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The Asia Pacific CRO

STATISTICAL ANALYSIS PLAN

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
Study Medication	OP-101 (dendrimer n-acetyl-cysteine)
Sponsor	Orpheris, Inc.
Original Protocol	V1.0 / 28 January 2020
Current Protocol	Final Version 2.0; 17 March 2020
SAP	V0.1 / May 28, 2020
Author	[redacted]

SAP APPROVAL

By my signature, I confirm that this SAP has been approved for use:

AUTHOR: [redacted]

Novotech (Australia) Pty Ltd

Signature: [redacted]

Email:

Signature Date

APPROVED BY: [redacted]

Novotech (Australia) Pty Ltd

Signature: [redacted]

Email:

Signature Date

[redacted]

Orpheris, Inc. (on behalf of Orpheris, Inc.)

Signature: [redacted]

Email:

Signature Date

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REVISION HISTORY

Document Version	**Document Date**	**Summary of Changes**
0.1	May 18, 2020	Original Draft
1.0	May 28, 2020	Final

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse Event
λ_z	First-order terminal elimination rate constant
%CV	Percent coefficient of variation
Ae	Cumulative amount of unchanged study drug excreted into the urine
Ae_{0-48}	Cumulative amount of unchanged study drug excreted into the urine from time 0 to 48 hours postdose
AUC	Area under the concentration-time curve
AUC_{0-48}	Area under the concentration-time curve from time 0 to 48 hours postdose
AUC_{0-inf}	Area under the concentration-time curve from time 0 extrapolated to infinity time
AUC_{0-last}	Area under the concentration-time curve from time 0 to the last quantifiable concentration
BMI	Body mass index
BP	Blood pressure
CL/F	Apparent total body clearance after SC administration
CL_r	Renal clearance
C_{max}	Maximum observed concentration directly from data
CNS	Central nervous system
CRO	Contract research organization
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
Fe_{0-48}	Fraction of the study drug excreted into the urine from time 0 to 48 hours
FIH	First-in-human
GI	Gastrointestinal
GLP	Good Laboratory Practice
GM	Geometric mean
ICF	Informed consent form
IL	Interleukin
IRB	Institutional Review Board
SC	Subcutaneous
KIM-1	Kidney injury molecule-1
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
NAC	N-acetyl-cysteine
NGAL	Neutrophil gelatinase-associated lipocalin
NOAEL	No observed adverse effect level
PAMAM	Polyamidoamine
PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
SRC	Safety review committee
$t_{½}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to reach maximum observed concentration directly from data
V_Z	Volume of distribution after IV administration
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) provides a detailed, technical elaboration of the statistical analysis of safety, pharmacokinetic (PK) and pharmacodynamic (PD) data as described in the study protocol OP-101-003 Version 2.0 dated 17 March 2020. Specifications for tables, listings, and figures are contained in a separate document. Any deviation from this analysis plan will be substantiated by sound statistical/PK rationale and will be documented in the final clinical study report.

2. STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objectives

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

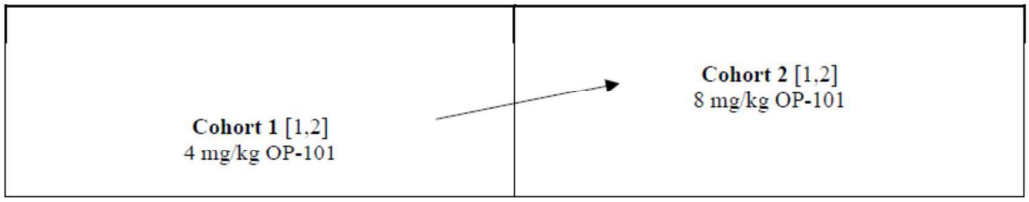
3. STUDY PLAN OVERVIEW

3.1 Study Design

This is a Phase 1, open-label, single-ascending dose study to evaluate the safety, tolerability, and PK of OP-101 after subcutaneous 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 up to 2 separate and sequential **subcutaneous Dose** cohorts (4 mg/kg, and 8 mg/kg) with at least 4 subjects in each cohort who complete Day 15.

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 Sample Collection for Pharmacokinetic Analysis

Plasma PK samples will be collected predose, at 30 and at 1, 2, 2.5, 3, 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 will 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 within 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.

3.3 Assessments of Safety

Safety will include adverse event monitoring, clinical laboratory tests (hematology, chemistry, and urinalysis), physical examinations, 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.

3.4 Treatment Groups

There will be 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 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.

3.5 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 1000mg/kg, have shown no adverse clinical signs or mortality. 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.

3.6 Dosage Form and Route of Administration

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.

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

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.

3.7 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. STUDY VARIABLES

5.1 Pharmacokinetic Parameters

The PK parameters listed below will be calculated from the individual plasma and urine OP-101 concentration-time profiles. Additional PK Parameters may be added if it is necessary to fully describe the plasma and urine PK profile.

Variables	Description
C_{max}	Maximum observed concentration directly from data
T_{max}	Time to reach maximum observed concentration directly from data
k_{el}	Apparent terminal elimination rate constant
$t_{½}$	Terminal elimination half-life, calculated as ln(2)/ λ_z
$AUC_{0\text{-last}}$	Area under the concentration versus time curve from time zero to the last quantifiable concentration (Clast)
$AUC_{0\text{-}48}$	Area under the concentration versus time curve from time zero to 48 hour post dose time point
$AUC_{0\text{-inf}}$	Area under the concentration versus time curve from time zero extrapolated to infinity time
CL/F	Apparent total body clearance (as Dose/AUC0-inf) after subcutaneous administration
V_z/F	Apparent volume of distribution (as Dose/ [λ_z *AUC0-inf]) after subcutaneous administration
$Ae_{0\text{-}48}$	Cumulative amount of unchanged study drug excreted into urine from Time 0 to 48 hours post-dose (Amount recovered in urine)

Variables	Description
%(Fe)	Fraction of the study drug excreted into urine in % (Fe) (as Ae/dose)
CL_r	Renal clearance of the drug from plasma utilizing the AUC and Ae to the same duration (as Amount recovered /AUC at 0-48 hours)

5.2 Safety Variables

The following safety evaluations will be performed during the study:

- Adverse event monitoring
- Vital signs (pulse rate, BP, respiration rate, and temperature).
- Physical examination
- Clinical laboratory tests (hematology, chemistry, and urinalysis)

6. GENERAL STATISTICAL CONSIDERATIONS

6.1 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.

6.2 Analysis Populations

6.2.1 Safety Population

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

6.2.2 PK Concentration Population

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.

6.2.3 Pharmacokinetic Parameter Population

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

7. STATISTICAL ANALYSIS

7.1 General Considerations

Continuous data will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], percent coefficient of variation [%CV], median, minimum, and maximum). The geometric Mean (GM) and CV% GM will be also be added for Cmax and AUCs. Any subjects with a value of 0 for a parameter will be excluded from the calculation of GM and GM CV%.

Categorical data will be summarized using frequency counts and percentages.

7.2 Summary of Study and Subject Information

7.2.1 Subject Disposition

Subject disposition information will be summarized by treatment in the Safety Population. Counts of subjects who receive any amount of drug as well as counts and percentages of subjects who complete each cohort and who withdraw early from the study will be presented in the summary table. The primary reasons for early withdrawal will also be included in the table. Percentages will be calculated using the number of Safety Population in each treatment as the denominator. Data will also be listed by treatment.

7.2.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics include, but are not limited to, age at informed consent, sex, race, ethnicity, height, body weight, and body mass index (BMI). Height, body weight, and body mass index (BMI) will be collected at screening. If a value at the scheduled baseline is not available, the last measurement prior to the first dose of study drug will be served as the baseline value.

Demographic and baseline characteristics will be summarized by treatment based on Safety Population. Data will also be listed by treatment for all subjects in the Safety Population.

7.2.3 Eligibility Criteria

Eligibility criteria (inclusion/exclusion) will be listed for the Safety Population.

7.2.4 Study Drug Administration

Study drug administration data will be listed by treatment in the Safety Population.

7.2.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded with the World Health Organization Drug Dictionary March 2018 Global B3 version.

Prior medications will be defined as those medications taken prior to the initial dose of study drug, and all medication taken on or after the first dose until the last PK sampling time in the last treatment period will be defined as concomitant medication.

All prior and concomitant medications will be listed and summarized for the Safety Population by treatment.

7.2.6 Medical History

Medical history will be collected at Screening. Data will be listed by treatment for the Safety Population. Medical/surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0.

7.2.7 Protocol Deviations

Subjects with protocol deviations will be listed by treatment for all subjects in the Safety Population.

7.2.8 Informed Consent

Informed consent will be collected before screening or first thing in screening visit. Date of informed consent will be listed by treatment for the Safety Population. By subject listing, corresponding analysis set will also be provided.

7.3 Pharmacokinetic Analysis

7.3.1 Handling Missing or Non-Quantifiable Data

Concentrations below the lower limit of quantitation (LLOQ) before the first measurable concentration will be assigned a value of zero. Any LLOQ values between measurable concentrations in a profile will be set to missing in the derivation of PK parameters, concentration summary, and the individual subject plots. Concentrations below the LLOQ which occur after the last measurable concentration will be set to missing in the derivation of PK parameters and in the individual subject plots but will be set as zero for the plasma concentration summary.

7.3.2 Pharmacokinetic Concentrations

Individual plasma concentrations of OP-101 will be listed by treatment at each time point. Plasma concentration of OP-101 will also be summarized by treatment at each nominal time based on PK Concentration Population. Mean concentrations of plasma OP-101 will be plotted on a linear and semi-logarithmic scale versus nominal time points by treatment. Individual plasma concentrations of OP-101 will be plotted on a linear and semi-log scale versus actual

sampling time points by treatment. The spaghetti plots of individual plasma OP-101 concentration on linear and semi-Log scale will also be presented.

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. Actual sampling times that are outside the sampling window will be listed but excluded from summary statistics.

Urine PK samples will be collected within 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. Urine concentrations and volumes will be listed and summarized by treatment and nominal time interval.

7.3.3 Pharmacokinetic Parameters Calculation

Standard non-compartmental methods (NCA) will be used for the calculation of PK parameters. The actual collection times will be used for evaluation of PK data. The Linear Up Log Down method (equivalent to the Linear Up/Log Down option in WinNonlin® Professional) will be used in the computation of AUCs.

The λz will not be presented for subjects who do not exhibit a terminal elimination phase in their concentration-time profiles. In order to estimate the first-order terminal elimination constant, λz, linear regression of the OP-101 concentration in logarithm scale vs. time will be performed using at least 3 data points. Uniform weighting will be selected to perform the regression analysis to estimate λ_z.

The constant λ_z will not be assigned if one of the following happens:

1. Tmax is equals to one of the 3 last data points,
2. The adjusted regression coefficient (adjusted R-squared) is less than 0.8,
3. The percent of $AUC_{0\text{-}inf}$ extrapolated exceeds 20%,
4. The estimated elimination rate indicates a positive slope, or
5. The terminal elimination phase is not linear (as appears in a semi-logarithmic scale) based on visual inspection.

In cases where the constant λ_z is not assigned, the values of associated variables (i.e., $T_{1/2}$, $AUC_{0\text{-}inf}$, CL/F, and V_z/F) may not be calculated.

PK parameters will be calculated based on PK Concentration Set.

7.3.4 Pharmacokinetic Parameters Summary and Analysis

The Plasma PK parameters will be summarized descriptively by treatment based on the PK

Parameter Population, including: C_{max}, T_{max}, $T_{1/2}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, CL/F, V_Z/F, $AUC_{0\text{-}48}$. Geometric Mean [GM]), and CV% GM will also be calculated for C_{max} and AUCs.

The urine PK parameters such as $Ae_{0\text{-}48}$, $Fe_{0\text{-}48}$ and CL_r will be calculated and summarized descriptively.

7.4 Safety Analyses

Safety analyses will be performed based on the Safety Population. Safety will be evaluated through assessments of AEs, treatment emergent adverse events (TEAE), vital signs, physical examinations, clinical laboratory tests.

7.4.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not

necessarily have a causal relationship with this treatment. Therefore, AEs include:

- the onset of new signs, symptoms, conditions, and illnesses;
- exacerbation of pre-existing conditions or illnesses;
- abnormal laboratory findings deemed clinically significant by the Investigator;
- physical examination changes deemed clinically significant by the Investigator; and
- Abnormal medical evaluation findings (e.g., ECG) that are not documented at the Screening Visit and/or, in the Investigator's opinion, represent a clinically significant change in the subject's health during study participation. Screening medical evaluation findings that were not previously provided as medical history, and can be determined as starting prior to the Screening Visit, are not considered AEs and will be recorded as medical history.

Adverse events will be coded using a latest version of Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0.

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 4.0. 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.

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.

The investigator will record the action taken and outcome for each AE according to the following:

Action Taken

- Dose not changed;
- Drug Interrupted;
- Drug withdrawn;
- Not applicable;
- Other (specify); or
- Unknown

Outcome

- Fatal;
- Not recovered or not resolved;
- Recovered or resolved;
- Recovered or resolved with sequelae;
- Recovering or resolving; or
- Unknown.

7.4.1.1 Serious Adverse Events

An SAE is any AE occurring at any dose that results in any of the following outcomes:

- Death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongs existing hospitalization;
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- Congenital anomaly/birth defect.

An important medical event that may not result in one of the above serious outcomes may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject or may require medical or surgical intervention to prevent one of the listed serious outcomes. 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 hospitalization, or development of drug dependency or drug abuse.

7.4.1.2 Treatment-Emergent Adverse Event

A TEAE is defined as an AE that emerges, having been absent prior to the study, or an AE that worsens in severity after the first dose of the study drug. Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe incident. Subjects reporting more than one type of event within a system organ class (SOC) will be counted only once for that SOC. Safety population will be used for all the safety analysis.

TEAEs will be summarized by SOC and preferred term (PT) for each treatment and overall. The number and percentage of subjects experiencing TEAEs will be tabulated. Specifically, the following summaries will be presented:

- Overall summary of TEAEs by treatment and overall, with a breakdown by AE grading;
- TEAEs by SOC and PT by treatment;
- TEAEs by SOC, PT, and relationship to the study drug by treatment;
- TEAEs by SOC, PT, and maximum severity by treatment; and
- TEAEs by SOC, PT, maximum severity, and the relationship to the study drug by treatment.

Separate listings will be prepared for SAEs, AEs leading to deaths, and AEs leading to study discontinuation.

7.4.2 Clinical Laboratory Tests

The clinical laboratory tests will include Hematology and Coagulation, Chemistry, and Urinalysis at Screening and other time points as specified in Appendix Table 1.

Observed values from Baseline and each time point, as well as change from Baseline to each time point will be summarized descriptively based on Safety Population by Treatment. Baseline is defined as reading on Day -1 (Check-in). If the reading on Study Day -1 is missing, the last reading before dosing will be used as baseline. A summary table representing abnormal value of safety laboratory tests will also be presented. Additional Urinary biomarkers include albumin, creatinine, KIM-1, and NGAL will also be listed and summarized similarly.

Tests for HIV, HBsAg, and HCVab will be completed at the Screening Visit to determine eligibility. The data will be listed by treatment for Safety Population. Coagulation test including aPTT, PTT, INR will be completed at the Screening visit, and the data will be listed by treatment for the Safety Population.

An FSH test will be performed at Screening for women who are post-menopausal, with amenorrhea for at least 2 years.

7.4.3 Vital Signs

Vital signs included blood pressure, heart rate, respiratory rate, and temperature and will be taken after a 5-minute seated rest at Screening, Check-in, and other time points as specified in Appendix Table 1.

Observed values and change from baseline to each time point will be summarized descriptively by treatment based on Safety Population. Baseline is defined as reading at predose. If the reading at predose is missing, the last reading before dosing will be used as baseline.

The data for vital signs will be also listed based on the Safety Population.

7.4.4 Physical Examination

Complete physical examinations will be performed at screening, on Day -21 to -2, 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.

Physical examination data will be listed by treatment for the Safety Population.

7.4.5 Pregnancy Test

Serum and urine pregnancy test will be performed at Screening and Check-in. Data will be listed by visit and treatment for the Safety Population.

7.4.6 Urine Drug Screen and Breath Alcohol Test

Urine screen for drugs, cotinine screen and a breath alcohol test, will be performed at screening and on Study Day –1. Data will be listed by treatment for the Safety Population.

8 GENERAL REPORTING CONVENTIONS

8.1 Statistical Software

The creation of analysis datasets and all statistical analyses will be done using SAS® Version 9.4 or higher. Novotech standard operating procedures will be followed for the generation and validation of all programs and outputs.

Phoenix WinNonlin version 7.0 or higher will be used in the determination of the PK terminal phase and the calculation of PK parameters. All the PK parameters will also be calculated via SAS® and verified with the Phoenix WinNonlin results.

8.2 Format

The format of tables, listings, and figures will be described in a stand-alone programming specifications document.

9 APPENDICES

Table 1: SCHEDULE OF PROCEDURES-Cohort 1and 2

Study Procedure	Screening Period	Check-In	Treatment Period			Follow-Up Visits [1]		Early Termination Visit
	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	
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 laboratory tests (chemistry, hematology, and urinalysis) [6]	X	X	X	X	X [3]	X	X	X
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]								
Assess adverse events	X	X	X	X	X[3]	X	X	X
Discharge from investigational site								

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

[1]Follicle-stimulating hormone

[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
Leukocyte esterase	[1]Microscopy
Nitrite	pH
Protein (calculation of eGFR)	Specific gravity
Urobilinogen	

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

Urinalysis

Albumin	Creatinine
Kidney injury molecule-1	Neutrophil gelatine-associated lipocalin

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.

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