Calibr
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Research

CLINICAL STUDY PROTOCOL

A Two-Part Phase 1 Study to Assess the Safety, Tolerability, and Pharmacokinetics of PDM608 in Healthy Adult Subjects

Sponsor Study Number: CBR-PDM608-3001

IND Number: 163942

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1.0	Original Protocol	30 Jan 2023

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3 Synopsis

Sponsor:	Investigational Medicinal Product:	IND No.:
Calibr, a Division of Scripps Research	PDM608	**163942**

Title of Study: A two-part Phase 1 study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of PDM608 in healthy adult subjects

Study Center: Quotient Sciences – Miami, Inc., 3898 NW 7th Street, Miami, FL 33126, USA

Objectives and Endpoints: Please see Section 7 of the protocol

Methodology and Study Design:

This is a 2-part, single-center, first-in-human study of single ascending doses (SAD; Part 1) and multiple ascending doses (MAD; Part 2) of PDM608 in healthy adult subjects.

Part 1 is a double-blind, randomized, placebo-controlled assessment of subcutaneous (SC) SAD administrations of PDM608 across 5 cohorts of subjects. All SAD cohorts will follow a sentinel design. Following completion of each cohort, safety and tolerability data will be reviewed to determine whether to progress to the next dose level and the dose level for the next cohort. Anticipated SAD cohort PDM608 dose levels are described in Table 2; see Section 8.1.1 for further details.

Part 2 is a double-blind, randomized, placebo-controlled assessment of SC MAD administrations (once weekly for 4 weeks) of PDM608 across up to 4 cohorts of subjects. Following completion of each cohort the safety and tolerability data will be reviewed to determine whether to progress to the next dose level and the dose level to be administered. MAD cohorts will receive PDM608 regimens as described in Table 3; see Section 8.1.2 for further details.

A Safety Advisory Committee (SAC) (Section 8.2) will oversee decisions to dose the next dose level for SAD and MAD cohorts, and the initiation of Part 2 (MAD). MAD cohorts will not include a sentinel design unless requested by the SAC.

Number of Subjects Planned:

It is planned to enroll 40 healthy adult subjects into up to 5 cohorts of 8 subjects each in Part 1 (SAD) to ensure data in a minimum of 6 evaluable subjects per cohort. Up to 2 replacement subjects per cohort may be enrolled into Part 1 of the study.

It is planned to enroll up to 48 healthy adult subjects into up to 4 cohorts of 12 subjects each (MAD Cohort 4 is optional) in Part 2 (MAD) to ensure data in a minimum of 8 evaluable subjects per cohort. Up to 3 replacement subjects per cohort may be enrolled into Part 2 of the study.

See Section 8.4 for further details.

Duration of Study:

In Part 1 (SAD), subjects will receive a single administration on one occasion. The estimated time from consent until the follow-up visit is 7 weeks.

In Part 2 (MAD), subjects will receive multiple administrations (4 doses) across a period of 4 weeks (once weekly dosing). The estimated time from consent until the follow-up visit is 13 weeks.

Main Inclusion Criteria:

Healthy men and non-pregnant, non-lactating healthy women of non-childbearing potential, aged 18 to 65 years inclusive at time of signing informed consent. See Section 10.

Body mass index of 18.0 to 33.0 kg/m^2 as measured at screening.

Investigational Medicinal Product, Dose and Mode of Administration:
The following investigational medicinal products (IMPs) will be used in this clinical study:

- PDM608 solution - 25 mg/mL
- Placebo for PDM608 - 0 mg/mL

See Section 5.2 and Pharmacy Manual for further IMP details.

Pharmacokinetic Assessments:

Blood samples will be collected throughout each study part for PK analysis. Analysis of PDM608 plasma concentration data will be performed using appropriate non-compartmental techniques to obtain estimates of the PK parameters detailed in Table 4, where possible and appropriate.

Immunogenicity Assessments:

Blood samples will be collected throughout each study part for detection and titering of antidrug antibodies (ADA) using a validated assay.

Pharmacodynamic Assessments:

Blood samples will be collected throughout each study part for pharmacodynamic (PD) analysis, which include the number of immunologic cell types and the concentration of cytokines.

Safety Assessments:

The safety assessments to be conducted include adverse event monitoring, clinical laboratory tests (clinical chemistry, hematology and urinalysis), physical examinations, 12-lead electrocardiograms and vital signs.

Statistical Methodology:

No formal statistical analysis will be performed on the safety and tolerability data for this study. Descriptive statistics are considered adequate for a study of this type. Descriptive summaries for all PK and PD data by cohort will be provided. In addition, formal statistical analyses will be performed to assess dose proportionality (Part 1 and Part 2), accumulation following multiple dosing (Part 2) and changes in the numbers of Treg cells. See Section 14.4 for further information.

Sample Size and Power:

Based on experience from previous similar studies, the target numbers of subjects to be enrolled (N = 8 and N = 12) should be sufficient to achieve a minimum of 6 and 8

evaluable subjects in each cohort in Part 1 and Part 2, respectively. Based on sargramostim treatment of Parkinson's Disease patients (Gendelman 2017), the MAD sample size is sufficient to detect an increase of 5% in mean Treg percentages compared with pooled placebo subjects, which is considered a meaningful treatment effect for future patient studies (Section 14.1). Similar sample sizes have detected changes in WBC, MNC, monocytes and eosinophils in healthy volunteers (Lane 1995; Fishmeister 1999).

An evaluable subject for Part 1 is defined as a subject who has received the IMP dose and completed relevant safety and tolerability assessments (inclusive of all scheduled hematology assessments) through 96 hours post-dose.

An evaluable subject for Part 2 is defined as a subject who has received all 4 doses of IMP and completed relevant safety and tolerability assessments (inclusive of all scheduled hematology assessments) through 96 hours post-final dose (Dose 4).

4 List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibodies
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	accumulation ratio
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CK	creatine kinase
CLcr	creatinine clearance
COVID-19	Coronavirus Disease 2019
CRF	case report form
CSF	colony-stimulating factor
CSPM	Clinical Sample Processing Manual
CV%	coefficient of variation
CYP	cytochrome P450
DC	discontinuation
DMP	Data Management Plan
ECG	electrocardiogram
eCRF	electronic case report form
F	absolute bioavailability
FDA	US Food and Drug Administration
FIH	first in human
FSH	follicle stimulating hormone
GCP	good clinical practice
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony stimulating factor
HBsAg	hepatitis B surface antigen
HCV Ab	hepatitis C virus antibody
HED	human equivalent dose

Abbreviation	Definition
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	50% inhibition of activity
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	investigational medicinal product
IRB	Institutional Review Board
ISF	Investigator Site File
IV	intravenous
MAD	multiple ascending dose
NOAEL	no-observed-adverse-effect-level
NSAOD	nonsteroidal anti-inflammatory
PAD	pharmacologically active dose
PD	pharmacodynamic
PK	pharmacokinetic(s)
QA	quality assurance
QTcF	Corrected QT interval by Fridericia's formula
RAP	Reporting and Analysis Plan
SAC	safety advisory committee
SAD	single ascending dose
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBS	short bowel syndrome
SC	subcutaneous
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TMF	trial master file
Treg	T-regulatory cells
ULN	upper limit of normal
WOCBP	woman of childbearing potential
WONCBP	woman of non-childbearing potential

The pharmacokinetic definitions used in this study are presented in Section 14.3.

5 Background Information

5.1 Introduction

Granulocyte-macrophage colony stimulating factor (GM-CSF; also known as colony-stimulating factor 2, CSF2) is a glycoprotein cytokine secreted by macrophages, T cells, mast cells, natural killer cells, endothelial cells and fibroblasts. It is an important hematopoietic growth factor and immune modulator that has profound effects on the function of circulating peripheral leukocytes. GM-CSF binds with high affinity to the GM-CSF receptor, a heterodimeric receptor expressed by granulocyte-monocyte progenitors, monocyte progenitors and most innate immune cells including granulocytes, monocytes, macrophages, dendritic cells and microglia.

Sargamostim (Leukine®) is a yeast-derived, recombinant GM-CSF (rGM-CSF) agonist used to treat neutropenia, to mobilize stem cells for hematopoietic stem cell transplant, to accelerate myeloid reconstitution following bone marrow transplant and to facilitate recovery from myelosuppression. Recent clinical studies suggest that sargramostim may also provide clinical benefits for patients with Alzheimer's disease and Parkinson's disease (Gendelman 2017, Olson 2021, Potter 2021). These effects may be mediated at least in part by selective increases in Treg numbers (Chen 2016, Gendelman 2017, Kosloski 2013, Olson 2020). Sargramostim treatment is generally safe and well-tolerated; however, sargramostim has a short half-life, and chronic treatment for these and other indications is possible only with daily subcutaneous (SC) injections. This dosing regimen is burdensome for patients.

Calibr is developing PDM608, a novel molecule consisting of rGM-CSF fused to the complementarity-determining region (CDR) of the immunoglobulin heavy chain of the clinically approved human trastuzumab (branded Herceptin®) antibody. Protein design was optimized by incorporating wild-type GM-CSF peptide into an engineered, de-immunized antibody scaffold with optimized linkers. PDM608 has a substantially longer half-life in animals (~200-300 hours in rat) and improved pharmacokinetic/pharmacodynamic (PK/PD) profile over sargramostim. PDM608 is being developed as a once-weekly injectable therapy for neurodegenerative, autoimmune and immuno-oncology applications.

5.2 Investigational Medicinal Product(s)

The investigational medicinal products (IMPs) that will be used in this clinical study are presented in Table 1.

Table 1 Investigational Medicinal Products

Investigational Medicinal Product Name:	PDM608 solution for SC injection	Matching placebo for PDM608 solution for SC injection
Product Type:	Test	Placebo
Dosage Formulation:	Solution	Solution
Unit Dose Strength(s)/ Dosage Level(s):	25 mg/mL	0 mg/mL
Route of Administration:	SC	SC

Dosing instructions:	Administered as a SC injection to the abdomen	Administered as a SC injection to the abdomen
Packaging and Labeling:	Each vial is individually labelled. Each box contains 100 vials.	Each vial is individually labelled. Each box contains 36 vials.
Storage and Handling:	-20°C, excursions permitted between -15°C to -25°C	-20°C, excursions permitted between -15°C to -25°C
Manufacturer:	Manufactured by Wuxi	Manufactured by Wuxi

SC: subcutaneous. Further information will be provided in the Pharmacy Manual.

The PDM608 solutions for SC and matching placebo injections are un-licensed medicinal products for use only in the proposed clinical trial.

Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments will be stored in a secure, environmentally-controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

IMPs will be reconciled and destroyed in accordance with the applicable standard operating procedures (SOPs).

5.3 Previous Study Findings

This is a first-in-human study. Full details of non-clinical study findings can be found in the Investigator's Brochure (IB). A summary of the non-clinical findings is provided below.

5.3.1 Nonclinical Findings

5.3.1.1 Nonclinical Pharmacokinetics,Metabolism and Toxicology

In vivo pharmacokinetics (PK), toxicokinetics and *in vitro* metabolism of PDM608 and toxicology have been evaluated and PDM608 exhibited a low clearance (< 0.1 mL/min/kg) and volume of distribution (< 0.2 L/kg) in mice, rats, and monkeys following IV administration. The half-life of PDM608 in mice, rats, and monkeys were 21.4 hr, 211 hr and 19.8 hr, respectively. SC bioavailability was > 44%.

Following IV and SC administration at 5 mg/kg to cynomolgus monkeys, the number of lymphocyte subpopulations in cynomolgus monkey peripheral blood showed a transient increase in Total T cells, Helper T cells, Regulatory Helper T cells, Cytotoxic T cells, Regulatory Cytotoxic T cells and B cells, and then decreased close to baseline.

The PK, PD, and safety pharmacology of PDM608 were assessed following repeat dosing SC administration to naïve male cynomolgus monkeys at 0.1, 0.5, or 5 mg/kg PDM608 (once weekly for 22 days). The systemic exposure of PDM608 increased proportional to dose or greater than dose proportional. PDM608 induced a dose-proportional increase in TREG. Most PDM608-treated animals at all doses were positive for ADAs from 336 through 672 hours.

In a non-GLP 14-day dose range-finding toxicity study in cynomolgus monkeys, the toxicity profile and PK of PDM608 was accessed at doses of 0, 5, 30, or 120 mg/kg (actual doses were 0, 6.2, 37.3, and 149.3 mg/kg) over 14 days by SC injection on Days 1, 4, 7, 10, and 13. The systemic exposure increased proportional to dose or greater than dose

proportional. The systemic exposure was lower at the end of study than Day 1, likely due to the immunogenicity response.

In a 4-week GLP toxicity study in cynomolgus monkeys (CBR-PDM608-0106), PDM608 was administered once every 3 days by SC injection at dose levels of 0, 2, 6, or 18 mg/kg/dose. The systemic exposure increased dose proportionally. On Day 13 and 28, plasma concentrations were below the lower limit of quantification in most of the animals, likely due to high ADA.

The NOAEL with PDM608 effect for this study was considered to be 18 mg/kg/dose. There was no NOAEL identified for the effects of ADA induced by PDM608.

Overall, no marked sex difference was observed in systemic exposure.

5.3.1.2 Clinical Findings

Effects of PDM608 in humans have not yet been characterized. It is anticipated that PDM608 will stimulate immune cells and cytokine production in a similar fashion to the short-acting GM-CSF, sargramostim, which shares a similar mechanism of action. Please see the Investigator's Brochure for a brief description of the safety of GM-CSF in different populations.

Because it is a protein biologic, treatment with PDM608 could be associated with the generation of anti-drug antibodies (ADAs). ADAs have been observed in patients treated with rGM-CSF produced in *E. coli* and with sargramostim; these antibodies were associated with decreased treatment efficacy but not with increased likelihood of AEs (Ragnhammar 1994, Leukine package insert).

6 Rationale

6.1 Study Rationale

This Phase 1 study will evaluate the safety, tolerability, PK and PD of single ascending doses (SAD; Part 1) and multiple ascending doses (MAD; Part 2) of PDM608.

This study is placebo-controlled to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment. Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment groups and to enhance the validity of comparisons across dose groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

As this study will be the first time PDM608 has been administered to humans, sentinel dosing will be used for all SAD cohorts. The first two subjects of each cohort (i.e., one subject receiving active and one subject receiving placebo) will be dosed prior to the remaining subjects (sentinel group). After review of the safety data up to 72 hours post-dose the Investigator will decide whether to proceed with dosing the remaining subjects in the cohort (main group).

6.2 Dose Rationale

The recommendations of the following guidelines have been considered when setting the starting dose and escalation rules for this trial:

- Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with IMPs (EMEA/Committee for Medicinal Products for Human Use [CHMP]/SWP/28367/07 Rev. 1), 20 July 2017

Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). July 2005

PDM608 will be administered by SC injection to healthy participants beginning in Part 1 with a single starting dose of 350 µg (flat dose) with subsequent single dose escalation to anticipated doses of 1050, 3150, 6300, up to 12600 µg. The safety of PDM608 by this route has been assessed in non-GLP and GLP nonclinical toxicology studies in monkeys, and PD studies have been conducted in monkeys and was considered safe and well tolerated. A broad dose range was selected for adult healthy volunteers to ensure a safe starting dose, to assess the safety of PDM608 across the anticipated clinical range of drug exposures, and to provide PK and PD data for further clinical development.

The FIH starting dose for PDM608 was calculated using toxicology data together with a pharmacologically active dose (PAD)-based approach. The proposed starting dose of 350 µg in humans is adequately supported by data from the toxicology study in cynomolgus monkeys (CBR-PDM608-0106). Using the NOAEL of 18 mg/kg in monkeys, the HED-based safety factor is approximately 1161. With the predicted human PK at 350 µg, the dose-based, concentration (Cmax)-based, and exposure (AUC)-based safety factors are estimated to be 3600, 8333, and 857, respectively. This proposed starting dose is also expected to be lower than the PAD in humans based on the PD response in cynomolgus monkeys (a single dose of 0.5 mg/kg (IV/SC) achieved an increase in TReg Cells of ~1% (CBR- PDM608-0110)). Of note, as PDM608 is not cross-reactive in rats or mice but is fully cross-reactive in cynomolgus monkeys, monkeys are considered the pharmacologically relevant species. It should also be noted that PDM608 may be eliminated faster than projected at low doses, including the starting dose, due to the impact of target on PK (i.e., target-mediated drug disposition), which provides an additional safety margin for this FIH dose.

GM-CSF has demonstrated clinical activity in patients with PD at 6 µg/kg/day Leukine (1). The HED of PDM608 was calculated by matching the molar exposure of Leukine (6 µg/kg/day) and the lowest efficacious dose is 1.21 µg/kg (Q1W, based on Cmax). Considering that PDM608 is about 22-fold less potent than recombinant human GM-CSF, the lowest HED of PDM608 is projected to be 27 µg/kg for every week [1.21 µg/kg (lowest HED of PDM608) x 22 = 27 µg/kg].

The proposed starting dose level of PDM608 at 350 µg (5 µg/kg for a 70 kg subject) is expected to be lower than the dose likely to have efficacy in humans. Escalation between cohorts will be limited to a maximum of 3-fold between SAD cohorts and a maximum of 3-fold between MAD cohorts. This is considered appropriate in the context of dose/exposure-toxicity and dose/exposure-effect relationship defined in non-clinical studies. Emerging clinical data relating to the safety and PK/PD and profile of PDM608 may also be considered, as appropriate and available, when dose decisions are made throughout the study.

Based on the maximum allowed escalations and anticipated PD activity, the highest anticipated dose will be 12600 µg. Using the NOAEL of 18 mg/kg in monkeys, the HED-based safety factor is approximately 32, With the predicted human PK at 12600 µg (assuming 70kg patients and 90% SC bioavailability), the dose-based, concentration (Cmax)-based, and exposure (AUC)-based safety factors are estimated to be 100, 231, and 24, respectively.

Doses administered will be predicted not to exceed a mean C_{max} of 103,950 ng/mL and a mean $AUC_{(0\text{-}24h)}$ of 1,775,000 ng.h/mL, which is the sex-averaged mean NOAEL exposure limits after the first dose of 18 mg/kg in the cynomolgus NOAEL 28-day good laboratory practice (GLP) toxicology study, in any individual subject.

The non-clinical program, containing pharmacology, PK, PD, and toxicology data of PDM608, supports the initiation of a human clinical study for the treatment of neurodegenerative diseases.

6.3 Population Rationale

As this is a Phase I study assessing the PK, PD, tolerability and safety of PDM608, the most relevant population is healthy volunteers. Subjects who are non-smokers without a history of alcohol, drug abuse or regular co-medication are proposed to avoid interaction on drug metabolism and noncompliance.

It is not known whether PDM608 can cause fetal harm when administered to pregnant women, affect male or female fertility, or whether it is secreted in human milk. Therefore, women of childbearing potential will not be enrolled in this study, men will be allowed to participate as long as they comply with the contraception requirements as detailed in Section 9.4, and men with pregnant partners will be excluded from the study (see Section 9.3).

Based on the above considerations and target population, healthy non-pregnant and non-lactating women of non-childbearing potential (WONCBP) and healthy men aged 18 to 65 years are considered suitable subjects for this study. GM-CSF preparations have previously been studied in healthy volunteers (Lane 1995; Fishmeister 1999).

6.4 Pharmacodynamic Rationale

GM-CSF is approved for peripheral blood mobilization of CD34+ stem cells for transplantation. The approved dose of sargramostim for autologous mobilization is 250 mcg/m2/day SC (6-7 mcg/kg) which greatly increases precursor cell frequencies. For allogeneic transplant, donors are often prepared with four daily doses of GM-CSF followed by apheresis.

One goal of the PDM608 early development program is to identify a safe, tolerated dose of PDM608 that increases peripheral blood Tregs, which can be profiled in neurodegenerative diseases, such as Parkinson's disease. Short-acting GM-CSF appears to increase various cell lineages with roughly similar kinetics, with the degree of change dependent on the cell type. We will take advantage of the known pharmacodynamic effects of GM-CSF to inform dose escalation decisions.

GM-CSF at a dose of 5-10 mcg/kg/day for 4-5 days increased numerous cell lineages in peripheral blood of healthy volunteers, with increases in WBC, MNC, PMN, monocytes,

and eosinophils (Lane 1995; Fishmeister 1999): WBC increased greater than 3-fold, MNC and monocytes increased greater than 2-fold and eosinophils increased greater than 7-fold. The time course of Treg elevation in humans is not well-known, but was increased two-fold after 2 weeks daily exposure to GM-CSF in persons with Parkinson's disease (Gendelman 2017). A preclinical PKPD study with PDM608 demonstrated dose-dependent elevation of Regulatory Helper T cells and Regulatory Cytotoxic T Cells in cynomolgus monkey 10 days after weekly dosing (CBR-PDM608-110).

An increase of 5% in mean Treg percentages compared with pooled placebo subjects may be considered a meaningful treatment effect for future patient studies (Section 14.1), thus dose escalation will be optimized through analysis of Tregs as a pharmacodynamic parameter.

Pharmacodynamic analysis may include immunophenotyping by flow cytometry to determine numbers/percentages of certain immune cells, and cytokine analysis (section 12), as well as analysis of a subset of the safety hematology labs (WBC, monocyte, and eosinophil values) as an indicator of pharmacodynamic activity.

The maximum PDM608 dose administered in either part of this trial will not exceed a dose that is more than two-fold above the dose at which any two of the following three pharmacodynamic activities are observed in a sample that includes a minimum 5 of 6 PDM608-treated subjects in SAD or 7 of 9 PDM608-treated subjects in MAD, treated within the same cohort, and observed at any laboratory timepoint up to and including 96 hours post-dose (SAD) and post-final dose (MAD):

- An increase in mean WBC from pre-dose baseline by ≥ 3-fold
- An increase in mean monocytes from pre-dose baseline by ≥ 2-fold
- An increase in mean eosinophils from pre-dose baseline by ≥ 7-fold

The above three hematologic parameters will be described and made available for review by the SAC when making dose level decisions.

Intra-subject changes are considered because of the wide-variability of hematological parameters between subjects, and because smaller numbers of subjects are allocated to placebo treatment. Multiple pharmacodynamic endpoints are selected to minimize the impact of outliers on mean values. A statistical test is not applied to these pharmacodynamic effects. Dose escalation beyond this point (as described above) is permitted in order to obtain pharmacokinetic and pharmacodynamic margin for subsequent patient studies. This pharmacodynamic limit assumes that PDM608 remains safe as defined by the other stopping rules in Section 8.5.

6.5 Safety Rationale

The major risks of PDM608 administration to humans are excessive pharmacology of stimulation of GM-CSF activity and the consequences of development of ADA against the product. The pharmacology of GM-CSF is outlined in the Investigator's Brochure. Common AE in clinical studies with sargramostim include injection site reactions, headache, bone pain, flu-like symptoms and increased blood leukocyte levels (Leukine USPI). This protocol specifies white count as an adverse event of special interest (Section

13.5). This protocol allows the use of acetaminophen if the Investigator believes it is appropriate to manage AE (Section 11.3). Sargramostim, a yeast derived GM-CSF, has been associated with the development of ADA, but there is little evidence that these antibodies result in AE, and the evidence that they reduce pharmacological activity of sargramostim is mixed (see the Investigator's Brochure). PDM608 is designed to have low immunogenicity in humans. This protocol will measure ADA with a validated assay. Serum sickness-like reactions, which may be a consequence of ADA, will be monitored through vital signs, laboratory safety testing and AE. This protocol instructs the Investigator to contact the Sponsor if a rash develops that may be part of a serum sickness-like reactions (Section 13.5).

6.6 Risks and Benefits

6.6.1 Risks Associated with PDM608 Administration

Human data have yet to be generated for PDM608. However, over 30 years of clinical data for sargramostim suggests that GM-CSF is safe and well-tolerated. Please see the IB for details of risks and benefits of PDM608 administration.

6.6.2 COVID-19 Related Risks and Risk Mitigation Measures

The following risks and risk mitigating measures apply to the time in which the study is conducted during the Coronavirus Disease 2019 (COVID-19) pandemic.

6.6.2.1 IMP Related Risk

Against the background of the COVID-19 pandemic, the potential risk of a subject developing COVID-19 has been considered in terms of the risk-benefit evaluation. The mode of action of the IMP – as a GM-CSF agonist – has been considered alongside available nonclinical and clinical data (including class effects) and it is considered that a subject would not be at increased risk of either becoming infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the virus that causes COVID-19) or experiencing a more severe illness. That is, the IMP has no known immunomodulatory effect that would confer an increased risk to healthy subjects enrolled in the study.

6.6.2.2 General COVID-19 Related Risks and Risk Mitigation Measures

General risk mitigation against COVID-19 will be implemented in accordance with Quotient's monitoring and prevention control measures.

The risk mitigation measures, where applicable, will be amended based on emerging government guidance.

6.6.2.3 COVID-19 Vaccine-Related Risk

Approved (including health authority conditional marketing authorization) COVID-19 vaccines (e.g., killed, inactivated, peptide, DNA and RNA vaccines) may be permitted according to the investigator's discretion and as per local guidance.

Based on the mechanism of action of the IMP, as a GM-CSF agonist, there is no perceived impact on the safety of the study subjects or on the study objectives for subjects who may receive these vaccines. It is also anticipated to be very unlikely that administration of the IMP would interfere with COVID19 vaccination response; however, no specific preclinical or clinical investigations have been conducted at this point with

PDM608. Therefore, no COVID-19 vaccines will be permitted within 14 days prior to first dose until a subject's final visit on this trial, and COVID19 vaccinations are not acceptable concomitant medications.

6.6.3 General Risks and Overall Risk-Benefit Assessment

PDM608 shares its mechanism of action with GM-CSF, sargramostim. The safety of sargramostim in various populations including healthy volunteers is outlined in the Investigator's Brochure. Flu-like symptoms and injection site rash were reported with a dose of 5-10 mcg/kg/day in these studies, while GM-CSF at 15 mcg/kg/day was not tolerated by donors, with 2 of 21 donors experiencing fever, chills and capillary leak syndrome (Devine 2005). This protocol allows the Investigator to manage headache, bone pain and flu-like symptoms as described in Section 11.3.

Therapeutic proteins may cause the development of ADA, which might cause AE(s). Antibodies to GM-CSF have been associated with loss of pharmacodynamic activity in humans, but not with an increase in adverse events. ADA to GM-CSF have been shown to clear with time (Ragnhammar 1994, Leukine package insert).

Collecting a blood sample from a vein may cause pain, swelling, bruising, lightheadedness, fainting and, very rarely, clot formation, nerve damage and/or infection at the site of the needle stick.

Electrocardiogram (ECGs) stickers on the subjects' chests and limbs may cause some local irritation and may be uncomfortable to remove but subjects will be closely monitored to ensure any local irritation does not persist.

There is no anticipated clinical benefit to the subjects taking part in this study. The development of a product to treat neurodegenerative, autoimmune and oncological diseases may be of benefit to future patients.

The overall risk benefit balance is considered to be acceptable.

7 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety, tolerability and PK of single (Part 1) and multiple (Part 2) SC doses of PDM608	• Incidence of AEs, change from baseline for physical examinations and vital signs, electrocardiograms (ECGs) and laboratory safety tests including ADA in blood • PK parameters for PDM608
Secondary	
To assess immunogenicity following single and multiple doses of PDM608	Incidence of ADA in blood
Exploratory[a]	
To assess PD following administration of single (Part 1) and multiple (Part 2) ascending SC doses of PDM608	• Individual baseline corrected leukocyte, Treg and other immune cell numbers/percentages • Individual baseline corrected cytokine levels

[a] Exploratory PD biomarker objectives may be reported separately to the Clinical Study Report.

8 Study Design

8.1 Study Plan

This is a 2-part, single-center, first-in-human study of SAD (Part 1) and MAD (Part 2) doses of PDM608 in healthy adult subjects. The 2 parts are not required to be conducted entirely sequentially provided that this is justified by safety data obtained from completed cohorts. The first MAD cohort will not be dosed until a minimum 3 SAD cohorts have undergone review by the SAC, and dosing for each MAD cohort will be at a dose level 2-3 fold lower than the highest SAD cohort dose deemed safe by the SAC at the time of each MAD cohort initiation.

8.1.1 Study Plan: Part 1 Single Ascending Doses

Part 1 is a double-blind, randomized, placebo-controlled assessment of SC PDM608 SAD administrations. Subjects will be enrolled sequentially into 1 of up to 5 cohorts, each containing 8 subjects. Within each cohort, 6 subjects will be randomly assigned to receive PDM608 and 2 subjects will be randomly assigned to receive matching placebo. An evaluable subject for Part 1 is defined as a subject who has received the IMP dose and undergone all safety and tolerability assessments (inclusive of all scheduled hematology assessments) out to 96 hours post.

All SAD Cohorts will follow a sentinel design. On the first day of dosing only 2 (sentinel) subjects will be dosed. The randomization schedule will be constructed such that 1 of the subjects dosed on the first day will receive PDM608 and 1 will receive placebo. After review of the safety data from the 72 hours post-dose period the Investigator will decide whether to proceed with dosing the remaining subjects in the cohort (main group; 5 subjects randomized to receive PDM608 and 1 subject randomized to receive placebo).

Following completion of each cohort the safety and tolerability assessments through 96 hours post-dose (Day 5) will be reviewed by the SAC to determine whether to progress to the next dose level and the dose level for the next cohort, with a maximum 3-fold increase in dose level between SAD cohorts.

Following dosing of at least 3 SAD cohorts, the SAC will also decide whether to progress to MAD Part 2 of the study and, if so, on the starting dose for the first MAD cohort. Part 2 may be dosed in parallel with Part 1, but the decision to proceed to Part 2 can only be made following interim review of safety and tolerability data from doses through SAD Cohort 3. Full details of the interim data reviews are provided in Section 8.2.

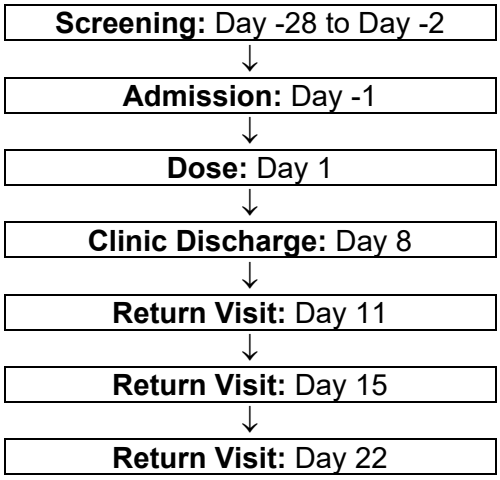
Table 2 Description of Dosing: Part 1 Single Ascending Doses

SAD Cohort	Investigational Medicinal Product	Dose[a, b]
1	PDM608 or matching placebo	350 µg
2	PDM608 or matching placebo	1050 µg
3	PDM608 or matching placebo	3150 µg
4	PDM608 or matching placebo	6300 µg
5	PDM608 or matching placebo	12600 µg

Details of the IMP are provided in Section 5.2.
[a] Anticipated doses. The actual doses to be administered in this study will be determined following interim review by the SAC.
[b] Administration detailed in the Pharmacy Manual.

Each cohort will follow the same study design (Figure 1), detailed in the Schedule of Assessments (Appendix 2).

Figure 1 Study Sequence: Part 1 Single Ascending Doses



8.1.2 Study Plan: Part 2 Multiple Ascending Doses

Part 2 is a double-blind, randomized, placebo-controlled assessment of SC PDM608 MAD administrations. Subjects will be enrolled sequentially into 1 of up to 4 cohorts, each containing 12 subjects. Within each cohort, 9 subjects will be randomly assigned to receive PDM608 and 3 subjects will be randomly assigned to receive matching placebo. MAD Cohort 4 is optional; the decision on whether to dose this cohort will be based on interim review of preceding MAD Cohorts 1 to 3.

Part 2 may be dosed in parallel with Part 1, but can only proceed following interim review of safety and tolerability data from at least the first 3 SAD cohorts in Part 1. Dosing for each MAD cohort will be at a dose level 2-3 fold lower than the highest SAD cohort dose deemed safe by the SAC at the time of each MAD cohort initiation.

An evaluable subject for Part 2 is defined as a subject who has received all 4 doses of IMP and undergone all safety and tolerability assessments out to 96 hours post-final dose (dose 4). Sentinel dosing is not planned for MAD cohorts, but the SAC may implement a sentinel design if deemed appropriate.

Following completion of each cohort, the safety and tolerability assessments out to 96 hours post-final dose (Day 26) will be reviewed to determine whether to progress to the next dose level and the dose to be administered. Full details of the interim data reviews are provided in Section 8.2.

Table 3 Description of Dosing: Part 2 Multiple Ascending Doses

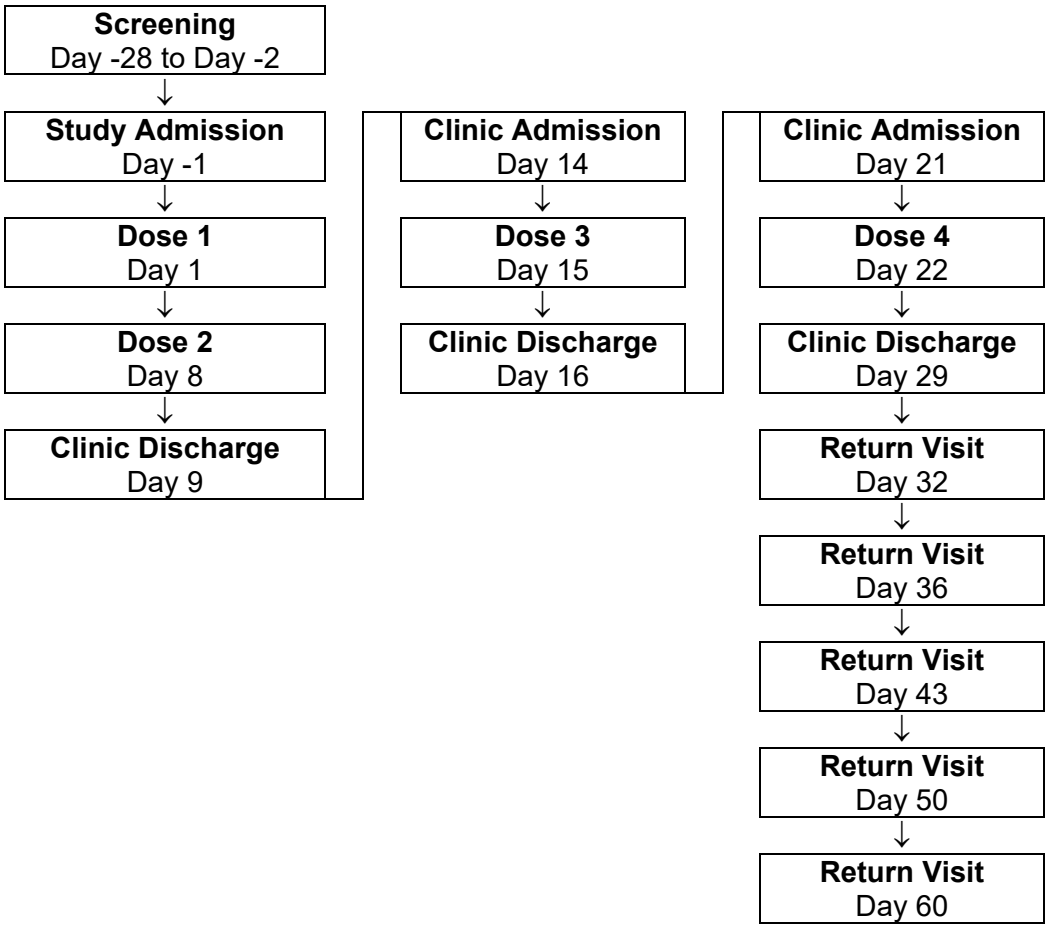
MAD Cohort	Investigational Medicinal Product	Dose[a, b]	Dosing Schedule
1	PDM608 or matching placebo	XX µg	Once weekly for 4 weeks
2	PDM608 or matching placebo	XX µg	Once weekly for 4 weeks
3	PDM608 or matching placebo	XX µg	Once weekly for 4 weeks

4 (optional)[c]	PDM608 or matching placebo	XX µg	Once weekly for 4 weeks

Details of the IMPs are provided in Section 5.2.
[a] MAD cohort dose levels will be determined following interim review by the SAC.
[b] Administration detailed in the Pharmacy Manual.
[c] The decision on whether to dose MAD Cohort 4 will be based on interim review of preceding MAD Cohorts 1 to 3.

Each cohort will follow the same study design (Figure 2), detailed in the Schedule of Assessments (Appendix 3).

Figure 2 Study Sequence: Part 2 Multiple Ascending Doses



8.2 Criteria for In-Study Decisions

In-study decisions will be made by the safety advisory committee (SAC) which will always comprise the Sponsor, investigator (or delegate), the Sponsor's representative medical monitor (or delegate) and a PK expert, where PK expertise is required.

8.2.1 Decision Points

For all cohorts where a sentinel dosing strategy is utilized, the decision to proceed with dosing of the main group will be made by the investigator based on safety data through 72 hours post-dose of the sentinel subjects. The investigator will inform the Sponsor of any safety concerns.

The following in-study decisions will be made by the SAC during this study:

- Whether to progress to the next dose level
- Dose level selection for each SAD and MAD regimen
- After at least SAD Cohort 3 has been dosed: whether to progress to MAD Part 2 of the study
- When progressing to MAD Part 2 of the study, whether a loading dose is required and the amount of the loading dose: loading doses will be chosen based on PK/PD (if available) and safety data and will not exceed the highest dose given in the SAD study
- After MAD Cohorts 1 to 3: whether optional MAD Cohort 4 is required
- Changes to safety and/or PK and/or PD time points if there is reason to believe that the change might improve the quality of the data based on review of emerging data. These changes may also be implemented by the Sponsor alone.

8.2.2 Criteria for Dose Decision

Progression to the next dose group will be permitted after review of defined safety and tolerability data suggests that it is safe to do so. All SAC decisions will be documented and signed by the investigator and Sponsor medical monitor or delegate. Evidence of the decision will be retained in the Trial Master File (TMF).

For dose escalation in the SAD phase to proceed data must be available from a minimum of 6 subjects who have completed the planned safety and tolerability assessments out to 96 hours post-dose (Day 5), to ensure at least 4 subjects receive active IMP. For dose escalation in the MAD phase to proceed data must be available from a minimum of 8 subjects who have completed the planned safety and tolerability assessments out to 96 hours post-final dose (Day 26) to ensure at least 6 subjects receive active IMP.

It is planned that the dose will be escalated for each subsequent cohort; however, the SAC may also agree to enroll additional subjects for an intermediate dose level if warranted or may agree to reduce the dose with no limit on the possible extent of reduction. Any decision to investigate an intermediate or reduced dose level will be fully documented.

The decision to proceed to the next dose level will be based on safety and tolerability and data. The following data are required:

- AEs
- Vital signs
- Safety laboratory, including review of PD hematology parameters outlined in Section 6.4

- 12-lead ECG
- Physical examinations

The SAC may also consider additional data as it becomes available and as relevant to decisions, including ADA, PD, and PK.

Rules for dose decision are as follows:

- Dose escalation will not be more than 3-fold between SAD cohorts. Anticipated SAD dose levels are described in Table 2.
- Dose escalation will not be more than 3-fold between MAD cohorts.
- Dosing for each MAD cohort will be at a dose level 2-3 fold lower than the highest SAD cohort dose deemed safe by the SAC at the time of each MAD cohort initiation.
- Doses administered will be predicted not to exceed a mean C_{max} of 103,950 ng/mL and a mean $AUC_{(0\text{-}24h)}$ of 1,775,000 ng.h/mL, which is the sex-averaged mean NOAEL exposure limits after the first dose of 18 mg/kg in the cynomolgus NOAEL 28-day good laboratory practice (GLP) toxicology study, in any individual subject.
- The predicted mean steady state exposures in the MAD (C_{max} and AUC) factoring the potential for accumulation will not be anticipated to exceed mean maximal exposures observed in the SAD that were confirmed to be safe and well tolerated.
- The maximum PDM608 dose administered in either part of this trial will not exceed a dose that is more than two-fold above the dose at which any two of the following three pharmacodynamic activities are observed in a sample that includes a minimum 5 of 6 PDM608-treated subjects in SAD or 7 of 9 PDM608-treated subjects in MAD, treated within the same cohort, and observed at any laboratory timepoint up to and including 96 hours post-dose (SAD) and post-final dose (MAD):
    - An increase in mean WBC from pre-dose baseline by ≥ 3-fold
    - An increase in mean monocytes from pre-dose baseline by ≥ 2-fold
    - An increase in mean eosinophils from pre-dose baseline by ≥ 7-fold
- The study will be halted and further dose decisions will be paused:
    - One or more subjects experience a possibly IMP-related serious adverse event (SAE)
    - Two or more subjects experience a possibly IMP-related non-serious AE of severe severity in one cohort in the same organ system class

  The decision to reinitiate dosing will be made by the Sponsor in consultation with the investigator after review of safety data and notification to the Institutional Review Board (IRB).

If, following review by the SAC, it is deemed acceptable to continue dose escalation above a defined exposure limit, a substantial amendment with relevant data will be submitted for approval to the regulatory authorities and IRB.

8.3 Subject Withdrawal

A subject may withdraw his/her participation from the study at any time or may be discontinued for any of the reasons below. In either case, every reasonable effort will be made by Quotient to complete a final assessment/discharge procedures and to provide medical follow-up as indicated. Quotient will advise the Sponsor of the withdrawal of any subject from the study.

Early withdrawal is defined as the date of the decision to withdraw the subject from the study. Subject completion is defined as the date of the last procedure conducted or last contact (e.g., phone call or unscheduled visit) for that subject.

If a subject requests to leave the clinical unit earlier than the planned discharge time (e.g., due to unforeseen personal circumstances) but aims to return to the clinical unit to complete the study, this will be documented as a subject self-discharge and a protocol deviation. The subject must complete the planned assessments/discharge procedures before discharge from the clinical unit and will return for the next study period/assessments, as planned following agreement between the Sponsor and the investigator.

Part 1 is a single dose assessment; therefore, after an individual subject has received a dose of IMP withdrawal of that subject from further dosing is not possible. Subjects will be monitored for the criteria detailed below which may require their withdrawal from some or all study procedures if continuation is not in their best interests, except when the withdrawal is a result of withdrawal of consent.

Part 2 is a multiple dose assessment; therefore, subjects will be withdrawn from the study drug(s) for the reasons detailed below.

- Experiencing a SAE, severe AE or laboratory abnormality including but not limited to:
    - corrected QT interval by Fridericia's formula (QTcF) interval of >500 msec or increase in QTcF interval of >60 msec from baseline at a value of >450 msec (confirmed following a repeat ECG)
    - alanine aminotransferase (ALT) concentration >3 × the upper limit of the reference range (confirmed following a repeat ALT blood test)
    - proteinuria, hematuria and/or hyaline casts in urine (confirmed following a repeat urinalysis)
    - other clinically significant laboratory abnormalities that necessitate study discontinuation in the opinion of the investigator and medical monitor
- Pregnancy
- Termination of the study by the Sponsor, regulatory agency or IRB
- Upon the subject's request (withdrawal of consent)
- Significant deviation from the protocol, as determined by the Investigator and Sponsor
- Significant concurrent illness or requirement for prohibited medication

- Subject non-compliance
- At the discretion of the investigator

Baseline will be considered the last available assessment prior to first dose for the purpose of withdrawal criteria.

Every effort will be made to ensure that subjects who discontinue IMP administration because of an IMP-related AE will complete all safety follow-up procedures.

Early withdrawal for any of the above reasons should be documented and distinguished from withdrawal of consent by the subject to participate in any further activities.

8.4 Subject Replacement

Up to 2 replacement subjects per cohort may be enrolled into Part 1 (SAD). The maximum number of subjects that may be dosed is 50.

Up to 3 replacement subjects per cohort may be enrolled into Part 2 (MAD). The maximum number of subjects that may be dosed is 60.

Any subject withdrawn due to an IMP-related AE will not be replaced. Subjects withdrawing for other reasons may be replaced as required by agreement between the investigator and Sponsor to ensure sufficient evaluable subjects.

8.5 Stopping Criteria

The study will be halted, and the risk to other subjects evaluated, if any of the following criteria are met:

- A serious adverse reaction (i.e., a SAE considered at least possibly related to the test product) in one subject
- Severe adverse reactions (i.e., severe AEs considered as at least possibly related to the test product) in two subjects in the same cohort, within the same system organ class.
- There is evidence of drug-induced liver injury in any subject:
    - ALT or aspartate aminotransferase (AST) >3 × upper limit of normal (ULN) and total bilirubin >2 × ULN or INR >1.5 with no alternative etiology OR
    - ALT or AST >3 ULN with fatigue, nausea, vomiting, right upper quadrant (RUQ) pain/tenderness, fever, rash and/or eosinophilia with no alternative etiology OR
    - ALT or AST >8 × ULN with no alternative etiology

Relatedness to IMP will be determined by the investigator.

The IRB will be notified if the study is halted. The study may be resumed or terminated; however, it will not be resumed until a further notice to resume the study is submitted and approved by the IRB.

Also see the pharmacodynamic criteria to cap dose escalation in SAD or MAD in the Pharmacodynamic Rationale Section 6.4.

8.6 Study Termination

The study may be terminated by the Sponsor at any time. Notification of termination must be provided to the IRB as soon as possible, clearly explaining the reasons for termination. A description of follow-up measures taken for safety reasons, if applicable, should also be provided.

If the study is abandoned prior to commencement of any protocol activities, the investigator must notify the IRB outlining the reasons for abandonment of the trial.

The study will be completed as planned unless there is a need for temporary suspension or early termination of the study secondary to any of the following:

- Occurrence of stopping events otherwise defined in this protocol.
- New information regarding the safety of the IMP that indicates that the risk/benefit profile is no longer acceptable.
- Significant violation of Good Clinical Practice (GCP) that compromises subject safety or the ability to achieve the primary study objectives.

If any of the above occur the study will be terminated if careful review of the overall risk/benefit analysis described in Section 6.6 demonstrates that the assumptions have changed and that the overall balance is no longer acceptable. The IRB will be informed of study termination.

If it becomes necessary to consider termination of the study, dosing may be suspended pending discussion between the investigator and Sponsor.

The study may be terminated or suspended at the request of the IRB.

8.7 Lost to Follow-Up

A subject will be considered lost to follow-up if they fail to return for scheduled visits and cannot be contacted by the clinical unit.

If a subject fails to return to the clinical unit for a required study visit:

- The clinical unit must attempt to contact the subject and reschedule the missed visit as soon as possible
- The investigator or designee must make every effort to regain contact with the participant (e.g., three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the subjects' electronic case report form (eCRF)
- If the subject cannot be contacted, they will be considered lost to follow-up

8.8 Subject Selection List and Randomization

This is a double-blind, randomized, placebo-controlled study; therefore, a randomization schedule will be produced for each study part.

A subject selection list will be produced for each study part prior to dosing using the randomization schedule and will be retained in the Investigative Site File (ISF).

In Part 1, for sentinel dosing, a group of 2 subjects will be dosed ahead of the remaining subjects in each cohort. A randomization schedule will be used such that the first 2 subject numbers will be allocated to active or placebo in a 1:1 ratio (i.e., 1 subject will be randomly assigned to receive PDM608 and 1 subject will be randomly assigned to receive matching placebo). The remaining 6 subject numbers will be allocated to active or placebo in a 5:1 ratio (i.e., 5 subjects will be randomly assigned to receive PDM608 and 1 subject will be randomly assigned to receive matching placebo).

For Part 2, a randomization schedule will be used to allocate subject numbers to PDM608 or placebo in a 3:1 ratio (i.e., in each cohort, 9 subjects will be randomly assigned to receive PDM608 and 3 subjects will be randomly assigned to receive matching placebo).

Subjects will be randomized prior to administration of the first dose.

8.8.1 Subject Numbers

Four-digit subject numbers will be allocated prior to initial dosing according to a code established by Quotient. Replacement subjects will be allocated subject numbers where the last three digits are the same as those of the original subject (e.g., if Subject 1005 withdraws, the replacement will have Subject Number 9005 and will receive the same regimen as Subject 1005).

8.8.2 Blinding

This is a double-blind study; treatment assignment will not be known to the subjects, the Sponsor or the staff involved in the clinical evaluation of the subjects and the analysis of data. The randomization schedule and disclosure envelopes will be generated by an unblinded statistician at Quotient according to Quotient's SOPs. The unblinded statistician will not be involved in any decisions relating to populations for analysis prior to unblinding. Prior to database lock and unblinding, all original randomization materials including the original final signed and dated randomization schedule will be held by the Quality Assurance (QA) department at Quotient. The Data Sciences department will not have access to the randomization schedule before database lock and unblinding.

Interim PK parameter estimations will be performed using bioanalytical data applied with subject aliases to maintain blinding.

There may be instances where interim data have the potential to reveal treatment (e.g., missed blood sampling occasions). In these cases, every effort will be made by the unblinded pharmacokineticist to maintain blinding by appropriate presentation of data to the study team. Data demonstrating extremes of exposure will always be presented regardless of the potential to break blinding. To permit selection of the appropriate dose, individual data if judged necessary will be presented to the review committee, regardless of the potential to reveal blinding.

The unblinded Pharmacist or designee at the clinical site will receive a copy of the final randomization schedule for preparation of the study drug and preparation of the subject selection list. A copy of the randomization schedule will also be made available to the laboratory performing the bioanalysis to allow selective analysis of drug concentrations and to the pharmacovigilance provider for analysis of pharmacovigilance.

Two sets of disclosure envelopes (i.e., sealed envelopes containing individual subject randomization details) will be provided. One set will be held in the clinical area and the other retained in the ISF. These may be used in the event of an emergency by the investigator. Any request for information on the randomization schedule after initial issue must be made using a randomization disclosure form to the designee of the randomization except in the case of emergency unblinding, which must be recorded on the emergency unblinding form including details of timing, those unblinded and scope of unblinding. Access to study drug assignment will be immediately available if the investigator deems it necessary to break blinding in the interest of a subject's medical safety, in case of a medical emergency or if warranted during scheduled safety reviews. The medical monitor must be contacted within 24 hours following disclosure of study drug assignment.

Details of any disclosure of the randomization schedule will be documented and retained in the ISF. The Sponsor will be notified if blinding is broken.

For each individual study part blinding will be broken after the study database has been locked and the safety and necessary populations have been defined.

9 Selection of Subjects

9.1 Informed Consent

The investigator or delegated, qualified study staff member will explain and review the IRB approved informed consent form (ICF) with each subject. Subjects will then be given the opportunity to ask questions and will be informed of their right to withdraw from the study without prejudice. After this explanation and before any study specific procedures are performed the subject will voluntarily sign and date the IRB approved ICF.

9.2 Inclusion Criteria

Informed Consent and Compliance

1. Must be able to understand a written informed consent, which must be obtained prior to initiation of study procedures
2. Must be willing and able to comply with all study requirements

Demographics and Contraception

3. Aged 18 to 65 years inclusive at time of signing informed consent
4. Must agree to use an adequate method of contraception (as defined in Section 9.4)

Baseline Characteristics

5. Healthy men or non-pregnant, non-lactating healthy women of non-childbearing potential
6. Body mass index (BMI) of 18.0 to 33.0 kg/m^2 as measured at screening
7. Weight ≤100 kg at screening

Inclusion criterion 5 from the list above will be re-assessed at admission/pre-dose on Day 1.

9.3 Exclusion Criteria

Medical/Surgical History and Mental Health

1. Serious adverse reaction or serious hypersensitivity to any drug or the formulation excipients
2. Presence or history of clinically significant allergy requiring treatment as judged by the investigator. Hay fever is allowed unless it is active
3. Significant serious skin disease, including rash, food allergy, eczema, psoriasis or urticaria
4. History of clinically significant autoimmune, cardiovascular, renal, hepatic, chronic respiratory or GI disease (except cholecystectomy), neurological or psychiatric disorder, illness/infection/hospitalization or surgical procedure within 30 days prior to first dose of study drug or any uncontrolled medical illness as judged by the investigator

Physical Examination

5. Have poor venous access that limits phlebotomy

Diagnostic Assessments

6. Evidence of current SARS-CoV-2 infection or exposure to confirmed infection within 10 days prior to the first dose of study drug
7. Clinically significant abnormal clinical chemistry, hematology or urinalysis as judged by the investigator (laboratory parameters are listed in Appendix 1). Subjects with Gilbert's Syndrome are allowed
8. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab), human immunodeficiency virus (HIV) antibody results or positive tuberculosis (TB) screening test
9. Evidence of renal impairment at screening, as indicated by an estimated creatinine clearance (CLcr) of <90 mL/min using the Cockcroft-Gault equation
10. Subjects with a QTcF interval of >450 msec at screening or first admission. At screening, QTcF will be based on a single 12-lead ECG; this single ECG can be repeated once if parameters are outside the limits for confirmation. At admission, this value will be from the mean of triplicate values
11. Positive highly sensitive serum pregnancy test at screening or highly sensitive urine pregnancy test at first admission. Those who are pregnant or lactating will be excluded

Prior Study Participation

12. Subjects who have received any IMP in a clinical research study within 5 half-lives or within 30 days prior to first dose (whichever is longer)

13. Subjects who have previously been administered IMP in this study. Subjects who have taken part in Part 1 are not permitted to take part in Part 2

Prior and Concomitant Medication

14. Subjects who are known to have received an antibody (as a treatment or as a participant in another study) may be eligible to participate after review by Investigator and/or Sponsor, to limit subjects who may have baseline anti-human antibodies
15. Subjects who are taking, or have taken, any prescribed or over-the-counter drug or herbal remedies (other than up to 4 g per day acetaminophen and HRT) in the 14 days or 5 half-lives (whichever is longer) before IMP administration (see Section 11.3). Exceptions may apply on a case-by-case basis if considered not to interfere with the objectives of the study as determined by the investigator
16. Subjects who have had a COVID-19 vaccine within 14 days prior to first dose or have a COVID-19 vaccine scheduled between their first dose of IMP and anticipated final study visit

Lifestyle Characteristics

17. History of any drug or alcohol abuse in the past 2 years, as determined by the Investigator according to the definitions of alcohol use disorder and substance abuse disorder in the Diagnostic and Statistical Manual (DSM)-5
18. Regular alcohol consumption in men >21 units per week and women >14 units per week (1 unit = 12 oz 1 bottle/can of beer, 1 oz 40% spirit or 5 oz glass of wine)
19. A confirmed positive alcohol urine test at screening or first admission
20. Current smokers and those who have smoked within the last 12 months or a confirmed positive urine cotinine test at screening or first admission
21. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months
22. Positive drugs of abuse test result (drugs of abuse tests are listed in Appendix 1)

Other

23. Men with pregnant or lactating partners
24. Donation of blood for transfusion within 2 months or donation of plasma within 7 days prior to first dose of study medication
25. Subjects who are, or are immediate family members of, a study site or Sponsor employee
26. Failure to satisfy the investigator of fitness to participate for any other reason

Exclusion criteria 6, 7, 10, 11, 12, 14, 16, 19, 20, 21, 22, 23, 24 and 26 from the list above will be re-assessed at admission/pre-dose on Day 1.

Healthy subjects who do not meet the inclusion/exclusion criteria for the study will not be enrolled.

9.4 Contraception and Restrictions

Men with Partners of Childbearing Potential

Men who are sexually active with a partner of childbearing potential must use, with their partner, a condom plus an approved method of highly effective contraception from the time of informed consent until 175 days after last IMP administration.

The following methods are acceptable:

- Partner's use of combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- Partner's use of progestogen-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - injectable/implantable
    - intrauterine hormone-releasing system
- Partner's use of intrauterine device
- Vasectomized
- Partner's bilateral tubal occlusion

Men with Partners of Non-childbearing Potential

There is an unknown risk of drug exposure through ejaculate (which also applies to vasectomized men) that might be harmful to sexual partners. Therefore, even if a man is sexually active with a partner of non-childbearing potential they will be required to use a condom from the time of informed consent until 175 days after last IMP administration (approximately 2.5 sperm turnover rate).

All Men

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Women of Non-Childbearing Potential

Women who are not of childbearing potential do not need to use any methods of contraception. A woman is considered of childbearing potential (WOCBP) unless post-menopausal or permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause and confirmed by a follicle stimulating hormone (FSH) result of ≥40 IU/L.

9.4.1 Sperm Donation

Men should not donate sperm from the time of informed consent until 175 days after last IMP administration (approximately 2.5 sperm turnover rate).

9.4.2 Egg Donation

Women should not participate in egg donation from dosing, from the time of informed consent until 115 days after last IMP administration.

9.5 Pregnancy

Subjects will be instructed that if they/their partner becomes pregnant during the study this should be reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject/subject's partner is subsequently found to be pregnant after the subject is included in the study, then consent will be sought from the subject/partner and, if granted, any pregnancy will be followed and the status of mother and/or child(ren) will be reported to the Sponsor after delivery. Any subject reporting a pregnancy during the study will be discontinued from study treatment and every reasonable effort will be made by Quotient to follow up the pregnancy until delivery.

A pregnancy notification form and follow-up will be completed.

9.6 Additional Study Restrictions

The following additional restrictions will be in place for the duration of the study:

- Subjects must abstain from alcohol during the 24 hours prior to screening and the 24 hours prior to admission until 48 hours post-final IMP dose
- Subjects should refrain from eating food containing poppy seeds for 48 hours prior to screening and for 48 hours prior to admission until 48 hours post-final IMP dose
- Subjects must not take part in any unaccustomed strenuous exercise from the 72 hours before the screening visit and then from 72 hours prior to admission until discharge from the study
- Subjects must not donate blood or plasma (outside of this study) from clinical unit admission, throughout the study duration, and for at least 30 days following last dose of study medication

The additional restrictions above are not exclusion criteria; if non-compliance occurs, the Sponsor will be contacted and each deviation will be assessed on a case by case basis.

10 Study Procedures

Study procedures will be performed as detailed in the study schedule of assessments Appendix 2 (Part 1) and Appendix 3 (Part 2), and in accordance with Quotient's SOPs unless otherwise stated in this protocol.

10.1 Screening

Within the 28 days preceding first dose all subjects will be required to undergo screening procedures. Screening procedures will be carried out in accordance with the schedule of assessments in Appendix 2 (Part 1) and Appendix 3 (Part 2).

If the start of the study is delayed for any reason so that the interval between screening and first dose exceeds 28 days all or part of the screening procedures will be repeated at the discretion of the investigator.

Screening safety procedures such as safety bloods, ECGs, vital signs, urine alcohol, urine cotinine, urine drug screen and urinalysis can be repeated as clinically indicated under the discretion of the investigator or sub-investigator if there is a concern regarding a subject's safety or eligibility to participate in the trial.

10.1.1 Subject Re-Screening

This study permits the re-screening of a subject who has discontinued the study as a pre-treatment failure (i.e., subject has not been randomized); the reason for failure must be temporary and expected to resolve. If re-screened, the subject must be re-consented.

10.2 Admission and Pre-dose Procedures

The identity of the subjects will be confirmed at admission and pre-dose.

In addition, the ongoing eligibility of subjects will be re-assessed at admission/pre-dose, as described in Sections 9.2 and 9.3.

Admission/pre-dose safety procedures such as safety blood tests, ECGs, vital signs, urinalysis and drugs of abuse tests can be repeated as clinically indicated under the discretion of investigator or sub-investigator if there is a concern regarding a subject's safety or eligibility to participate in the clinical trial.

Alternative subjects for the first dose occasion, in any cohort, will not require admission procedures to be repeated if dosing is within 2 days of their prior admission.

If dosing is delayed, subjects who have completed admission procedures do not need admission procedures to be repeated if dosing is within 2 days and the subjects have remained resident in the clinical unit.

The admission and pre-dose procedures are presented in Appendix **2** (Part 1) and Appendix 3 (Part 2).

10.3 Study Day Procedures

10.3.1 Blood Volume

The total blood volume for each subject will not exceed 550 mL in an 8-week period (based on a representative healthy subject weighing at least 110 pounds). See the study Lab Manual for further details on sample volumes and collection and processing requirements. The number and timing of samples may be amended following review by the Sponsor and/or SAC.

10.3.2 Timing of Procedures

There are times where the protocol requires more than one procedure to be completed at the same time point. In these instances, the following will apply to post-dose time points:

- ECGs should be taken prior to vital signs when both measurements are scheduled at the same time point.
- PK/PD samples should take priority (i.e., taken at the nominal time point) over other procedures scheduled at the same time point.
- Other assessments (e.g., physical examinations) will be performed within the required time windows.

As guidance, the preferred order of assessments is:

ECGs	→	**Vitals**	→	**PK/PD/ADA blood sampling (nominal time)**	→	**Other assessments (e.g., physical examinations)**

All safety assessments will be timed and performed relative to the start of dosing.

10.3.3 Discharge from the Clinical Unit

Subjects will be discharged from the clinical unit following completion of study-specific procedures as detailed in Appendix 2 (Part 1) and Appendix 3 (Part 2). However, the investigator may ask a subject to remain domiciled for additional safety observation and monitoring (e.g., as indicated for an AE).

10.3.4 Return Visits

Subjects in Part 1 and Part 2 will be required to return to the clinical unit at specified time points for the assessments described in Appendix 2 (Part 1) and Appendix 3 (Part 2); the acceptable deviations for the return visit are also described in these appendices.

10.3.5 Medical Supervision

A physician will be responsible for the clinical aspects of the study and will be available at all times during the study.

10.3.6 Follow-up

If a subject reports any AEs that can present a cause for concern, they will be required to attend the clinical unit for a further follow-up assessment (as an unscheduled visit) and will be followed up until the AE has resolved. Completion of the last scheduled return visit or unscheduled follow-up call/visit will be considered the end of the study.

11 Dosing of Subjects

11.1 Food and Fluid Intake

Subjects will be allowed water up to 1 hour before each scheduled dosing time and will be provided with 240 mL of water at 1 h post-dose (to ensure adequate hydration). Thereafter, water will be allowed ad libitum after 1 h post-dose. Decaffeinated fluids will be allowed ad libitum from lunch time on the day of dosing.

The calorie/fat content of meals are not required to be controlled. Subjects will be provided with a standardized menu. See also the food and liquid restrictions detailed in Section 9.6. Meals will be provided at appropriate times.

11.2 Dosing Compliance

Subjects will be observed by study staff during all clinical phases of the study to assure compliance to all study procedures including dose administration.

Doses will be administered by trained staff to ensure dosing compliance.

The date and time that each subject is dosed will be recorded in the subject's eCRF. Any violation of compliance will require evaluation by the investigator and Sponsor to determine if the subject can continue in the study.

11.3 Prior and Concomitant Medications

No prescribed medications, over-the-counter medications or herbal remedies will be permitted from 14 days or 5 half-lives (whichever is longer) before IMP administration until a subject's final visit except HRT, up to 4 g per day of acetaminophen, and those deemed necessary by the investigator to treat AEs (see also Section 9.3). Any medications used will be recorded in the eCRF.

No COVID-19 vaccines will be permitted within 14 days prior to first dose until a subject's final visit on this trial. COVID-19 vaccinations are not acceptable concomitant medications.

Emergency equipment and drugs will be available within the clinical unit as per current standard procedures. In the unlikely event that they are required, their use will be documented.

12 Pharmacokinetic and Pharmacodynamic Blood Sampling

Venous blood samples for analysis by a bioanalytical lab for PK and PD analysis will be collected from the subjects by a trained member of the clinical team.

Samples will be sent for laboratory testing in linked anonymized form (subject number only). This information can be linked directly to the subject by the Quotient research team and study monitor but not by the laboratory staff or Sponsor.

Venous blood samples will be withdrawn via venipuncture according to the Schedule of Assessments presented in Appendix 2 (Part 1) and Appendix 3 (Part 2). The acceptable deviations from the nominal blood sampling times are detailed in the schedules.

The timing and number of the samples may be amended by the Sponsor and/or SAC, including collection over a longer duration. Any changes to blood sampling time points will be documented and retained in the TMF.

Samples will be collected into appropriate tubes as specified by the bioanalytical laboratory. Details of sample tubes and processing will be contained in the Clinical Sample Processing Manual (CSPM).

Pharmacodynamic parameters analyzed by the bioanalytical lab may include the following:

- Immunophenotyping by flow cytometry to determine numbers/percentages of the following immune cells:
    - Total T cells (CD45+CD3+)

- Helper T cells (CD45+CD3+CD4+CD8-)
- Cytotoxic T cells (CD45+CD3+CD4-CD8+)
- Regulatory Helper T cells (CD45+CD3+CD4+CD8-CD25+Foxp3+)
- Regulatory Cytotoxic T cells (CD45+CD3+CD4-CD8+CD25+Foxp3+)
- Macrophages (CD45+CD14+CD11b+)
- Dendritic cells (CD45+CD123+HLA-DR+CD11c+)

- Cytokine analysis:
  - Panel 1: IL-1α, IL-1B, IL-1RA, IL-12/IL-23p40, IFN-α2a, MCP-1
  - Panel 2: IL-1β, IL-6, IL-10, IL-12p70, IFN-ɣ, GM-CSF, TNF-α

As described in Section 6.4 Pharmacodynamic Rationale, a subset of the safety hematology labs (WBC, monocyte, and eosinophil values) will be analyzed as an indicator of pharmacodynamic activity to aid in defining the maximum dose level to be administered to subjects in this trial.

13 Assessment of Safety

13.1 Definition and Classification of Adverse Events

An AE is any untoward medical occurrence in a subject that occurs either before dosing (referred to as a pre-dose AE) or once a medicinal product has been administered, including occurrences that are not necessarily caused by or related to that product.

An adverse drug reaction (ADR) is any AE where a causal relationship with the IMP is at least a reasonable possibility (possibly related or related).

AEs will be monitored from the time the subject signs the ICF until 30 days after the final dose of study drug. The severity of AEs should be assessed as follows:

Mild An AE that is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities

Moderate An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed

Severe An AE that prevents normal everyday activities; treatment or other intervention usually needed

13.2 Assessment of Causality

Every effort should be made by the investigator to try to explain each AE and assess its relationship, if any, to the IMP. The temporal relationship of the event to IMP administration should be considered in the causality assessment (i.e., if the event starts soon after IMP administration and resolves when the IMP is stopped).

Causality should be assessed using the following categories:

Unrelated: Clinical event with an incompatible time relationship to IMP administration and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the IMP

Possibly related: Clinical event with a reasonable time relationship to IMP administration that is unlikely to be attributed to concurrent disease or other drugs or chemicals

Related: Clinical event with plausible time relationship to IMP administration that cannot be explained by concurrent disease or other drugs or chemicals

The degree of certainty with which an AE is attributed to IMP administration (or alternative causes such as natural history of the underlying disease or concomitant therapy) will be determined by how well the experience can be understood in terms of one or more of the following:

- Known pharmacology of the IMP
- Reactions of a similar nature have been previously observed with the IMP or this class of drug
- The experience being related by time to IMP administration, terminating with IMP withdrawal or recurring on rechallenge
- Alternative cause

13.3 Recording Adverse Events

AEs will be recorded from the time of providing written informed consent until 30 days after the last dose of study drug. During each study visit the subject will be questioned directly regarding the occurrence of any adverse medical event according to the schedule in eCRF. All AEs, whether ascribed to study procedures or not, will be documented immediately in the subject's eCRF. This will include the date and time of onset, a description of the AE, severity, seriousness, duration, actions taken, outcome and an investigator's current opinion on the relationship between the study drug and the event. A diagnosis and final opinion on the relationship between the study drug and the event will be provided at the end of the study by the investigator.

Any subject who withdraws from the study due to an AE will be followed until the outcome is determined and written reports are provided by the investigator.

13.4 Serious Adverse Events

13.4.1 Definition of Serious Adverse Events

A SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is an important medical event as recognized by the investigator

SAEs must be reported to the Sponsor and IRB within 24 hours of site awareness.

13.4.2 Definition of Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are believed to be related to a test product and are both unexpected (i.e., the nature or severity is not expected from the information provided in the IB) and serious. SUSARs are subject to expedited reporting to the IRB (see Section 15.3.2 for details on reporting SUSARs).

13.5 Adverse Events of Special Interest (AESI)

The following AESI must be reported to the Sponsor within 24 hours of site awareness irrespective of seriousness, severity or causality:

- Serum sickness-like reaction – a type III hypersensitivity reaction presenting with a constellation of symptoms including fever, pruritic rash, joint pain/tenderness/edema/erythema, muscle pain, edema of the lips and/or eyelids, GI symptoms (nausea, vomiting, abdominal cramps, diarrhea), headache and dyspnea
- A new vasculitic rash, a fixed, erythematous, non-blanching rash. Vasculitic rashes may be accompanied by fever, fatigue and diffuse aches or pain
- Urticarial reaction
- Leucocytosis with WBC > 50,000/uL

In the event of a suspected serum sickness-like reaction blood samples will be collected within 1 hour of the event to assess CBC, ESR, urinalysis, serum chemistries, C3, C4 and fibrinogen.

The subsequent course of therapy may include NSAIDs, antihistamines and/or corticosteroids depending on institutional guidelines and the severity of the event.

The investigator is encouraged to discuss with the Sponsor medical monitor all AESI as defined above.

13.6 Safety Laboratory Measurements

Venous blood and urine samples will be collected from subjects by a trained member of the clinical team.

Safety laboratory tests and virology will be carried out on blood samples, and drugs of abuse tests and urinalysis will be carried out on urine samples. The research will not involve analysis or use of human DNA.

Blood samples will be sent for laboratory testing in linked anonymized form (subject number only). This information can be linked directly to the subject by the Quotient research team and study monitor but not by the laboratory staff or Sponsor.

Blood and urine sample results will be reviewed by a physician and acted upon before the subject is dosed, receives their next dose or is released from the study, as appropriate. A list of the laboratory parameters measured is presented in Appendix 1.

13.6.1 Hematology and Clinical Chemistry

Laboratory tests will be performed by Quotient Sciences Labs according to the Schedule of Assessments presented in Appendix 2 (Part 1) and Appendix 3 (Part 2). Blood samples will be collected and processed as detailed in the CSPM. Scheduled blood samples will be taken following an overnight fast of a minimum of 8 hours. Samples taken due to early withdrawal do not need to be fasted. The acceptable deviations from the nominal blood sampling times are detailed in the schedules.

CLcr will be calculated at screening by Quotient Sciences Labs using the Cockcroft-Gault equation and body weight for eligibility purposes:

$$\text{CLcr (mL/min)} = \frac{(140\text{-age [years]}) \times \text{body weight [kg]} \text{ (x 0.85, if female)}}{72 \times \text{serum creatinine (mg/dL)}}$$

13.6.2 Anti-Drug Antibodies

Venous blood samples will be withdrawn via venipuncture according to the Schedule of Assessments presented in Appendix 2 (Part 1) and Appendix 3 (Part 2). The acceptable deviations from the nominal blood sampling times are detailed in the schedules.

The timing and number of the samples may be amended by the Sponsor, including collection over a longer duration. Any changes to blood sampling time points would be documented and retained in the TMF.

Samples will be collected into appropriate tubes as specified by the bioanalytical laboratory. Details of sample tubes and processing will be contained in the CSPM.

13.6.3 Urinalysis

Urinalysis will be performed by Quotient Sciences Labs according to the Schedule of Assessments presented in Appendix 2 (Part 1) and Appendix 3 (Part 2). Urine samples will be collected and processed as detailed in the CSPM. Microscopic analysis of sediment for bacteria, casts, crystals, epithelial cells, red blood cells and white blood cells will be performed, as required. The acceptable deviations from the nominal urine sampling times are detailed in the schedules.

13.6.4 Pregnancy Test

Serum and urine pregnancy tests will be performed as detailed in Appendix 2 (Part 1) and Appendix 3 (Part 2). The samples will be collected and processed as detailed in the CSPM.

13.6.5 Follicle-Stimulating Hormone Test

Serum FSH tests will be performed as detailed in Appendix 2 (Part 1) and Appendix 3 (Part 2). The samples will be collected and processed according to the CSPM.

13.6.6 Alcohol, Cotinine, and Drug Screen

A urine alcohol, cotinine and drug screen will be performed by Quotient Sciences Labs according to the Schedule of Assessments presented in Appendix 2 (Part 1) and Appendix 3 (Part 2). The sample will be collected and processed according to the CSPM.

Subjects will be screened for the drugs of abuse listed in Appendix 1. A positive result will exclude the subject from dosing for the remainder of the study.

13.6.7 Abnormal Laboratory Findings

In cases where laboratory findings are outside the normal range and the investigator believes that the results may be of clinical significance, repeat sampling may be requested as clinically indicated. If the abnormal finding is clinically significant, the Sponsor and Medical Monitor may be consulted and appropriate actions will be taken (e.g., the subject will not be entered into or may be withdrawn from the study). The subject will be referred to their primary care provider or other appropriate provider for further care if necessary. The same will apply if the results of the HBsAg, HCV Ab or HIV test are positive and in addition the investigator will ensure that adequate counselling is available if requested.

Abnormal results at follow-up assessments will also require repeat testing if the investigator believes the results may be of clinical significance.

Any clinically significant laboratory finding, including changes from baseline, must be reported as an AE.

Additional blood and/or urine samples may be taken for safety tests. Furthermore, additional assays outside those specified in the protocol may be performed for safety reasons as requested by the investigator.

13.7 Vital Signs Measurements

Blood pressure and heart rate will be measured by an automated recorder after the subject has been in a supine position for a minimum of 5 minutes and body temperature and respiratory rate will be measured according to the Schedule of Assessments presented in Appendix 2 (Part 1) and Appendix 3 (Part 2). The acceptable deviations from the nominal vital signs assessment times are detailed in the schedules.

If a subject shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the investigator or sub-investigator.

Any clinically significant abnormality, including changes from baseline, must be reported as an AE.

13.8 12-Lead Electrocardiogram Measurements

Single 12-lead ECGs will be measured after the subject has been in the supine position for a minimum of 5 minutes, and triplicate 12-lead ECG measurements will be performed approximately 2 min apart after the subject has been in the supine position for a minimum of 5 min, according to the Schedule of Assessments presented in Appendix 2 (Part 1) and Appendix 3 (Part 2). The acceptable deviations from the nominal ECG assessment times are detailed in the schedules.

If a subject shows an abnormal assessment at any stage repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the investigator or sub-investigator.

Any clinically significant abnormality, including changes from baseline, will be reported as an AE.

13.9 Body Weight, Height and Body Mass Index

The subject's body weight and height will be measured and their BMI calculated according to the Schedule of Assessments presented in Appendix 2 (Part 1) and Appendix 3 (Part 2).

13.10 Physical Examination

Subjects will undergo a physical examination according to the Schedule of Assessments presented in Appendix 2 (Part 1) and Appendix 3 (Part 2).

13.11 Additional Safety Procedures

Additional non-invasive procedures that are already specified in the protocol may be performed if it is believed that an important effect of the IMP is occurring, may occur at a time when no measurements are scheduled or if extra procedures are needed in the interests of safety.

Additional blood samples, urine samples or other diagnostic tests for safety assessments may be taken if required by the investigator or sub-investigator at any point.

14 Statistics and Data Analysis

14.1 Sample Size Justification

Based on experience from previous similar studies, the target numbers of subjects to be enrolled (N = 8 and N = 12) should be sufficient to achieve a minimum of 6 and 8 evaluable subjects in each cohort in Part 1 and Part 2, respectively. Six evaluable subjects in SAD is customarily sufficient to assess cohorts for dose escalation. The sample size of 12 in MAD is supported by results of daily sargramostim (6 mcg/kg/day) for 8 weeks administered to 20 persons with Parkinson's Disease in a randomized (1:1), placebo-controlled trial (Gendelman 2017). A significant transient increase of 5% CD4+Treg counts (Mann-Whitney U test p=0.05-0.01) and Treg activity was identified at 2-4 weeks with data from 5-9 sargramostim treated patients). GM-CSF at a dose of 5-10 mcg/kg/day for 4-5 days significantly increased numerous cell lineages in peripheral blood of 5-8 healthy volunteers, with increases in CD34+ mononuclear cells, WBC, MNC, PMN, monocytes, and eosinophils (Lane 1995; Fishmeister 1999). PD patients also have increases in PMN and eosinophils in response to sargramostim (Gendelman 2017). These results suggest the MAD sample size is sufficient to detect an increase of 5% in mean Treg percentages compared with pooled placebo subjects. The sample size is also adequate to identify expected pharmacodynamic changes in hematology laboratory tests.

14.2 Data Management

Data management will be performed by Quotient.

Study data will be managed using a validated eCRF database system and subjected to data consistency and validation checks. Data queries will be raised within the study eCRF

database by data management staff and resolved with the assistance of clinical staff. The database is compliant with 21 Code of Federal Regulations (CFR) Part 11 guidelines.

AEs, medical histories and medications will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version to be specified in the Data Management Plan [DMP]) and the World Health Organization (WHO) Drug Dictionary Global Drug Reference (version to be specified in the DMP), respectively. An independent coding review will also be performed within the Data Sciences department.

Clinical chemistry and hematology data (and other safety laboratory data) will be collected by Quotient Labs and Quest Diagnostics Clinical Laboratories Inc and stored electronically in their laboratory information system. The data will be transferred electronically to Quotient and all demographic details and sample dates will be cross-referenced with the corresponding data on the study database. All queries will be resolved with the assistance of laboratory staff, or if necessary, clinical staff.

The database will be closed after all queries have been resolved. The database will be locked when all criteria listed in the DMP are met.

Further details are addressed in the DMP.

14.3 Pharmacokinetic Data Analysis

The PK data for PDM608 will be analyzed by Quotient, using Phoenix WinNonlin v8.0 or a more recent version (Certara USA, Inc., USA).

PK analysis of the concentration time data obtained will be performed using appropriate non-compartmental techniques to obtain estimates of the PK parameters presented in Table 4, where possible and appropriate.

Table 4 Pharmacokinetic Parameters

Parameter	Definition
Part 1 SAD	
t_{max}	Time of maximum observed concentration
C_{max}	Maximum observed concentration
C_{max}/Dose	Maximum observed concentration divided by dose
$AUC_{(0\text{-}24)}$	Area under the curve from time 0 to 24 hr
$AUC_{(0\text{-last})}$	Area under the curve from time 0 to the time of last measurable concentration
$AUC_{(0\text{-last})}$/Dose	Area under the curve from time 0 to the time of last measurable concentration divided by dose
$AUC_{(0\text{-inf})}$	Area under the curve from time 0 extrapolated to infinity
$AUC_{(0\text{-inf})}$/Dose	Area under the curve from time 0 extrapolated to infinity divided by dose
AUC_{extrap}	Area under the curve from time of the last measurable concentration to infinity as a percentage of the area under the curve extrapolated to infinity

Parameter	Definition
$T_{1/2}$	Terminal elimination half-life
Lambda-z	First order rate constant associated with the terminal (log-linear) portion of the curve
CL/F	Total body clearance calculated after extravascular administration where F (fraction of dose bioavailable) is unknown
Vz/F	Apparent volume of distribution based on the terminal phase calculated using $AUC_{(0\text{-}inf)}$ after a single extravascular administration where F (fraction of dose bioavailable) is unknown
Part 2 MAD – Dose 1, Dose 2, and Dose 3	
T_{max}	Time of maximum observed concentration
C_{max}	Maximum observed concentration
$AUC_{(0\text{-}24)}$	Area under the curve from time 0 to 24 hr
$AUC_{(tau)}$	Area under the curve for the defined interval between doses (tau)
Part 2 MAD – Dose 4	
t_{max}	Time of maximum observed concentration
C_{max}	Maximum observed concentration
$AUC_{(0\text{-}24)}$	Area under the curve from time 0 to 24 hr
$AUC_{(tau)}$	Area under the curve for the defined interval between doses (tau)
$T_{1/2}$	Terminal elimination half-life
Lambda-z	First order rate constant associated with the terminal (log-linear) portion of the curve
AR C_{max}*	Accumulation Ratio based on C_{max} last dose / C_{max} first dose
AR AUC*	Accumulation Ratio based on $AUC_{(0\text{-}tau)}$ last dose / $AUC_{(0\text{-}tau)}$ first dose
Vz/F	Apparent volume of distribution based on the terminal phase after extravascular administration where F (fraction of dose bioavailable) is unknown

*These parameters will not be calculated if Dose 1 is a loading dose.

Further details of the PK data analysis will be included in the Reporting and Analysis Plan (RAP).

14.4 Statistical Data Analysis

Statistical analysis and production of summary tables, figures and listings for this study will be performed by Quotient using the statistical package SAS (v9.4 or more recent version).

In general terms, categorical data (including treatment-emergent AEs) will be presented using counts and percentages, while continuous variables will be presented using the mean, median, standard deviation, minimum and maximum. Additional statistics will be provided for PK-related data including coefficient of variation (CV%), geometric mean and geometric CV%.

Descriptive summaries for all safety data (AEs, vital signs, ECGs and safety laboratory assessments) by treatment will be provided (including changes from baseline as required).

Descriptive summaries for all PK and PD data by treatment will be provided, including changes from baseline in PD variables. The number and percentage of subjects with confirmed ADA response will be presented, both prevalence and incidence.

All safety, PK and PD data will be listed.

The following formal statistical analysis may be performed:

Dose proportionality for SC doses - assessed using a power model using log-transformed $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$ (Part 1), and $AUC_{(0\text{-tau})}$ (Part 2) and C_{max} values (e.g., a linear model with log dose as a covariate). The resulting estimated slope (b) is a measure of dose proportionality (e.g., the relationship is dose proportional when b=1). Dose proportionality will be assessed on each of Day 1/Dose 1 (SAD and MAD) and Dose 4 (MAD only).

Accumulation - assessed in Part 2 on log-transformed parameters $AUC_{(0\text{-tau})}$ and C_{max} values using a mixed effects model with terms for treatment (e.g., dose level) and day as fixed effects, a day by treatment interaction term and subject as a random effect. Ratios of geometric means and 90% CI will be provided for Dose 2/3/4 versus Dose 1. Accumulation ratios will not be calculated if Dose 1 is a loading dose.

Pharmacodynamics – Leukocyte numbers/percentages and Treg numbers/percentages will be compared between the active treatment and placebo groups using t-tests. Non-parametric statistics may be used for comparison if the data distribution suggest they are more appropriate. Changes from baseline in both groups will be summarized descriptively. Specific PK/PD modelling (e.g., Emax model fit) may be performed.

Populations and analysis sets will be determined for safety, PK , ADA and PD (if applicable) after database lock using the criteria defined in the RAP; the RAP will be signed off prior to database lock.

The safety and PD populations and analysis sets will be defined after database lock but prior to study unblinding; all other populations will be defined after database lock when the relevant data are available.

Further details relating to the statistical analysis will be included in the RAP including the following:

- Criteria to be used to define each of the population and analysis sets
- Additional detail covering the analyses and/or description of primary and secondary analyses and safety data
- Handling of missing data, unused or spurious data
- Handling of data from withdrawn subjects

14.5 Interim Analysis

No formal interim analyses are planned for this study. Interim Data Reviews will be performed as detailed in Section 8.2.

15 Safety Reporting to Institutional Review Board and Regulatory Authorities

15.1 Events Requiring Expedited Reporting

SUSARs (Section 13.4.2) are subject to expedited reporting to the IRB and regulatory authorities.

In addition to SUSARs, other safety issues may qualify for expedited reporting where they might materially alter the current benefit-risk assessment of an IMP or that would be sufficient to consider changes in the IMPs' administration or in the overall conduct of the study, for instance:

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction which is judged to be clinically important
- SAEs that occur after the subject has completed the clinical study where the Sponsor considers them to be a SUSAR
- New events related to the conduct of the study or the development of the IMPs and likely to affect the safety of the subjects

An SAE that could be associated with study procedures and could modify study conduct

A major safety finding from a newly completed animal study (e.g., carcinogenicity)

Any anticipated end or temporary halt of a study for safety reasons and conducted with the same IMPs in another country by the same Sponsor

15.2 Urgent Safety Measures

If Quotient or any of its staff or contractors becomes aware of an actual or potential urgent safety issue the Sponsor must be contacted immediately so that appropriate urgent safety measures can be agreed. An urgent safety issue is defined as:

- An immediate hazard to the health or safety of subjects participating in a clinical study
- A serious or potentially serious risk to human health

An urgent safety issue may include issues with an investigational drug or comparators, study procedures, inter-current illness (including pandemic infections), concomitant medications, concurrent medical conditions or any other issues related to the safe conduct of the study or that pose a risk to study subjects.

In exceptional circumstances of imminent hazard and to safeguard the health or safety of individuals, Quotient may take urgent safety measures before informing the Sponsor. The Sponsor must be informed immediately after the hazard has resolved.

The Sponsor will take responsibility for informing the FDA of any urgent safety issue. Investigators will be responsible for notifying their IRB of any urgent safety matter.

15.3 Reporting

15.3.1 Reporting Serious Adverse Events and AESI

The investigator is required to notify the study Sponsor and pharmacovigilance provider if appropriate within 24 hours of becoming aware of the occurrence of a SAE or AESI. A copy of the written report of the event should promptly be sent to the study Sponsor for information purposes in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for GCP.

15.3.2 Reporting of Suspected Unexpected Serious Adverse Reactions

It is the responsibility of the Sponsor to determine whether a reported SAE fits the classification of a SUSAR and to notify the investigator of their decision as soon as possible.

15.3.3 Expedited Reporting of Events

It is the responsibility of the Sponsor to determine whether an event requires expedited reporting and to notify the investigator of their decision as soon as possible.

Where expedited reporting is required, the following procedures should be followed.

Fatal or life-threatening SUSARs

It is the responsibility of the investigator and Sponsor to report fatal or life-threatening SUSARs to the IRB and relevant regulatory authorities, respectively, as soon as possible but no later than 7 calendar days after they first became aware of the reaction. Any additional relevant information should be sent within 8 days of the report. The task of reporting fatal or life-threatening SUSARs may be delegated to the pharmacovigilance provider.

Other SUSARs

It is the responsibility of the investigator and Sponsor to report other SUSARs to the IRB and relevant regulatory authorities, respectively, as soon as possible but no later than 15 calendar days after they first became aware of the reaction. The task of reporting other SUSARs may be delegated to the pharmacovigilance provider.

15.3.4 Reporting of Urgent Safety Issues

The Sponsor is required to inform the appropriate regulatory authorities and investigators and the investigator is responsible for informing the IRB, within 3 calendar days of the urgent safety issue.

15.4 Reporting Other Serious Important Medical Events

Events should be reported when they do not fit other outcomes but may jeopardize the subject and/or may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of reportable medical events.

16 Protocol Amendments and Deviations

16.1 Amendments

Protocol amendments will be submitted to the FDA and IRB as required by current regulations.

If the ICF is updated as a result of the substantial amendment the new approved version will be used to re-consent currently enrolled subjects (as required by the IRB) and must be provided to newly enrolled subjects prior to their entry into the study.

16.2 Protocol Deviations

The study must be conducted in accordance with the clinical protocol. Should a protocol deviation occur it must be promptly assessed to decide whether any non-compliance should be reported to the IRB.

Protocol waivers are not acceptable.

Important protocol deviations will be promptly reported to and discussed with the Sponsor to assess the impact on the study.

17 Regulatory

17.1 Compliance

This study will be conducted in accordance with the protocol and with the following legislation:

- ICH GCP Guidelines approved by the Committee for Medicinal Products for Human Use (CHMP) on 17 Jul 1996, which came into force on 17 Jan 1997, updated Jul 2002, Integrated Addendum E6 (R2) dated 09 Nov 2016
- US CFR Title 21
- The ethical principles outlined in the World Medical Association Declaration of Helsinki and its amendments

17.2 Ethical Approval

Prior to the initiation of the study, the protocol and associated documentation must be approved by an IRB. A copy of this written approval and any correspondence with the IRB will be provided to the Sponsor.

17.3 Investigator Responsibilities

The investigator will be responsible for the following:

- Providing written summaries of the study status to the IRB annually or more frequently in accordance with the requirements, policies and procedures established by the IRB
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB and all other applicable local regulations

- Notifying the Sponsor of any requests for inspections by a regulatory authority

17.4 Source Data

A study-specific source document identification list will be finalized with the Sponsor prior to the start of the clinical phase of the study. The document will identify what data should be considered source data for this study.

For this study, electronic data capture will be used where possible and data will be automatically recorded into an eCRF. In instances where paper source documents are used data to be transcribed into the eCRF will be identified using a Source Document Identification List as governed by Quotient's SOPs.

17.5 Declaration of the End of the Study

The end of the study is defined as the point at which the Sponsor determines that any remaining optional groups are not required to meet the objectives of the trial (i.e., signed dose decision document or the completion of the last follow-up visit or unscheduled follow-up assessment for the final cohort/subject dosed, whichever occurs later). The Sponsor can also declare an end of the study if business reasons indicate that the development of PDM-608 cannot proceed, with orderly collection of follow-up data at safety visits from enrolled subjects. If all optional groups are utilized, completion of the last follow-up visit or unscheduled follow-up call/visit will be considered the end of the study. Any changes to this definition will be notified as a substantial amendment.

17.6 Document Storage and Archiving

All documentation and correspondence pertaining to the study (eCRF, raw data, letters, etc.) will be kept in accordance with 21 CFR and the ICH guidelines for GCP 1996, updated 2002, Integrated Addendum E6 (R2) dated 09 Nov 2016 (ICH GCP Section 4.9.5)

All study related documents will be retained for a period of at least 2 years following the date a marketing application is approved for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified; or 8 years after completion of the study, whichever is longer. After this time, the Sponsor will be contacted to ascertain whether continued storage or destruction is required in accordance with current regulations.

17.7 Protection of Personal Data and Confidentiality

Personal data are securely stored to prevent unauthorized access, disclosure, dissemination, alteration or loss of information and unauthorized personal data processing.

Access to personal information is restricted so that only personnel who are required to access personal data as part of their job role can do so. All personnel who access personal information are bound by a duty of confidentiality.

Technical arrangements surrounding the electronic storage and use of data are as follows:

- Computers storing electronic personal data are protected by antivirus software and the network on which computers are linked are protected by industry grade firewalls

- Off-site personnel can only access networked computers through a virtual private network
- Electronic access of data is limited according to user roles
- All data are stored on password protected computers

Organizational arrangements are as follows:

- All buildings are secured by key-card access
- Manual files of personal data are stored within restricted areas of the clinical unit that can only be accessed by authorized personnel
- Data security and/or confidentiality provisions are utilized in agreements with third parties
- Documented back-up and disaster recovery procedures are in place
- Internal audit and compliance functions provide regulatory oversight

The Sponsor shall be the data controller of study subject personal data collected in connection with the study and shall act in accordance with the relevant data protection laws in relation to the collection and processing of those personal data. Records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Anonymized personal data shall be collected and processed for the purposes of the study and may also be added to research databases and used in the future by the Sponsor and its affiliates for certain additional clinical research, product regulation, safety reporting purposes and for ensuring compliance with legal requirements. The study subjects' anonymized personal data may be processed for such purposes by other parties including the Sponsor's affiliates and licensing partners, its business partners, regulatory agencies, other health authorities and the IRB. The study subjects' authorization for such use and disclosure shall be obtained by the study subjects signing the ICF for the study.

Additionally, Quotient personnel are contractually bound by a duty of confidentiality and receive training on this matter.

18 Quality Control and Quality Assurance

Quality control of all data collected from this study will be performed in accordance with Quotient's SOPs. This study (or elements thereof) may be subject to Quotient QA audit in line with current internal auditing procedures. Similarly, the study (or elements thereof) may be subject to Sponsor QA audit.

18.1 Monitoring

GCP requires that studies are adequately monitored. The Sponsor should determine the appropriate extent and nature of monitoring. A study monitor, independent of Quotient, will be appointed to verify that the study is conducted in accordance with current GCP, regulatory requirements, the protocol and that the data are authentic, accurate and complete.

The investigator agrees to receive visits from a study monitor and provide assistance to verify protocol implementation, eCRF completion, document storage and AE reporting.

Quotient will extend the professional privilege of access to the subjects' clinical source documents to the study monitor, IRB, regulatory bodies or other authorized personnel (e.g., auditor) for the purposes of source data verification.

Following completion of the study all study related documents and subject data, unless mandated by law and federal agencies, will be stored by Quotient, either on site or in long term storage site under Quotient's responsibility. In the interests of confidentiality subjects will not be identified on any such documents or data, and specific subject consent for such a disposition will be obtained as required by law.

19 Publication

Please refer to the Master Services Agreement for information on publication.

Quotient shall have the right to publish the results of the research, subject to the Sponsor's prior written consent, which shall not be unreasonably withheld or delayed. Following the receipt of such consent Quotient shall submit a copy of the proposed publication to the Sponsor who shall have 30 days in which to request amendments thereto which, to the extent that such proposed amendments are reasonable, Quotient shall be obliged to incorporate prior to such publication.

The Sponsor undertakes that, prior to publication of any information, article, paper, report or other material concerning the research, it will submit a copy of such publication to Quotient who shall have 30 days in which to request amendments thereto which, to the extent that such proposed amendments are reasonable, the Sponsor shall be obliged to incorporate prior to such publication.

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Investigator's Brochure: PDM608. Calibr. V1.0 / 03 Mar 2018.

Leukine (sargramostim) for injection, for subcutaneous use or intravenous use. Highlights of Prescribing Information. Initial U.S. approval: 1991; revised: May 2019.

Appendix 1 Clinical Laboratory Parameters

Hematology	Clinical Chemistry	Virology	Urinalysis	Drugs of Abuse
Basophils Eosinophils Hematocrit Hemoglobin Lymphocytes Mean Cell Hemoglobin (MCH) Mean Cell Hemoglobin Concentration (MCHC) Mean Cell Volume (MCV) Monocytes Neutrophils Platelet Count Red Blood Cell (RBC) Count White Blood Cell (WBC) Count	Alanine Aminotransferase (ALT) Albumin Alkaline Phosphatase (ALP) Aspartate Aminotransferase (AST) Bilirubin (Total) Bilirubin (Direct) Blood urea nitrogen (BUN) Calcium Carbon Dioxide (CO_2) Chloride Creatine Kinase (CK) Creatinine CLcr will be calculated at screening only using the Cockcroft-Gault equation for eligibility purposes Follicle Stimulating Hormone (FSH; post-menopausal female subjects only at screening) Gamma Glutamyl Transferase (GGT) Glucose (unscheduled time points)[a] Glucose (Fasting) Human Chorionic Gonadotropin (hCG) (female subjects when indicated) Potassium Phosphate (Inorganic) Protein (Total) Sodium Triglycerides (fasted)	Hepatitis B Surface Antigen Hepatitis C Virus Antibody HIV Antibody QuantiFERON®-TB Gold test	Bilirubin Blood Glucose Ketones Leukocytes Nitrites pH Protein Specific gravity Urobilinogen **Based on urinalysis results** Microbiology Urine Microscopy (analysis of sediment for: bacteria, casts, crystals, epithelial cells, red blood cells and white blood cells) **Urine Pregnancy** Human Chorionic Gonadotropin (hCG) (female subjects when indicated)	Amphetamines[b] Antidepressants Barbiturates Benzodiazepines Cocaine Cotinine[c] Ethanol Marijuana/Cannabis Methadone Morphine/Opiates Phencyclidine Tricyclic s

Samples taken due to early withdrawal do not need to be fasted.
[a] Fasting is not a requirement for unscheduled samples.
[b] Refers to a group of drugs that includes methamphetamine/MDMA (commonly known as Ecstasy)
[c] Urine cotinine at screening and admission only (for Part 2, this is the Day -1 admission)

Appendix 2 Schedule of Assessments: Part 1 Single Ascending Dose

Study Day →	SCRN	D -1	D1					D2	D3	D4	D5	D6	D7	D8	D11	D15	D22	Premature
Time Relative to IMP Admin→		Admit	Pre-Dose	0H	1H	3H	12H	24H	48H	72H	96H	120H	144H	168H	240H	336H	504H	
Window →	D-28 to -2	Day of	1H[j]	n/a	±10M	±10M	±1H	±2H	±2H	±2H	±2H	±2H	±2H	±2H	±24H	±24H	±24H	
Assessments ↓																		
Informed Consent	X																	
Medical History	X	X[a]																
Weight, Height, BMI	X	X[b]																
Vein Assessment	X	X																
Urine Alcohol, Cotinine, Drug Screen	X	X																
Serum Pregnancy	X[c]																	
Urine Pregnancy		X[d]																
Randomization			X[e]															
IMP Administration[f]				X														
Physical Exam	X							X			X			X				X
Hem & Chem[m]	X	X					X	X	X		X			X		X		X
Virology & TB Test	X																	
FSH[g]	X																	
CLcr	X						X	X	X		X			X		X		X
Urinalysis	X		X[k]					X	X	X	X	X	X	X				
Single ECG	X	X													X	X	X	X
Triplicate ECG			X		X	X	X	X	X	X	X	X	X	X				

Study Day →	SCRN	D -1	D1					D2	D3	D4	D5	D6	D7	D8	D11	D15	D22	Premature
Time Relative to IMP Admin→		Admit	Pre-Dose	0H	1H	3H	12H	24H	48H	72H	96H	120H	144H	168H	240H	336H	504H	
Window →	D-28 to -2	Day of	1H[j]	n/a	±10M	±10M	±1H	±2H	±2H	±2H	±2H	±2H	±2H	±2H	±24H	±24H	±24H	
Assessments ↓																		
Vital Signs[h]	X	X	X				X	X	X	X	X	X	X	X				X
PK			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD			X					X			X			X	X	X	X	X
ADA			X											X		X	X	X
Adverse Events	X																	
Concomitant Medications	X																	
Clinical Residency		Clinical Residency admit Day -1, discharge Day 8													RV	RV	RV	

RV = Return Visit

Appendix 2 Footnotes

a Update of medical history

b Weight only

c All female subjects

d All female subjects, except those confirmed menopausal/post-menopausal by FSH ≥ 40 IU/L at screening

e Subjects will be randomized on Day 1 prior to dosing (1 hour window not applicable)

f See Pharmacy Manual for details on SC IMP administration

g Menopausal/post-menopausal female subjects only, to confirm childbearing potential status

h Vital signs to include blood pressure, heart rate, body temperature, and respiratory rate

j Within 1 hour prior to IMP administration

k Urinalysis within 2 hours prior to IMP administration

m Scheduled blood samples will be taken following an overnight fast of a minimum of 8 hours

Appendix 3 Schedule of Assessments: Part 2 Multiple Ascending Dose

Screening through Day 16

Study Day →	SCRN	D -1	D1					D2	D3	D4	D5	D6	D7	D8	D9	D14	D15	D16
Time Relative to D1 →		Admit	Pre-Dose	0H	1H	3H	12 H	24 H	48 H	72 H	96 H	120 H	144 H	168 H	192 H	Admit	336H	360H
Time Relative to Prior Dose →														0H	24H		0H	24H
Window Relative to Prior Dose →	D-28 to -2	Day of	≤1H[i]	n/a	±10M	±10M	±1 H	±2 H	±2 H	±2 H	±2 H	±2H	±2H	≤1H[i]	Day of	Day of	≤1H[i]	Day of
Assessments ↓																		
Informed Consent	X																	
Medical History	X	X[a]																
Weight, Height, BMI	X	X[b]																
Vein Assessment	X	X																
Urine Alcohol, Cotinine, Drug Screen	X	X														X		
Serum Pregnancy	X[c]																	
Urine Pregnancy		X[d]											X[d]			X[d]		
Randomization			X[e]															
IMP Administration[f]				X										X			X	
Physical Exam	X																	
Hem & Chem[k]	X	X					X			X			X	X		X		
Urinalysis	X	X					X	X		X			X	X		X		
Virology and TB Test	X																	
FSH	X[g]																	

Study Day →	SCRN	D -1	D1					D2	D3	D4	D5	D6	D7	D8	D9	D14	D15	D16
Time Relative to D1 →		Admit	Pre-Dose	0H	1H	3H	12 H	24 H	48 H	72 H	96 H	120 H	144 H	168 H	192 H	Admit	336H	360H
Time Relative to Prior Dose →														0H	24H		0H	24H
Window Relative to Prior Dose →	D-28 to -2	Day of	≤1H[i]	n/a	±10M	±10M	±1 H	±2 H	±2 H	±2 H	±2 H	±2H	±2H	≤1H[i]	Day of	Day of	≤1H[i]	Day of
Assessments ↓																		
CLcr	X						X						X	X				
Single ECG	X															X		
Triplicate ECG		X	X		X	X	X	X	X	X	X	X	X	X			X	
Vital Signs[h]	X	X	X				X	X	X	X	X	X	X	X	X	X	X	X
PK			X		X	X	X	X	X	X	X	X	X	X			X	
PD			X					X			X			X			X	
ADA			X											X			X	
Adverse Events	X																	
Concomitant Medications	X																	
Clinical Residency		Admit Day -1, Discharge D9														Admit D14, D/C D16		

Day 21 through 60 and Premature Discontinuation

Study Day →	D21	D22				D23	D24	D25	D26	D27	D28	D29	D32	D36	D43	D50	D60	Premature DC
Time Relative to D1 →	Admit	n/a				528H	552H	576H	600H	624H	648H	672H	744H	840H	1008H	1176H	1416H	
Time Relative to Prior Dose →		0H	1H	3H	12H	24H	48H	72H	96H	120H	144H	168H	240H	336H	504H	672H	912H	
Window Relative to Prior Dose →	Day of	≤1H[i]	±10M	±10M	±1H	±2H	±2H	±2H	±2H	±2H	±2H	±2H	±24H	±24H	±24H	±24H	±24H	
Assessments ↓																		
Urine Alcohol, Cotinine, Drug Screen	X																	
Urine Pregnancy	X[d]																	
IMP Administration[f]		X																
Physical Exam								X										X
Hem & Chem[k]	X							X				X	X	X	X	X	X	X
Urinalysis	X				X	X		X			X	X						
Single ECG														X			X	
Triplicate ECG	X	X			X	X		X		X		X						X
Vitals Signs[h]	X	X			X						X	X						
PK		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD		X					X			X		X	X	X	X			X
ADA											X				X		X	X
Adverse Events	X																	X
Concomitant Medications	X																	X
Clinical Residency	Admit D21, Discharge 29												RV	RV	RV	RV	RV	

RV = Return Visit

Appendix 3 Footnotes

a Update of medical history

b Weight only

c All female subjects

d All female subjects, except those confirmed menopausal/post-menopausal by FSH ≥ 40 IU/L at screening

e Subjects will be randomized on Day 1 prior to dosing (1 hr window not applicable)

f See Pharmacy Manualfor details on IMP administration

g Menopausal/post-menopausal female subjects only, to confirm childbearing potential status

h Vital signs to include blood pressure, heart rate, temperature, and respiratory rate

i Within 1 hour prior to IMP administration

k Scheduled blood samples will be taken following an overnight fast of a minimum of 8 hours

Signatures for Quotient Sciences

CONFIDENTIALITY AND GCP COMPLIANCE STATEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the Sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 15.3.1 of this protocol.

Information taken from the study protocol may not be disseminated or discussed with a third party without the express consent of the Sponsor.

Principal Investigator Print Name	Signature
	Date of Signature

Signatures for Sponsor

DocuSigned by:
Chan Beals
0A6F4FF3560E4D0...

Chan Beals MD PhD

Chief Medical Officer
Calibr, a Division for Scripps Research

Signature

1/30/2023

Date