CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 22-0027
Study Title:
A Randomized, Double Blind, Placebo-Controlled, Multiple Ascending Dose, Phase 1 Study of SLV213 in Healthy Volunteers

NCT06146374

Version 1.0

DATE: 18-NOV-2024

RESTRICTED

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 22-0027**
Development Phase:	Phase 1
Products:	SLV213 100 mg (capsules containing K777 hydrochloride, the drug substance) Matched Placebo (capsules containing Microcrystalline celluloid)
Form/Route:	Oral
Indication Studied:	COVID-19
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	March 12, 2024
Clinical Trial Completion Date:	July 08, 2024
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Version Number:	1.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration-time curve
$AUC_{(0\text{-}t)}$	AUC from time zero to the last time with a concentration greater than or equal to the validated limit of quantitation of the assay
$AUC_{(0\text{-}\infty)}$	AUC from time zero to infinity
$AUC_{(0\text{-}12)}$	AUC from 0h (time zero [pre-dose]) to 12h after dosing
$AUC_{(0\text{-}48),ss}$	AUC from 0h (time zero [pre-dose]) to 48h after dosing at steady state
$AUC_{(0\text{-}last)}$	AUC from time zero to the last concentration above the LLOQ
$AUC_{(0\text{-}tau)}$	AUC from time zero to the end of the dosing interval
$AUC_{(0\text{-}tau),ss}$	AUC from time zero to the end of the dosing interval at steady state
BID	Bis In Die (twice a day)
BMI	Body Mass Index
BP	Blood Pressure
bpm	Breaths Per Minute
BQL	Below Quantifiable Limit
BUN	Blood Urea Nitrogen
C	Celsius
C_{avg}	Average concentration during the dosing interval
CHEM	Chemistry
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL_T	Total clearance
C_{max}	Observed maximum concentration

List of Abbreviations *(continued)*

$C_{max,ss}$	Observed maximum concentration at steady state
C_{min}	Observed minimum concentration at the end of the dosing interval
$C_{min,ss}$	Observed minimum concentration at the end of the dosing interval at steady state
CO_2	Carbon Dioxide
COAG	Coagulation
COVID	Corona Virus Disease (SARS-CoV-2)
CRF	Case Report Form
CSR	Clinical Study Report
CTU	Clinical Trial Unit
CV%	Coefficient of Variation
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicity
DMID	Division of Microbiology and Infectious Diseases
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
F	Fahrenheit
FDA	Food and Drug Administration
GM	Geometric Mean
h	Hour
HBsAg	Hepatitis B Virus Surface Antigen
HCG	β-Human Chorionic Gonadotropin (pregnancy hormone)
HCV	Hepatitis C Virus
HEM	Hematology
HIV	Human Immunodeficiency Virus
HLGT	Higher Level Group Term
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

List of Abbreviations *(continued)*

IND	Investigational New Drug
IQR	Interquartile Range
Ke	Terminal phase elimination rate constant (λ_z)
kg	Kilograms
L	Liters
lbs	Pounds
LFT	Liver Function Test
LLOQ	Lower Limit of Quantitation
m	Meters
M/F	Male to Female (ratio)
MAAE	Medically Attended Adverse Event
MAD	Multiple Ascending Dose
mg	Milligrams
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MH	Medical History
mITT	Modified Intention to Treat
mL	Milliliter
MTD	Maximum Tolerate Dose
MO	Medical Officer
MOP	Manual of Procedures
N	Number (typically refers to participants)
NCA	Noncompartmental Analysis
ng	Nanogram
NIH	National Institutes of Health
OTC	Over-the-Counter
PD	Pharmacodynamics
PE	Physical Examination
PI	Principal Investigator
PK	Pharmacokinetics

List of Abbreviations *(continued)*

PO	Per Os (by mouth, orally)
PT	Preferred Term
PT INR	Prothrombin Time International Normalized Rate
Q1	First Quartile (25th Percentile)
Q12h	Every 12 hours (twice daily)
Q3	Third Quartile (75th Percentile)
QD	Quaque Die (once a day)
QNS	Quantity Not Sufficient
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red Blood Cell
Rsq	Coefficient of determination (R-Squared or R^2)
RAUC	Accumulation ratio of AUC
SAE	Serious Adverse Event
SAD	Single Ascending Dose
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOC	System Organ Class
SRC	Safety Review Committee
SS	Steady state
SOC	System Organ Class
SOP	Standard Operating Procedures
$t_{1/2}$	Terminal half-life
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time of maximum concentration
$T_{max,ss}$	Time of maximum concentration at steady state
T_{min}	Time of minimum concentration
UA	Urinalysis

List of Abbreviations *(continued)*

UDS	Urine Drug Screening
ULN	Upper Limit of Normal
UP	Unanticipated Problem
Vd	Volume of distribution
Vd,ss	Volume of distribution at steady state
VS	Vital Signs
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Randomized, Double Blind, Placebo-Controlled, Multiple Ascending Dose, Phase 1 Study of SLV213 in Healthy Volunteers" (DMID Protocol 22-0027) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports) [**1**], and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) [**2**] and Topic E9 (Statistical Principles for Clinical Trials) [**3**]. The structure and content of the SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association [**4**] and the Royal Statistical Society [**5**] for statistical practice.

This document contains four sections: (1) a review of the study design, (2) general statistical considerations, (3) comprehensive statistical analysis methods for pharmacokinetics (PK), tolerability, and safety outcomes, and (4) a list of proposed tables and figures. Within the table, figure, and listing mock-ups (**Appendix 1**, **Appendix 2**, and **Appendix 3**), references to CSR sections are included. Any deviation from this SAP will be described and justified in protocol amendments and/or in the CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2. INTRODUCTION

2.1. Purpose of the Analyses

These analyses will assess the safety, tolerability, and PK of multiple ascending doses (MAD) of SLV213 in healthy male and female participants, 18-65 years of age. These analyses will help to select the most likely suitable dose (e.g., at Maximum Tolerated Dose [MTD]) for treatment of patients with COVID-19 in a pivotal study. This double blind, placebo-controlled study was designed to enroll three sequential cohorts of 12 participants each (8 SLV213 and 4 placebo) at doses of 400 mg every 12 hours (Q12h), 600 mg Q12h, and 800 mg Q12h administered per os (PO) (by mouth, orally) for 7 days.

This study was terminated after Cohort 1 and will not proceed with sequential cohorts.

3. STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVE	ENDPOINTS (OUTCOME MEASURES)
Primary	**Primary**
To evaluate the safety and tolerability of multiple ascending doses SLV213 for 7 days in healthy participants.	**Safety:** Type, incidence, severity, and relatedness to study drug of all treatment-emergent systemic, laboratory and electrocardiographic (ECG) adverse events (AEs) and serious adverse events (SAEs) in each treatment cohort from the first dose (Day 1) through the last visit (Day 28 ± 2 days). **Tolerability:** Summarized by dose cohort and include: • Number (and percentage) of participants who: 1) Terminate early or are withdrawn due to treatment-emergent AEs assessed as related to intake of study medication. 2) Have at least 1 treatment-emergent adverse event (TEAE), total and per dose level. 3) Meet Grade 3 abnormal criteria for safety laboratory tests at least once post-dose. 4) Meet Grade 3 abnormal criteria for vital sign measurements at least once post-dose. 5) Meet Grade 3 criteria for safety electrocardiogram (ECG) parameters at least once post-dose. • Proportion of oral medication doses completed.
Secondary	**Secondary**
To characterize the multiple dose pharmacokinetics (PK) of SLV213 in healthy participants.	The following single-dose plasma PK parameters will be computed (if estimable) from the plasma total concentration-time data over the 12-hour period following the morning dose on Day 1 for each cohort: • C_{max}: Observed maximum concentration • T_{max}: Time of maximum concentration • C_{min}: Observed minimum concentration at the end of the dosing interval • $AUC_{(0-t)}$: Area under the plasma concentration - time curve (AUC) to the last time with a concentration greater than or equal to the validated limit of quantitation of the assay • $AUC_{(0-\infty)}$: Area under the plasma concentration-time curve to infinity • $AUC_{(0-12)}$: Area under the plasma concentration - time curve from 0h (pre-dose) to 12 h after dosing • $AUC_{(0-last)}$: Area under the plasma concentration - time curve from time zero to the last concentration above the lower limit of quantitation (LLOQ) • $AUC_{(0-tau)}$: Area under the plasma concentration - time curve to the end of the dosing interval • $t_{1/2}$: Terminal half-life • CL_T: Total clearance • Ke: terminal phase elimination rate constant • Vd: Volume of distribution • Dose-normalized exposure parameters ($AUC_{(0-tau)}$/Dose and C_{max}/Dose)

OBJECTIVE	ENDPOINTS (OUTCOME MEASURES)
	The following multiple-dose plasma PK parameters will be computed (if estimable) from the drug total concentration-time data over the 48-hour dosing interval following the evening dose on Day 7 for each cohort. • $C_{max,ss}$: observed maximum concentration at steady state (ss) • $C_{min,ss}$: observed minimum concentration at the end of the dosing interval at steady state • C_{avg}: calculated average concentration during the dosing interval • $T_{max,ss}$: Time of maximum concentration (C_{max}) at steady state • T_{min}: Time to minimum concentration (C_{min}) • $AUC_{(0-48),ss}$: area under the plasma concentration - time curve from 0h (pre-dose) to 48 h after dosing at steady state • $AUC_{(0-tau),ss}$: Area under the plasma concentration - time curve to the end of the dosing interval at steady state • $t_{1/2}$: Terminal half-life • CL_T: Total clearance • Vd,ss: Volume of distribution at steady state • Linearity Index: $AUC_{(0-tau),ss}$ (Day 7) / $AUC_{(0-\infty)}$ (Day 1) • RAUC: Accumulation ratio for AUC estimated as $AUC_{(0-tau)}$ (Day 7) / $AUC_{(0-tau)}$ (Day 1) • RC_{max}: Accumulation ratio for C_{max} estimated as C_{max} (Day 7) / C_{max} (Day 1). • Dose-normalized exposure parameters ($AUC_{(0-tau)}$/Dose and C_{max}/Dose) Calculate trough plasma concentrations of total SLV213 at 12h after each morning and evening dose from Day 1 through Day 7.

3.1. Study Definitions and Derived Variables

Adverse Events

All AEs collected in this study will be considered unsolicited. Treatment-emergent AEs (TEAEs) are defined as AEs that occur or worsen after beginning study drug administration.

Treatment Groups

Results for safety and PK analyses will be presented by study product and dosage. Participants who received placebo will be pooled together and presented as a single treatment group. The treatment groups will be presented in the order of 400 mg SLV213 and Placebo. Results from placebo participants will not appear in the PK analyses. 600 mg SLV213 and 800 mg SLV213 treatment groups will not be enrolled.

Baseline

Any systemic medical condition and last vital sign (VS), electrocardiogram (ECG), and clinical safety laboratory test value that are recorded prior to dosing on Day 1 (Check-in/Enrollment and/or Day 1 Pre-Dose 1) will be considered a baseline finding for the purpose of data analysis. If multiple measurements are available, the last measurement prior to dosing will be used as baseline.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This Phase 1 double blind, placebo-controlled study will consist of three sequential inpatient cohorts of 12 healthy participants each (8 SLV213 and 4 placebo), at doses of 400 mg Q12h, 600 mg Q12h, and 800 mg Q12h for 7 days administered PO. After each cohort has been dosed, a Safety Review Committee (SRC) will evaluate the safety of the regimen to Day 15 before proceeding to dose the next cohort. The study will be carried out in the United States at a single clinical trial unit site (CTU). Participants who have consented to participate in the study, as evidenced by signing the informed consent form (ICF), will undergo study procedures to determine their eligibility to receive study drug. An overall schematic of the study design is shown in **Figure 1**.

After the 400 mg SLV213 treatment group met multiple halting rules, it was recommended by the SMC to not proceed with the next sequential dose. The 600 mg SLV213 and 800 mg SLV213 treatment groups will not be enrolled.

Upon meeting Inclusion/Exclusion criteria, participants will begin dosing with SLV213 or placebo per their allotted cohort. Participants will take their study drug orally Q12h in the fasted state, prior to morning and evening meals. AEs will be noted and graded per the protocol Toxicity Grading Tables (**Table 6**, **Table 7**, **Table 8**, and **Table 9**). Visit assessments are shown in the schedule of events (**Table 2**).

Participants will be assigned to receive their treatment according to the randomization carried out by the clinical site. For each dosing cohort, randomized participants will be assigned a unique number. Participants will be replaced if lost to follow up prior to Day 1 of treatment. The replacement participant would receive the same treatment that the participant being replaced would have received. A unique number will be the only participant identifier used on all sample collections and return of results. The site's unblinded pharmacist or qualified designee will provide each participant's study drug to blinded clinical staff at the participating site. All doses will be administered to the participant at the site by delegated staff under the observation of licensed clinical staff authorized to administered study drug (PI, or sub-investigator or licensed clinicians listed in Form 1572). The investigational drug blind is maintained by the dispensing pharmacist through a randomization schedule.

Full details about timing of analyses are found in **Section 6.2**.

4.2. Discussion of Study Design, Including the Choice of Control Groups

Given that the present study constitutes a follow-up to a completed single ascending dose (SAD) Phase 1 safety trial, a placebo control will also be utilized for the current multiple ascending dose (MAD) study. In light of this, healthy volunteers aged 18 to 65 years old will be selected in a randomized fashion to constitute a representative sample of the broader population affected by COVID-19. Due to the MAD nature of this trial, the study will allow for an assessment of safety and PK following multiple doses of SLV213 through 28 days post the first dose.

4.3. Selection of Study Population

This study will enroll healthy volunteers 18 to 65 years old. Participants will be enrolled in an equitable way with best practices to balance sex and age applied to the study population. Recruitment of not more than 5/3 or less than 3/5 Male-to-Female (M/F) ratio for each experimental group and not more than 3/1 or less than 1/3 M/F ratio for each placebo group may be obtained. Should a participant replacement be necessary within a

cohort, the replacement participant will receive the same treatment, and attempts will be made to be of the same gender as the withdrawn participant. Participant Inclusion and Exclusion Criteria must be confirmed by a study clinician licensed to make medical diagnoses. No exemptions are granted on Participant Inclusion/Exclusion Criteria in DMID-sponsored studies.

4.3.1. Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form.
2. Able to understand and willing to be available for all study visits and comply with all study procedures including Lifestyle Considerations (see Protocol v4.0 Section 5.4) throughout the study.
3. Male and Female individuals, age 18-65 inclusive at time of enrollment.
4. Good general health by medical history (MH), physical examination (PE), and vital signs (VS), clinical laboratory tests and ECG within normal reference range.[1]
    - *Note 1: Lab exceptions include: lab test values that are within Grade 1 range per the Toxicity Table (**Table 8**) are acceptable if not considered to be clinically significant by the investigator (PI, sub-investigator, or authorized clinician), with the exception of liver function tests (LFT) (transaminases alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), total and direct bilirubin, serum creatinine, estimated glomerular filtration rate (eGFR) per the CKD-EPI formula, and urine protein, which must be within the laboratory normal reference range.*
    - *Note 2: Screening laboratory values that fall outside the laboratory normal reference ranges and the ranges are not listed within the Toxicity Table (**Table 8**) (e.g., decrease activated partial thromboplastin time [aPTT]) that are deemed Not Clinically Significant by the PI will be acceptable.*
5. Ability to take oral medication and be willing to adhere to the dosing regimen.
6. Women of childbearing potential[1] must have practiced or use true abstinence[2] or use at least one acceptable primary form of contraception[3] for specified periods[4] before, during and after dosing.
    - *Note 1: Not of childbearing potential – post-menopausal females (defined as having a history of amenorrhea for at least one year) or a documented status as being surgically sterile (hysterectomy, bilateral oophorectomy, salpingectomy, tubal ligation, or Essure® placement with a history of documented radiological confirmation test at least 90 days after the procedure).*
    - *Note 2: True abstinence is 100% of the time without sexual intercourse (the male's penis enters the female's vagina). Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).*
    - *Note 3: Acceptable forms of primary contraception include a monogamous relationship with a vasectomized partner who has been vasectomized for 180 days or more before the participant receiving the study product, tubal ligation, non-hormonal intrauterine device, and if in a monogamous relationship with a male partner who uses a barrier method without spermicide.*
    - *Note 4: Specified periods include at least 30 days prior to screening, during the period between screening and completion of dosing, and until at least 30 days following receipt of the last dose of study product.*
7. Women of childbearing potential must have a negative serum β-human chorionic gonadotropin (HCG) pregnancy test at screening and a negative urine HCG pregnancy test at check-in (Day-1) within 24 hours before receiving the initial study product.

8. Male participants receiving the study product must use acceptable contraception and refrain from donating sperm from the day of first dose until 30 days after the last dose or be vasectomized.[1]
    - *Note 1: Acceptable contraception includes abstinence from intercourse with a female of childbearing potential or use of a male condom without spermicide when engaging in any activity that allows for the passage of ejaculate to a female during the intervention period and for at least 30 days after ending study dosing, or surgical sterilization for 180 days or more.*
9. Willing to avoid excessive physical exercise starting within 48 h prior to dosing and until discharge from the CTU on Day 9.
10. No history of acute febrile or infectious illness for at least 7 days prior to the administration of study drug.

4.3.2. Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Pregnant or lactating.
2. History of any chronic disease that may increase risk to subject or interfere with endpoint assessment.[1]:
    - *Note 1: With the exception of stable chronic medical conditions that do not require prescribed oral or injectable medications (e.g., Type 2 diabetes managed by diet only).*
3. History of bradycardia, orthostatic hypotension or orthostatic tachycardia, Long COVID or history of dysautonomia.[1]
    - *Note 1: Exception is sinus bradycardia (HR <60 bpm) in healthy participants (e.g., conditioned athletes) could be enrolled per investigator's clinical judgement.*
4. Known history of a clinically significant food or drug allergy/hypersensitivity including known allergy/ hypersensitivity to ingredients of the study drug or placebo.
5. Current seasonal allergies with ongoing symptoms for more than a week prior to dosing requiring glucocorticoids and/or frequent use of antihistamines for treatment.
6. History of any clinically significant disease or disorder, medical/surgical procedure, or trauma within 4 weeks prior to initiation of administration of study product(s).
7. History of any psychiatric condition that has required hospitalization in the last 12 months or subject is considered psychologically unstable by the investigator.
8. History of any substance use disorder or positive urine drug screening (UDS) test for illicit substances listed in Protocol v4.0 Section 8.1 at Screening or Check-in (Day -1)[1].
    - *Note 1: Any approved medical use of amphetamines, barbiturates, benzodiazepines, cannabis, tricyclic antidepressants and opiates will not be acceptable.*
9. History of alcoholism or of binge[1] or heavy alcohol drinking[2] at any time in the 6 months before study product administration or positive urine alcohol test at Screening or Check-in (Day -1).
    - *Note 1: Binge drinking is defined as 5 or more drinks during a single occasion if male, or 4 or more if female.*
    - *Note 2: Heavy drinking of alcohol is defined as consumption of more than 14 drinks of alcohol per week if male, or more than 7 drinks if female.*
10. History of ≥10 pack-years of nicotine product[1] consumption in the 5-year period before screening, or positive urine cotinine screen at Check-in (Day -1)[2].

- *Note 1: Nicotine products include cigarettes, e-cigarettes, pipe, cigar, chewing tobacco, nicotine patch.*
- *Note 2: Positive urine cotinine at Screening is allowed if negative at Check-in (Day -1).*

11. Body mass index (BMI) ≤ 18 kg/m^2 or ≥ 32 kg/m^2, or weight ≤ 100 lbs at Screening.
12. Prior exposure to SLV213 or K777 or K11777.
13. Use of any prohibited prescription or non-prescription medication within 14 days or 5 half-lives of the drug, whichever is longer, prior to study Check-in. (See **Section 4.4.7**)
14. Use of any investigational drug product within 30 days or 5 half-lives (whichever is longer) before investigational product administration in this study.
15. Planned participation in a clinical research study that requires treatment with a study drug, blood draws or other invasive assessments during the study period (screening until final visit).
16. Blood or plasma donation of 500 mL within 3 months or more than 100 mL within 30 days before signing informed consent or planned donation prior to completion of this trial.
17. Positive viral serology tests for Human Immunodeficiency Virus (HIV), hepatitis B virus, or hepatitis C virus (HCV) at screening[1] (See Protocol v4.0 Section 8.1) with one exception[2]:
    - *Note 1: Viral serology tests include HIV 1 and HIV 2 antibodies, Hepatitis B virus surface antigen (HBsAg), and HCV antibodies.*
    - *Note 2: Do not exclude participants with HCV antibodies who have been successfully treated for Hepatitis C, do not take any treatment medications currently, do not use prohibited medications, have normal transaminases and are generally healthy.*
18. Positive SARS-CoV-2 (COVID-19) molecular diagnostic test (Cue Care™ test) at Check-in (Day -1).

4.3.2.1. Exclusion of Specific Populations

Because the effects on the fetus are not known, pregnant women will not be eligible for the trial. Women of childbearing potential must utilize a highly effective method of contraception and will be required to have a negative urine pregnancy test on Check-in (Day -1) (within 24 h prior to initiation of study drug administration).

Children will not be included in this trial as presently there are no safety or efficacy data in adults. Should the outcome of this trial be deemed acceptable, additional trials may be initiated, including those in other populations.

4.4. Treatments

4.4.1. Treatments Administered

Study intervention:

- SLV213 capsules containing 100 mg of a refined powder of drug substance K777 hydrochloride.
- Matching placebo capsules containing 62.5 mg microcrystalline celluloid.

Each participant will be randomly assigned to receive SLV213 or placebo (SLV213:placebo ratio 2:1) by mouth as follows: 4 capsules Q12h in Cohort 1, 6 capsules Q12h in Cohort 2, and 8 capsules Q12h in

Cohort 3. The SLV213 dose will be 400 mg Q12h, 600 mg Q12h and 800 mg Q12h for participants in Cohorts 1, 2 and 3, respectively, for 7 days.

This study was terminated after Cohort 1 and will not proceed with sequential cohorts.

4.4.2. Identity of Investigational Product(s)

In this SAP, the term "study drug" refers to all or any of the drugs defined below:

Product 1: SLV213 in 100 mg capsules

SLV213 drug substance (K777) is 4-methylpiperazine-1-carboxylic acid [1-(3-benzenesulfonyl-1-phenethyl-allycarbamoyl)-2-phenylethyl]-amid) as hydrochloride salt. SLV213 is a white to tan powder of the drug substance without excipients or stabilizer that will be packed into Swedish orange opaque size 1 capsules. It is an investigational drug product that is being used to accordance with approved labeling.

Drug Substance Characteristics

Molecular weight	*611.19 (574.73 free base)*
Molecular formula	*$C_{32}H_{39}C_{l}N_{4}O_{4}S$*
Calculated pKa	*7.02*

Product 2: Matched Placebo

Placebo for SLV213 drug product is manufactured as microcrystalline cellulose in a size 1 orange hard gelatin capsule.

4.4.3. Method of Assigning Participants to Treatment Groups (Randomization)

Participants in each cohort will be randomized 2:1 to drug versus placebo before dosing on Day 1 and receive assigned treatment at each dose.

4.4.4. Selection of Doses in the Study

Selva has conducted a Phase 1 randomized double-blind placebo-controlled SAD study in healthy volunteers to evaluate the safety, tolerability, and PK of SLV213 following oral administration (Study SLV213-01). Following randomization, 5 cohorts of 8 participants each (6 active, 2 placebo) received a single dose of the active compound SLV213 or placebo at 50 mg, 100 mg, 200 mg, 400 mg, or 800 mg PO daily (QD). A SRC evaluated the blinded results of each successive cohort before proceeding to dose the next cohort. Although a clinically significant episode of orthostatic hypotension was observed 30 minutes (min) after dosing in one participant at the 200 mg dose level, this was not seen in this participant at subsequent time points, nor in any other participant at the 400 mg or 800 mg dose levels. The SRC therefore concluded that no dose limiting toxicity (DLT) had been seen at any of the dose levels. PK analyses demonstrated dose dependent C_{max} and AUC. Preliminary modeling of 400 mg and 800 mg BID using predicted blood levels showed exposures comparable to concentrations measured in preclinical efficacy models. It is therefore concluded that 400 mg Q12h, 600 mg Q12h and 800 mg Q12h dosing should be well tolerated. Further description of the results of the SLV213-01 study is provided in the investigator's brochure (IB).

This study was terminated after Cohort 1 (400 mg) and will not proceed with sequential cohorts (600 mg and 800 mg).

4.4.5. Selection and Timing of Dose for Each Participant

Participants will take their study drug prior to morning and evening meals in the fasted state with at least 240 mL (8 fluid ounces) or more of tap or bottled water under the supervision of the site staff. Participants will not be re-dosed outside of the standard schedule of events. A list of study products by cohort is available in **Table 1**.

Dose modifications are not planned unless mandated by the SMC.

4.4.6. Blinding

The study will be double-blinded, placebo-controlled. Placebo capsules are made to mimic study drug to avoid unblinding. Study drug and placebo are in matched bottles with matched capsule sizes. Administration of drug and placebo is controlled by the CTU as designated on the Delegation of Authority Log.

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is essential for the medical treatment of the participant. If possible, the DMID Medical monitor should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

For unblinding a participant, the investigational drug blind can be obtained by contacting the dispensing pharmacist. The emergency unblinding information will be obtained from the statistical and data coordinating center (SDCC). The sponsor (investigational new drug [IND] holder) must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents. Details will be presented in the study-specific manual of procedures (MOP).

4.4.7. Prior and Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, and supplements.

Information about prior medications, including hormonal contraceptives, taken by the participant in the 30 days prior to initiation of dosing with study product(s) will be recorded on the appropriate CRF.

Concomitant medications include all medications (prescription and over-the-counter [OTC] medications, supplements, and vaccines), except study products, taken by the participant from the time of the first dose of study product(s) to the end of the study. At each study visit following dosing, including telephone calls, participants will be queried about new ConMeds and changes to existing medications. The following medications are prohibited during the study:

- No medications are allowed after enrollment until completion of all study assessments with the exception of up to 1,000 mg acetaminophen daily for up to 3 days for the relief of common, temporary symptoms (headache, musculoskeletal pain, etc.) if approved by the site PI or authorized clinician.
- Any medications known to be strongly metabolized by CYP3A4 or CYP2D6, or strongly inhibit or induce these enzymes might interfere with the evaluation of the investigational product and should not be used by the participant for 14 days or 5 half-lives of the drug, whichever is longer, prior to and during the study. (See Protocol v4.0 Appendix C for a partial list).

- Participant should refrain from OTC supplements, such as vitamins and herbal supplements (e.g., Saint John's Wort), for 14 days or 5 half-lives of the supplement, whichever is longer, prior to and for the duration of the trial.

In the event medical conditions dictate the use of medications during the in-patient period, appropriate treatment may be prescribed by authorized/licensed clinician. For events during the out-patient period, participants are encouraged to notify the investigator or, if they seek care by their personal healthcare provider, to comply with the course of therapy as prescribed and inform the study investigator as soon as practical.

Any drug or vaccine used or received by the participant during the trial should be recorded on the appropriate CRF.

For additional lifestyle restrictions, see Protocol v4.0 Section 5.4.

4.4.8. Treatment Compliance

Participants will be directly observed at the time of dosing by a member of the clinical research team who is licensed and authorized to administer the study product (PI, sub-investigator or licensed clinician listed in Form 1572, or staff listed in the study Delegation of Authority Log). Each dose of study product will be administered by a member of the clinical research team that is delegated to administer the study product.

Study product administration date and time will be documented on site source document and recorded on the appropriate eCRF.

4.5. Safety and Pharmacokinetic Variables

The following section describes the safety and PK variables of the study. As this study is a Phase 1 clinical trial in healthy adult participants, there will be no assessment of drug efficacy.

4.5.1. Safety Variables

Venipuncture schedule and blood volumes are shown in schedule of assessments (**Table 3**). The following safety endpoints will be assessed:

- Chemistry (CHEM), Hematology (HEM), Coagulation (COAG), and Urinalysis (UA) clinical laboratory result safety parameters will be collected at Screening, Day -1, and prior to the morning dose on Days 2, 4, and 6, and on Day 8 or at early termination.
    - CHEM parameters: Electrolytes (sodium, potassium, total carbon dioxide [CO_2]), calcium, chloride, creatinine, blood urea nitrogen (BUN), fasting glucose, total protein, albumin, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), amylase, lipase, magnesium, and inorganic phosphorus.
        - Note 1: Estimate glomerular flow rate (eGFR) and direct bilirubin will be collected but not graded.
    - HEM parameters: Hemoglobin, platelets, white blood cells (WBC), neutrophils, lymphocytes, monocytes, basophils, and eosinophils.
        - Note 1: Red blood cells (RBC) will be collected but not graded.
    - COAG parameters: Prothrombin time and activated partial thromboplastin time (aPTT).

        - Note 1: Prothrombin time international normalized rate (PT INR) will be collected but not graded.
    - UA parameters: Nitrite, urine protein, and urine glucose via dipstick.
        - Note 1: pH, specific gravity, bilirubin, and occult blood will be collected but not graded.
        - Note 2: If urine dipstick is abnormal for blood, protein, glucose, and nitrites, urine microscopy will be performed (for WBC, RBC, and bacteria), and the results will supersede those of the dipstick UA.
- Vital signs (VS) will be collected at Screening, Day -1, within 30 minutes before and 2 hours (± 10 minutes) after each dose on Day 1 through Day 7, and the mornings of Days 8 and 9.
    - Supine VS parameters: Body temperature (oral), systolic blood pressure (SBP), diastolic BP (DBP), pulse, and respiratory rate.
        - Note 1: BP will be taken after at least 5 minutes of resting.
    - Orthostatic VS parameters: SBP, DBP, and pulse
        - Note 1: Orthostatic parameters will be measured 1 minute ± 15 seconds and 3 minutes ± 15 seconds after standing.
- Electrocardiogram (ECG) results will be collected at Screening, Day -1, and prior to the morning dose on Day 4, and Day 8 (before 12h PK timepoint after Day 7 evening dose) or at early termination.
    - ECG parameters: PR interval, QRS interval, QT interval, QT interval corrected for heart rate using Fridericia's formula (QTcF correction), RR interval, and ventricular rate.

Incidence, relatedness, and severity of TEAEs and SAEs will be recorded from the time of dosing to the final visit on the appropriate eCRF. All AEs will be graded for severity and relationship to the study product by a trained and qualified member of the study team. All AEs and SAEs will be considered unsolicited events. Abnormal clinical assessments should be submitted in the appropriate AE form. If a participant had an event with graded severity after enrollment on Day -1 but before dosing on Day 1, then the event will be reported in an updated medical history (MH) form and will be considered an AE only if it increases in severity grade after dosing.

4.5.2. PK Variables

Blood (plasma) samples for PK analysis will be collected according to the schedule of assessment (**Table 3**). Plasma concentrations of SLV213 will be quantitated using validated assays and study drug concentration data will be transferred to SDCC (Emmes) from the bioanalytical lab, KCAS, for reporting and PK analysis. PK parameters to be estimated for single dose and multiple dose plasma samples are described in **Section 10**.

5. SAMPLE SIZE CONSIDERATIONS

The sample size chosen of a total of 36 participants (12 per cohort: 8 to receive active drug and 4 placebo) is considered to be sufficient for evaluation of safety, tolerability and PK data for this study; the sample size was not based on statistical power considerations (**Table 4**).

Participants will be replaced if they withdraw or are withdrawn prior to Day 1 of treatment. The replacement participant would receive the same treatment that the participant would have received.

Participants who withdraw or are withdrawn from this study after receiving at least one dose of study product and prior to Day 9 for reasons not related to TEAEs or study drug intolerance may be replaced, at the recommendation of the Site PI and concurrence by the DMID MO, with a participant who will receive the same treatment as the withdrawn participant, and an effort will be made to also be of the same gender as the participant who is replaced. The SDCC must be contacted prior to enrolling any replacement participants.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum, and minimum. The frequency and percentages (based on analysis population sample size, unless otherwise stated) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by treatment group, participant, parameter, and time point as applicable.

The Safety Population will be the primary population used for summaries of safety endpoints. The PK Analysis Population will be used for summaries of PK endpoints. Analyses of primary and secondary endpoints will be done for each dose of SLV213 and compared with a placebo group.

6.2. Timing of Analyses

The primary clinical database for this study will consist of safety data including unsolicited events, and abnormal laboratory values, as well as baseline/demographic data. Once the last participant has completed the final visit, the primary clinical database will be cleaned, monitored, and locked. After clinical database lock and receipt of secondary endpoint data, a set of topline tables will be generated, including summaries of clinical safety and secondary PK data. The topline report will be made available to the study team for planning subsequent trials and may be presented in a public forum or used for publication in collaboration with the lead PI. These analyses will be considered final and will be included in the Clinical Study Report (CSR).

Interim Analysis

Blinded safety and tolerability data will be periodically reviewed by DMID and the site PI or authorized study clinician (listed on FDA Form 1572) to assess whether rules for halting progression to the next study cohort have been met. An *ad hoc* SMC meeting will review safety data if halting criteria have been met. The SMC will receive data in aggregate. The SMC may request to receive data by study product vs. placebo in a closed session. The SMC may also request that the blind be broken for individual participants, as needed, to assess safety issues. The SMC will be asked to recommend early termination or modification only when there is clear and substantial evidence of a treatment difference. More details about the interim analyses are described below, as well as in a separate guidance document for the SMC.

Interim Safety Analyses

Interim safety analysis is not planned. Safety data may be summarized for *ad hoc* review as requested by the SMC. Top level safety parameters will be assessed between cohorts as needed.

After one participant experienced a moderate allergic reaction, further dosing was discontinued in four participants. As a result, four replacement participants were added at the advice of the SMC. One of these replacement participants also had a moderate allergic reaction to the study product. After meeting a halting rule criterion, the study was halted, and the SMC reviewed data of the two participants who reported a moderate allergic reaction. Under the advisement of the SMC, the study will not proceed with Cohort 2 and Cohort 3.

Interim Pharmacokinetics, Pharmacodynamic, Microbiological Activity, or Efficacy Review

An interim PK and pharmacodynamics (PD) analysis is not planned. If concentration versus time or PK data are available, top-level concentration versus time curves or PK parameters will be assessed between cohorts as needed.

Final Analyses

Final analysis will be completed after study completion and database lock. No formal study data will be provided prior to this final analysis.

6.3. Analysis Populations

6.3.1. Full Analysis Population

The Full Analysis population will include all randomized participants, including replacement participants, and analyzed according to the treatment as randomized. This population is analogous to an intent-to-treat population.

6.3.2. Modified Intention-to-Treat (mITT) Population

The mITT population will include all randomized participants, including replacement participants, who meet eligibility criteria and receive at least one dose of any study treatment. Participants will be excluded from the mITT population, if they fail to meet eligibility criteria or if they do not receive any study treatment. Analysis will be performed according to the treatment as randomized.

6.3.3. Safety Population

The Safety population will include all randomized participants, including replacement participants, who received at least one dose of any study treatment, and analysis will be performed according to the treatment actually received.

6.3.4. Pharmacokinetics (PK) Population

The PK population will include all randomized participants, including replacement participants, who received at least one dose of study treatment and have at least one quantifiable post-dosing plasma concentration to use for the PK analysis.

6.4. Covariates and Subgroups

The protocol does not define any formal subgroup analyses, and the study is not adequately powered to perform subgroup analyses.

6.5. Handling of Missing Data, Outliers, and BQL Data

6.5.1. Missing Data

All attempts will be made to collect all data per protocol. No imputation will be performed for missing values.

6.5.2. Outliers

Outliers will not be excluded from the primary analyses. Outliers identified during the PK analysis will be discussed in the analysis report. Outliers will be defined as any values of plasma concentration for a given

treatment group that fall outside the interquartile fences of their respective distribution. Given an interquartile range (IQR) of Q3-Q1, where Q3 is the 75th percentile and Q1 is the 25th percentile, outliers will be those that are greater than Q3 + (1.5 x IQR) or those less than Q1 – (1.5 x IQR).

6.5.3. BQL Data

PK sample concentrations below the quantitative limit (BQL) will be imputed as zero if they did not come after a PK sample concentration that is above the lower limit of quantitation (LLOQ). The first PK sample that's BQL will be imputed as ½ LLOQ if it came after a PK sample concentration above LLOQ and all PK samples after are also BQL. Otherwise, PK sample concentrations that are BQL will be imputed as missing.

6.6. Interim Analyses and Data Monitoring

Refer to **Section 6.2**.

6.7. Multicenter Studies

This is a single-site study.

6.8. Multiple Comparisons/Multiplicity

The objectives of the study are to obtain safety data and plasma PK data for 3 escalating doses of SLV213 administered PO daily Q12h for seven days. There are no formal hypotheses being tested in this Phase 1 trial.

This study was terminated after Cohort 1 (400 mg) and will not proceed with sequential cohorts (600 mg and 800 mg).

7. STUDY SUBJECTS

7.1. Disposition of Participants

The composition of analysis populations, including reasons for participant exclusion, by treatment group, is presented in **Table 11**.

The disposition of participants in the study will be tabulated by treatment group (**Table 10**). The table shows the total number of participants enrolled, included in Safety Population (receiving at least 1 dose), received all planned doses, included in the mITT population, included in PK population (having at least one quantifiable post dose plasma concentration), completed all PK blood draws, and completed follow-up.

A flowchart showing the disposition of study participant will be included (**Figure 2**). This figure will present the number of participants screened, enrolled, dosed, completed the study and/or lost to follow-up, and analyzed by treatment group.

A listing of participants who discontinued dosing or terminated from study follow-up and the reason will be included in **Listing 2**. A listing of participants who were excluded from certain analysis populations and the reasons are included in **Listing 5**.

7.2. Protocol Deviations

A summary of participant-specific protocol deviations will be presented by the reason for the deviation, the deviation category, and treatment group for all participants in the Safety Population (**Table 5**). All participant-specific protocol deviations and non-participant specific protocol deviations will be included in **Appendix 3** as data listings (**Listing 3** and **Listing 4** respectively).

8. EFFICACY EVALUATION

There are no efficacy endpoints for this trial.

9. SAFETY EVALUATION

All safety analyses will be performed using the Safety Population and will be presented by Treatment Group.

TEAEs will be presented in listings and summarized. Individual results of laboratory tests, VS, and ECGs will be listed and baseline, post dose, and changes from baseline to post dose laboratory, VS, and ECG data will be summarized.

In general, TEAEs, including abnormal laboratory values, will be graded according to the FDA Guidance: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (https://www.fda.gov/media/73679/download). Grading scales are provided for AEs (**Table 6**), supine vital signs (**Table 7**), clinical laboratory results (**Table 8**), and ECG results (**Table 9**). Abnormal PE findings will be presented in data listings (**Listing 18**).

Clinical laboratory tests and VS at Screening Visit and Check-in (Day -1) should be within site normal reference range with exceptions as allowed per **Section 4.3.1**, inclusion criterion #4 and outlined in the Manual of Procedures (MOP). Grade 1 measurements acceptable at baseline will only be considered a TEAE post-baseline if condition worsened.

All TEAEs will be summarized using frequency counts and percentages. The following summaries will be presented for TEAEs and SAEs:

- Overall (i.e., regardless of severity or relationship to treatment).
- By severity grade (mild, moderate, severe, or life-threatening).
- By relationship to study drug.
- By MedDRA level hierarchy (system organ class [SOC], higher level group term [HLGT], and preferred term [PT]).

Unless otherwise specified, at each level of participant summarization in reporting the incidence of TEAEs, a participant will be counted once if the participant reported one or more TEAEs. If more than one occurrence of a TEAE is reported, the TEAE of the worst severity or the worst-case relationship assessment will be summarized.

9.1. Demographic and Other Baseline Characteristics

Summaries of sex, gender assigned at birth, ethnicity, and race and of age, height, weight, and BMI will be presented by treatment group (**Table 12** and **Table 13** respectively). Ethnicity is categorized as Hispanic or Latino, or Not Hispanic or Latino. In accordance with NIH reporting policy, participants may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as “No” to each racial option.

Individual participant listings (**Appendix 3**) will be presented for all demographics, including weight, height, and BMI **(Listing 6**), pre-existing medical conditions (**Listing 7**), and concomitant medications (**Listing 21**).

9.1.1. Prior and Concurrent Medical Conditions

All current illnesses and pre-existing medical conditions will be Medical Dictionary for Regulatory Activities (MedDRA) coded using MedDRA dictionary version 24.1 or higher.

Individual participant listings will be presented for all medical conditions (**Listing 7**).

9.1.2. Prior and Concomitant Medications

All medications will be coded to the Anatomical Therapeutic Classification (ATC) using the current version of the World Health Organization (WHO) Drug Dictionary.

Individual participant listings will be presented for all concomitant medications (**Listing 21**).

9.2. Measurements of Treatment Compliance

Information on whether a participant missed a dose and reason, if provided, for missing a dose are included in **Listing 8**.

9.3. Adverse Events

All AEs collected will be considered unsolicited. Unsolicited AEs collected after receiving the first dose will be considered TEAEs.

An overall summary of TEAEs by treatment group will be presented in **Table 22** including number and percentage of participants who experienced at least one TEAE and at least one SAE. The number and percentage of participants and the number of events will be presented for SAEs and AEs in **Table 23**.

The following summaries of AEs will be presented by treatment group, SOC, HLGT, and PT:

- The number and percentage of participants, its corresponding 95% Confidence Interval (CI), and the number of events will be presented in **Table 24**. The 95% CI will be calculated using exact Clopper-Pearson methodology.
- The number and percentage of participants will be presented by the maximum severity of each relationship to the study treatment (related or not related) in **Table 25**.
- The frequency and incidence of related TEAEs are presented graphically in **Figure 9** and **Figure 10**, respectively.

Individual participant listings will be presented for all TEAEs (**Listing 12**).

9.4. Deaths, Serious Adverse Events and other Significant Adverse Events

A complete listing of SAEs will be presented in **Table 26**. Other non-serious, unsolicited, moderate or greater severity TEAEs are listed in **Table 27**. A listing of adverse events of special interest (AESIs), medically attended adverse events (MAAEs), and unanticipated problems (UPs) will be presented in **Table 28**.

9.5. Pregnancies

Individual data listings of pregnancy reports will be provided if a pregnancy occurs post dosing:

- Maternal information will be presented in **Listing 22**.
- Gravida and para information will be presented in **Listing 23**.
- Live birth outcomes will be presented in **Listing 24**, and still birth outcomes will be presented in **Listing 25**.
- Spontaneous, elective, or therapeutic abortion outcomes will be presented in **Listing 26**.

9.6. Clinical Laboratory Evaluations

Venipuncture schedule and blood volumes are shown in schedule of assessments (**Table 3**). Unscheduled clinical laboratory evaluations will be included in listings of all clinical laboratory results but will be excluded from tabular and graphical summaries by time point, except when calculating the maximum severity post baseline. All clinical laboratory results will be listed for each participant from time of screening to last study visit. Any abnormal laboratory result at Screening or Check-in (Day -1) (baseline) with values in the Grade 1 range but deemed acceptable for enrollment per **Section 4.3.1**, inclusion criterion #4, will be presented in listings but will only be reported as a TEAE if severity worsens. Clinical laboratory parameters that have grading criteria for both decreases (result lower than normal range) and increases (result higher than normal range) will be summarized separately by direction.

Laboratory results will be presented for chemistry, hematology, coagulation, and urinalysis separately. All safety laboratory results, severity, and change from baseline will be listed for each participant by treatment group, parameter, and time point in **Listing 13**, **Listing 14**, **Listing 15**, and **Listing 16**. Abnormal laboratory results (laboratory results outside the site normal range) will be presented in **Table 29**, **Table 30**, **Table 31**, and **Table 32**. Laboratory results outside of normal range but not within toxicity grading ranges will be listed as "ONR" (out of normal range) for severity.

The sort order for CHEM parameters will be as follows: Sodium, Potassium, Total Carbon Dioxide, Calcium, Chloride, Creatinine, eGFR, Blood Urea Nitrogen, Fasting Glucose, Total Protein, Albumin, Total Bilirubin, Direct Bilirubin, Alanine Aminotransferase, Aspartate Aminotransferase, Alkaline Phosphatase, Amylase, Lipase, Magnesium, and Inorganic Phosphorus.

The sort order for HEM parameters will be as follows: Hemoglobin, Platelets, Red Blood Cells, White Blood Cells, Neutrophils, Lymphocytes, Monocytes, Basophils, and Eosinophils.

The sort order for COAG parameters will be as follows: PT INR, Prothrombin Time, and aPTT.

The sort order for UA parameters will be as follows: pH, Specific Gravity, Bilirubin, Nitrite, Urine Protein, Urine Glucose, Occult Blood, White Blood Cell Count, Red Blood Cell Count, and Bacteria.

Laboratory results will be summarized for baseline, Day 2, Day 4, Day 6, and Day 8 in tables and figures:

- Number and percentage of participants with none, mild, moderate, severe, or life-threatening laboratory results both low (decrease) and high (increase) by parameter, time point, and treatment group for CHEM (**Table 33**), HEM (**Table 34**), COAG (**Table 35**), and UA (**Table 36**).

9.7. Vital Signs and Physical Evaluations

Unscheduled supine or orthostatic VS measurements will be included in listings but will be excluded from tabular and graphical summaries by time point, except when calculating the maximum severity post baseline. If VS measurements are repeated due to technical errors, the initial measurements made in error will not be used for analysis but will be listed. The following rules will be used to determine which supine VS measurement to use for analyses if repeat measurements occur:

1. If the first replicate is normal, then it will be used for analysis.
2. If the first and second replicates are both abnormal, then the replicate with the higher severity will be used for analysis.
3. If the first replicate is abnormal, the second replicate is normal, and the third replicate was not performed, then the first replicate will be used in the analysis.

4. If the first replicate is abnormal, the second replicate is normal, and the third replicate is normal, then the second replicate will be used in the analysis.
5. If the first replicate is abnormal, the second replicate is normal, and the third replicate is abnormal, then the abnormal replicate with the higher severity will be used for analysis.

Any supine VS assessment at Screening or Check-in (Day -1) with values in the Grade 1 range but deemed acceptable for enrollment per **Section 4.3.1**, inclusion criterion #4, will be presented in listings but will only be reported as a TEAE if severity worsens. VS assessments that have grading criteria for both decreases (result lower than normal range) and increases (result higher than normal range) will be summarized separately by direction.

The sort order for VS will be as follows: Oral Temperature, SBP, DPB, Pulse, and Respiratory Rate.

Supine VS results will be summarized in tables:

- Number and percentage of participants with mild, moderate, severe, or life-threatening VS results both low (decrease) and high (increase) by parameter, time point, dose (morning or evening), and treatment group (**Table 37**).

Following supine measurements, orthostatic measurements of blood pressure and heart rate (pulse) were taken at 1 min (±15s) and 3 min (±15s) after standing. These measurements were evaluated relative to the supine measurements that were taken before standing up. The criteria for an abnormal VS orthostatic response include the following:

- Orthostatic hypotension, defined as an SBP decrease of at least 20 mm/Hg **and/or** a DBP decrease of at least 10 mm/Hg from supine baseline,
- **And** an increase in orthostatic pulse defined as an increase of at least 30 beats/min above supine baseline or any time there was there was tachycardia with a pulse above 120 beats/min.

Abnormal VS orthostatic response meeting these criteria will be summarized as a TEAE. Orthostatic BP and HR are not included in VS tables. If orthostatic measurements were repeated, then supine measurements were repeated first.

All supine and orthostatic VS measurements will be presented in **Listing 17**.

Abnormal physical exams will be submitted and counted as an AE. A listing of abnormal physical exams will be presented in **Listing 18**.

9.8. Concomitant Medications

Refer to **Section 9.1.2**.

9.9. Other Safety Measures

9.9.1. 12-Lead Standard Electrocardiogram

Unscheduled ECG measurements will be included in listings but will be excluded from tabular and graphical summaries by time point, except when calculating the maximum severity post baseline. Baseline is defined in **Section 3.1**. Individual interval measurements and overall interpretations will be presented in **Listing 19** and **Listing 20**, respectively.

The sort order for ECG interval measurements will be as follows: PR Interval, QRS Interval, QT Interval, QTcF Interval, RR Interval, and Ventricular Rate.

12-lead standard ECG results will be summarized in tables and figures:

- Summary of 12-lead standard ECG change in overall interpretation from baseline will be shown by treatment group and time point (**Table 38**).
- Number and percentage of participants with mild, moderate, severe, or life-threatening ECG results by parameter, time point, and treatment group (**Table 39**).

9.9.2. Tolerability

Tolerability to study product is summarized by treatment group in **Table 14**. The table includes number and percentage of participants who (1) were terminated early or withdrawn due to TEAE related to study product; (2) had at least one TEAE; (3) had at least one Grade 3 abnormal lab test, VS measurement, or ECG parameter; (4) completed all oral medication doses.

10. PHARMACOKINETICS

The PK Analysis Population will be used when summarizing plasma drug concentrations and will be used to conduct noncompartmental analysis (NCA). Concentrations collected that are BQL before the first measurable PK concentration above the LLOQ will be treated as 0 for plotting and for all calculations including NCA and concentration summary statistics. The first BQL concentration after the last measurable PK concentration will be imputed as ½ LLOQ. Otherwise, BQL concentrations will be imputed as missing. Otherwise, PK sample concentrations that are BQL will be imputed as missing.

There will be no imputation for missing concentrations. The geometric mean (GM) of concentrations will be calculated using non-missing values after imputations.

Collection of plasma samples outside of the protocol defined time window for the time point, determined by exact rather than nominal time of collection, will not result in exclusion of the sample result from NCA. Plasma samples collected out of window will be evaluated on a case-by-case basis. Results from PK plasma samples that were collected substantially outside of the protocol-defined time window will be excluded from concentration summary statistics by nominal time points and plots of mean concentration by nominal time point. Substantially out-of-window samples will be defined as twice the size of the protocol-defined windows. Plasma will be drawn at the following time points to measure the concentration of SLV213 and analyze PK parameters:

- On Day 1 MORNING DOSE: Within 30 min before the morning dose (t=0), and at 0.5h (±5 min), 1h (±5 min), 2h (±5 min), 4h (±5 min), 6h (±10 min), 8h (±10 min), and 12h (±15 min) after the morning dose. (The 12h time point is the same as the pre-dose time point (t=0) before the evening dose on Day 1)
- On Day 1 EVENING DOSE: Before (t=0) and 12h (±15 min) after the evening dose. (The 12h time point is the same as the pre-dose time point before the morning dose on Day 2).
- On Days 2 to 6: Within 30 min before the morning and evening doses (t=0) and at 12h (±15 min) after the morning and evening doses on each day. (The PK time point before each dose on Days 2 to 6 is the same as the 12h time point of the previously received dose.)
- On Day 7 MORNING DOSE: Within 30 min before the morning dose (t=0), and 12h (±15 min) after the morning dose. (The 12h time point is the same as the pre-dose time point (t=0) before the evening dose on Day 7)
- On Day 7 EVENING DOSE: Within 30 min before the evening dose (t=0), and at 0.5h (±5 min), 1h (±5 min), 2h (±5 min), and 4h (±5 min) after the evening dose on Day 7.
- On Day 8: At 6h (±10 min), 8h (±10 min), 12h (±15 min) and 24h (±15 min) after the evening dose on Day 7.
- On Day 9: At 36h (±15 min) and 48h (-2 hours) after the evening dose on Dose 7.

If the exact time of plasma PK sample collection is not recorded, then the collection time will be imputed as the planned time for analysis, as long as it is not known that the sample was collected outside of the protocol-defined window. Rationale for excluding results from analysis will be described in the CSR. Results from samples with imputed collection times will be indicated in listing of PK sample concentrations.

Participant-level SLV213 concentration listings will include separate columns for concentrations reported by the lab and concentrations used for analysis (**Listing 9**). The lab reported concentrations may include codes

such as "BQL" or "QNS" (Quantity Not Sufficient), while the analysis concentrations will contain numeric data only, including imputed values such as 0 for pre-dose time points and BQL samples prior to the first quantifiable sample. Listing will also indicate nominal time (i.e., planned time point) and actual time post dose in hours and minutes (e.g., 12H 10M). The listing will also indicate sample times that were collected out of window or imputed.

Individual concentrations for all participants in the PK population will be presented in tables and figures:

1. Summary statistics of SLV213 concentrations in plasma are presented for each nominal time point on Day 1 (morning dose) (**Table 15** and [by sex] **Table 16**), Day 1 (evening dose) to Day 7 (morning dose) (**Table 17** and [by sex] **Table 18**), and Day 7 (evening dose) to Day 9 (**Table 19** and [by sex] **Table 20**).
2. Individual SLV213 concentrations in plasma profiles are presented graphically for Day 1 (morning dose) (**Figure 3**) and Day 7 (evening dose) (**Figure 4**).
3. Individual trough SLV213 concentrations in plasma profiles are presented for Day 1 (morning dose) through Day 7 (evening dose) (**Figure 5**).
4. Semi-log individual SLV213 concentrations in plasma profiles are presented for Day 1 (morning dose) (**Figure 6**) and Day 7 (evening dose) (**Figure 7**).
5. Semi-log individual trough SLV213 concentrations in plasma profiles are presented for Day 1 (morning dose) to Day 7 (evening dose) (**Figure 8**).

10.1. Noncompartmental Analysis

PK parameters from plasma PK data will be estimated through NCA using version 8.3.4 or higher of Phoenix WinNonlin®. Actual post dose times will be used for estimation of plasma PK parameters instead of nominal time. In case of imputed sample collection times, the imputed time will be included in NCA. Any outliers identified in the PK analysis will be discussed in the analysis report. Outliers will not be excluded from the noncompartmental PK analysis.

All estimable participant-specific PK parameters for single-dose and multiple dose are included in **Listing 10** and **Listing 11**, respectively.

Summary statistics for SLV213 PK parameters are presented by Day 1, Single Dose and Day 7, Multiple Dose for the 400 mg SLV213 treatment group (**Table 21**) for participants in the PK population with a measurable Ke (terminal elimination rate constant) at the given dose.

The definition of coefficient of variation (CV%) is described below:

For an independent identically distributed random sample $\{x_1, x_2, \ldots, x_n\}$ from a log-normal distribution, let s^2 be the sample variance statistic of the natural log-transformed values of the sample. The CV% will be defined as:

$$CV\% = \sqrt{\exp(s^2) - 1} \times 100\%$$

Phoenix WinNonlin® NCA will use the following settings to compute parameters from plasma PK data:

- Linear Up Log Down calculation method
- Uniform weighting
- Ke Acceptance Criteria
  - Rsq_adjusted $\geq$ 0.90

- Includes at least 3 time points after T_{max}

10.1.1. Single-Dose Plasma PK Parameters

These parameters will be computed (if estimable) from the plasma drug concentration-time data over the 12-hours following Dose 1 (Day 1, morning dose) for each study drug:

C_{max}

C_{max} is defined as the maximum drug or metabolite concentration observed in plasma over all PK sample concentrations. It will be obtained from the *Cmax* parameter calculated by WinNonlin®. If there is no measurable concentration in the participant's PK profile, then C_{max} will be missing for that participant. C_{max} will be reported in units of ng/mL. The dose-normalized parameter C_{max}/Dose will also be reported from *Cmax_D* in WinNonlin®.

C_{min}

C_{min} is defined as the observed minimum concentration at the end of the dosing interval. It will be obtained from the *Clast* parameter calculated by WinNonlin®.

T_{max}

Time of maximum concentration (T_{max}) is defined as the time at which the C_{max} occurs. It will be obtained from the *Tmax* parameter calculated by WinNonlin®. If there is no measurable C_{max} in the participant's PK profile, then T_{max} will be missing for that participant. T_{max} will be reported in units of h.

Ke

The terminal phase elimination rate constant (Ke) is defined as the first-order rate constant describing the rate of decrease of drug or metabolite concentration in the terminal phase (defined as the terminal region of the PK curve where drug or metabolite concentration follows first-order elimination kinetics). Ke will be computed as the slope of a terminal region consisting of $\geq$ 3 points in the plot of log-transformed concentration data versus time. Ke will be estimated using uniform weighting.

Time points used in the estimation of Ke will be initially selected using the WinNonlin® automatic algorithm. Manually chosen time points may be used at the discretion of the PK analyst after examination of the automatically chosen points in the context of the semi-log profile to improve estimation of Ke on a case-by-case basis. The set of points chosen must contain only time points after T_{max}, include at least 3 time points, and satisfy the Ke Acceptance Criteria described above. Otherwise, the elimination rate constant and all derived parameters (apparent terminal elimination half-life [$t_{1/2}$], AUC Extrapolated to Infinity [$AUC_{0-\infty}$], total clearance [CL_T], and apparent volume of distribution during terminal phase [Vd]) will be treated as missing.

This parameter will be represented by the *Lambda_z* parameter calculated by WinNonlin®. Ke will be reported in units of 1/h.

$t_{1/2}$

The $t_{1/2}$ is defined as the time required for the drug or metabolite concentration to decrease by a factor of one-half in the terminal phase. The $t_{1/2}$ can be estimated as ln(2)/ Ke. It will be obtained from the *HL_Lambda_z* parameter calculated by WinNonlin®. Terminal half-life will be reported in units of h.

AUC

$AUC_{0\text{-last}}$ is defined as the area under the concentration-time curve from dosing (t=0) to the time of the last measured concentration. $AUC_{0\text{-last}}$ will be estimated using the Linear Up Log Down calculation method and obtained from the *AUClast* parameter calculated by WinNonlin®.

$AUC_{0\text{-}\infty}$is defined as the total area under the concentration-time curve from dosing (t=0) taken to the limit as the end time becomes arbitrarily large. $AUC_{0\text{-}\infty}$ can be calculated by adding $AUC_{0\text{-last}}$ to an extrapolated value equal to the last measured concentration greater than the LLOQ divided by Ke:

$$AUC_{0-\infty} = AUC_{0-\text{last}} + \frac{C_{\text{last}}}{Ke}$$

Where C_{last} is the last measured concentration ≥ LLOQ. $AUC_{0\text{-}\infty}$ will be obtained from the *AUCINF_obs* parameter calculated by WinNonlin®.

$\%AUC_{ex}$ is defined as percentage of $AUC_{0\text{-}\infty}$ obtained by extrapolation from time of the last measured concentration to infinity. $\%AUC_{ex}$ can be calculated by dividing AUC from time of the last measured concentration to infinity by $AUC_{0\text{-}\infty}$:

$$\%AUC_{ex} = \frac{AUC_{0-\infty} - AUC_{0-\text{last}}}{AUC_{0-\text{inf}}},$$

If $\%AUC_{ex}$ is >20%, the estimated $AUC_{0\text{-}\infty}$ will be excluded from statistical summaries of PK parameter estimates and downstream calculations. $\%AUC_{ex}$ will be obtained from the *AUC_%Extrap_obs* parameter calculated by WinNonlin®.

$AUC_{0\text{-}12}$ will be calculated as the AUC extrapolated to 12 h after dosing. This will be obtained from the WinNonlin® *AUC0_12* parameter.

$AUC_{0\text{-tau}}$ will be calculated as the AUC to the end of the dosing interval. The dose-normalized parameter $AUC_{0\text{-tau}}$/Dose will also be reported. These parameters will be obtained from the *AUC_tau* and *AUC_tau_D* parameters in WinNonlin®, respectively.

All AUCs will be reported in units of ng*h/mL.

CL_T

Total clearance (CL_T) will be obtained from Dose/AUC_{∞}. If $\%AUC_{ex}$ is >20%, the estimated CL_T value will be excluded from statistical summaries of parameter estimates and downstream calculations. CL_T will be obtained from the *CL_F_obs* parameter calculated by WinNonlin®. Clearance will be reported in units of L/h.

Vd

Apparent volume of distribution (Vd) will be calculated as (CL_T)/ Ke. If $\%AUC_{ex}$ is >20%, the estimated Vd value will be excluded from statistical summaries of parameter estimates and downstream calculations. Vd will be obtained from *Vz_F_obs* calculated by WinNonlin®. Volume will be reported in units of L.

10.1.2. Multiple-Dose Plasma PK Parameters

These parameters will be computed (if estimable) from the plasma drug concentration-time data over the 48-hour dosing interval following Dose 14 (Day 7, evening dose) for each study drug. Note that these parameter estimates assume that steady state has been achieved.

$C_{max,ss}$

$C_{max,ss}$ is the observed maximum concentration at steady state. This will be obtained from the *Cmax* parameter calculated by WinNonlin® for Dose 14.

$C_{min,ss}$

$C_{min,ss}$ is the observed minimum concentration at the end of the dosing interval at steady state. This will be obtained from the *Clast* parameter calculated by WinNonlin® for Dose 14.

C_{avg}

C_{avg} is the calculated average concentration during the dosing interval. It is calculated as $AUC_{0\text{-}tau,ss}$/tau. This will be obtained from the *Cavg* parameter calculated by WinNonlin® for Dose 14.

$T_{max,ss}$

$T_{max,ss}$ is the time of maximum concentration (C_{max}) at steady state. This will be obtained from the *Tmax* parameter calculated by WinNonlin® for Dose 14.

T_{min}

T_{min} is the time to minimum concentration (C_{min}). This will be obtained from the *Tlast* parameter calculated by WinNonlin® for Dose 14.

Ke

Ke is the first-order rate constant describing the rate of decrease of drug or metabolite concentration in the terminal phase (see **Section 10.1.1** for additional details). This will be obtained from the *Lambda_z* parameter calculated by WinNonlin® for Dose 14.

$AUC_{(0\text{-}48),ss}$

$AUC_{(0\text{-}48),ss}$ is calculated as the area under the plasma concentration - time curve extrapolated to 48 h after dosing (see **Section 10.1.1** for additional details).

$AUC_{(0\text{-}tau),ss}$

$AUC_{(0\text{-}tau),ss}$ is calculated as the area under the plasma concentration-time curve to the end of the dosing interval at steady state.

$t_{1/2}$

$t_{1/2}$ will be obtained from the *HL_Lambda_z* parameter calculated by WinNonlin® for Dose 14 (see **Section 10.1.1** for additional details).

CL_T

CL_T will be obtained from the *CL_F_obs* parameter calculated by WinNonlin® (see **Section 10.1.1** for additional details).

$Vd_{,ss}$

$Vd_{,ss}$ is the volume of distribution at steady state. It will be obtained from *Vz_F_obs* in WinNonlin®.

Linearity Index

The Linearity Index is calculated as $AUC_{(0\text{-}tau),ss}$ (Dose 14 [Day 7 Evening Dose]) / $AUC_{(0\text{-}\infty)}$ (Dose 1 [Day 1 Morning Dose]).

RAUC

RAUC is the accumulation ratio for AUC, which is estimated as $AUC_{(0\text{-}tau),ss}$ (Dose 14 [Day 7 Evening Dose]) / $AUC_{(0\text{-}tau)}$ (Dose 1 [Day 1 Morning Dose]) where $AUC_{(0\text{-}tau),ss}$ (Dose 14 [Day 7 Evening Dose]) and $AUC_{(0\text{-}tau)}$ (Dose 1 [Day 1 Morning Dose]) are taken from the 0-12h interval on their respective days.

RC_{max}

RC_{max} is the accumulation ratio for C_{max}, which is estimated as C_{max} (Dose 14 [Day 7 Evening Dose]) / C_{max} (Dose 1 [Day 1 Morning Dose]).

11. IMMUNOGENICITY

Not applicable.

12. OTHER ANALYSES

Not applicable.

13. REPORTING CONVENTIONS

P-values >0.001 and <0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001" The mean, standard deviation, and other statistics will be reported to 1 decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as 2 decimal places; values greater than zero but <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values greater than zero but "<1" will be presented as "<1"; values greater than 99% but less than 100% will be reported as ">99". Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

14. TECHNICAL DETAILS

SAS version 9.4 or above and R versions 3.2 or above will be used to generate tables, figures, and listings. PK parameters will be estimated through NCA using Phoenix® WinNonlin® version 8.3.4 or later.

15. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

If there are any changes to the planned analyses prior to final data lock and after finalization of the SAP, they may be added to the SAP as an addendum. The SAP will not be amended after final data lock.

Changes from Protocol v4.0:

The study did not continue enrollment after Cohort 1 (See **Section 6.2**). This SAP provides shells for an abbreviated CSR that will assess 400 mg SLV213 and placebo treatment groups from Cohort 1 only.

16. REFERENCES

1. ICH Harmonised Tripartite Guideline. Structure and Content of Clinical Study Reports E3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 1995. Retrieved from: https://database.ich.org/sites/default/files/E3_Guideline.pdf.
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5. Royal Statistical Association Guideline. Code of Conduct. The Royal Statistical Association. 2014. Retrieved from: https://rss.org.uk/RSS/media/File-library/About/2019/RSS-Code-of-Conduct-2014.pdf.

17. LISTING OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in **Appendix 1**, **Appendix 2**, and **Appendix 3**, respectively.

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

List of Tables *(continued)*

9.1 Overall Study Design and Plan Description

Table 1: Dosing and Administration

Cohort	Product Name	Dose	Route	Frequency of Administration	Duration of Treatment
1	SLV213	400 mg (4x 100 mg capsules)	Oral	Q12 hours	7 Days
	Matched Placebo	4 capsules			
2 (not enrolled)	SLV213	600 mg (6x 100 mg capsules)	Oral	Q12 hours	7 Days
	Matched Placebo	6 capsules			
3 (not enrolled)	SLV213	800 mg (8x 100 mg capsules)	Oral	Q12 hours	7 Days
	Matched Placebo	8 capsules			

Note: The study was terminated prior to enrollment to Cohorts 2 and 3

9.5.1 Immunogenicity and Safety Measurements Assessed and Flow Chart

Table 2: Schedule of Assessments

	Screening Period		In-patient at the CTU					Out-patient		
Procedures **Study Day**	**Screening** **Day -28 to Day -2**	**Check-in/ Enrollment** **Day -1**	**Randomization/ Drug Administration and Monitoring** **Day 1**	**Drug Administration and Monitoring** **Day 2- Day 6**	**Drug Administration and Monitoring** **Day 7:**	**Monitoring** **Day 8:**	**Discharge** **Day 9**	**Interim and Closeout Visits (by phone)[t]** **Days 15, 21, 28 (each ± 2 days)**	**Unscheduled visit(s)[w]**	**Early Termination**
Informed Consent[a]	x									
Demographics	x									
Eligibility confirmation[b]	x	x [b]	x [b]							
Medical History (MH)[c]	x[c]	x[c]	x[c]							
Prior and Concomitant Medication[d]	x	x	x	x	x	x	x	x	x[w]	x
Complete Physical Examination (PE)[e]	x	x					x			x
Focused PE[f]			x	x	x	x			x[w]	
Height and Weight and Body Mass Index (BMI)	x									
Body weight		x								
Vital Signs (VS)[g]	x	x	x	x	x	x	x		x[w]	x
Pregnancy Test[h]	x	x								
Follicle-stimulating hormone (FSH) in post-menopausal women[i]	x									
Urine Drug Screen (UDS) and alcohol test[j]	x	x								
Cotinine test in urine[k]	x	x								
HIV(1 and 2) and Hepatitis B and C Serology tests[l]	x									
SARS-CoV-2 (COVID-19) test[m]		x								
Blood (serum) Clinical Laboratory Assessments[n]	x	x		x		x			x[w]	x
Urinalysis (UA)[o]	x	x		x		x			x[w]	x

Table 2: Schedule of Assessments *(continued)*

	Screening Period		In-patient at the CTU					Out-patient		
Procedures **Study Day**	**Screening** **Day -28 to Day -2**	**Check-in/ Enrollment** **Day -1**	**Randomization/ Drug Administration and Monitoring** **Day 1**	**Drug Administration and Monitoring** **Day 2- Day 6**	**Drug Administration and Monitoring** **Day 7:**	**Monitoring** **Day 8:**	**Discharge** **Day 9**	**Interim and Closeout Visits (by phone)[t]** **Days 15, 21, 28 (each ± 2 days)**	**Unscheduled visit(s)[w]**	**Early Termination**
ECG[p]	x	x		x		x			x[w]	x
Enrollment / Randomization[q]		x	x							
Record time of last meal consumed before initiation of predose fasting		x	x	x	x					
Drug Administration[r]			x	x	x					
Adverse Events[s]			x	x	x	x	x	x	x[w]	x
Telephone Call[t]								x		
PK Assessments and Future tests[u]			x	x	x	x	x			x
Check patency of IV blood draw line – replace if needed			x	x	x	x	x			
Counselling[v]	x	x	x	x	x	x	x	x		X

(a) Informed consent to occur and informed consent form (ICF) signed prior to any study related procedures.
(b) Eligibility for Admission in the CTU confirmed on Day-1 after review of assessments and for Dosing on Day 1 before administration of the first dose.
(c) MH obtained at Screening and updated on Day-1 and before dosing on Day 1.
(d) Prior Medications include any medications used prior to first dose. Concomitant medications include any new medications taken only after initiation of first dose on Day 1.
(e) Complete PE includes assessments described in Protocol v4.0 Section 8.1.1. It will be completed at Screening, Check-in (Day -1) and on Day 9.
(f) Focused PE is a symptom directed PE performed as needed to assess new symptoms reported from the time of Admission on Day-1 to before the first dose, and after first dose on Day 1 to the end of the study to assess treatment-emergent AEs as needed, except on Day 9 when a complete PE is performed.
(g) VS include blood pressure (BP), heart rate (HR), respiratory rate (RR) and temperature (T) and assessed resting supine at Screening, Day-1, within 30 min before and 2 h (± 10 min) after each dose on Days 1 to 7, and once daily in the morning on Day 8 and on Day 9, or ET (See Protocol v4.0 Section 8.1.1 and Section 8.3.1). Orthostatic blood pressure and heart rate are also assessed in the standing position for 1 minute ± 15 seconds and 3 minutes ± 15 seconds. **NOTE: VS are taken before drawing blood for safety lab tests, plasma PK, and serum for future research if consented. Supine VS are taken before orthostatic BP and HR.**
(h) Serum pregnancy test at Screening and Urine pregnancy test on Day-1 (See Protocol v4.0 Section 8.1.2).
(i) FSH to confirm menopause in women with amenorrhea of 12 or more months at Screening.
(j) UDS screening for illicit drugs described in Protocol v4.0 Section 8.1.2 and urine alcohol test.
(k) Urine cotinine test for nicotine use at Screening and Day-1.
(l) HIV antibody (HIV 1 and HIV 2), Hepatitis B virus surface antigen (HBsAg) and Hepatitis C virus antibody (HCV) tests at Screening Visit (see Protocol v4.0 Section 8.1.2).
(m) SARS-CoV-2 (Covid-19) molecular diagnostic Cue Care™ test at Check-in Visit (Day-1) (see Protocol v4.0 Section 8.1.2).
(n) Clinical laboratory tests at Screening, Day-1, before the first (morning) dose on dosing Days 2, 4 and 6, and on Day 8, or ET. (See Protocol v4.0 Section 8.1.2 and Section 8.3.2).

Table 2: Schedule of Assessments *(continued)*

(o) UA by dipstick at Screening, Day-1, and on Days 4 and 8, or ET. If abnormal for blood, protein, glucose and nitrites, a microscopic UA will be done. The results of microscopic UA will supersede the results of dipstick UA. UA will be postponed in a menstruating female (See Protocol v4.0 Section 8.1.2 and Section 8.3.2).

(p) 12-lead ECGs at Screening, Day-1, before the morning dose on Day 4 and at Day 8 (before the 12h PK timepoint after evening dose on Day 7), unscheduled as indicated or ET (See Protocol v4.0 Section 8.1.1 and Section 8.3.1).

(q) Enrollment will occur on Day-1 after eligibility is confirmed. **NOTE: Randomization will occur before administration of the morning dose on Day 1.**

(r) Dose administration Q12h (±15 min) for all doses following Day 1 first dose on Day 1 to Day 7. Each dose is ingested with approximately 240 mL (8 oz) or more of tap or bottled water in the fasted state. See Protocol v4.0 Section 6.2.5 for the duration of fast and restriction of fluid intake before and after dosing. Meals to be scheduled to accommodate dosing schedule and restrictions.

(s) Treatment-emergent adverse events (TEAEs) and serious AEs (SAEs) will be reported and followed from the first dose (Day 1) to the last visit (Day 28 ± 2 days). (See Protocol v4.0 Section 8.5 for AE and SAE definition, evaluation, and reporting.). **NOTE: Monitoring for AEs starts upon ingestion of the first capsule on Day 1.**

(t) The interim and close-out outpatient visits on Day 15 (± 2 days), 21 (± 2 days) and 28 (± 2 days) may be conducted by phone to collect information about new AEs and SAEs and medication use since the previous visit. (See footnote (v) for unscheduled visits during the outpatient period)

(u) Blood will be drawn at the following timepoints to measure the concentration of study drug and analyze PK parameters (plasma PK) and, if consented, secondary future research (serum) (See Protocol v4.0 Section 8.3.4). **NOTE: Start recording time for PK collections after ingestion of the last capsule at each dose daily. Collect blood after measurement of VS and ECG recording.**

- On Day 1 MORNING DOSE: Within 30 min before the morning dose (t=0), and at 0.5h (±5 min), 1h (±5 min), 2h (±5 min), 4h (±5 min), 6h (±10 min), 8h (±10 min), and 12h (±15 min) after the morning dose. (The 12h timepoint after the morning dose on Day 1 is the same as the predose timepoint before the evening dose on Day 1).
- On Day 1 EVENING DOSE: Before the evening dose (t=0), and 12h (±15 min) after the evening dose. (The 12h timepoint after the evening dose on Day 1 is the same as the predose timepoint before the morning dose on Day 2).
- On Days 2 to 6: Within 30 min before the morning and evening doses and 12h (±15 min) after the morning and evening doses. (The PK timepoint before each dose on Days 2 to 6 is the same as the 12h timepoint of the previously received dose.).
- On Day 7 MORNING DOSE: Within 30 min before the morning dose and at 12h (±15 min) after the morning dose. (The 12h timepoint is the same as the predose timepoint before the evening dose on Day 7).
- On Day 7 EVENING DOSE: Within 30 min before the evening dose (t=0), and at 0.5h (±5 min), 1h (±5 min), 2h (±5 min), and 4h (±5 min) after the evening dose on Day 7.
- On Day 8: At 6h (±10 min), 8h (±10 min), 12h (±15 min), and 24h (±15 min) after the evening dose on Day 7.
- On Day 9: At 36h (±15 min) and 48h (-2 hours) after the evening dose on Day 7.

(v) Participant counseled to avoid prohibited lifestyle activities and prescription and non-prescription medications and use recommended contraception methods after Screening and, if enrolled and dosed, for the duration of study. Before or at discharge from the in-patient phase on Day 9, participants must be counseled to use recommended contraception and avoid pregnancy for at least 30 days after the last study dose. Male participants must be counseled to avoid donating sperm for 30 days after the last dose received in the study.

(w) An unscheduled visit to the CTU may be initiated by study staff after each outpatient follow up by phone call for evaluation of any new AEs assessed as moderate or above or SAEs or AESIs by the study PI or authorized clinician. The evaluation will consist of a history of the AE, any ConMeds taken, focused PE and, as needed, clinical laboratory tests, ECG and other tests as indicated. Any ongoing AEs after discharge from the CTU on Day 9 may also be followed with as needed assessments during unscheduled visits.

Table 3: Laboratory Samples and Estimated Total Blood Volume (mL)

Study Periods	Out-patient	In-patient	In-patient Period (Days 1 – 9)									
Study Visit	Screen	Check-in	Dosing							In-patient FU	Discharge	ET
Study Day [a]	-28 to -2	-1	1	2	3	4	5	6	7	8	9	
HEMATOLOGY [1]	4	4		4		4		4		4		4
COAGULATION [1]	2.7	2.7		2.7		2.7		2.7		2.7		2.7
CHEMISTRY [1]	8.5	8.5		8.5		8.5		8.5		8.5		8.5
Serum β-HCG and FSH [1,2]	0											
Viral Serology (HIV, HBsAg, HCV) [3]	8.5											
PK (plasma) [4]			48	12	12	12	12	12	36	24	12	6
Future research (serum)[5]			28	7	7	7	7	7	21	14	7	3.5
Total blood volume/visit	23.7	15.2	76	34.2	19	34.2	19	34.2	57	53.2	19	24.7
Cumulative total blood volume	23.7	38.9	114.9	149.1	168.1.	202.3	221.3	255.5	312.5	365.7	384.7	

[a] Study Days shown correspond to days in each study period. For a view of the cumulative numbering of study days, please refer to Protocol Section 8.1.

[1] Clinical Safety blood tests (HEM, CHEM, COAG) are drawn at Screening Visit, on Day -1, pre-dose on Days 2, 4 and 6, on Day 8, and ET if needed. The CHEM test includes serum β-HCG and FSH at Screening.

[2] Serum pregnancy test (β-HCG) in all women at Screening. FSH at Screening only in post-menopausal women.

[3] Viral serology tests are drawn at Screening.

[4] PK (plasma) samples (6 mL total blood per sample) are drawn on:

- On Day 1: MORNING DOSE: Within 30 min before the dose (t=0), and at 0.5h (±5 min), 1h (±5 min), 2h (±5 min), 4h (±5 min), 6h (±10 min), 8h (±10 min), and 12h (±15 min) after the morning dose. And EVENING DOSE: Before and 12h (±15 min) after the dose.
  - NOTE: Starting with the Evening Dose on Day 1, the timepoint before each dose is the same as the 12h timepoint after the previous dose.
- On Days 2 to 6: Within 30 min before the morning and evening doses and 12h (±15 min) after the morning and evening doses.
- On Day 7 MORNING DOSE: Within 30 min before the morning dose (t=0), and at 12h (±15 min) after the morning dose.
- On Day 7 EVENING DOSE: Within 30 min before the evening dose (t=0), and at 0.5h (±5 min), 1h (±5 min), 2h (±5 min), and 4h (±5 min) after the evening dose.
- On Day 8: At 6h (±10 min) 8h (±10 min), 12h (±15 min), and 24h (±15 min) after the evening dose on Day 7.
- On Day 9: At 36h (±15 min) and 48h (-2 hours) after the evening dose on Day 7.

[5] Future research (serum) samples (3.5 mL total blood per sample) are drawn if subject consented to their collection at the same timepoints as PK (plasma) samples from Day 1 to Day 9.

9.7.1 Sample Size

Table 4: Sample Size

Study Treatment Group	No. of Participants
400 mg SLV213	6
600 mg SLV213 (not enrolled)	6
800 mg SLV213 (not enrolled)	6
Placebo	18
Note: The sample size chosen was not based on statistical power considerations. The study was terminated prior to enrollment of 600 mg SLV213 and 800 mg SLV213 treatment groups and their associated placebo groups.	

10.2 Protocol Deviations

Table 5: Distribution of Protocol Deviations by Category, Type, and Treatment Group, Full Analysis Population

[Implementation Note: If no participants experienced the deviation type, then that row will be omitted. If there is only one deviation type within a category, then "Any type" row will be omitted. All categories should be present. If there are no deviation types within a category, then only the "Any type" row will be present for the category.]

Category	Deviation Type	400 mg SLV213 (N=X)		Placebo (N=X)	
		No. of Part.	No. of Dev.	No. of Part.	No. of Dev.
Major Deviation					
Eligibility/enrollment	Any type				
	Did not meet inclusion criterion	x	x	x	x
	Met exclusion criterion				
	ICF not signed prior to study procedures				
	Other				
Treatment administration schedule	Any type				
	Out of window visit				
	Missed visit/visit not conducted				
	Missed treatment administration				
	Delayed treatment administration				
	Other				
Follow-up visit schedule	Any type				
	Out of window visit				
	Missed visit/visit not conducted				
	Other				
Protocol procedure/assessment	Any type				
	Incorrect version of ICF signed				
	Blood not collected				
	Urine not collected				
	Stool not collected				
	Other specimen not collected				
	Too few aliquots obtained				
	Specimen result not obtained				
	Required procedure not conducted				
	Required procedure done incorrectly				

Table 5: Distribution of Protocol Deviations by Category, Type, and Treatment Group *(continued)*

Category	Deviation Type	400 mg SLV213 (N=X)		Placebo (N=X)	
		No. of Part.	No. of Dev.	No. of Part.	No. of Dev.
	Study product temperature excursion				
	Specimen temperature excursion				
	Other				
Treatment administration	Any type				
	Required procedure done incorrectly				
	Study product temperature excursion				
	Other				
Blinding policy/procedure	Any type				
	Treatment unblinded				
	Other				
[Repeat for Minor Deviations]					
Note: N = Number of participants randomized (Full Analysis Population).					

12.2.2 Displays of Adverse Events

Adverse events will be graded per FDA Guidance (https://www.fda.gov/media/73679/download) unless otherwise specified.

Table 6: Adverse Event Grading Scale

Parameter	Grade 1/Mild	Grade 2/Moderate	Grade 3/Severe	Grade 4/ Potentially Life-Threatening
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as Grade 5.

Table 7: Vital Sign Grading Scale

Parameter	Grade 1/Mild	Grade 2/Moderate	Grade 3/Severe	Grade 4/ Potentially Life-Threatening
Supine (at rest)				
Fever[1] (°C) (°F)	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.1	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia – bpm	101 – 115	116-130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia[2] – bpm, when baseline HR 60-100 bpm	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Sinus Bradycardia[2] – bpm, when baseline HR <60 bpm	45 – 49	40 – 44	<40	Life-threatening consequences, urgent intervention indicated
Hypertension (diastolic) – mmHg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypertension (systolic) – mmHg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mmHg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – BPM	17 – 20	21 – 25	> 25	Intubation

[1] Oral temperature; no recent hot or cold beverages or smoking.
[2] Use clinical judgement when characterizing bradycardia among some healthy participant populations (e.g., conditioned athletes).

Note: Isolated/individual abnormalities of VS would not be considered toward halting criteria. Abnormalities of VS will be described as "increased X" or "decreased X" (X = HR, BP, RR, temperature) if asymptomatic, transient, and not associated with a systemic or organ-specific disorder and coded by MedDRA within the System Organ Class (SOC) "Investigations." These abnormalities will be graded per criteria in this table, but not considered in determining whether study stopping criteria have been met. On the other hand, abnormalities of VS that are either secondary to systemic or organ-specific clinical syndrome or primary disorders will be coded in the appropriate SOC (e.g., "cardiac disorders", "respiratory disorders", "immunological disorders", etc.). These abnormalities will be considered in determining whether stopping criteria have been met.

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Table 8: Laboratory Adverse Event Grading Scale

Parameter	Grade 1/Mild	Grade 2/Moderate	Grade 3/Severe	Grade 4/ Potentially Life-Threatening
Chemistry				
Sodium increase – mmol/L	144 – 145	146 – 147	148 – 150	> 150
Sodium decrease – mmol/L	132 – 134	130 – 131	125 – 129	< 125
Potassium increase – mmol/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium increase – mmol/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Carbon Dioxide increase – mEq/L	32.1 – 36.0	36.1 – 40.0	> 40.0	Intervention indicated
Carbon Dioxide decrease – mEq/L	17.0 – 21.9	14.0 – 16.9	< 14.0	Metabolic acidosis Invention indicated
Calcium increase – mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Calcium decrease – mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Creatinine increase – mg/dL	1.50 – 1.79	1.80 – 2.00	2.01 – 2.50	> 2.50
BUN increase – mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Glucose (fasting) increase – mg/dL	100 - 110	111 - 125	>125	Insulin requirements or hyperosmolar coma
Glucose (fasting) decrease – mg/dL	65 – 69	55 – 64	45 – 54	< 45
Total Protein decrease – g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Albumin decrease – g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Bilirubin increase – mg/dL, when LFT[1] normal	1.5 – 2.1	2.2 – 2.7	2.8 – 4.2	> 4.2
Total Bilirubin increase – mg/dL, when LFT[1] increased	1.5 – 1.6	1.7 – 2.1	2.2 – 2.4	> 2.4
Alanine Aminotransferase (SPGT/ALT) increase – U/L, female male	44 – 100 60 – 137	101 – 200 138 – 275	201 – 400 276 – 550	> 400 > 500
Aspartate Aminotransferase (SGOT/AST) increase – U/L, female male	38 – 87 55 – 125	88 – 175 126 – 250	176 – 350 251 – 500	> 350 > 500
Alkaline Phosphatase (ALP) increase – U/L, female male	114 – 208 141 – 258	209 – 312 259 – 387	313 – 1040 388 – 1290	> 1040 > 1290
Amylase increase – U/L	110 – 150	151 – 200	201 – 500	> 500
Lipase increase – U/L	66 – 90	91 – 201	121 - 300	> 300
Magnesium decrease – mg/dL	1.30 – 1.50	1.10 – 1.29	0.90 – 1.09	< 0.90
Phosphorus (inorganic) decrease – mg/dL	2.3-2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
Hematology				
Hemoglobin decrease – g/dL, female male	11.0 – 12.0 12.5 – 13.5	9.5 – 10.9 10.5 – 12.4	8.0 – 9.4 8.5 – 10.4	< 8.0 < 8.5
Hemoglobin decrease – g/dL,	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0

Table 8: Laboratory Adverse Event Grading Scale *(continued)*

Parameter	Grade 1/Mild	Grade 2/Moderate	Grade 3/Severe	Grade 4/ Potentially Life-Threatening
change from baseline				
Platelets decrease – $x10^3/\mu L$	125 – 140	100 – 124	25 – 99	< 25
Leukocytes (WBC) increase – $x10^3/\mu L$	10.80 – 15.00	15.01 – 20.00	20.01 – 25.00	> 25.00
Leukocytes (WBC) decrease – $x10^3/\mu L$	2.50 – 3.50	1.50 – 2.49	1.00 – 1.49	< 1.00
Lymphocytes decrease – $x10^3/\mu L$	0.75 – 1.00	0.50 – 0.74	0.25 – 0.49	< 0.25
Monocytes increase – $x10^3/\mu L$	1.01 – 2.00	2.01 – 3.00	> 3.00	Intervention indicated
Basophils increase – $x10^3/\mu L$	0.16 – 0.50	0.51 – 0.80	> 0.80	Intervention indicated
Eosinophils increase – $x10^3/\mu L$	0.65 – 1.50	1.51 – 5.00	> 5.0	Hyper-eosinophilic
Neutrophils decrease – $x10^3/\mu L$	1.50 – 2.00	1.00 – 1.49	0.50 – 0.99	< 0.50
Coagulation				
Prothrombin Time – sec	11.2 – 12.3	12.4 – 13.4	13.5 – 14.0	> 14.0
Activated Partial Thromboplastin Time (aPTT) – sec	35.0 – 42.0	42.1 – 49.0	49.1 – 52.5	> 52.5
Urine Dipstick				
Nitrite	1+	2+	>2+	--
Urine Protein	Trace	1+	2+	Hospitalization or dialysis
Urine Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Urine Microscopy[2]				
White blood cells (WBC) per HPF	0 – 10	11 – 50	> 50 or gross	Hospitalization of intervention
Red blood cells (RBC) per HPF	1 – 10	11 – 50	> 50 or gross	Hospitalization or packed red blood cells (PRBC) transfusion
Bacteria (microscopic)	Few	Moderate	Many	Hospitalization or intervention

[1] Liver function tests (LFT) include ALT and AST.
[2] Urine microscopy was only performed if urine dipstick was abnormal for blood, protein, glucose, and nitrites. The results of the urine microscopy would supersede the results of the urine dipstick.

Table 9: ECG Adverse Event Grading Scale

ECG interval abnormality	Grade 1/Mild	Grade 2/Moderate	Grade 3/Severe	Grade 4/ Potentially Life-Threatening
QTcF interval prolonged (msec): • Male • Female	Asymptomatic, QTcF • 451 – 479 msec • 471 – 479 msec	Asymptomatic, QTcF 480 – 500 msec OR increase in interval 30 – 59 msec above baseline	Asymptomatic, QTcF >500 msec OR Increase in interval >60 msec above baseline	QTcF >500msec, Life threatening signs or symptoms (e.g., arrhythmia, hypotension, syncope); Torsade de pointes
PR interval prolonged (msec)	211 – 250 msec	>250 msec	Type II 2nd degree AV block OR Ventricular pause >3.0 msec	Urgent Intervention indicated

14.1 Description of Study Participants

14.1.1 Disposition of Participants

Table 10: Participant Disposition by Treatment Group, Full Analysis Population

Participant Disposition	400 mg SLV213 (N=X)		Placebo (N=X)	
	n	%	n	%
Enrolled/Randomized	x	100	x	100
Included in Safety Population (Received at least One Dose of Study Product)	x	xx	x	xx
Included in the mITT Population (Received at least One Dose of Study Product and Meet Eligibility Criteria)				
Received All Planned Doses of Study Product[a]	x	xx	x	xx
Included in the PK Population[b] (Had at least One Quantifiable Post-Dosing Plasma Concentration)				
Completed all PK Blood Draws (Study Day 1 through Study Day 9)				
Completed Follow-up (Study Day 28)[a]				

Note: A total of X participants were screened from [study start date] to [date last enrollment].
N = Number of participants randomized (Full Analysis Population); n = Number of participants meeting the disposition criteria.
[a] Refer to **Listing 2**: 16.2.1 Early Terminations or Discontinued Participants for reasons participants discontinued or terminated early.
[b] Refer to **Listing 5**: 16.2.3 Participants Excluded from Analysis for reasons participants are excluded from the analysis populations.

Table 11: Analysis Populations by Treatment Group, Full Analysis Population

[Implementation Note: Participants can be counted for more than one reason. If no participants were excluded for the given reason, then that row will be omitted. If there is only one reason within a category, then "Any reason" row will be omitted. All analysis populations should be present. If there are no reasons within an analysis population, then only the "Any reason" row will be present for the category.]

Analysis Populations	Reason Participants Excluded	400 mg SLV213 (N=X)		Placebo (N=X)	
		n	%	n	%
Safety Population	Did not receive study product	x	xx	x	xx
mITT Population	Any Reason				
	Exclusion from Safety Population				
PK Analysis Population	Any Reason				
	Exclusion from Safety Population				
	No quantifiable post-dosing plasma concentration				

Note: N = Number of participants randomized (Full Analysis Population); n = Number of participants excluded entirely from the specified analysis population for the given reason.

14.1.2 Demographic Data by Study Group

Table 12: Summary of Categorical Demographic and Baseline Characteristics by Treatment Group, Full Analysis Population

[Implementation Note: If there are no records of "Other", "Not Reported", "Decline to State", and "Unknown", then the characteristics will be omitted, respectively.]

Variable	Characteristic	400 mg SLV213 (N=X)		Placebo (N=X)	
		n	%	n	%
Sex	Male	x	xx	x	xx
	Female				
Sex Assigned at Birth	Male				
	Female				
	Intersex				
Gender Identity	Cisgender Man				
	Cisgender Woman				
	Genderqueer				
	Gender Non-binary				
	Gender Non-conforming				
	Transgender Man				
	Transgender Woman				
	Other				
	Decline to State				
Ethnicity	Not Hispanic or Latino	x	xx	x	xx
	Hispanic or Latino				
	Not Reported				
	Unknown				
Race	American Indian or Alaska Native	x	xx	x	xx
	Asian				
	Native Hawaiian or Other Pacific Islander				
	Black or African American				
	White				
	Multi-Racial				
	Unknown				
Note: N = Number of participants randomized (Full Analysis Population); n = Number of participants with the given characteristic.					

Table 13: Summary of Continuous Demographic and Baseline Characteristics by Treatment Group, Full Analysis Population

Variable	Statistic	400 mg SLV213 (N=X)	Placebo (N=X)
Age (years)	Mean (SD)	xx.x	xx.x
	Median	xx.x	xx.x
	Minimum, Maximum	xx, xx	xx, xx
Weight (kg)	Mean (SD)	xx.xx	xx.x
	Median	xx.xx	xx.x
	Minimum, Maximum	xx.x, xx.x	xx, xx
Height (cm)	Mean (SD)	xx.xx	xx.x
	Median	xx.xx	xx.x
	Minimum, Maximum	xx.x, xx.x	xx, xx
BMI (kg/m^2)	Mean (SD)	xx.xx	xx.x
	Median	xx.xx	xx.x
	Minimum, Maximum	xx.x, xx.x	xx, xx

Note: N = Number of participants randomized (Full Analysis Population).
SD = Standard Deviation.

14.2 Tolerability Data

Table 14: Tolerability by Treatment Group, Safety Population

Participants who:	**400 mg SLV213 (N=X)**		**Placebo (N=X)**	
	n	**%**	**n**	**%**
Terminated early or withdrawn due to TEAE related to study product	x	xx	xx	xx
Have at least one TEAE				
Met Grade 3 abnormal criteria at least once post-dose for				
Safety laboratory tests				
VS measurements				
Safety ECG parameters				
Completed all oral medication doses				
Note: N = Number of participants in the Safety Population; n = Number of participants meeting each tolerability category criteria.				

14.3 Pharmacokinetic Data

Table 15: Summary Statistics for SLV213 Concentrations in Plasma, 400 mg SLV213 PK Population – Day 1, Morning Dose (Single Dose)

[Implementation Note: SLV213 plasma concentrations will be summarized for Study Day 1 for 400 mg SLV213 treatment group. Nominal time points are t=0, 0.5, 1, 2, 4, 6, 8, and 12 hours post morning dose.]

Statistic	Nominal Time[a] (h)							
	0	0.5	1	2	4	6	8	12
n	x	x	x	x	x	x	x	x
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Geometric Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
CV%	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

Note: Concentrations are reported in units of ng/mL. Time points where data was not collected are denoted by "-". Time points where data was not estimable are denoted by "NE".
BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ. The first BQL value after the last PK sample concentration that is above the LLOQ is imputed as ½ LLOQ. All other BQL values are treated as missing.
n = Number of data points used to compute summary statistics.
SD = Standard Deviation; CV = Coefficient of Variance.
[a] Times are relative to time of dosing. Time 0 concentrations are drawn within 30 minutes prior to dosing.

Tables with similar format:

Table 16: Summary Statistics for SLV213 Concentrations in Plasma by Sex, 400 mg SLV213 PK Population – Day 1, Morning Dose (Single Dose)

[Implementation Note: Row headers will be included labeled as "Male" and "Female".]

Table 17: Summary Statistics for SLV213 Concentrations in Plasma by Time Point and Dose, 400 mg SLV213 PK Population – Day 1, Evening Dose to Day 7, Morning Dose

[Implementation Note: SLV213 plasma concentrations will be summarized for each study day from Day 1 (evening dose) to Day 7 (morning dose) for 400 mg SLV213 treatment group, and each dosing period (morning and evening). Nominal time points are t=0 and 12 hours post morning dose and evening dose. The 12-hour time point is the same as the pre-dose time point of the previously received dose. Thus only t=12 hours will be shown for each dose except for Day 1 (evening dose), which will also show t=0 hours.]

Time Point	Dose[a]	Statistic	400 mg SLV213 (N=X)
Day 1	Evening (0 h)	n	x
		Mean (SD)	xx.x (xx.x)
		Geometric Mean	xx.x
		CV%	xx.x
		Median	xx.x
		Minimum, Maximum	xx, xx
	Evening (12 h)	n	
	…	…	
Day 2	Morning (12 h)	n	x
		Mean (SD)	xx.x (xx.x)
		CV%	xx.x
		Median	xx.x
		Minimum, Maximum	xx, xx
	Evening (12 h)	n	x
		…	
Day 3	Morning (12 h)	n	
…	…	…	
Day 7	Morning (12 h)	n	
		…	

Note: Concentrations are reported in units of ng/mL. Time points where data was not collected are denoted by "-". Time points where data was not estimable are denoted by "NE".
BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ. The first BQL value after the last PK sample concentration that is above the LLOQ is imputed as ½ LLOQ. All other BQL values are treated as missing.
n = Number of data points used to compute summary statistics.
SD = Standard Deviation; CV = Coefficient of Variance.

[a] Times are relative to time of dosing. Time 0 concentrations are drawn within 30 minutes prior to dosing. The 12-hour time point is the same as the pre-dose time point of the next received dose.

Tables with similar format:

Table 18: Summary Statistics for SLV213 Concentrations in Plasma by Sex, Time Point, and Dose, 400 mg SLV213 PK Population – Day 1, Evening Dose to Day 7, Morning Dose

[Implementation Note: Row headers will be included labeled as “Male” and “Female”.]

Table 19: Summary Statistics for SLV213 Concentrations in Plasma, 400 mg SLV213 PK Population – Day 7, Evening Dose to Day 9 (Multiple Doses)

[Implementation Note: SLV213 plasma concentrations will be summarized for Study Day 7 (evening dose) for 400 mg SLV213 treatment group. Nominal time points are t=0, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, and 48 hours post evening dose.]

Statistic	Nominal Time[a] (h)									
	0	**0.5**	**1**	**2**	**4**	**6**	**12**	**24**	**36**	**48**
n	x	x	x	x	x	x	x	x	x	x
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
SD	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
CV%	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
n										
…										
n										
…										

Note: Concentrations are reported in units of ng/mL. Time points where data was not collected are denoted by "-". Time points where data was not estimable are denoted by "NE". BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ.
The first BQL value after the last PK sample concentration that is above the LLOQ is imputed as ½ LLOQ. All other BQL values are treated as missing.
n = Number of data points used to compute summary statistics.
SD = Standard Deviation; CV = Coefficient of Variance.

[a] Times are relative to time of dosing. Time 0 concentrations are drawn within 30 minutes prior to dosing.

Tables with similar format:

Table 20: Summary Statistics for SLV213 Concentrations in Plasma by Sex, 400 mg SLV213 PK Population – Day 7, Evening Dose to Day 9 (Multiple Doses)

[Implementation Note: Row headers will be included labeled as "Male" and "Female".]

Table 21: Summary Statistics for SLV213 PK Parameters by Dose, 400 mg SLV213 PK Population

[Implementation Note: PK parameters will only be summarized for participants with a measurable Ke at the specified dosing day.]

PK Parameter (Units)	N	Mean (SD)	GM (CV%)	Median	Minimum, Maximum
Day 1, Single Dose					
C_{max} (ng/mL)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
C_{max}/Dose (ng/mL/mg)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
C_{min} (ng/mL)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
T_{max} (h)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
$AUC_{(0-t)}$ (ng*h/mL)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
$AUC_{(0-\infty)}$ (ng*h/mL)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
$AUC_{(0-12)}$ (ng*h/mL)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
$AUC_{(0-last)}$ (ng*h/mL)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
$AUC_{(0-tau)}$ (ng*h/mL)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
$AUC_{(0-tau)}$/Dose (ng*h/mL/mg)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
$t_{1/2}$ (h)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
CL_T (L/h)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
Ke (1/h)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
Vd (L)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
Day 7, Multiple Doses					
$C_{max,ss}$ (ng/mL)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
C_{max}/Dose (ng/mL/mg)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
$C_{min,ss}$ (ng/mL)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
C_{avg} (ng/mL)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
RC_{max}[a]	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
$T_{max,ss}$ (h)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
T_{min} (h)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
$AUC_{(0-48),ss}$ (ng*h/mL)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
$AUC_{(0-tau),ss}$ (ng*h/mL)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
$AUC_{(0-tau)}$/Dose (ng*h/mL/mg)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
Linearity Index[b]	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx

PK Parameter (Units)	N	Mean (SD)	GM (CV%)	Median	Minimum, Maximum
RAUC[c]	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
$t_{1/2}$ (h)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
CL_T (L/h)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx
Vd,ss (L)	x	xx.x (xx.x)	xx.x (xx.x)	xx.x	xx, xx

Note: Single-dose parameters are calculated over the 12-hour period following the morning dose (Dose 1) on Day 1. Multiple-dose parameters are calculated over the 48-hour period following the evening dose (Dose 14) on Day 7.
N = Number of participants with an estimable Ke for the given dose used to calculate summary statistics.
SD = Standard Deviation; GM = Geometric Mean; CV = Coefficient of Variance.
[a] RC_{max} is defined as the accumulation ratio for C_{max} estimated as C_{max} (Day 7, Evening Dose)/C_{max} (Day 1, Morning Dose).
[b] Linearity index is estimated as $AUC_{(0\text{-}tau),ss}$ (Day 7, Evening Dose)/$AUC_{(0\text{-}\infty)}$ (Day 1, Morning Dose)
[c] RAUC is defined as the accumulation ratio for AUC estimated as $AUC_{(0\text{-}tau)}$ (Day 7)/$AUC_{(0\text{-}tau)}$ (Day 1).

14.4 Safety Data

14.4.1 Displays of Adverse Events

Table 22: Overall Summary of Adverse Events, Safety Population

[Implementation Note: An "adverse event" includes laboratory AEs, ECG AEs, TEAEs, and other unsolicited AEs.]

	400 mg SLV213 (N=X)		Placebo (N=X)		All Participants (N=X)	
Participants[a] with	n	%	n	%	n	%
At least one adverse event	x	xx	x	xx	x	xx
At least one related adverse event	x	xx	x	xx	x	xx
Mild (Grade 1)	x	xx	x	xx	x	xx
Moderate (Grade 2)	x	xx	x	xx	x	xx
Severe (Grade 3)	x	xx	x	xx	x	xx
At least one severe (Grade 3) adverse event	x	xx	x	xx	x	xx
Related	x	xx	x	xx	x	xx
Unrelated	x	xx	x	xx	x	xx
At least one serious adverse event[b]	x	xx	x	xx	x	xx
At least one related, serious adverse event	x	xx	x	xx	x	xx
At least one adverse event leading to early termination[c]	x	xx	x	xx	x	xx
At least one adverse event of special interest						
At least one medically attended adverse event	x	xx	x	xx	x	xx
At least one unanticipated problem						

Note: N = Number of participants in the Safety Population.
[a] Participants are counted once for each category regardless of the number of events.
[b] Refer to Listing of Serious Adverse Events.
[c] As reported on the Adverse Event eCRF.

Table 23: Serious Adverse Events and Adverse Events by MedDRA System Organ Class and Preferred Term, and Treatment Group, Safety Population

[Implementation Note: If there is only one PT within a given SOC, then "Any PT" row will be omitted. An "adverse event" includes laboratory AEs, ECG AEs, TEAEs, and other unsolicited AEs. Serious adverse events will be displayed regardless of percentage of participants.]

MedDRA System Organ Class	MedDRA Preferred Term	400 mg SLV213 (N=X)			Placebo (N=X)			All Participants (N=X)		
		n	%	Events	n	%	Events	n	%	Events
Serious Adverse Events										
Any SOC	Any PT	x	xx	x	x	xx	x	x	xx	x
[SOC 1]	Any SOC	x	xx	x	x	xx	x	x	xx	x
	[PT 1]	x	xx	x	x	xx	x	x	xx	x
	[PT 2]	x	xx	x	x	xx	x	x	xx	x
	…									
[SOC 2]	Any SOC	x	xx	x	x	xx	x	x	xx	x
	[PT 1]	x	xx	x	x	xx	x	x	xx	x
…	…	x	xx	x	x	xx	x	x	xx	x
[Repeat for Other (non-serious) Adverse Events]										

Note: N = Number of participants in the Safety Population (number of participants at risk).
n = Number of participants reporting event.
Events = Total frequency of events reported.

14.3.1.2 Treatment-Emergent Adverse Events

Table 24: Summary of Treatment Emergent Adverse Events by MedDRA System Organ Class, High Level Group Term, Preferred Term, and Treatment Group, Safety Population

[Implementation Note: If there is only one PT within a given SOC and HLGT, then "Any PT" row will be omitted. Similarly, if there is only one HLGT within a given SOC, then "Any HLGT" row will be omitted.]

Treatment Group	MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	n (%)	95% CI[a]	Number of Events
400 mg SLV213 (N=X)	Any SOC	Any HLGT	Any PT	x (xx)	xx, xx	x
	[SOC 1]	Any HLGT	Any PT	x (xx)	xx, xx	x
		[HLGT 1]	Any PT	x (xx)	xx, xx	x
			[PT 1]	x (xx)	xx, xx	x
	[SOC 2]	Any HLGT	Any PT	x (xx)	xx, xx	x
		[HLGT 1]	Any PT	x (xx)	xx, xx	x
			[PT 1]	x (xx)	xx, xx	x
Placebo (N=X)	…	…	…	x (xx)	xx, xx	x
	…	…	…	x (xx)	xx, xx	x
All Participants (N=X)	…	…	…	x (xx)	xx, xx	x
	…	…	…	x (xx)	xx, xx	x

Note: N = Number of participants in the Safety Population in the specified treatment group.
n = Number of participants reporting adverse events within each SOC/HLGT/PT.
A participant is only counted once per PT.
[a] Exact Clopper-Pearson Confidence Interval.

Table 25: Treatment Emergent Adverse Events by MedDRA System Organ Class, High Level Group Term, Preferred Term, Maximum Severity, Relationship, and Treatment Group, Safety Population

[Implementation Note: If there is only one PT within a given SOC and HLGT, then "Any PT" row will be omitted. Similarly, if there is only one HLGT within a given SOC, then "Any HLGT" row will be omitted. Life-threatening severity will only be included as applicable. The highest severity for each relationship status will be reported, e.g., a participant may be counted for Mild Related and Severe Not Related for the same PT.]

Treatment Group	MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term	Severity	Relationship to Study Treatment	
					Related n (%)	Not Related n (%)
400 mg SLV213 (N=X)	Any SOC	Any HLGT	Any PT	Any Severity	x (xx)	x (xx)
				Mild	x (xx)	x (xx)
				Moderate	x (xx)	x (xx)
				Severe	x (xx)	x (xx)
				Life-Threatening	x (xx)	x (xx)
	[SOC 1]	Any HLGT	Any PT	Any Severity	x (xx)	x (xx)
				…	x (xx)	x (xx)
		[HLGT 1]	Any PT	Any Severity	x (xx)	x (xx)
				…	x (xx)	x (xx)
			[PT 1]	Any Severity	x (xx)	x (xx)
				…	x (xx)	x (xx)
Placebo (N=X)	…	…	…		x (xx)	x (xx)
	…	…	…		x (xx)	x (xx)
All Participants (N=X)	…	…	…		x (xx)	x (xx)
	…	…	…		x (xx)	x (xx)

Note: N = Number of participants in the Safety Population in the specified treatment group.
n = Number of participants reporting adverse events within each SOC/HLGT/PT with the specified maximum severity.
A participant is only counted once per PT. A participant highest reported severity for each relationship to study treatment is reported.

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 26: Listing of Serious Adverse Events

[Implementation Note: If the event is ongoing (i.e., no stop date), indicate "ongoing" for "Duration". If there are no comments, then indicate "None" for "Comments". Listing should be sorted by Treatment Group, Participant ID, and AE Number.]

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	No. of Days Post Dose the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term
Treatment Group: , Participant ID: , AE Number:													
Comments:													
Treatment Group: , Participant ID: , AE Number:													
Comments:													

Table 27: Listing of Non-Serious, Unsolicited, Moderate or Greater Severity Adverse Events

[Implementation Note: If the event is ongoing (i.e., no stop date), indicate "ongoing" for "Duration". If there are no comments, then indicate "None" for "Comments". Listing should be sorted by Treatment Group, Participant ID, and AE Number.]

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term
Treatment Group: , Participant ID: , AE Number:											
Comments:											
Treatment Group: , Participant ID: , AE Number:											
Comments:											

Table 28: Listing of Adverse Events of Special Interest, Medically Attended Adverse Events, and Unanticipated Problems

[Implementation Note: This table is for any AESIs, MAAEs, and UPs. If the event is ongoing (i.e., no stop date), indicate "ongoing" for "Duration of Event". If there are no comments, then indicate "None" for "Comments". Listing should be sorted by Treatment Group, Participant ID, and AE Number.]

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose	Duration of Event	Severity	MedDRA System Organ Class	AESI?	MAAE?	UP?	Relationship	Outcome
Treatment Group: , Participant ID: , AE Number:										
Comments:										
Treatment Group: , Participant ID: , AE Number:										
Comments:										

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

(not included in SAP, but this is a placeholder for the CSR)

14.3.4 Abnormal Laboratory Value Listings (by Participant)

Table 29: Listing of Abnormal Laboratory Results – Chemistry

[Implementation Note: This listing is for any chemistry lab result outside of normal range, including ONRs and graded events. Listing will be sorted by Treatment Group, Participant ID, Laboratory Parameter, and Planned Time Point. Refer to **Section 9.6** for parameter sort order.]

Treatment Group	Participant ID	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Participant Discontinued Due to Result?

Table 30: Listing of Abnormal Laboratory Results – Hematology

[Implementation Note: This listing is for any hematology lab result outside of normal range, including ONRs and graded events. Listing will be sorted by Treatment Group, Participant ID, Laboratory Parameter, and Planned Time Point. Refer to **Section 9.6** for parameter sort order.]

Treatment Group	Participant ID	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Participant Discontinued Due to Result?

Table 31: Listing of Abnormal Laboratory Results – Coagulation

[Implementation Note: This listing is for any coagulation lab result outside of normal range, including ONRs and graded events. Listing will be sorted by Treatment Group, Participant ID, Laboratory Parameter, and Planned Time Point. Refer to **Section 9.6** for parameter sort order.]

Treatment Group	Participant ID	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Participant Discontinued Due to Result?

Table 32: Listing of Abnormal Laboratory Results – Urinalysis

[Implementation Note: This listing is for any urinalysis lab result outside of normal range, including ONRs and graded events. Listing will be sorted by Treatment Group, Participant ID, Laboratory Parameter, and Planned Time Point. Refer to **Section 9.6** for parameter sort order.]

Treatment Group	Participant ID	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Participant Discontinued Due to Result?

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 33: Chemistry Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group, Safety Population

[Implementation Note: Chemistry results will be presented for Check-In (Day -1)(baseline), 2, 4, 6, and 8 and for each treatment group.

If there are no life-threatening/grade 4 chemistry results reported, then the rows will be omitted. If there is not at least one graded event for a treatment group within a parameter, then only "None" row will be shown. If there are more than one graded event within a parameter for a specified time point, then report the maximum severity.

If the grade is zero counts, then populate the cell with "-".

Parameters will be shown in the following order: Any Chemistry Parameter, Sodium, Potassium, Total Carbon Dioxide, Calcium, Creatinine, Blood Urea Nitrogen, Fasting Glucose, Total Protein, Albumin, Total Bilirubin, Alanine Aminotransferase, Aspartate Aminotransferase, Alkaline Phosphatase, Amylase, Lipase, Magnesium, and Inorganic Phosphorus.

Parameters will specify increase or decrease. If a parameter can both increase and decrease, then the parameter decrease will be listed first.

The following parameters may decrease: Sodium, Potassium, Total Carbon Dioxide, Calcium, Total Protein, Albumin, Magnesium, and Inorganic Phosphorus.

The following parameters may increase: Sodium, Potassium, Total Carbon Dioxide, Calcium, Creatinine, Blood Urea Nitrogen, Fasting Glucose, Total Bilirubin, Alanine Aminotransferase, Aspartate Aminotransferase, Alkaline Phosphatase, Amylase, and Lipase.]

Severity	Treatment Group	Day -1 (Baseline)		Day 2		Day 4		Day 6		Day 8		Any Time Post Baseline	
		n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Any Chemistry Parameter													
None	400 mg SLV213	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
	Placebo												
	All Participants												
Mild	400 mg SLV213												
…	…												

Table 33: Chemistry Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group, Safety Population *(continued)*

Severity	Treatment Group	Day -1 (Baseline)		Day 2		Day 4		Day 6		Day 8		Any Time Post Baseline	
		n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Moderate	400 mg SLV213												
	…												
Severe	400 mg SLV213												
	…												
Life-Threatening	400 mg SLV213	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	…												
Sodium, Decrease													
None	400 mg SLV213												
…	…												
Mild	400 mg SLV213												
	…												
Moderate	400 mg SLV213	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	…												
Severe	400 mg SLV213												
	…												
Life-Threatening	400 mg SLV213												
	…												

Table 33: Chemistry Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group, Safety Population *(continued)*

Severity	Treatment Group	Day -1 (Baseline)		Day 2		Day 4		Day 6		Day 8		Any Time Post Baseline	
		n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Sodium, Increase													
None	400 mg SLV213												
…	…												
[Repeat for each chemistry parameter]													

Note: The "Any Time Post Baseline" column indicates the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. Abnormal laboratory events were only considered an adverse event if the graded severity worsened from baseline.

N = Number of participants in the Safety Population with the laboratory result assessed at the respective time point; n = Number of participants with the maximum grade experienced for the specified parameter and time point.

14.3.5.2 Hematology Results

Table 34: Hematology Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group, Safety Population

[Implementation Note: This table will be a similar format to **Table 33**.

Parameters will be shown in the following order: Any Hematology Parameter, Hemoglobin, Platelets, White Blood Cells, Neutrophils, Lymphocytes, Monocytes, Basophils, and Eosinophils.

The following parameters may decrease: Hemoglobin, Platelets, White Blood Cells, Neutrophils, and Lymphocytes.

The following parameters may increase: Hemoglobin, White Blood Cells, Monocytes, Basophils, and Eosinophils.]

14.3.5.2 Coagulation Results

Table 35: Coagulation Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group, Safety Population

[Implementation Note: This table will be a similar format to **Table 33**.

Parameters will be shown in the following order: Any Coagulation Parameter, Prothrombin Time, and Activated Partial Thromboplastin Time (aPTT).]

14.3.5.3 Urinalysis Results

Table 36: Urinalysis Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group, Safety Population

[Implementation Note: This table will be a similar format to **Table 33**. Urinalysis will be presented for Days -1 (baseline), 4, and 8 and for each treatment group. Headers will not be split into Low and High, e.g., "Mild/Grade 1".

Parameters will be shown in the following order: Any Urinalysis Parameter, Bilirubin, Nitrite, Urine Protein, Urine Glucose, White Blood Cell Count, Red Blood Cell Count, and Bacteria.

Urine microscopy parameters (WBC Count, RBC Count, and Bacteria) were only collected conditionally and thus will only be included if at least 5 participants reported a graded event. Otherwise refer to **Table 32**.]

14.3.6 Displays of Vital Signs

Table 37: Supine Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group, Safety Population

[Implementation Note: Vital signs will be presented for Days 1 (pre-dose 1)(baseline) through Day 9 for each treatment group. Dosing days (Days 1 through 7) will be separated by pre- and post- Morning and Evening dose. Follow-up assessments and Maximum Post Baseline will be Any Time.

If there are no life-threatening/grade 4 vital signs reported, then the columns will be omitted. If there is not at least one graded event for a treatment group within a parameter, then only "Max Severity Post Baseline" will be shown. If there are more than one graded event within a parameter for a specified time point, then report the maximum severity.

For grading not applicable to the specified parameter, then populate the cell with "N/A". Otherwise, if the grade is zero counts, then populate the cell with "-". Assessments will be shown in the following order: Any Vital Sign Assessment, Oral Temperature, Systolic Blood Pressure, Diastolic Blood Pressure, Pulse, and Respiratory Rate.

Assessments will specify low or high. If an assessment can be both high and low, then the low assessment will be listed first.

The following assessments may be low: Systolic Blood Pressure, Diastolic Blood Pressure, and Pulse.

All assessments may be high.]

Time Point	Dose	Treatment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life-Threatening/ Grade 4	
				n	%	n	%	n	%	n	%	n	%
Any Vital Sign Assessment													
Day 1	Pre-Morning (Baseline)	400 mg SLV213	x	x	xx	x	xx	x	xx	x	xx	x	xx
		Placebo											
		All Participants											
	Post-Morning	400 mg SLV213											
		…											
	Pre-Evening	400 mg SLV213											
		…											
	Post-Evening	400 mg SLV213											
		…											

Table 37: Supine Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group, Safety Population *(continued)*

Time Point	Dose	Treatment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life-Threatening/ Grade 4	
				n	%	n	%	n	%	n	%	n	%
Day 2	Pre-Morning	400 mg SLV213											
		…											
	Post-Morning	400 mg SLV213											
		…											
	Pre-Evening	400 mg SLV213											
		…											
	Post-Evening	400 mg SLV213											
		…											
…	…	…											
Day 8	N/A	400 mg SLV213											
		…											
Day 9	N/A	400 mg SLV213											
		…											
Max Severity Post Baseline	Any Time	400 mg SLV213											
		…											
Oral Temperature													
Day 1	Pre-Morning (Baseline)	400 mg SLV213	x	x	xx	x	xx	x	xx	x	xx	x	xx
	…	…											
Day 9	N/A	400 mg SLV213											
		…											

Table 37: Supine Vital Signs by Assessment, Maximum Severity, Time Point, and Treatment Group, Safety Population *(continued)*

Time Point	Dose	Treatment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life-Threatening/ Grade 4	
				n	%	n	%	n	%	n	%	n	%
Max Severity Post Baseline	Any Time	400 mg SLV213											
		…											
Systolic Blood Pressure, Low													
Day 1	Pre-Morning (Baseline)	400 mg SLV213	x	x	xx	x	xx	x	xx	x	xx	x	xx
	…	…											
Day 9	N/A	400 mg SLV213											
		…											
Max Severity Post Baseline	Any Time	400 mg SLV213											
		…											
[Repeat for all vital sign assessments]													

Note: The "Max Severity Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments.
N = Number of participants in the Safety Population with the laboratory result assessed at the respective time point; n = Number of participants with the maximum grade experienced for the specified assessment and time point.
Vital signs were collected prior to and after each dose (morning and evening) on Days 1 through Day 9 and collected in the morning during follow-up visits (Day 8 and Day 9).

14.3.7 Displays of 12-Lead Standard Electrocardiograms

Table 38: Summary of Post Dose Electrocardiograms Change in Overall Interpretations from Baseline by Treatment Group and Time Point, Safety Population

Change from Baseline in ECG Interpretation	400 mg SLV213 (N=X)		Placebo (N=X)		All Participants (N=X)	
	n	%	n	%	n	%
Day 4						
Normal at Both Times	x	xx	x	xx	x	xx
Normal to Abnormal, NCS						
Normal to Abnormal, CS						
Day 8						
Normal at Both Times	x	xx	x	xx	x	xx
Normal to Abnormal, NCS						
Normal to Abnormal, CS						

Note: N = Number of participants in the Safety Population with ECG measurements; n = Number of participants with the change from baseline interpretations.

NCS = Not clinically significant; CS = Clinically significant.

Table 39: ECG Results by Parameter, Severity, Treatment Group, and Time Point, Safety Population

[Implementation Note: ECGs will be presented for Days -1 (baseline), 4, and 8 for each treatment group.

If there are no life-threatening/grade 4 vital signs reported, then the columns will be omitted. If there is not at least one graded event for a treatment group within a parameter, then only "Max Severity Post Baseline" will be shown. If there are more than one graded event within a parameter for a specified time point, then report the maximum severity.

Parameters will be shown in the following order: Any ECG Parameter, PR Interval, and QTcF Interval.]

Time Point	Treatment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life-Threatening/ Grade 4	
			n	%	n	%	n	%	n	%	n	%
Any ECG Parameter												
Day -1 (Baseline)	400 mg SLV213	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo											
	All Participants											
Day 4	400 mg SLV213											
	…											
Day 8	400 mg SLV213											
	…											
Max Severity Post Baseline	400 mg SLV213											
	…											
PR Interval												
Day -1 (Baseline)	400 mg SLV213	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Placebo											
	All Participants											
Day 4	400 mg SLV213											
	…											

Table 39: ECG Results by Parameter, Severity, Treatment Group, and Time Point, Safety Population *(continued)*

Time Point	Treatment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Life-Threatening/ Grade 4	
			n	%	n	%	n	%	n	%	n	%
Day 8	400 mg SLV213											
	…											
Max Severity Post Baseline	400 mg SLV213											
	…											
QTcF Interval												
Day -1 (Baseline)	400 mg SLV213	x	x	xx	x	xx	x	xx	x	xx	x	xx
	…											
Day 4	400 mg SLV213											
	…											
Day 8	400 mg SLV213											
	…											
Max Severity Post Baseline	400 mg SLV213											
	…											

Note: The “Max Post Baseline” rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments.
N = Number of participants in the Safety Population with the laboratory result assessed at the respective time point; n = Number of participants with the maximum grade experienced for the specified parameter and time point.

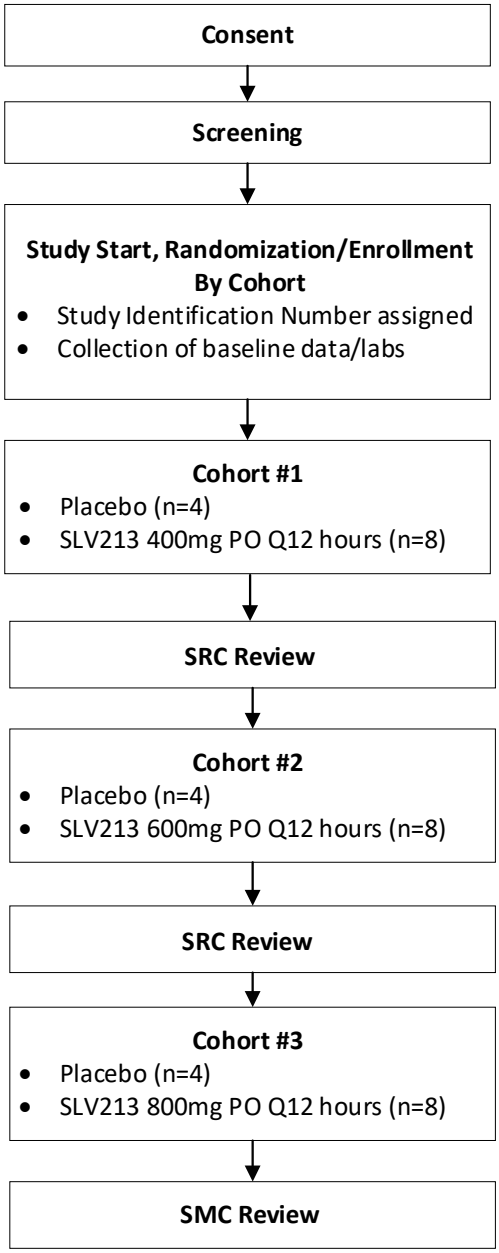
APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

9.5.1 Safety Measurements Assessed and Flow Chart

Figure 1: Schematic of Study Design

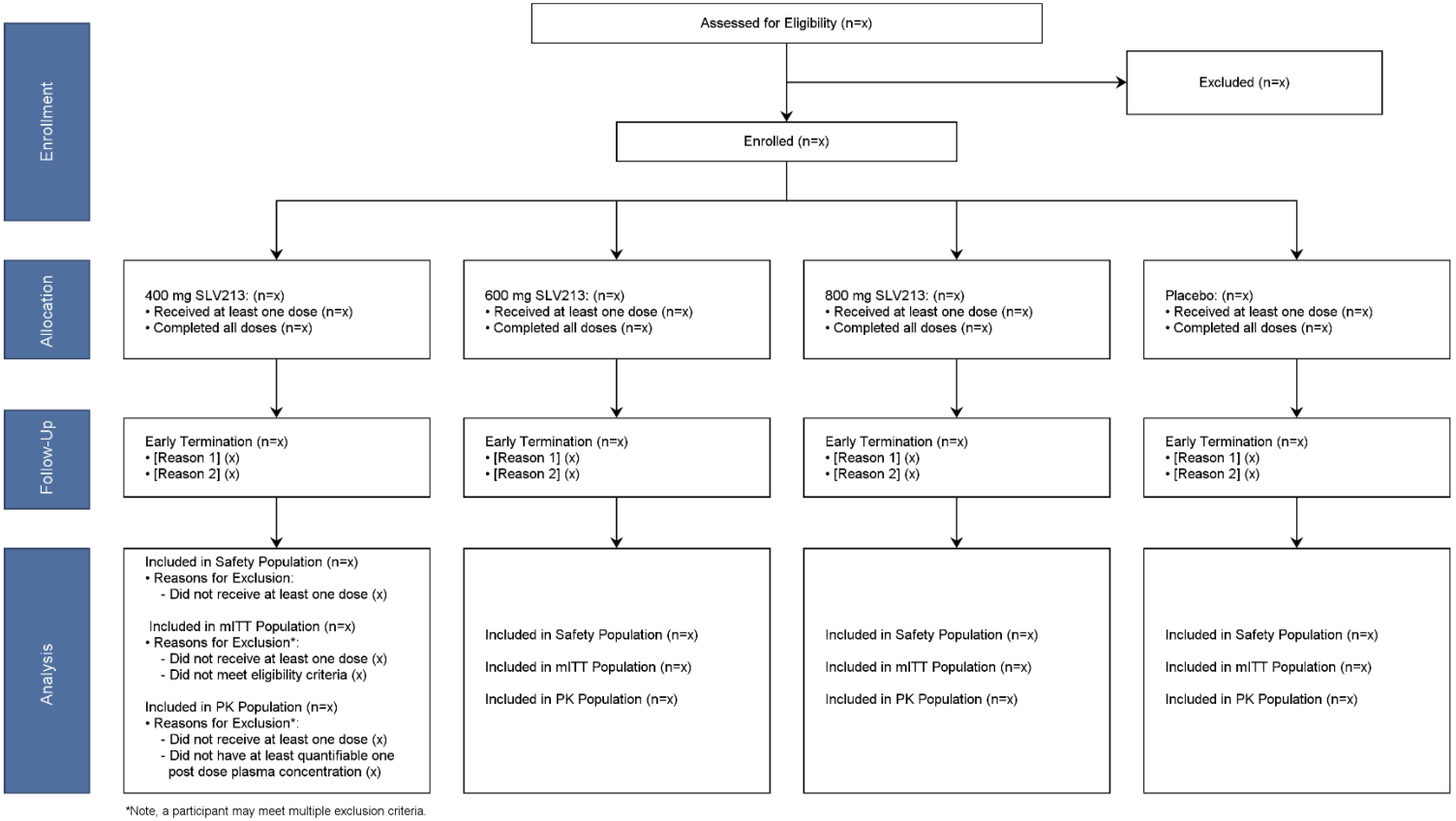
[Implementation Note: Pulled from Protocol v4.0 Section 1.3.]



10.1 Disposition of Participants

Figure 2: CONSORT Flow Diagram

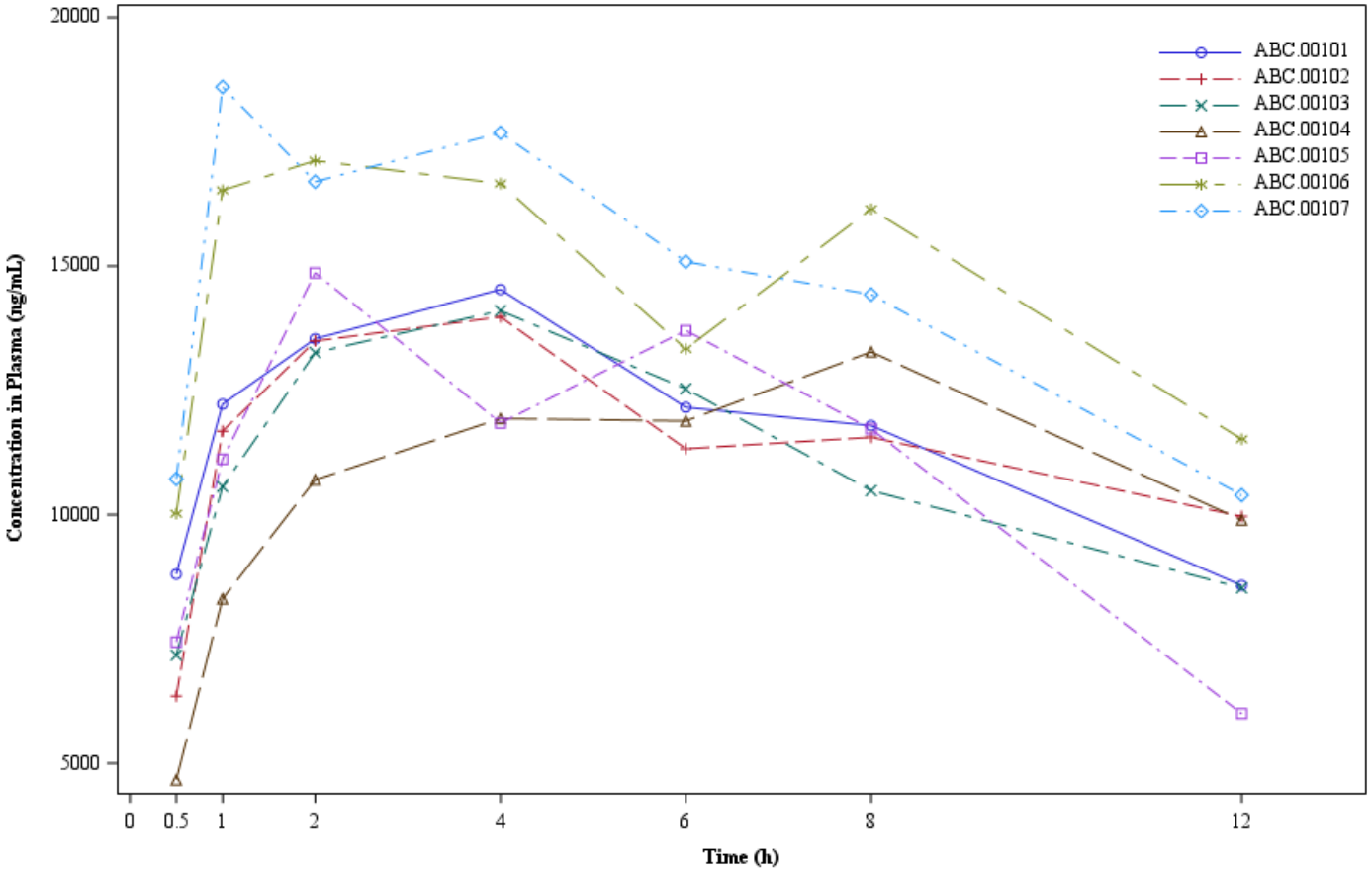
[Implementation Note: Treatment groups will be 400 mg SLV213 and Placebo. "Reasons for Exclusion" and the associated footnote will only be listed if at least one participant was excluded from the specified population for the specified reason in the given treatment group. 'x' will be replaced with the number of participants that meet the criteria. If any participants received the incorrect dose at any point in time, a footnote will be attached to "Completed all doses[a]" of the given treatment group and the following footnote will be added: "[a] X participants received at least one incorrect dose." The asterisks will be updated to footnote (b), if applicable. A footnote will be added before footnotes (a) and (b): "Note: The study was terminated prior to enrollment to Cohorts 2 (600 mg SLV213) and 3 (800 mg SLV213)."]



14.2.2 Pharmacokinetics

Figure 3: Individual SLV213 Concentration in Plasma Profiles – Day 1, Morning Dose

[Implementation Note: The figure will consist of individual concentrations at each nominal time point: t=0 (pre-dose), 1h, 2h, 4h, 6h, 8h, and 12h. The y-axis will be labeled "Concentration in Plasma (ng/mL)" with the maximum concentration as the max and the minimum concentration as the min. The x-axis will be labeled "Time (h)" with tick marks at each nominal time point. Data points should represent actual time of collection.]



Figures with similar format:

Figure 4: Individual SLV213 Concentration in Plasma Profiles – Day 7, Evening Dose

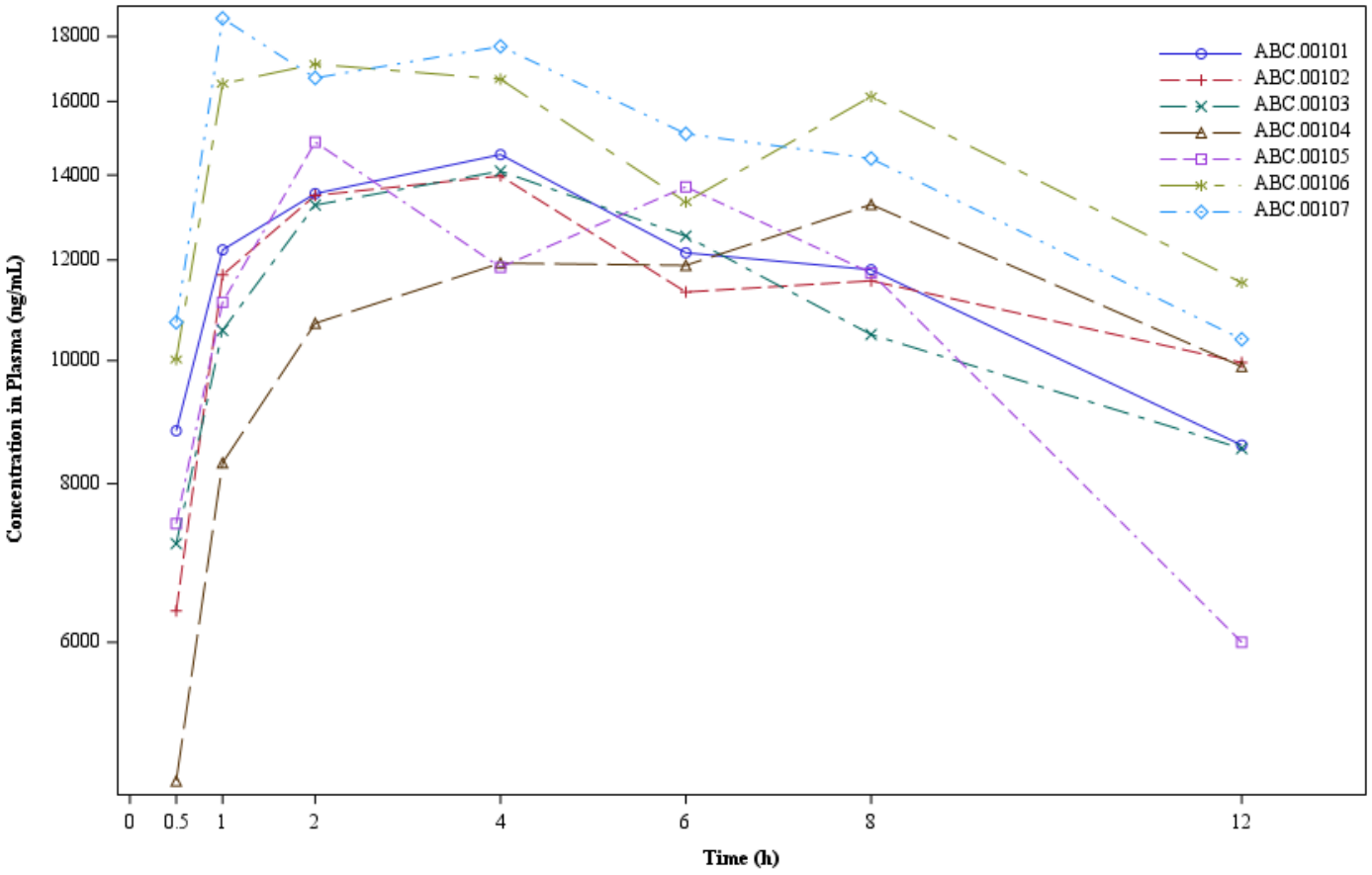
[Implementation Note: Dose 14 nominal time points are t=0 (pre-dose), 1h, 2h, 4h, 6h, 8h, 12h, 24h, 36h, and 48h.]

Figure 5: Individual Trough SLV213 Concentration in Plasma Profiles – Day 1 to Day 7, All Doses

[Implementation Note: Trough concentrations are defined as concentrations collected 12 hours after each morning and evening dose. Note, 12 hours post dose will also be considered as t=0 (pre-dose) for the proceeding dose. The x-axis label will be "Doses" with a tick mark for each dose number.]

Figure 6: Semi-Log Individual SLV213 Concentration in Plasma Profiles – Day 1, Morning Dose

[Implementation Note: The figure will consist of individual concentrations at each nominal time point: t=0 (pre-dose), 1h, 2h, 4h, 6h, 8h, and 12h. The y-axis will be in the log-10 scale and labeled "Concentration in Plasma (ng/mL)" with the maximum concentration as the max and the minimum concentration as the min. The x-axis will be labeled "Time (h)" with tick marks at each nominal time point. Data points should represent actual time of collection.]



Figures with similar format:

Figure 7: Semi-Log Individual SLV213 Concentration in Plasma Profiles – Day 7, Evening Dose

[Implementation Note: Dose 14 nominal time points are t=0 (pre-dose), 1h, 2h, 4h, 6h, 8h, 12h, 24h, 36h, and 48h.]

Figure 8: Semi-Log Trough SLV213 Concentration in Plasma Profiles – Day 1 to Day 7, All Doses

[Implementation Note: Trough concentrations are defined as concentrations collected 12 hours after each morning and evening dose. Note, 12 hours post dose will also be considered as t=0 (pre-dose) for the proceeding dose. The x-axis label will be "Doses" with a tick mark for each dose number.]

14.3.1.2 Unsolicited Adverse Events

Figure 9: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity

[Implementation Note: This figure will include serious and non-serious unsolicited adverse events deemed related to the study product. It will be paneled by treatment group: 400 mg SLV213 and Placebo. The SOCs will be sorted by descending frequency with "Any SOC" at the top.]

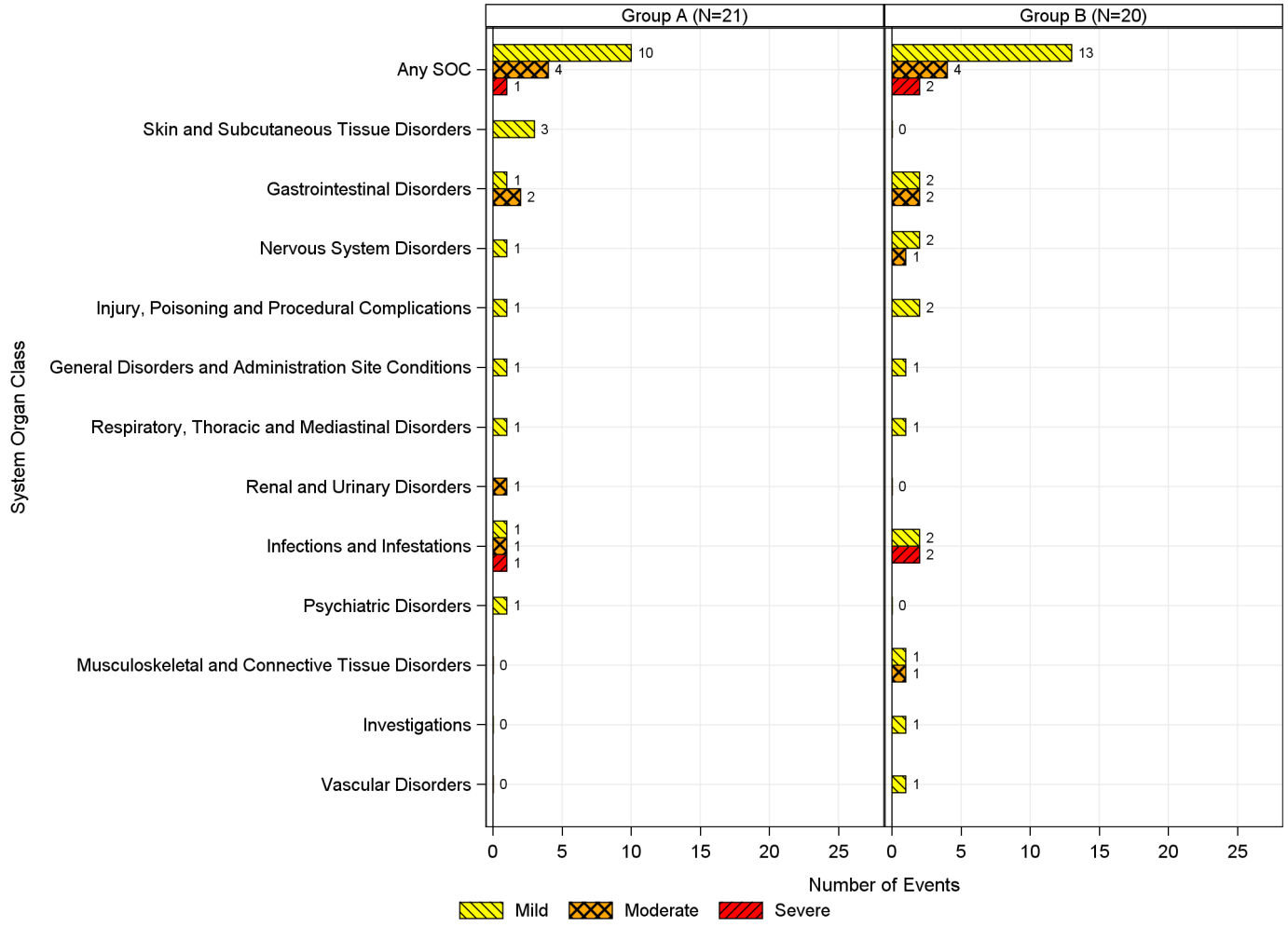
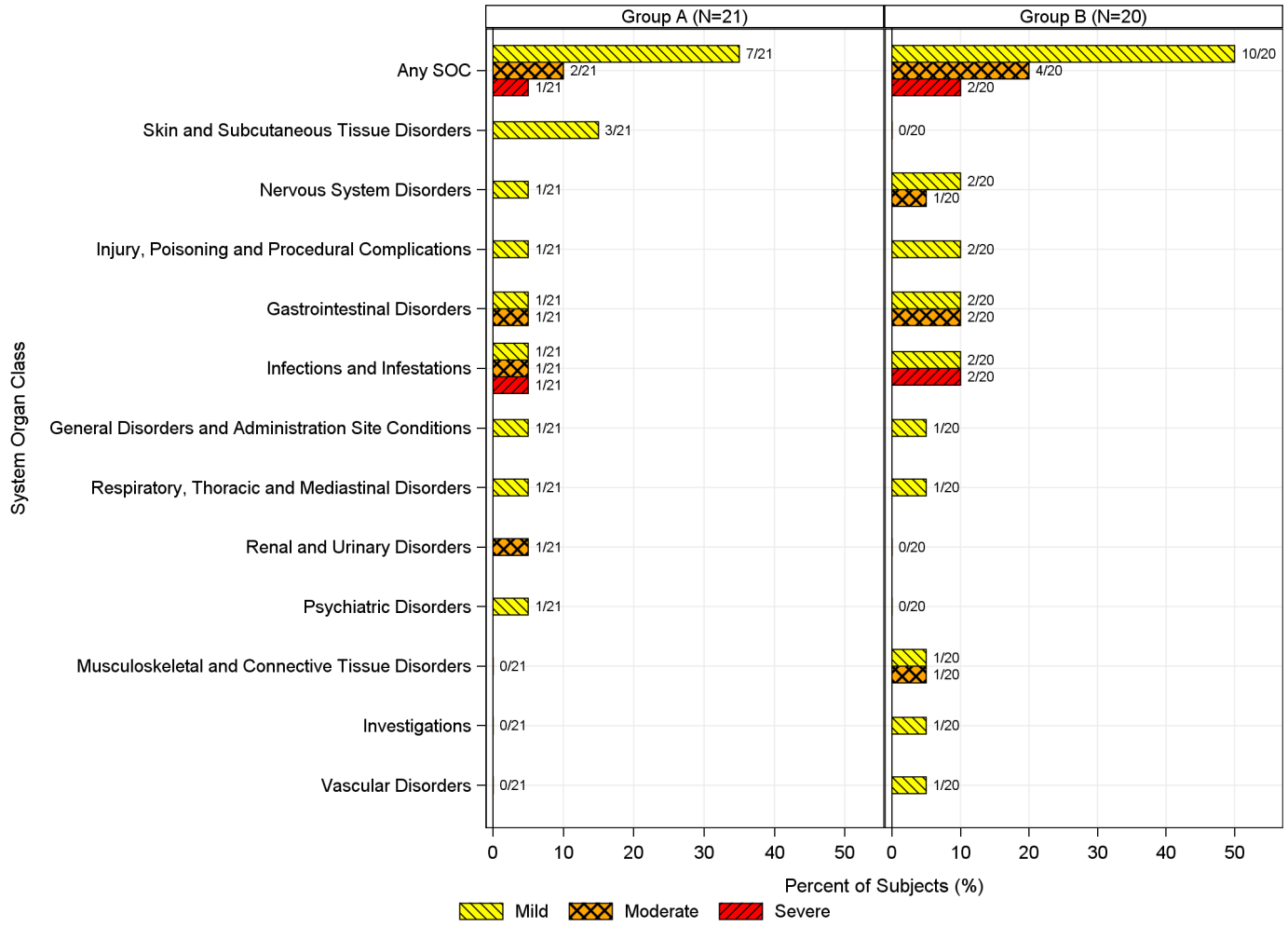


Figure 10: Incidence of Related Adverse Events by MedDRA System Organ Class and Maximum Severity

[Implementation Note: This figure will include serious and non-serious unsolicited adverse events deemed related to the study product. It will be paneled by treatment group: 400 mg SLV213 and Placebo. The SOCs will be sorted by descending incidence with "Any SOC" at the top.]



APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

Listing 1: **16.1.6: Listing of Participants Receiving Investigational Product**

[Implementation Note: Listing will be sorted by Treatment Group, Participant ID, Date, and Time.]

Treatment Group	Participant ID	Study Day (Dose)	Date	Time
		Day 1 (Morning)	ddMMMyyyy	hh:mm

16.2 Database Listings by Participant

16.2.1 Discontinued Participant

Listing 2: 16.2.1: Early Terminations or Discontinued Participants

[Implementation Note: Listing will be sorted by Treatment Group, Participant ID, Category, and Study Day.]

Treatment Group	Participant ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day

16.2.2 Protocol Deviations

Listing 3: 16.2.2.1: Participant-Specific Protocol Deviations

[Implementation Note: Listing will be sorted by Treatment Group, Participant ID, and DV Number.]

Treatment Group	Participant ID	DV Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Participant Termination?	Deviation Affected Product Stability?	Deviation Classification	Deviation Resolution	Comments

Listing 4: 16.2.2.2: Non-Participant-Specific Protocol Deviations

[Implementation Note: Listing will be sorted by Site, Start Date, and Deviation.]

DV Number	Deviation	Deviation Category	Start Date	End Date	Reason for Deviation	Deviation Resulted in Participant Termination?	Deviation Affected Product Stability?	Deviation Classification	Deviation Resolution	Comments

16.2.3 Participants Excluded from the Safety and/or PK Analysis

Listing 5: 16.2.3: Participants Excluded from Analysis Populations

[Implementation Note: This listing should be congruent with "Analysis Populations by Treatment Group" (**Table 11**). Only participants who were excluded from at least one analysis population will be included in this listing. Participants who were excluded from multiple analysis populations will have a separate line per analysis population excluded from in the listing.

Listing will be sorted by Treatment Group, Participant ID, Analyses Included, and Analyses Excluded.]

Treatment Group	Participant ID	Analyses in which Participant is Included	Analyses from which Participant is Excluded	Results Available?	Reason Participant Excluded
		[e.g., Full Analysis, Safety, mITT, PK]	[e.g., Safety, mITT, PK (All Visits)]		Safety: Did not receive study product mITT, PK: Excluded from Safety Population
Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.					

16.2.4 Demographic Data

Listing 6: 16.2.4.1: Demographic Data

[Implementation Note: If the participant is multi-racial, in the "Race" column, note "Multiple: (list races, separated by a comma)."

Listing will be sorted by Treatment Group and Participant ID.]

Treatment Group	Participant ID	Sex	Sex Assigned at Birth	Gender	Ethnicity	Race	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m^2)
		Male		Man/Cisgender Man	Not Hispanic or Latino	Multiple: Asian, White	20	85.5	180.1	26.4

Listing 7: 16.2.4.2: Pre-Existing and Concurrent Medical Conditions

[Implementation Note: "Condition Start Day" and "Condition End Day" are relative to enrollment (which is Day 1, day before enrollment is Day -1). Rather than use exact study days, categorize as follows:

- 5 years prior to enrollment
- 1-5 years prior to enrollment
- 1-12 months prior to enrollment
- Within 1 month of enrollment
- During study
- If ongoing, display "Ongoing" in the "Condition End Day" column

It may be appropriate to add another category, based on exclusion criteria that restrict conditions within a particular time period (e.g., within 3 years prior to enrollment).

Listing will be sorted by Treatment Group, Participant ID, and MH Number.]

Treatment Group	Participant ID	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term

16.2.5 Compliance and/or Drug Concentration Data (if available)

Listing 8: 16.2.5: Compliance Data

[Implementation Note: Only participants who missed at least one dose will be included in this listing. Each dose missed will be its own row. If no reason/comment was provided for the dose being missed, then fill "Reasons for Missing" with "Reason not given".

Listing will be sorted by Treatment Group and Participant ID.]

Treatment Group	Participant ID	Dose Missed	Reasons for Missing
		[e.g., Day 3, Day 3 (Morning), etc.]	

16.2.6 Pharmacokinetics

Listing 9: 16.2.6.1: Participant-Level SLV213 Concentrations in Plasma

[Implementation Note: Units of nominal time and actual time may vary by time point and will be provided for each time rather than in the column header. "Laboratory Reported Concentrations" will give the verbatim value reported by the lab (with minimal formatting, as needed) and will use the character value such as PC.PCORRES. "Analysis Concentrations" will report the value actually used for analysis and will use a numeric variable such as ADNCA.AVAL. If one or more samples are excluded from NCA, two additional columns will be provided in the PK report listing: "Excluded from NCA (Yes/No)" and "Reason for Exclusion from NCA".

In the actual time column, mark out-of-window times with one asterisk (*), substantially out of window visits with two asterisks (**), and imputed times with three asterisks (***). If there are no out-of-window times or imputed values, remove their respective footnotes.

Listing will be sorted by Treatment Group, Participant ID, Study Day, and Nominal Time.]

Treatment Group	Participant ID	Study Day (Dose)	Nominal Time	Actual Time	Laboratory Reported Concentrations (ng/mL)	Analysis Concentrations (ng/mL)
		Day 1 (Morning)	0	0	0	0
		Day 1 (Morning)	30M	28M	BQL	0
		Day 1 (Morning)	1H	1H 12M*	207	207

*Out-of-window collection time.

**Substantially out-of-window collection time.

***Imputed time.

Listing 10: 16.2.6.2: Participant-Specific Single-Dose SLV213 Plasma PK Parameters

[Implementation Note: This listing will include all estimable PK parameters regardless of Ke. Listing will be sorted by Treatment Group and Participant ID.]

Treatment Group	Participant ID	C_{max} (ng/mL)	C_{max}/Dose (ng/mL/mg)	C_{min} (ng/mL)	T_{max} (h)	T_{min} (h)	$AUC_{(0-t)}$ (ng*h/mL)	$AUC_{(0-\infty)}$ (ng*h/mL)	$AUC_{(0-12)}$ (ng*h/mL)	$AUC_{(0-last)}$ (ng*h/mL)	$AUC_{(0-tau)}$ (ng*h/mL)	$AUC_{(0-tau)}$/Dose (ng*h/mL)/mg)	$t_{1/2}$ (h)	CL_T (L/h)	Ke (1/h)	Vd (L)

Listing 11: 16.2.6.3: Participant-Specific Multiple-Dose SLV213 Plasma PK Parameters

[Implementation Note: This listing will include all estimable PK parameters regardless of Ke. Listing will be sorted by Treatment Group and Participant ID.]

Treatment Group	Participant ID	$C_{max,ss}$ (ng/mL)	$C_{max,ss}$/ Dose (ng/mL)/ mg)	$C_{min,ss}$ (ng/mL)	C_{avg} (ng/mL)	$T_{max,ss}$ (h)	T_{min} (h)	$AUC_{(0-48),ss}$ (ng*h/ mL)	$AUC_{(0-tau),ss}$ (ng*h/ mL)	$AUC_{(0-tau),ss}$/ Dose (ng*h/mL)/ mg)	$t_{1/2}$ (h)	CL_T (L/h)	Ke (1/h)	$Vd_{,ss}$ (L)	Linearity Index	RAUC	RC_{max}

16.2.7 Adverse Events

Listing 12: 16.2.7.3: Treatment Emergent Adverse Events

[Implementation Note: Listing will be sorted by Treatment Group, Participant ID, and AE Number.]

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	Severity	SAE?	TEAE?	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Participant Discontinued Due to AE?	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Treatment Group: , Participant ID: , AE Number:												
Comments:												
Treatment Group: , Participant ID: , AE Number:												
Comments:												
Note: For additional details about SAEs, see Listing of Serious Adverse Events.												

16.2.8 Individual Laboratory Measurements

[Implementation Note: These listings (for hematology, chemistry, coagulation, and urinalysis) include all laboratory results, scheduled and unscheduled. These listings are not color-coded, but the severity should be included in parentheses after the result for abnormal results, e.g., 16.2 (Mild).

Measurements outside the reference range but are not graded should show "ONR" for "Severity Grade". Change from Baseline column will be blank for non-numeric parameters and a dash (-) for baseline time point.

Refer to **Section 9.6** for sort order of laboratory parameters.

Listing will be sorted by Treatment Group, Participant ID, Parameter, Time Point, and Assessment Time. Refer to **Section 9.6** for parameter sort orders.]

Listing 13: 16.2.8.1: Clinical Laboratory Results – Chemistry

Treatment Group	Participant ID	Time Point	Assessment Date	Assessment Time	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Normal Range Low	Reference Normal Range High	Change from Baseline
400 mg SLV213	ABC.00101	Baseline	ddMMMyyyy	hh:mm	Male	22	Sodium (mmol/L)	138	133	145	-
		Day 2	ddMMMyyyy	hh:mm	Male	22	Sodium (mmol/L)	134 (Mild)	133	145	-4

Listings with similar format:

Listing 14: 16.2.8.2: Clinical Laboratory Results – Hematology

Listing 15: 16.2.8.2: Clinical Laboratory Results – Coagulation

Listing 16: 16.2.8.3: Clinical Laboratory Results – Urinalysis

[Implementation Note: The Change from Baseline column will not be included. A column will be added between Age and Laboratory Parameter columns and will be labelled as "Methodology". Options for this column include dipstick and microscopy.]

16.2.9 Vital Signs and Physical Exam Findings

Listing 17: 16.2.9.1: Vital Signs

[Implementation Note: This includes all vital sign assessments, scheduled and unscheduled. This listing is not color-coded, but the severity should be included in parentheses after the result for abnormal supine results, e.g., 141 (Mild).

Listing will be sorted by Treatment Group, Participant ID, Study Day, and Planned Time Point.]

Treatment Group	Participant ID	Study Day (Dose)	Planned Time Point	Actual Time Point	Temperature (°C)	Systolic Blood Pressure (mmHg)			Diastolic Blood Pressure (mmHg)			Pulse (beats/min)			Respiratory Rate (breaths/min)
						Supine	Standing (1 min)	Standing (3 min)	Supine	Standing (1 min)	Standing (3 min)	Supine	Standing (1 min)	Standing (3 min)	
		Day 1 (Morning)	-30M	-32M	36 (None)	120 (None)	116	112	60 (None)	68	57	60 (None)	68	70	12 (None)
		Day 1 (Morning)	2H	2H 5M											
		…	…	…											
		Day 8	-												
		Day 9	-												

Note: Systolic blood pressure, diastolic blood pressure, and pulse standing measurements that meet the criteria for an abnormal orthostatic response are graded according to Adverse Event Grading Scale and are included in **Listing 12**: 16.2.7.3 Treatment Emergent Adverse Events.

Time point refers to the amount of time before or after the associated dose that supine vital signs were collected. Standing vital signs were collected 1 min (±15 s) and 3 min (±15 s) after supine vital signs were collected.

Listing 18: 16.2.9.2: Abnormal Physical Exam Findings

[Implementation Note: Listing will be sorted by Treatment Group, Participant ID, Planned Time Point, and AE Number.]

Treatment Group	Participant ID	Planned Time Point	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)

16.2.10 12-Lead Electrocardiogram

Listing 19: 16.2.10: Electrocardiogram Interval Measurements

[Implementation Note: This included all ECG assessments, scheduled and unscheduled. These listings are not color-coded, but the severity should be included in parentheses after the result for abnormal results, e.g., 16.2 (Mild).

Refer to **Section 9.1.1** for sort order of ECG parameters.

Listing will be sorted by Treatment Group, Participant ID, Parameter, Time Point, and Assessment Time. Refer to **Section 9.1.1** for parameter sort order.]

Treatment Group	Participant ID	Sex	Parameter	Time Point	Assessment Date	Assessment Time	Result (Severity)	Change from Baseline
				Baseline	ddMMMyyyy	hh:mm		
				Day 4	ddMMMyyyy	hh:mm		

Listing 20: 16.2.10: Electrocardiogram Overall Interpretations and Comments

[Implementation Note: Listing will be sorted by Treatment Group, Participant ID and Time Point.]

Treatment Group	Participant ID	Sex	Time Point	Assessment Date	Interpretation	Change from Baseline	Morphological Abnormalities Present?	If Abnormal CS, AE No.	Comments
		Male	Baseline	ddMMMyyy	Normal NCS	-	No	-	Sinus Bradycardia
		Male	Day 4	ddMMMyyy	Abnormal NCS	NCB	Yes	-	Sinus Bradycardia

Note: NCS = Not clinically significant; CS = Clinically significant.
NCB = No change from baseline; NSB = Not clinically significant, change from baseline; CSB = Clinically significant change from baseline.

16.2.10 Concomitant Medications

Listing 21: 16.2.11: Concomitant Medications

[Implementation Note: Listing will be sorted by Treatment Group, Participant ID, and CM Number.]

Treatment Group	Participant ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Description; Number)	Taken for a condition on Medical History? (MH Description; Number)	ATC Level 1 (ATC Level 2)

16.2.12 Pregnancy Reports

[Implementation Note: Listings will be sorted by Treatment Group (as applicable), Participant ID, and Pregnancy Number or Fetus Number.]

Listing 22: 16.2.12.1: Pregnancy Reports – Maternal Information

Treatment Group	Participant ID	Pregnancy Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Mother's Weight Gain During Pregnancy	Tobacco, Alcohol, or Drug Use During Pregnancy?	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?
Note: Maternal Complications are included in the Adverse Event listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.											

Listing 23: 16.2.12.2: Pregnancy Reports – Gravida and Para

			Live Births												
Participant ID	Pregnancy Number	Gravida	Extremely PB[a]	Very Early PB[a]	Early PB[a]	Late PB[a]	Early TB[b]	Full TB[b]	Late TB[b]	Post TB[b]	Still Births	Spontaneous Abortion/ Miscarriage	Elective Abortions	Therapeutic Abortions	Major Congenital Anomaly with Previous Pregnancy?
Note: Gravida includes the current pregnancy, para events do not. [a] Preterm Birth [b] Term Birth															

Listing 24: 16.2.12.3: Pregnancy Reports – Live Birth Outcomes

Participant ID	Pregnancy Number	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Live Birth	Size for Gestational Age	Apgar Score, 1 minute	Apgar Score, 5 minutes	Cord pH	Congenital Anomalies?	Illnesses/ Hospitalizations within 1 Month of Birth?
Note: Congenital Anomalies are included in the Adverse Event listing.												

Listing 25: 16.2.12.4: Pregnancy Reports – Still Birth Outcomes

Participant ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Still Birth	Size for Gestational Age	Cord pH	Congenital Anomalies?	Autopsy Performed?	If Autopsy, Etiology for Still Birth Identified?

Listing 26: 16.2.12.5: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

Participant ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Gestational Age at Termination	Abnormality in Product of Conception?	Reason for Therapeutic Abortion