NCT04321980

CLINICAL STUDY PROTOCOL

A Phase 1 Open-Label Single-Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of OP-101 (dendrimer n-acetyl-cysteine) After Subcutaneous Administration in Healthy Volunteers

Investigational Product: OP-101 (dendrimer n-acetyl-cysteine)
Protocol Number: OP-101-003

Sponsor:
Orpheris, Inc.
1235 Radio Road, Suite 200
Redwood City, CA 94065
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Version Number: 2.0
Date: 17 March 2020

SIGNATURE PAGE

STUDY TITLE: A Phase 1 Open-Label Single-Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of OP-101 (dendrimer n-acetyl-cysteine) After Subcutaneous Administration in Healthy Volunteers

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
[redacted]	17/03/2020
[redacted] Orpheris, Inc.	
Medical Monitor	

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Orpheris to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Orpheris and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Orpheris, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure(s) (IB), Case Report Forms (CRFs), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Human Research Ethics Committee (HREC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the Ethics Committee, except where necessary to avert an immediate hazard to the participants.

I have read the protocol and agree that the study will be conducted in compliance with the protocol and in accordance with the principles of the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), and with the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research (2007, updated 2018). The conduct of the study will be in accordance with the Integrated Addendum to ICH E6 (R1), Guideline for GCP ICH E6 (R2), annotated with comments by the Australian Therapeutic Goods Administration (TGA) (2018).

I acknowledge that I am responsible for the overall study conduct. I agree to personally conduct or supervise the described clinical study. I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study at my site are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the conduct of the study.

_____ _____

Investigator’s Signature Date

_____

Investigator’s Printed Name

SYNOPSIS

TITLE: A Phase 1 Open-Label Single-Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of OP-101 (dendrimer n-acetyl-cysteine) After Subcutaneous Administration in Healthy Volunteers

PROTOCOL NUMBER: OP-101-003

INVESTIGATIONAL PRODUCT: OP-101 (dendrimer n-acetyl-cysteine)

PHASE: 1

INDICATION(S): Treatment of children with childhood cerebral adrenoleukodystrophy who are not eligible for hematopoietic stem cell transplantation.

OBJECTIVES:

The primary objective is to evaluate the safety and tolerability of OP-101 after single subcutaneous (SC) doses in healthy subjects.

The secondary objective is to determine the pharmacokinetic (PK) profile of OP-101 after single SC doses in healthy subjects.

POPULATION:

The population for this study includes men and women aged 18 to 65 years, inclusive, who are in good health as determined by screening medical history, a physical examination, vital sign measurements, and clinical laboratory tests (chemistry, hematology, and urinalysis). Subjects are to have a body mass index between 18 and 32 kg/m^2, inclusive.

STUDY DESIGN AND DURATION:

This is a Phase 1, open-label, single-ascending dose study to evaluate the safety, tolerability, and PK of OP-101 after SC administration in up to 8 healthy subjects at 1 site in Australia.

This study will consist of a 21-day Screening Period, a 2-day Treatment Period, and Follow-up Visits on Days 8 and 15. Subjects will sign an informed consent form before any study procedures are performed and must meet all of the inclusion and none of the exclusion criteria to participate in the study. Eligible subjects will be admitted to the investigational site on Day -1, dosed on Day 1, and discharged on Day 3.

There will be 2 separate and sequential SC cohorts (4 mg/kg and 8 mg/kg) with 4 subjects in each cohort who complete Day 15. Cohort 1 will enroll 4 subjects administered a single SC dose of 4 mg/kg. Dose escalation from Cohort 1 (4 mg/kg) to Cohort 2 (8 mg/kg) will be determined by the safety review committee (SRC), consisting of the Medical Monitor, the Principal Investigator (or delegate), and Sponsor representative after review of safety, tolerability, and any available PK data through Day 8 of Cohort 1. Cohort 2 will enroll 4 subjects administered a single SC dose of 8 mg/kg.

During the Treatment Period, plasma and urine samples will be collected for PK analysis. Plasma PK samples will be collected predose, at 30 minutes and at 1, 2, 4, 6, 8, 10, 12, 16, 24, and 30-36 hours after dosing, as well as on Day 3 (~48 hr). Blood samples for PK analysis can be obtained within ±5 minutes of the scheduled sampling time for sample times ≤1 hour, within ±10 minutes of the scheduled sampling time for sample times ≤12 hours, and within ±2 hours of the scheduled sampling times for sample times >12 hours.

Urine PK samples will be collected predose (spot sample) and between 0 to 4, 4 to 8, 8 to 12, 12 to 18, 18 to 24, and 24 to 48 hours.

Safety assessments will include adverse event monitoring, clinical laboratory tests (hematology, chemistry, and urinalysis), physical examinations, and vital signs (pulse rate, blood pressure [BP], respiration rate, and temperature). Coagulation testing will be performed at screening. Pregnancy testing will be performed at screening and Day -1.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Subjects in Cohort 1 will be administered 4 mg/kg OP-101 as a SC injection.

Subjects in Cohort 2 will be administered 8 mg/kg OP-101 as a SC injection.

PHARMACOKINETIC VARIABLES:

The PK variables will include the following:

- C_{max} – maximum plasma concentration,
- t_{max} – time to maximum plasma concentration,
- kel – apparent terminal rate constant,
- $t_{½}$ – apparent elimination half-life,
- AUC_{0-t} – area under the concentration-time curve based on the last measurable concentration,
- AUC_{0-inf} – area under the concentration-time curve from time zero to infinity, and
- CL – clearance of study drug.

SAFETY VARIABLES:

Safety assessments will include adverse event monitoring, clinical laboratory tests (hematology, chemistry, and urinalysis), physical examinations, and vital signs (pulse rate, BP, respiration rate, and temperature).

STATISTICAL ANALYSES:

The PK Concentration Population is defined as all subjects who received at least 1 dose of study drug and have at least 1 measurable concentration. The PK Parameter Population is defined as all subjects who received a dose of study drug and have at least 1 PK parameter. Plasma PK concentrations of OP-101 will be summarized with descriptive statistics (n, mean, standard deviation [SD], percent coefficient of variation [%CV], minimum, median, maximum, geometric mean, and %CV for the geometric mean) by nominal PK sampling time and treatment using the PK Concentration Population. Standard noncompartmental PK analysis will be used to calculate the PK parameters. Pharmacokinetic parameters will be summarized with descriptive statistics (n, mean, SD, %CV, minimum, median, maximum, geometric mean, and %CV for the geometric mean) by treatment using the PK Parameter Population.

The Safety Population is defined as all subjects who received at least 1 dose of study drug. Adverse events will be summarized overall and by system organ class and preferred term, and the relationship to the study drug received. A list of subjects who have SAEs and who discontinue from the study due to an adverse event will be provided. Deaths due to adverse events will also be provided. Safety laboratory tests will include chemistry, hematology, and urinalysis. Summary statistics for laboratory values will be provided at baseline, postbaseline, and for changes from baseline to postbaseline by treatment. Occurrence of significant laboratory abnormalities will be summarized by regimen for each treatment. Vital signs will be summarized in the same manner as clinical laboratory evaluations, and physical examination data will be listed.

SAMPLE SIZE DETERMINATION:

Up to 8 subjects will be enrolled and dosed in 2 cohorts with 4 subjects in each cohort who complete Day 15. The sample size in the study is based on clinical and practical considerations rather than statistical power.

SITES: 1 site in Australia.

SPONSOR:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
%CV	Percent coefficient of variation
ALD	Adrenoleukodystrophy
ANOVA	Analysis of variance
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time zero to infinity
$AUC_{0\text{-}t}$	Area under the concentration-time curve based on the last measurable concentration
BP	Blood pressure
ccALD	Childhood cerebral adrenoleukodystrophy
CFR	Code of Federal Regulations
CL	Clearance of study drug
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CRA	Clinical Research Associate
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
FSH	Follicle-stimulating hormone
GI	Gastrointestinal
GLP	Good Laboratory Practice
GSH	Glutathione
HBsAg	Hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HCVab	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
HREC	Human Research Ethics Committee
HSCT	Hematopoietic stem cell transplantation
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Institutional Ethics Committee
IL	Interleukin
IV	Intravenous
kel	Apparent terminal rate constant
KIM-1	Kidney injury molecule-1
NAC	N-acetyl-cysteine
NGAL	Neutrophil gelatinase-associated lipocalin
PAMAM	Polyamidoamine

Abbreviation	Definition
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
ROS	Reactive oxygen species
SAE	Serious adverse event
SD	Standard deviation
SRC	Safety review committee
$t_{½}$	Apparent elimination half-life
TGA	Therapeutic Goods Administration
t_{max}	Time to maximum plasma concentration

1 INTRODUCTION AND BACKGROUND INFORMATION

OP-101 is a new chemical entity consisting of a metabolically stable inactive dendrimer covalently coupled to n-acetyl-cysteine (NAC). Upon intravenous (IV) administration, OP-101 is selectively taken up by reactive microglia and reactive astrocytes in the brain through fluid phase endocytosis. The active component of OP-101, NAC, is released upon uptake into reactive microglia and astrocytes. Upon intracellular release from OP-101, NAC acts to reduce oxidative stress and neuroinflammation in the brain. Following release of NAC, the dendrimer component is excreted from the cells and cleared without further metabolism.

Specifically, OP-101 consists of a generation-4 hydroxyl-terminated polyamidoamine (PAMAM) dendrimer linked to NAC using a disulfide bond. PAMAM is a class of dendrimer made of repetitive reactions of methyl acrylate and ethylene diamine. The PAMAM dendrimer contains an ethylene diamine core, amidoamine repeat units ([$CH_2CH_2CONHCH_2CH_2N$]), and 64 hydroxyl end groups (chemical formula: $C_{622}H_{1184}N_{186}O_{188}$). Approximately 20 of the 64 hydroxyls are subsequently converted to amine groups and then to a thiol group for eventual conjugation with NAC using a disulfide bond. The active metabolite of OP-101, NAC, comprises approximately 16% of the total mass of OP-101.

In vitro and in vivo nonclinical studies have demonstrated that the PAMAM dendrimer is metabolically stable and rapidly excreted via the kidney. Upon IV administration, OP-101 is endocytosed by reactive microglia and astrocytes in animal models of neuroinflammation. After endocytosis, the reducing environment inside these cells results in release of NAC and a normalization of glutathione (GSH) levels. As the active metabolite of OP-101, NAC reduces oxidative stress and related proinflammatory cytokines (via the nuclear receptor, NFκβ pathway), decreasing neuroinflammation and central nervous system (CNS) toxicity. Pharmacology studies support the specific targeting of OP-101 to microglia and the intracellular release of NAC (Kurtoglu 2009; Navath 2008), as well as the ability of OP-101 to significantly reduce a proinflammatory response as compared with unconjugated free NAC (Dai 2010; Kambhampati 2015; Kannan 2012; Lesniak 2013; Mishra 2014; Nance 2015; Nemeth 2017).

NAC, the active metabolite of OP-101, is an approved product and marketed under Acetadote®, and the putative mechanism of action of OP-101 is related to the chemical and biological properties of NAC. NAC has been approved for use as a mucolytic agent and for the treatment of acetaminophen intoxication in addition to other conditions and disorders, including doxorubicin-induced cardiotoxicity, radio-contrast-induced nephropathy, and chemotherapy-induced toxicity (Samuni 2013). NAC has been shown to interact with several metabolic pathways including regulation of cell cycle and apoptosis, but the main clinical effect of NAC is attributed mainly to its ability to scavenge reactive oxygen species (ROS) and elevate cellular GSH levels. NAC is recognized to suppress microglial activation (Tsai 2009) and inhibit NFκB-mediated proinflammatory cytokines by macrophages and glial cells (Pahan 1998). Examples of CNS effects of NAC include reduced levels of proinflammatory cytokines tumor necrosis factor-alpha, interleukin (IL)-1beta in rodent models of traumatic brain injury and cerebral ischemia (Chen 2008; Khan 2004), and IL-6 and IL-10 in lipopolysaccharide-treated rat fetal brain (Beloosesky 2012). The human safety profile for NAC, based on the collective experience with Acetadote, supports human testing of OP-101.

OP-101 is being developed as a possible treatment for patients with advanced childhood cerebral adrenoleukodystrophy (ccALD) who are not considered eligible for hematopoietic stem cell

transplantation (HSCT). Adrenoleukodystrophy (ALD) is an X-linked disease caused by mutations in the *ABCD1* that result in oxidative stress and neuroinflammation in several critical CNS cell types (Deon 2016). The disease affects cerebral white matter, spinal cord, and peripheral nerves, with some pediatric phenotypes suffering rapid progression leading to death in early childhood (Moser 2000; Moser 2007). About 35% of all hemizygous males between 3 and 10 years of age develop a form of ALD that manifests with progressive neuroinflammation resulting in widespread demyelination and rapid neurological deterioration. This phenotype is referred to as ccALD and typically leads to death within 2 to 5 years after onset of symptoms. While HSCT may stabilize patients in the very early stages of ALD, there is no effective therapy for patients who present with advanced stages of ccALD where HSCT is contraindicated. Therefore, OP-101 is being investigated as a potential treatment for patients with advanced ccALD who present with signs of progressive neuroinflammation potentially reversible by OP-101 and who are not candidates for HSCT.

1.1 Rationale

A first-in-human study has been completed to evaluate the safety, tolerability, and pharmacokinetics (PK) of IV administered OP-101 in normal healthy humans. This study indicated that treatment with a single IV dose of OP-101 at 20 and 40 mg/kg was generally well tolerated in healthy subjects based on an assessment of clinical and laboratory adverse events. The half-life of OP-101 in this study (5.5 hr) demonstrated the need for development of a more convenient dosing route (e.g. subcutaneous). This study is being conducted to enable selection of the starting dose and regimen in a planned Phase 1/2/3 study in patients with ccALD. Currently, ccALD patients with progressive disease not treatable with HSCT have no therapeutic options, and reactive microglia are a recognized cause of the neuroinflammation associated with progression in ccALD. OP-101 has been demonstrated to selectively target reactive microglia and astrocytes in animal models of neuroinflammation, and has also been shown ex vivo to be effective in normalizing activated macrophages cells derived from ccALD patients. By targeting the reactive microglia, OP-101 has the potential to stop or slow neurodegeneration in ccALD patients through antioxidant and anti-inflammatory mechanisms and may provide clinical benefit to ccALD patients not eligible for HSCT. Reversing the neuroinflammation driving the white matter injury in ccALD patients could stabilize the disease course and preserve neurological, developmental, and cognitive function.

The safety and PK data collected in this subcutaneous dosing study will permit identification of the starting dose and regimen for the Phase 1/2/3 study in ccALD and support further clinical development of OP-101.

1.2 Risk/Benefit

This study is a follow up to the completed Phase 1 single ascending IV dosing study in healthy volunteers. In the completed Phase 1 study, treatment with a single IV dose of OP-101 at 20 and 40 mg/kg was generally well tolerated in healthy subjects based on an assessment of clinical and laboratory adverse events. There were no clinically meaningful changes from baseline in laboratory parameters except changes in the urinalysis parameters of proteinuria and the presence of granular urinary casts. Transient elevations in KIM-1 and NGAL were observed, and subjects who experienced an increase in KIM-1 or NGAL at Day 15 underwent additional follow-up, at the recommendation of the SRC. The additional measurements in either KIM-1 or NGAL were

conducted as a precautionary measure and the values subsequently returned to baseline. There were no clinically meaningful changes in vital signs or ECGs. OP-101 has also been tested in nonclinical studies with no adverse clinical changes observed across multiple species and models. The anticipated risks associated with OP-101 may be categorized as potentially related to the PAMAM dendrimer and/or NAC. In vitro studies have demonstrated that the dendrimer is not systemically metabolized in human hepatocytes or human plasma and is rapidly cleared by the kidney. Good Laboratory Practice toxicity studies with repeat dosing of OP-101 in juvenile and adult rats have shown partial dose-dependent changes of proximal tubular cells characterized by mild intracellular basophilia and mild single-cell necrosis, but no associated clinical adverse events, mortality, or change in electrolytes. Toxicology studies in rats with single-doses of OP-101 have demonstrated resolution of the single-cell necrosis by 2 weeks postdosing and no adverse clinical observations or changes in urinalysis parameters. In summary, the renal clearance of OP-101 and the effects on proximal tubular cells in nonclinical studies indicate that renal function should be carefully assessed in human studies.

The active metabolite of OP-101, NAC, is an approved product and marketed under Acetadote. NAC is only released from OP-101 under intracellular GSH levels, and lower levels of GSH in plasma are insufficient to release NAC systemically. Regardless, the total level of NAC, if completely released from the highest possible human OP-101 dose, is well below the total systemic NAC typically administered for acetaminophen toxicity. Thus, the risks associated with Acetadote are relevant but unlikely to manifest given the projected low systemic exposure to NAC, even if fully released upon administration. For completeness, the major adverse events associated with IV NAC administration have been categorized as anaphylactoid reactions, with most either mild or moderate in degree. The most common adverse effects associated with NAC infusion were minor anaphylactoid reactions, including rash, urticarial, hypotension, and wheezing or shortness of breath. Literature reports indicate that adverse reactions consistent with hypersensitivity have been easily treated with antihistamines, epinephrine, and/or slowing of the drug infusion. Other reported adverse events related to IV NAC administration include tachycardia, nausea, and emesis. The frequency of adverse events has been reported to be between 0.2% and 20.8% and most commonly occur during the initial IV infusion of Acetadote (Acetadote Prescribing Information, Cumberland Pharmaceuticals Inc.).

In summary, clinical risks associated with the proposed subcuntaneous (SC) doses of OP-101 are considered low based on the lack of clinical adverse events observed at 3-5 fold higher doses administered IV in healthy volunteers. In addition, the human safety profile established for NAC, which is the active moiety in OP-101, further predicts a favorable safety profile and low risk with human investigation.

There is no expected benefit of IV OP-101 administration for normal healthy subjects. Although safety and efficacy of OP-101 have not yet been evaluated in clinical studies, the collective efficacy observed in nonclinical studies indicate the potential to reverse neuroinflammation by targeting the reactive microglia in patients with ccALD. Because of the central role of neuroinflammation in driving disease progression in ccALD, the potential benefit in the intended patient population could include stabilization of white matter injury, and therefore the preservation of motor, cognitive, and developmental functions similar to the treatment effect after successful HSCT.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to evaluate the safety and tolerability of OP-101 after single SC doses in healthy subjects.

2.2 Secondary Objective

The secondary objective is to determine the pharmacokinetic (PK) profile of OP-101 after single SC doses in healthy subjects.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 1, open-label, single-ascending dose study to evaluate the safety, tolerability, and PK of OP-101 after SC administration in up to 8 healthy subjects at 1 site in Australia.

This study will consist of a 21-day Screening Period, a 2-day Treatment Period, and Follow-up Visits on Days 8 and 15. Subjects will sign an informed consent form (ICF) before any study procedures are performed and must meet all of the inclusion and none of the exclusion criteria to participate in the study. Eligible subjects will be admitted to the investigational site on Day -1, dosed on Day 1, and discharged on Day 3.

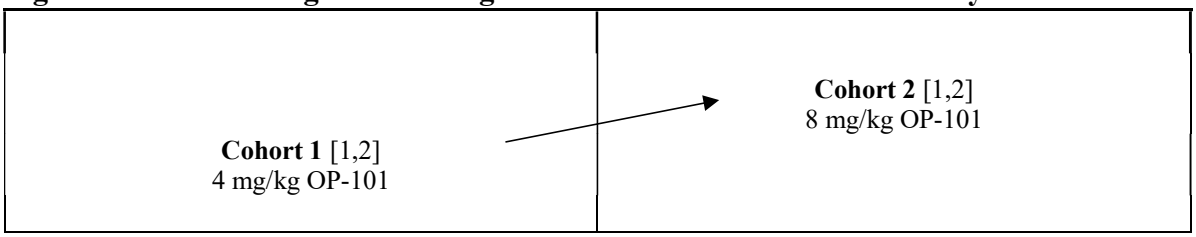
Figure 1 presents the cohort dosing schematic. There will be 2 separate and sequential SC cohorts (4 mg/kg and 8 mg/kg) with 4 subjects in each cohort who complete Day 15. Cohort 1 will enroll 4 subjects administered a single SC dose of 4 mg/kg. Dose escalation from Cohort 1 (4 mg/kg) to Cohort 2 (8 mg/kg) will be determined by the safety review committee (SRC), consisting of the Medical Monitor, the Principal Investigator (or delegate), and Sponsor representative after review of safety, tolerability, and any available PK data through Day 8 of Cohort 1. Cohort 2 will enroll 4 subjects administered a single SC dose of 8 mg/kg.

During the Treatment Period, plasma and urine samples will be collected for PK analysis. Plasma PK samples will be collected predose, at 30 minutes and at 1, 2, 4, 6, 8, 10, 12, 16, 24, and 30-36 hours after dosing, as well as on Day 3 (~48 hr). Blood samples for PK analysis can be obtained within ±5 minutes of the scheduled sampling time for sample times ≤1 hour, within ±10 minutes of the scheduled sampling time for sample times ≤12 hours, and within ±2 hours of the scheduled sampling times for sample times >12 hours.

Urine PK samples will be collected predose (spot sample) and between 0 to 4, 4 to 8, 8 to 12, 12 to 18, 18 to 24, and 24 to 48 hours.

Safety assessments will include adverse event monitoring, clinical laboratory tests (hematology, chemistry, and urinalysis), physical examinations, and vital signs (pulse rate, blood pressure [BP], respiration rate, and temperature). Coagulation testing will be performed at screening. Pregnancy testing will be performed at screening and Day -1.

Figure 1. OP-101 Single-Ascending Subcutaneous Dose Schedule – Day 1



1. Cohort enrollment will be separate and sequential with 4 subjects in each cohort who complete Day 15.
2. Cohort 1 will enroll 4 subjects administered a single SC dose of 4 mg/kg OP-101. Dose escalation to Cohort 2 (8 mg/kg) will be determined by the SRC after review of safety, tolerability and any available PK data through Day 8 of Cohort 1. Cohort 2 will enroll 4 subjects administered a single SC dose of 8 mg/kg.

PK = pharmacokinetic(s); SRC = safety review committee.

3.2 Study Stopping Rules

This study will stop and no further dosing and/or dose escalation will occur until safety information can be reviewed in the event that:

- 1 subject within a dose cohort has a drug-related Grade 3 adverse event or serious adverse event (SAE), or
- ≥2 subjects within the same dose cohort have a drug-related Grade 2 adverse event.

3.3 Study Indication

OP-101 is being developed for the treatment of children with ccALD who are not eligible for HSCT.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects who meet all of the following criteria will be eligible to participate in the study:

1. Is a healthy man or woman age 18 to 65 years, inclusive, at the Screening Visit;
2. Has the ability to understand and sign the written ICF and local medical privacy authorization forms, which must be obtained prior to any study related procedures being completed;
3. Body mass index (BMI) between 18 and 32 kg/m^2, inclusive;
4. Is in general good health, based upon the results of a medical history assessment, physical examination, vital signs, and laboratory profile, as judged by the Investigator;
5. Female subjects of non-childbearing potential must be either surgically sterile (hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks before the Screening Visit) or postmenopausal, defined as spontaneous amenorrhea for at least 2 years, with follicle-stimulating hormone (FSH) in the postmenopausal range at screening, based on the central laboratory's ranges;
6. Female subjects of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) and all male subjects must use a medically accepted contraceptive regimen (including hormonal contraceptives) during their participation in the study and for 30 days after the last administration of study drug. Medically accepted contraceptive methods are defined as those with 90% or greater efficacy;
7. Acceptable methods of contraception for male subjects enrolled in the study include the following:

   - Condoms or surgical sterilization of subject at least 26 weeks before the Screening Visit (vasectomy);

   Acceptable methods of contraception for female subjects enrolled in the study include the following:

   - Surgical sterilization of subject at least 26 weeks before the Screening Visit (includes hysterectomy or bilateral tubal ligation, oophorectomy, or salpingectomy);
   - Intrauterine device for at least 12 weeks before the Screening Visit;
   - Hormonal contraception (oral, implant, injection, ring, or patch) for at least 12 weeks before the Screening Visit; or
   - Diaphragm;
8. If male, subjects must agree to abstain from sperm donation through 90 days after administration of the last dose of study drug;
9. Female subjects may not be pregnant, lactating, or breastfeeding;
10. Female subjects of childbearing potential must have negative result for pregnancy test at screening and Check-in;

11. Subjects must have a negative test result for hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCVab), and human immunodeficiency virus (HIV) antibody at screening;
12. Subjects must have an estimated glomerular filtration rate (eGFR) of ≥90 mL/min/1.73m^2 at screening;
13. Subjects must have a negative urine test for drugs of abuse (opiates, benzodiazepines, amphetamines, cannabinoids, cocaine, barbiturates, and phencyclidine), cotinine, and breath alcohol test at screening and Check-in; and
14. Subjects must be willing and able to abide by all study requirements and restrictions.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Evidence of clinically significant hematologic, renal, endocrine, pulmonary, cardiac, gastrointestinal (GI), hepatic, psychiatric, neurologic, immunologic, allergic disease (including multiple or clinically significant drug allergies), or any other condition that, in the opinion of the Investigator, might significantly interfere with the absorption, distribution, metabolism, or excretion of study drug, or place the subject at an unacceptable risk as a participant in this study;
2. History of malignancy (other than successfully treated basal cell or squamous cell skin cancer);
3. History or presence of an abnormal ECG that, in the opinion of the Investigator, is clinically significant;
4. Laboratory results (serum chemistry, hematology, coagulation, and urinalysis) outside the normal range at screening and Check-in and considered clinically significant in the opinion of the Investigator. Any elevation of aspartate transaminase (AST) and alanine transaminase (ALT) above the upper limit of normal at screening and/or Check-in is exclusionary. One retest of an exclusionary laboratory result is allowed at the discretion of the Investigator;
5. Has had an acute illness considered clinically significant by the Investigator within 30 days prior to screening;
6. History of alcoholism or drug abuse within 2 years prior to screening;
7. Has used any product containing nicotine within 90 days prior to screening or intends to use any product containing nicotine during the course of the study;
8. Has had any immunizations (live vaccines) in the 4 weeks prior to screening;
9. Has used medications that affect GI motility or gastric emptying; such as metoclopramide, proton pump inhibitors, and H2 blockers; within 30 days prior to Day 1;
10. Has used any prescription or over-the-counter medication (with exception of acetaminophen), vitamins/herbal supplements (with the exception of hormonal contraceptives) within 14 days prior to Day 1;
11. Has used any other study drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to Day 1;
12. Has lost or donated >450 mL of whole blood or blood products within 30 days prior to screening;

13. Investigator has reason to believe that the subject may be unable to fulfill the protocol visit schedule or requirements;
14. Has any finding that, in the view of the Investigator or Medical Monitor, would compromise the subject's safety requirements; or
15. Is employed by the Sponsor, the Contract Research Organization (CRO), or the study site (permanent, temporary contract worker, or designee responsible for the conduct of the study), or is a family member (spouse, parent, sibling, or child) of the Sponsor, CRO, or study site employee.

4.3 Withdrawal Criteria

Participation of a subject in this clinical study may be discontinued for any of the following reasons:

- The subject withdraws consent or requests discontinuation from the study for any reason;
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol;
- Any SAE, clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the subject;
- Pregnancy;
- Requirement of prohibited concomitant medication;
- Subject failure to comply with protocol requirements or study-related procedures;
- Termination of the study by the Sponsor or the regulatory authority; or
- Subject noncompliance.

If a subject withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the Early Termination Visit. The reason for subject withdrawal must be documented in the electronic case report form (eCRF).

If a subject is withdrawn from the study due to an adverse event, the subject will be asked to return to the site for, at a minimum, the evaluations scheduled for the Early Termination Visit. If the adverse event has still not resolved, additional follow-up will be performed, as appropriate, based on the Investigator's judgment, and documented in the subject's medical records. As a minimum requirement, SAEs should be followed for 30 days after the subject's last dose of study drug.

Withdrawn subjects will be replaced if the subject is withdrawn prior to dosing. Withdrawn subjects may be replaced after dosing if adequate PK data is not available for that subject at the discretion of the Investigator and Medical Monitor.

5 STUDY TREATMENTS

5.1 Treatment Groups

There will 2 separate and sequential SC cohorts with 4 subjects in each cohort. The population will include healthy men and women aged 18 to 65 years, inclusive.

Dose escalation from Cohort 1 to Cohort 2 will be determined by the SRC, consisting of the Medical Monitor, the Principal Investigator (or delegate), and Sponsor representative after review of safety, tolerability, and any available PK data through Day 8 of Cohort 1.

Dosing with OP-101 is planned for the cohorts as follows:

- Cohort 1: Single SC dose of 4 mg/kg, and
- Cohort 2: Single SC dose of 8 mg/kg.

5.2 Rationale for Dosing

The safety of OP-101 is supported by the completed Phase 1 IV dosing study in healthy volunteers at 20 and 40 mg/kg (3-5 fold higher than the planned SC doses in this study). In addition, a series of nonclinical studies previously conducted with the active agent in OP-101, NAC, and numerous clinical studies that have been performed with NAC provide further support for the proposed dosing. The overall toxicological profile of OP-101 is expected to be comparable to NAC, which has been evaluated in nonclinical toxicity studies in support of the approval of Acetadote.

Good Laboratory Practice toxicology studies conducted with OP-101 in juvenile and adult rats, incorporating repeat IV doses up to 2000 mg/kg or single IV doses up to 1000 mg/kg, have shown no adverse clinical signs or mortality. The predominant finding in the toxicology studies was microscopic changes in the kidney that were generally localized to the proximal tubule. The findings included tubular degeneration/regeneration, mineralization, basophilic granules/tubules, and/or single cell necrosis, which increased in severity with increasing dose. While a defined NOAEL was not identified in the repeat-dose studies, the single-dose study in adult male rats, demonstrated a NOAEL of 200 mg/kg based upon the absence of single cell necrosis by 2 weeks after dosing and minimal-to-mild severity of this finding noted at earlier time points. Of note, no effects were observed for urinalysis or urine chemistry parameters, and no changes in other urinary biomarkers (kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, albumin, cystatin C, and β-microglobulin) were detected.

From the completed IV dosing study in healthy volunteers it was determined that the clearance of OP-101 was rapid with no detectable drug in the plasma after 24 hours. There were also no clinical adverse events in subjects administered IV doses of 20 or 40 mg/kg OP-101. To enable chronic dosing, SC dosing is being evaluated in this study. The SC dosage formulation has been optimized to enable a single SC dose of 400-500 mg. Higher doses may require two SC injections to achieve the desired dose if necessary. The selection of 4 and 8 mg/kg SC doses enable the majority of the subjects to receive only one injection and is 3-5 fold lower dose than the previous IV study in healthy volunteers. Exposure to NAC at the proposed starting dose and subsequent dose cohorts in this study is orders of magnitude less than that demonstrated to be safe in humans following oral or IV administration.

5.3 Randomization and Blinding

This open-label study consists of 2 separate and sequential SC cohorts. Randomization and blinding methods will not be used in this study.

Cohort 1 will enroll 4 subjects administered a single SC dose of 4 mg/kg. Dose escalation from Cohort 1 (4 mg/kg) to Cohort 2 (8 mg/kg) will be determined by the safety review committee (SRC), consisting of the Medical Monitor, the Principal Investigator (or delegate), and Sponsor representative after review of safety, tolerability, and any available PK data through Day 8 of Cohort 1. Cohort 2 will enroll 4 subjects administered a single SC dose of 8 mg/kg.

If an eligible subject is not used in the first cohort and is outside the screening window for a future cohort, the subject may be rescreened.

5.4 Breaking the Blind

This is an open-label study. Study drug assignment will be known by subjects, investigational site staff, and the Sponsor.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

OP-101 study drug is provided as lyophilized powder in Schott Glass, 5 cc/13 mm Type 1 clear glass vials with West, 13 mm, single vent lyophilizer grey butyl chloride stoppers, and West 13 mm flip-top matte white caps. Each vial is filled to deliver 500 ± 50 mg OP-101. Each vial is reconstituted 0.7 mL sterile water for injection to yield 400 mg/mL OP-101 in 20 mM histidine, pH 5.5 and 80 mg/mL trehalose. Vials of study drug will be supplied in boxes labeled for this study. Vials will be reconstituted with sterile water for injection prior to use.

OP-101 will be stored at 2 to 8°C and must not be frozen. Reconstituted OP-101 is stable at room temperature for up to 7 days if the vial seal is not compromised.

5.5.2 Study Drug Preparation and Dispensing

Trained and qualified site personnel will administer OP-101 to subjects within the clinical facility. Site personnel should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by Orpheris and outlined in the Pharmacy Manual. Instructions for OP-101 preparation are documented in the pharmacy manual.

5.5.3 Study Drug Administration

Study drug will be administered on Day 1 as a SC injection under the supervision of the site personnel.

<u>Dose Escalation</u>

Cohort 1 will enroll 4 subjects administered a single SC dose of 4 mg/kg. Dose escalation from Cohort 1 (4 mg/kg) to Cohort 2 (8 mg/kg) will be determined by the safety review committee (SRC), consisting of the Medical Monitor, the Principal Investigator (or delegate), and Sponsor representative after review of safety, tolerability, and any available PK data through Day 8 of Cohort 1. Cohort 2 will enroll 4 subjects administered a single SC dose of 8 mg/kg.

5.5.4 Treatment Compliance

Study drug will be administered at the investigational site by site staff.

5.5.5 Storage and Accountability

Study drug will be stored in a secure, temperature-controlled location. Study drug will only be prepared and dispensed by authorized site personnel at the clinical site.

Documentation will be performed for the receipt, storage, dispensing, and retention of study drug during the conduct of study to ensure complete accountability. Used study drug vials will be retained for monitoring purposes.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

Subjects who have lost or donated >450 mL of whole blood or blood products within 30 days prior to screening will be excluded.

See Section 4.2 for exclusion criteria.

5.6.2 Restricted Medications and/or Procedures

Subjects are not permitted to take prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 14 days (14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the Day 15 Follow-up Visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study or is required out of medical necessity.

See Section 4.2 for exclusion criteria.

5.6.3 Restricted Cigarette Use

Subjects are not permitted to use any product containing nicotine during the course of this study and may not have used any product containing nicotine within 90 days prior to screening.

5.6.4 Permitted Medications

Nonsteroidal anti-inflammatory drugs (eg, ibuprofen or naproxen) may be considered for use during the study on a case-by-case basis by the Investigator in consultation with the Orpheris Medical Monitor if required.

Hormonal contraception (oral, implant, injection, ring, or patch) for at least 12 weeks before the Screening Visit is permitted.

5.6.5 Documentation of Prior and Concomitant Medication Use

All medications administered during the study must be documented on the concomitant medication eCRF.

6 STUDY PROCEDURES

A 30-minute window for vital signs and all postdose procedures is allowed.

When multiple procedures are scheduled at the same time point, the order of procedures should be as follows: obtain vital signs, collect blood sample (drawn at nominal time), and obtain urine sample.

Blood samples for PK analysis can be obtained within ±5 minutes of the scheduled sampling time for sample times ≤1 hour, within ±10 minutes of the scheduled sampling time for sample times ≤12 hours, and within ±2 hours of the scheduled sampling times for sample times >12 hours.

6.1 Screening Visit (Days -21 to -1)

The following procedures will be performed at screening:

- Obtain informed consent;
- Evaluate inclusion/exclusion criteria;
- Obtain demographics and medical history;
- Record prior and concomitant medications;
- Perform physical examination including height and weight;
- Measure height and weight and calculate BMI;
- Record vital signs;
- Perform breath alcohol test;
- Collect urine sample for urine drug screen, cotinine, and urinalysis;
- Obtain fasting blood sample for safety laboratory tests, coagulation (activated partial thromboplastin time [aPTT], partial thromboplastin time [PTT], and international normalized ratio [INR]) serum (beta human chorionic gonadotropin [HCG]) pregnancy test (women of childbearing potential only), FSH (only for women of non-childbearing potential who are not surgically sterile), HIV, HBsAg, and HCVab screen; and
- Assess adverse events.

6.2 Check-in (Day -1)

The following procedures will be performed at Day -1:

- Admit subject to investigational site;
- Record prior and concomitant medications;
- Perform physical examination including weight for dose determination;
- Record vital signs;
- Perform breath alcohol test;

- Collect urine sample for urine drug screen, cotinine, urinary albumin, urinary creatinine, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL) and urinalysis;
- Collect urine sample for pregnancy test women of childbearing potential only;
- Obtain fasting blood sample for safety laboratory tests; and
- Assess adverse events.

6.3 Treatment Period (Days 1 to 3)

6.3.1 Day 1

The following procedures will be performed on Day 1:

- Record prior and concomitant medications;
- Record vital signs (predose, 30 and 60 minutes and at 2, 4, and 12 hours after SC dosing);
- Collect urine sample for urinalysis predose;
- Obtain fasting blood sample for safety laboratory tests within 30 minutes prior to dosing;
- Administer study drug;
- Collect plasma PK samples (collected within 30 minutes prior to dosing, and at 30 minutes and 1, 2, 4, 6, 8, 10, 12, and 16 hours);
- Collect urine PK sample (within 60 to 30 minutes prior to dosing [spot sample] and between 0 to 4, 4 to 8, 8 to 12, 12 to 18, and 18 to 24 hours after dosing);
- Assess adverse events.

6.3.2 Day 2

The following procedures will be performed on Day 2:

- Record prior and concomitant medications;
- Perform physical examination;
- Record vital signs at 24 hours;
- Collect urine sample for urinary albumin, urinary creatinine, KIM-1, NGAL and urinalysis at 24 hours;
- Obtain fasting blood sample for safety laboratory tests at 24 hours;
- Collect plasma PK sample (24 and 30-36 hours after dosing);
- Collect urine PK sample (between 24 to 48 hours after dosing); and
- Assess adverse events.

6.3.3 Day 3

The following procedures will be performed on Day 3:

- Record prior and concomitant medications;
- Perform physical examination;
- Record vital signs at 48 hours;
- Collect urine sample for urinary albumin, urinary creatinine, KIM-1, NGAL and urinalysis at 48 hours;
- Collect plasma PK sample (48 hours after dosing);
- Collect urine PK sample up to 48 hours;
- Obtain fasting blood sample for safety laboratory tests at 48 hours;
- Assess adverse events; and
- Discharge subject from the investigational site.

6.4 Follow-up Visit (Day 8)

The following procedures will be performed at the Follow-up Visit on Day 8:

- Record prior and concomitant medications;
- Perform physical examination;
- Record vital signs;
- Collect urine sample for urinary albumin, urinary creatinine, KIM-1, NGAL and urinalysis;
- Obtain fasting blood sample for safety laboratory tests; and
- Assess adverse events.

6.5 Follow-up Visit (Day 15)

The following procedures will be performed at the Follow-up Visit on Day 15:

- Record prior and concomitant medications;
- Perform physical examination;
- Record vital signs;
- Collect urine sample for urinary albumin, urinary creatinine, KIM-1, NGAL and urinalysis;
- Obtain fasting blood sample for safety laboratory tests; and
- Assess adverse events.

6.6 Early Termination Visit and Withdrawal Procedures

The end of treatment for subjects completing the study is Day 15. For subjects who are withdrawn from the study prior to completion, the following procedures will be performed at the Early Termination Visit:

- Record prior and concomitant medications;

- Perform physical examination;
- Record vital signs;
- Collect urine sample for urinary albumin, urinary creatinine, KIM-1, NGAL and urinalysis;
- Obtain fasting blood sample for safety laboratory tests; and
- Assess adverse events.

7 PHARMACOKINETIC ASSESSMENTS

The actual PK blood sampling times will be captured on the eCRF. The actual dosing time will also be captured on the eCRF.

During the Treatment Period, plasma and urine samples will be collected for PK analysis. Plasma PK samples will be collected predose, at 30 min and 1, 2, 4, 6, 8, 10, 12, 16, 24, and 30-36 hours after SC injection, as well as on Day 3 (~48 hr). Blood samples for PK analysis can be obtained within ±5 minutes of the scheduled sampling time for sample times ≤1 hour, within ±10 minutes of the scheduled sampling time for sample times ≤12 hours, and within ±2 hours of the scheduled sampling times for sample times >12 hours.

Urine PK samples will be collected predose (spot sample) and between 0 to 4, 4 to 8, 8 to 12, 12 to 18, 18 to 24, and 24 to 48 hours after dosing.

7.1 Pharmacokinetic Parameters

Pharmacokinetic parameters will include the following:

- C_{max} – maximum plasma concentration,
- t_{max} – time to maximum plasma concentration,
- kel – apparent terminal rate constant,
- $t_{½}$ – apparent elimination half-life,
- AUC_{0-t} – area under the concentration-time curve based on the last measureable concentration,
- AUC_{0-inf} – area under the concentration-time curve from time zero to infinity, and
- CL – clearance of study drug.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent until study participation is complete. Subjects should be instructed to report any adverse event that they experience to the Investigator. Beginning with the screening visit, the Investigator should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure.

Any medical condition already present at screening should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline (pre-dose) changes in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, (ie, the relationship cannot be ruled out).

8.1.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information in the Investigator’s Brochure.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event as mild, moderate, or severe, and will also categorize each adverse event as to its potential relationship to study drug using the categories of yes or no.

The severity of all adverse events should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. These criteria can be found at http://ctep.cancer.gov/reporting/ctc.html. For those adverse events not listed in the CTCAE, the following grading system should be used:

- Mild (CTCAE Grade 1): Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with subject's daily activities.
- Moderate (CTCAE Grade 2): Marked signs/symptoms that interfere with subject's usual activities, but still acceptable.
- Severe (CTCAE Grade 3): Incapacitating signs/symptoms which cause considerable interference with the subject's daily activities, unacceptable.
- Life-threatening (CTCAE Grade 4): Life threatening or disabling adverse event.
- Death (CTCAE Grade 5): Death-related adverse event.

Causality Assessment

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes (related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-
  - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases-
  - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant drug-
  - The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug-
    - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses-
    - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug-
    - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.2 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
    - NOTE: An adverse event or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations,
    - NOTE: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly/birth defect, or
- An important medical event.
    - NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to safety@clinical.net.au within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after the 30-day follow-up period must be reported to the Sponsor.

If the event meets serious criteria, send an email of the paper SAE form to safety@clinical.net.au or call the CNS Clinical Research Associate (CRA) or Project Manager (PM) within 24 hours of awareness. The SAE information must be entered within the EDC within 24 hours of the system becoming available.

Safety Contact Information: safety@clinical.net.au

Follow-Up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit the updated SAE Paper form and any supporting documentation (eg, subject discharge summary or autopsy reports) to CNS via e-mail at safety@clinical.net.au.

8.4 Pregnancy Reporting

If the subject or partner of a subject participating in the study becomes pregnant during the study or within 30 days of discontinuing study drug, the Investigator should report the pregnancy to CNS within 24 hours of being notified via safety@clnical.net.au and cc the CRA and PM. CNS will then forward the Pregnancy Notification Form to the Investigator for completion.

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed.

The subject or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify CNS Safety via safety@clinical.net.au and cc CRA and PM.. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the TGA, and in any case no later than 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information will subsequently be communicated within an additional 8 days.

All other suspected unexpected serious adverse reactions will be reported to the TGA as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will also inform the Investigator as required.

8.6 Clinical Laboratory Evaluations

Standard clinical laboratory profiles for chemistry, hematology, and urinalysis will be evaluated at screening, Day -1, and on Days 1 (pre-dose), 2 & 3. Samples will also be collected on Day 8, Day 15, and at the Early Termination Visit. Note, the eGFR will be determined for each time point above to assess any potentially acute effects on kidney clearance.

See Appendix B for a list of clinical laboratory analytes.

Tests for HIV, HBsAg, and HCVab will be completed at screening to determine eligibility.

Coagulation (aPTT, PTT, and INR) will be assessed at screening.

A serum (beta HCG) pregnancy test will be performed at screening for female subjects of childbearing potential only. A urine pregnancy test will be performed at Day -1 for female subjects of childbearing potential only. A test for FSH level will be performed at screening only for women of non-childbearing potential who are not surgically sterile.

A urine drug, cotinine, and breath alcohol test will be administered at screening and Check-in.

8.7 Vital Signs

Vital signs (pulse rate, respiration rate, body temperature, and BP) will be recorded at all study visits and the Early Termination Visit after the subject has been seated or supine for ≥5 minutes.

During the Treatment Period, vital signs will be measured predose, 30 and 60 minutes and at 2, 4, 12, and 24, and 48 hours after dosing. Vital signs will also be measured at the Follow-up Visits on Days 8 and 15.

8.8 Physical Examinations

Complete physical examinations will be performed at screening, on Day -1, Day 2, Day 3, Day 8, and Day 15, or at the Early Termination Visit. Body weight and height will be measured at screening and used to calculate BMI.

9 STATISTICS

9.1 Analysis Populations

The Safety Population is defined as all subjects who received at least 1 dose of study drug.

The PK Concentration Population is defined as all subjects who received at least 1 dose of study drug and have at least 1 measurable concentration.

The PK Parameter Population is defined as all subjects who received a dose of study drug and have at least 1 PK parameter.

9.2 Statistical Methods

A detailed Statistical Analysis Plan (SAP) describing the methodology to be used in the final analysis will be prepared and finalized prior to database lock. Statistical methods described here may be changed based on advances in research. If changes in the statistical methods are made which change the principal features of the protocol, a protocol amendment will be required. Any deviation from the planned statistical analyses in the protocol will be fully described in the SAP.

9.2.1 Analysis of Efficacy

Not applicable.

9.2.2 Analysis of Pharmacokinetics

Plasma PK concentrations of OP-101 will be summarized with descriptive statistics (n, mean, standard deviation [SD], percent coefficient of variation [%CV], minimum, median, maximum, geometric mean, and %CV for the geometric mean) by nominal PK sampling time and treatment using the PK Concentration Population.

Standard noncompartmental PK analysis will be used to calculate the PK parameters.

Pharmacokinetic parameters will be summarized with descriptive statistics (n, mean, SD, %CV, minimum, median, maximum, geometric mean, and %CV for the geometric mean) by treatment using the PK Parameter Population.

9.2.3 Analysis of Safety

Safety will be assessed using the Safety Population.

9.2.3.1 Adverse events

Adverse events will be summarized overall and by system organ class and preferred term, and the relationship to the study drug received. A list of subjects who have SAEs and who discontinue from the study due to an adverse event will be provided. Deaths due to adverse events will also be provided.

9.2.3.2 Clinical laboratory evaluations

Safety laboratory tests will include chemistry, hematology, and urinalysis. Summary statistics for laboratory values will be provided at baseline, postbaseline, and for changes from baseline to postbaseline by treatment. Occurrence of significant laboratory abnormalities will be summarized by regimen for each treatment.

9.2.3.3 Vital signs

Vital signs will be summarized in the same manner as clinical laboratory evaluations.

9.2.3.4 Physical examinations

Physical examination data will be listed.

9.2.4 Protocol Deviations

Subjects with protocol deviations will be listed for the Safety Population.

9.2.5 Medical History

Medical history will be listed for each treatment for the Safety Population.

9.2.6 Subject Disposition

Subject disposition information will be tabulated for each treatment based on the enrolled subjects. Counts of subjects enrolled, as well as counts and percentages of subjects who completed each period and the study, and who withdrew early from the study will be presented. The primary reasons for early withdrawal will also be tabulated.

9.2.7 Demographic and Baseline Characteristics

Demographic and baseline characteristics data will be summarized for each treatment.

9.2.8 Prior and Concomitant Medications

Concomitant medication will be summarized for each treatment. A listing of all medications including the reported term, dictionary term, start and stop dates, and other relevant data will be provided.

9.2.9 Interim Analysis

Not applicable.

9.3 Sample Size Determination

8 subjects will be enrolled and dosed in 2 cohorts with 4 subjects in each cohort to complete Day 15. The sample size in the study is based on clinical and practical considerations rather than statistical power.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the latest versions of the following thesauri will be used:

- Medical Dictionary for Regulatory Activities for medical history and adverse events, and
- World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Ethics Committee (IEC) or Human Research Ethics Committee (HREC)

The Institutional Ethics Committee (IEC) or Human Research Ethics Committee (HREC) will review all appropriate study documentation in order to safeguard the rights, safety, and wellbeing of subjects. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject or subject's legal guardian must be approved by the IRB.

No drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each subject before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the Medical Monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable

data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to the Investigator. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by Regulatory authorities, the Sponsor or their designee, applicable foreign health authorities, and the IEC/HEC as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.8 Financial Disclosure

The Investigator is required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, the Investigator must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigator by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IEC/HREC, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IEC/HREC within 5 working days.

12.2 Address List

12.2.1 Sponsor

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12.2.3 Serious Adverse Event Reporting

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12.2.4 Biological Specimens

TBC

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APPENDIX A: SCHEDULE OF PROCEDURES

Table 1. Schedule of Procedures – Cohorts 1 and 2

	Screening Period	Check-In	Treatment Period			Follow-Up Visits [1]		Early Termination Visit
Study Procedure	Days -21 to -2	Day -1	Day 1	Day 2	Day 3	Day 8	Day 15	
Informed consent	X							
Admit to investigational site		X						
Inclusion/exclusion criteria	X	X						
Medical history	X							
Demographics	X							
Prior/concomitant medications	X	X	X	X	X [3]	X	X	X
BMI calculation [2]	X							
Physical examination (complete)	X	X		X	X [3]	X	X	X
Vital signs [4]	X	X	X	X	X [3]	X	X	X
Breath alcohol screen	X	X						
Pregnancy test [5]	X	X						
FSH [5]	X							
Urine drug and cotinine screen	X	X						
Safety	X	X	X	X	X [3]	X	X	X

laboratory tests (chemistry, hematology, and urinalysis) [6]								
aPTT, PTT, INR	X							
HIV, HBsAg, HCVab screen	X							
Plasma PK sampling [7]			X	X	X[3]			
Urine PK sampling [8]			X	X	X[3]			
Administer study drug [9]			X					
Assess adverse events	X	X	X	X	X[3]	X	X	X
Discharge from investigational site					X			

Footnotes appear on the following page.

A 30-minute window for vital signs and all postdose procedures is allowed.
When multiple procedures are scheduled at the same time point, the order of procedures should be as follows: obtain vital signs, collect blood sample (drawn at nominal time), and obtain urine sample.

1. There will be a ±1-day visit window for Days 8 and 15.
2. Body weight and height will be measured at screening and used to calculate BMI.
3. Assessments will be performed prior to discharge.
4. Vital signs (pulse rate, respiration rate, body temperature, and BP) will be recorded at all study visits after the subject has been seated or supine for ≥5 minutes. During the Treatment Period, vital signs will be measured predose, 30 and 60 minutes and at 2, 4, 12, 24 and 48 hours after SC dosing.
5. A serum (beta HCG) pregnancy test will be performed at screening for female subjects of childbearing potential only. A urine pregnancy test will be performed at Day -1 for female subjects of childbearing potential only. A test for FSH level will be performed only for women of non-childbearing potential who are not surgically sterile.
6. Safety laboratory tests will be performed under fasting conditions (at least 8 hours). Day 1 sample will be taken within 30 minutes prior to dosing. See Appendix B for the list of analytes assessed; eGFR will be assessed with each sample and will be based on the subject's creatinine level, age, sex, and race. KIM-1 and NGAL will be evaluated from urine collected on Day -1, Day 2, Day 3, Day 8, Day 15 and on Early Termination. Additional chemistry parameters (i.e., glycosylated haemoglobin and homocysteine) will only be assessed at screening.
7. Plasma PK samples will be collected within 30 minutes prior to dosing, and at 30 min and 1, 2, 4, 6, 8, 10, 12, 16, 24, and 30-36 hours after SC injection, as well as on Day 3 (~48 hr). Blood samples for PK analysis can be obtained within ±5 minutes of the scheduled sampling time for sample times ≤1 hour, within ±10 minutes of the scheduled sampling time for sample times ≤12 hours, and within ±2 hours of the scheduled sampling times for sample times >12 hours.
8. Urine PK samples will be collected 60 to 30 minutes prior to dosing (spot sample) and between 0 to 4, 4 to 8, 8 to 12, 12 to 18, 18 to 24, and 24 to 48 hours after dosing.
9. Cohort dosing will be separate and sequential. Dose escalation from Cohort 1 (4 mg/kg) to Cohort 2 (8 mg/kg) will be determined by the SRC after review of safety, tolerability up to Day 8, and any available PK data from Cohort 1.

aPTT = activated partial thromboplastin time; BMI = body mass index; BP = blood pressure; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; PTT = partial thromboplastin time; SRC = safety review committee.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine [1]	Estimated glomerular filtration rate (eGFR)
Gamma-glutamyl transferase	Glucose
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin
Total protein	Uric acid

1. eGFR will be assessed with each safety chemistry panel according to a mathematically derived formula based on the subject's serum creatinine level, age, sex, and race.

Additional Chemistry Parameters

Glycosylated hemoglobin	Homocysteine

Endocrinology

Follicle-stimulating hormone [1]

1. Follicle-stimulating hormone (only for female subjects of non-childbearing potential who are not surgically sterile).

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential	

Coagulation

Activated partial thromboplastin time
International normalized ratio
Partial thromboplastin time

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Kidney injury molecule-1 (KIM-1)	Leukocyte esterase
Microscopy [1]	Nitrite
Neutrophil gelatinase-associated lipocalin (NGAL)	pH
Protein (calculation of eGFR)	Specific gravity
Urobilinogen	

1. Microscopy is performed only as needed based on positive dipstick test results.

Pregnancy Test

A serum (beta human chorionic gonadotropin) pregnancy test will be performed for female subjects of childbearing potential at screening only. A urine pregnancy test will be performed at Day -1 for female subjects of childbearing potential only.

Urine drug, cotinine, and Breath Alcohol Tests

Urine drug, cotinine, and breath alcohol tests will be performed at screening and Check-in.

- Amphetamine
- Barbiturates
- Benzodiazepines
- Cocaine
- Cannabinoids
- Opiates
- Phencyclidine

Serology

Hepatitis B, hepatitis C, and human immunodeficiency virus at screening only.

OP-101-003 Protocol v2.0_17Mar20

Final Audit Report 2020-03-17

Created:	2020-03-17
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Status:	Signed
Transaction ID:	[redacted]

"OP-101-003 Protocol v2.0_17Mar20" History

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2020-03-17 - 4:10:38 AM GMT

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