ECG parameters of ventricular heart rate, PR interval, QRS duration, QT interval, and QTcF were to be noted on the eCRF. All CS findings were to be recorded as AEs.

Abnormal ECGs that were NCS could be repeated at the Investigator's discretion. Abnormal ECGs that were CS were to be repeated. In the case of evident bad quality of the tracing (e.g., muscle tremor), an ECG was to be repeated. Repeat assessments were to be performed in triplicate.

9.5.3.7 Stool Diary

A stool diary was completed by participants starting on Day 1 until discharge on Day 4 (Part A, SAD) or on Day 18 (Part B, MAD) to monitor effects of study treatment on gastrointestinal function.

9.5.3.8 Simplified Nutritional Appetite Questionnaire

A simplified nutritional appetite questionnaire (SNAQ) based on appetite assessment was evaluated on Day -1 after dinner, and again on Day 15 after dinner was completed by participants in Part B (MAD) only.

The SNAQ consisted of four questions, assessing the participants appetite as follows:

My appetite is:

- a = Very poor; b = Poor; c = Average; d = Good; e = Very good

When I eat, I feel full after:

- a = Eating only a few mouthfuls
- b = Eating about a third of a plateful
- c = Eating over half a plateful
- d = Eating most of the food
- e = Hardly ever

Food tastes:

- a = Very bad; b = Bad; c = Average; d = Good; e = Very good

Normally I eat:

- a = Less than one full meal a day
- b = One meal a day
- c = Two meals a day
- d = Three meals a day
- e = More than three meals a day, including snacks

9.5.4 Pharmacokinetic Assessments

Blood and urine samples were collected in both Part A and Part B of the study for assessment of MVD1 and main metabolite M1 concentrations and PK parameters. Clinical staff were to collect each blood and urine PK sample at the scheduled timepoints within the windows indicated in the SoA (Table 9-D and Table 9-E) and in Table 9-G and Table 9-H (below) for Part A and Part B, respectively.

All PK samples were assayed by validated bioanalytical methods, which were specific for the measurement of the analytes for this study. The method validation conducted by the appointed bioanalytical laboratory addressed (at a minimum) method accuracy, precision, reproducibility, specificity, recovery and sample stability, and other parameters as appropriate.

Samples from all participants who received a dose of any of the study treatments were analysed. Repeat analysis may have been carried out according to pre-defined criteria as described in standard operating procedures of the bioanalytical laboratory who conducted the PK analysis for this study.

Details regarding the collection, processing, storage, and transfer of blood samples are outlined in the study Laboratory Manual, which is provided in the TMF.

Table 9-G Pharmacokinetic Sampling Timepoints for Part A (SAD Cohorts S1 to S3)

Day	Study Event	Timepoint	Time Window (minutes)	Plasma PK Sample No.	Urine PK Sample No.
-1		Predose ~ 10 pm			1*
1		Predose	*Within 15 min prior to dosing*	1	
	Dose	***0***			
		0.25 h post-dose	±5	2	2**
		0.5 h post-dose	±5	3	
		1 h post-dose	±5	4	
		2 h post-dose	±5	5	
		3 h post-dose	±15	6	
		4 h post-dose	±15	7	
		6 h post-dose	±15	8	
		8 h post-dose	±15	9	
		10 h post-dose	±15	10	
		12 h post-dose	±15	11	
2		24 h post-dose	±15	12	
3		48 h post-dose	±30	13	
4		72 h post-dose	±30	14	

Abbreviations: PK = pharmacokinetic.

*Pooled urine collected from ~10 pm on Day -1 to pre-dose on Day 1.

**Pooled urine collected for 24 hours post-dose on Day 1.

Table 9-H Pharmacokinetic Sampling Timepoints for Part B (MAD Cohorts M1 to M3)

Day	Study Event	Timepoint (hour)	Time Window (minutes)	Plasma PK Sample No.	Urine PK Sample No.
-1		Predose (~ 10 pm)			1*
		Predose	*Within 15 min prior to dosing*	1	
	Dose 1	***0 (~ 8 am)***			
		0.25 h post-dose 1	±5	2	
		0.5 h post-dose 1	±5	3	
		1 h post-dose 1	±5	4	
		2 h post-dose 1	±5	5	
		3 h post-dose 1	±15	6	
		4 h post-dose 1	±15	7	
		6 h post-dose 1	±15	8	
1		8 h post-dose 1	±15	9	
		10 h post-dose 1	±15	10	
		Pre-dose 2	*Within 15 min prior to dosing*	11	
	Dose 2	***0 (~ 8 pm)***			
		0.25 h post-dose 2	±5	12	
		0.5 h post-dose 2	±5	13	
		1 h post-dose 2	±5	14	
		2 h post-dose 2	±5	15	
		3 h post-dose 2	±15	16	
		4 h post-dose 2	±15	17	
		6 h post-dose 2 (D1)	±15	18	
2		8 h post-dose 2 (D1)	±15	19	
		10 h post-dose 2 (D1)	±15	20	
		Pre-dose 1 (D2)	Within 15 min prior to dosing	21	
4		Pre-dose 1 (D4)	Within 15 min prior to dosing	22	
7		Pre-dose 1 (D7)	Within 15 min prior to dosing	23	
10		Pre-dose 1 (D10)	Within 15 min prior to dosing	24	
		Pre-dose	*Within 15 min prior to dosing*	25	
	Final Dose	***0 (~ 8 am)***			
		0.25 h post-dose	±5	26	
15		0.5 h post-dose	±5	27	
		1 h post-dose	±5	28	
		2 h post-dose	±5	29	2**
		3 h post-dose	±15	30	
		4 h post-dose	±15	31	

Day	Study Event	Timepoint (hour)	Time Window (minutes)	Plasma PK Sample No.	Urine PK Sample No.
		6 h post-dose	±15	32	
		8 h post-dose	±15	33	
		10 h post-dose	±15	34	
		12 h post-dose	±15	35	
16		24 h post-dose	±15	36	
17		48 h post-dose	±30	37	
18		72 h post-dose	±30	38	

Abbreviations: PK = pharmacokinetic.

*Pooled urine collected from ~10 pm on Day -1 to pre-dose on Day 1.

**Pooled urine collected for 24 hours post final dose on Day 15.

9.5.5 Pharmacodynamic Assessments (Part B Only)

9.5.5.1 Body Weight

Body weight was measured on Day -1 (check-in) prior to dose administration, pre-dose on Day 15 (within 3 hours) and on Day 22 (EoS) to investigate drug induced body weight reduction.

9.5.5.2 Serum Biomarkers

Blood samples were to be collected in Part B only for assessment of PD biomarkers including:

- Glucose
- Insulin
- C peptide
- hsCRP
- Fructosamine
- Glycohemoglobin (Cohort MAD 1 and MAD 2 only)
- Free fatty acids
- Triglycerides
- Leptin levels

Timepoints for PD biomarker sampling in Part B are provided in Table 9-I, below.

All samples were assayed by bioanalytical methods, which were specific for the measurement of the analytes relevant to this study and fit for purpose.

Samples of all participants who received a dose of any of the study treatments were analysed. Repeat analysis may have been carried out according to pre-defined criteria as described in standard operating procedures of the bioanalytical laboratory who conducted the PD sample analysis for this study.

Instructions for collection, processing, storage, and transfer of PD blood samples are provided in the study Laboratory Manual, available in the TMF.

Table 9-I Pharmacodynamic Sampling Timepoints for Part B (MAD Cohorts M1 to M3)

Sampling Windows for Blood Pharmacodynamic Samples					
Day	**Timepoint**	**Time Window (minutes)**	**Pharmacodynamic marker**		
			Biochemistry Blood Sample No.	**OGTT blood sample**	**Adipose tissue biopsy sample**
-1	Pre glucose drink	*Just prior to glucose drink*	-	1	-
	1 hour post glucose drink	*± 5 min*	-	2	-
	2 hours post glucose drink	*± 5 min*	-	3	-
1	Predose 1	*Within 2-3 hours prior to dosing*	1	-	-
7	2 hours post-dose 1	± 1 hour	2	-	1
15	2 hours post-dose	± 1 hour	3	-	-
16	24 hours post-dose	± 1 hour	4	-	-
	Pre glucose drink	*Just prior to glucose drink*	-	4	-
	1 hour post glucose drink	*± 5 min*	-	5	-
	2 hours post glucose drink	*± 5 min*	-	6	-

Abbreviations: OGTT = Oral glucose tolerance test; No. = number.

All OGTT tests to be conducted following overnight fast of at least 8 hours.

Biochemistry blood samples include Leptin, C peptide, hsCRP, glycohemoglobin, triglycerides, free fatty acids, fasting glucose, insulin.

9.5.5.3 Oral Glucose Tolerance Test

An OGTT was conducted on Day -1 (the day prior to the first dose of study drug) and on Day 16, the day following the last dose of study drug. The glucose tolerance test was conducted following an overnight fast of at least 8 hours. After an initial blood sample had been collected to establish baseline fasting glucose, participants were required to consume ~ 75 grams of glucose administered in 250 mL water within a 10-minute timeframe. Blood samples were obtained at 1 hour and 2 hours post glucose challenge to determine glucose tolerance. No food was to be consumed during the test.

9.5.6 Exploratory Assessments

9.5.6.1 White Adipose Tissue Sampling

In Part B (MAD) cohorts M1 to M3 only, a single sample of WAT was obtained by needle biopsy approximately 2 hours (± 1 hour) following the morning dose of study drug on Day 7. During the procedure, approximately 1.0 mL of subcutaneous fat was aspirated from the abdominal area using a needle under local anesthesia.

9.5.6.2 Patients General Impression of Change Questionnaire

A PGIC questionnaire was to be completed by participants in Part B only on Day 16 (the day following the last dose of study drug). The questionnaire was comprised of a single question

that rated the participants perception of change following treatment by a seven-point scale ranging from very much improved to very much worse, as follows:

Since the start of the study, my general health is:

1 = Very Much Improved
2 = Much Improved
3 = Slightly Improved
4 = No Change
5 = Slightly Worse
6 = Much Worse
7 = Very Much Worse

9.5.7 Appropriateness of Measurements

Sample collection and safety assessment timepoints were considered appropriate to achieve the objectives of this study.

The PK sampling schedule was designed to provide an adequate estimation of the planned PK parameters.

The planned PD sampling schedule, and timing of exploratory assessments was designed to provide a preliminary assessment of changes in response over time.

Procedures, assessments, and study drug administration were required to be performed as close as possible to the designated timepoint, within the allowable windows as specified in the protocol.

9.6 DATA QUALITY ASSURANCE

The Sponsor (or designee) performed the quality assurance and quality control activities for this study. However, the responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lay with the Investigator (and delegate[s]) generating the data.

9.6.1 Study Monitoring

The Sponsor was responsible for assuring the proper conduct of the study with regards to protocol adherence and validity of the data recorded in the eCRF.

During the course of the study, the Sponsor (or designee) visited the study site and/or performed remote monitoring at regular intervals. The Investigator was required to make themselves available to the Study Monitor during an on-site (or remote) monitoring visit to enable discussion on any arising issues relating to the study. The purpose of the monitoring was to ensure that the eCRF was completed correctly, the protocol was being adhered to, to perform source data verification, and to monitor drug accountability.

The PI agreed to allow the Study Monitor direct access to relevant source documents (original documents, data, and records). Direct access included permission to examine, analyze, verify, and reproduce any record(s) and report(s) that were important to evaluation of the clinical study. The PI also agreed to allocate their time and the time of their staff to the Study Monitor to discuss findings and any relevant issues.

Participant confidentiality was required to be maintained during all monitoring activities conducted by the Sponsor (or delegate).

In accordance with applicable regulations and ICH GCP, Avance Clinical (contracted by the study Sponsor, Eolo Pharma Pty Ltd) was responsible for assigning a Study Monitor who contacted the site to organize an on-site (or remote) visit prior to participant enrolment to review the protocol and data collection procedures with site staff. In addition, the assigned Study Monitor periodically contacted the site, including conducting on-site and remote visits. The extent, nature and frequency of on-site visits was based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrolment rate.

During these site visits, the Study Monitor:

- Checked the progress of the study
- Reviewed study data collected
- Conducted source document verification
- Identified any issues and addressed their resolution
- Checked study treatment accountability records
- Reviewed biological samples collected for the study and ensured that they were labelled and stored correctly
- Verified that:
    - The data were authentic, accurate, and complete
    - Safety and rights of participants were being protected
    - Study was conducted in accordance with the currently approved protocol (and any amendments), ICH GCP and all applicable regulatory requirements

At study closure, a Study Monitor conducted the following activities in conjunction with the PI or site staff as appropriate:

- Ensured that all data queries had been resolved
- Conducted final accountability and reconciliation for study treatment supplies including inventory and final disposition (e.g., destruction, shipping to repository, etc)
- Reviewed site study records for completeness

As this was a blinded study, a blinded Study Monitor was assigned to visit the site pharmacy during the study and at study completion, to review the randomization schedule in comparison to the dispensing log in order to verify correct randomization of study drug.

9.6.2 Quality Assurance and Quality Control

To ensure compliance with ICH GCP and all applicable regulatory requirements, the Sponsor (or a designated third party), could conduct a quality assurance audit of the study site. Regulatory agencies could also conduct a regulatory inspection of this study. Such audits/inspections could occur at any time during or after completion of the study. If an audit or inspection occurred, the Investigator and Institution agreed to notify the Sponsor as soon as possible following awareness of an impending regulatory inspection. The Investigator and Institution agreed to allow the auditor/inspector direct access to all relevant documents and

allocated their time and the time of their staff to the auditor/inspector to discuss findings and any relevant issues.

There were no Sponsor audits or regulatory inspections undertaken for this study.

9.6.3 Data Quality Control

The accuracy and reliability of data were ensured by the selection of qualified Investigators and investigational site, review of protocol procedures with the Investigator and associated personnel before the study commenced and conduct of periodic monitoring visits by the Sponsor (or designee). Written instructions were provided for collection, preparation, and shipment of biological samples collected for the purposes of this study. The Study Monitor reviewed electronic data for accuracy and completeness during on-site (or remote) monitoring visits and any discrepancies were resolved with the Investigator or designee, as appropriate. The data was entered into the clinical study eCRF and verified for accuracy.

This CSR has been prepared from data listings, summary tables and data analyses generated from the final locked study database and has been reviewed by a qualified independent Avance Clinical staff member and audited by the Avance Clinical Quality Assurance group. A Quality Audit Certificate is provided in Appendix 16.1.8.

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical and Analytical Plans

A Statistical Analysis Plan (SAP) (Final version 3.0, dated 08 May 2024) for this study is provided in Appendix 16.1.9.

9.7.1.1 Analysis Populations

There were 4 analysis sets for this study, as described below:

All-Randomised Analysis Set

The All-Randomised Analysis Set (ARS) included all participants randomised. Participants were analysed according to the treatment allocation at randomization.

Safety Analysis Set

The Safety Analysis Set (SS) included all participants who received at least one dose of study drug or placebo and had at least one post-dose safety assessment. Participants were analysed according to treatment received.

Pharmacokinetic Analysis Set

The PK Analysis Set (PKS) included all participants in the SS who had at least one post-dose plasma concentration data.

Pharmacodynamic Analysis Set

The PD Analysis Set (PDS) included all participants in the SS who had at least one observed post-dose pharmacodynamic parameter.

9.7.1.2 Participant Enrolment and Disposition

Counts and percentages of enrolment and disposition were summarised for participants included in the ARS.

Listings were provided for participant enrolment and disposition sorted by participant ID information for the ARS.

9.7.1.3 Demographic and Baseline Data Analysis

Demographic variables (age, sex, WOCBP, race, ethnicity, height, weight, and BMI) were summarised using descriptive statistics by treatment group for the ARS and SS. Demographic variables were listed by treatment group for the ARS and sorted by Participant ID.

Pregnancy test, FSH, alcohol breath test, urine drug screen, cotinine, serology, and COVID-19 test data were displayed in listings by treatment group for the SS.

Medical history was displayed in listings by treatment group for the ARS.

9.7.1.4 Protocol Deviations

All data recorded in the protocol deviation dataset were summarised. Counts (events and participants) and percentages for participants with any protocol deviations, participants with major protocol deviations, and participants with different deviation categories were provided by treatment group for the ARS.

A listing of all protocol deviations was provided by treatment group for the ARS.

9.7.1.5 Treatment Compliance and Exposure

All study drug administration information is displayed in data listings and includes all information collected. Listings are presented by the treatment groups, sorted by participant ID and date/time of administration for the SS, along with ages, sex, race and baseline weight of the participant

For Part B treatment groups, treatment compliance and duration were summarised.

Treatment compliance is defined as:

$$\frac{total\ number\ of\ tablets\ administered}{Expected\ number\ of\ tablets\ to\ be\ taken} \times 100\%$$

Compliance was summarised using descriptive statistics for the SS and Part B treatment groups. In addition, the number and percentage of participants in the following categories were summarised: 100% compliance and <100% compliance.

Treatment exposure (duration of treatment) in days was defined as:

- Date of last dose of study drug – date of first dose of study drug + 1

Overall duration of treatment (days) was summarised using descriptive statistics for the SS and Part B treatment groups.

9.7.1.6 Prior and Concomitant Medication

All medications were coded using the World Health Organization Drug Dictionary (WHO-DD) (WHODRUG GLOBAL B3 September 2022).

The definitions of prior and concomitant medications are provided in Section 9.4.7.

Medications stopped prior to the day of first study drug administration were not considered concomitant medication, but they were coded by WHO-DD and listed. If a clear determination could not be made as whether the medication was concomitant or not due to missing or incomplete data, the medication would be treated as concomitant medication taken during the study.

The number and percentage of participants using at least one concomitant medication was displayed together with the number and percentage of participants using at least one medication within each anatomical therapeutic class (ATC-Level 1) and preferred name. These were summarised under the SS for treatment groups and repeated for prior medication. Where ATC-Level and preferred name were reported, the display would be sorted by the descending order of the total counts by ATC-Level 1 and then by preferred term (PT) in the overall treatment group.

A listing of full details of prior and concomitant medications were provided by the treatment group, for the ARS.

Listing of full details of concomitant procedures (procedure, date, indication) is provided by the treatment groups, sorted by participant ID and date for the SS.

9.7.1.7 Safety Data Analysis

Adverse Events

AE verbatim terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 25.1).

The definitions of AEs are provided in Section 9.5.3.1. All AE summaries were restricted to TEAEs only and were summarised as follows:

- Overall Summary of TEAEs
  - TEAEs
  - TEAEs by Severity (Grade 1 to Grade 5)
  - Treatment Related TEAEs
  - Serious TEAEs
  - Serious Treatment Related TEAEs
  - TEAEs leading to death
  - TEAEs leading to study drug discontinuation
  - TEAEs leading to study withdrawal.
- TEAE summary by system organ class (SOC) and PT
- TEAE summary by SOC, PT and Severity
- Treatment Related TEAE summary by SOC and PT
- Treatment Related TEAE summary by SOC, PT and Severity
- Serious TEAE summary by SOC and PT

- Serious Treatment Related TEAEs summary by SOC and PT
- TEAE summary of events leading to study drug discontinuation, or study withdrawal by SOC and PT
- TEAE summary of events leading to death

The following table summaries were presented by PT by treatment groups:

- TEAE summary by PT
- Treatment Related TEAE summary by PT

The above was presented using summary tables, which included the number of participants and percentage (%) experiencing an event and the number of events. If a participant experienced the same AE multiple times, this was only counted once for the purpose of counting the number of participants who experienced the event. Maximum severity was considered when counting participants in the summary tables by SOC, PT and severity, while all occurrences were counted according to their severity. When seriousness and relation to treatment were reported with different values in records related to the same occurrence of an AE, i.e., the worst case among the records was assigned to the AE occurrence. Summary tables were done for the SS for treatment groups. Where SOC and PT were reported, the display was sorted in descending order by the total count of SOC and then by PT in the Overall treatment group.

All AEs were listed and included the verbatim term, SOC, PT, SAE, TEAE, start/end date/time, severity, relationship to study treatment, outcome, action taken, and study withdrawal.

Key participant listings were created for SAEs, any deaths, AEs leading to study drug discontinuation of AEs leading to withdrawal from the study.

Safety Laboratory Assessments

For haematology, coagulation and serum chemistry continuous data summary statistics were presented for values and change from baseline values at baseline and each scheduled post baseline visit. Where applicable, clinical assessment results (normal, abnormal NCS, and abnormal CS, unable to evaluate) was summarised by counts and percentages for baseline and each scheduled visit. In addition, shift tables from baseline to each visit for haematology, chemistry, and coagulation lab parameters (low, normal, and high) were presented using counts and percentages. A shift table from baseline to worst outcome on treatment was also presented.

For urinalysis, discrete data summary statistics were presented for the counts and percentages of normal, abnormal CS and NCS results at each visit at baseline and each schedules post baseline visit. A shift table from baseline to worst outcome on treatment is also presented.

The summary tables were based on the SS for treatment groups.

All available laboratory assessment results were displayed in a data listing and included all information collected. In addition, the observations that were used as the baseline record (value) for each parameter was flagged, and the change from baseline values (where applicable) at each scheduled post baseline (scheduled and unscheduled) visit was presented.

Vital Sign Measurements

Observed values and changes from baseline for vital signs (systolic and diastolic BP, HR and body temperature) were summarised at each baseline and scheduled post-baseline visit using descriptive statistics and tabulated for each dose group. In addition, overall clinical interpretation (normal, abnormal NCS, abnormal CS) was summarised. A shift table from baseline to worse outcome on treatment for clinical interpretation was also presented by treatment group for the SS.

For Part B, a summary of change between post-dose and pre-dose values was also presented for each dose and time point.

All available vital signs results were displayed in a data listing and included all information collected for the SS.

Electrocardiograms

The following ECG parameters were analysed; PR interval, QT interval, QRS duration, QTcF and ventricular HR. Observed values and changes from baseline for ECG parameters were summarised at each scheduled timepoint using descriptive statistics and tabulated for each dose group for the SS. In addition, clinical results of ECG interpretations (Normal, Abnormal NCS, and Abnormal CS) were summarised by counts and percentages for baseline and for each scheduled post baseline visit. A shift table from baseline to worse outcome on treatment for clinical interpretation was also presented by treatment group for the SS. For Part B, a summary of change between post-dose and pre-dose values was also presented for each dose and time point.

Physical Examinations

All physical examination data was listed. The listing is presented by the treatment groups sorted by participant ID and visit for the Safety Analysis Set, along with age, sex, race and baseline weight of the participant.

Stool Diary

All available stool diary results were listed. The listing is presented by the treatment groups sorted by participant ID and visit for the Safety Analysis Set, along with age, sex, race and baseline weight of the participant.

Simplified Nutritional Appetite Questionnaire

All available results were listed, presented by the treatment groups sorted by participant ID and visit for the Safety Analysis Set, along with age, sex, race and baseline weight of the participant.

9.7.1.8 Pharmacokinetic Data Analysis

Pharmacokinetic data was analysed using the PKS.

Plasma and Urine Concentration Data

Individual plasma and urine concentrations of MVD1 and metabolites were used for analyses as supplied by the laboratory (including units). The actual sampling time and date, if

available, were listed for plasma, by participant and nominal sampling time, with time deviation (difference in hours between nominal and actual sampling times) calculated. Individual plasma concentrations of MVD1 and metabolites over actual time were plotted by cohort with the concentration result (y-axis) displayed for the PKS on a linear and semi-logarithmic scale.

Pharmacokinetic Parameter Calculation

A non-compartmental analysis was conducted in plasma using Phoenix WinNonlin software version 8.3. Following oral (capsule) route of administration, MVD1 and metabolites were analysed using the extravascular model. Parameters were generated following dosing on Day 1 (Parts A and B) and Day 15 (Part B), using actual sampling times and doses, if available. For the purpose of the PK parameter calculations, concentrations that are BQL were treated as zero. Following the 1st dose on Day 1, pre-dose samples will be assigned a value of zero. If pre-dose is not present following repeat dosing, Cmin within the tau period (where tau = 12) may be duplicated as pre-dose.

Plasma and urine PK parameters calculated are presented and defined in Table 9-J and Table 9-K, respectively.

Table 9-J Plasma Pharmacokinetic Parameters

Parameter	Definition
C_{max}	Individual maximum concentration values, directly determined from the plasma concentration time profiles for each participant.
C_{min}	Individual minimum concentration values, directly determined from the plasma concentration time profiles for each participant, following repeat dosing only.
t_{max}	The time to attain maximum concentration. If the same C_{max} concentration occurs at different time points, t_{max} is assigned to the first occurrence of C_{max}.
t_{last}	Time of last measurable observed concentration.
AUC_{last}	The area under the plasma concentration-time curve from time zero to the last time point with measurable concentration using the linear trapezoidal.
AUC_{0-12}	The area under the plasma concentration time curve from time zero to 12 hours post dose, using the linear trapezoidal rule.
R_{AUC}	Accumulation ratio calculated as AUC_{last} repeat dose/AUC_{last} single dose using the same the same or similar t_{last}.
R_{Cmax}	Accumulation ratio calculated as C_{max} repeat dose/C_{max} single dose
M:P C_{max}	Metabolite to parent drug ratios of C_{max} calculated in mol units.
M:P AUC_{last}	Metabolite to parent drug ratios of AUC_{last} calculated in mol units.

The above PK parameters were calculated for each administration as well as for the overall sampling period, within each sampling occasion.

Parameter	Definition
AUC_{inf}	The area under the plasma concentration-time curve over the time interval from time 0 extrapolated to infinity, after each administration on Day 1.
$t_{1/2}$	The terminal elimination half-life.
CL/F	Plasma clearance following oral route of administration, defined as the volume of plasma cleared of drug per unit of time, where F is the fraction of drug absorbed following subcutaneous administration.
V_z/F	The apparent volume of distribution in plasma, determined from the terminal elimination phase during terminal phase following oral route of administration, where F is the fraction of drug absorbed following administration.

Where data allowed the calculation of slope parameters, the following parameters were included.

Table 9-K Urine Pharmacokinetic Parameters

Parameter	Definition
A_e	Total amount of parent drug excreted unaltered in urine, calculated as a cumulative sum of the amount excreted across collection intervals.
CL_r	Renal clearance, calculated as the total amount of parent drug excreted in urine, divided by the AUC calculated up to the end of the last collection interval.

The following were considered for reporting the PK parameters:

- All AUC_{last} and C_{max} were set to zero for descriptive statistics purposes if all concentrations were below the limit of quantification.
- No value of AUC_{inf}, $t_{½}$, CL/F and V_z/F were reported for cases that did not exhibit a terminal log-linear phase in the concentration versus time profile. Criteria which may have indicated a failure to exhibit a terminal log-linear phase in the concentration-versus-time profile included:
    - Positive slope for log regression fit.
    - $r^2adj < 0.85$.
    - Time points in the interval used in estimating the half-life span less than 1.5 half-lives.

The PK parameters which were not determined from PK analyses due to inadequate concentration data or missing data were considered as ‘not estimable (NE)’. The details of

extrapolation for the determination of slope related parameters, including the number of timepoints used, λz, Adujsted Rsq, AUC percentage extrapolated, interval and interval/$t_{1/2}$ were listed.

Reasons for exclusion of a participant or a sample from the descriptive statistics at the discretion of the PK analyst may have included, but were not limited to, the following:

- Noncompliance with study procedures affecting PK (e.g., concomitant medication, over or underdosing).
- Too few collected samples to reliably estimate at least 1 PK parameter (e.g., participants who did not complete PK sample collection).
- Vomiting between administration and up to t_{max} or within 2 hours following administration.

Individual plasma and urine PK parameters are listed, in the units supplied by the laboratory, except for CL/F, CLr and Vz/F that may have been reported in different units, if deemed necessary. All PK parameters are reported to three significant figures.

Statistical Analysis of Plasma and Urine Concentrations and Pharmacokinetic Parameters

Plasma and urine concentrations and PK parameters were summarised using descriptive statistics (number of non-missing observation [n], arithmetic mean, standard deviation, coefficient of variation [CV%], geometric mean, median, minimum and maximum and geometric CV%) for each time point and summarised by treatment cohorts. Urine Concentrations were summarised by interval rather than timepoint. Concentrations below the lower limit of quantification (BLQ) were treated as zero in the calculation of summary statistics, except geometric mean. BLQ values were excluded from the calculation of geometric mean.

When reporting descriptive statistics for concentration and PK parameter, data was reported to three significant figures. Mean plasma concentrations over scheduled time on Day 1 and 15 as well as over the scheduled time from Day 1 to the end of the last administration on Day 15 were plotted with the concentration result (y-axis) displayed for the PK Analysis set on a linear and semi-logarithmic scale.

Dose proportionality was assessed using the power model for all dosed cohorts. Natural log-transformed PK parameter overall C_{max}, total AUC_{last} and AUC_{inf} on Days 1 (Parts A and B) and Day 15 (Part B) as following each administration on Day 1 (Part B), and natural log-transformed dose was used to estimate the slope parameter and the 90% confidence interval for the slope.

Plasma PK parameters were assessed by fitting the following power model and testing the null hypothesis of linearity, that $\beta = 1$, by a general linear model approach using the GLM procedure in SAS:

$$\ln(\text{Parameter}) = \alpha + \beta \times \ln(\text{Dose}) + \text{random error}$$

Dose proportionality was generally concluded if the 90% CI around the slope estimate (β) included the value of 1. R square was also computed.

The relationship between PK parameters and dose was also presented graphically. All tables and figures were produced using SAS.

9.7.1.9 Pharmacodynamic Data (Part B only)

Pharmacodynamic data was analysed using the PDS and presented for Part B only.

Body Weight

Body weight was measured on Day -1 (check-in) prior to dose administration, pre-dose on Day 15 (within 3 hours) and on Day 22 (EoS) to investigate drug induced body weight reduction.

Serum Biomarkers

The following biomarkers assessed were taken at timepoints specified in the SoA:

- Glucose, Insulin, C peptide, hsCRP, Fructosamine, Glycohemoglobin (Cohort MAD 1 and MAD 2 only), Free fatty acids, Triglycerides, Leptin levels. Continuous data summary statistics were presented for values and change from baseline value at baseline and each scheduled post baseline visit. A figure is presented showing mean values over time for each parameter.
- All serum biomarker results are presented in a data listing and include all information collected. In addition, observations that were used as the baseline record (value) for each parameter were flagged, and the change from baseline values (where applicable) at each scheduled post baseline (scheduled and unscheduled) visit are presented.

Oral Glucose Tolerance Test

An OGTT was conducted on Day -1 and on Day 16. The OGTT was conducted following an overnight fast of at least 8 hours. After an initial blood sample had been collected to establish baseline fasting glucose, participants were required to consume ~75 grams of glucose administered in 250 mL water. Blood samples were obtained at 1 hour and 2 hours post glucose challenge to determine glucose tolerance.

Continuous data summary statistics are presented for values and change from baseline value at baseline and each scheduled post baseline visit. A figure is also presented showing mean values at each visit and time point with all treatment groups presented on the same page.

All OGTT results are presented in a data listing and include all information collected. In addition, the observations that are used as the baseline record (value) for each parameter were flagged, and the change from baseline values (where applicable) at each scheduled post baseline (scheduled and unscheduled) visit are presented.

9.7.1.10 Exploratory Analyses

All exploratory endpoints were analysed using the SS.

White adipose tissue sampling

A single sample of white adipose tissue was obtained by punch biopsy approximately 2 hours following the morning dose of study drug on Day 7 (Part B) which was analysed for the presence of MVD1.

All white adipose tissue sampling results are displayed in a data listing and include all information collected, including presence of MVD1. This listing is presented by the treatment groups, sorted by participant ID and visit, along with age, sex, race, and baseline weight of the participant.

Patient General Impression of Change

The PGIC is a scale that asks the participant to rate how much their disease has improved or worsened relative to a baseline state after starting an intervention. PGIC was assessed at the time points specified in the study procedure schedule.

Since the start of the study, my general health is:

1 = Very Much Improved
2 = Much Improved
3 = Slightly Improved
4 = No Change
5 = Slightly Worse
6 = Much Worse
7 = Very Much Worse

All PGIC results are displayed in a data listing and include all information collected. This listing is presented by the treatment groups, sorted by participant ID and visit, along with age, sex, race, and baseline weight of the participant.

9.7.2 Determination of Sample Size

This study was a FIH study with MVD1 and as such no formal sample size calculation was performed. A total of 42 healthy volunteers were planned to be enrolled. Part A: 3 cohorts of 6 participants per cohort (2:1 active: placebo) and Part B: 3 cohorts of 8 participants per cohort (3:1 active: placebo) which was considered sufficient to address the objectives of the study.

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

9.8.1 Changes in the Conduct of the Study

The study was initiated on Protocol Version 2.0, dated 08 Dec 2022. There were 2 amendments to the protocol, and 7 Protocol Clarification Memorandums implemented during the study. Three participants were screened and consented under Protocol Version 2.0, but were then reconsented under Protocol Version 3.0, prior to dosing.

All SAD patients were dosed and completed the study under Protocol Version 3.0.

All MAD patients were screened, dosed, and completed the study under Protocol Version 4.0.

The changes are summarised in Table 9-L .

Table 9-L A Summary of Protocol Amendments and Participant Enrolment

Protocol Version and Date	Summary of Key Changes	Number of Participants Enrolled
Protocol V2.0_08 Dec 2022 (IEC approved on 20 Dec 2022)	Not Applicable	3 (SAD)
Protocol V3.0_16 Feb 2023 (IEC approved on 23 Feb 2023)	1. Clarification that triplicate mean ECG parameters would be used, procedure and assessment window updated. 2. Addition of topical ointment, vitamins and dietary supplements to the list of excluded medications. 3. Inclusion of fasting requirements prior to admission to the clinical facility on Day -1. 4. Medical history removed from data analysis parameters. 5. Clarification around the amount of microcrystalline cellulose in placebo capsules (equivalent to dose level of API). 6. Storage conditions range updated. 7. Clarification that all vitals would be taken in supine position within 1.5 hours of dosing. 8. Clarification of the time of physical examination assessments. 9. Clarification on timing of nutritional appetite questionnaire and update of name to SNAQ. 10. Clarification that body weight assessment was required on Day -1. 11. Clarification on timing and assessment requirements for symptom directed physical examinations. 12. Clarification that screen failed participants would not be presented. 13. Definition of PGIC amended to align with definition used in Australia. 14. Associated updates to SoA (SAD and MAD).	17 (SAD)
Protocol Clarification Memo_01_16 Mar 2023 (IEC approved on 21 Mar 2023	1. Recording of AEs and SAEs wording amended to remove requirement to record any increase in the severity of an AE as a separate AE. 2. Clarification that only available safety and PK data would be used by the SRC when making dose escalation. 3. Escalation to the next dose level in Part A would occur after SRC review of available safety data up to day 4 and available PK data from all participants at the current dose level.	

Protocol Version and Date	Summary of Key Changes	Number of Participants Enrolled
	4. Escalation to the next dose level in Part B would occur after SRC review of available safety data up to day 18 and available PK data from all participants at the current dose level. 5. Typographical error in the spelling of the word Capsule was fixed, and the size of the capsule updated to Size 0 or 000.	
Protocol V4.0_27 Aug 2023 (IEC approved on 05 Sep 2023)	1. Allowable medications amended to include medications for hayfever rather than nasal spray (as the risk of drug-drug interaction (DDI) between hayfever medications and MVD1 was deemed low and may have impacted recruitment. 2. Clarification that WAT sampling on day 7 for all part B (MAD) cohorts was to demonstrate MVD1 target engagement. 3. Clarification that only a 2 hour fast is required prior to first dose administration on Day 1 for all part B (MAD) cohorts. 4. Clarification that a needle will be used for sampling of white adipose tissue for all part B (MAD) cohorts and that this should be obtained on day 7 approximately 2 hours (± 1hour) post morning dose of study drug. 5. Update of PK sampling timepoints for part B (MAD) in Appendix 10 to include pre-dose 2 PK sample on Day 1 of dosing and PK timepoint at 8 hours post dose 2 on Day 1 of dosing. 6. Update of Investigational product Section 8.1 to include 100 mg MVD1 drug product dose strength. 7. Associated updates to SoA (MAD). 8. Clarification regarding the recording of AEs and SAEs, update of wording to “available” safety and PK data reviewed by SRC when deciding to escalate between dose levels and proceed from Part A to B. Clarification around the size of capsule used for both MVD1 and Placebo (000). (These changes were outlined in Protocol Clarification Memo_01_16 Mar 2023 (IEC approved on 21 Mar 2023)).	20 (MAD)
Protocol Clarification Memo_02_14 Nov 2023 (IEC approved on 22 Nov 2023)	1. SRC review/dose escalation to was allowed to proceed in the event that data from < 8 participants was available for review at the time of the SRC meeting. 2. Time windows for PD sampling timepoints in Part B (MAD) were increased (to 3 hours) to allow increased flexibility for sites.	

Protocol Version and Date	Summary of Key Changes	Number of Participants Enrolled
	3. The definition of baseline for QTcF was clarified (Two or more participants with ≥ 60 msec increase over baseline (Day -1) in QTcF (the mean of the triplicates should be used).	
Protocol Clarification Memo_03_19 Dec 2023 (IEC approved on 21 Dec 2023)	1. Body weight was added as a pre-dose assessment on the morning of Day 15 and 22 (to investigate drug induced body weight reduction). 2. Clarification that PK samples that were not used for PK analysis at the central laboratory would be shipped to an overseas facility to explore target engagement of the study drug in relation to the adipose tissue sample and to measure further drug-induced effects on biochemical pathways of MVD1 in plasma in the MAD cohorts.	
Protocol Clarification Memo_04_03 Jan 2024 (IEC approved on 09 Jan 2024)	1. Addition of a WAT biopsies on Day -1 (in addition to post-dose on Day 7).	
Protocol Clarification Memo_05_12 Jan 2024 (IEC approved on 15 Jan 2024)	1. Fructosamine sampling was added to serum biomarker assessment. (in place of Glycoalbumin) 2. Glycohemoglobin was removed for Cohort MAD 3	
Protocol Clarification Memo_06_09 Feb 2024 (IEC approved on 27 Mar 2024)	1. Section 11 of the protocol was updated to include the ± 30-min window, as only the SoA was updated when Protocol V4.0 was drafted. 2. Clarification that there was a transcription error when transcribing the original wording from the Protocol to the Protocol Clarification Memo #04 – "Adipose tissue biopsy sample will be collected on Day 7, post-dose" was incorrectly transcribed as "Adipose tissue biopsy sample will be collected on Day 7, pre-dose." The intention of protocol clarification emo #04 was to add a Day -1 adipose tissue biopsy, rather than change the Day 7 sample collection from post-dose to pre-dose.	
Protocol Clarification Memo_07_05 Jun 2024 (IEC approved on 27 Mar 2024)	Amendment of Protocol/Study Title to correctly reflect the patient populations recruited into the study. Original Wording:	

Protocol Version and Date	Summary of Key Changes	Number of Participants Enrolled
	• A Phase 1, Randomised, Double-blind, Placebo-controlled, First in Human Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single and Multiple Doses of MVD1 in Healthy Adult Volunteers Revised Wording: • A Phase 1, Randomised, Double-blind, Placebo-controlled, First in Human Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single *Doses of MVD1 in Normal Weight or Overweight Healthy Adult Volunteers* and Multiple Doses of MVD1 in *Overweight or Obese* Healthy Adult Volunteers	
Abbreviations: AE = Adverse event; API = Active Pharmaceutical Ingredient; ECG = Electrocardiogram; IEC = Independent Ethics Committee; MAD = Multiple Ascending Dose; PCL = Protocol Clarification Letter; PD = Pharmacodynamic; PK = Pharmacokinetics; SAD = Single Ascending Dose; SNAQ = Simplified Nutritional Appetite Questionnaire; SoA = Schedule of Assessments; WAT = white adipose tissue.		

There were no other changes to the conduct of the study.

9.8.2 Changes in the Planned Analyses

The SAP version 3.0, dated 08 May 2024, was finalised prior to database lock (DBL), which occurred on 21 May 2024.

Changed to the analyses outlined in the SAP (V3.0, 08 May 2024) included:

- Section 14.2 Pharmacokinetic Parameter Calculation: AUC_{0-12} was included for Part B on Day 15 as well for the comparison with Part B Day 1 AUC_{0-12}.

There were no other changes to the analyses as described in the SAP (Version 3.0 dated 08 May 2024) provided in Appendix 16.1.9.

10. STUDY PARTICIPANTS

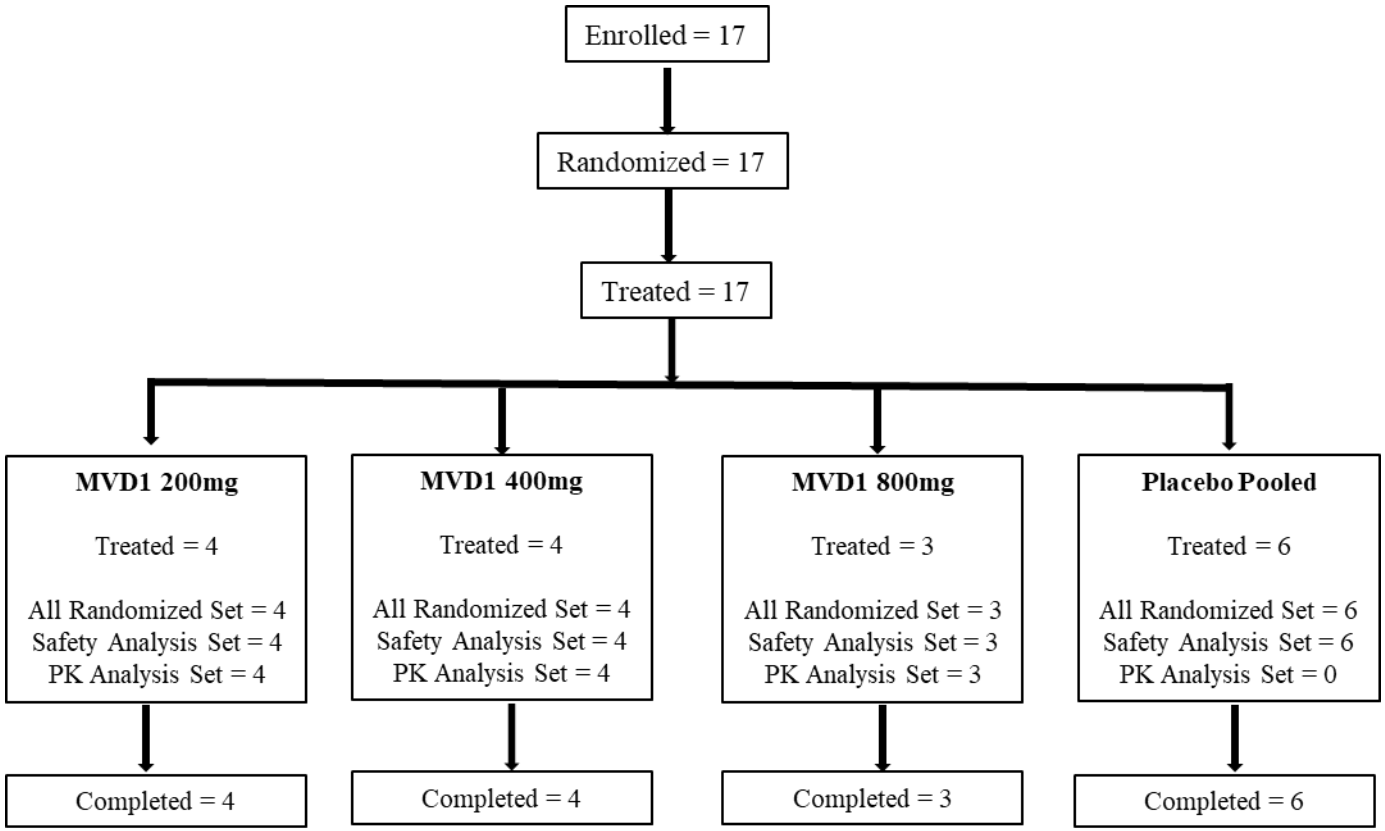
10.1 ENROLMENT AND DISPOSITION OF PARTICIPANTS

A summary of participant enrolment and disposition is provided in Section 14.1 (Table 14.1.1A and Table 14.1.1B) and presented in Figure 10-A and Figure 10-B. A complete list of enrolment and disposition by participant is provided in Appendix 16.2.1 (Listing 16.2.1.1A and Listing 16.2.1.1B and Listing 16.2.1.2A and Listing 16.2.1.2B). Participant Pre-dose eligibility reviews are listed in Listing 16.2.1.3A and Listing 16.2.1.3B.

Overall, 17 participants were considered eligible, enrolled into Part A (SAD) of the study and randomised to MVD1 or placebo. Eleven participants were administered MVD1 (4 participants for each of 200 mg and 400 mg MVD1 groups and 3 participants for the 800 mg MVD1 group). Six participants were administered placebo (2 in each dose cohort). All participants randomised and dosed with study drug completed the study.

Overall, 24 participants were considered eligible, enrolled into Part B (MAD) of the study and randomised to MVD1 or placebo. Eighteen participants were administered MVD1 (6 participants for each of 200 mg, 300 mg and 400 mg MVD1 groups). Six participants were administered placebo (2 in each dose cohort). Two participants did not complete the study (one in the 200 mg MVD1 group due to an AE and the other in the pooled placebo group due to a major protocol deviation).

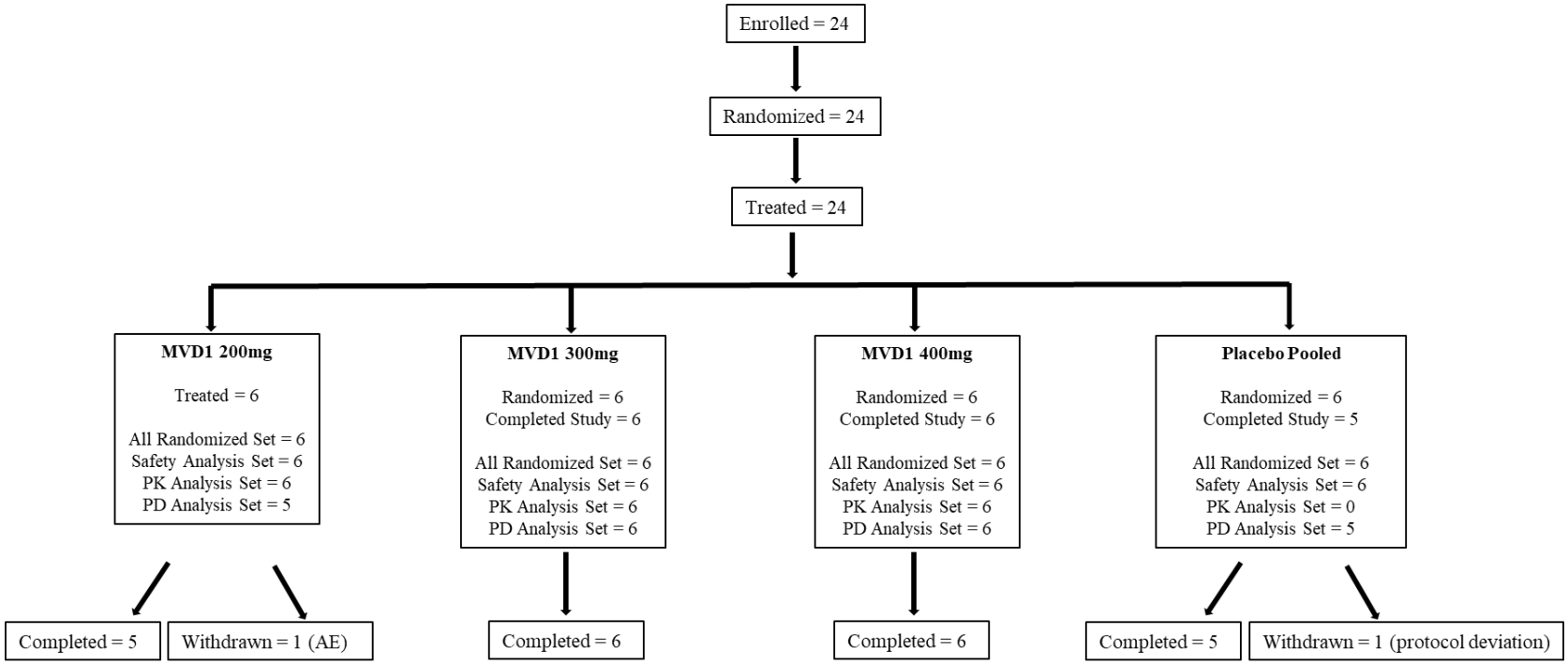
Figure 10-A Enrolment, Disposition, and Analysis Populations (Part A – SAD)



Abbreviations: PK = Pharmacokinetic; SAD = Single Ascending Dose

References: Table 14.1.1A and Table 14.1.2A

Figure 10-B Enrolment, Disposition, and Analysis Populations (Part B – MAD)



Abbreviations: MAD = Multiple Ascending Dose; PD = Pharmacodynamics; PK = Pharmacokinetic

References: Table 14.1.1B and Table 14.1.2B

10.2 PROTOCOL DEVIATIONS

A summary of protocol deviations is provided in Section 14.1 (Part A: Table 14.1.3A and Part B: Table 14.1.3B). A complete list of protocol deviations is provided in Appendix 16.2.2 (Part A: Listing 16.2.2.1A and Part B: Listing 16.2.2.1B) and general comments by participant is provided in Listing 16.2.2.2A (Part A) and Listing 16.2.2.2B (Part B).

In Part A (SAD), there were 43 protocol deviations reported in 16 (94.1%) of 17 participants in the study, with 40 protocol deviations for 15 (88.2%) participants considered to be minor protocol deviations.

There were 3 protocol deviations in 2 (11.8%) participants that were considered to be major protocol deviations as follows:

- There were 2 procedures/tests deviations in 1 participant in the 200 mg MVD1 group, where the Day 1 (6-hours post-dose) and Day 4 (72-hours post-dose) PK samples did not have acetonitrile added to the aliquot. As per the analytical laboratory, these samples were presented as neat plasma and were not able to be analysed.
- There was 1 major inclusion/exclusion deviation in 1 participant in the 400 mg MVD1 group of any exclusion criterion met by a randomised and dosed participant. The participant reported at Screening an alcohol consumption history of 3 standard drinks per day, >10 standard drinks per week which was exclusionary per Exclusion Criterion#13. The participant was deemed to be eligible for the study in error and was enrolled into the trial. The participant was dosed and completed the study with no safety signals of concern.

The majority of protocol deviations were related to study procedures/tests (23 protocol deviations in 12 [70.6%] participants). Other protocol deviations included laboratory (18 protocol deviations in 10 [58.8%] participants, visit schedule (1 protocol deviation for 1 [5.9%] participant) and 1 inclusion/exclusion protocol deviation. There were no protocol deviations related to COVID-19 reported during Part A of the study.

In Part B (MAD), there were 120 protocol deviations reported in 24 (100%) of 24 participants in the study, with 116 protocol deviations for 24 (100%) participants considered to be minor protocol deviations.

There were 4 protocol deviations for 4 (16.7%) participants that were considered to be major protocol deviations as follows:

- There were 3 major study procedures/tests deviations in 2 participants in the 200 mg MVD1 group and 1 participant in the placebo group of efficacy assessments not performed as per protocol: Day 1 PD glycoalbumin testing was not performed. A suitable plasma sample was available at site and shipped to the analysis facility for fructosamine testing. Site believed that the sample that was sent had acetonitrile added.
- There was 1 major inclusion/exclusion deviation in 1 participant in the placebo group of any exclusion criterion met by a randomised /dosed participant. The participant was 19 years of age at screening so did not meet Inclusion Criterion #2 for Part B which stated participants needed to be between 25-60 years of age (inclusive) at the time of

screening. The participant was randomised and received 3 doses of placebo before being withdrawn from the study.

The majority of all protocol deviations were related to study procedures/tests (85 protocol deviations in 23 [95.8%] participants). Other protocol deviations included laboratory (18 protocol deviations in 16 [66.7%] participants), IP dosing and or accountability (6 protocol deviations in 3 (12.5%) participants), source data (5 protocol deviations in 4 (16.7%) participants), other (3 protocol deviations in 3 (12.5%) participants) and 1 protocol deviation for 1 [4.2%] participant each for inclusion/exclusion criteria, informed consent and visit schedule. There were no protocol deviations related to COVID-19 reported during Part B of the study. Of note, the IP dosing and or accountability protocol deviations were as follows:

- One participant in 300 mg MVD1 group with a deviation of Failure to modify doses according to protocol on Day 5 (Dose 1) Pre-dose and Day 6 (Dose 1) Urinalysis Dipstick (Protein) results were positive but participant dosing was not suspended. PI was aware and happy to continue dosing with reason, currently menstruating, occurring in the setting of menses and asymptomatic bacteriuria, and has settled with ongoing dosing, hence NCS.
- Two participants one in 200 mg MVD1 group and one in the placebo group with a deviation in non-compliance with study drug dosing. One participant in the 200 mg MVD1 group, Day 8 (dose 2), Day 10 (dose 2) and Day 12 (dose 2), did not fast for the required 2 hours post-dose. The other participant (placebo), Day 10 (dose 2) did not fast for the required 2 hours post-dose.

10.3 DATA SETS ANALYSED

A summary of analysis sets is provided in Section 14.1 (Part A: Table 14.1.2A and Part B: Table 14.1.2B). A complete list of analysis sets by participant is provided in Appendix 16.2.3 (Part A: Listing 16.2.3.1A and Part B: Listing 16.2.3.1B).

In Part A (SAD), all 17 participants who were randomised and dosed with study drug were included in the ARS and SS. All 11 participants who received MVD1 were included in the PKS (Figure 10-A).

In Part B (MAD), all 24 participants who were randomised and dosed with study drug were included in the ARS and SS. All 18 participants who received MVD1 were included in the PKS. All 22 participants who completed the study were included in the PDS. (Figure 10-B).

10.4 MEASUREMENTS OF TREATMENT COMPLIANCE AND EXPOSURE

A summary of treatment compliance and exposure for Part B (MAD) is provided in Section 14.1 (Part B: Table 14.1.7B). A complete list of study drug administration, treatment compliance and exposure by participant is provided in Appendix 16.2.5 (Part A: Listing 16.2.5.1A and Part B: Listing 16.2.5.1B).

In Part A (SAD), all doses of MVD1 and placebo were administered as per the protocol.

In Part B (MAD), the mean (SD) duration of treatment (in days) for participants administered MVD1 was 14.3 (3.06) days for 18 participants, with a mean of 12.8 (5.31) days for 6 participants administered placebo.

Overall, in Part B (MAD), mean (SD) treatment compliance for participants administered MVD1 was 93.5% (21.51), with 15 (83.3%) participants having an overall treatment compliance rate of 100%. There were 3 (16.7%) participants with less than 100% overall treatment compliance rate who were administered MVD1. Overall mean (SD) treatment compliance for participants administered placebo was 84.5% (36.35), with 4 (66.7%) participants having an overall treatment compliance rate of 100%. There were 2 (33.3%) participants with less than 100% overall treatment compliance rate who were administered placebo. As per Listing 16.2.5.1B, all doses that were given were administered as per the protocol.

There were 5 participants who did not receive all the scheduled doses of study drug as follows:

- 1 participant in the 200 mg MVD1 group did not receive Dose 1 on Day 7 (i.e., received 28 of the 29 scheduled doses) due to the dose being temporarily paused as a safety precaution. This participant had elevated ACR and treatment was stopped on Day 7. The morning dose was not given, however the ACR returned to normal, and dosing recommenced Day 7 Dose 2.
- 1 participant in the 200 mg MVD1 group had study drug withdrawn after Dose 1 on Day 2 (i.e., received 3 of the 29 scheduled doses) due to an AE of proteinuria (refer to Section 12.2.2) and was subsequently withdrawn from the study.
- 1 participant in the 400 mg MVD1 group did not receive doses from Dose 1 on Day 2 to Dose 1 on Day 5, inclusive (i.e., received 22 of the scheduled 29 doses), as the PI decided to interrupt dosing due to an elevated ACR which was associated with an AE of proteinuria (refer to Section 12.2.2).
- 1 participant in the placebo group did not receive Dose 1 on Day 8 (i.e., received 28 of the 29 scheduled doses) due to a false positive result for protein in urine. The

participant had dosing stopped temporarily while ACR testing was done, when results returned to normal the PI confirmed dosing could resume on Day 8 Dose 2.

- 1 participant in the placebo group did not receive a dose of study drug from Dose 2 on Day 2 to the final dose on Day 15 (i.e., received 3 of the 29 scheduled doses) as the participant was withdrawn from the study due to a major inclusion/exclusion protocol deviation i.e., was younger than 25 years of age at screening (refer to Section 10.1).

10.5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

10.5.1 Demographics

A summary of demographics is provided in Section 14.1 (Part A: Table 14.1.4A and Part B: Table 14.1.4B) and presented in

Table 10-A and

Table 10-B.

A complete list of demographics by participant is provided in Appendix 16.2.4 (Part A: Listing 16.2.4.1A and Part B: Listing 16.2.4.1B).

In Part A (SAD), the demographic characteristics of participants across dose cohorts in the SAS were broadly similar. Overall, participants had a median age (minimum;maximum) of 31.0 years (18;58) which was higher in the participants administered placebo (33.5 years [18;53]) compared to MVD1 (31.0 years [21;58]). Mean (SD) BMI for all participants was 24.96 kg/m^2 (2.666), which was similar for participants administered MVD1 and placebo (mean BMI [SD] 24.38 kg/m^2 [2.435] and 26.02 kg/m^2 [2.967], respectively). The were a total of 9 (52.9%) of 17 participants that were male with a similar number and percentage that were female (8 [47.1%]). Of these 8 female participants, there were 7 (87.5%) participants of childbearing potential. The majority of participants were White (15 [88.2%] of 17 participants). One (5.9%) of 17 participants was Asian, and 1 participant was reported as 'other'. Four (23.5%) of 17 participants were Hispanic or Latino.

In Part B (MAD), the demographic characteristics of participants across dose cohorts in the SAS were broadly similar. Participants had a median age (minimum;maximum) of 31.0 years (19;55) which was higher in the participants administered placebo (33.0 years [19;47]) compared to MVD1 (30.5 years [27;55]). Mean (SD) BMI for all participants was 31.03 kg/m2 (2.005), which was similar for participants administered MVD1 and placebo (mean BMI [SD] 30.95 kg/m2 [1.968] and 31.25 kg/m2 [2.292], respectively). The majority of participants were male (19 [79.2%] of 24 participants). Five (20.8%) of 24 participants were female, of these there were 5 (100%) participants of childbearing potential. The majority of participants were White (14 [58.3%] of 24 participants). Seven (29.2%) of 24 participants were Asian, and 1 (4.2%) of 24 participants each were reported as American Indian or Alaska Native, Black or African American or unknown. Four (16.7%) of 24 participants were Hispanic or Latino.

Table 10-A Summary of Demographics – Part A (SAD) (Safety Analysis Set)

Variable Statistics	MVD1 200 mg (N = 4)	MVD1 400 mg (N = 4)	MVD1 800 mg (N = 3)	MVD1 Pooled (N = 11)	Placebo Pooled (N = 6)	Overall (N = 17)
Age (years)						
Mean	42.3	30.8	33.3	35.6	35.5	35.6
SD	13.23	18.17	6.81	13.76	13.66	13.30
Median	44.0	22.0	31.0	31.0	33.5	31.0
Minimum	56	58	41	58	53	58
Maximum	25	21	28	21	18	18
Sex, n (%)						
Male	1 (25.0)	4 (100)	2 (66.7)	7 (63.6)	2 (33.3)	9 (52.9)
Female	3 (75.0)	0	1 (33.3)	4 (36.4)	4 (66.7)	8 (47.1)
Women of Child-bearing Potential, n (%)						
n	3	0	1	4	4	8
Yes	3 (100)	0	1 (100)	4 (100)	3 (75.0)	7 (87.5)
No	-0	0	0	0	1 (25.0)	1 (12.5)
Post-menopausal	0	0	0	0	1 (100%)	1 (100%)
Race, n (%)						
White	4 (100)	3 (75.0)	3 (100)	10 (90.9)	5 (83.3)	15 (88.2)
Asian	0	1 (25.0)	0	1 (9.1)	0	1 (5.9)
Other	0	0	0	0	1 (16.7)	1 (5.9)
Ethnicity, n (%)						
Hispanic or Latino	1 (25.0)	0	1 (33.3)	2 (18.2)	2 (33.3)	4 (23.5)
Not Hispanic or Latino	3 (75.0)	4 (100)	2 (66.7)	9 (81.8)	4 (66.7)	13 (76.5)
BMI (kg/m^2) at Screening						
Mean	24.80	24.93	23.10	24.38	26.02	24.96
SD	2.719	2.644	2.163	2.435	2.967	2.666
Median	25.25	24.50	23.70	24.90	25.20	24.90
Minimum	27.6	28.1	24.9	28.1	29.7	29.7
Maximum	21.1	22.6	20.7	20.7	23.1	20.7
Weight (kg) at Baseline (Day -1)						
Mean	72.47*	80.71	65.67	73.73	75.02	74.16
SD	3.778	18.016	7.182	12.911	14.834	13.055
Median	73.00	80.13	68.50	72.00	68.50	71.00
Minimum	76.0	102.2	71.0	102.2	96.7	102.2
Maximum	68.5	60.4	57.5	57.5	61.2	57.5

Abbreviations: BMI = body mass index; SAD = single ascending dose; SD = standard deviation
Denominator for women of child-bearing potential was based on female participants.
Denominator for reasons of no child-bearing potential was based on non child-bearing female participants.
*n = 3, not all participants were included at this timepoint for the 200 mg MVD1 group.
**n = 5, not all participants were included at this timepoint for the placebo group.
Source: Listing 16.2.4.1.a

Reference: Table 14.1.4A

Table 10-B Summary of Demographics – Part B (MAD) (Safety Analysis Set)

Variable Statistics	MVD1 200 mg (N = 6)	MVD1 300 mg (N = 6)	MVD1 400 mg (N = 6)	MVD1 Pooled (N = 18)	Placebo Pooled (N = 6)	Overall (N = 24)
Age (years)						
Mean	38.8	33.5	31.7	34.7	32.2	34.0
SD	9.95	8.87	5.65	8.45	9.39	8.55
Median	37.5	30.0	29.5	30.5	33.0	31.0
Minimum	55	51	43	55	47	55
Maximum	28	27	28	27	19	19
Sex, n (%)						
Male	6 (100)	4 (66.7)	4 (66.7)	14 (77.8)	5 (83.3)	19 (79.2)
Female	0	2 (33.3)	2 (33.3)	4 (22.2)	1 (16.7)	5 (20.8)
Women of Child-bearing potential, n (%)						
n	0	2	2	4	1	5
Yes	0	2 (100)	2 (100)	4 (100)	1 (100)	5 (100)
No	0	0	0	0	0	0
Race, n (%)						
White	3 (50.0)	3 (50.0)	4 (66.7)	10 (55.6)	4 (66.7)	14 (58.3)
American Indian or Alaska Native	0	0	1 (16.7)	1 (5.6)	0	1 (4.2)
Asian	2 (33.3)	2 (33.3)	1 (16.7)	5 (27.8)	2 (33.3)	7 (29.2)
Black or African American		1 (16.7)	0	1 (5.6)	0	1 (4.2)
Unknown	1 (16.7)	0	0	1 (5.6)	0	1 (4.2)
Ethnicity, n (%)						
Hispanic or Latino	1 (16.7)	1 (16.7)	2 (33.3)	4 (22.2)	0	4 (16.7)
Not Hispanic or Latino	4 (66.7)	5 (83.3)	4 (66.7)	13 (72.2)	6 (100)	19 (79.2)
Not reported	1 (16.7)	0	0	1 (5.6)	0	1 (4.2)
BMI (kg/m^2) at Screening						
Mean	32.10	30.28	30.47	30.95	31.25	31.03
SD	1.790	2.122	1.750	1.968	2.292	2.005
Median	32.70	29.85	30.10	30.40	31.15	30.55
Minimum	33.8	34.3	32.7	34.3	34.4	34.4
Maximum	29.2	28.3	28.4	28.3	28.1	28.1
Weight (kg) at Baseline (Day -1)						
Mean	96.45	87.47	94.22	92.71	95.18	93.33
SD	7.444	12.536	4.271	9.128	11.427	9.548
Median	99.05	82.40	93.15	93.15	96.35	93.15
Minimum	104.1	109.1	102.4	109.1	108.3	109.1
Maximum	84.7	77.1	91.0	77.1	82.4	77.1

Abbreviations: BMI = body mass index; MAD = multiple ascending dose; N = ; n = SD = standard deviation
Denominator for women of child-bearing potential is based on female subjects.
Denominator for reasons of no child-bearing potential is based on non child-bearing female subjects.
Source: Listing 16.2.4.1.b Reference: Table 14.1.4B

10.5.2 Baseline Disease Characteristics

All participants were healthy adults as defined by the inclusion and exclusion criteria in Section 9.3.

10.5.3 Medical History

A complete list of medical history by participant is provided in Appendix 16.2.4 (Part A: Listing 16.2.4.2A and Part B: Listing 16.2.4.2B).

10.5.4 Prior Medication

A summary of the use of prior medication is provided in Section 14.1 (Part A: Table 14.1.5A and Part B: Table 14.5.1B). A complete list of prior medication use by participant is provided in Appendix 16.2.10 (Part A: Listing 16.2.10.1A and Part B: Listing 16.2.10.1B).

In Part A (SAD), there was 1 (5.9%) of 17 participants who reported the use of at least 1 prior medication (i.e., any medication where the use was started prior to the start date/time of the first study drug administration). One participant (800 mg MVD1) took ibuprofen (for dysmenorrhea/200 mg/once/oral). The use of prior medication in the 10 days prior to dosing of study drug was not reported in any other participant.

In Part B (MAD), there were 3 (12.5%) of 24 participants who reported the use of at least 1 prior medication (i.e., any medication where the use was started prior to the start date/time of the first study drug administration). Two (11.1%) of 18 participants in the MVD1 group (pooled) reported the use of prior medication, and one (16.7%) of 6 participants reported use in the placebo group. Two participants took paracetamol for a medical history of headache, one in the 200 mg MVD1 group (2 g/once/oral) and one in the placebo group (500 mg/once/oral). One participant (300 mg MVD1) took mometasone for grass and dust mite allergies (one spray each nostril, once daily/nasal) and herbal Nos and vitamins Nos (1 tablet, once daily, oral).

10.5.5 Other Baseline Assessments

A summary of body weight and body mass index are presented in Table 14.3.5.3A and Table 14.3.5.3B. A complete list of body weight and BMI is presented in Listing 16.2.9.4A and Listing 16.2.9.4B.

A complete list of participant pre-dose eligibility reviews are provided in Listing 16.2.1.3A and Listing 16.2.1.3B.

A complete list of pregnancy and FSH test by participant is provided in Appendix 16.2.4 (Part A: Listing 16.2.4.3A and Part A: Listing 6.2.4.3B).

A complete list of substance abuse history is presented in Listing 16.2.4.8A and Listing 16.2.4.8B.

In Part A (SAD), all serum pregnancy tests at Screening and EoS, and urine pregnancy tests at Day-1 were negative (one participant had an Equivocal result at EoS). Only one participant had menopause confirmed.

In Part B (MAD), all serum pregnancy tests at Screening and EoS, and urine pregnancy tests at Day-1 were negative. No participants had menopause confirmed.

Complete lists (for Part A and B) of alcohol breath test, urine drug screen and cotinine test by participant is provided in Appendix 16.2.4 (alcohol breath test: Part A: Listing 16.2.4.4A and Part B: Listing 16.2.4.4B and drug screen/cotinine test: Part A: Listing 16.2.4.5A and Part B: Listing 16.2.4.5B). All alcohol breath tests at screening, Day -1, and unscheduled visits were negative for all participants. Urine test for amphetamines, barbiturates, benzodiazepines, cocaine, methadone, methamphetamines, opiates, THC, and tricyclic antidepressants, and cotinine at screening and Day -1 were negative for all participants.

Complete lists of serology and COVID-19 test by participant is provided in Appendix 16.2.4 (serology: Part A: Listing 16.2.4.6A and Part B: Listing 16.2.4.6B and COVID-19:

Part A: Listing 16.2.4.7A and Part B: Listing 16.2.4.7B). All participants in Part A (SAD) and Part B (MAD) were negative for hepatitis B virus surface antigen, not reactive for HCV antibody, and did not have HIV antibody detected at screening.

In Part A (SAD), 7 participants (3 participants in the MVD1 200 mg, 2 in placebo, 1 in MVD1 400 mg and 1 in MVD1 800 mg) had a COVID-19 test at screening or Day -1, the result of which was negative.

In Part B (MAD), one participant (MVD1 200 mg) had a COVID-19 test at Day -1, the result of which was negative. Substance (alcohol and tobacco) usage history is listed in Part B: Listing 16.2.4.8.B.

11. PHARMACOKINETIC, PHARMACODYNAMIC AND EXPLORATORY EVALUATION

11.1 PHARMACOKINETIC ANALYSIS IN PLASMA

11.1.1 Plasma Concentration Data

Concentrations in plasma of MVD1, and also its metabolite M1, were determined for all participants receiving MVD1. The lower limit of quantification was 50 ng/mL for MVD1 and 25 ng/mL for M1.

In Part A (SAD), there were two missing PK blood samples/analyses for the participants included in the PKS.

- RS01002 (Cohort 1 200 mg) at 6 hours and 72 hours (Subject) – collected not analysed

In Part B (MAD), there were missing PK blood samples/analyses for 3 participants in the PKS, as follows

- RM01007 (Cohort 4 200 mg) samples were not collected beyond Day 2 pre-dose
- RM01008 (Cohort 4 200 mg) samples were not collected for Day 1 12.5 hour, and not analysed for Day 1 (dose 2) 0.5 hour
- RM3003 (Cohort 6 400 mg) Day 15 at 0.25 hour

The actual collection times of PK blood samples for all participants in the PKS are presented in Listing 16.2.6.1.1.A and Listing 16.2.6.1.1.B for Part A (SAD), Part B (MAD), respectively. These listings also include the plasma concentrations of MVD, and the metabolite M1, along with calculated time relative to dose administration. Individual profiles of plasma concentrations over time by treatment and analyte are presented in Figure 16.2.6.1.2.A and Figure 16.2.6.1.3.A for participants in Part A (SAD), and in Figure 16.2.6.1.2.B and Figure 16.2.6.1.3.B for participants in Part B (MAD), with concentrations displayed on linear and logarithmic scales, respectively. Individual plasma concentrations over time from Day 1 to Day 15 are presented in Figure 16.2.6.1.4B (Linear Scale) and in Figure 16.2.6.1.5B (Log-Linear Scale).

For participants administered placebo, blood samples were collected at all timepoints. The pre-dose and 1 hour post dose samples were analysed to confirm that there was no quantifiable plasma concentration of any analyte. These data are not included in the listings and figures of individual PK concentration data.

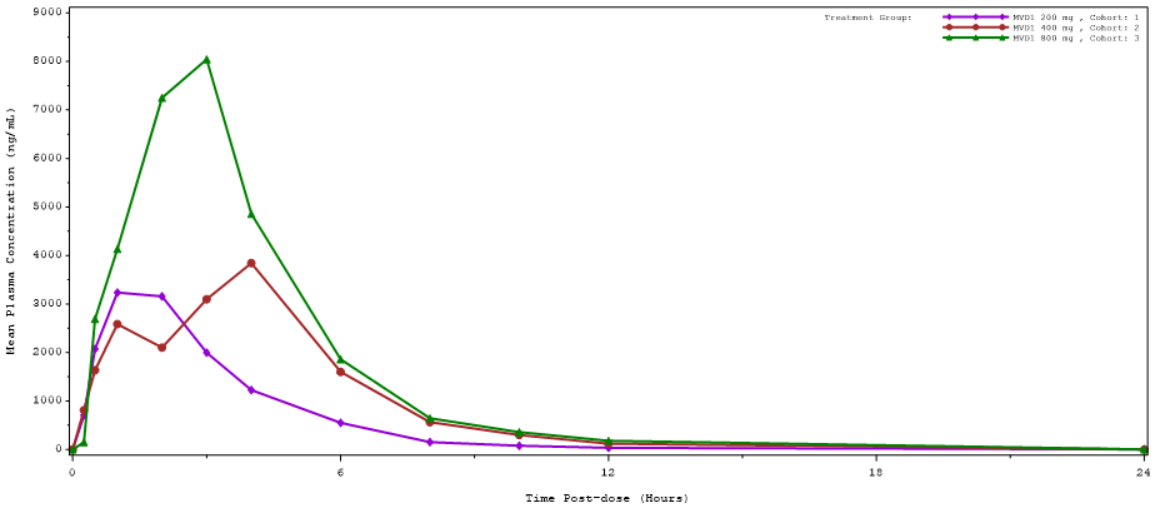
11.1.2 Analysis of Plasma Concentration Data

11.1.2.1 Part A (SAD)

Plasma concentrations of MVD1 and M1 at each sampling time in Part A (SAD) are summarised by treatment and analyte in Table 14.2.1.1.A. Mean plasma concentration-time profiles over time post-dose are presented by analyte in Figure 14.2.1.2.A and Figure 14.2.1.3.A, with concentration shown on linear and logarithmic scale, respectively.

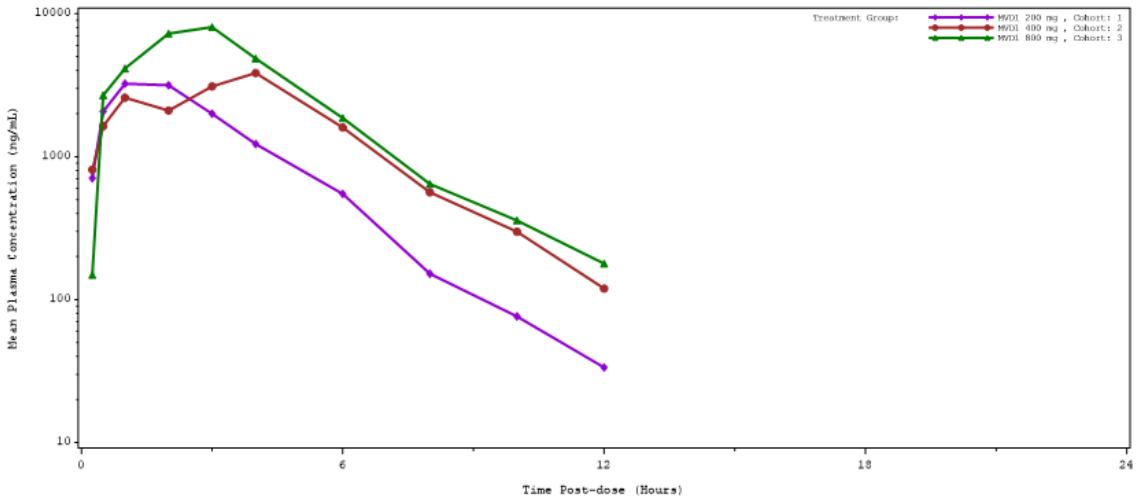
Mean plasma concentration profiles of MVD1 by SAD dose level are also presented below in Figure 11-A and Figure 11-B with concentrations shown on a linear and logarithmic scale, respectively. Mean plasma concentration profiles of its metabolite M1 by SAD dose level are presented below in Figure 11-Cand Figure 11-D with concentrations shown on a linear and logarithmic scale, respectively.

Figure 11-A Mean Plasma Concentrations of MVD1 by Treatment (Linear) – Part A (SAD) (Pharmacokinetic Analysis Set)



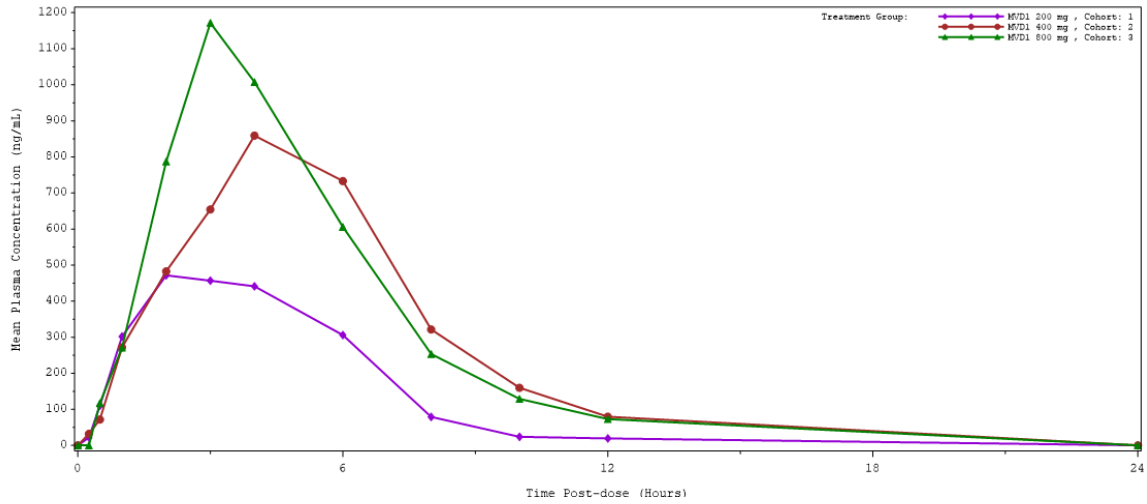
Source: Table 14 2.1.1.A and Figure 14.2.1.2.A

Figure 11-B Mean Plasma Concentrations of MVD1 by Treatment (Semi-log) – Part A (SAD) (Pharmacokinetic Analysis Set)



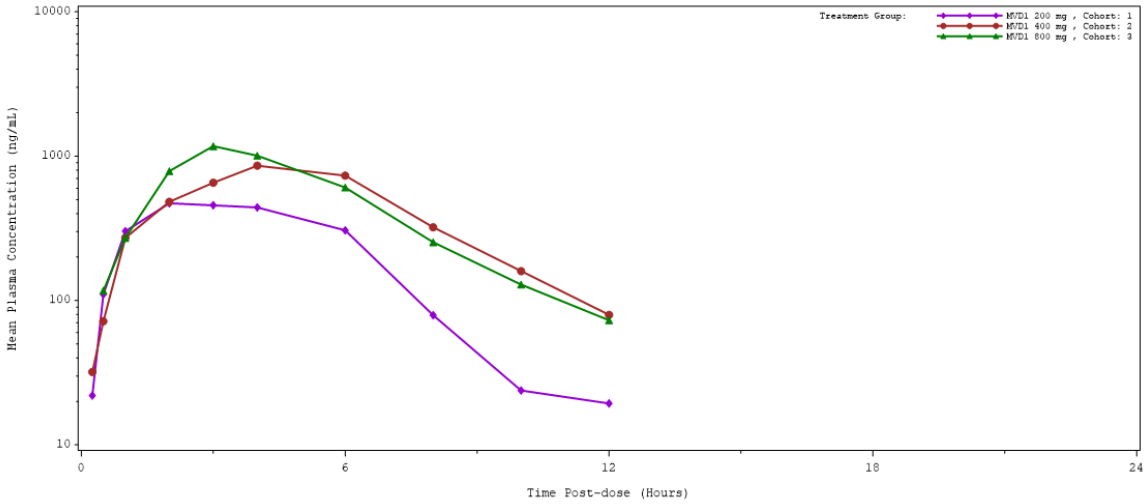
Source: Table 14 2.1.1.A and Figure 14.2.1.3.A

Figure 11-C Mean Plasma Concentrations of Metabolite M1 by Treatment (Linear) – Part A (SAD) (Pharmacokinetic Analysis Set)



Source: Table 14 2.1.1.A and Figure 14.2.1.2.A

Figure 11-D Mean Plasma Concentrations of Metabolite M1 by Treatment (Semi-log) – Part A (SAD) (Pharmacokinetic Analysis Set)



Source: Table 14 2.1.1.A and Figure 14.2.1.3.A

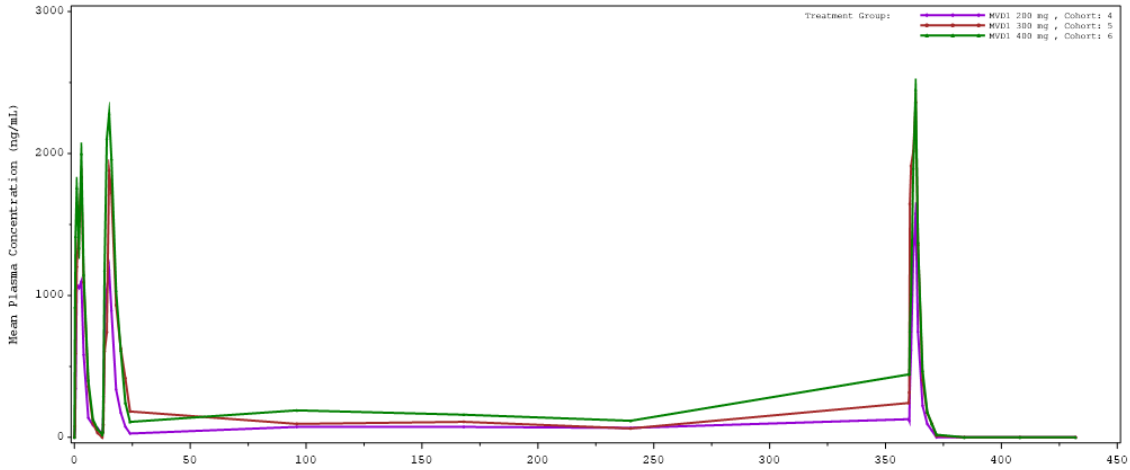
11.1.2.2 Part B (MAD)

Plasma concentrations of MVD1 and M1 at each sampling time in Part B (MAD) are summarised by treatment and analyte in Table 14.2.1.1.B. Mean plasma concentration-time profiles over time post-dose on Day 15 are presented by analyte in Figure 14.2.1.2.B and Figure 14.2.1.3.B, with concentration shown on linear and logarithmic scale, respectively.

Mean plasma concentrations over time from Day 1 to 15 are presented by analyte in Figure 14.2.1.4.B and Figure 14.2.1.5.B, with concentration shown on linear and logarithmic scale, respectively.

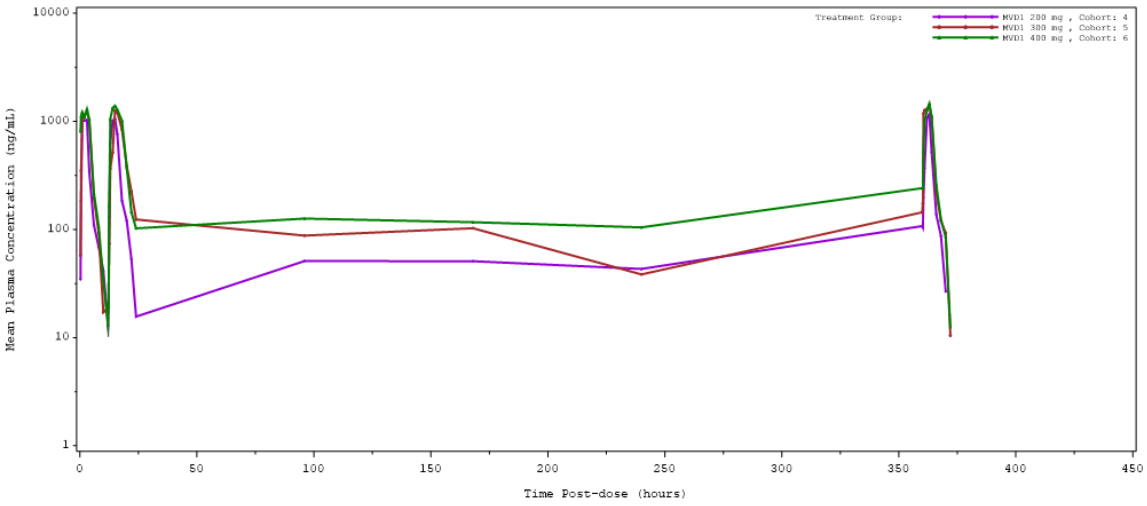
Mean plasma concentration profiles of MVD1 by MAD dose level on Day 1 to Day 15 are also presented below in Figure 11-E and Figure 11-F, with concentrations shown on a linear and logarithmic scale, respectively. Mean plasma concentration profiles of metabolite M1 by MAD dose level on Day 1 to Day 15 are also presented below in Figure 11-G and Figure 11-H with concentrations shown on a linear and logarithmic scale, respectively. It is noted that mean plasma concentrations of MVD1were BLQ for the majority of participants at Day 1, pre dose 2. All other pre-dose concentrations from Day 2 onwards were generally quantifiable except for Day 2 in Cohort 1 where half of the samples were still BLQ.

Figure 11-E Mean Plasma Concentrations of MVD1 by Treatment on Day 1 to Day 15 (Linear) – Part B (MAD) (Pharmacokinetic Analysis Set)



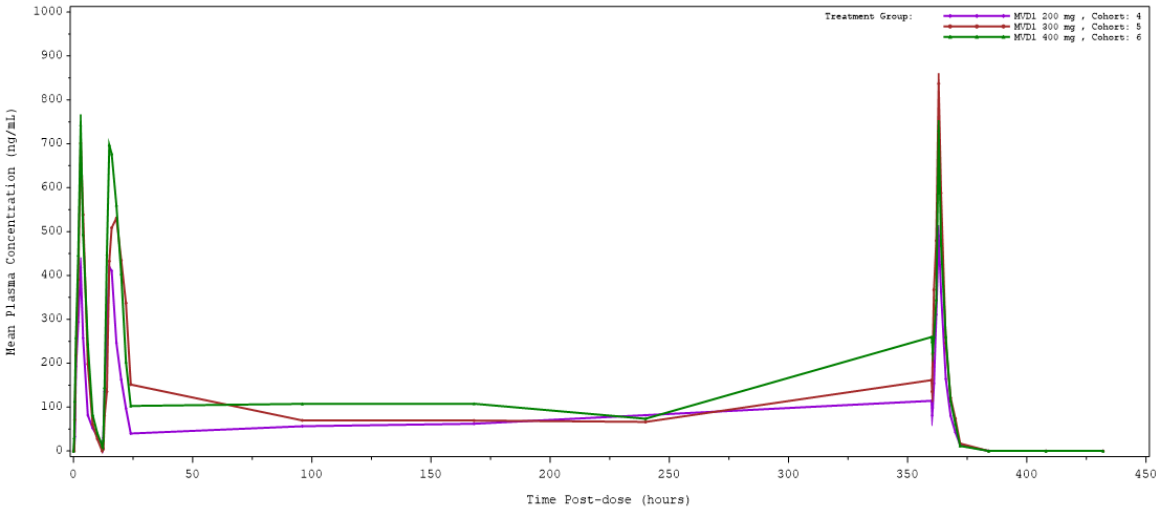
Source: Table 14 2.1.1.B and Figure 14.2.1.4.B

Figure 11-F Mean Plasma Concentrations of MVD1 by Treatment on Day 1 to Day 15 (Semi-log) – Part B (MAD) (Pharmacokinetic Analysis Set)



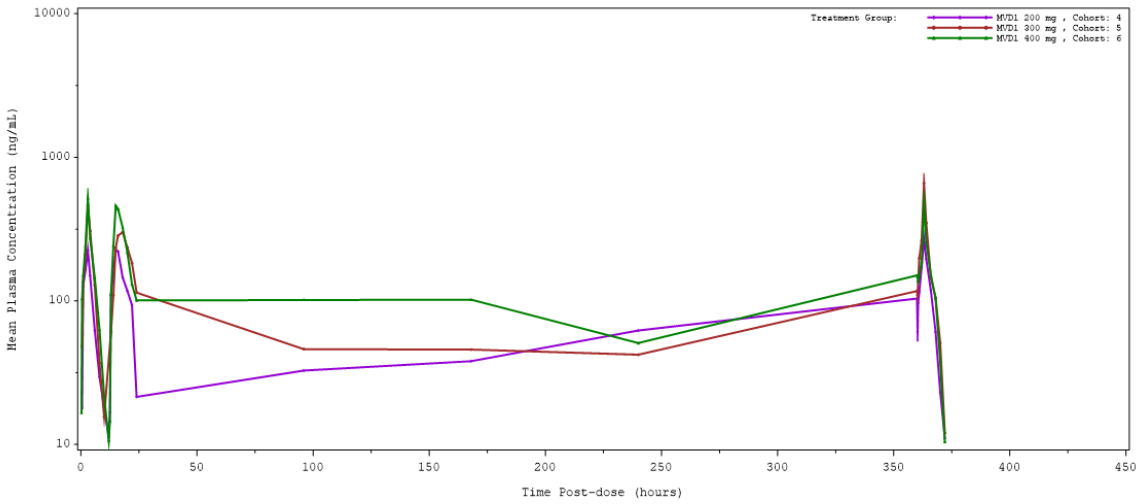
Source: Table 14 2.1.1.B and Figure 14.2.1.5.B

Figure 11-G Mean Plasma Concentrations of Metabolite M1 by Treatment on Day 1 to Day 15 (Linear) – Part B (MAD) (Pharmacokinetic Analysis Set)



Source: Table 14 2.1.1.B and Figure 14.2.1.4.B

Figure 11-H Mean Plasma Concentrations of Metabolite M1 by Treatment on Day 1 to Day 15 (Semi-log) – Part B (MAD) (Pharmacokinetic Analysis Set)



Source: Table 14 2.1.1.B and Figure 14.2.1.5.B

11.1.3 Plasma Pharmacokinetic Parameters

Plasma PK parameters of MVD1 and M1 were determined using Phoenix WinNonlin Version 8.3. Actual sampling time post-dose was used in the determination of PK parameters.

11.1.3.1 Part A (SAD)

For Part A (SAD), the individual plasma PK parameters by analyte for all participants who received MVD1 are presented in Listing 16.2.6.1.6.A. Details of extrapolation for determination of the terminal elimination rate by regression analysis using logarithmic transformed concentration data for each individual profile by analyte are provided in Listing 16.2.6.1.7.A. All profiles of MVD1 gave acceptable goodness of fit estimates from WinNonlin for terminal elimination rate constant. Terminal elimination rate constant of M1 was estimable for most participants, with the exception being 1 participant at a dose level of 200 mg MVD1.

Pharmacokinetic parameters for Part A (SAD) are summarised by treatment and analyte in Table 14.2.1.6.A for Cohorts 1-3. The arithmetic mean (coefficient of variation [CV]) of key plasma PK parameters of exposure by treatment, along with median and range for T_{max}, are also presented below in Table 11-A for MVD1, and in Table 11-B for M1.

Table 11-A Summary of Pharmacokinetic Parameters of MVD1 – Part A (SAD) (Pharmacokinetic Analysis Set)

		Median (range)	Arithmetic mean (coefficient of variation [CV])			
Analyte	**MVD1 Dose Level**	**T_{max} (h)**	**C_{max} (ng/mL)**	**AUC_{last} (h*ng/mL)**	**$t_{1/2}$ (h)**	**AUC_{inf} (h*ng/mL)**
MVD1	**Cohort 1: 200 mg (N=4)**	1.50 (1.00-2.00)	4090 (16.6%)	11900 (9.7%)	1.59 (16.2%)	12000 (9.7%)
	Cohort 2: 400 mg (N=4)	4.00 (1.00-4.00)	4450 (32.4%)	18600 (25.7%)	1.69 (4.2%)	18900 (25.4%)
	Cohort 3: 800 mg (N=3)	3.00 (3.00-4.00)	8080 (28.2%)	32600 (16.6%)	1.93 (13.2%)	33100 (16.4%)

Source: Table 14 2.1.6.A

Table 11-B Summary of Pharmacokinetic Parameters of Metabolite M1 – Part A (SAD) (Pharmacokinetic Analysis Set)

		Median (range)	Arithmetic mean (coefficient of variation [CV])			
Analyte	**MVD1 Dose Level**	**T_{max} (h)**	**C_{max} (ng/mL)**	**AUC_{last} (h*ng/mL)**	**$t_{1/2}$ (h)**	**AUC_{inf} (h*ng/mL)**
M1	**Cohort 1: 200 mg (N=4)**	1.50 (1.00-4.00)	611 (73.9%)	2570 (87.3%)	1.83[a] (3.0%)	3120[a] (84.3%)
	Cohort 2: 400 mg (N=4)	5.00 (3.00-6.00)	969 (52.9%)	5170 (54.0%)	1.82 (9.3%)	5390 (55.0%)
	Cohort 3: 800 mg (N=3)	3.00 (3.00-4.00)	1320 (30.1%)	5750 (29.0%)	2.17 (18.3%)	5980 (27.8%)

a:n=3

Source: Table 14 2.1.6.A

11.1.3.2 Part B (MAD)

For Part B (MAD), the individual plasma PK parameters by analyte on Day 1 and Day 15 for all subjects who received MVD1 are presented in Listing 16.2.6.1.6.B. Details of extrapolation for determination of the terminal elimination rate by regression analysis using logarithmic transformed concentration data for each individual profile by analyte and study day are provided in Listing 16.2.6.1.7.B. Most profiles gave acceptable goodness of fit estimates from WinNonlin for terminal elimination rate with the exceptions being:

- 200 mg –
  - Day 1 Dose 1: MVD1 for 2 participants, M1 for 2 participants
  - Day 15: MVD1 for 2 participants, M1 for 1 participant
- 300 mg –
  - Day 1 Dose 1: MVD1 for 3 participants, M1 for 1 participant
  - Day 1 Dose 2: MVD1 for 1 participant, M1 for 2 participants
- 400 mg –
  - Day 1 Dose 1: M1 for 1 participant
  - Day 1 Dose 2: M1 for 2 participants

Pharmacokinetic parameters for Part B (MAD) are summarised by treatment and analyte for Day 1 and Day 15 in Table 14.2.1.6.B for Cohorts 4-6. The arithmetic mean (coefficient of variation [CV]) and geometric mean of key plasma PK parameters of exposure by treatment, along with median and range for T_{max}, for Day 1 and 2 combined are also presented below in Table 11-C for MVD1, and in Table 11-D for the metabolites. In order to assess the PK parameters of exposure over a 24 hour period based on twice daily dosing (BID) dosing, the summary for Part B (MAD) is based on Dose 1 and Dose 2 combined.

Table 11-C Summary of Pharmacokinetic Parameters of MVD1 Day 1 Dose 1 & Dose 2 Combined – Part B (MAD) (Pharmacokinetic Analysis Set)

		Median (range)	Arithmetic mean (coefficient of variation [CV])		
Analyte	**MVD1 Dose Level, Day**	**T_{max} (h)**	**C_{max} (ng/mL)**	**AUC_{last} (h*ng/mL)**	**$t_{1/2}$ (h)**
MVD1	**Cohort 4: 100 mg BID (200 mg daily total) (N=6)**	14.50 (1.00-16.00)	1860 (24.9%)	9990 (25.0%)	1.77 (21.1%)
	Cohort 5: 150 mg BID (300 mg daily total) (N=6)	15.00 (2.00-18.33)	2360 (16.3%)	16900 (19.1%)	1.90[a] (14.6%)
	Cohort 6: 200 mg BID (400 mg daily total) (N=6)	3.00 (0.50-15.00)	2970 (29.4%)	20600 (16.7%)	1.65 (10.9%)

Key: a: n=5

Source: Table 14 2.1.6.B

Table 11-D Summary of Pharmacokinetic Parameters of M1 Day 1 Dose 1 & Dose 2 Combined – Part B (MAD) (Pharmacokinetic Analysis Set)

		Median (range)	Arithmetic mean (coefficient of variation [CV])		
Analyte	**MVD1 Dose Level, Day**	**T_{max} (h)**	**C_{max} (ng/mL)**	**AUC_{last} (h*ng/mL)**	**$t_{1/2}$ (h)**
M1	**Cohort 4: 100 mg BID (200 mg daily total) (N=6)**	8.50 (2.00-16.00)	564 (37.7%)	4060 (43.9%)	2.05 (14.8%)
	Cohort 5: 150 mg BID (300 mg daily total) (N=6)	9.50 (2.00-18.33)	802 (44.9%)	6770 (45.2%)	2.43[a] (19.7%)
	Cohort 6: 200 mg BID (400 mg daily total) (N=6)	12.17 (3.00-20.00)	965 (52.3%)	7630 (47.7%)	1.56[a] (23.4%)

Key: a: n=4;

Source: Table 14 2.1.6.B

Summaries of the accumulation ratios (Day 15)/(Day 1) for $AUC_{0-12}$and C_{max} by treatment and analyte, showing arithmetic mean and CV, are presented in Table 11-E.

Table 11-E Summary of Accumulation Ratios of MVD1 – Part B (MAD) (Pharmacokinetic Analysis Set)

		Arithmetic mean (coefficient of variation [CV])	
Analyte	**MVD1 Daily Dose Level, Day**	**RC_{max}**	**$R_{AUC0-12}$**
MVD1	**Cohort 4: 200 mg Day 15 (N=5)**	0.984 (26.8%)	1.18 (15.0%)
	Cohort 5: 300 mg Day 15 (N=6)	1.28 (26.2%)	1.38 (16.9%)
	Cohort 6: 400 mg Day 15 (N=6)	1.01 (37.9%)	1.10 (19.4%)
M1	**Cohort 4: 200 mg Day 15 (N=5)**	0.966 (39.6%)	1.47 (30.5%)
	Cohort 5: 300 mg Day 15 (N=6)	1.15 (28.2%)	1.32 (27.3%)
	Cohort 6: 400 mg Day 15 (N=6)	0.865 (53.8%)	1.18 (35.0%)

Source: Table 14 2.1.6.B

A summary of the metabolite to parent ratio for C_{max} and AUC_{0-12} for Day 1 Dose 1, Day 1 dose 2 and Day 1 dose 1 and dose 2 combined, and Day 15 are summarised below in Table 11-F. The ratio of metabolite M1 to MVD1 remained constant at approximately 30-40% as the dose of MVD1 increased.

Table 11-F Summary of Metabolite to Parent Ratio – Part B (MAD) (Pharmacokinetic Analysis Set)

Arithmetic mean (Coefficient of variation [CV])		
MVD1 Dose Level, Day	**Metabolite:Parent C_{max}**	**Metabolite:Parent AUC_{0-12}**
Cohort 4: 100 mg BID Day 1 Dose 1 (N=6)	0.29 (35.1%)	0.34 (25.3%)
Cohort 4: 100 mg BID Day 1 Dose 2 (N=6)	0.29 (36.1%)	0.43 (32.3%)
Cohort 4: 100 mg BID (200 mg daily total) Day 1 Dose 1 & Dose 2 Combined (N=6)	0.30 (36.3%)	0.35 (24.7%)
Cohort 4: 100 mg BID Day 15 (N=5)	0.30 (32.3%)	0.40 (22.4%)
Cohort 5: 150 mg BID Day 1 Dose 1 (N=6)	0.35 (45.4%)	0.36 (31.1%)
Cohort 5: 150 mg BID Day 1 Dose 2 (N=6)	0.33 (43.8%)	0.39 (29.3%)
Cohort 5: 150 mg BID (300 mg daily total) Day 1 Dose 1 & Dose 2 Combined (N=6)	0.33 (38.7%)	0.37 (31.8%)
Cohort 5: 150 mg BID Day 15 (N=6)	0.30 (39.6%)	0.34 (25.7%)
Cohort 6: 200 mg BID Day 1 Dose 1 (N=6)	0.29 (76.3%)	0.33 (50.9%)
Cohort 6: 200 mg BID Day 1 Dose 2 (N=6)	0.32 (25.5%)	0.38 (28.4%)
Cohort 6: 200 mg BID (400 mg daily total) Day 1 Dose 1 & Dose 2 Combined (N=6)	0.33 (51.3%)	0.33 (50.6%)
Cohort 6: 200 mg BID Day 15 (N=6)	0.24 (16.0%)	0.32 (19.8%)

Abbreviation: BID = twice a day

Source: Table 14 2.1.6.B

11.1.4 Analysis of Plasma Pharmacokinetic Parameters

11.1.4.1 Part A (SAD)

For Part A (SAD), dose proportionality was assessed for C_{max}, AUC_{0-12}, AUC_{last} and AUC_{inf} for each analyte using the power model for logarithmic transformed parameters. The results of the analysis are presented in Table 14.2.1.8.A. A summary is also presented below in Table 11-G, including the upper and lower confidence limits for the 90% CI for the estimate of the slope, beta.

Table 11-G Analysis of Dose Proportionality of Pharmacokinetic Parameters – Part A (SAD) (Pharmacokinetic Analysis Set)

Analyte	Pharmacokinetic Parameter	No. of Observations	Beta Estimate	Lower CL	Upper CL	r^2
MVD1	Log(C_{max})	11	0.457	0.158	0.757	0.47
	Log(AUC_{0-12})	11	0.720	0.531	0.909	0.84
	Log(AUC_{last})	11	0.720	0.531	0.909	0.84
	Log(AUC_{inf})	11	0.720	0.532	0.908	0.85
M1	Log(C_{max})	11	0.669	0.130	1.208	0.37
	Log(AUC_{0-12})	11	0.746	0.169	1.323	0.38
	Log(AUC_{last})	11	0.746	0.169	1.323	0.38
	Log(AUC_{inf})	10	0.614	-0.005	1.232	0.30

Key: CL = Confidence Limit

Source: Table 14 2.1.8.A

The mean exposure parameters increased monotonically by dose level in an approximately dose proportional manner for MVD1 as shown in Figure 14.2.1.7.A however the power model analyses did not meet criteria for dose proportionality.

11.1.4.2 Part B (MAD)

For Part B (MAD), dose proportionality was assessed for C_{max} andAUC_{0-12}, on Day 1 and C_{max} and AUC_{0-12} on Day 15 for each analyte using the power model for logarithmic transformed parameters. The analysis is presented in Table 14.2.1.8.B, with a summary for, Day 1– Dose 1 & Dose 2 Combined in Table 11-H and Day 15 in Table 11-I.

Table 11-H Analysis of Dose Proportionality of Pharmacokinetic Parameters on Day 1– Dose 1 & Dose 2 Combined; Part B (MAD) (Pharmacokinetic Analysis Set)

Analyte	Pharmacokinetic Parameter	No. of Observations	Beta Estimate	Lower CL	Upper CL	r^2
MVD1	Log(C_{max})	18	0.671	0.337	1.005	0.44
	Log(AUC_{last})	18	1.085	0.766	1.404	0.69
M1	Log(C_{max})	18	0.743	0.115	1.371	0.21
	Log(AUC_{last})	18	0.942	0.284	1.600	0.28

Key: CL = Confidence Limit

Source: Table 14 2.1.8.B

Table 11-I Analysis of Dose Proportionality of Pharmacokinetic Parameters on Day 15– Part B (MAD) (Pharmacokinetic Analysis Set)

Analyte	Pharmacokinetic Parameter	No. of Observations	Beta Estimate	Lower CL	Upper CL	r^2
MVD1	$Log(C_{max})$	17	0.727	0.120	1.335	0.23
	$Log(AUC_{0-12})$	17	0.843	0.365	1.320	0.39
M1	$Log(C_{max})$	17	0.499	-0.167	1.165	0.10
	$Log(AUC_{0-12})$	17	0.537	-0.122	1.196	0.12

Key: CL = Confidence Limit

Source: Table 14 2.1.8.B

The power model analyses did not indicate dose proportionality of exposure for multiple dosing of MVD1 twice daily for 15 days. The power model accounted for less than 50% of the variability in exposure versus dose except for MVD1 AUC_{0-12} on Day 1. As shown in Figure 14.2.1.7.B, the mean exposure parameters increased monotonically for Day 1 by dose level, however the dose dependence was not monotonic on Day 15. Increase in exposure from 100 mg BID and 150 mg BID was approximately dose proportional, however there was no apparent further increase in AUC for 200 mg BID on Day 15.

11.1.5 Amount of Drug Excreted in Urine

Concentrations in urine of MVD1 and the metabolite M1, were determined on Day 1 at pre-dose, and 0-24 hours post-dose for all participants in Part A (SAD), and on Day 1 at pre-dose, 0-24 hours post-dose on Day 15 for participants in Part B (MAD).

As noted in Table 14.2.2.1.A, there were no participants with missing urine collections in Part A (SAD of the study. In Part B (MAD) there was 1 participant who has no sample collected on Day 1 (except pre-dose) and was only collected on Day 15 (0-24 hours).

The collection times of PK urine samples for all subjects, as well as urine concentrations of MVD1 and metabolites, along with urine volume and calculated amount excreted, are presented in Listing 16.2.6.1.8.A for Part A (SAD) and Listing 16.2.6.1.8.B for Part B(MAD). The amount excreted in urine per interval is summarised in Table 14.2.2.1.A for Day 1 of Part A (SAD), Table 14.2.2.1.B for Day 1 pre-dose and Day 15 of Part B (MAD).

Urine pharmacokinetic parameters of MVD1 and M1 are summarised by treatment and study day in Table 14.2.2.2.A for Day 1 of Part A (SAD), Table 14.2.2.2.B for Day 1 and Day 15 of Part B (MAD).

The amount of MVD1 excreted in urine and the fraction of drug excreted unchanged is also presented below in Table 11-J, and Table 11-K for Part A (SAD), Part B (MAD) respectively.

Table 11-J Summary of Urine Excretion of MVD1 – Part A (SAD) (Pharmacokinetic Analysis Set)

Arithmetic mean (coefficient of variation [CV])				
	MVD1			M1
MVD1 Dose Level	Amount excreted (mg)	Fraction excreted (%)	CLr (L/h)	Amount excreted (mg)
Cohort 1: 200 mg (N=4)	12.43 (45.03%)	6.216 (45.03%)	1.026 (42.19%)	18.73 (23.22%)
Cohort 2: 400 mg (N=4)	31.57 (84.41%)	7.893 (84.41%)	1.550 (84.28%)	46.88 (37.29%)
Cohort 3: 800 mg (N=3)	30.07 (41.02%)	3.758 (41.02%)	0.871 (31.64%)	31.15 (28.94%)

Key: CLr = renal clearance

Source: Table 14 2.2.2.A

Table 11-K Summary of Urine Excretion of MVD1 – Part B (MAD) (Pharmacokinetic Analysis Set)

Arithmetic mean (coefficient of variation [CV])				
	MVD1			M1
MVD1 Daily Dose Level, Day	Amount excreted Day 15 (mg)	Fraction excreted (%)	CLr (L/h)	M1 amount excreted (mg)
Cohort 4: 200 mg Day 15 (N=5)	6.045[a] (56.66%)	6.045 (56.66%)	1.374[a] (93.35%)	15.25[a] (57.72%)
Cohort 5: 300 mg Day 15 (N=6)	14.27 (59.81%)	9.514 (59.81%)	1.386 (57.28%)	23.28 (59.02%)
Cohort 6: 400 mg Day 15 (N=6)	13.37 (45.02%)	6.683 (45.02%)	1.416 (27.28%)	25.68 (50.76%)

Key: CLr = renal clearance

Source: Table 14 2.2.2.B

There was little MVD1 excreted unchanged in urine (< 10%). It is noted that there was no noticeable increase in amount excreted at the highest dose level for single and multiple dosing. More of the drug was excreted in urine as metabolite M1 than as unchanged MVD1

11.2 EXPLORATORY ANALYSIS

11.2.1 Body Weight

Body weight was measured on Day -1 (check-in) prior to dose administration, pre-dose on Day 15 (within 3 hours) and on Day 22 (EoS) to investigate drug induced body weight reduction. Body weight changes from baseline are listed by participant in Listing 16.2.9.4B and summarised in Table 14.3.5.3B and below in Table 11-L.

A reduction in body weight was observed on Day 15 following administration of MVD1 (MAD, 300 mg) with an average reduction of 1.5% (mean % body weight reduction) when adjusted for placebo. Following administration of multiple ascending doses of MVD1 (300 mg) a weight loss improvement trend was observed.

A significant reduction in body weight was observed on Day 15 following administration of MVD1 (MAD cohort 3) with an average reduction of 2.7% (mean % body weight reduction) when adjusted for placebo. After treatment was stopped on Day 15, those treated with MVD1 demonstrated early signs of sustained weight loss. Treatment with MVD1 (MAD, 400 mg) demonstrated significant weight loss improvement when compared to placebo.

Table 11-L Summary of Change from Baseline for Body Weight and BMI – Part B (MAD) (Safety Analysis Set)

Variable Visit Statistic	MVD1 200 mg (N = 6)	MVD1 300 mg (N = 6)	MVD1 400 mg (N = 6)	MVD1 Pooled (N = 18)	Placebo Pooled (N = 6)	Overall (N = 24)
Weight (kg)						
Day 15						
n	1	1	6	8	2	10
Mean	-3.10	-1.60	-2.57	-2.51	-0.50	-2.11
SD	NA	NA	1.612	1.424	0.566	1.527
Median	-3.10	-1.60	-2.35	-2.35	-0.50	-1.75
Minimum	-3.1	-1.6	-0.5	-0.5	-0.1	-0.1
Maximum	-3.1	-1.6	-5.1	-5.1	-0.9	-5.1
EoS						
n	1	6	6	13	3	16
Mean	-2.90	-0.22	-1.38	-0.96	-0.07	-0.79
SD	NA	1.701	1.459	1.665	0.451	1.541
Median	-2.90	-0.15	-1.20	-1.10	-0.10	-0.50
Minimum	-2.9	2.4	0.4	2.4	0.4	2.4
Maximum	-2.9	-2.6	-3.7	-3.7	-0.5	-3.7

Abbreviations: MAD = multiple ascending dose; SD = standard deviation
*Baseline was defined as the last observation (including unscheduled assessments) prior to study drug administration on Day 1.
Source: Listing 16.2.9.4.b

Reference: Table 14.3.5.3.B

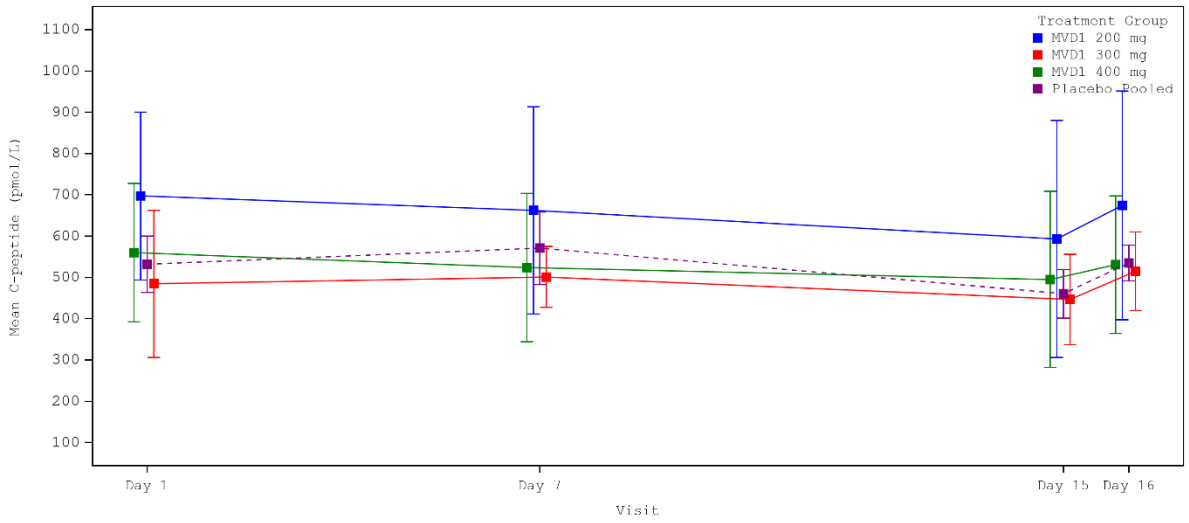
11.2.2 Serum Pharmacodynamic Biomarkers

In Part B (MAD) only, the effects of MVD1 on serum PD biomarkers were assessed. Summary Tables, Listings and Figures for rerum biomarkers are provided in Section 14.3.1. (Table 14.2.3.1.B; Listing 16.2.6.2.1.B, Listing 16.2.6.2.2B and Figure 14.2.3.2.B). The biomarkers assessed included:

- Glucose
- Insulin
- C-peptide
- hsCRP
- Fructosamine
- Glycohemoglobin (Cohort MAD 1 and MAD 2 only)
- Free fatty acids
- Triglycerides
- Leptin levels

Mean C-peptide (pmol/L) levels were higher in the 200 mg MVD1 group compared to all other MVD1 groups and placebo at baseline (Day 1) and were consistently higher over time (Figure 11-I). There did not appear to be any treatment- or dose-related trends in mean C-peptide levels over time. There appeared to be an increase in mean CRP (mg/L) levels in MVD1 groups when compared to placebo at Day 7 (Table 11-M and Figure 11-J). However, this did not appear to be maintained through to Day 16. There was no apparent difference between the MVD1 or placebo groups in mean free fatty acid (mmol/L) or mean fructosamine (µmol/L) levels over time (Figure 11-K and Figure 11-L). Free-fatty acid levels increased at Day 7 for all groups including placebo but returned to baseline levels by Day 16. Mean glucose (mmol/L) levels were higher in the 200 mg and 400 mg MVD1 groups at baseline (Day 1) when compared to the 300 mg MVD1 group and placebo and were consistently higher over time (Figure 11-M). Mean insulin (mU/L) levels at baseline (Day 1) were higher in the 200 mg MVD1 group when compared to all other MVD1 groups and placebo but did not continue with this trend over time. Mean insulin levels increased at Day 16 for all MVD1 groups and placebo cohorts (Figure 11-N). Mean leptin (µg/L) levels were lower at baseline for the 200 mg MVD1 cohort when compared to other MVD1 cohorts and placebo, however this was not maintained over time. No treatment- or dose- related trends in leptin levels were observed (Figure 11-O). Over time, the mean triglyceride (mmol/L) levels were lower in the 400 mg MVD1 group when compared to the other MVD1 groups and placebo (Figure 11-P).

Figure 11-I Mean C-peptide Over Time (Linear Scale) – Part B (MAD) (Pharmacodynamic Population)



Abbreviations: MAD = multiple ascending doses.
Notes: ± Bars denote Standard Deviation.
If lower limit (mean minus standard error) was less than zero, then it was set to zero.
For visual comparison purposes, the result of different treatment levels was staggered on the x-axis timepoint.
Source: Table 14.2.3.1.B

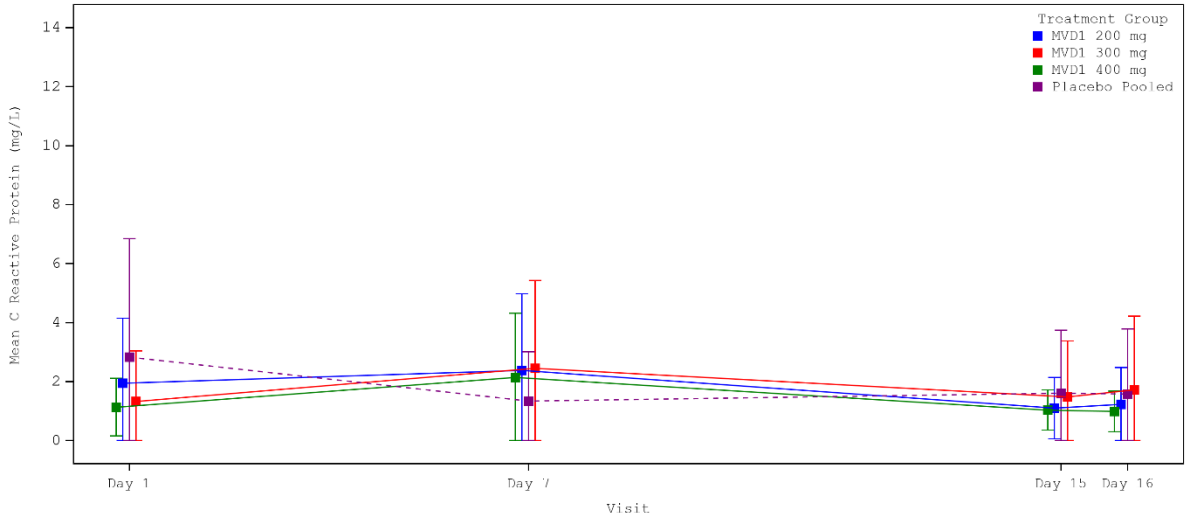
Reference: Figure 14.2.3.2B

Table 11-M Summary of Mean C Reactive Protein – Part B (MAD) (Pharmacodynamics Analysis Set)

Visit Statistic	MVD1 200 mg (N = 5)		MVD1 300 mg (N = 6)		MVD1 400 mg (N = 6)		Placebo Pooled (N = 5)	
	Actual Result (pmol/L)	Change from Baseline (pmol/L)	Actual Result (pmol/L)	Change from Baseline (pmol/L)	Actual Result (pmol/L)	Change from Baseline (pmol/L)	Actual Result (pmol/L)	Change from Baseline (pmol/L)
Baseline*								
Mean (SD)	1.94 (2.206)	-	1.32 (1.717)	-	1.13 (0.983)	-	2.82 (4.027)	-
Day 7								
Mean (SD)	2.38 (2.597)	0.44 (0.439)	2.45 (2.983)	1.13 (2.297)	2.13 (2.184)	1.00 (2.091)	1.34 (1.664)	-1.48 (4.198)
Day 15								
Mean (SD)	1.10 (1.039)	-0.84 (1.203)	1.48 (1.894)	0.17 (0.216)	1.03 (0.680)	-0.10 (0.613)	1.60 (2.140)	-1.22 (4.641)
Day 16								
Mean (SD)	1.22 (1.256)	-0.72 (1.008)	1.72 (2.506)	0.40 (0.797)	0.98 (0.685)	-0.15 (0.609)	1.58 (2.198)	-1.24 (4.644)

Abbreviations: MD = multiple ascending dose; N = ; SD = Standard Deviation.
* Baseline was defined as the latest observation (including unscheduled assessment) prior to study drug administration on Day 1.
Source: Listing 16.2.6.2.1.B Reference: Table 14.2.3.1.B

Figure 11-J Mean C Reactive Protein Over Time (Linear Scale) – Part B (MAD) (Pharmacodynamic Population)

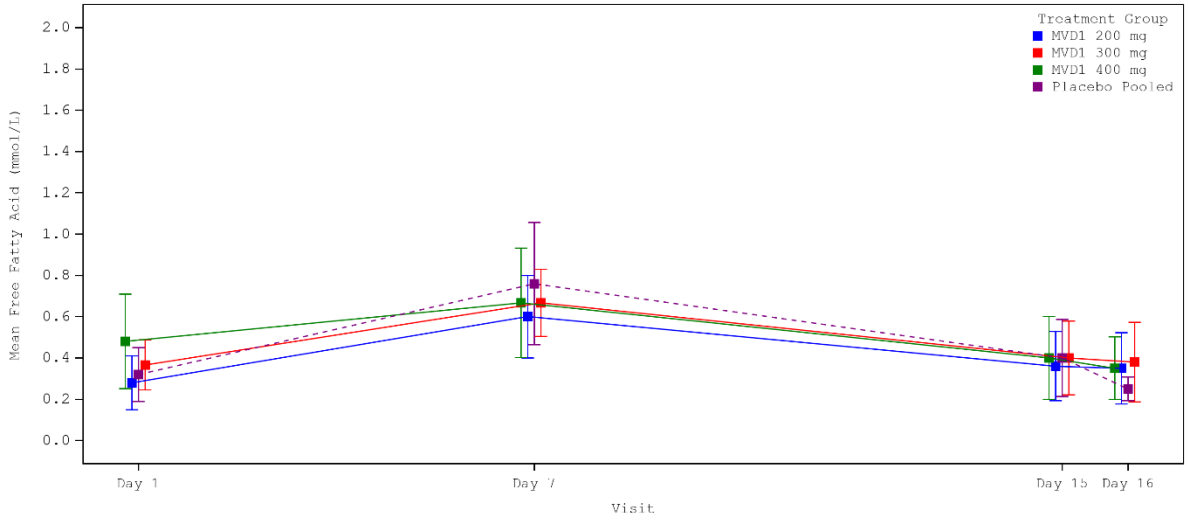


Abbreviations: MAD = multiple ascending dose
Notes: ± Bars denote Standard Deviation. If lower limit (mean minus standard error) was less than zero, then it was set to zero.

For visual comparison purposes, the result of different treatment levels were staggered on the x-axis timepoint.
Source: Table 14.2.3.1.B

Reference: Figure 14.2.3.2.B

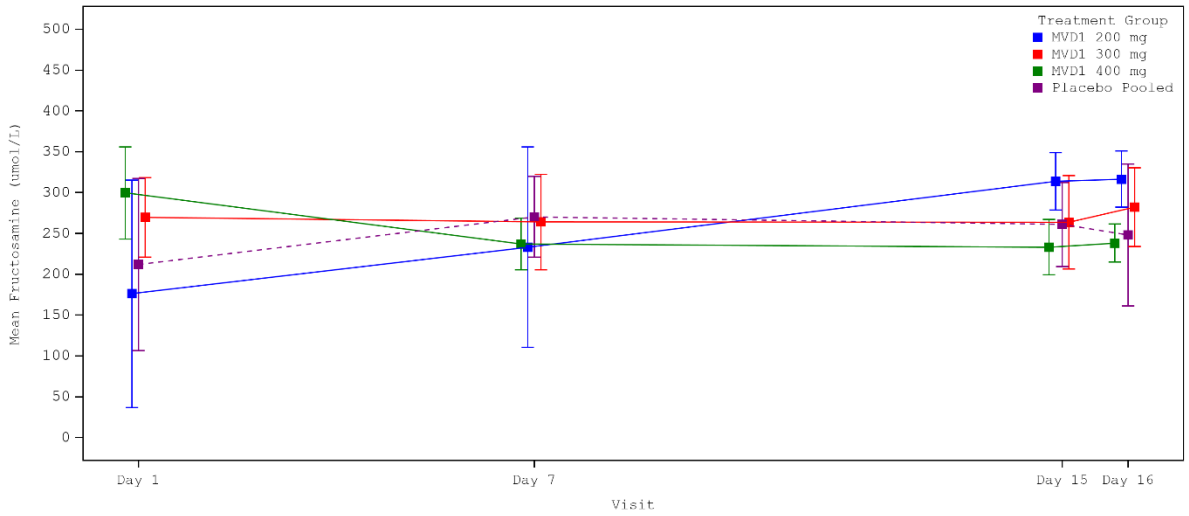
Figure 11-K Mean Free Fatty Acid Over Time (Linear Scale) – Part B (MAD) (Pharmacodynamic Population)



Abbreviations: MAD = multiple ascending dose
Notes: ± Bars denote Standard Deviation.
If lower limit (mean minus standard error) was less than zero, then it was set to zero.
For visual comparison purposes, the result of different treatment levels were staggered on the x-axis timepoint.
Source: Table 14.2.3.1.B

Reference: Figure 14.2.3.2.B

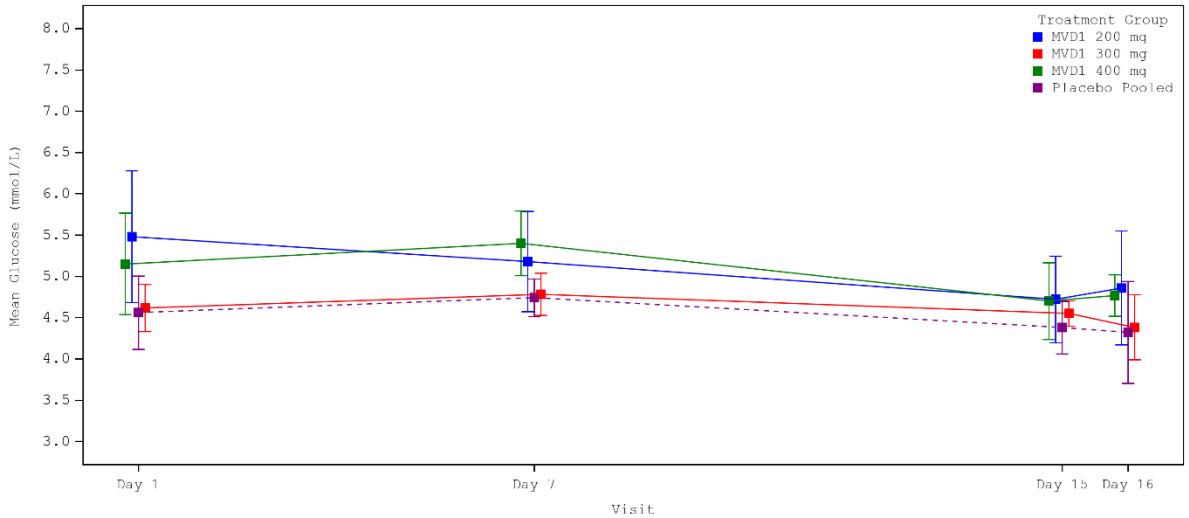
Figure 11-L Mean Fructosamine Over Time (Linear Scale) – Part B (MAD) (Pharmacodynamic Population)



Abbreviations: MAD = multiple ascending dose
Notes: ± Bars denote Standard Deviation.
If lower limit (mean minus standard error) was less than zero, then it was set to zero.
For visual comparison purposes, the result of different treatment levels were staggered on the x-axis timepoint.
Source: Table 14.2.3.1.B

Reference: Figure 14.2.3.2.B

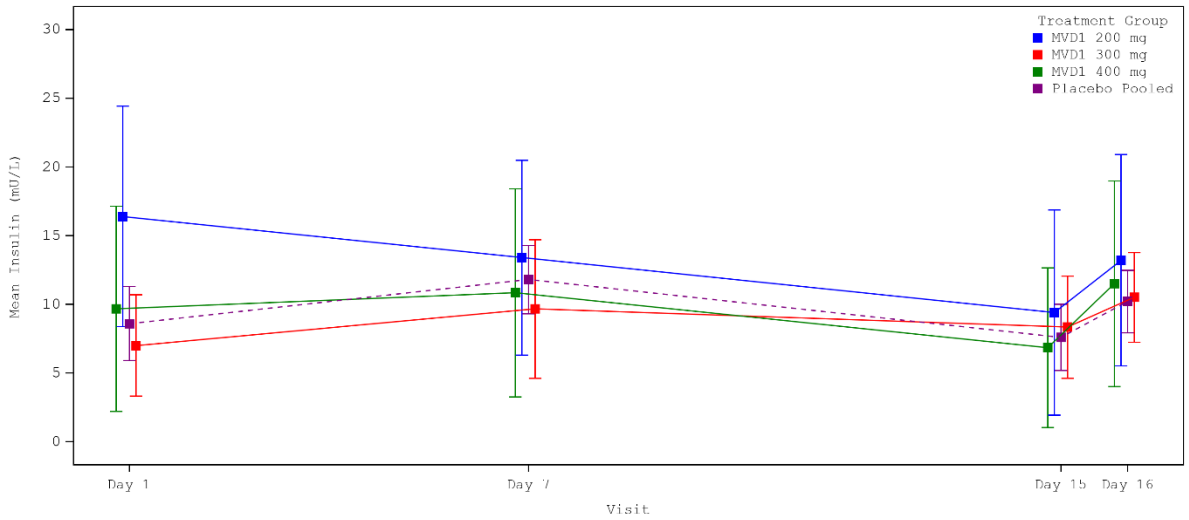
Figure 11-M Mean Glucose Over Time (Linear Scale) – Part B (MAD) (Pharmacodynamic Population)



Abbreviations: MAD = multiple ascending dose
Notes: ± Bars denote Standard Deviation.
If lower limit (mean minus standard error) was less than it was zero, then set to zero.
For visual comparison purposes, the result of different treatment levels were staggered on the x-axis timepoint.
Source: Table 14.2.3.1.B

Reference: Figure 14.2.3.2.B

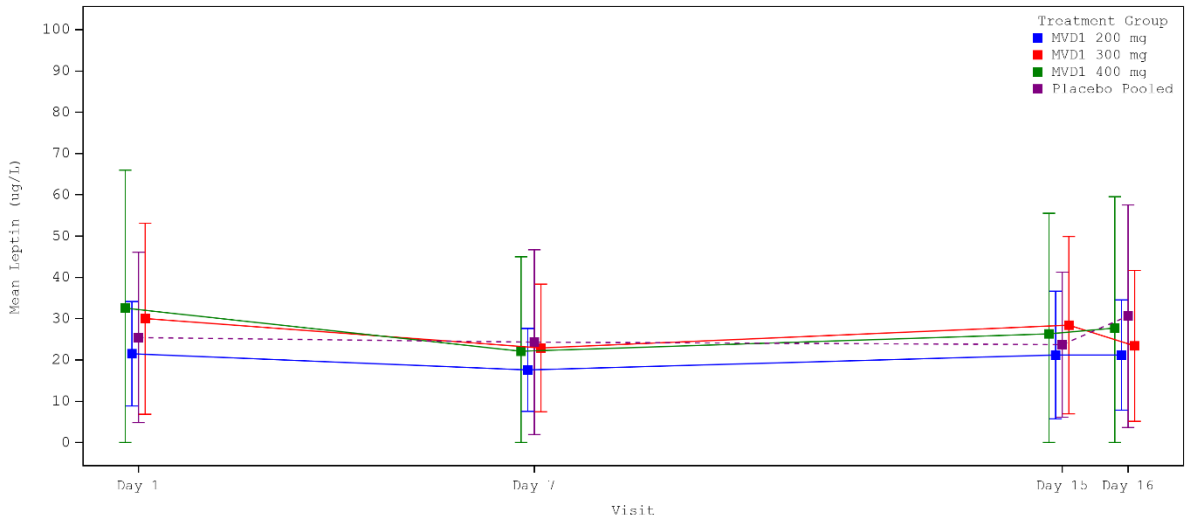
Figure 11-N Mean Insulin Over Time (Linear Scale) – Part B (MAD) (Pharmacodynamic Population)



Abbreviations: MAD = multiple ascending dose
Note: ± Bars denote Standard Deviation.
If lower limit (mean minus standard error) was less than zero, then it was set to zero.
For visual comparison purposes, the result of different treatment levels were staggered on the x-axis timepoint.
Source: Table 14.2.3.1.B

Reference: Figure 14.2.3.2.B

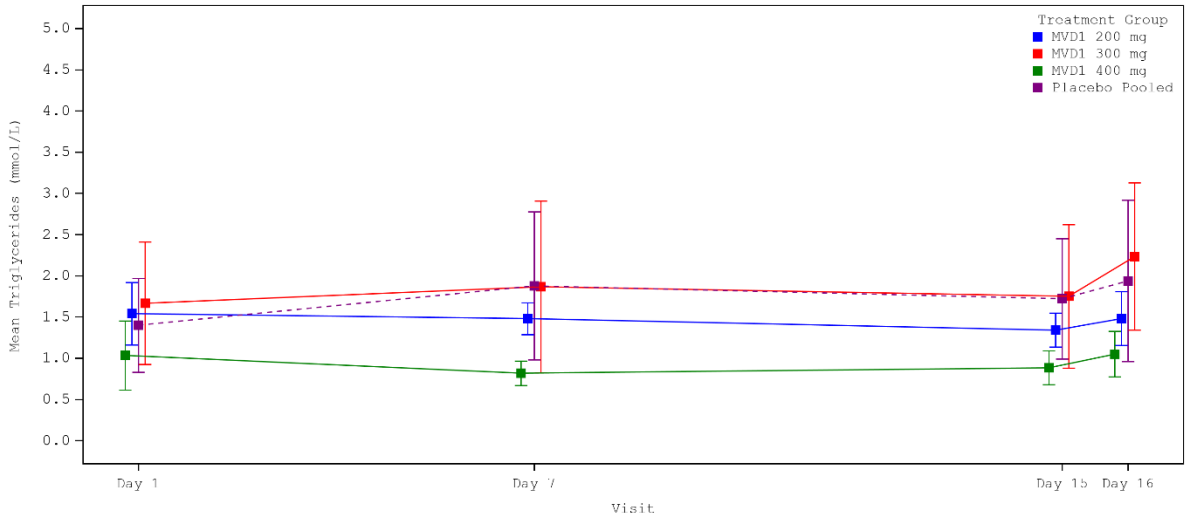
Figure 11-O Mean Leptin Over Time (Linear Scale) – Part B (MAD) (Pharmacodynamic Population)



Abbreviations: MAD = multiple ascending dose
Note: ± Bars denote Standard Deviation.
If lower limit (mean minus standard error) was less than zero, then it was set to zero.
For visual comparison purposes, the result of different treatment levels were staggered on the x-axis timepoint.
Source: Table 14.2.3.1.B

Reference: Figure 14.2.3.2.B

Figure 11-P Mean Triglycerides Over Time (Linear Scale) – Part B (MAD) (Pharmacodynamic Population)



Abbreviations: MAD = multiple ascending dose
Note: ± Bars denote Standard Deviation.
If lower limit (mean minus standard error) was less than zero, then it was set to zero.
For visual comparison purposes, the result of different treatment levels were staggered on the x-axis timepoint.
Source: Table 14.2.3.1.B

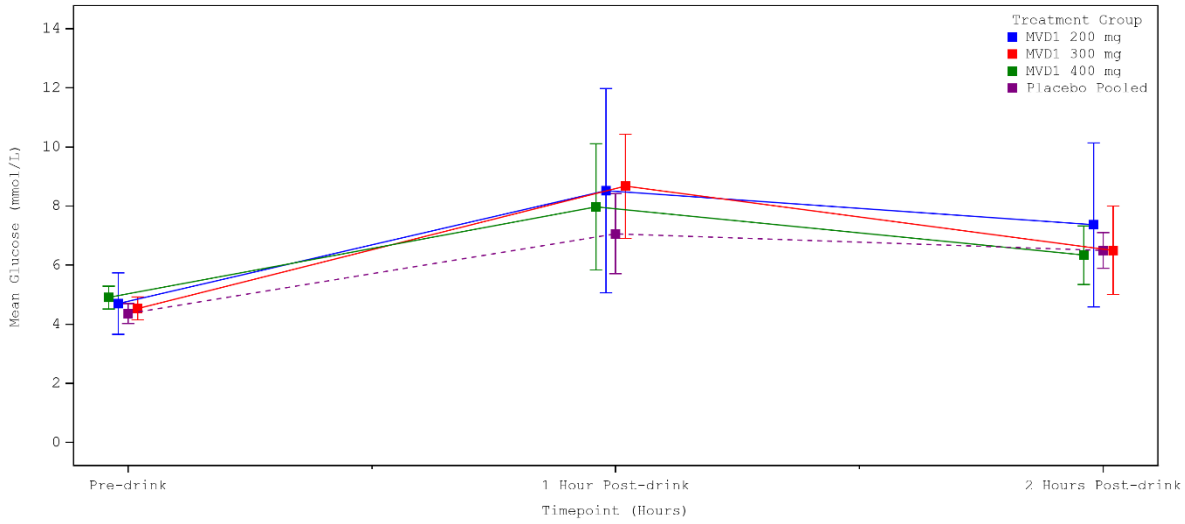
Reference: Figure 14.2.3.2.B

11.2.3 Oral Glucose Tolerance Test

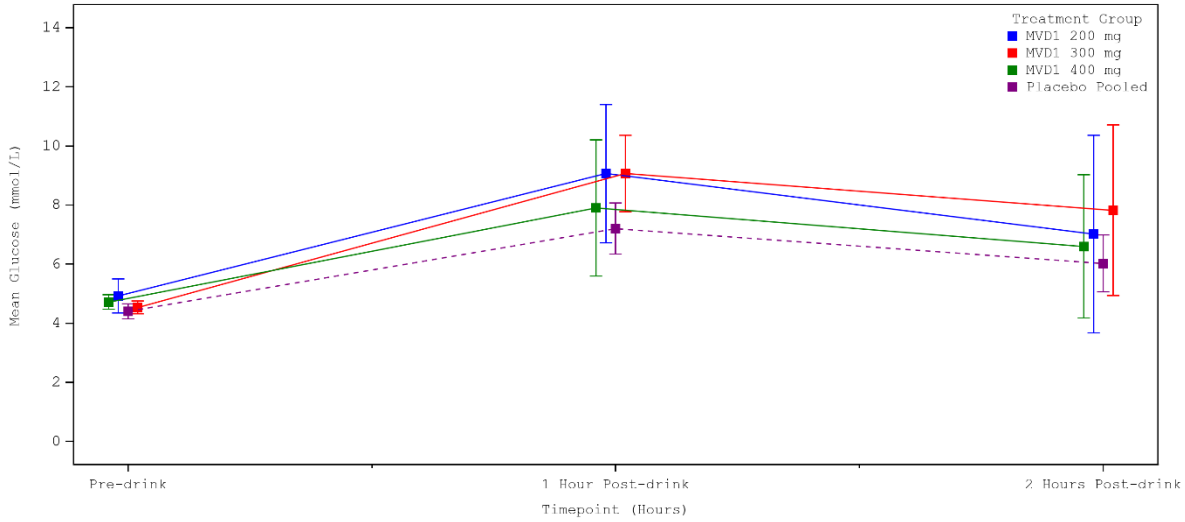
The OGTT was conducted on Day -1 and on Day 16 in Part B (MAD) only. A summary of oral glucose tolerance tests and mean values are provided in Section 14.3.1 (Part B: Table 14.2.3.3.B and Table 14.2.3.5.B). The test was conducted following an overnight fast of at least 8 hours. An initial blood sample was collected to establish a baseline fasting glucose, after which participants were required to consume approximately 75 grams of glucose administered in 250 mL water. Blood samples were collected at 1 hour and 2 hours post glucose challenge to determine glucose tolerance. No food was consumed during the test. Mean oral glucose (mmol/L) was lower at 1-hour post-drink in the pooled placebo cohort when compared to all MVD1 cohorts at Day -1 and at Day 16. With no apparent difference between MVD1 treated cohorts and placebo at 2 hours post-drink on Day -1 or Day 16 (Figure 11-Q). Mean oral glucose (mmol/L) at Day 16 was lower in the 400 mg MVD1 group pre-drink, 1-hour post- drink and 2 hours post-drink on Day -1 (baseline) and when compared to placebo.

Figure 11-Q Mean Oral Glucose Tolerance Test Over Time (Linear Scale) – Part B (MAD) (Pharmacodynamic Population)

Day -1



Day 16



Abbreviations: MAD = multiple ascending dose
Note: ± Bars denote Standard Deviation.
For visual comparison purposes, the results of different treatment levels were staggered on the x-axis timepoint.
Source: Table 14.2.3.3.B

Reference: Figure 14.2.3.4.B

11.2.4 Oral Glucose Tolerance Test

A nutritional questionnaire was completed by participants in Part B only, to assess the effects of study treatments on appetite. The responses to the SNAQ questionnaire are presented in Listing 16.2.9.6B.

11.2.5 White Adipose Tissue Sampling

In Part B (MAD) only, a single sample of WAT was obtained by needle biopsy at check-in on Day -1 and approximately 2 hours (±1 hour) following the morning dose of study drug on Day 7. During the procedure, approximately ~1.0 mL of subcutaneous fat was aspirated from the abdominal area using a needle under local anesthesia. The presence of MVD1 was not detected in white adipose samples of participants in any of the MAD (M1 – M3) cohorts on Day -1 or Day 7.

The results of the white adipose tissue sampling are presented in Listing 16.2.6.2.3B.

11.2.6 Patient Global Impression of Change Questionnaire

A PGIC questionnaire was completed by participants on Day 16 (i.e., the day after the last dose of study drug) in Part B (MAD) only. The questionnaire was comprised of a single question rating the participants perception of change following treatment using a seven-point scale ranging from very much improved, to very much worse. All participants who received placebo reported 'No Change' in their perception of change. There was 1 participant in each of the MVD1 dose groups who reported improvement, and 2 participants in the 200 mg MVD1 group and 1 participant in the 400 mg MVD1 group reporting their perception of change being slightly worse.

The PGIC questionnaire responses are listed by participant in Listing 16.2.9.5B.

11.3 STATISTICAL AND ANALYTICAL ISSUES

11.3.1 Adjustments for Covariates

Not applicable.

11.3.2 Handling of Dropouts or Missing Data

All data was analysed as collected and missing values were not imputed or replaced unless stated otherwise.

Adverse Events Missing Data Rules: For adverse events, with unknown intensity (severity) or unknown relationship to study treatment, these were imputed as follows:

- If the intensity (severity) of an adverse event was unknown/missing, the intensity was imputed for the summary of adverse events as "Severe (Grade 3)".
- If the relationship to investigational product of an adverse event was unknown/missing, the relationship was imputed for the summary of adverse events as being the least favorable relationship, i.e., "Definitely".

For AEs, where either the onset time or resolution date was unknown, time since first dose and duration were imputed as follows:

- If onset date was unknown, and it could not be confirmed that onset was prior to the start of dose administration, then the AE was classified as treatment-emergent (TE), with unknown time since first dose.
- If either the date of onset or the date of resolution was unknown, then duration was shown as unknown.
- If onset time is unknown:
    - If the date of onset was known to be the date of first dose administration, then the AE was classified as TE.
    - AE Duration was only calculated for Adverse events with complete dates and times.
- If resolution time was unknown:
    - If the date of resolution was known to be the date of first dose administration, then the AE was classified as TE.

11.3.3 Interim Analysis

No formal interim analysis was planned or conducted, however as previously discussed in Section 6.2, the SRC reviewed blinded data prior to the escalation to the next dose level cohort, and between SAD and MAD parts of the study, in accordance with the protocol.

11.3.4 Multicentre Studies

Not applicable.

11.3.5 Multiple Comparisons and Multiplicity

Not applicable. There was no hypothesis testing conducted in this study.

11.3.6 Efficacy Subset

Not applicable.

11.3.7 Examination of Subgroups

Not applicable.

11.3.8 Tabulation of Individual Response Data

Not applicable.

11.4 PHARMACOKINETIC, PHARMACODYNAMIC AND EXPLORATORY CONCLUSIONS

Pharmacokinetic Conclusions

Single dose PK characteristics of MVD1 were assessed in 11 participants, for ascending dose levels of 200, 400 and 800 mg. Multiple dose PK characteristics of MVD1 were assessed in 18 participants, for ascending total daily dose levels of 200, 300, and 400 mg.

The average elimination half-life of MVD1 was approximately 1.5-2.0 hours. There was minimal accumulation over the 15 days of multiple dosing BID, with pre-dose trough levels of MVD1 from Day 2 onwards generally quantifiable but quite low.

For the metabolite M1, the average elimination half-life was 1.5-2.5 hours. There was minimal accumulation for the metabolites, with pre-dose trough levels of M1 generally quantifiable but quite low. The ratio of metabolite M1 to MVD1 remained constant at approximately 30-40% as the dose of MVD1 increased.

For single dose, the mean exposure parameters increased monotonically by dose level in an approximately dose proportional manner, however the power model analyses did not meet criteria for dose proportionality for MVD1. For multiple dosing, the power model accounted for less than 50% of the variability in exposure versus dose except for MVD1 AUC_{0-12} on Day 1 and also dose dependence was noted to be non-monotonic on Day 15.

Median T_{max} varied across dose levels with no dose related trend.

There was little MVD1 excreted unchanged in urine (< 10%). It is noted that there was no noticeable increase in amount excreted at the highest dose level for single and multiple dosing. More of the drug was excreted in urine as metabolite M1 than as unchanged MVD1.

Pharmacodynamic and Exploratory Conclusions

There were no treatment- or dose- related trends over time observed in any of the PD biomarkers assessed. Despite some changes observed in PD biomarkers from baseline, these changes were not maintained over time (i.e., to Day 16). MVD1 did appear to increase plasma levels of the following biomarkers when compared to placebo: mean C-peptide (pmol/L), CRP (mg/L) and mean glucose (mmol/L).

Mean oral glucose (mmol/L) was lower at 1-hour post-drink in the pooled placebo cohort when compared to all MVD1 dose cohorts at Day -1 and at Day 16. There was no apparent difference between MVD1 treated cohorts and placebo at 2 hours post-drink on Day -1 or Day 16.

The presence of MVD1 was not detected in white adipose samples of participants in any of the MAD (M1 – M3) cohorts on Day -1 or Day 7.

All participants who received placebo reported ‘No Change’ in their perception of change. There was one participant in each of the MVD1 groups who reported improvement, with 2 participants in the 200 mg MVD1 group and 1participant in the 400 mg MVD1 group reporting their perception of change being slightly worse.

Following multiple administrations of MVD1 (400 mg) after 15 days of treatment significant body weight reduction was observed, demonstrating encouraging efficacy of MVD1.

12. SAFETY EVALUATION

12.1 ADVERSE EVENTS

Adverse events by individual are provided in Appendix 16.2.7 (Part A: Listing 16.2.7.1A and Part B: Listing 16.2.7.1B).

12.1.1 Brief Summary of Adverse Events

Part A (SAD)

An overall summary of TEAEs is provided in Section 14.3.1 (Part A: Table 14.3.1.1A) and presented below in Table 12-A.

Across study Part A (SAD), 18 TEAEs were reported in 6 (35.3%) of 17 participants, the incidence of which was similar in participants administered MVD1 (12 events in 4 [36.4%] of 11 participants) and placebo (6 events in 2 [33.3%] of 6 participants). There was a higher incidence of TEAEs in the MVD1 800 mg group (5 TEAEs reported in 2 [66.7%] of 3 participants) compared to the 200 mg and 400 mg groups (5 TEAEs reported in 1 [25.0%] of 4 participants and 2 TEAEs reported in 1 [25.0%] of 4 participants, respectively). There were no serious TEAEs or TEAEs resulting in study drug discontinuation, withdrawal from the study or death. The majority of TEAEs were mild in severity (13 TEAEs in 3 [17.6%] of 17 participants) and 5 TEAEs were of moderate severity reported in 3 [17.6%] of 17 participants (2 administered MVD1 and 1 administered placebo). There were no severe or life threatening TEAEs reported. There were 8 TEAEs in 5 [29.4%] of 17 participants considered related to study drug. The majority of the related TEAEs were mild in severity (6 related TEAEs in 3 (17.6%) of 17 participants) with 2 related TEAEs in 2 (11.8%) participants of moderate severity.

Table 12-A Overall Summary of Treatment-emergent Adverse Events – Part A (SAD) (Safety Analysis Set)

	MVD1 200 mg (N = 4) n (%) M	MVD1 400 mg (N = 4) n (%) M	MVD1 800 mg (N = 3) n (%) M	MVD1 Pooled (N = 11) n (%) M	Placebo Pooled (N = 6) n (%) M	Overall (N = 17) n (%) M
Participants with:						
Any TEAEs	1 (25.0) 5	1 (25.0) 2	2 (66.7) 5	4 (36.4) 12	2 (33.3) 6	6 (35.3) 18
Any Serious TEAEs	0	0	0	0	0	0
Any TEAEs Leading to Study Drug Discontinuation	0	0	0	0	0	0
Any TEAEs Leading to Study Withdrawal	0	0	0	0	0	0
Any TEAEs Leading to Death	0	0	0	0	0	0
Severity of TEAEs						
Grade 1 - Mild	0 (0) 2	1 (25.0) 2	1 (33.3) 4	2 (18.2) 8	1 (16.7) 5	3 (17.6) 13
Grade 2 - Moderate	1 (25.0) 3	0	1 (33.3) 1	2 (18.2) 4	1 (16.7) 1	3 (17.6) 5

	MVD1 200 mg (N = 4) n (%) M	MVD1 400 mg (N = 4) n (%) M	MVD1 800 mg (N = 3) n (%) M	MVD1 Pooled (N = 11) n (%) M	Placebo Pooled (N = 6) n (%) M	Overall (N = 17) n (%) M
≥Grade 3 - ≥Severe	0	0	0	0	0	0
Participants with:						
Any Treatment-related TEAEs	0	1 (25.0) 1	2 (66.7) 4	3 (27.3) 5	2 (33.3) 3	5 (29.4) 8
Severity of Treatment-related TEAEs:						
Grade 1 - Mild	0	1 (25.0) 1	1 (33.3) 3	2 (18.2) 4	1 (16.7) 2	3 (17.6) 6
Grade 2 - Moderate	0	0	1 (33.3) 1	1 (9.1) 1	1 (16.7) 1	2 (11.8) 2

Abbreviations: SAD = single ascending dose; TEAE = treatment-emergent adverse event
TEAEs were defined as AEs that occurred or worsened from the first administration of study drug (MVD1 or placebo), up to the end of study.
Treatment-related TEAEs were defined as any TEAEs reported with the causality of related to study treatment (MVD1 or placebo), up to the end of study.
For severity/causality of TEAE, the number of events was counted by each severity/causality in Events (M) column, while the number of participants is counted once for the worst/highest severity/causality in Participant count (n).
Percentages were calculated (the denominator used for the calculation) based on the number of participants of each treatment group (N).
Source: Listing 16.2.7.1.A

Reference: Table 14.3.1.1A

Part B (MAD)

An overall summary of TEAEs is provided in Section 14.3.1 (Part B: Table 14.3.1.1B) and presented below in Table 12-B.

Across study Part B (MAD), 107 TEAEs were reported in 24 (100%) of 24 participants, the incidence of which was the same in participants administered MVD1 (76 events in 18 [100%] of 18 participants) and placebo (31 events in 6 [100%] of 6 participants). There appeared to be an increase in the number of TEAEs with increasing dose of MVD1 although the incidence of events in each group was the same (200 mg had 16 TEAEs reported in 6 [100%] of 6 participants, 300 mg had 26 TEAEs reported in 6 [100%] of 6 participants, and 400 mg MVD1 had 34 TEAEs reported in 6 [100%] of 6 participants). There were no serious TEAEs or TEAEs resulting in death. There was one TEAE in 1 (16.7%) of 6 participants leading to study drug discontinuation and study withdrawal in the 200 mg MVD1 group. The majority of TEAEs were mild in severity (102 TEAEs in 19 [79.2%] of 24 participants) and 5 TEAEs of moderate severity reported in 5 [20.8%] of 24 participants. Four moderate TEAEs were reported in 4 (22.2%) of 18 participants administered MVD1, 2 (33.3%) of each of the 6 participants in the 300 mg MVD1 and 400 mg MVD1 treatment groups. One moderate TEAE was reported for 1 (16.7%) of 6 participants in the placebo group. There were no severe or life threatening TEAEs reported. There were 18 TEAEs for 13 [54.2%] of 24 participants considered related to study drug. The majority of the related TEAEs were mild in severity (17 related TEAEs in 12 (50.0%) of 24 participants) with 1 related TEAE in 1 (4.2%) participant of moderate severity.

Table 12-B Overall Summary of Treatment-emergent Adverse Events – Part B (MAD) (Safety Analysis Set)

	MVD1 200 mg (N = 6) n (%) M	MVD1 300 mg (N = 6) n (%) M	MVD1 400 mg (N = 6) n (%) M	MVD1 Pooled (N = 18) n (%) M	Placebo Pooled (N = 6) n (%) M	Overall (N = 24) n (%) M
Participants with:						
Any TEAEs	6 (100) 16	6 (100) 26	6 (100) 34	18 (100) 76	6 (100) 31	24 (100) 107
Any Serious TEAEs	0	0	0	0	0	0
Any TEAEs Leading to Study Drug Discontinuation	1 (16.7) 1	0	0	1 (5.6) 1	0	1 (4.2) 1
Any TEAEs Leading to Study Withdrawal	1 (16.7) 1	0	0	1 (5.) 1	0	1 (4.2) 1
Any TEAEs Leading to Death	0	0	0	0	0	0
Severity of TEAEs						
Grade 1 - Mild	6 (100) 16	4 (66.7) 24	4 (66.7) 32	14 (77.8) 72	5 (83.3) 30	19 (79.2) 102
Grade 2 - Moderate	0	2 (33.3) 2	2 (33.3) 2	4 (22.2) 4	1 (16.7) 1	5 (20.8) 5
≥Grade 3 - ≥Severe	0	0	0	0	0	0
Participant with:						
Any Treatment-related TEAEs	4 (66.7) 4	2 (33.3) 4	3 (50.0) 5	9 (50.0) 13	4 (66.7) 5	13 (54.2) 18
Any Treatment-related TEAEs leading to Study Drug Discontinuation	0	0	0	0	0	0
Any Treatment-related TEAEs leading to Study Withdrawal	0	0	0	0	0	0
Treatment-related Severity of TEAEs:						
Grade 1 - Mild	4 (66.7) 4	2 (33.3) 4	2 (33.3) 4	8 (44.4) 12	4 (66.7) 5	12 (50.0) 17
Grade 2 - Moderate	0	0	1 (16.7) 1	1 (5.6) 1	0	1 (4.2) 1

Abbreviations: MAD = multiple ascending dose; TEAE = treatment-emergent adverse event
TEAEs were defined as AEs that occurred or worsened from the first administration of study drug (MVD1 or placebo), up to the end of study.
Treatment-related TEAEs were defined as any TEAEs reported with the causality of related to study treatment (MVD1 or placebo), up to the end of study.
For severity/causality of TEAE, the number of events was counted by each severity/causality in Events (M) column, while the number of participants is counted once for the worst/highest severity/causality in Participant count (n).
Percentages were calculated (the denominator used for the calculation) based on the number of participants of each treatment group (N).
Source: Listing 16.2.7.1.B

Reference: Table 14.3.1.1B

12.1.2 Display of Adverse Events

12.1.2.1 Treatment-emergent Adverse Events

Part A (SAD)

A summary of TEAEs by SOC and PT, and PT only are provided in Section 14.3.1 (Part A: Table 14.3.1.2A and Table 14.3.1.6A) and presented in Table 12-C.

The most commonly reported TEAEs in participants administered MVD1 by PT were diarrhoea, nausea and renal tubular injury with all events only reported in participants who received MVD1 (2 events in 2 [18.2%] of 11 participants for each PT). Headache was the only event to be reported in both the MVD1 group (1 event in 1 [9.1%] of 11 participants) and the placebo group (2 events in 2 [33.3%] of 6 participants). All other events were reported only once and included catheter site bruise, musculoskeletal stiffness, photophobia, presyncope and vomiting in the MVD1 group, and catheter site pain, fatigue, head discomfort and vessel puncture site swelling in the placebo group.

Overall, in Part A (SAD), the incidence was similar in participants administered MVD1 (12 events in 4 [36.4%] of 11 participants) and placebo (6 events in 2 [33.3%] of 6 participants). There was a higher incidence of TEAEs in the MVD1 800 mg group (5 TEAEs reported in 2 [66.7%] of 3 participants) compared to the 200 mg and 400 mg groups (5 TEAEs reported in 1 [25.0%] of 4 participants and 2 TEAEs reported in 1 [25.0%] of 4 participants, respectively).

The most commonly reported TEAEs in participants who received MVD1 by SOC were Gastrointestinal Disorders (5 events in 3 [27.3%] of 11 participants), which were only reported in participants who received MVD1. Treatment-emergent AEs by PT in this SOC were diarrhoea reported in 1 participant each administered 400 mg MVD1 and 800 mg MVD1; nausea reported in 1 participant each administered 200 mg MVD1 and 800 mg MVD1; and vomiting reported in 1 participant administered 200 mg MVD1.

The next most reported TEAEs in the MVD1 group by SOC were Nervous System Disorders and Renal and Urinary Disorders. Nervous System Disorders were reported at a higher incidence in participants administered placebo (3 events in 2 [33.3%] of 6 participants) compared to MVD1 (2 events in 2 [18.2%] of 11 participants). The majority TEAEs in this SOC by PT were headache (2 events in 2 [33.3%] participants in the placebo group and 1 event in 1 (9.1%) participant in the 200 mg MVD1 group). Other TEAEs reported included 1 event each of head discomfort in the placebo group and presyncope in the 800 mg MVD1 group. Renal and Urinary Disorders were only reported in participants who received MVD1 (2 events in 2 [18.2%] of 11 participants), with renal tubular injury the only TEAE reported in this SOC (2 events in 800 mg MVD1).

Table 12-C Summary of Treatment-emergent Adverse Event by PT – Part A (SAD) (Safety Analysis Set)

Preferred Term	MVD1 200 mg (N = 4) n (%) M	MVD1 400 mg (N = 4) n (%) M	MVD1 800 mg (N = 3) n (%) M	MVD1 Pooled (N = 11) n (%) M	Placebo Pooled (N = 6) n (%) M	Overall (N = 17) n (%) M
Participants with at least one TEAE	**1 (25.0) 5**	**1 (25.0) 2**	**2 (66.7) 5**	**4 (36.4) 12**	**2 (33.3) 6**	**6 (35.3) 18**
Headache	1 (25.0) 1	0	0	1 (9.1) 1	2 (33.3) 2	3 (17.6) 3
Diarrhoea	0	1 (25.0) 1	1 (33.3) 1	2 (18.2) 2	0	2 (11.8) 2
Nausea	1 (25.0) 1	0	1 (33.3) 1	2 (18.2) 2	0	2 (11.8) 2
Renal tubular injury	0	0	2 (66.7) 2	2 (18.2) 2	0	2 (11.8) 2
Catheter site bruise	0	1 (25.0) 1	0	1 (9.1) 1	0	1 (5.9) 1
Catheter site pain	0	0	0	0	1 (16.7) 1	1 (5.9) 1
Fatigue	0	0	0	0	1 (16.7) 1	1 (5.9) 1
Head discomfort	0	0	0	0	1 (16.7) 1	1 (5.9) 1
Musculoskeletal stiffness	1 (25.0) 1	0	0	1 (9.1) 1	0	1 (5.9) 1
Photophobia	1 (25.0) 1	0	0	1 (9.1) 1	0	1 (5.9) 1
Presyncope	0	0	1 (33.3) 1	1 (9.1) 1	0	1 (5.9) 1
Vessel puncture site swelling	0	0	0	0	1 (16.7) 1	1 (5.9) 1
Vomiting	1 (25.0) 1	0	0	1 (9.1) 1	0	1 (5.9) 1

Abbreviations: SAD = single ascending dose; PT = preferred term; TEAE = treatment-emergent adverse event
TEAEs were defined as AEs that occurred or worsened from the first administration of study drug (MVD1 or placebo), up to the end of study.
Percentages were calculated (the denominator used for the calculation) based on the number of participants of each treatment group (N).
If a participant had multiple occurrences of a TEAE, the participant was presented only once in the Participant count (n) column for a given PT. Occurrences were counted each time in the Events (M) column.
TEAEs were sorted by descending order of the counts (M) of PT in the Overall column, and alphabetically thereafter.
Coding: Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1
Source: Listing 16.2.7.1.A Reference: Table 14.3.1.6A

Part B (MAD)

A summary of commonly occurring TEAEs (i.e., reported in at least 2 or more participants in a treatment group) by SOC and PT is provided in Section 14.3.1 (Part B: Table 14.3.1.2b) and presented in Table 12-D.

Overall, in Part B (MAD), the number of TEAEs appeared to increase with increasing MVD1 dose although the incidence of events in each MVD1 group (200 mg had 16 TEAEs reported in 6 [100%] of 6 participants, 300 mg had 26 TEAEs reported in 6 [100%] of 6 participants,

and 400 mg MVD1 had 34 TEAEs reported in 6 [100%] of 6 participants) and the placebo group was the same (31 events in 6 [100%] of 6 participants).

The most commonly reported TEAEs in participants who received MVD1 by SOC were Injury, Poisoning and Procedural Complications (34 events in 16 [88.9%] of 18 participants), which were reported at a similar incidence in the participants administered placebo (12 events in 6 [100%] of 6 participants). Commonly occurring TEAEs (reported in at least 2 or more participants in the MVD1 group) in this SOC by PT were as follows: post procedural contusion (19 events in 13 [72.2] of 18 participants), procedural pain (8 events in 6 [33.3%] of 18 participants) and post procedural haematoma (3 events in 3 [16.7%] of 18 participants), which were all reported at the same or slightly higher incidence in the placebo group.

The next most reported TEAEs in the MVD1 group by SOC were Gastrointestinal Disorders (17 events in 9 [50.0%] of 18 participants), which were reported at a slightly lower incidence in the placebo group (3 events in 2 [33.3%] of 6 participants). Commonly occurring TEAEs (reported in at least 2 or more participants in the MVD1 group) in this SOC by PT were diarrhoea (5 events in 5 [27.8%] of 18 participants), nausea (4 events in 3 [16.7%] of 18 participants) and constipation (2 events in 2 [11.1%] of 18 participants), with constipation the only event that was also reported in the placebo group (2 events in 1 [16.7%] of 6 participants).

General Disorders and Administration Site Conditions were reported at a similar incidence in the MVD1 group (8 events in 7 [38.9%] of 18 participants) and placebo group (6 events in 2 [33.3%] of 6 participants). Commonly occurring TEAEs (reported in at least 2 or more participants in the MVD1 group) in this SOC by PT were catheter site pain (3 events in 3 [16.7%] of 18 participants), fatigue (2 events in 2 [11.1%] of 18 participants), both of which were not reported in the placebo group.

Nervous System Disorders were also reported at a similar incidence in the MVD1 group (6 events in 5 [27.8%] of 18 participants) and placebo group (3 events in 2 [33.3%] of 6 participants). Commonly occurring TEAEs (reported in at least 2 or more participants in the MVD1 group) in this SOC by PT were headache and dizziness (both 3 events in 3 [16.7%] of 18 participants), with only headache also reported in the placebo group (2 events in 2 [33.3%] of 6 participants).

Treatment-emergent AEs in the SOCs of Musculoskeletal and Connective Tissue Disorders, Infections and Infestations, Renal and Urinary Disorders, Respiratory, Thoracic and Mediastinal Disorders, Skin and Subcutaneous Tissue Disorders, Skin and Subcutaneous Tissue Disorders and Investigations were reported in ≤ 2 participants in the MVD1 group.

Table 12-D Summary of Treatment-emergent Adverse Events Occurring in ≥2 Participants in a Treatment Group by SOC and PT – Part B (MAD) (Safety Analysis Set)

System Organ Class Preferred Term	MVD1 200 mg (N = 6) n (%) M	MVD1 300 mg (N = 6) n (%) M	MVD1 400 mg (N = 6) n (%) M	MVD1 Pooled (N = 18) n (%) M	Placebo Pooled (N = 6) n (%) M	Overall (N = 24) n (%) M
Participants with at least one TEAE	**6 (100) 16**	**6 (100) 26**	**6 (100) 34**	**18 (100) 76**	**6 (100) 31**	**24 (100) 107**
Injury, Poisoning and Procedural Complications	**5 (83.3) 6**	**6 (100) 10**	**5 (83.3) 18**	**16 (88.9) 34**	**6 (100) 12**	**22 (91.7) 46**
Post procedural contusion	5 (83.3) 6	3 (50.0) 4	5 (83.3) 9	13 (72.2) 19	5 (83.3) 6	18 (75.0) 25
Procedural pain	0	2 (33.3) 2	4 (66.7) 6	6 (33.3) 8	3 (50.0) 3	9 (37.5) 11
Post procedural haematoma	0	3 (50.0) 3	0	3 (16.7) 3	1 (16.7) 1	4 (16.7) 4
Gastrointestinal Disorders	**2 (33.3) 3**	**3 (50.0) 6**	**4 (66.7) 8**	**9 (50.0) 17**	**2 (33.3) 3**	**11 (45.8) 20**
Diarrhoea	2 (33.3) 2	1 (16.7) 1	2 (33.3) 2	5 (27.8) 5	0	5 (20.8) 5
Constipation	0	0	2 (33.3) 2	2 (11.1) 2	1 (16.7) 2	3 (12.5) 4
Nausea	1 (16.7) 1	2 (33.3) 3	0	3 (16.7) 4	0	3 (12.5) 4
General Disorders and Administration Site Conditions	**3 (50.0) 3**	**2 (33.3) 3**	**2 (33.3) 2**	**7 (38.9) 8**	**2 (33.3) 6**	**9 (37.5) 14**
Catheter site pain	1 (16.7) 1	1 (16.7) 1	1 (16.7) 1	3 (16.7) 3	0	3 (12.5) 3
Fatigue	2 (33.3) 2	0	0	2 (11.1) 2	0	2 (8.3) 2
Nervous System Disorders	**2 (33.3) 2**	**1 (16.7) 1**	**2 (33.3) 3**	**5 (27.8) 6**	**2 (33.3) 3**	**7 (29.2) 9**
Headache	1 (16.7) 1	0	2 (33.3) 2	3 (16.7) 3	2 (33.3) 2	5 (20.8) 5
Dizziness	1 (16.7) 1	1 (16.7) 1	1 (16.7) 1	3 (16.7) 3	0	3 (12.5) 3
Musculoskeletal and Connective Tissue Disorders	0	**1 (16.7) 1**	**1 (16.7) 1**	**2 (11.1) 2**	**2 (33.3) 3**	**4 (16.7) 5**
Back pain	0	1 (16.7) 1	1 (16.7) 1	2 (11.1) 2	1 (16.7) 1	3 (12.5) 3
Renal and Urinary Disorders	**1 (16.7) 1**	0	**1 (16.7) 1**	**2 (11.1) 2**	0	**2 (8.3) 2**
Proteinuria	1 (16.7) 1	0	1 (16.7) 1	2 (11.1) 2	0	2 (8.3) 2

Abbreviations: MAD = multiple ascending dose; SOC = system organ class; PT = preferred term; TEAE = treatment-emergent adverse event

TEAEs were defined as AEs that occurred or worsened from the first administration of study drug (MVD1 or placebo), up to the end of study.

Percentages were calculated (the denominator used for the calculation) based on the number of participants of each treatment group (N).

If a participant had multiple occurrences of a TEAE, the participant was presented only once in the Participant count (n) column for a given SOC and PT. Occurrences were counted each time in the Events (M) column.

TEAEs are sorted by descending order by the counts (M) of SOC and PT in the Overall column, and alphabetically thereafter.

Coding: Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1

Source: Listing 16.2.7.1.B

Reference: Table 14.3.1.2B

A summary of commonly occurring TEAEs (i.e., reported in at least 2 or more participants in a treatment group) by PT is provided in Section 14.3.1 (Part B: Table 14.3.1.6B) and presented in Table 12-E.

The most commonly reported TEAEs by PT in participants administered MVD1 were post procedural contusion (19 events in 13 [72.2%] of 18 participants), procedural pain (8 events in 6 [33.3%] of 18 participants), diarrhoea (5 events in 5 [27.8%] of 18 participants), headache (3 events in 3 [16.7%] of 18 participants), constipation (2 events in 2 [11.1%] of 18 participants), nausea (4 events in 3 [16.7%] of 18 participants), post procedural haematoma (3 events in 3 [16.7%] of 18 participants), back pain (2 events in 2 [11.1%] of 18 participants), catheter site pain (3 events in 3 [16.7%] of 18 participants), dizziness (3 events in 3 [16.7%] of 18 participants), fatigue (2 events in 2 [11.1%] of 18 participants) and proteinuria (2 events in 2 [11.1%] of 18 participants). Of the above TEAEs, diarrhoea, nausea, catheter site pain, dizziness, fatigue and proteinuria were only reported in the MVD1 group with the other events reported at the same or a slightly higher incidence in the placebo group. All other events by PT were reported only once.

Table 12-E Summary of Treatment-emergent Adverse Event Occurring in ≥2 Participants by PT – Part B (MAD) (Safety Analysis Set)

Preferred Term	**MVD1 200 mg (N = 6) n (%) M**	**MVD1 300 mg (N = 6) n (%) M**	**MVD1 400 mg (N = 6) n (%) M**	**MVD1 Pooled (N = 18) n (%) M**	**Placebo Pooled (N = 6) n (%) M**	**Overall (N = 24) n (%) M**
Participants with at least one TEAE	**6 (100) 16**	**6 (100) 26**	**6 (100) 34**	**18 (100) 76**	**6 (100) 31**	**24 (100) 107**
Post procedural contusion	5 (83.3) 6	3 (50.0) 4	5 (83.3) 9	13 (72.2) 19	5 (83.3) 6	18 (75.0) 25
Procedural pain	0	2 (33.3) 2	4 (66.7) 6	6 (33.3) 8	3 (50.0) 3	9 (37.5) 11
Diarrhoea	2 (33.3) 2	1 (16.7) 1	2 (33.3) 2	5 (27.8) 5	0	5 (20.8) 5
Headache	1 (16.7) 1	0	2 (33.3) 2	3 (16.7) 3	2 (33.3) 2	5 (20.8) 5
Post procedural haematoma	0	3 (50.0) 3	0	3 (16.7) 3	1 (16.7) 1	4 (16.7) 4
Constipation	0	0	2 (33.3) 2	2 (11.1) 2	1 (16.7) 2	3 (12.5) 4
Nausea	1 (16.7) 1	2 (33.3) 3	0	3 (16.7) 4	0	3 (12.5) 4
Back pain	0	1 (16.7) 1	1 (16.7) 1	2 (11.1) 2	1 (16.7) 1	3 (12.5) 3
Catheter site pain	1 (16.7) 1	1 (16.7) 1	1 (16.7) 1	3 (16.7) 3	0	3 (12.5) 3
Dizziness	1 (16.7) 1	1 (16.7) 1	1 (16.7) 1	3 (16.7) 3	0	3 (12.5) 3
Fatigue	2 (33.3) 2	0	0	2 (11.1) 2	0	2 (8.3) 2
Proteinuria	1 (16.7) 1	0	1 (16.7) 1	2 (11.1) 2	0	2 (8.3) 2

Abbreviations: MAD = multiple ascending dose; PT = preferred term; TEAE = treatment-emergent adverse event.

TEAEs were defined as AEs that occurred or worsened from the first administration of study drug (MVD1 or placebo), up to the end of study.
Percentages were calculated (the denominator used for the calculation) based on the number of participants of each treatment group (N).
If a participant had multiple occurrences of a TEAE, the participant was presented only once in the Participant count (n) column for a given PT. Occurrences were counted each time in the Events (M) column.
TEAEs were sorted by descending order of the counts (M) of PT in the Overall column, and alphabetically thereafter.
Coding: Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1
Source: Listing 16.2.7.1.B

Reference: Table 14.3.1.6B

12.1.3 Analysis of Adverse Events

12.1.3.1 Severity

A summary of TEAEs for severity by SOC and PT is provided in Section 14.3.1 (Part A: Table 14.3.1.3A and Part B: Table 14.3.1.3B) and TEAEs ≥ moderate severity are presented in Table 12-F and Table 12-G.

Part A (SAD)

The majority of TEAEs reported across Part A (SAD) of the study were mild (Grade 1) in severity (13 events in 3 [17.6%] of 17 participants). There were 5 TEAEs which were moderate (Grade 2) in severity in 3 [17.6%] participants: 3 moderate TEAEs were reported for 1 participant in the 200 mg MVD1 group, 1 moderate TEAE in 1 participant in the 800 mg and 1 moderate TEAE in 1 participant in the placebo group. The moderate TEAEs were as follows:

- The 3 moderate (Grade 2) TEAEs experienced by a participant in the 200 mg MVD1 group were:
    - Headache lasting approximately 2.5 days, nausea lasting 3 days and photophobia lasting approximately 2.5 days. These events were not serious and deemed to be unrelated to study drug by the Investigator. The headache was treated with a cold pack and paracetamol (1000 mg, 3 times, orally) or Panadeine forte (1 tablet, 3 times, orally), nausea was treated with an Ondansetron wafer (4 mg, twice sublingual,) and photophobia treated with the participant in a room with curtains closed and lights off. All events were considered recovered/resolved. This participant did not have a history of headache, nausea, or photophobia.
- The moderate TEAE experienced by a participant in the 800 mg MVD1 group was diarrhoea lasting approximately 9 hours, which was not serious, deemed possibly related to study drug by the Investigator and considered resolved on the same day as onset with no concomitant medication or other action taken.
- The moderate TEAE experienced by a participant in the placebo group was head discomfort lasting 6 hours, which was not serious, deemed possibly related to study drug by the Investigator and considered resolved on the same day as onset with no concomitant medication or other action taken.

There were no severe (Grade 3) or life-threatening (Grade 4) TEAEs, or TEAEs resulting in death (Grade 5) reported.

Table 12-F Summary of Treatment-emergent Adverse Events for Severity by PT – Part A (SAD) (Safety Analysis Set)

Severity/ Preferred Term	MVD1 200 mg (N = 4) n (%) M	MVD1 400 mg (N = 4) n (%) M	MVD1 800 mg (N = 3) n (%) M	MVD1 Pooled (N = 11) n (%) M	Placebo Pooled (N = 6) n (%) M	Overall (N = 17) n (%) M
Participants with at least one TEAE						
Grade 1 - Mild	0 (0) 2	1 (25.0) 2	1 (33.3) 4	2 (18.2) 8	1 (16.7) 5	3 (17.6) 13
Grade 2 - Moderate	1 (25.0) 3	0	1 (33.3) 1	2 (18.2) 4	1 (16.7) 1	3 (17.6) 5
Participants with at least one TEAE ≥moderate						
Diarrhoea	0	0	1 (33.3) 1	1 (9.1) 1	0	1 (5.9) 1
Nausea	1 (25.0) 1	0	0	1 (9.1) 1	0	1 (5.9) 1
Headache	1 (25.0) 1	0	0	1 (9.1) 1	0	1 (5.9) 1
Head discomfort	0	0	0	0	1 (16.7) 1	1 (5.9) 1
Photophobia	1 (25.0) 1	0	0	1 (9.1) 1	0	1 (5.9) 1

Abbreviations: PT = preferred term; SAD = single ascending dose; SOC = System organ class; TEAE = treatment-emergent adverse event.
TEAEs were defined as AEs that occurred or worsened from the first administration of study drug (MVD1 or placebo), up to the end of study.
For severity/causality of TEAE, the number of events were counted by each severity in Events (M) column, while the number of participants were counted once for the worst severity in Participant count (n).
Percentages were calculated (the denominator used for the calculation) based on the number of participants of each treatment group (N).
TEAEs were sorted by descending order of the counts (M) of SOC and PT in the Overall column, and alphabetically thereafter.
Coding: Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1
Source: Listing 16.2.7.1.A

Reference: Table 14.3.1.3A

Part B (MAD)

The majority of TEAEs reported across Part B (MAD) of the study were mild (Grade 1) in severity (102 events in 19 [79.2%] of 24 participants). There were 5 TEAEs which were moderate (Grade 2) in severity in 5 [20.8%] participants: 2 moderate TEAEs were reported for 2 participants in the 300 mg MVD1 group and 2 participants in the 400 mg MVD1 group, and 1 moderate TEAE was reported for 1 participant in the placebo group. The moderate TEAEs were as follows:

- Two moderate TEAEs experienced by 2 participants in the MVD1 300 mg group were reported as:
    - Cystitis, deemed unrelated to study drug, was not serious, lasted for 11 days and resolved with no concomitant medication or action with the study drug taken.
    - Back pain, deemed unrelated to study drug, was not serious, lasted for 25 minutes and resolved with no concomitant medication or action with the study drug taken.

- Two moderate TEAEs experienced by 2 participants in the MVD1 400 mg group were reported as:
    - Constipation, deemed unrelated to study drug, was not serious, lasted for 14 days, no action was taken with study drug and the event resolved after treatment with prune juice.
    - Headache, deemed possibly related to study drug, was not serious, lasted approximately 1 day, no action was taken with study drug and the event resolved after treatment with a cold pack.
- One moderate TEAE experienced by 1 participant in the placebo group was reported as post procedural contusion, deemed unrelated to study drug, was not serious, lasted for 27 days and resolved with no concomitant medication or action with the study drug taken.

There were no severe (Grade 3) or life-threatening (Grade 4) TEAEs, or TEAEs resulting in death (Grade 5) reported.

Table 12-G Summary of Treatment-emergent Adverse Events for Severity by PT – Part B (MAD) (Safety Analysis Set)

Severity/ Preferred Term	MVD1 200 mg (N = 6) n (%) M	MVD1 300 mg (N = 6) n (%) M	MVD1 400 mg (N = 6) n (%) M	MVD1 Pooled (N = 18) n (%) M	Placebo Pooled (N = 6) n (%) M	Overall (N = 24) n (%) M
Participants with at least one TEAE						
Grade 1 - Mild	6 (100) 16	4 (66.7) 24	4 (66.7) 32	14 (77.8) 72	5 (83.3) 30	19 (79.2) 102
Grade 2 - Moderate	0	2 (33.3) 2	2 (33.3) 2	4 (22.2) 4	1 (16.7) 1	5 (20.8) 5
Participants with at least one TEAE ≥moderate						
Post procedural contusion	0	0	0	0	1 (16.7) 1	1 (4.2) 1
Constipation	0	0	1 (16.7) 1	1 (5.6) 1	0	1 (4.2) 1
Headache	0	0	1 (16.7) 1	1 (5.6) 1	0	1 (4.2) 1
Back pain	0	1 (16.7) 1	0	1 (5.6) 1	0	1 (4.2) 1
Cystitis	0	1 (16.7) 1	0	1 (5.6) 1	0	1 (4.2) 1

Abbreviations: MAD = multiple ascending dose; SOC = system organ class; PT = preferred term; TEAE = treatment-emergent adverse event.
TEAEs were defined as AEs that occurred or worsened from the first administration of study drug (MVD1 or placebo), up to the end of study.
For severity/causality of TEAE, the number of events were counted by each severity in Events (M) column, while the number of participants were counted once for the worst severity in Participant count (n).
Percentages are calculated (the denominator used for the calculation) based on the number of participants of each treatment group (N).
TEAEs were sorted by descending order of the counts (M) of SOC and PT in the Overall column, and alphabetically thereafter.
Coding: Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1
Source: Listing 16.2.7.1.B

Reference: Table 14.3.1.3B

12.1.3.2 Relationship to Study Drug Administration

Part A (SAD)

A summary of treatment-related TEAEs by severity by SOC and PT is provided in Section 14.3.1 (Part A: Table 14.3.1.4A) and presented by PT in Section 14.3.1 (Part A: Table 14.3.1.7A) and below in Table 12-H.

In Part A (SAD), there were 5 [29.4%] of 17 participants with at least one treatment-related TEAE with a total of 8 related TEAEs. Related TEAEs reported only in participants who received MVD1 were in the SOC of Gastrointestinal Disorders (3 events in 2 [18.2%] of 11 participants), and Renal and Urinary Disorders (2 events in 2 [18.2%] of 11 participants). Related TEAEs in the remaining SOCs of Nervous System Disorders, and General Disorders and Administration Site Conditions were reported in the placebo group only.

The treatment-related TEAEs reported only in the MVD1 group by PT were diarrhoea (a total 2 events in 2 [18.2%] of 11 participants); renal tubular injury (a total 2 events in 2 [18.2%] of 11 participants) and nausea (1 event in 1 [9.1%] of 11 participants). These related events were reported in the 400 mg and/or 800 mg MVD1 groups. All other treatment-related TEAEs were single events reported in the placebo group of head discomfort, headache and fatigue.

Table 12-H Summary of Treatment-related Treatment-emergent Adverse Events by PT – Part A (SAD) (Safety Analysis Set)

	MVD1 200 mg (N = 4) n (%) M	MVD1 400 mg (N = 4) n (%) M	MVD1 800 mg (N = 3) n (%) M	MVD1 Pooled (N = 11) n (%) M	Placebo Pooled (N = 6) n (%) M	Overall (N = 17) n (%) M
Participants with at least one treatment-related TEAE	**0**	**1 (25.0) 1**	**2 (66.7) 4**	**3 (27.3) 5**	**2 (33.3) 3**	**5 (29.4) 8**
Diarrhoea	0	1 (25.0) 1	1 (33.3) 1	2 (18.2) 2	0	2 (11.8) 2
Renal tubular injury	0	0	2 (66.7) 2	2 (18.2) 2	0	2 (11.8) 2
Fatigue	0	0	0	0	1 (16.7) 1	1 (5.9) 1
Head discomfort	0	0	0	0	1 (16.7) 1	1 (5.9) 1
Headache	0	0	0	0	1 (16.7) 1	1 (5.9) 1
Nausea	0	0	1 (33.3) 1	1 (9.1) 1	0	1 (5.9) 1

Abbreviations: PT = preferred term; SAD = single ascending dose; SOC = system organ class; TEAE = treatment-emergent adverse event.
TEAEs were defined as AEs that occurred or worsened from the first administration of study drug (MVD1 or placebo), up to the end of study.
Treatment-related TEAEs were defined as any TEAEs reported with the causality of related to study treatment (MVD1 or placebo).
Percentages were calculated (the denominator used for the calculation) based on the number of participants of each treatment group (N).
If a participant had multiple occurrences of a TEAE, the participant was presented only once in the Participant count (n) column for a given PT. Occurrences were counted each time in the Events (M) column.

TEAEs were sorted by descending order of the counts (M) of PT in the Overall column, and alphabetically thereafter.
Coding: Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1
Source: Listing 16.2.7.1.A

Reference: Table 14.3.7.1A

A summary of treatment-related TEAEs by severity is provided in Section 14.3.1 (Part A: Table 14.3.1.5A) and presented in Table 12-I.

Overall, in Part A, the majority of treatment-related TEAEs were mild in severity with 6 TEAEs for 3 [17.6%] of 17 participants. There were 2 moderate, related TEAEs in 2 participants (one each in the MVD1 and placebo treatment groups) as follows:

- One participant in 800 mg MVD1 group experienced a moderate TEAE of diarrhoea on Day 1 that lasted approximately 9 hours, was deemed possibly related to study drug and was considered resolved on the same day. No concomitant medication or other action was taken.
- One participant in the placebo group experienced a moderate TEAE of head discomfort on Day 1 that lasted 6 hours, was deemed possibly related to study drug and was considered resolved on the same day. No concomitant medication or other action was taken.

Table 12-I Summary of Treatment-related Treatment-emergent Adverse Events for Severity by PT – Part A (SAD) (Safety Analysis Set)

Severity/ Preferred Term	MVD1 200 mg (N = 4) n (%) M	MVD1 400 mg (N = 4) n (%) M	MVD1 800 mg (N = 3) n (%) M	MVD1 Pooled (N = 11) n (%) M	Placebo Pooled (N = 6) n (%) M	Overall (N = 17) n (%) M
Participants with at least one treatment-related TEAE						
Grade 1 - Mild	0	1 (25.0) 1	1 (33.3) 3	2 (18.2) 4	1 (16.7) 2	3 (17.6) 6
Grade 2 - Moderate	0	0	1 (33.3) 1	1 (9.1) 1	1 (16.7) 1	2 (11.8) 2
Participants with at least one treatment-related TEAE ≥ moderate						
Diarrhoea	0	0	1 (33.3) 1	1 (9.1) 1	0	1 (5.9) 1
Head discomfort	0	0	0	0	1 (16.7) 1	1 (5.9) 1

Abbreviations: PT = preferred term; SAD = single ascending dose; SOC = system organ class; TEAE = treatment-emergent adverse event.
TEAEs were defined as AEs that occurred or worsened from the first administration of study drug (MVD1 or placebo), up to the end of study.
Treatment-related TEAEs were defined as any TEAEs reported with the causality of related to study treatment (MVD1 or placebo).
Percentages were calculated (the denominator used for the calculation) based on the number of participants of each treatment group (N).
If a participant had multiple occurrences of a TEAE, the participant was presented only once in the Participant count (n) column for a given SOC and PT. Occurrences were counted each time in the Events (M) column.
TEAEs were sorted by descending order of the counts (M) of SOC and PT in the Overall column, and alphabetically thereafter.
Coding: Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1

Source: Listing 16.2.7.1.A

Reference: Table 14.3.1.5A

Part B (MAD)

A summary of treatment-related TEAEs by severity by SOC and PT is provided in Section 14.3.1 (Table 14.3.1.4B) and presented by PT in Section 14.3.1 (Part B: Table 14.3.1.7B) and below in Table 12-J and Table 12-K.

In Part B (MAD), there were 13 [54.2%] of 24 participants with at least one treatment-related TEAE with a total of 18 TEAEs. The majority of treatment-related TEAEs were in the SOC of Gastrointestinal Disorders (9 events in 7 [29.2%] of 24 participants) and Nervous System Disorders (7 events in 6 [25.0%] of 24 participants), with incidence of related TEAEs similar in the MVD1 group and placebo group for both SOCs. In the remaining SOCs of General Disorders and Administration Site Conditions and Renal and Urinary Disorders treatment-related TEAEs were singles events reported in either the MVD1 or placebo group.

The most commonly reported treatment-related TEAEs in the MVD1 group by PT were headache (3 events in 3 [16.7%] of 18 participants) which were reported in the 200 mg MVD1 Group (1 event) and 400 mg MVD1 Group (2 events); diarrhoea (3 events in 3 [16.7%] of 18 participants) which were reported in the 200 mg MVD1 group (2 events) and the 300 mg MVD1 group (1 event); and dizziness (2 events in 2 [11.1%] of 18 participants) which were reported in the 200 mg and 400 mg MVD1 groups (1 event each). All the above related TEAEs were reported only in the MVD1 group except for headache which was also reported in the placebo group however at a higher incidence (2 events in 2 [33.3%] of 6 participants). All other treatment-related TEAEs were single events reported in either the MVD1 or placebo group.

Table 12-J Summary of Treatment-related Treatment-emergent Adverse Event by SOC and PT – Part B (MAD) (Safety Analysis Set)

System Organ Class Preferred Term	**MVD1 200 mg (N = 6) n (%) M**	**MVD1 300 mg (N = 6) n (%) M**	**MVD1 400 mg (N = 6) n (%) M**	**MVD1 Pooled (N = 18) n (%) M**	**Placebo Pooled (N = 6) n (%) M**	**Overall (N = 24) n (%) M**
Participants with at least one treatment-related TEAE	**4 (66.7) 4**	**2 (33.3) 4**	**3 (50.0) 5**	**9 (50.0) 13**	**4 (66.7) 5**	**13 (54.2) 18**
Gastrointestinal Disorders	**2 (33.3) 2**	**2 (33.3) 4**	**1 (16.7) 1**	**5 (27.8) 7**	**2 (33.3) 2**	**7 (29.2) 9**
Diarrhoea	2 (33.3) 2	1 (16.7) 1	0	3 (16.7) 3	0	3 (12.5) 3
Abdominal pain	0	1 (16.7) 1	0	1 (5.6) 1	0	1 (4.2) 1
Abdominal pain upper	0	1 (16.7) 1	0	1 (5.6) 1	0	1 (4.2) 1
Constipation	0	0	0	0	1 (16.7) 1	1 (4.2) 1
Dysphagia	0	0	0	0	1 (16.7) 1	1 (4.2) 1
Faeces soft	0	0	1 (16.7) 1	1 (5.6) 1	0	1 (4.2) 1
Nausea	0	1 (16.7) 1	0	1 (5.6) 1	0	1 (4.2) 1

System Organ Class Preferred Term	MVD1 200 mg (N = 6) n (%) M	MVD1 300 mg (N = 6) n (%) M	MVD1 400 mg (N = 6) n (%) M	MVD1 Pooled (N = 18) n (%) M	Placebo Pooled (N = 6) n (%) M	Overall (N = 24) n (%) M
Nervous System Disorders	**2 (33.3) 2**	**0**	**2 (33.3) 3**	**4 (22.2) 5**	**2 (33.3) 2**	**6 (25.0) 7**
Headache	1 (16.7) 1	0	2 (33.3) 2	3 (16.7) 3	2 (33.3) 2	5 (20.8) 5
Dizziness	1 (16.7) 1	0	1 (16.7) 1	2 (11.1) 2	0	2 (8.3) 2
General disorders and administration site conditions	**0**	**0**	**0**	**0**	**1 (16.7) 1**	**1 (4.2) 1**
Thirst	0	0	0	0	1 (16.7) 1	1 (4.2) 1
Renal and urinary disorders	**0**	**0**	**1 (16.7) 1**	**1 (5.6) 1**	**0**	**1 (4.2) 1**
Proteinuria	0	0	1 (16.7) 1	1 (5.6) 1	0	1 (4.2) 1

Abbreviations: AE = adverse event; MAD = multiple ascending dose; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
TEAEs were defined as AEs that occurred or worsened from the first administration of study drug (MVD1 or placebo), up to the end of study.
Treatment-related TEAEs were defined as any TEAEs reported with the causality of related to study treatment (MVD1 or placebo).
Percentages were calculated (the denominator used for the calculation) based on the number of participants of each treatment group (N).
If a participant had multiple occurrences of a TEAE, the participant were presented only once in the Participant count (n) column for a given SOC and PT. Occurrences were counted each time in the Events (M) column.
TEAEs were sorted by descending order of the counts (M) of SOC and PT in the Overall column, and alphabetically thereafter.
Coding: Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1
Source: Listing 16.2.7.1.B

Reference: Table 14.3.1.4B

A summary of treatment-related TEAEs by severity is provided in Section 14.3.1 (Part B: Table 14.3.1.5B) and presented in Table 12-K.

Table 12-K Summary of Treatment-related Treatment-emergent Adverse Event for Severity by SOC and PT – Part B (MAD) (Safety Analysis Set)

System Organ Class Severity/ Preferred Term	MVD1 200 mg (N = 6) n (%) M	MVD1 300 mg (N = 6) n (%) M	MVD1 400 mg (N = 6) n (%) M	MVD1 Pooled (N = 18) n (%) M	Placebo Pooled (N = 6) n (%) M	Overall (N = 24) n (%) M
Participants with at least one treatment-related TEAE						
Grade 1 - Mild	4 (66.7) 4	2 (33.3) 4	2 (33.3) 4	8 (44.4) 12	4 (66.7) 5	12 (50.0) 17
Grade 2 - Moderate	0	0	1 (16.7) 1	1 (5.6) 1	0	1 (4.2) 1
Participants with at least one treatment-related TEAE ≥moderate						
Nervous system disorders						
Headache	0	0	1 (16.7) 1	1 (5.6) 1	0	1 (4.2) 1

Abbreviations: AE = adverse event; MAD = multiple ascending dose; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
TEAEs were defined as AEs that occurred or worsened from the first administration of study drug (MVD1 or placebo), up to the end of study.
Treatment-related TEAEs were defined as any TEAEs reported with the causality of related to study treatment (MVD1 or placebo).
Percentages were calculated (the denominator used for the calculation) based on the number of participants of each treatment group (N).
If a participant had multiple occurrences of a TEAE, the participant was presented only once in the Participant count (n) column for a given SOC and PT. Occurrences are counted each time in the Events (M) column.
TEAEs were sorted by descending order of the counts (M) of SOC and PT in the Overall column, and alphabetically thereafter.
Coding: Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1
Source: Listing 16.2.7.1.B Reference: Table 14.3.1.5B

Overall, in Part B, the majority of treatment-related TEAEs were mild in severity with 17 TEAEs for 12 [50.0%] of 24 participants. There was 1 moderate related TEAE of headache in 1 participant (400 mg MVD1). The moderate TEAE of headache, was deemed possibly related to study drug, commenced on Day 12, lasted approximately 1 day before resolving. A cold pack was used to treat this event.

12.1.3.3 Ongoing Adverse Events

Across Part A (SAD) and Part B (MAD) all TEAEs were considered resolved/recovered. There were no ongoing TEAEs at the completion of the study.

12.1.3.4 Concomitant Medications and Procedures

A summary of the use of concomitant medication is provided in Section 14.1 (Part A: Table 14.1.6A and Part B: Table 14.1.6B). A complete list of concomitant medication use by participant and concomitant procedures by participant is provided in Appendix 16.2.10 (Part A: Listing 16.2.10.2A and Part B: Listing 16.2.10.2B and in Part A: Listing 16.2.10.3A and Part B: Listing 16.2.10.3B).

In Part A (SAD), 5 (29.4%) of 17 participants reported the use of at least 1 concomitant medication, with a similar incidence in the MVD1 (3 [27.3%] of 11 participants) and placebo group (2 [33.3%] of 6 participants).

Concomitant medications ongoing from before dosing were contraceptives and were used by 3 (17.6%) of 17 participants. Ibuprofen was used by 1 (5.9%) of 17 participants to treat a pre-existing condition of dysmenorrhea.

There were 2 participants who reported the use of concomitant medication for the treatment of TEAEs as follows:

- 1 participant (200 mg MVD1) reported the use of;
  - Paracetamol (1000 mg/ 3 times/ orally), for the treatment of headache, which was reported as a TEAE on Day 1;
  - Codeine phosphate; paracetamol (1 tablet/ 3 times/ orally), for the treatment of headache, which was reported as a TEAE on Day 1;
  - Ondansetron hydrochloride (4 mg/ twice/ sublingually) for the treatment of nausea.

- 1 participant (Placebo) reported the use of;
    - Paracetamol (1000 mg/ once/ orally), for the treatment of headache, which was reported as a TEAE on Day 1;

There were no concomitant procedures reported in Part A (SAD).

In Part B (MAD), 7 (29.2%) of 24 participants reported the use of at least 1 concomitant medication, with a similar incidence in the MVD1 (5 [27.8%] of 18 participants) and placebo group (2 [33.3%] of 6 participants).

Concomitant medications ongoing from before dosing were contraceptives used by 2 (8.3%) of 24 participants. Other concomitant medications used were citric acid; sodium bicarbonate; sodium citrate; tartaric acid (ural) used by 1 (4.2%0 of 24 participants, paracetamol in 2 (8.3%) of 24 participants, cetrizine used by 1 (4.2%) of 24 participants, docusate sodium; sennoside A+B used by 1 (4.2%) of 24 participants and cefalexin used by 1 (4.2%) of 24 participants.

There were 5 participants who reported the use of concomitant medication for the treatment of TEAEs as follows:

- Two participants (200 mg and 400 mg MVD1) took paracetamol for a headache (1000 mg/ once/ orally).
- One participant (300 mg MVD1) took;
    - Citric acid; sodium bicarbonate; sodium citrate; tartaric acid (4 mg/ once/ orally) on three occasions for a urinary tract infection.
    - Cefalexin (500 mg/ BID/ orally) on 5 occasions for a urinary tract infection.
- One participant (400 mg MVD1) took docusate sodium; sennoside A+b for constipation for four days (2 tablets/ BID/ orally).
- One participant (Placebo) took cetirizine for ongoing dust allergy (intermittent hay fever) on two occasions (10 mg /orally).

There were no concomitant procedures reported in Part B (MAD).

12.1.4 Listing of Adverse Events by Participant

A complete list of AEs reported by participant is presented in Appendix 16.2.7 (Part A: Listing 16.2.7.1A and Part B: Listing 16.2.7.1B).

12.2 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

12.2.1 Deaths and Other Serious Adverse Events

There were no SAEs reported in Part A (Listing 16.2.7.2A and Table 14.3.2.1A and Table 14.3.2.2A) or Part B (Listing 16.2.7.2B and Table 14.3.2.1B and Table 14.3.2.2B).

There were no deaths reported in Part A (Listing 16.2.7.4A and Listing 16.2.9.6A and Table14.3.2.4A) or Part B (Listing 16.2.7.4B and Listing 16.2.9.8B and Table 14.3.2.4B).

12.2.2 Other Significant Adverse Events

Part A (SAD)

There were no TEAEs leading to study drug discontinuation or study withdrawal in Part A (SAD) (Listing 16.2.7.3A and Table 14.3.2.3A).

Part B (MAD)

In Part B (MAD), one participant in the 200 mg MVD1 group experienced a TEAE of proteinuria with a duration of 2 days. The TEAE was deemed mild and unrelated to study treatment. The participant had abnormal clinically significant ACR results on Day 2 dose 2 with increased ACR seen on Day 3 dose 2. ACR levels returned to baseline for the remainder of the study. Under PI advice the study drug was withdrawn after the first dose on Day 2 and the participant discontinued from the study (Listing 16.2.7.3.B and Table 14.3.2.3B).

One participant in the 400 mg MVD1 group experienced a TEAE of proteinuria with a duration of 2 days. The TEAE was deemed mild and probably related to study treatment. The participant had abnormal clinically significant ACR results on Day 1 dose 2, abnormal not clinically significant ACR levels on Day 2, dose 1. ACR levels returned to baseline for the remainder of the study. Dosing with the study drug was interrupted with the participant not receiving MVD1 doses after Day 1 dose 2 until being re-administered on Day 5 dose 2.

One participant in the placebo group did not receive a dose of study drug from Dose 2 on Day 2 to the final dose on Day 15 (i.e., received 3 of the 29 scheduled doses) as the participant was withdrawn from the study due to a major inclusion/exclusion protocol deviation i.e., was younger than 25 years of age at screening (Section 10.2).

12.3 CLINICAL LABORATORY EVALUATION

12.3.1 Listing of Individual Laboratory Measurements by Participant and Each Abnormal Laboratory Value

A complete list of laboratory parameters including abnormal CS results reported by participant are provided in Appendix 16.2.8 (Haematology: Part A: Listing 16.2.8.1A and Part B: Listing 16.2.8.1B, Clinical Chemistry: Part A: Listing 16.2.8.2A and Part B: Listing 16.2.8.2B, Coagulation: Part A: Listing 16.2.8.3A and Part B: Listing 16.2.8.3B, Urinalysis: Part A: Listing 16.2.8.4A and Part B: Listing 16.2.8.4B, Urine Microscope: Part A: Listing 16.2.8.5A and Part B: Listing 16.2.8.5B, Urinalysis (Protein Dipstick): Part B: Listing 16.2.8.6B, Urinalysis (ACR): Part B: Listing 16.2.8.7B).

12.3.2 Evaluation of Haematology, Serum Chemistry, Coagulation, and Urinalysis Parameters

A summary of laboratory parameters is provided in Section 14.3.4 (Haematology: Part A: Table 14.3.4.1.1A and Part A: Table 14.3.4.1.1B, Part A: 14.3.4.1.2A and Part B: Table 14.3.4.1.2B, Part A: 14.3.4.1.3A and Part B: Table 14.3.4.1.3B; Clinical Chemistry: Part A: Table 14.3.4.2.1A and Part B: Table 14.3.4.2.1B, Part A: Table 14.3.4.2.2A and Part B: Table 14.3.4.2.2B and Part A: Table 14.3.4.2.3A and Part B: Table 14.3.4.2.3B; Coagulation: Part A: Table 14.3.4.3.1A and Part B: Table 14.3.4.3.1B, Part A: Table 14.3.4.3.2A and Part B: Table14.3.4.3.2B and Part A: Table 14.3.4.3.3A and Part B: Table 14.3.4.3.3B; Urinalysis:

Part A: Table 14.3.4.4.1A and Part B: Table 14.3.4.4.1B and Part A: Table 14.3.4.4.2A and Part B: Table 14.3.4.4.2B).

Across Part A of the study, there were no abnormalities in hematology, serum chemistry or coagulation parameters which were deemed by the PI to be CS or met the criteria of an AE. Abnormalities in hematology parameters that were NCS did not appear to have any trend with increasing MVD1 dose.

Across Part A of the study, 2 (11.8%) of 17 participants had abnormal urinalysis results. There were 2 (66.7%) of 3 participants administered 800 mg MVD1 that had CS abnormal results for Glucose on Day 2 and 3 (which were NCS by Day 4). Two (66.7%) of 3 participants administered 800 mg MVD1 had abnormal CS protein results on Day 2 (Day 3 - unscheduled) and Day 4. The CS abnormal results in protein were associated with 2 TEAEs of renal tubular injury, considered mild in severity. The TEAE lasted for 6 days in both participants and was deemed by the PI to be definitely related to study treatment.

Across Part B of the study, there were two abnormalities in hematology parameters which were deemed by the PI to be CS or met the criteria of an AE. One participant who received 300 mg MVD1 had an abnormally high leukocyte value of 12.3×10^9/L (normal range 4.0, 11.0×10^9/L) on Day 11 and an abnormally high neutrophil value of 9.3×10^9/L (normal range 2.0, 8.0×10^9/L) on Day 11. Both values returned within the normal range by Day 18. The increased leukocyte values were associated with a moderate TEAE of cystitis (which occurred for 11 days). The TEAE was considered not to be related to MVD1 administration.

Across Part B of the study, there were no abnormalities in serum chemistry or coagulation parameters which were deemed by the PI to be CS or met the criteria of an AE. Abnormalities that were NCS did not appear to have any trend with increasing MVD1 dose.

Across Part B of the study, 1 (4.2%) of 24 participants had abnormal urinalysis results. There was 1 (16.7%) of 6 participants administered 300 mg MVD1 that had abnormal CS results for leukocyte esterase on Days 5, 6, and 7 and returned to normal by Day 18. These abnormal results were associated with a moderate (unrelated) TEAE of cystitis, which was considered recovered/resolved after treatment with cefalexin and citric acid; sodium bicarbonate; sodium citrate; tartaric acid.

12.4 VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

12.4.1 Vital Signs

A summary of vital signs is provided in Section 14.3.5 (Part A: Listing 16.2.9.1A and Part B: 16.2.9.1B; Part A: Table 14.3.5.1.1A and Part B: Table 14.3.5.1.1B, Part A: Table 14.3.5.1.2A and Part B: Table 14.3.5.1.2B, Part A: Table 14.3.5.1.3A and Part B: Table 14.3.5.1.3B, Part B: Table 14.3.5.1.4B).

Across Part A of the study, there were no abnormalities in vital signs which were deemed by the PI to be CS or met the criteria of an AE. Vital sign parameters were within normal range at Baseline for all participants. Abnormal vital sign parameters did occur after study drug was administered but were all NCS and did not appear to increase in incidence with increasing

MVD1 dose. There were no apparent treatment-related trends (MVD1 versus placebo) and no apparent trends in vital sign changes over time.

In Part B (MAD), there were abnormalities in vital signs (increased temperature [38.1°C]) on Day 4 (pre-dose) deemed by the PI to be CS in 1 (16.7%) of 6 participants in the 300 mg MVD1 group. Vital sign parameters were within normal range at Baseline for all participants in this part of the study. Abnormal vital sign parameters did occur after study drug was administered but did not appear to increase in incidence with increasing MVD1 dose. There were no apparent treatment related trends (MVD1 versus placebo) and no apparent trends in vital sign changes post-dose 1 or 2 or trends over time.

12.4.2 Physical Examinations

A complete list of physical examination results by participant are provided in Appendix 16.2.8 (Part A: Listing 16.2.9.3A and Part B: Listing 16.2.9.3B).

In Part A (SAD), there were no abnormal physical examination findings deemed by the PI to be CS or met the criteria of an AE.

In Part B (MAD), there were CS abnormal physical examination findings post-dose which were reported as TEAEs.

12.4.3 Electrocardiography

Across Part A and Part B of the study, there were no abnormalities in ECG parameters which were deemed by the PI to be CS or met the criteria of an AE. ECG parameters were normal at Baseline for all participants in this part of the study. Abnormal ECG parameters did occur after study drug was administered but were all NCS and did not appear to increase in incidence with increasing MVD1 dose. There were no apparent treatment related trends (MVD1 vs Placebo) and no apparent trends in ECG changes over time. A summary of ECG data is provided in Section 14.3.5 (Part A: Listing 16.2.9.2A and Part B: Listing 16.2.9.2B; Part A: Table 14.3.5.2.1A and Part B: Table 14.3.5.2.1B, Part A: Table 14.3.5.2.2A and Part B: Table 14.3.5.2.2B, Part A: Table 14.3.5.2.3A and Part B: Table 14.3.5.2.3B and Table 14.3.5.2.4B).

12.4.4 Stool Diary

Stool diary assessments by participant are listed in Listing 16.2.9.5A (Part A [SAD]) and Listing 16.2.9.7B (Part B [MAD]).

The effects of study treatments on the gastrointestinal system were monitored using a stool diary. Participants completed the stool diary starting on Day 1 until discharge on Day 4 (Part A) or Day 18 (Part B).

In Part A (SAD), there were 3 participants in the 200 mg MVD1 group who had no change in their stool score. The greatest stool score change was in the 400 mg MVD1 group where 1 participant reported a change from 2 to 7 (5-point change); 2 participants in this group had no change. The 800 mg MVD1 group had 1 participant who experienced a change from a stool score of 3 to 7 (4-point change). No overt changes in stool scores were observed for participants who received placebo.

In Part B (MAD), in each of the MVD1 groups (200 mg, 300 mg and 400 mg) 1 participant had a stool score change from 1 to 7 (6-point change). Two participants in the 400 mg MVD1 group had a change of 5-points in their stool scores (from 1 to 6 and 2 to 7, respectively). Most of the participants in the 200 mg MVD1 group had a stool score change of 4 points, with only 1 participant in each of the 300 mg MVD1 and 400 mg MVD1 groups having this degree of change. Only 1 participant in the 300 mg MVD1 group had no change to their stool score.

12.4.5 Nutritional

In Part B (MAD) only, a SNAQ was completed by participants to assess the effects of study treatments on appetite. The questionnaire was completed on Day -1 after dinner, and again on Day 15, after dinner (refer to Section 9.5.3.8).

When appetite was assessed, most participants in the 200 mg MVD1 group reported their appetite improving over time. One participant in the 300 mg MVD1 group reported their appetite reduced from Day -1 to Day 15 (fullness reduced from eating most of the food to eating about a third of a plateful), their fullness score did not change over time. Half of the participants in the 400 mg MVD1 group reported their appetite improving, with the other half reporting a reduction in their appetite from Day -1 to Day 15 (fullness reduced). Placebo results demonstrated a wide range of both improved and reduced appetite over time. One participant in the 300 mg MVD1 and one participant in the 400 mg MVD1 group reported a reduction in the number of meals consumed a day (3 meals a day to 2 meals a day).

12.5 SAFETY CONCLUSIONS

Part A (SAD)

Part A (SAD) of the study demonstrated that a single oral administration of MVD1 at doses ranging from 200 mg to 800 mg in healthy normal weight and overweight adult volunteers was generally well tolerated. There was no dose related trend in TEAE incidence, no serious TEAEs or TEAEs resulting in discontinuation from the study or death were observed. The majority of TEAEs were mild in severity. Three participants, one in each of the MVD1 treatment groups experienced moderate TEAEs. There were no severe or life threatening TEAEs reported.

Across study Part A (SAD), the most commonly reported TEAEs by SOC were Nervous System disorders which were reported at a higher incidence in the participants administered placebo compared to participants administered MVD1. The majority of TEAEs in this SOC were headache. Other TEAEs reported included head discomfort and presyncope. The next most reported TEAEs by SOC were Gastrointestinal disorders which were diarrhoea reported in participants administered MVD1 (1 participant each administered 400 mg MVD1 and 800 mg MVD1). Moderate TEAEs experienced by participants who received MVD1 were headache deemed not related to study drug while head discomfort and diarrhoea, both deemed related to administration of MVD1. Two out of three participants treated with 800 mg MVD1 experienced mild TEAEs of renal tubular damage, both considered related to study treatment and resolved/recovered at the end of study.

Across Part A of the study, there were no abnormalities in vital signs which were deemed by the PI to be CS or met the criteria of an AE.

In Part A (SAD), the greatest stool score change was in the 400 mg MVD1 group where 1 participant reported a change from 2 to 7 (5-point change). The 800 mg MVD1 group had one participant who experienced a change from a stool score of 3 to 7 (4-point change). No overt changes in stool scores were observed for participants who received placebo.

Part B (MAD)

Part B (MAD) of the study demonstrated that multiple oral administrations of MVD1 at doses ranging from 200 mg to 400 mg in healthy overweight or obese adult volunteers was well tolerated. There appeared to be an increase in the incidence of TEAEs with increasing MVD1 dose, however, no serious TEAEs were reported. No deaths were reported. The majority of TEAEs were mild in severity. Four participants (2 in 300 mg MVD1 and 2 in 400 mg MVD1 cohorts) experienced moderate TEAEs. There were no severe or life threatening TEAEs reported. One participant in the 200 mg MVD1 group had baseline proteinuria, which worsened with the use of MVD1. The participant experienced a TEAE (proteinuria) resulting in study drug being withdrawn and their discontinuation from the study. One participant in the 400 mg MVD1 group had study drug interrupted due to a TEAE of proteinuria (mild, probably related to study drug), however recommenced dosing and completed the study on PI advice.

The most commonly reported TEAEs by SOC were Injury, poisoning and procedural complications, which were reported at a lower incidence in the participants administered placebo compared to participants administered MVD1. Commonly occurring TEAEs (reported in at least 2 or more participants in a treatment group) were post procedural contusion, procedural pain, post procedural hematoma, diarrhoea, constipation, nausea, catheter site pain, fatigue, headache, dizziness, back pain and proteinuria. Moderate TEAEs experienced by participants who received MVD1 were headache deemed related to study drug, cystitis, constipation and procedural contusion, deemed not related to administration of MVD1.

In Part B (MAD), there were abnormalities in vital signs on Day 4 (pre-dose) deemed by the PI to be CS in 1 (16.7%) of 6 participants in the 300 mg MVD1 group.

In Part B (MAD), most of the participants in the 200 mg MVD1 group had a stool score change of 4 points, with only one participant in each of the 300 mg MVD1 and 400 mg MVD1 groups having this degree of change. In each of the MVD1 groups (200 mg, 300 mg and 400 mg) one participant had a stool score change from 1 to 7 (6-point change). Two participants in the 400 mg MVD1 group had a change of 5-points in their stool scores (from 1 to 6 and 2 to 7, respectively). Only 1 participant in the 300 mg MVD1 group had no change to their stool score.

When appetite was assessed, approximately half of the participants administered MVD1 reported their appetite improved over time. Participants administered placebo reported a wide range of both improved and reduced appetite over time.

Overall, MVD1 when administered orally as a single or multiple doses was safe and generally well tolerated in healthy normal weight, overweight and obese adults.

13. DISCUSSION AND OVERALL CONCLUSIONS

This was a Phase 1, FIH, single and multiple dose escalation clinical study conducted in normal weight or overweight healthy adult, and healthy overweight or obese adult volunteers, respectively. The safety, tolerability, PK and PD of MVD1 following single and multiple oral dose administrations was evaluated using a randomised, double-blind, placebo-controlled study design.

The safety and tolerability data from Part A and Part B of the study suggest that MVD1 was well tolerated and appeared safe when administered as single oral doses of up to 800 mg and multiple oral doses up to 400 mg in healthy adult normal weight or overweight and overweight or obese participants, respectively.

Single dose PK characteristics of MVD1 were assessed in 11 participants, for ascending dose levels of 200, 400 and 800 mg. Multiple dose PK characteristics of MVD1 were assessed in 18 participants, for ascending total daily dose levels of 200, 300, and 400 mg.

The average elimination half-life of MVD1 was approximately 1.5-2.0 hours. There was minimal accumulation over the 15 days of multiple dosing BID, with pre-dose trough levels of MVD1 from Day 2 onwards generally quantifiable but quite low.

For the metabolite M1, the average elimination half-life was 1.5-2.5 hours. There was minimal accumulation for the metabolites, with pre-dose trough levels of M1 generally quantifiable but quite low. The ratio of metabolite M1 to MVD1 remained constant at approximately 30-40% as the dose of MVD1 increased.

For single dose, the mean exposure parameters increased monotonically by dose level in an approximately dose proportional manner, however the power model analyses did not meet criteria for dose proportionality for MVD1. For multiple dosing, the power model accounted for less than 50% of the variability in exposure versus dose except for MVD1 AUC_{0-12} on Day 1 and also dose dependence was noted to be non-monotonic on Day 15.

Median T_{max} varied across dose levels with no dose related trend.

There was little MVD1 excreted unchanged in urine (< 10%). It is noted that there was no noticeable increase in amount excreted at the highest dose level for single and multiple dosing. More of the drug was excreted in urine as metabolite M1 than as unchanged MVD1.

Pharmacodynamic data from Part B suggest there appeared to be no overall changes in the PD biomarkers assessed (i.e., glucose, insulin, C-peptide, fructosamine, free fatty acids, triglycerides, leptin levels, OGTT and cytokines) when participants were given multiple doses of MVD1. After single administration, there was a treatment effect on the Bristol stool chart scores with at least a 4-point change in stool scores observed in both the 400 mg and 800 mg MVD1 group. Following multiple administrations of MVD1, the largest change in stool scores was 6 points seen for three participants following 200 mg, 300 mg and 400 mg of MVD1.Bristol stool scores demonstrated at least a 4-point change after multiple MVD1 administrations. Following multiple administrations of MVD1 at doses of at least 300 mg/day, particularly at 400 mg/day, after 15 days of treatment a significant body weight reduction compared to placebo was observed demonstrating encouraging efficacy of MVD1.

The presence of MVD1 was not detected in white adipose samples of participants in any of the MAD (M1 – M3) cohorts on Day -1 or Day 7.

All participants who received placebo reported 'No Change' in their perception of change to their health following multiple doses of MVD1. There was one participant in each of the MVD1 groups who reported improvement, with 2 participants in the 200 mg MVD1 group and one participant in the 400 mg MVD1 group reporting their perception of change being slightly worse.

In conclusion, single and multiple doses of MVD1 up to 800 mg demonstrated an overall favourable safety and tolerability profile and demonstrating encouraging efficacy of MVD1 in normal weight, overweight and obese adults.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Table 14.1.1.A Summary of Participant Disposition – Part A (SAD) (All Randomised Analysis Set)

Table 14.1.1.B Summary of Participant Disposition – Part B (MAD) (All Randomised Analysis Set)

Table 14.1.2.A Summary of Analysis Populations – Part A (SAD) (All Randomised Analysis Set)

Table 14.1.2.B Summary of Analysis Populations – Part B (MAD) (All Randomised Analysis Set)

Table 14.1.3.A Summary of Protocol Deviations – Part A (SAD) (All Randomised Analysis Set)

Table 14.1.3.B Summary of Protocol Deviations – Part B (MAD) (All Randomised Analysis Set)

Table 14.1.4.A Summary of Demographics – Part A (SAD) (All Randomised Analysis Set)

Table 14.1.4.B Summary of Demographics – Part B (MAD) (All Randomised Analysis Set)

Table 14.1.5.A Summary of Prior Medications – Part A (SAD) (Safety Analysis Set)

Table 14.1.5.B Summary of Prior Medications – Part B (MAD) (Safety Analysis Set)

Table 14.1.6.A Summary of Concomitant Medications – Part A (SAD) (Safety Analysis Set)

Table 14.1.6.B Summary of Concomitant Medications – Part B (MAD) (Safety Analysis Set)

Table 14.1.7.B Summary of Treatment Compliance and Exposure – Part B (MAD) (Safety Analysis Set)

14.2 Pharmacokinetic and Pharmacodynamic Data

14.2.1 Pharmacokinetic Plasma Concentration Summaries

Table 14.2.1.1.A Individual and Summary of Plasma Concentrations over time by Treatment and Analyte – Part A (SAD) (Pharmacokinetic Analysis Set)

Table 14.2.1.1.B Individual and Summary of Plasma Concentrations over time by Treatment and Analyte – Part B (MAD) (Pharmacokinetic Analysis Set)

Table 14.2.1.6.A Summary of Plasma Pharmacokinetic Parameters by Treatment and Analyte – Part A (SAD) (Pharmacokinetic Analysis Set)

Table 14.2.1.6.B Summary of Plasma Pharmacokinetic Parameters by Treatment and Analyte – Part B (MAD) (Pharmacokinetic Analysis Set)

Table 14.2.1.8.A Assessment of Dose Proportionality – Part A (SAD) (Pharmacokinetic Analysis Set)

14.3 Safety Data – Adverse Events

14.3.1 Adverse Event Summaries

Table 14.3.1.1.A Overall Summary of Treatment Emergent Adverse Event – Part A (SAD) (Safety Analysis Set)

Table 14.3.1.1.B Overall Summary of Treatment Emergent Adverse Event – Part B (MAD) (Safety Analysis Set)

Table 14.3.1.2.A Summary of Treatment Emergent Adverse Event by System Organ Class and Preferred Term – Part A (SAD) (Safety Analysis Set)

Table 14.3.1.2.B Summary of Treatment Emergent Adverse Event by System Organ Class and Preferred Term – Part B (MAD) (Safety Analysis Set)

Table 14.3.1.3.A Summary of Treatment Emergent Adverse Events for Severity by System Organ Class and Preferred Term – Part A (SAD) (Safety Analysis Set)

Table 14.3.1.3.B Summary of Treatment Emergent Adverse Events for Severity by System Organ Class and Preferred Term – Part B (MAD) (Safety Analysis Set)

Table 14.3.1.4.A Summary of Treatment-Related Treatment Emergent Adverse Event by System Organ Class and Preferred Term – Part A (SAD) (Safety Analysis Set)

Table 14.3.1.4.B Summary of Treatment-Related Treatment Emergent Adverse Event by System Organ Class and Preferred Term – Part B (MAD) (Safety Analysis Set)

Table 14.3.1.5.A Summary of Treatment-Related Treatment Emergent Adverse Events for Severity by System Organ Class and Preferred Term – Part A (SAD) (Safety Analysis Set)

Table 14.3.1.5.B Summary of Treatment-Related Treatment Emergent Adverse Events for Severity by System Organ Class and Preferred Term – Part B (MAD) (Safety Analysis Set)

Table 14.3.1.6.A Summary of Treatment Emergent Adverse Event by Preferred Term – Part A (SAD) (Safety Analysis Set)

Table 14.3.1.6.B Summary of Treatment Emergent Adverse Event by Preferred Term – Part B (MAD) (Safety Analysis Set)

Table 14.3.1.7.A Summary of Treatment-Related Treatment Emergent Adverse Event by Preferred Term – Part A (SAD) (Safety Analysis Set)

Table 14.3.1.7.B Summary of Treatment-Related Treatment Emergent Adverse Event by Preferred Term – Part B (MAD) (Safety Analysis Set)

14.3.2 Deaths, Other Serious and Significant Adverse Events

Table 14.3.2.1.A Serious Treatment Emergent Adverse Event by System Organ Class and Preferred Term – Part A (SAD) (Safety Analysis Set)

14.3.3 Narratives of Deaths, Other Serious, and Certain Other Significant Adverse Events

Not Applicable

14.3.4 Clinical Laboratory Assessments

14.3.5 Vital Signs

15. REFERENCE LIST

1. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-Specific Excess Deaths Associated With Underweight, Overweight, and Obesity. JAMA. 2007;298(17):2028–2037. Doi:10.1001/jama.298.17.2028
2. Goldfine A.B, Silver R, Aldhahi W, *et al*., (2008), Use of Salsalate to Target Inflammation in the Treatment of Insulin Resistance and Type 2 Diabetes. Clinical and Translational Science, 1: 36-43. https://doi.org/10.1111/j.1752-8062.2008.00026.x
3. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993 Jan 1;259(5091):87-91. Doi: 10.1126/science.7678183. PMID: 7678183.
4. Zatterale F, Longo M, Naderi J, Raciti GA, Desiderio A, Miele C, Beguinot F. Chronic Adipose Tissue Inflammation Linking Obesity to Insulin Resistance and Type 2 Diabetes. Front Physiol. 2020 Jan 29;10:1607. doi: 10.3389/fphys.2019.01607. PMID: 32063863; PMCID: PMC7000657.
5. Goldfine AB, Fonseca V, Jablonski KA, *et al*., Targeting Inflammation Using Salsalate in Type 2 Diabetes Study Team. Salicylate (salsalate) in patients with type 2 diabetes: a randomised trial. Ann Intern Med. 2013 Jul 2;159(1):1-12. doi: 10.7326/0003-4819-159-1-201307020-00003. PMID: 23817699; PMCID: PMC4128629.
6. Goldfine AB, Fonseca V, Jablonski KA, *et al*., TINSAL-T2D (Targeting Inflammation Using Salsalate in Type 2 Diabetes) Study Team. The effects of salsalate on glycemic control in patients with type 2 diabetes: a randomised trial. Ann Intern Med. 2010 Mar 16;152(6):346-57. doi: 10.7326/0003-4819-152-6-201003160-00004. PMID: 20231565; PMCID: PMC3138470.
7. Salastekar N, Desai T, Hauser T, *et al*., TINSAL-CVD study team. Salsalate improves glycaemia in overweight persons with diabetes risk factors of stable statin-treated cardiovascular disease: A 30-month randomised placebo-controlled trial. Diabetes Obes Metab. 2017 Oct;19(10):1458-1462. doi: 10.1111/dom.12940. Epub 2017 Jul 6. PMID: 28295931; PMCID: PMC5599319.
8. Dapueto R, Rodriguez-Duarte J, Galliussi G, et al., A novel nitroalkene vitamin E analogue inhibits the NLRP3 inflammasome and protects against inflammation and glucose intolerance triggered by obesity. Redox Biol. 2021 Feb;39:101833. doi: 10.1016/j.redox.2020.101833. Epub 2020 Dec 15. PMID: 33352465; PMCID: PMC7750735.
9. Ibarburu S, Kovacs M, Varela V, et al., A Nitroalkene Benzoic Acid Derivative Targets Reactive Microglia and Prolongs Survival in an Inherited Model of ALS via NF-κB Inhibition. Neurotherapeutics. 2021 Jan;18(1):309-325. doi: 10.1007/s13311-020-00953-z. Epub 2020 Oct 28. PMID: 33118131; PMCID: PMC8116482.
10. Rodriguez-Duarte J, Galliussi G, Dapueto R, et al., A novel nitroalkene-α-tocopherol analogue inhibits inflammation and ameliorates atherosclerosis in Apo E knockout mice. Br J Pharmacol. 2019 Mar;176(6):757-772. doi: 10.1111/bph.14561. Epub 2019 Feb 3. PMID: 30588602; PMCID: PMC6393233.

11. Villacorta L, Gao Z, Schopfer FJ, et al., Nitro-fatty acids in cardiovascular regulation and diseases: characteristics and molecular mechanisms. Front Biosci (Landmark Ed). 2016 Jan 1;21(4):873-89. doi: 10.2741/4425. PMID: 26709810; PMCID: PMC4748372.

12. Batthyany C, Schopfer FJ, Baker PR, et al., Reversible post-translational modification of proteins by nitrated fatty acids in vivo. J Biol Chem. 2006 Jul 21;281(29):20450-63. doi: 10.1074/jbc.M602814200. Epub 2006 May 8. PMID: 16682416; PMCID: PMC2169497.

13. Kelley EE, Baust J, Bonacci G, *et al.*, Fatty acid nitroalkenes ameliorate glucose intolerance and pulmonary hypertension in high-fat diet-induced obesity. Cardiovasc Res. 2014 Mar 1;101(3):352-63. doi: 10.1093/cvr/cvt341. Epub 2014 Jan 2. PMID: 24385344; PMCID: PMC3928004.

14. Rom O, Xu G, Guo Y, *et al*., Nitro-fatty acids protect against steatosis and fibrosis during development of nonalcoholic fatty liver disease in mice. EBioMedicine. 2019 Mar;41:62-72. doi: 10.1016/j.ebiom.2019.02.019. Epub 2019 Feb 13. PMID: 30772307; PMCID: PMC6444056.

15. Khoo NKH, Fazzari M, Chartoumpekis DV, *et al*., Electrophilic nitro-oleic acid reverses obesity-induced hepatic steatosis. Redox Biol. 2019 Apr;22:101132. doi: 10.1016/j.redox.2019.101132. Epub 2019 Feb 1. PMID: 30769284; PMCID: PMC6375063.

16. APPENDICES

16.1 STUDY INFORMATION

16.1.1 Protocol and Protocol Amendments

- Protocol Version 2.0, dated 08 Dec 2022
- Protocol Version 3.0, dated 16 Feb 2023
- Protocol Clarification Memo_01, dated 16 Mar 2023
- Protocol Version 4.0, dated 27 Aug 2023
- Protocol Clarification Memo_02, dated 14 Nov 2023
- Protocol Clarification Memo_03, dated 19 Dec 2023
- Protocol Clarification Memo_04, dated 03 Jan 2024
- Protocol Clarification Memo_05, dated 12 Jan 2024
- Protocol Clarification Memo_06, dated 09 Feb 2024
- Protocol Clarification Memo_07, dated 05 Jun 2024

16.1.2 Sample Case Report Form

- MVD1-AU-001 Unique Blank CRF Version 5.0 dated 16Feb2024

16.1.3 List of IECs or IRBs (Plus the Name of the Committee Chair if Required by the Regulatory Authority) –Written Information for Participants and Consent Forms

Bellberry Human Research Ethics Committee

123 Glen Osmond Road

Eastwood, South Australia 5063

Please refer to Trial Master File for PICFs.

16.1.4 List and Description of Investigators and Other Important Participants in the Study, Including Brief (1 Page) CVs or Equivalent Summaries of Training and Experience Relevant to the Performance of the Clinical Study

ROLE	NAME
Sponsor	Eolo Pharma Pty Ltd Level 5, 63 Pirie Street, Adelaide SA 5000, Australia
Local Sponsor	Avance Clinical Pty Ltd 213 Glynburn Road, Firle SA 5070, Australia
Principal Investigator	Professor Sepehr Shakib
Clinical Research Unit	CMAX Ground Floor, 21-24 North Terrace, Adelaide SA 5000, Australia
Study Management	Avance Clinical Pty Ltd 213 Glynburn Road, Firle SA 5070, Australia
Clinical Laboratory Safety Sample Analysis and Pharmacodynamic Blood Chemistry	• Australian Clinical Labs 1 Bulter Road, Adelaide SA 5095, Australia • Ashford Hospital Laboratory (Out of Hours) 55 Anzac Highway, Ashford SA 5035, Australia
Oral Glucose Tolerance Test	Australian Clinical Labs 1 Bulter Road, Adelaide SA 5095, Australia
Bioanalysis of Pharmacokinetic and Pharmacodynamic Samples	Agilex Biolabs 31 Dalgleish Street, Thebarton SA 5031, Australia
Adipose Tissue Biopsy Processing and Analysis	Institut Pasteur de Montevideo Mataojo 2020 CP 11400 Montevideo, Uruguay
Data Management	Avance Clinical Pty Ltd 213 Glynburn Road, Firle SA 5070, Australia
Statistician	Benjamin Raymond Avance Clinical Pty Ltd 213 Glynburn Road, Firle SA 5070, Australia
Pharmacometrician	Oriol Peris Serrano Avance Clinical Pty Ltd 213 Glynburn Road, Firle SA 5070, Australia
Clinical Study Report Author	Yolandi Starczak, PhD Avance Clinical Pty Ltd 213 Glynburn Road, Firle SA 5070, Australia

16.1.5 Signatures for Approval of the CSR of Principal or Coordinating Investigator(s) or Sponsor's Responsible Medical Officer

- Signature of Principal Investigator
- Signature of Sponsor's responsible Medical Officer

16.1.6 List of Investigational Products Batch Numbers

	Batch/Lot Number	Date of Manufacture	Re-test Date
MVD1 (API)	CM-BPR-N4661-02-001-20-RPK1	25 Aug 2020	24 Aug 2024
Placebo	D104210348	Apr 2021	Mar 2026

	Batch/Lot Number	Date of Labelling/Manufacture	Expiry Date
SAD Cohort 1 – MVD1	SYN.23.0052/0053	27 Feb 2023	24 Aug 2023
SAD Cohort 1 – Placebo			
SAD Cohort 2 – MVD1	SYN.23.0082/0083	28 Mar 2023	24 Aug 2023
SAD Cohort 2 – Placebo			
SAD Cohort 3 – MVD1	SYN.23.0118/0119	28 Apr 2023	24 Aug 2023
SAD Cohort 3 – Placebo			
MAD Cohort 1 – MVD1	SYN.23.0345/0346	25-26 Sep 2023	24 Aug 2024
MAD Cohort 1 – Placebo	SYN.23.0345/0346	22-25 Sep 2023	24 Aug 2024
MAD Cohort 2 – MVD1	SYN.23.0396/0397	29-30 Nov 2023	24 Aug 2024
MAD Cohort 2 – Placebo	SYN.23.0396/0397	28 Nov 2023	24 Aug 2024
MAD Cohort 3 – MVD1	SYN.24.0035/0036	18-19 Dec 2023	24 Aug 2024
MAD Cohort 3 – Placebo	SYN.24.0035/0036	17 Jan 2024	24 Aug 2024

16.1.7 Randomisation Scheme and Codes (Participant Identification and Treatment Assigned)

- MVD1-AU-001_Randomisation_SAD_09_Feb_2023

- MVD1-AU-001_Randomisation_MAD_09_Feb_2023

16.1.8 Audit Certificates

- Quality Audit Certificate dated 01_Oct_2024

16.1.9 Documentation of Statistical Methods

- Statistical Analysis Plan (Version 3.0, dated 08May2024)

16.1.10 Documentation of Inter-laboratory Standardisation Methods and Quality Assurance Procedures If Used

Not applicable

16.1.11 Publications Based on the Study

There are no publications at the time of writing this report.

16.1.12 Important Publications Referenced in the Report

Not applicable

16.2 PARTICIPANT LISTINGS

16.2.1 Participant Disposition

Listing 16.2.1.1.A Participant Enrolment – Part A (SAD) (All-Randomised Analysis Set)

Listing 16.2.1.1.B Participant Enrolment – Part B (MAD) (All-Randomised Analysis Set)

Listing 16.2.1.2.A Participant Disposition - Part A (SAD) (All-Randomised Analysis Set)

Listing 16.2.1.2.B Participant Disposition - Part B (MAD) (All-Randomised Analysis Set)

Listing 16.2.1.3.A Participant Pre-Dose Eligibility Review - Part A (SAD) (All-Randomised Analysis Set)

Listing 16.2.1.3.B Participant Pre-Dose Eligibility Review - Part B (MAD) (All-Randomised Analysis Set)

16.2.2 Protocol Deviations

Listing 16.2.2.1.A Protocol Deviations – Part A (SAD) (All-Randomised Analysis Set)

Listing 16.2.2.1.B Protocol Deviations – Part B (MAD) (All-Randomised Analysis Set)

Listing 16.2.2.2.A Comments Part A (SAD) (All-Randomised Analysis Set)

Listing 16.2.2.2.B Comments Part B (MAD) (All-Randomised Analysis Set)

16.2.3 Analysis Population

Listing 16.2.3.1.A Analysis Populations – Part A (SAD) (All-Randomised Analysis Set)

Listing 16.2.3.1.B Analysis Populations – Part B (MAD) (All-Randomised Analysis Set)

16.2.4 Demographics and Baseline Information

Listing 16.2.4.1.A Demographics – Part A (SAD) (All-Randomised Analysis Set)

Listing 16.2.4.1.B Demographics – Part B (MAD) (All-Randomised Analysis Set)

Listing 16.2.4.2.A Medical History – Part A (SAD) (All-Randomised Analysis Set)

Listing 16.2.4.2.B Medical History – Part B (MAD) (All-Randomised Analysis Set)

Listing 16.2.4.3.A Pregnancy and Follicle Stimulating Hormone Test – Part A (SAD) (Safety Analysis Set)

Listing 16.2.4.3.B Pregnancy and Follicle Stimulating Hormone Test – Part B (MAD) (Safety Analysis Set)

Listing 16.2.4.4.A Alcohol Breath Test – Part A (SAD) (Safety Analysis Set)

Listing 16.2.4.4.B Alcohol Breath Test – Part B (MAD) (Safety Analysis Set)

Listing 16.2.4.5.A Urine Drug Screen and Cotinine – Part A (SAD) (Safety Analysis Set)

Listing 16.2.4.5.B Urine Drug Screen and Cotinine – Part B (MAD) (Safety Analysis Set)

Listing 16.2.4.6.A Serology – Part A (SAD) (Safety Analysis Set)

16.2.5 Treatment Administration

16.2.6 Pharmacokinetic and Pharmacodynamic Data

16.2.7 Safety Data–Adverse Events

16.2.8 Safety Data–Laboratory Parameters

16.3.2 Other CRFs Submitted

None

STATISTICAL ANALYSIS PLAN

A PHASE 1, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, FIRST IN HUMAN STUDY OF THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF SINGLE AND MULTIPLE DOSES OF MVD1 IN HEALTHY ADULT VOLUNTEERS

Protocol No.: MVD1-AU-001

Sponsor Name and Address:	Eolo Pharma Pty Ltd Level 5, 63 Pirie Street, Adelaide SA 5000, Australia
Date of Issue:	08-May-2024
Status and Version:	V3.0
Version Date:	08-May-2024
Author and Affiliation:	Kayne Sellen Biostatistician Avance Clinical Pty Ltd 213 Glynburn Road, Firle 5070, Australia

Authorisation Page:

Role	Name	Company	Signature and Date
Biostatistician	Kayne Sellen	Avance Clinical Pty Ltd	DocuSigned by: Kayne Sellen Signer Name: Kayne Sellen Signing Reason: I am the author of this document Signing Time: 10-May-2024 | 10:51:10 ACST B99F86DD9E3F45E2A700E0BC47183D2B
QC Biostatistician	Ben Raymond	Avance Clinical Pty Ltd	DocuSigned by: Benjamin Raymond Signer Name: Benjamin Raymond Signing Reason: I have reviewed this document Signing Time: 10-May-2024 | 10:44:14 ACST 239A792BFBA74B9A955D9412862E2454
QC Pharmacokineticist	Oriol Serrano	Avance Clinical Pty Ltd	DocuSigned by: Oriol Peris Serrano Signer Name: Oriol Peris Serrano Signing Reason: I approve this document Signing Time: 13-May-2024 | 14:59:20 ACST BCEA6730BBB54CFA87FC7554AA437588
Sponsor	Carlos Batthyány	Eolo Pharma Pty Ltd	DocuSigned by: Carlos Batthyány Signer Name: Carlos Batthyány Signing Reason: I have reviewed this document Signing Time: 09-May-2024 | 19:28:05 PDT 73C10B7DFEE84C8DB3D8DCA3EE13D72F

SAP Amendments before database lock

Version	Issue Date	Applicable Sections	Revision/ Addition	Rationale
1	16-Jan-2024		V1.0 Signed off	N/A
2	22-Mar-2024	Section 2.2.3 and 15	Updated PD parameter to be included	To be consistent with Protocol Clarification Memo 05 12Jan2024
3	08-May-2024	4.6 Treatment Group and Visit Display Conventions	Updated the Dose 1 and Dose 2 representation in Part B	For clearer representation of data in outputs
		4.5 Handling of Missing Data	Adverse Events Missing Data Rules were added.	For handling scenarios with missing causality/ severity and unknown onset time or resolution date
		13.6 Body Weight and BMI	Added BMI calculation based on Height at Screening	To be consistent with Protocol v4.0
		15.2 Oral Glucose Tolerance Test (OGTT)	Added clarity on pre-drink and post-drink continuous summary and inclusion of continuous summary for difference between Day -1 and Day 16	As per sponsor request

Table of Contents

List of Abbreviations

Abbreviation	Description
ACR	Albumin:Creatinine ratio
ADR	Adverse Drug Reaction
Ae	Cumulative amount of unchanged drug excreted
AEs	Adverse Events
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Class
AUC_{0-12}	Area Under the Concentration-Time Curve From 0 to 12 hours
AUC_{inf}	Area Under the Concentration-Time Curve From 0 to Infinity
AUC_{last}	Area Under the Concentration-Time Curve From 0 to Time of Last Quantifiable Concentration
BLQ	Below The Limit of Quantifiable
BMI	Body Mass Index
CL/F	Total Apparent Body Clearance
CLr	Renal clearance
C_{min}	Minimum Observed Concentration
C_{max}	Maximum Observed Concentration
COVID	Coronavirus Disease
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
CV	Coefficient of Variation
DBL	Database Lock
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRFs	Electronic Case Report Forms
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
ID	Identification
INR	International Normalized Ratio
ITT	Intent to Treat Analysis Set
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LLOQ	Lower Limit of Quantitation

MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
OGTT	Oral Glucose Tolerance Test
PD	Pharmacodynamic
PDS	Pharmacodynamic Analysis Set
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
PKS	Pharmacokinetic Analysis Set
PT	Preferred Terms
PT	Prothrombin Time
SAD	Single Ascending Dose
SAEs	Serious Adverse Events
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SNAQ	Simplified Nutritional Assessment Questionnaire
SOC	System Organ Class
SOPs	Standard Operating Procedures
SS	Safety Analysis Set
$t_{1/2}$	Apparent Terminal Elimination Half-Life
TEAEs	Treatment Emergent Adverse Events
TFLs	Tables, Listings, And Figures
t_{last}	Time of last measurable observed concentration.
t_{max}	Time To Cmax
ULOQ	Upper Limit of Quantitation
UN	Unknown
UNK	Unknown
Vz/F	Apparent Volume of Distribution
WAT	White Adipose Tissue
WBC	White Blood Cells
WHO-DD	World Health Organization Drug Dictionary
λz	Terminal Elimination Rate Constant

1 INTRODUCTION

This Statistical Analysis Plan (SAP) provides the outline for the statistical analysis of the data collected for Eolo Pharma Pty Ltd study protocol titled: "A Phase 1, Randomised, Double-blind, Placebo-controlled, First in Human Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single and Multiple Ascending Doses of MVD1 in Healthy Adult Volunteers" version 4.0, dated 27 Aug 2023.

The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock, reasons for such deviations, and all alternatives or additional statistical analyses that may be performed will be described the Clinical Study Report (CSR).

If the SAP differs the statistical considerations in the protocol, details will be given in section 17.

2 PROJECT OVERVIEW

2.1 Description of Study Design

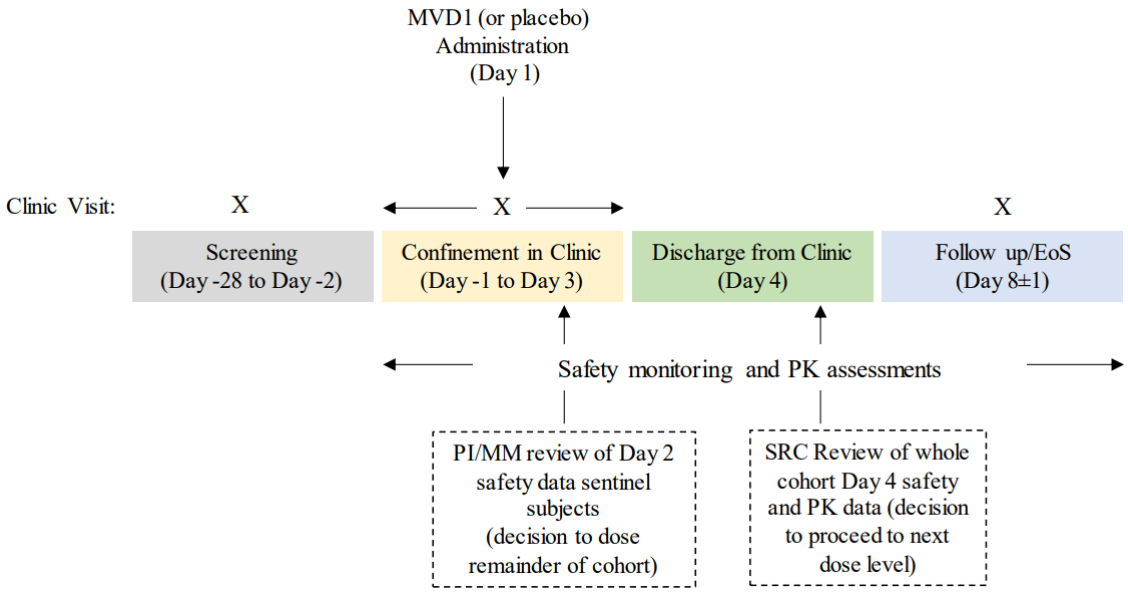
This is a double-blind, randomised, placebo-controlled, Phase I study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and multiple ascending doses of MVD1 in healthy adult volunteers. The study will be conducted in 2 parts: Part A, a single ascending dose (SAD) study in healthy adults and Part B, a multiple ascending dose (MAD) study in healthy but obese adults. The decision to escalate between dose levels in Part A and proceed from Part A to Part B will be based on a review of the safety and available PK data by the study safety review committee (SRC).

Part A (SAD) will be conducted in up to a total of 3 cohorts (Cohorts S1 to S3). Six participants will be enrolled in each cohort with 4 participants randomised to receive MVD1 and 2 participants randomised to receive placebo. MVD1 dose levels planned for each cohort Part A are:

- Cohort S1: 200 mg (single dose)
- Cohort S2: 400 mg (single dose)
- Cohort S3: 800 mg (single dose)

For all study cohorts in Part A, MVD1 or placebo will be administered under fasting conditions. Screening for study eligibility will occur between Day -28 and Day -2 inclusive. Eligible participants will be admitted to the clinical facility on Day -1. Following confirmation of eligibility on Day 1, participants will be enrolled in Cohorts S1, S2, or S3 and randomised to receive either MVD1 or placebo. In Part A, the confinement period will commence on Day -1, followed by dosing on Day 1 with placebo or active drug in a double-blind manner. Participants will be discharged from the clinical facility on Day 4 following completion of study assessments and will be required to attend the clinic for a final follow-up visit on Day 8.

Figure 1: Part A (SAD) Study Schedule Outline



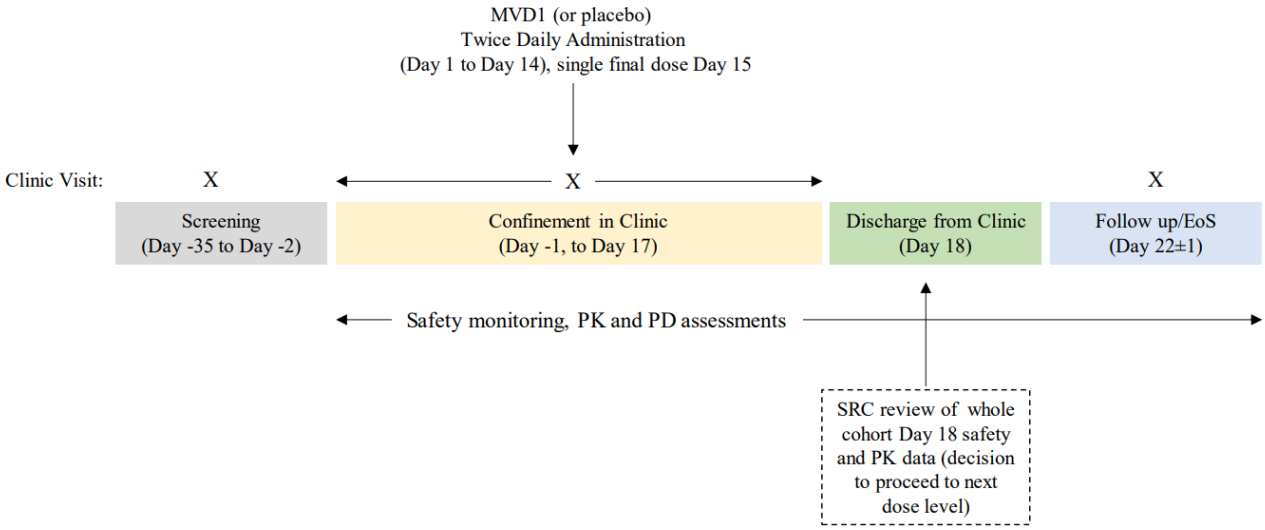
Part B (MAD) will be conducted in up to 3 cohorts (M1 to M3) of healthy obese adult volunteers. Eight participants will be enrolled in each cohort with six participants randomised to receive MVD1 and 2 participants randomised to receive placebo administered as two daily doses (administered 12 hours apart, 1 in the morning and 1 in the evening) for fourteen consecutive days and a final single dose administered on the morning of Day 15. MVD1 dose levels planned for each cohort in Part B are:

- Cohort M1: 200 mg (2 x 100 mg)
- Cohort M2: 300 mg (2 x 150 mg)
- Cohort M3: 400 mg (2 x 200 mg)

A dose level will only be evaluated in Part B if determined to be safe based on a review of safety, tolerability and PK data in Part A by the SRC. Based on this data, actual dose levels evaluated in Part B may need to be adjusted.

Screening for study eligibility in Part B will occur between Day -35 and Day -2 inclusive. Eligible participants will be admitted to the clinical facility on Day -1 and following confirmation of eligibility on Day 1, participants will be enrolled in Cohorts M1, M2, or M3 and randomised to receive either MVD1 or placebo. In Part B, the confinement period will commence on Day -1, followed by dosing on Day 1 with placebo or active drug in a double-blind manner. Participants will be discharged from the clinical facility on Day 18 following completion of study assessments and will be required to attend the clinic for a final follow-up visit on Day 22.

Figure 2: Part B (MAD) Study Schedule Outline



2.2 Objectives

2.2.1 Primary Objectives and Endpoints

The primary objective of this study is:

- To assess the safety and tolerability of single and 15-day repeat oral doses of MVD1 in healthy adult volunteers and healthy but obese adult volunteers respectively.

The primary endpoints of this study are:

- Safety endpoints as change from baseline and where appropriate over time and versus placebo include:
    - Incidence, severity, and relationship of adverse events (AEs)/serious AEs (SAEs) (including withdrawals due to AEs).
    - Change in vital signs.
    - Change in electrocardiogram (ECG) parameters.
    - Change in clinical laboratory parameters (hematology, serum chemistry, coagulation, and urinalysis).
    - Stool diary.
    - Nutritional appetite questionnaire (Part B only).

2.2.2 Secondary Objectives and Endpoints

The secondary objective of this study is:

- To assess the PK of MVD1 and metabolites in plasma and urine following administration of single and 15-day repeat oral doses in healthy volunteers.

The plasma MVD1 and metabolite M1 PK endpoints of this study will include (but will not be limited to):

- Maximum observed plasma concentration (C_{max}).
- Time to C_{max} (T_{max}).
- Area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration (AUC_{last}).
- Area under the plasma concentration-time curve from time 0 extrapolated to infinity (AUC_{0-inf}) following single dose only.
- Apparent terminal elimination half-life ($t_{1/2}$).
- Terminal elimination rate constate (λz).
- Apparent clearance (CL/F).
- Apparent volume of distribution (V_z/F) (Part A only).
- Minimum observed concentration C_{min} (Day 15) (Part B only).
- Area under the plasma concentration-time curve from time 0 to 12 hours(AUC_{0-12})

The urine PK endpoints of this study will include (but will not be limited to):

- Cumulative amount of unchanged drug excreted (Ae) in urine.
- Renal clearance (CLr).

2.2.3 Exploratory Objectives and Endpoints (Part B only)

The exploratory objectives of this study are:

- To investigate biomarker changes following multiple oral doses of MVD1 in healthy obese adult volunteers.
- To investigate MVD1 exposure in white adipose tissue.
- To evaluate the participant's impression of change following study treatment.

The MVD1 PD endpoints of this study will include (but will not be limited to) a change from baseline in the following serum biomarkers:

- Glucose
- Oral Glucose Tolerance Test (OGTT)
- Insulin
- C Peptide
- High Sensitivity C Reactive Protein (hsCRP)
- Fructosamine
- Glycohemoglobin (Cohort MAD 1 and MAD 2 only)
- Free fatty acids
- Triglycerides
- Leptin levels

Additional exploratory endpoints will include:

- MVD1 target engagement in white adipose tissue sampled using a single needle biopsy on Day -1 and 7.
- Body Weight (day -1, day 15 and day 22)
- Patient global impression of change (PGIC) questionnaire to be completed by study participants at the end of the study treatment period.

3 SAMPLE SIZE

42 participants will be randomised and allocated in Part A in a 4:2 ratio in each cohort (1:1 in sentinels and 3:1 in the main group of each cohort) to receive MVD1 or placebo to achieve a total of n=6 per cohort, and in Part B in a 6:2 ratio to received MVD1 or placebo to achieve a total of n=8 per cohort.

A formal sample size calculation was not performed. Rather, as the first study of MVD1 in people, the chosen sample size is deemed adequate to evaluate all study endpoints.

4 STATISTICAL CONSIDERATIONS

4.1 Standard Operating Procedures and Software

Data will be handled and processed per the sponsor representative's (Avance) Standard Operating Procedures (SOPs), which are written based on the principles of Good Clinical Practice (GCP).

All data conversions and statistical analyses will be performed using SAS® <Version 9.4> or higher (SAS Institute, Cary, North Carolina, USA) with program code prepared specifically for the study by qualified Avance statisticians and SAS® programmers.

4.2 General Considerations

All data collected during the study (data originating from the electronic Case Report Forms (eCRFs) or electronic transfers will be presented in the data listings. Event-based listings will be sorted by cohort, participant identifier and event start date/time (i.e., Adverse Event (AE) start date/time). Assessment-based listings will be sorted by cohort, parameter name (alphabetically unless specifically stated otherwise), participant identifier, visit and time point (if applicable).

Each study part will be presented separately in the table summaries.

Unless otherwise stated, the following methods will be applied:

- Continuous variables: Descriptive statistics will include the number of non-missing values (n), arithmetic mean, standard deviation, median, minimum and maximum values.

  The minimum and maximum values will be displayed to the same decimal precision as the source data, the arithmetic mean and median values will be displayed to one more decimal than the source data, and the SD values will be displayed to two more decimals than the source data for the specific variable.

  The appropriate precision for derived variables will be determined based on the precision of the data on which the derivations are based, and statistics will be presented in accordance with the above mentioned rules.

- Categorical variables: Descriptive statistics will include frequencies and percentages per category. The denominator in all percentage calculations will be the number of Participants in the relevant analysis population (by treatment group) with non-missing data, unless specifically stated otherwise. Percentages will be rounded to one decimal place and will not be displayed for zero frequencies.

- Presentation of p-values and confidence intervals: 95% confidence intervals will be computed, and reported to four significant figures, p-values will be displayed up to three decimal places and as "<0.001" if the value is below 0.001.

- Repeat/unscheduled assessments: Only values collected at scheduled study visits/time points will be presented in summary tables. If a repeat assessment was performed, the result from the original assessment will be presented as the result at the specific visit/time point. All collected data will be included in the data listings. If an unscheduled visit was intended to replace the missing assessment for a scheduled visit this should be documented clearly before values are carried forward as a scheduled visit assessment.

- Assessment windows: All assessments will be included in the data listings and the protocol specified visit windows will not be applied to exclude assessments that were not performed on the protocol specified visit days. Protocol visit windows will be as per Case Report Form (CRF) data collection.
- Result display convention: Results will be centre aligned in all summary tables and listings. Participant numbers, visit, and parameter labels and comments may be left aligned if required.

  Conversion of categorical values:

  Any quantitative safety assessments that are given as '<xx' or '>xx' in the database will be imputed with the absolute value of the number without the sign (e.g., <2.2 will be imputed as 2.2) for the calculation of the changes from baseline and for the descriptive statistics. In the listings, no imputations will be performed, and all data will be displayed as recorded in the database.
- Date and time display conventions: The following display conventions will be applied in all outputs where dates and/or times are displayed:
  - Date only: DD-MMM-YYYY
  - Date and time: DD-MMM-YYYY/HH:MM

  If only partial information is available, unknown components of the date or time will be presented as UN (Unknown) or UNK (Unknown), for example "UN-UNK-2020" or "UN:UN" for time.

4.3 Key Definitions

The following definitions will be used:

- Date of the First Study Treatment Administration: The date of the first study treatment administration is defined as the earliest date on which a study treatment was administered.
- Date of the Last Study Treatment Administration: The date of the last study treatment administration is defined as the latest known date on which a study treatment was administered.
- Baseline: The Baseline value is defined as the last available valid, non-missing observation for each Participant prior to first study treatment administration on Day 1. For ECG triplicates, the baseline is defined as the mean of the ECG triplicate performed prior to first study treatment administration. Repeat and unscheduled assessments will be included in the derivation of the Baseline values only if Baseline value is missing.
- Change from Baseline: The change from Baseline value is defined as the difference between the result collected/derived at a particular visit and the Baseline value.

  The change from Baseline value at each visit will be calculated for all continuous parameters using the following formula:

  Change from Baseline Value = Result at specified visit – Baseline Value

  The change from Baseline value will only be calculated if the specific visit result and the Baseline value for the parameter are both available and will be treated as missing otherwise.

- Percentage Change from Baseline: The percentage change from Baseline value is defined as the percentage of the difference between the result collected/derived at a particular visit and the Baseline value.

  – Percentage Change from Baseline Value = (Result at specified visit – Baseline Value)/(Baseline Value)

  The percentage change from Baseline value will only be calculated if the specific visit result and the Baseline value for the parameter are both available and will be treated as missing otherwise. If Baseline value is 0, then percentage of change from baseline will be undefined and removed from the analysis.

- Study Day: The study day of an event is defined as the relative day of the event starting with the date of the first study treatment administration (reference date) as Day 1 (there will be no Day 0).

  The study day of events occurring before the first study treatment administration will be calculated as:

  Study Day = (Date of Event - Date of First Study Treatment Administration)

  For events occurring on or after Day 1, study day will be calculated as:

  Study Day = (Date of Event - Date of First Study Treatment Administration) + 1

  Study days will only be calculated for events with complete dates and will be undefined for events that are 'Ongoing' at the end of the study.

- Actual Time from First Dose (hours) in PK related outputs is defined as:

  (Date/Time of PK Sample collection) – (Date/Start Time of First Dose on Day 1).

- Actual Time Deviation (hours) in PK related outputs is defined as:

  (Actual PK Sample Collection Time Post Dose) – (Scheduled PK Sample Collection Time Post Dose).

- AE Duration: Adverse event duration (in days, to two decimal places), calculated as

  (Resolution Date + Resolution Time) – (Onset Date + Onset Time) AE duration will only be calculated for events with complete dates/times and will be undefined for events that are 'Ongoing' at the end of the study.

- Low/Normal/High indicator for Laboratory Parameters:

  The L/N/H indicator will be derived, where both the lower and upper limit of the reference range was provided, by following derivation:
  - If the result is less than the lower limit of the reference range, the indicator will be set as "Low".
  - If the result is greater than the upper limit of the reference range, the indicator will be set as "High".
  - If the result is greater or equal to the lower limit of the reference range and less or equal to the upper limit of the reference range, the indicator will be set as "Normal".

4.4 Multiple Comparisons and Multiplicity

No multiplicity adjustment will be carried out for this study.

4.5 Handling of Missing Data

In general, all data will be analysed as collected and missing values will not be imputed or replaced unless stated otherwise.

Adverse Events Missing Data Rules: For adverse events, with unknown intensity (severity) or unknown relationship to study treatment, these will be imputed as follows:

- If the intensity (severity) of an adverse event is unknown/missing, the intensity will be imputed for the summary of adverse events as "Severe (Grade 3)".
- If the relationship to investigational product of an adverse event is unknown/missing, the relationship will be imputed for the summary of adverse events as being the least favorable relationship, i.e., "Definitely".

For adverse events, where either the onset time or resolution date is unknown, time since first dose and duration will be imputed as follows:

- If onset date is unknown, and it cannot be confirmed that onset was prior to the start of dose administration, then the AE will be classified as treatment-emergent (TE), with unknown time since first dose.
- If either the date of onset or the date of resolution is unknown, then duration will be shown as unknown.
- If onset time is unknown:
    - If the date of onset is known to be the date of first dose administration, then the AE will be classified as TE.
    - AE Duration will only be calculated for Adverse events with complete dates and times.
- If resolution time is unknown
    - If the date of resolution is known to be the date of first dose administration, then the AE will be classified as TE.

4.6 Treatment Group and Visit Display Conventions

Summary Tables:

In summary tables, the representation as below:

Part A:

- MVD1 200 mg
- MVD1 400 mg
- MVD1 800 mg
- Pooled MVD1

- Placebo
- Overall

Part B:

- MVD1 200 mg
- MVD1 300 mg
- MVD1 400 mg
- Pooled MVD1
- Placebo
- Overall

Data Listings:

In data listings, the following labels will be used:

Part A:

- Cohort S1: MVD1 200 mg
- Cohort S1: Placebo
- Cohort S2: MVD1 400 mg
- Cohort S2: Placebo
- Cohort S3: MVD1 800 mg
- Cohort S3: Placebo

Part B:

- Cohort M1: MVD1 200 mg
- Cohort M1: Placebo
- Cohort M2: MVD1 300 mg
- Cohort M2: Placebo
- Cohort M3: MVD1 400 mg
- Cohort M3: Placebo

Visit labels:

The following visit labels will be used:

Part A

- Screening (Listing only)
- Day -1 (Listing only)
- Baseline (Table only)
- Day 1

Part B

- Screening (Listing only)
- Day -1 (Listing only)
- Baseline (Table only)
- Day 1

Part A

- Pre-dose
- 0.25 hours post-dose
- 0.5 hours post-dose
- 1-hour post-dose
- 2 hours post-dose
- 3 hours post-dose
- 4 hours post-dose
- 6 hours post-dose
- 8 hours post-dose
- 10 hours post-dose
- 12 hours post-dose

- Day 2, Day 3, Day 4
- End of Study
- Unscheduled (Listing only)
- Early Termination (Listing only)

Part B

- (Dose 1 representation)
  - Pre-dose 1
  - 0.25 hours post-dose 1
  - 0.5 hours post-dose 1
  - 1-hour post-dose 1
  - 2 hours post-dose 1
  - 3 hours post-dose 1
  - 4 hours post-dose 1
  - 6 hours post-dose 1
  - 8 hours post-dose 1
  - 10 hours post-dose 1
  - 12 hours post-dose 1
- (Dose 2 representation)
  - Pre-dose 2
  - 0.25 hours post-dose 2
  - 0.5 hours post-dose 2
  - 1-hour post-dose 2
  - 2 hours post-dose 2
  - 3 hours post-dose 2
  - 4 hours post-dose 2
  - 6 hours post-dose 2
  - 8 hours post-dose 2
  - 10 hours post-dose 2
  - 12 hours post-dose 2

- Day 2, Day 4, Day 10
  - (Dose 1 representation)

Part A	Part B
	▪ Pre-dose 1 ▪ 4 hours post-dose 1 o (Dose 2 representation) ▪ Pre-dose 2 ▪ 4 hours post-dose 2 • Day 7 o (Dose 1 representation) ▪ Pre-dose 1 ▪ 2 hours post-dose 1 ▪ 4 hours post-dose 1 o (Dose 2 representation) ▪ Pre-dose 2 ▪ 4 hours post-dose 2 • Day 3, Day 5, Day 6, Day 8, Day 9, Day 11, Day 12, Day 13, Day 14 o Pre-dose o Post-dose • Day 15 o Pre-dose o 2 hours post-dose o 4 hours post-dose • Day 16, Day 17, Day 18 • End of Study • Unscheduled (Listing only) • Early Termination (Listing only)

For listings, these labels will be used, with visit representing baseline (either screening/baseline or unscheduled visit marked as "*" with a footnote indicating it is baseline value). These visit displays will be sorted by date of visit within each Participant:

5 ANALYSIS POPULATIONS

5.1 All-Randomized Analysis Set (ARS)

The All-Randomized Analysis Set will include all participants randomized. Participants will be analysed according to the treatment allocated at randomization.

5.2 Safety Analysis Set (SS)

The Safety Analysis Set will include all participants who received at least one dose of study drug or placebo and have at least one post-dose safety assessment. Participants will be analysed according to treatment received.

5.3 Pharmacokinetic Analysis Set (PKS)

The Pharmacokinetic Analysis Set will include all participants in the Safety Analysis Set who have at least one post-dose plasma concentration data.

5.4 Pharmacodynamic Analysis Set (PDS)

The Pharmacodynamic Analysis Set will include all participants in the Safety Analysis Set who have at least one observed post-dose pharmacodynamic parameter.

6 PARTICIPANT ENROLMENT AND DISPOSITION

The following participant enrolment and disposition information will be reported:

Summary of Enrolment:

- Number of Participants Randomized
- Number of Participants Treated (to receive at least one dose of study drug)

Summary of Disposition:

- Number of Participants Completed
- Number of Participants Not Completed
- Reason for Non-Completion (percentage denominator based on number of withdrawn Participants)

Counts and percentages will be reported for summary of enrolment and disposition and will be provided using All-Randomized Analysis Set for treatment groups defined in Section 4.6.

Listings will be provided for summary of enrolment along with the date the participant provided informed consent/reconsent, eligibility, date of randomization/randomization number, reason for screen failure, date received study drug and sorted by participant ID for All-Randomized Analysis Set.

Listings will be provided for summary of disposition along with the date the participant provided informed consent/reconsent, the date of study completion/discontinuation and the primary reason for non-completion. The listing will be provided by treatment groups (Section 4.6) sorted by participant ID for the All-Randomized Analysis Set

7 ANALYSIS SET

The following analysis set information will be reported:

- Participants included in All-Randomized Population Set
- Participants included in Safety Analysis Set
- Participants included in Pharmacokinetic Analysis Set
- Participants included in Pharmacodynamic Analysis Set

Counts and percentages for these participants under different population sets will be provided using the All-Randomized Analysis Set for treatment groups defined in Section 4.6.

Listings will be provided by treatment groups (Section 4.6) sorted by Participant ID for the All-Randomized Analysis Set.

8 PROTOCOL DEVIATIONS

Prior to database lock, all protocol deviations will be reviewed between Avance medical monitors and the Sponsor and subjects excluded from the analysis sets based on type of deviation.

The number of participants with at least one protocol deviations and with at least one major protocol deviations and the category and grading of protocol deviations will be summarized in accordance with Section 4.2 using the All-Randomized Analysis Set for treatment groups defined in Section 4.6.

Listing of all protocol deviations will be provided by treatment group (Section 4.6) sorted by participant ID for the All-Randomized Analysis Set.

9 DEMOGRAPHICS

The demographics variables to be reported are listed below:

- Age (years)
- Sex
- Women of child-bearing potential
- Race
- Ethnicity
- Height (cm) at screening
- Weight (kg) at screening
- Body Mass Index (BMI) (kg/m^2) at screening

These variables will be summarized using descriptive statistics in accordance with Section 4.2 under the Safety Analysis Set for treatment groups defined in Section 4.6. Demographics variables will also be listed by treatment groups (Section 4.6) under the All-Randomized Analysis Set sorted by Participant ID.

9.1 Pregnancy and Follicle Stimulating Hormone (FSH) Test

All available pregnancy and FSH test results will be displayed in a data listing and include all information collected. The listing will be presented by the treatment groups defined in section 4.6, sorted by participant ID for the Safety Analysis Set, along with age, sex, race and baseline weight of the participant.

9.2 Alcohol Breath Test

All available alcohol breath test results will be displayed in a data listing and include all information collected. The listing will be presented by the treatment groups defined in section 4.6, sorted by participant ID for the Safety Analysis Set, along with age, sex, race and baseline weight of the participant.

9.3 Urine Drug Screen

All available urine drug screen (including methamphetamine, opiates, cocaine, tetrahydrocannabinol, benzodiazepines, barbiturates, methadone, tricyclic antidepressants, and amphetamines) and cotinine results will be displayed in a data listing and include all information collected. The listing will be presented by the treatment groups defined in section 4.6, sorted by participant ID for the Safety Analysis Set, along with age, sex, race and baseline weight of the participant.

9.4 Substance Use History

All available substance use history (including alcohol and tobacco use) results will be displayed in a data listing and include all information collected. The listing will be presented by the treatment groups defined in section 4.6, sorted by participant ID for the Safety Analysis Set, along with age, sex, race and baseline weight of the participant.

9.5 Serology Assessment

All available serology results (including human immunodeficiency virus (HIV)-1, HIV-2, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody) will be displayed in a data listing and include all information collected. The listing will be presented by the treatment groups defined in section 4.6, sorted by participant ID for the Safety Analysis Set, along with age, sex, race and baseline weight of the participant.

9.6 COVID-19 Assessment

All available COVID-19 assessment (rapid antigen test (RAT) or polymerase chain reaction (PCR)) results will be displayed in a data listing and include all information collected. The listing will be presented by the treatment groups defined in section 4.6, sorted by participant ID for the Safety Analysis Set, along with age, sex, race and baseline weight of the participant.

10 MEDICAL HISTORY

All available participant medical history information will be displayed in a data listing and include all information collected. The listing will be provided by the treatment groups defined in section 4.6, sorted by participant ID for the All-Randomized Analysis Set, along with age, sex, race and baseline weight of the participant.

11 PRIOR AND CONCOMITANT MEDICATION

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD) (the version of WHODRUG GLOBAL B3 September 2022).

- Prior Medications: Prior medications are defined as any medication where the use was started prior to the start date/time of first study drug administration.
- Concomitant Medications: Concomitant medications are defined as medications (other than the study drug) taken at least once after the start of first study drug administration.

  Medications stopped prior to the day of first study drug administration will not be considered concomitant medications, but they will be coded by WHO-DD and listed. If a clear determination cannot be made as to whether the medication is concomitant or not due to missing or incomplete data, the medication will be treated as concomitant medication taken during the study.

The number and percentage of participants using at least one concomitant medication will be displayed together with the number and percentage of participants using at least one medication within each anatomical therapeutic class (ATC-Level 1) and preferred name. These will be summarized under the Safety Analysis Set for treatment groups defined in Section 4.6 and repeated for prior medication. Where ATC-Level 1 and preferred name are reported, the display will be sorted by the descending order of the total counts by ATC-Level 1 and then by PT in the overall treatment group.

Listing of full details of prior and concomitant medications (medication taken, therapeutic class, start and stop dates/ongoing status, indication, routes, frequency, dosage and unit) will be provided by the treatment groups defined in section 4.6, sorted by participant ID and start date for the All-Randomized Analysis Set, along with age, sex, race and baseline weight of the participant.

Listing of full details of concomitant procedures (procedure, date, indication) will be provided by the treatment groups defined in section 4.6, sorted by participant ID and date for the Safety Analysis Set.

12 TREATMENT COMPLIANCE AND EXPOSURE

All study drug administration information will be displayed in a data listing and include all information collected. Listings will be presented by the treatment groups defined in section 4.6, sorted by participant ID and date/time of administration for the Safety Analysis Set, along with age, sex, race and baseline weight of the participant.

For Part B treatment groups, treatment compliance and duration will be summarized.

Treatment Compliance during the treatment period is defined as:

$$\frac{\text{total number of tablets administered}}{\text{Expected number of tablets to be taken}} * 100\%$$

The total number of tablets expected for all Part B treatment groups is 29 (Day 1-14 twice daily, single dose on day 15).

Compliance will be summarized using descriptive statistics in accordance to Section 4.2 for the Safety Analysis Set and Part B treatment groups defined in Section 4.6. In addition the number and percentage of subjects in the following categories will be summarised: 100% compliance and <100% compliance.

Treatment exposure (duration of treatment) in days is defined as:

- Date of last dose of study drug – date of first dose of study drug + 1

Overall duration of treatment (days) will be summarized using descriptive statistics in accordance to Section 4.2 for the Safety Analysis Set and Part B treatment groups defined in Section 4.6.

13 SAFETY

All safety endpoints will be analyzed using the Safety Analysis Set.

13.1 Adverse Events

AE verbatim terms will be coded using the version 25.1 of the Medical Dictionary for Regulatory Activities (MedDRA). AEs and SAEs are defined in the study protocol.

- Treatment Emergent Adverse Events (TEAEs) are defined as adverse events that occurred or worsened after the first administration of study drug. If determination cannot be made as to whether the event is treatment emergent due to missing or incomplete data, the adverse event will be treated as treatment emergent.
- Treatment-Related are defined as any TEAEs reported with the causality of "Possibly", "Probably", "Definitely" to study treatment.
- For summaries participants with multiple incidents of events for a given PT and SOC will be counted only once. Similarly, if a participant experiences multiple incidents of events for a given PT and SOC, the highest severity will be used in the summaries presenting the number of subjects by severity. In addition to participant count, the total number of occurrences will be displayed.

All AE summaries will be restricted to TEAEs only.

The TEAE summaries will include:

- Overall Summary of TEAEs
    - TEAEs
    - Serious TEAEs
    - Serious Treatment Related TEAEs
    - TEAEs leading to study drug discontinuation
    - TEAEs leading to study withdrawal
    - TEAEs leading to death
    - TEAEs by Severity (Grade 1 to Grade 5)
    - Treatment Related TEAEs

The following table summaries will be presented by SOC and PT by treatment groups defined in Section 4.6:

- TEAE summary by SOC and PT
- TEAE summary by SOC, PT and Severity
- Treatment Related TEAE summary by SOC and PT
- Treatment Related TEAE summary by SOC, PT and Severity
- Serious TEAE summary by SOC and PT
- Serious Treatment Related TEAEs summary by SOC and PT

- TEAE summary of events leading to study drug discontinuation, or study withdrawal by SOC and PT
- TEAE summary of events leading to death

The following table summaries will be presented by PT by treatment groups defined in Section 4.6:

- TEAE summary by PT
- Treatment Related TEAE summary by PT

The above items will be presented using summary tables, which will include the number of participants (%) experiencing an event and the number of events. If a participant experienced the same adverse event multiple times, this will only be counted once for the purpose of counting the number of participants experiencing that adverse event. Maximum severity will be considered when counting subjects in the summary tables by SOC, PT and severity, while all occurrences will be counted according to their severity. If an AE occurrence changes in severity it will only be counted once by the maximum severity. Similarly, will be done when seriousness and relation to treatment are reported with different values in records related to the same occurrence of an AE, i.e. the worst case among the records will be assigned to the AE occurrence. Summary tables will be done for the Safety Analysis Set for treatment groups defined in Section 4.6. Where SOC and PT are reported, the display will be sorted by the descending order by the total count of SOC and then by PT in the Overall treatment group.

All AEs will be listed and will include the verbatim term, SOC, PT, SAE, TEAE, start/end date/time, severity, relationship to study treatment, outcome, action taken, and study withdrawal. Key subject listings will be created for SAEs, any deaths, AEs leading to study drug discontinuation or AEs leading to withdrawal from study .These listings will be presented by treatment groups (Section 4.6) sorted by participant ID and AE start date for the Safety Analysis Set, along with age, sex, race, and baseline weight of the participant.

13.2 Safety Laboratory Assessments

The following laboratory measurements will be taken at the time points specified in the study procedure schedule (Section 19):

- Hematology: Hematocrit, hemoglobin, mean cell hemoglobin (MCH), mean cell volume (MCV), mean corpuscular hemoglobin concentration (MCH), monocytes, platelet count, mean platelet volume (MPV), red cell count, red cell distribution width, WBC count with differential (neutrophils count, eosinophils count, basophils count, lymphocytes count).
- Chemistry: Anion gap, bicarbonate, calcium (adjusted), calcium, chloride, ionised calcium, phosphorus, potassium, sodium, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, indirect bilirubin, gamma-glutamyl transferase (GGT), albumin, cholesterol, creatinine, estimated glomerular filtration rate (eGFR), globulin, glucose, lactate dehydrogenase (LDH), protein, urea, uric acid.
- Coagulation: Activated partial thromboplastin time (aPTT), international normalized ratio (INR), prothrombin time (PT)

- Urinalysis and Urine Microscopy: bilirubin, blood, glucose, ketones, protein, albumin-creatine ratio (ACR), specific gravity, leukocyte esterase, pH, nitrite, urobilinogen, proteinuria (Part B only)

For the hematology, chemistry, and coagulation results, continuous data summary statistics (as described in Section 4.2) will be presented for values and change from baseline value at baseline and each scheduled post baseline visit. Where applicable, clinical result (Normal, Abnormal not clinically significant, abnormal clinically significant, unable to evaluate) will be also summarized by counts and percentages for baseline and for each scheduled visit.

In addition, shift tables from baseline at each visit for hematology, chemistry, and coagulation lab parameters (low, normal, and high) will also be presented using counts and percentages. A shift table from baseline to worst outcome on treatment will also be presented.

For urinalysis, discrete data summary statistics (as described in Section 4.2) will be presented for the counts and percentages of normal, abnormal clinically significant (CS) and non-clinically significant (NCS) at each visit results at baseline and each schedule post baseline visit. A shift table from baseline to worst outcome on treatment will also be presented.

These summary tables will be based on the Safety Analysis Set for treatment groups defined in section 4.6.

All available laboratory assessment results (hematology, chemistry, coagulation, and urinalysis including dipstick and ACR) will be displayed in a data listing and include all the information collected. In addition, the observations that are used as the baseline record (value) for each parameter will be flagged, and the change from baseline values (where applicable) at each scheduled post baseline (scheduled and unscheduled) visit will be presented. These listings will be presented by the treatment groups defined in section 4.6, sorted by participant ID and visit for the Safety Analysis Set, along with age, sex, race, and baseline weight of the participant.

13.3 Vital Sign Assessments

The following vital signs measurements will be taken at the time points specified in the study procedure schedule (section 19):

- Systolic blood pressure (SBP) (mmHg) [Reference range: 110-140 mmHg]
- Diastolic blood pressure (DBP) (mmHg) [Reference range: 70-90 mmHg]
- Heart Rate (beats/min) [Reference range: 50-90 beats/min]
- Body Temperature (tympanic) (ºC) [Reference range: 36.5 - 37.2 ºC]
- Overall Clinical Interpretation:
    - Normal
    - Abnormal NCS (Not Clinically Significant)
    - Abnormal CS (Clinically Significant)

The parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, ‘Systolic Blood Pressure (mmHg)’. Parameters will be sorted in the order that the measurements were collected in on the Vital Signs eCRF page within the tables and listings.

Summary statistics for vital sign parameters in accordance to Section 4.2 will be presented for baseline and for each scheduled post baseline visit (which also includes change from baseline). In addition, overall clinical interpretation result (Normal, Abnormal not clinically significant, Abnormal and clinically significant,) will be summarized by counts and percentages for baseline and each scheduled post baseline visit. A shift table from baseline to worst outcome on treatment for clinical interpretation will also be presented. These summary tables will be prepared for the Safety Analysis Set for treatment groups defined in Section 4.6.

In addition for Part B MAD treatment groups only, a summary of change between post-dose and pre-dose values will be presented for each dose and time point. For example Day 1 post-dose 1 will show change from Day 1 pre-dose 1. Similarly, Day 1 post-dose 2 will show change from Day 1 pre-dose 2.

All available vital signs results will be displayed in a data listing and include all information collected. In addition, the observations that are used as the baseline record for each parameter will be flagged, and the change from baseline values at each post baseline (scheduled and unscheduled) visit will be presented. This listing will be presented by the treatment groups defined in section 4.6, sorted by participant ID and visit for the Safety Analysis Set, along with age, sex, race, and baseline weight of the participant.

13.4 Electrocardiogram (ECG)

The following ECG measurements will be taken at the time points specified in the study procedure schedule (section 19):

- Heart Rate (bpm)
- PR interval (msec)
- QRS duration (msec)
- QT interval (msec)
- QTcF internal (msec)
- Clinical Interpretation
    - Normal
    - Abnormal NCS
    - Abnormal CS

The mean/average of ECG triplicates at applicable visit/timepoints for each participant will be captured in the CRF and displayed in the data listing along with the original triplicates. For overall clinical interpretation will be captured in the CRF and displayed in the mean of ECG triplicate.

In summary tables, the mean of ECG triplicates for each scheduled visit will be used, and the baseline of ECG triplicates is as defined in section 4.3.

Summary statistics for ECG parameters in accordance with section 4.2 will be presented for baseline and for each scheduled post baseline scheduled visit (which also includes the change from baseline). In addition, clinical result of ECG interpretation (*Normal, Abnormal NCS, and Abnormal CS*) will be summarized by counts and percentages for baseline and for each scheduled at post baseline visit. A shift table from baseline to worst outcome on treatment for clinical interpretation will also be

presented. These summary tables will be done for the Safety Analysis Set for the treatment groups defined in section 4.6.

In addition for Part B MAD treatment groups only, a summary of change between post-dose and pre-dose values will be presented for each dose and time point. For example Day 1 post-dose 1 will show change from Day 1 pre-dose 1. Similarly, Day 1 post-dose 2 will show change from Day 1 pre-dose 2.

All available ECG results will be displayed in a data listing and include all information collected. In addition, the observations that are used as the baseline record (value) for each parameter will be flagged, and the change from baseline values at each post baseline (scheduled and unscheduled) visit will be presented. This listing will be presented by the treatment groups defined in section 4.6, sorted by participant ID and visit for the Safety Analysis Set, along with the age, sex, race and baseline weight of the participant.

13.5 Physical Examinations

Physical examinations will be conducted at the time points specified in the study procedure schedule (section 19). Full physical examinations will include, at a minimum, assessment of the following: general appearance, head, ears, eyes, nose and throat, neck (including thyroid and lymph nodes), respiratory system, cardiovascular system, gastrointestinal system, renal system, neurological condition, musculoskeletal system, skin, and any other focused assessments suggested by the presence of specific symptoms. Symptom directed physical examinations will be performed if clinically indicated, as determined by the Investigator.

All available physical examination results will be displayed in a data listing and include all information collected. This listing will be presented by the treatment groups defined in Section 4.6, sorted by participant ID and visit for the Safety Analysis Set, along with age, sex, race and baseline weight of the participant.

13.6 Body Weight and BMI

Body weight will be assessed at the time points specified in the study procedure schedule (section 19). All available body weight results and the corresponding BMI calculated using Height at Screening will be displayed in a data listing. This listing will be presented by the treatment groups defined in Section 4.6, sorted by participant ID and visit for the Safety Analysis Set, along with age, sex, race and baseline weight of the participant.

In addition, for MAD cohort 2 and 3, body weight will be measured at day-1, day 15 and day 22 and corresponding BMI would be calculated using formula as below:

$$\text{Body Mass Index (kg/m}^2\text{)} = \frac{Weight\ (kg)}{[\text{Height (m) at Screening}]^2}$$

For these treatment groups summary statistics in accordance with section 4.2 will be presented for baseline and for each scheduled post baseline scheduled visit (which also includes the change from baseline).

13.7 Simplified Nutritional Appetite Questionnaire

A Simplified Nutritional Appetite Questionnaire (SNAQ) will be taken at the time points specified in the study procedure schedule (Section 19). The SNAQ consists of four questions assessing the participant's appetite:

- My appetite is:
  - a = Very poor; b = Poor; c = Average; d = Good; e = Very good
- When I eat, I feel full after:
  - a = Eating only a few mouthfuls
  - b = Eating about a third of a plateful
  - c = Eating over half a plateful
  - d = Eating most of the food
  - e = Hardly ever
- Food tastes:
  - a = Very bad; b = Bad; c = Average; d = Good; e = Very good
- Normally I eat:
  - a = Less than one full meal a day
  - b = One meal a day
  - c = Two meals a day
  - d = Three meals a day
  - e = More than three meals a day, including snacks

All available SNAQ results will be displayed in a data listing and include all information collected. The listings will be presented by the treatment groups defined in section 4.6, sorted by participant ID and visit for the Safety Analysis Set, along with age, sex, race and baseline weight of the participant.

13.8 Stool Diary

A stool diary will be completed by participants starting on Day 1 until discharge to monitor effects of study treatment on gastrointestinal function.

All available stool diary results will be displayed in a data listing and include all information collected. This listing will be presented by the treatment groups defined in Section 4.6, sorted by participant ID and visit for the Safety Analysis Set, along with age, sex, race and baseline weight of the participant.

13.9 Death details

In the event of a participant death all details will be captured in a separate form. A listing will be provided detailing date of death, primary cause of death and if an autopsy was performed.

14 PHARMACOKINETICS

14.1 Plasma and Urine Concentration Data

Individual plasma and urine concentrations of MVD1 and metabolites will be used as supplied by the laboratory. The units of concentration will be presented as they are received from the laboratory. The actual sampling, if available, date and time will be listed for plasma, by participant and nominal sampling time, with time deviation (difference in hours between nominal and actual sampling times) calculated. Individual plasma concentrations of MVD1 and metabolites over actual time will be plotted by cohort with the concentration result (y-axis) displayed for the PK Analysis set on a linear and semi-logarithmic scale.

14.2 Pharmacokinetic Parameter Calculation

A non-compartmental analysis consistent with the oral route of administration will be conducted in plasma using Phoenix WinNonlin software version 8.3. Following oral (capsule) route of administration, MVD1 and metabolites will be analysed using the extravascular model. Parameters will be generated following dosing on Day 1(Parts A and B) and Day 15 (Part B), using actual sampling times and doses, if available. For the purpose of the PK parameter calculations, concentrations that are BQL will be treated as zero. Following the 1st dose on Day 1, predose samples will be assigned a value of zero. If predose is not present following repeat dosing, C_{min} within the tau period (where tau = 12) may be duplicated as predose.

The following PK parameters will be calculated for each administration as well as for the overall sampling period , within each sampling occasion:

Parameter	**Definition**
C_{max}	Individual maximum concentration values, directly determined from the plasma concentration time profiles for each participant.
C_{min}	Individual minimum concentration values, directly determined from the plasma concentration time profiles for each participant, following repeat dosing only.
t_{max}	The time to attain maximum concentration. If the same C_{max} concentration occurs at different time points, t_{max} is assigned to the first occurrence of C_{max}.
t_{last}	Time of last measurable observed concentration.
AUC_{last}	The area under the plasma concentration-time curve from time zero to the last time point with measurable concentration using the linear trapezoidal.
AUC_{0-12}	The area under the plasma concentration time curve from time zero to 12 hours post dose, using the linear trapezoidal rule. (Part A only)
R_{AUC}	Accumulation ratio calculated as AUC_{last} repeat dose/AUC_{last} single dose using the same the same or similar t_{last}.
R_{Cmax}	Accumulation ratio calculated as C_{max} repeat dose/C_{max} single dose
M:P C_{max}	Metabolite to parent drug ratios of C_{max} calculated in mol units.
M:P AUC_{last}	Metabolite to parent drug ratios of AUC_{last} calculated in mol units.

Where data allows the calculation of slope related parameters, the following parameters will be included:

AUC_{inf}	The area under the plasma concentration-time curve over the time interval from time 0 extrapolated to infinity, after each administration on Day 1.
$t_{½}$	The terminal elimination half-life.
CL/F	Plasma clearance following oral route of administration, defined as the volume of plasma cleared of drug per unit of time, where F is the fraction of drug absorbed following subcutaneous administration.
V_z/F	The apparent volume of distribution in plasma, determined from the terminal elimination phase during terminal phase following oral route of administration, where F is the fraction of drug absorbed following administration.

Urine concentrations will be used to determine the following PK parameters:

A_e	Total amount of parent drug excreted unaltered in urine, calculated as a cumulative sum of the amount excreted across collection intervals.
F_e	Fraction of the dose excreted in urine across collection intervals.
CL_r	Renal clearance, calculated as the total amount of parent drug excreted in urine, divided by the AUC calculated up to the end of the last collection interval.

The following will be considered for reporting the PK parameters:

- All AUC_{last} and C_{max} will be set to zero for descriptive statistics purposes if all concentrations were below the limit of quantification.
- No value of AUC_{inf}, $t_{½}$, CL/F and V_z/F will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile. Criteria which may indicate a failure to exhibit a terminal log-linear phase in the concentration-versus-time profile include:
    - Positive slope for log regression fit.
    - $r^2_{adj} < 0.85$.
    - Time points in the interval used in estimating the half-life span less than 1.5 half-lives.

The PK parameters which are not determined from PK analyses due to inadequate concentration data or missing data will be considered as 'not estimable (NE)'. The details of extrapolation for the determination of slope related parameters, including the number of timepoints used, λ_z, Adujsted Rsq, AUC percentage extrapolated, interval and interval/$t_{1/2}$ will be listed.

Reasons for exclusion of a participant or a sample from the descriptive statistics at the discretion of the PK analyst may include, but are not limited to, the following:

- Noncompliance with study procedures affecting PK (e.g., concomitant medication, over or underdosing).
- Too few collected samples to reliably estimate at least 1 PK parameter (e.g. participants who did not complete PK sample collection).
- Vomiting between administration and up to t_{max} or within 2 hours following administration.

Individual plasma and urine PK parameters will be listed, in the units supplied by the laboratory, except for CL/F, CL_r and V_z/F that may be reported in different units, if deemed necessary. All PK parameters will be reported to three significant figures.

14.3 Statistical Analysis of Plasma and Urine Concentrations and PK parameters

Plasma and urine concentrations and PK parameters will be summarized (number of non-missing observation [n], arithmetic mean, standard deviation, coefficient of variation [CV%], geometric mean, median, minimum and maximum and geometric CV%) will be calculated for each time point and summarized by treatment cohorts. Urine Concentrations will be summarised by interval rather than timepoint. Concentrations below the lower limit of quantification (BLQ) will be treated 0 in the calculation of summary statistics, except geometric mean. BLQ values will be excluded from the calculation of geometric mean.

When reporting descriptive statistics for concentration and PK parameter, data will be reported to three significant figures. Mean plasma concentrations over scheduled time on Day 1 and 15 as well as over the scheduled time from Day 1 to the end of the last administration on Day 15 will be plotted with the concentration result (y-axis) displayed for the PK Analysis set on a linear and semi-logarithmic scale.

Dose proportionality will be assessed using the power model for all dosed cohorts. Natural log-transformed PK parameter overall C_{max}, total AUC_{last} and AUC_{inf} on Days 1 (Parts A and B) and Day 15 (Part B) as following each administration on Day 1 (Part B), and natural log-transformed dose will be used to estimate the slope parameter and the 90% confidence interval for the slope.

Plasma PK parameters will be assessed by fitting the following power model and testing the null hypothesis of linearity, that $\beta = 1$, by a general linear model approach using the GLM procedure in SAS:

$$\ln(Parameter) = \alpha + \beta \times \ln(Dose) + random\ error$$

Dose proportionality is generally concluded if the 90% confidence interval around the slope estimate (β) includes the value of 1. R square will also be computed.

The relationship between PK parameters in plasma and dose will also be presented graphically. All tables and figures will be produced.

15 PHARMACODYNAMICS

All pharmacodynamic endpoints will be analyzed using the Pharmacodynamic Analysis Set and presented for Part B only.

15.1 Serum Biomarkers

The following biomarkers to be assessed will be taken at the time points specified in the study procedure schedule (Section 19):

- Glucose, Insulin, C peptide, hsCRP, Fructosamine, Glycohemoglobin (Cohort MAD 1 and MAD 2 only), Free fatty acids, Triglycerides, Leptin levels

Continuous data summary statistics (as described in Section 4.2) will be presented for values and change from baseline value at baseline and each scheduled post baseline visit. A figure will also be presented showing mean values over time for each parameter, with all treatment groups presented on the same page.

All serum biomarker results will be presented in a data listing and include all information collected. In addition, the observations that are used as the baseline record (value) for each parameter will be flagged, and the change from baseline values (where applicable) at each scheduled post baseline (scheduled and unscheduled) visit will be presented. This listing will be presented by the treatment groups defined in section 4.6, sorted by participant ID and visit, along with age, sex, race, and baseline weight of the participant.

15.2 Oral Glucose Tolerance Test (OGTT)

An Oral Glucose Tolerance Test will be conducted on Day -1 and on Day 16. The OGTT will be conducted following an overnight fast of at least 8 hours. After an initial blood sample has been collected to establish baseline fasting glucose, participants will be required to consume ~75 grams of glucose administered in 250 mL water. Blood samples will be obtained at 1 hour and 2 hours post glucose challenge to determine glucose tolerance.

Continuous data summary statistics (as described in Section 4.2) will be presented for glucose tolerance value and change from pre-drink value at each scheduled post drink timepoint, separately for Day -1 and Day 16. A figure will also be presented showing mean values at each visit and time point with all treatment groups presented on the same page. Additionally, a summary of day 16 individual glucose results minus the Day -1 results for each applicable drink timepoint will be provided. All OGTT results will be presented in a data listing and include all information collected. In addition, the observations that are used as the baseline record (value) for each parameter will be flagged, and the change from baseline values (where applicable) at each scheduled post baseline (scheduled and unscheduled) visit will be presented. This listing will be presented by the treatment groups defined in section 4.6), sorted by participant ID and visit, along with age, sex, race, and baseline weight of the participant.

16 EXPLORATORY

All exploratory endpoints will be analyzed using the Safety Analysis Set.

16.1 White Adipose Tissue Sampling

A single sample of white adipose tissue will be obtained by punch biopsy approximately 2 hours following the morning dose of study drug on Day 7 (Part B) which will be analysed for the presence of MVD1.

All white adipose tissue sampling results will be displayed in a data listing and include all information collected, including presence of MVD1. This listing will be presented by the treatment groups defined in section 4.6, sorted by participant ID and visit, along with age, sex, race, and baseline weight of the participant.

16.2 Patient Global Impression of Change (PGIC)

The PGIC is a scale that asks the participant to rate how much their disease has improved or worsened relative to a baseline state after starting an intervention. PGIC will be assessed at the time points specified in the study procedure schedule (Section 19).

- Since the start of the study, my general health is:

  1 = Much better
  2 = A little better
  3 = No change
  4 = A little worse
  5 = Much worse

All PGIC results will be displayed in a data listing and include all information collected. This listing will be presented by the treatment groups defined in section 4.6, sorted by participant ID and visit, along with age, sex, race, and baseline weight of the participant.

17 CHANGES TO THE PLANNED ANALYSIS

There are currently no changes to the planned analysis in the study protocol.

18 INTERIM AND FINAL ANALYSIS

18.1 Interim Analysis

No formal interim analyses are planned for this study.

18.2 Final Analysis (End of Study)

The final analysis will be conducted after all Participants have completed the study, the clinical database has been locked, and the analysis populations have been approved.

The final analysis will be based on the final version of the SAP. Any deviations from the planned analysis will be documented in the CSR.

19 APPENDIX 1 TIME AND EVENTS SCHEDULE

19.1 Part A (SAD)

STUDY TIME SCHEDULE																		
STUDY PERIODS►	**Screen**	**Confinement**																**EoS/ETV**
STUDY DAY►	**-28 to -2**	**-1**	**1**												**2**	**3**	**4**	**8 (± 1 day)**
STUDY HOUR			**Pre**	**0**	**0.25**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**24**	**48**	**72**	**1**
VISIT & FOLLOW UP SCHEDULE																		
CLINIC VISIT	X	X																X
Informed Consent	X																	
Eligibility Criteria [1]	X	X	X															
Randomisation [2]			X															
Demographics	X																	
Medical History	X																	
Height [3]	X																	
Body Weight [3]	X	X																
Concomitant Medication Assessment [4]	X	X	X												X	X	X	X
Alcohol breath test	X	X																
Urine drugs of abuse and cotinine	X	X																
Serology (HIV/Hepatitis)	X																	
COVID-19 test [5]	X	X																
12 Lead ECG [6]	X	X	X			X		X			X			X	X	X	X	X
Physical Examination (Full) [7]	X																	X
Physical Examination (Symptom directed) [8]		X	X	X														
Vital Signs (BP, HR, temp) [9]	X	X	X			X		X			X			X	X	X	X	X
Pregnancy Test (Serum) [10]	X																	X
Pregnancy Test (Urine) [10]		X																
Serum FSH test [11]	X																	
Clinical Laboratory Blood and Urine Tests [12]	X	X													X		X	
PK Blood sampling [13]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
PK Urine sampling [14]		X			X													
AEs [15]		X																
Stool Diary [16]			X															
Dose administration [17]				X														

Abbreviations: AEs = adverse events; BL = baseline; BP = blood pressure; EoS = end of study; ETV = early termination visit; HR = heart rate; Temp = temperature; ECG = electrocardiogram; FSH = Follicle stimulating hormone, HIV = Human immunodeficiency virus; SAD = single ascending dose; PK = pharmacokinetic.

Notes: Schedule of Assessments Part A, (SAD Cohorts S1 to S3)

1 Eligibility to be confirmed on Day 1 prior to dosing after completion of all eligibility assessments.

2 Randomisation to be performed after eligibility confirmation on Day 1.

3 Body mass index to be calculated using the height and body weight values recorded at screening.

4 To be evaluated throughout the study as indicated

5 A COVID-19 polymerase chain reaction or rapid antigen test to be performed at screening and again on admission to the clinical facility on Day -1 as required by clinical study site and state health policy. A COVID-19 test may also be required at other times throughout the study if clinically indicated.

6 All ECGs will be in triplicate, conducted within 5 minutes with each recording separated by at least 1 minute. ECGs will be taken after participants have been resting quietly in a supine position for at least 5 minutes. Predose ECGs should be performed within 1.5 hours prior to dosing. All postdose ECGs should be performed within a ± 20-minute window of the scheduled timepoint except for assessments performed at EoS/ETV where this time window does not apply.

7 Full physical examinations will include, at a minimum, assessment of the following: general appearance, head, ears, eyes, nose and throat, neck (including thyroid and lymph nodes), respiratory system, cardiovascular system, gastrointestinal system, renal system, neurological condition, musculoskeletal system, skin and any other focused assessments suggested by the presence of specific symptoms.

8 Symptom directed physical examination (focused assessments suggested by the presence of specific symptoms) will be performed if clinically indicated, as determined by the Investigator. A symptom-directed physical examination assessment will be performed on Day -1 (Check-in) and within 1.5 hours prior to dosing on Day 1.

9 Participants should be resting in a supine position for at least 5 minutes prior to and during vital signs measurements. Predose vital signs assessments should be performed within 1.5 hours prior to dosing. All postdose vital signs assessments should be performed within a ± 20-minute window of the scheduled timepoint except for assessments performed at the EoS/ETV where this time window does not apply.

10 For women of childbearing potential only. If the urine test is positive it will be confirmed by a serum pregnancy test.

11 Follicle- stimulating hormone (FSH) levels will be measured in female participants who report as postmenopausal. If serum FSH levels are below the cut-off limit as defined by the local testing laboratory, participants will be considered to be of childbearing potential and will be required to use appropriate contraception for the duration of the study.

12 To be conducted at screening and on Day -1 to determine study eligibility. Laboratory test results will be assessed by the investigator, or medically qualified nominee, before confirmation of eligibility on Day 1. Any deviation in laboratory values that are confirmed on re-examination to be clinically significant by the investigator, or medically qualified nominee (i.e. would jeopardize the safety of the participant or impact on the validity of the study results), will result in exclusion of that participant. A blood and urine test will also be conducted postdose on Day 2 and Day 4 as part of the drug safety assessment.

13 Blood PK sampling to be conducted throughout the study as indicated in Appendix 9.

14 Pooled urine will be collected overnight (from approximately 10 pm) on Day -1 up to predose on Day 1 for predose PK assessment and for up to 24 hours postdose for postdose PK assessment

15 Assessment to be performed throughout the study as indicated

16 Stool diary to be completed starting on Day 1 until discharge on Day 4.

17 Single oral dose to be administered following an overnight fast of at least 8 hours. Fasting will be required for at least a further 4 hours postdose. During this time no food or beverages are to be consumed by the participant except for water.

19.2 Part B (MAD)

STUDY TIME SCHEDULE																							
STUDY PERIODS►	**Screen**	**Confinement**																					**EoS/ETV**
STUDY DAY►	**-35 to -2**	**-1**	**1**		**2,4**		**7**			**10**		**3, 5, 11**		**6, 8, 9, 12, 13,14**		**15**			**16**	**17**	**18**	**22 (± 1 day)**
STUDY HOUR[1]			**Pre**	**4**	**Pre**	**4**	**Pre**	**2**	**4**	**Pre**	**4**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**2**	**4**	**24**	**48**	**72**	
VISIT & FOLLOW UP SCHEDULE																							
CLINIC VISIT	X	X																					X
Informed Consent	X																						
Eligibility Criteria [2]	X	X	X																				
Randomisation [3]			X																				
Demographics	X																						
Medical History	X																						
Height [4]	X																						
Body Weight [4]	X	X																					
Concomitant Medication Assessment [5]	X	X	X		X		X			X		X		X		X			X	X	X	X	
Alcohol breath test	X	X																					
Urine drugs of abuse and cotinine	X	X																					
Serology (HIV/Hepatitis)	X																						
COVID-19 test [6]	X	X																					
12 Lead ECG [7]	X	X	X	X	X	X	X		X	X	X					X		X			X	X	
Physical Examination (Full) [8]	X																					X	
Physical Examination (symptom directed) [9]		X	X																				
Vital Signs (BP, HR, temp) [10]	X	X	X	X	X	X	X		X	X	X					X		X	X	X	X	X	
Pregnancy Test (Serum) [11]	X																					X	
Pregnancy Test (Urine) [11]		X																					
Serum FSH test [12]	X																						
Urine protein dipstick test [13]			X		X		X			X		X		X		X							
Urine albumin:creatinine ratio test [14]			X		X		X			X		X		X		X							
Clinical Laboratory Blood and Urine Tests [15]	X	X										X							X		X		
PK Blood sampling [16]			X													X							
PK Urine sampling [17]		X														X							

STUDY TIME SCHEDULE																							
STUDY PERIODS►	**Screen**	**Confinement**																					**EoS/ETV**
STUDY DAY►	**-28 to -2**	**-1**	**1**		**2,4**		**7**			**10**		**3, 5, 11**		**6, 8, 9, 12, 13,14**		**15**			**16**	**17**	**18**	**22 (± 1 day)**
STUDY HOUR			**Pre**	**4**	**Pre**	**4**	**Pre**	**2**	**4**	**Pre**	**4**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**2**	**4**	**24**	**48**	**72**	
VISIT & FOLLOW UP SCHEDULE																							
CLINIC VISIT	X	X																					X
PD Blood chemistry sampling [18]			X					X									X		X				
PD OGTT [19]		X																	X				
Adipose tissue Biopsy [20]								X															
PGIC questionnaire [21]																			X				
AEs [22]		X																					
SNAQ [23]		X															X						
Stool Diary [24]		X																					
Dose administration [25]			X		X		X			X		X		X		X							

Abbreviations: AEs = adverse events; BP = blood pressure; EoS = end of study; ETV = early termination visit; HR = heart rate; Temp = temperature; ECG = electrocardiogram, OGTT = Oral glucose tolerance test; PD = pharmacodynamic; PK = pharmacokinetic; Pre = predose administration; Post = postdose administration; WAT = White adipose tissue. Study hour indicates number of hours postdose; HIV = human immunodeficiency virus; MAD = multiple ascending dose; PGIC = Patient general impression of change; SNAQ = Simplified Nutritional Appetite Questionnaire

Notes: Schedule of Assessments Part B, (MAD Cohorts M1 to M3)

1 Pre and post assessments on dosing Days 1 to 15 apply to both the morning and evening dose of study drug on Day 1. On all other days pre and post dose assessments refer to the morning dose only.

2 Eligibility to be confirmed on Day 1 prior to dosing after completion of all eligibility assessments.

3 Randomisation to be performed after eligibility confirmation on Day 1.

4 Body mass index to be calculated using the height and body weight values recorded at screening.

5 To be evaluated throughout the study as indicated

6 A COVID-19 polymerase chain reaction or rapid antigen test to be performed at screening and again on admission to the clinical facility on Day -1 as required by clinical study site and state health policy. A COVID-19 test may also be required at other times throughout the study if clinically indicated.

7 All ECGs will be in triplicate, conducted within 5 minutes with each recording separated by at least 1 minute. ECGs will be taken after participants have been resting quietly in a supine position for at least 5 minutes. Predose ECGs should be performed within 1.5 hours prior to dosing. All postdose ECGs should be performed within a ± 30-minute window of the scheduled timepoint except for assessments performed at EoS/ETV where this time window does not apply. 4 hour postdose ECG assessment only required after both morning and evening dose on Day 1 and following the morning dose only on all other dosing days.

8 Full physical examinations will include, at a minimum, assessment of the following: general appearance, head, ears, eyes, nose and throat, neck (including thyroid and lymph nodes), respiratory system, cardiovascular system, gastrointestinal system, renal system, neurological condition, musculoskeletal system, skin and any other focused assessments suggested by the presence of specific symptoms.

9 Symptom directed physical examination (focused assessments suggested by the presence of specific symptoms) will be performed if clinically indicated, as determined by the Investigator. A symptom-directed physical examination assessment will be performed on Day -1 (Check-in) and within 1.5 hours prior to first (morning) dose administration on Day 1 to Day 15. Postdose assessments will also be performed if required.

10 Participants should be resting in a supine position for at least 5 minutes prior to and during vital signs measurements. Predose vital signs assessments should be performed within 1.5 hours prior to dosing. All postdose vital signs assessments should be performed within a ± 30-minute window of the scheduled timepoint except for assessments performed at the EoS/ETV where this time window does not apply. 4 hour postdose vital signs assessment only required after both morning and evening dose on Day 1 and following the morning dose only on all other dosing days.

11 For women of childbearing potential only. If the urine test is positive, it will be confirmed by a serum pregnancy test.

12 Follicle- stimulating hormone (FSH) levels will be measured in female participants who report as postmenopausal. If serum FSH levels are below the cut-off limit as defined by the local testing laboratory, participants will be considered to be of childbearing potential and will be required to use appropriate contraception for the duration of the study.

13	Test to be administered on first morning urine sample within 6 hours prior to first dose administration on Day 1. A urine dipstick protein test showing more than a trace of protein prior to first dose on Day 1 will result in participant exclusion. A first morning urine protein dipstick test will also be conducted prior to administration of the first daily dose of study drug on Days 2 to 15. Urine dipstick protein testing will also be required on Days 1 to 14 prior to administration of the second (evening) dose of study drug. First morning urine dipstick testing will also be required following the dosing period on Days 16 to 18. Detection of more than a trace of protein predose on Day 1 pre dose 2 and prior to any dose administered on Days 2 to Day 15 will result in suspension of dosing for the participant. All urine dipstick tests showing a trace of protein or less will be sent for urine ACR assessment.
14	Urine ACR to be assessed at the timepoints specified for all urine dipstick protein tests where dipstick test shows a trace of protein or less. This test will be in addition to urinalysis conducted as part of standard clinical safety laboratory assessments.
15	To be conducted at screening and on Day -1 to determine study eligibility. Clinical laboratory test results will be assessed by the investigator, or medically qualified nominee, before confirmation of eligibility on Day 1. Any deviation in laboratory values that are confirmed on re-examination to be clinically significant by the investigator, or medically qualified nominee (i.e. would jeopardize the safety of the participant or impact on the validity of the study results), will result in exclusion of that participant. A clinical laboratory blood and urine test will also be conducted prior to the first (morning) dose only on Days 3, 5 and 11 and at 24 hours and 72 hours post final (Day 15) dose on Day 16 and Day 18 respectively as part of the drug safety assessment.
16	Blood PK sampling to be conducted throughout the study as indicated in Appendix 10.
17	Pooled Urine will be collected overnight (from approximately 10 pm) on Day -1 up to predose 1 on Day 1 for predose urine PK assessment and on Day 15 for up to 24 hours post dose for postdose urine PK assessment
18	Blood chemistry PD sampling to be conducted predose 1 on Day 1, at approximately 2 hours postdose 1 on Day 7, at approximately 2 hours post final dose on Day 15, and 24 hours post final dose (Day 16). Blood PD markers will include: Leptin, C peptide, hsCRP, glycoalbumin/glycohaemoglobin, triglycerides, free fatty acids, fasting glucose, insulin in accordance with the sampling timepoints shown in Appendix 11.
19	Oral glucose tolerance test to be conducted in a fasted state on Day -1 and on Day 16 (day after final dose) as indicated in Appendix 11.
20	Single needle biopsy (aspiration) of subcutaneous white adipose tissue sampling to be obtained approximately 2 hours (± 1 hour) after first (morning) dose of study drug on Day 7
21	PGIC questionnaire to be evaluated on Day 16 only (the day after the last dose of study drug)
22	AEs to be monitored throughout the study as indicated
23	Simplified nutritional appetite questionnaire (SNAQ) based on appetite assessments at Day -1 after dinner, and again on Day 15 after dinner.
24	Stool diary to be completed starting on Day 1 until discharge on Day 18.
25	Two daily oral doses of study drug taken 12 hours apart (morning and evening) will be administered on Days 1 to 14. Final single dose administration will be on the morning of Day 15. All doses will be administered following a fasting for at least 2 hours. Fasting will be required for at least a further 2 hours after each dose on each dosing day. During this time no food or beverages are to be consumed by the participant except for water.