A Randomized, Double Blind, Placebo-Controlled, Multiple Ascending Dose, Phase 1 Study of SLV213 in Healthy Volunteers

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STATEMENT OF COMPLIANCE

Each institution engaged in this research will hold a current Federalwide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be registered with OHRP as applicable to the research.

The study will be carried out in accordance with the following as applicable:

- United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11 (Electronic Records and Electronic Signatures), and 21 CFR Part 312 (Investigational New Drug Application), and/or 21 CFR 812 (Investigational Device Exemptions)
- The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6(R2) Good Clinical Practice (GCP), and the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- The policies and procedures of National Institutes of Health (NIH) Office of Extramural Research and the Division of Microbiology and Infectious Diseases (DMID)
- The National Institute of Allergy and Infectious Diseases (NIAID) Terms of Award
- Any additional Federal, State, and Local Regulations and Guidance

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations, and ICH E6(R2) GCP guidelines.

Site Principal Investigator Signature:

Signed: _____ Date: _____

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1.1 Synopsis

Rationale

The outbreak of COVID-19, which is caused by the severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) has been declared a pandemic and represents a great threat to public health (CDC 2020). Well over 625 million individuals have been infected globally and more than 6.5 million confirmed deaths have been reported, numbers that are likely to continue to grow (Our World in Data 2020). Confirmed US cases have exceeded 102 million, with over 1 million deaths to date. Selva Therapeutics, Inc. is developing SLV213, 4-methylpiperazine-1-carboxylic acid [1-(3- benzenesulfonyl- 1- phenethylallyl-carbamoyl)-2-phenylethyl]-amide, a vinyl sulfone cysteine protease inhibitor for the treatment of subjects infected with SARS-CoV-2, to address an urgent medical need for the treatment of COVID-19.

SLV213 is an oral formulation (drug substance powder in capsules without excipients or stabilizers) of the drug substance K777 hydrochloride, which has been demonstrated to exhibit broad inhibitory properties against host cathepsins (e.g., Cathepsin L), which represent one of two types of proteases known to activate or "prime" the spike protein of coronaviruses. Priming by host Cathepsin L in the endosome is required to initiate the conformational change of the spike protein necessary to begin viral entry into host cells. This mechanism of entry is required for coronaviruses (e.g., SARS-CoV-2, Middle East respiratory syndrome coronavirus, Human coronavirus NL63) (Zhou, Vedantham et al. 2015). Crucially, due to SLV213's broad mechanism of action against host cathepsins as well as the conservation of the priming mechanism for coronaviruses, there is potential for SLV213 to be effective against future coronavirus outbreaks (Mellott, Tseng et al. 2021)

Study Design

The proposed study will evaluate the safety, tolerability, and pharmacokinetics (PK) of multiple ascending doses (MAD) of SLV213 in healthy male and female participants, 18-65 years of age. This study will help to select the most likely suitable dose (e.g., at Maximum Tolerated Dose [MTD]) for the treatment of patients with COVID-19 in a pivotal study. This double blind, placebo-controlled study will consist of 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 orally (PO) for 7 days. After each cohort, a Safety Review Committee (SRC) will evaluate the safety of the regimen before proceeding to dose the next cohort.

Randomization will occur into the respective cohorts as above. Upon meeting the Inclusion/Exclusion criteria, subjects will begin treatment with SLV213 or placebo per their assigned cohort. Participants will take their study drug in the fasted state prior to morning and evening meals and will remain as in-patient in the clinical trial unit (CTU) during all treatments and for approximately 48 hours (h) after the last dose for monitoring. After discharge from the CTU, participants will be monitored by CTU staff by telephone to assess for new adverse events (AEs) and use of concomitant medications (ConMeds) since the last visit or contact, approximately

weekly for three weeks. Participants will be asked to return to the CTU for further assessment of moderate or severe AEs. (For further information on study drug administration see Section 6.1.2. List of assessments from Screening to last study visit can be found in the Schedule of Assessments (SOA), Section 1.2, and in Section 8.1 and Section 8.3).

Objectives

- Primary: To evaluate the safety and tolerability of multiple ascending doses of SLV213 for 7 days in healthy participants.
- Secondary: To characterize the multiple dose PK of SLV213 in healthy participants.

Outcomes / Endpoints

- Primary:
  - 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: Proportion of participants experiencing any treatment-emergent AEs assessed as related to study drug vs. placebo.
- Secondary: PK parameter estimates and calculated exposure measures in plasma SLV213 following a single initial dose on Day 1 and after multiple Q12h dose administration for 7 days.

For a full list of Objectives and Outcomes/Endpoints, see Section 3.

Inclusion Criteria

See inclusion criteria in Section 5.1.

Exclusion Criteria

See exclusion criteria in Section 5.2.

Study Phase (if applicable)

Phase 1

Study Population

36 ambulatory healthy participants, age 18-65 years of age inclusive at the time of dosing.

Sites

One clinical site located in the United States.

Study intervention:

- SLV213 capsules containing 100 mg of a defined powder of drug substance K777 hydrochloride. The chemical structure, characteristics and formulation of SLV213 are provided in Section 6.1.1 and Section 6.2.3, and in Figure 2 and Table 1.
- Matching placebo capsules containing 62.5 mg microcrystalline celluloid. The chemical structure, characteristics and formulation are provided in Section 6.1.1 and Section 6.2.3, and in Figure 3 and Table 2

Each participant will be randomly assigned to receive SLV213 or placebo (SLV213: placebo ratio 2:1) orally (PO) as follows: 4 capsules Q12h in Cohort 1, 6 capsules Q12h in Cohort 2, and 8 capsules Q12h in Cohort 3 daily for 7 days. 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.

Study Duration

Screening can occur up to 28 days before the start of dosing. Dosing commences over a period of 7 days at the study site. Participants are followed for 28 (± 2) days after the first dose is administered. The study is expected to complete in 6 months.

Participant Duration

There will be a Screening period of 27 days (Day-28 to Day-2) to determine eligibility and a check-in visit (Day-1) to confirm eligibility for admission. Eligible participants will be monitored as in-patients in the CTU for 9 days, 7 days (Day 1 to Day 7) during active dosing, and for 2 days after dosing (Days 8 and 9) for in-patient follow-up, discharged on Day 9, and followed up to 21 days as out-patients after the last dose, on Days 15 (±2 days), 21 (±2 days) and 28 (±2 days) by phone, and as needed at the CTU for the evaluation of AEs/SAEs. The total participant duration including the screening and post-dosing periods would be up to 56 (±2 days).

Safety Monitoring

This protocol will utilize a safety monitoring committee (SMC) and a safety review committee (SRC).

The SMC will consist of independent experts and will advise the sponsor (Division of Microbiology and Infectious Diseases [DMID]) on the safety of the study. The SMC will have an organizational meeting and will conduct a review of safety data for dose escalation if a halting rule is met, as defined by the protocol, or if the internal SRC requests a review of the data, or *ad hoc* when requested by the sponsor, investigators, or SMC. The SMC will review the safety, tolerability, trial progress and final PK data at the conclusion of the trial to provide a recommendation on the dose of SLV213 to be used in a Phase 2 clinical trial.

The SRC will review combined safety data to study Day 15 in each cohort and recommend dose escalation if halting criteria are not met. The SRC will consist of a DMID Medical Monitor (MM), a DMID Medical Officer (MO), the clinical site principal investigator (PI) and the Pharmaceutical (Selva) MO. (See Section 10.1.6 for further details on safety oversight.)

1.2 Schedule of Assessments (SOA)

	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
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 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 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 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 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 Section 8.1.2).
(m) SARS-CoV-2 (Covid-19) molecular diagnostic Cue Care™ test at Check-in Visit (Day-1) (see 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 Section 8.1.2 and Section 8.3.2.
(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 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 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 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 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 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.**

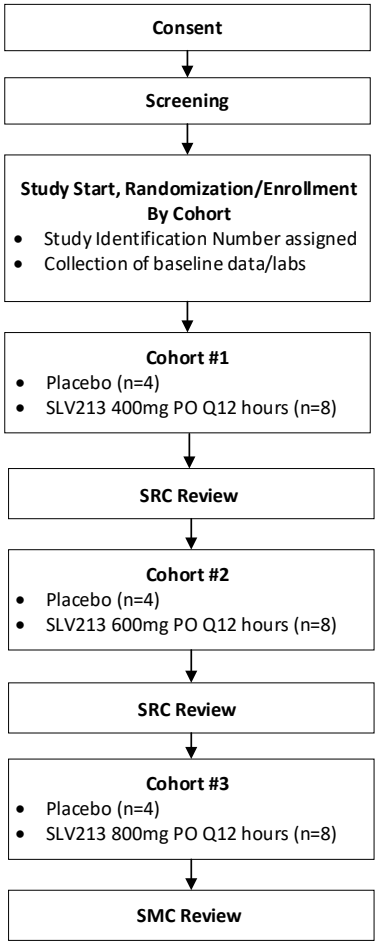
- On Day 1 MORNING DOSE: Within 30 min before the morning dose (t=0), and at 0.5h (±5 min), 1h (±5 min), 2h (±5 min), 4h (±5 min), 6h (±10 min), 8h (±10 min), and 12h (±15 min) after the morning dose. (The 12h timepoint after the morning dose on Day 1 is the same as the predose timepoint before the evening 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.

1.3 Study Schema

Figure 1: Study Schema



2. INTRODUCTION

2.1 Study Rationale

The outbreak of COVID-19, which is caused by SARS-CoV-2 has been declared a pandemic and represents a great threat to public health (CDC 2020). Well over 625 million individuals are already infected globally and more than 6.5 million confirmed deaths have been reported, numbers that are likely to continue to grow over (Our World in Data 2020). Confirmed US cases have exceeded 102 million, with over 1 million deaths to date.

The current standard of care for COVID-19 includes supportive care, such as oxygen therapy and fluid management, and the use of antiviral drugs like Remdesivir and Paxlovid. In more severe cases, corticosteroids are used to reduce inflammation and prevent damage to organs, such as the lungs. While these treatments can help manage symptoms and potentially reduce the severity of the disease, they do not provide a cure or prevent disease progression. Additionally, the use of

antivirals like Remdesivir has been associated with adverse effects, such as gastrointestinal problems and liver damage. Furthermore, the effectiveness of these treatments may vary depending on the severity of the disease and the timing of treatment. For example, corticosteroids may be effective in reducing inflammation and preventing damage to organs in severe cases, but they may not be effective in mild cases or may even exacerbate the disease in the early stages. There is a significant need for additional therapies that can target the underlying mechanisms of COVID-19 pathogenesis and reduce disease severity. For instance, host-targeted interventions that can block viral entry and replication could be promising therapeutic options for COVID-19 and other viral diseases.

Selva has conducted a Phase 1 randomized double-blind placebo-controlled single ascending dose (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 PO at 50 mg, 100 mg, 200 mg, 400 mg, or 800 mg 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. Pharmacokinetic analyses demonstrated dose dependent peak drug concentration (C_{max}) and area under the plasma concentration – time curve (AUC). Preliminary modeling of 400 mg and 800 mg QD suggested predicted blood levels were 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 Brochure (IB).

2.2 Background

Selva Therapeutics is developing SLV213, the oral formulation of the drug substance K777 hydrochloride. SLV213 is a vinyl-sulfone cysteine protease inhibitor that acts as a broad antiviral by inhibiting cathepsin-mediated cell entry (Zhou, Vedantham et al. 2015). Such entry is required for infection by coronaviruses, providing a mechanism-based rationale for investigating SLV213 as a potential treatment against COVID-19. Pharmaceutical development of SLV213 was previously focused on Chagas disease, and NIAID-sponsored activities have been ongoing for two decades, including Good Laboratory Practice (GLP) and non-GLP studies conducted primarily at SRI International. Due to these efforts, extensive preclinical evaluation has been completed to assess the PK, metabolism, and toxicity of SLV213 in rodents, dogs, and non-human primates (McKerrow 2018).

A mechanism-based rationale for investigating SLV213 as a potential treatment against COVID-19 is supported by multiple lines of evidence. Investigators at University of Texas Medical Branch, University of California San Diego, and the Utah State University have generated *in vitro* data that demonstrate dose-dependent antiviral effects of K777 in several SARS-CoV-2-permissive mammalian cell lines (Mellott, Tseng et al. 2021). Supporting evidence has also been published

by Hoffman et al. (Hoffmann, Kleine-Weber et al. 2020, Nie, Qian et al. 2021), which demonstrated that inhibition of cysteine proteases by E-64d blocks SARS-CoV-2 from cell entry, strongly supporting the theory that SLV213 may be a potentially effective treatment of COVID-19.

Additionally, investigators at Tulane Primate Research Center have completed two non-human primate studies in which the safety and efficacy of K777 were evaluated. Data from African Green monkeys inoculated with SARS-CoV-2 indicate a reduction in viral loads and a corresponding reduction in measures of lung pathology in treated animals compared to untreated controls (Frueh, Maneval et al. 2021). Histological analysis showed that treated animals were protected against acute respiratory distress syndrome (ARDS)-like pathology that was seen in untreated animals.

Other clinical trials targeting other known host proteins involved in SARS-CoV-2 infection are ongoing; however, SLV213 represents the first opportunity to test the inhibition of host cysteine protease activity in humans. Evidence from the SLV213-01 Phase 1 trial, non-human primate studies, and emerging observations in the literature from COVID-19 patients further support the development of SLV213 for the treatment of COVID-19 (Nie, Qian et al. 2021).

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

SLV213

Cathepsin inhibitors have been safely used in the clinic (Drake, Clarke et al. 2017; Fuchs, Meta et al. 2020).

Preclinical:

SLV213 is the oral formulation of the drug substance, K777. All preclinical development was conducted with K777 (K11777). The K777 toxicology program included single-dose and repeat-dose oral dose toxicity studies in rats and dogs. Pivotal studies included a 14-day GLP toxicity study in rats, a 28-day GLP toxicity study in dogs as well as standard GLP *in vitro* tests for genotoxicity. Non-GLP studies were also conducted in cynomolgus and rhesus monkeys. In general, K777 was well tolerated in all species after oral administration. The liver was identified as the target organ of toxicity. Reversible increases in transaminases (e.g., aspartate aminotransferase [AST], alanine aminotransferase [ALT]) were reported in all species at high doses. In the GLP 14-day rat toxicity study, the highest dose administered (150 mg/kg/day) produced mild effects on liver enzymes (2-fold elevation) that were not confirmed by histopathologic evaluation of the liver. In the 28-day GLP dog toxicity study, modest reversible elevations in serum transaminases were also observed. In addition, reversible microscopic changes were detected in the brain (100 mg/kg dose; females only) and in lymphoid tissues. These reversible changes were considered non-adverse due to lack of histopathologic, clinicopathologic, and clinical evidence suggestive of an organ or organismal functional impairment.

Modest depressions in food consumption and weight gain were also observed in several studies, but effects were reversible and not considered adverse. Emesis was frequently reported in the dog

at oral K777 doses ~100 mg/kg and was also reported after intravenous (IV) dosing in a recent dog safety pharmacology study. Changes in hematological parameters were not typically observed or not considered of toxicological significance. *In vitro* and *in vivo* GLP studies did not demonstrate genotoxic effects of K777.

The oral administration of K777 at doses of 15, 50, and 150 mg/kg did not induce any significant effects on pulmonary function or neurobehavioral responses in conscious male rats. Potential cardiovascular effects of K777 *in vivo* were further investigated in a GLP dog safety pharmacology study. To maximize systemic exposure of K777, conscious telemetered dogs received K777 weekly IV at doses of 0, 5, 15, and 25 mg/kg. The IV administration of K777 did not induce any biologically relevant effects on blood pressure, ECG morphology, ECG measurements, or body temperature. Moderate increases in heart rate were observed during dosing of K777 at 15 and 25 mg/kg, and effects were resolved immediately following dosing.

Clinical:

Selva has conducted a Phase 1 randomized, double-blind, placebo-controlled, SAD study to evaluate the safety, tolerability, and PK of SLV213 following oral administration (Study SLV213-01). An SRC concluded that no DLT had been seen at any of the dose levels. Occasional, transient, mild, treatment-emergent adverse events (TEAEs) were observed at all dose levels. A clinically significant episode of orthostatic hypotension was observed 30 min after dosing in one participant at the 200 mg dose level, but this was not seen in that participant at subsequent time points, nor in any other participant at the 400 mg or 800mg dose levels. No SAEs were noted, and no participants discontinued the trial because of an AE. No clinically significant changes from participants' baseline values were seen in liver function enzymes (alkaline phosphatase [ALP], ALT, AST, gamma-glutamyl transferase [GGT]) or in ECG parameters at any dose level. Preliminary PK modeling of BID dosing predicted blood levels at 400 mg BID to be well below the 800 mg single dose C_{max} and comparable to concentrations measured in preclinical efficacy models, and supported the conclusion that 400 mg, 600 mg, and 800 mg Q12h dosing should be well tolerated.

2.3.2 Known Potential Benefits

The participants will have no direct benefit from participating in the study.

The development of a host-targeted therapeutic for COVID-19 would provide significant benefits over the current standard treatment of care. COVID-19 is a highly infectious and life-threatening disease that has caused a worldwide pandemic. While vaccines have been developed to prevent the disease, they are not entirely effective, and not all individuals can receive them. As such, the availability of a host-targeted therapeutic would be critical for those who contract the disease, particularly those at high risk of severe illness or death.

The current standard treatment for COVID-19 involves supportive care, such as oxygen therapy and fluid management, and the use of antiviral drugs like Remdesivir and Paxlovid. While these treatments can manage symptoms and potentially reduce disease severity, they do not provide a cure or prevent disease progression. A host-targeted therapeutic for COVID-19 would provide a novel approach to improving the standard of care for the disease. Host-targeted therapies are

designed to target the host's cellular pathways and processes that the virus relies on for survival and replication, rather than directly targeting the virus itself. This approach has the potential to address and reduce the underlying mechanisms of COVID-19 pathogenesis and other viral disease severity (Mahajan, Choudhary et al. 2021; Dwek, Bell et al. 2022).

For example, investigators at Tulane Primate Research Center have completed two non-human primate studies in which the safety and efficacy of SLV213 were evaluated. Data from African Green monkeys inoculated with SARS-CoV-2 indicate a reduction in viral loads and a corresponding reduction in measures of lung pathology in treated animals compared to untreated controls (Frueh, Maneval et al. 2021). Histological analysis showed that treated animals were protected against ARDS-like pathology that was seen in untreated animals.

Another potential advantage of host-targeted therapies is that they could be effective against multiple strains of the virus, including emerging variants, whereas traditional antiviral therapies may only target specific strains. Additionally, host-targeted therapies could reduce the potential for the development of drug resistance, which is a concern with traditional antiviral therapies.

Host-targeted therapies could also be used in combination with other treatments, such as vaccines and antivirals, to provide a more comprehensive approach to COVID-19 treatment (Wagoner, Herring et al. 2022). For example, host-targeted therapies could be used in combination with antivirals to reduce the viral load and prevent the spread of the virus, while also targeting the host response to reduce inflammation and other damaging effects of the disease.

Furthermore, host-targeted therapies could potentially address the long-term consequences of COVID-19, such as post-acute sequelae of SARS-CoV-2 infection or "long COVID." These conditions are characterized by persistent symptoms and can have a significant impact on an individual's quality of life. Host-targeted therapies could potentially target the underlying mechanisms of these conditions and provide relief for individuals who are experiencing prolonged symptoms.

Additionally, the development of a therapeutic would help alleviate the burden on healthcare systems and resources that are currently overwhelmed by the number of COVID-19 cases. With an effective therapeutic, hospitalization rates could potentially be reduced, freeing up hospital beds and resources for those who need them most. The development of a host-targeted therapeutic for COVID-19 would be a significant advancement in the fight against this deadly disease and could save numerous lives.

2.3.3 Assessment of Potential Risks and Benefits

- Available pre-clinical and clinical data support further clinical development of SLV213. The study aim is to determine the maximum tolerated dose of SLV213 after multiple doses in order to determine a possible therapeutic dose to test in an efficacy trial.
- Risk will be minimized by housing the participants in a CTU and participants will be monitored throughout the trial by trained staff.

- Potential risks that were identified in animal studies were not evidenced in the Phase 1 clinical trial. No DLTs or SAEs were noted/occurred in the Phase 1 SAD at the highest single dose tested (800 mg). There may be other side effects or risks that are not yet known.

3. 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 (h) • 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

OBJECTIVE	ENDPOINTS (OUTCOME MEASURES)
	• $AUC_{(0\text{-last})}$: Area under the plasma concentration - time curve from time zero to the last concentration above the lower limit of quantitation • $AUC_{(0\text{-tau})}$: Area under the plasma concentration - time curve to the end of the dosing interval • $t_{1/2}$: Terminal half-life • CLT: Total clearance • Ke: terminal phase elimination rate constant • Vd: Volume of distribution • Dose-normalized exposure parameters ($AUC_{(0\text{-tau})}$/Dose and C_{max}/Dose) 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 • $C_{min,ss}$: 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}) • $AUC_{(0\text{-}48),ss}$: area under the plasma concentration - time curve from 0h (pre-dose) to 48 h after dosing at steady state • $AUC_{(0\text{-tau}),ss}$: Area under the plasma concentration - time curve to the end of the dosing interval at steady state • $t_{1/2}$: Terminal half-life • CLT: Total clearance • Vd,ss: Volume of distribution at steady state • Linearity Index: $AUC_{(0\text{-tau}),ss}$ (Day 7) / $AUC_{(0\text{-}\infty)}$ (Day 1) • RAUC: Accumulation ratio for AUC estimated as $AUC_{(0\text{-tau})}$ (Day 7) / $AUC_{(0\text{-tau})}$ (Day 1) • RC_{max}: Accumulation ratio for C_{max} estimated as C_{max} (Day 7) / C_{max} (Day 1). • Dose-normalized exposure parameters ($AUC_{(0\text{-tau})}$/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.

4. STUDY DESIGN

4.1 Overall Design

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 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 US at a single clinical trial unit (CTU). Subjects 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.

Upon meeting Inclusion/Exclusion criteria, participants will begin dosing with SLV213 or placebo per their allotted cohort. Participants will take their study drug prior to morning and evening meals. AEs will be noted and graded per the protocol Toxicity Grading Tables (See Appendix A). Visit assessments are shown in the schedule of events (Section 1.2) and Section 8.1 and Section 8.3.

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 they withdraw or are withdrawn 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 supervision of licensed clinical staff authorized to administer study drug (PI, or sub-investigator or licensed clinicians listed on Form FDA 1572). The investigational drug blind is maintained by the dispensing pharmacist through a randomization schedule.

A schematic of the study design is presented in Section 1.3. The schedule of activities is in Section 1.2.

Full details about timing of analyses are found in Section 9.3.2.

Details of the SMC oversight are found in Section 10.1.6.

4.2 Dose Escalation

Participants will be enrolled in MAD cohorts. Dosing to the next cohort will be done sequentially only after the safety assessments to Day 15 have been completed to ensure adequate time for review of all available safety and tolerability data and the safety review committee (SRC) confirms that Halting Criteria have not been met.

4.3 Scientific Rationale for Study Design

Given that the present study constitutes a follow-up to a completed SAD Phase 1 safety trial, a placebo control will also be utilized for the current MAD study. In light of this, healthy volunteers

aged 18 - 65 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 of multiple doses of SLV213 over a period of 7 days.

4.4 Justification for Dose

Selva has conducted a Phase 1 randomized double-blind placebo-controlled single ascending dose study in healthy volunteers to evaluate the safety, tolerability, and PK of SLV213 following oral administration (Study SLV213-01). Following randomization, five 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. 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 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 DLT had been seen at any of the dose levels. Pharmacokinetic 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 IB.

5. STUDY POPULATION

This study will enroll healthy volunteers 18-65 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 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.

5.1 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 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 (Appendix A) 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 ALT, 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 (Appendix A) (e.g., decrease 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.

5.2 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 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 6.5)
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 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).

5.2.1 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.

5.3 Inclusion of Vulnerable Participants

Not applicable

5.4 Lifestyle Considerations

During this study, participants are asked to:

- Refrain from consumption of red wine, Seville oranges, grapefruit, or grapefruit juice, [pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices] from 7 days before the start of the study until discharge on Day 9.
- Refrain from alcohol use 7 days before starting dosing and for the duration of the trial.
- Refrain from using nicotine products from a week before starting dosing to discharge from the inpatient phase on Day 9.
- Refrain from treatment with any prescription medications including medications known to be strongly metabolized by CYP3A4 or CYP2D6 or inhibit or induce both these enzymes for 14 days or 5 half-lives of the drug, whichever is longer, prior to starting dosing and for the duration of the trial. (See Appendix C for a partial list of drugs. CTU to obtain a careful medication history.)
- Refrain from illicit (non-medical) use of amphetamines, barbiturates, benzodiazepines, cocaine, opiates, cannabis, and nicotine.
- Any approved medical use of tricyclic antidepressants, amphetamines, barbiturates, benzodiazepines, opiates, and cannabis will not be acceptable.
- Refrain from over the counter (OTC) non-prescription medications, supplements such as vitamins and herbal supplements (e.g., Saint John's Wort) for at least 14 days or 5 half-lives of the drug, whichever is longer, prior to starting dosing with study drug and for the duration of the trial.

- Refrain from eating or drinking anything hot or cold within 10 minutes prior to taking oral temperature.
- Refrain from consuming food or drink containing poppy seeds within 72 h of the screening visit and the Check-in (Day -1) visit as this could cause a false positive urine drug screen result.
- Agree to Section 5.1 inclusion criteria relating to pregnancy, contraception, or sexual activity, and to Section 5.2, exclusion criterion relating to breastfeeding.
- Abstain from strenuous exercise within 48 h prior to dosing, for the duration of the 7 days of dosing and 2 days of in-patient follow up until discharge on Day 9. Participants may participate in light recreational activities (e.g., watching television, reading) during those periods of the study.
- After enrollment in this study (but before Day 1 of this study), the participant should notify study staff of their intention to enroll in any other clinical study prior to enrollment in that study.
- Agree to consume food and beverages served by the CTU. Carry-out is not permitted.
- Agree to abide by the restrictions on food and fluid intake before and after each dose. (See. Section 6.2.5)

5.5 Screen Failures

After the screening evaluations have been completed, the PI, sub-investigator or authorized clinician is to review the inclusion/exclusion criteria and determine the participant's eligibility for the study.

Only the following information will be collected on screen failures: demographics (age, screen number, sex, ethnicity, and race) and reason(s) for ineligibility. Participants who are found to be ineligible will be told the reason for ineligibility.

A participant may be rescreened if there is a transient disease status or short-term treatment with a medication within exclusionary window and the eligibility criteria could be met by rescreening at a later date. No participant may be screened more than twice due to a screening failure result as defined above. All other individuals who do not meet the criteria for participation in this study may not be rescreened for the study. (See Section 8.1.4).

5.6 Strategies for Recruitment and Retention

5.6.1 Recruitment

Potential participants will learn about the study via Institutional Review Board (IRB)-approved recruitment strategies, including direct mailing, recruitment from an IRB-approved trial registry and local advertisements/flyers. Recruiting may begin with a brief IRB-approved telephone call between study staff and the potential participant. Information about the study will be presented to

potential participants, questions about their health and ability to comply with the study visit schedule will be asked of potential participants to determine eligibility. Information about the participant may be recorded from interviews or medical records. Appointments will be made at the research clinic for potential participants who are interested in further screening procedures and additional protocol-specific information.

5.6.2 Retention

Study retention strategies will include education and explanation of the study schedule and procedures during screening and enrollment visits and restriction of enrollment to persons who can attend all study visits. Participants will be reminded of subsequent visits during each visit, and study staff will contact participants for follow up appointments. Study staff will contact participants who miss appointments to encourage them to return for completion of safety evaluations.

5.6.3 Compensation Plan for Participants

Participants may be compensated for their participation in this trial. Compensation will be in accordance with local IRB requirements, and participant to IRB approval. Reimbursements will be disbursed at specific timepoints during the study with the amount contingent on completing study procedures.

5.6.4 Costs

There is no cost to participants for the research tests, procedures, and study product while taking part in this trial. Procedures and treatment for clinical care may be billed to the participant, participant's insurance or third party.

6. STUDY PRODUCT

6.1 Study Product(s) and Administration

6.1.1 Study Product Description

In this protocol, 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- allylcarbamoyl)-2-phenylethyl]-amide) as a 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 in accordance with approved labeling.

Product 2: Matched Placebo

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

6.1.2 Dosing and Administration

Cohort	Product Name	Dose	Route	Frequency of Administration	Duration of Treatment
1	SLV213	400mg (4x 100mg capsules)	Oral	Q12 hours	7 days
2	SLV213	600mg (6x 100mg capsules)	Oral	Q12 hours	7 days
3	SLV213	800mg (8x 100mg capsules)	Oral	Q12 hours	7 days

Cohort	Product Name	Dose	Route	Frequency of Administration	Duration of Treatment
1	Matched Placebo	4 capsules	Oral	Q12 hours	7 days
2	Matched Placebo	6 capsules	Oral	Q12 hours	7 days
3	Matched Placebo	8 capsules	Oral	Q12 hours	7 days

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.

6.1.3 Dose Modifications

Dose modifications are not planned unless mandated by the SMC.

6.1.4 Criteria for Redosing

Participants will not be re-dosed outside of the standard schedule of events.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition

Product 1: SLV213

Will be provided by Selva Therapeutics to the DMID Clinical Materials Services (DMID CMS).

Product 2: Matched Placebo

Will be provided by Selva Therapeutics to the DMID CMS.

Study products (SLV213 and placebo) from DMID CMS will be distributed to the CTU upon request and approval from DMID.

DMID Clinical Materials Services Contract
Fisher BioServices

20439 Seneca Meadows Parkway
Germantown, MD 20876

6.2.2 Accountability

Product 1: SLV213

The participating site PI is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The participating site PI may delegate to the participating site's research pharmacist responsibility for study product accountability. The participating site's research pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, storage conditions, and final disposition of the study product(s).

Study product accountability records and dispensing logs should include, but are not limited to the following:

- DMID protocol number
- Name
- Dosage form
- Strength of the study product
- Capture bottle numbers assigned sequentially by the pharmacists as bottles are used (number uniquely, do not start over at 1 or repeat numbers)
- Manufacturer or other source
- Control, lot number, or other identification number
- Expiration or retest date
- Date of receipt of the study product
- Quantity received from supplier; participant identification number
- Quantity dispensed as amount or dose per participant
- Balance of study product currently available
- Disposition of study product if not dispensed to a study participant (e.g., retuned to supplier as per protocol)
- Date of study product preparation/administration
- Time of product administration to the participant will be recorded on the appropriate subject record.

All study product(s), including the amount of SLV213, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. The

sponsor's monitoring staff will verify the participating site's study product accountability records and dispensing logs per the DMID-approved Clinical Monitoring Plan.

Once all participant dosing is complete, the pharmacy staff should retain the remaining product and complete study product accountability procedures in accordance with site-specific standard operating procedures. This applies to unused SLV213 bottles and/or capsules. Upon completion of the trial or termination of the study and after the final monitoring visit, any remaining unused test article will be returned to Selva in accordance with the disposition plan provided by the DMID Clinical Project Manager.

Product 2: Matched Placebo

Placebo will be supplied and documented in the same manner as the study product listed above.

6.2.3 Formulation, Appearance, Packaging, and Labeling

Product 1: SLV213

SLV213 drug product is manufactured as size 1 orange hard gelatin capsules containing 100 mg K777. SLV213 drug product (100-mg dosage strength) is packaged at 30 capsules per bottle in 40cc high density polyethylene (HDPE) bottles with a desiccant (silica gel pack) and secured with a 33 mm child-resistant closure and induction foil seal.

Figure 2: Structure of K777

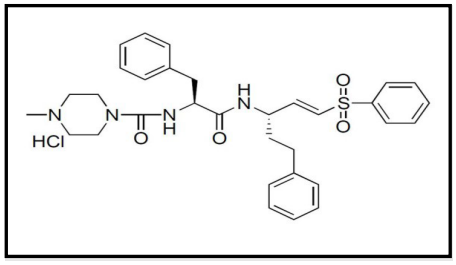


Table 1: Drug Substance Characteristics

Attribute	Result
Appearance	White powder
Molecular weight	611.19 (574.73 free base)
Molecular formula	$C_{32}H_{39}C_lN_4O_4S$
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. The capsules are packaged in 40 cc HDPE bottles closed with a 33 mm child resistant cap and an induction foil seal. One 0.75 g silica gel desiccant Pillowpak is added to each bottle. The composition of the placebo is provided in Figure 3.

Figure 3: Structure of Matched Placebo

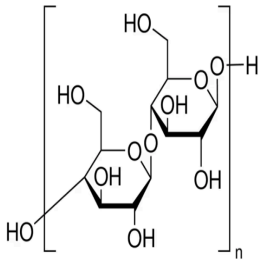


Table 2: Matched Placebo Composition

Component	Quality	Quantity per Capsule
Microcrystalline cellulose	NF, Ph. Eur., JP	62.5 mg
Size 1 orange gelatin capsule	Per manufacturer's specification	1 capsule

6.2.4 Product Storage and Stability

Drug will be kept in HDPE bottles stored at the appropriate temperature listed in the storage conditions section before administration.

Product 1: SLV213

Investigational drug must be kept in a limited-access, secure place at controlled room temperature between (15-25°C [59-77˚F]) and protected from light until it is used or returned to the sponsor or designee for destruction. Investigational drug must be stored under the conditions specified on the label and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day while the drug is still in the CTU.

Product 2: Matched Placebo

Placebo must be kept in a limited-access, secure place at controlled room temperature between (15-25°C [59-77˚F]) until it is used or returned to the sponsor or designee for destruction. Matched placebo must be stored under the conditions specified on the label and remain in the original container and protected from light until dispensed. A daily temperature log of the matched placebo storage area must be maintained every working day while the matched placebo is still in the CTU.

6.2.5 Preparation

The unblinded pharmacist will prepare each dose from the HDPE bottles. Participants will receive dosing Q12h daily (morning and evening) on Days 1 to 7 at the CTU. The first dose of the study drug will be received in the morning of Day 1 and every subsequent dose administered every 12 h (± 15 min). The study product will be administered orally with at least 240 mL (8 fluid ounces) of water by blinded delegated site staff under the supervision of the blinded PI or sub-investigator or authorized clinicians listed on Form FDA 1572.

All participants are required to fast for at least 8h before and 4h after the morning dose on Day 1 and the evening dose on Day 7, and at least 2h before dose to 1h after evening dose on Day 1, both

doses on Days 2-6 and the morning dose on Day 7. The meal schedule will be structured to restrict meals before each dose as required. Standard meals are provided at the appropriate times before and after drug administration and the time of last meal consumed before and after each dose will be recorded. Fluids will be allowed except at least 1h before and 1h after each scheduled dose.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Treatment Assignment Procedures

Per ICH guideline E6(R2): GCP, screening records will be kept at the participating site to document the reason why an individual was screened, but failed trial entry criteria. The reasons why individuals failed screening will be recorded in the Statistical and Data Coordinating Center's (SDCC) Advantage eClinical^{SM} (Electronic Data Capture System).

Consented participants who met eligibility criteria at screening and confirmed to be eligible at check-in (Day-1) Visit will be enrolled into the study.

6.3.2 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.

6.3.3 Blinding and Masking Procedures

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 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 MM and DMID MO 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 SDCC. The sponsor (DMID, the Investigational New Drug [IND] Application 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).

6.4 Study Intervention Compliance

Participants will be observed at the time of dosing by a member of the clinical research team who is licensed and authorized to administer study product (PI, sub-investigator or delegated clinicians) listed on Form FDA 1572. 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 electronic Case Report Form (eCRF).

6.5 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 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 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 Section 5.4.

6.5.1 Rescue Medicine

Not Applicable.

6.5.2 Non-Research Standard of Care

If at any time during the inpatient facility stay, the participant develops illness requiring medical care that is beyond the care available in this facility, the participant will be transferred to a hospital capable of providing this level of care. The hospital and physicians accepting the participant for care will be informed of the participant's participation in this research study so that the participant can be managed according to appropriate precautions per standard of care.

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Halting Criteria and Discontinuation of Study Intervention

7.1.1 Study Halting Criteria

Cohort Halting Rules

If any of the following criteria occur, dosing of subsequent participants in the cohort will be halted and could resume after blinded review by the SMC at an *ad hoc* meeting:

- One participant experiences a treatment-related SAE assessed as related to the investigational study product, with the exception of accidental injury.
- One participant experiences a treatment-related Grade 3 or higher adverse event.
- Two or more participants experience a Grade 2 or higher systemic AE in the same higher level group term (HLGT) per MedDRA classification assessed as related to the study product.
- One participant develops QT prolongation on a post dose ECG, defined as a QT interval with Fridericia correction method (QTcF) > 500 msec (Grade 3).
- One participant develops clinically significant abnormal liver function tests as follows:
    - ALT and/or AST > 5 × upper limit of normal (ULN) in the absence of a total bilirubin increase.
    - ALT and/or AST elevations > 3 × ULN in the presence of a total bilirubin increase > 2 × ULN or an international normalized ratio (INR) > 1.5 without findings of cholestasis or other alternate etiology to explain the elevations (i.e., "Hy's Law cases").
    - Symptomatic ALT and/or AST elevations > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5% of total WBC count).

7.1.2 Individual Halting Criteria

A participant will be discontinued from further dosing and the cohort dosing will be stopped for the SRC review or SMC *ad hoc* meeting if any of the following criteria are met:

- A participant experiences an SAE, regardless of the relationship to the study product, with the exception of accidental injury.
- A participant experiences clinically significant Grade 3 or higher AE (laboratory or systemic) assessed as related to the study product.
- A participant develops anaphylaxis within 24 hours after receiving the study product.
- A participant experiences a suspected drug-related hypersensitivity AE Grade 2 or higher.
- A participant develops QT prolongation on a post dose ECG, defined as a QT interval with QTcF > 500 msec (Grade 3).
- In the opinion of the PI, further dosing would not be in the best interest of the participant.

7.1.3 Follow Up for Participants Who Discontinued Study Intervention

Discontinuation from the investigational drug product does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the PI, sub-investigator, or licensed clinician will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE. All other events will be monitored and collected even when drug administration has been discontinued.

See SOA, Early Termination (ET) (Section 1.2) for data to be collected at the time of study intervention discontinuation.

7.2 Participant Withdrawal from the Study and Replacement

7.2.1 Participant Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request for any reason.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Participant becomes pregnant.
- Study non-compliance that in the opinion of the investigator poses an increased risk (i.e., missing safety labs), or compromises the validity of the data.
- If any clinical, laboratory or ECG abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- If the participant met an exclusion criterion for participation in the study (either newly developed or not previously recognized) that precludes further study participation.

- Medical disease or condition, or new clinical finding(s) for which continued participation, in the opinion of the investigator might compromise the safety of the participant, interfere with the participant's successful completion of this study, or interfere with the evaluation of responses.
- Participant lost to follow-up.

Every effort should be made to encourage participants to remain in the study for the duration of their planned outcome assessments. Participants will be educated on the continued scientific importance of their data, even if they discontinue study drug.

Unless the participant withdraws consent, those who discontinue study drug early will remain in the study.

If the participant agrees, every attempt will be made to follow all AEs through resolution (return to baseline) or until defined as stable.

The reason for participant discontinuation or withdrawal from the study, whether the decision was made by investigator or participant, and the extent of the withdrawal (i.e., whether participant withdrew from all components of research study or just the study intervention) will be recorded on the CRF.

The investigator will inform the participant that already collected data will be retained and analyzed for this study even if the participant withdraws from this study. Biospecimens collected for the current study will still be used to analyze the study endpoints.

7.2.2 Participant Replacement

Participants who withdraw or are withdrawn from this study after receiving at least one dose of the 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.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she is unable to be contacted by the study site staff after three attempts. Extensive effort (i.e., generally three documented contact attempts via telephone calls, e-mail, etc., made on separate occasions) will be made to locate or recall the participant, or at least to determine the participant’s health status. These efforts will be documented in the participant’s study file.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Screening Procedures

There is a small amount of risk to participants who report that they are in good health but have an unknown health problem at the time of screening. Screening assessments can occur up to 28 days before the participant's first treatment (Day 1) and may occur in one or two visits. At the first visit, and prior to any other study-related activities, a delegated staff member at the participating site will provide the participant with detailed study information and will obtain written informed consent.

Individuals will have the opportunity to ask questions. The Site PI or authorized sub-investigator or clinician will also be available to answer questions. The site PI will review and approve eligibility criteria.

Some or all of the following assessments are performed during the Screening visit and confirmed at Check-in (Day -1) to determine eligibility requirements as specified in the inclusion (Section 5.1) and exclusion criteria (Section 5.2). Assessments are listed in the SOA (Section 1.2). Guidelines for documentation will be reported in the study-specific MOP and eCRF Instructions.

8.1.1 Clinical Procedures and Evaluations

- **Demographics:** Demographic information (date of birth, gender, ethnicity, and race) will be recorded on the subject's source documents and eCRF at Screening Visit. Name, address, phone number, and emergency contact information will be documented in the source documents only.
- **Eligibility Review:** A review of study inclusion and exclusion criteria will be completed within 28 days before study drug dosing at the Screening and Check-in (Day -1) visits. Confirmation of eligibility for dosing will be performed before dosing on Day 1.

  Screening failures and the reason for failure to meet the study eligibility requirements will be documented in source documents and eCRFs.
- **Medical History (MH):** A review of pertinent MH that may impact study participation will be obtained by direct interview of the subject. The MH will capture current disease processes, past disease processes, history of hospitalization, and history of surgery. Participants will be queried regarding a history of significant medical disorders of the head, eyes, ears, nose, throat (HEENT), mouth, skin, the cardiovascular, respiratory, gastrointestinal, renal, urological, nervous, hematological, lymphatic, endocrine, musculoskeletal and genital/reproductive systems. A history of allergies including allergies to medications, medication history, and history of substance and alcohol abuse will be obtained.

Participants will be queried about a history of orthostatic hypotension, any symptoms associated with position change, syncope or near syncope (i.e., dizziness, fainting), and symptoms related to transition from lying down to standing up (such as fast heart rate, dizziness, or fainting).

The MH will be obtained at Screening Visit and updated on Day -1 (Check-in) and before dosing on Day 1. After start of study drug dosing, any worsening of pre-dosing MH or new symptoms will be evaluated and reported as TEAEs.

- **Concomitant Medications (ConMeds):** Medication history will include prescription medication, including contraceptives, and non-prescription drugs, vitamins, supplements and herbal medication, and recent vaccinations including for COVID-19 used in the recent past, and include medications that are prohibited prior to dosing. (See Section 6.5).

  Medications history will be obtained at Screening, Check-in (Day-1) and updated prior to dosing on Day 1. Medications taken prior to dosing will be recorded as "Prior Medications".

- **Physical Exam (PE):** A Complete PE - except genital, breast, pelvic and rectal exams - will assess general appearance and the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) lymph nodes; and (10) neurological/neurosensory examination.

  Any abnormal finding on a screening examination assessment must be assessed as Not Clinically Significant (NCS) or Clinically Significant (CS) by the investigator (PI, sub-investigator, or authorized clinician) listed on Form FDA 1572 and recorded in the source document and eCRF.

  A complete PE will be performed at the Screening and Check-in (Day -1) visits.

- **Body Mass Index (BMI):** Consists of weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units according to the following formula: BMI = weight (kg)/[height (m)]^2.

  BMI will be measured and recorded at Screening. A subject will be excluded if BMI is ≤ 18 kg/m^2 or ≥ 32 kg/m^2, or weight $\leq$100 lbs at Screening.

  Body weight only (i.e., not including height or recalculation of BMI) will also be measured on Day-1

- **Vital Signs (VS)**: Include body temperature (oral), BP (resting more than 5 min), RR, and HR. Heart rate and BP will be measured at rest with the participant supine for at least 5 minutes.[1]. Repeat measurements with the participant supine may be allowed if the first measurement is abnormal (See Section 8.1.4)

Note 1: Orthostatic blood pressure and heart rate will be obtained and recorded after the supine VS, while a participant is in standing position with measurements taken at 1 minute ± 15 seconds and 3 minutes ± 15 seconds after standing.

VS will be measured before any blood draws at the Screening Visit and Check-in (Day -1).

- **Electrocardiogram (ECG)**: Standard twelve-lead ECG using an ECG machine that automatically calculates the HR and measures PR interval, RR interval, QRS interval, QT interval, and QT interval corrected by the Fridericia (QTcF) formula. QTcF may also be calculated manually by the site. Participants should be in a supine position and should have an approximate 10-minute rest period prior to the test. ECGs will be recorded before any blood draws.

  The ECGs will be reviewed by the PI or authorized sub-investigator or study clinician (listed on FDA Form 1572) for ECG interval and for morphologic abnormalities. If a question regarding ECG interpretation arises, the study investigators will have the ECG reviewed by a cardiologist. To be eligible for participation, the PR and QTcF interval must be within protocol reference range criteria (as shown in Appendix A) at Screening and Check-in (Day -1) and there must be no clinically significant ECG abnormalities.

- ECGs will be obtained at the Screening Visit and Check-in (Day -1).

8.1.2 Laboratory Evaluations

Venipuncture schedule and blood volumes are shown in Section 1.2 and Appendix B, Table 3, respectively.

- **Clinical Laboratory Assessments: (Hematology, Coagulation, Chemistry and Urinalysis):** Blood and urine samples for clinical laboratory tests will be collected at the Screening Visit and on Check-in (Day -1) to determine eligibility.

  Participants must be fasting at least for 4h before any blood draw for clinical laboratory assessments. These tests will include:

  - Hematology (HEM): Complete Blood Count with absolute differential cell count (CBC w/Diff). The panel will include total white blood cell count (WBC), absolute count for neutrophils, lymphocytes, monocytes, basophils, and eosinophils, red blood cell count (RBC), platelet count, and hemoglobin.
  - Coagulation (COAG): INR with prothrombin time (PT), activated partial thromboplastin time APTT).
  - Chemistries (CHEM): Albumin, blood urea nitrogen (BUN), calcium, phosphorous (inorganic), creatinine, estimated glomerular filtration rate (eGFR) calculated by the CKD-EPI formula, electrolytes (sodium, potassium, chloride, total carbon dioxide [CO2]), magnesium, glucose (fasting), total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase

(ALP), total protein, amylase, and lipase.

- Urinalysis (UA): Routine dipstick testing of clean-catch urine for occult blood, protein, glucose, nitrite, bilirubin, specific gravity, and pH.
  - If urine dipstick is abnormal for blood, protein, glucose, and nitrites, urine microscopy will be performed (for WBC, RBC, bacteria, and other cell counts), and the results will supersede those of the dipstick UA.
  - UA can be deferred until after the end of menses.

Clinical laboratory tests at the Screening Visit and Check-in (Day -1) should be in the normal reference range with exceptions. (See Section 5.2, Inclusion Criterion #4). Laboratory normal reference ranges are those included in the current version of the Manual of Procedures (MOP).

Other Exceptions to screening laboratory tests' normal reference ranges are:

a. Labs performed as part of a panel but not included among the listed tests are to be recorded in the source record. Examples include direct bilirubin, RBC, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), mean platelet volume (MPV), nucleated red blood cell count (NRBC CT), and % white blood cells types, which are included in a CBC with WBC differential, INR, and specific gravity and pH resulted by dipstick urinalysis (UA). If abnormal per the laboratory normal reference range, they are not exclusionary and are not to be graded per Toxicity table individually; however, the investigator would make a clinical decision about their clinical significance.

b. Menstruating females with a positive dipstick UA or microscopic UA may be retested following cessation of menses. Gross blood in urine that is confirmed due to menses is not a TEAE (but is for all other reasons).

- **Viral Serology Testing:** HIV antibody test (HIV 1 & HIV 2), Hepatitis B surface Ag (HBsAg, Hepatitis C virus (HCV antibody, and SARS-CoV-2 molecular diagnostic test (Cue Care™ test) for COVID-19.

  The HIV and hepatitis tests will be performed at the Screening Visit only and all results must be negative for study eligibility.

  The SARS-CoV-2 test will be performed at Check-in Visit (Day -1), and the result must be negative for study eligibility.

- **Pregnancy Test (females of child-bearing potential only):** A *serum β-HCG pregnancy test* will be done at the Screening Visit and a *urine pregnancy test* will be done at Check-in (Day -1) within 24 hours before receiving the initial study product. The results must be negative for determining eligibility and dosing with study drug(s).

- **Serum follicle stimulating hormone (FSH)**: The test will be performed to confirm post-menopausal status in female participants at the initial Screening Visit only.
- **Urine Drug Screen (UDS):** Urine drug screen to assess for illicit (non-medical) use of amphetamines, cocaine metabolites, barbiturates, benzodiazepines, opiates, cannabinoids, tricyclic antidepressants, and phencyclidine. Urine creatinine will be measured as part of the profile to assess quality of collected sample.

  UDS will be performed at Screening Visit and on Day -1. Results must be negative for study eligibility. Participants using any of these substances for medical reasons will also be excluded.
- **Urine Alcohol Test**: The test will be performed at Screening and Check-in (Day -1). Results must be negative for study eligibility.
- **Urine Cotinine Test**: The test will be performed at Screening and Check-in (Day -1). A positive result at Screening in a participant without history of heavy consumption of nicotine products is acceptable. The result of test done at Check-in (Day -1) must be negative for study eligibility.

8.1.3 Evaluation of Screening Data

The overall eligibility of the participant to participate in the study will be assessed once all screening values are available. The screening process can be suspended prior to complete assessment at any time if exclusions are identified by the study team.

Study participants who qualify for inclusion will be contacted and scheduled for a Check-in visit (Day-1) to evaluate continuing eligibility for enrollment within the window for enrollment.

8.1.4 Procedures to be Followed in the Event of Abnormal Clinical Laboratory Test Values or Abnormal Clinical Findings During Screening

During screening, if a physiologic parameter, e.g., vital signs (VS) or clinical laboratory value, is outside of the protocol-specified range, then the measurement may be repeated if, in the judgment of the investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition (e.g., stress, anxiety, or "white coat syndrome") or if there is a technical problem with the measurement caused by malfunctioning or an inappropriate measuring device (i.e., inappropriate-sized blood pressure cuff), or error in collecting, and processing the clinical laboratory sample). An abnormal laboratory value may be repeated once. An abnormal vital sign should be repeated as described below.

Procedure followed for Abnormal Supine Vital Signs (Screening, Day -1, pre-dose on Day 1):

- Abnormal supine VS that are either due to technical or procedural error or the result of an acute, short-term condition as assessed by the PI (e.g., stress, anxiety, white coat syndrome) may be repeated up to twice more at rest and at least 5 min after previous measurement.

- If the second measurement is abnormal, it will be reported at the highest grade/value of severity of the two measurements and will be used for assessment of eligibility (per Inclusion Criterion #4).
- If the second measurement is normal, a third measurement will be taken at least 5 minutes after second measurement.
- If the third measurement is normal, the subject is eligible. If the third measurement is abnormal, the value with the highest grade of severity between the first and the third measurements will be reported and will be used for assessment of eligibility (per Inclusion Criterion #4).

Re-screening:

Rescreening is not allowed, except in the following circumstances:

- Prospective participants may not be re-screened due to laboratory values except to verify accuracy of an aberrant value.
- A participant may be re-screened if there is a transient disease status (e.g., participant complained of a "cold or fever" and met a temporary delaying enrollment criterion of acute illness or fever), or if a protocol eligibility criterion that is not met at the initial time of screening, will be met by rescreening at a later date (e.g., a medication taken within exclusionary window at the time of first screening that would not be within exclusionary window at a later rescreen).
- No participant may be screened more than twice due to a screening failure result as defined above.

Participants who failed screening will be provided any of their abnormal clinical laboratory results if requested and will be counselled to follow up with their primary healthcare provider for further evaluation and treatment as needed.

8.2 Efficacy Assessments

Not Applicable

8.2.1 Efficacy Evaluations

Not applicable

Management of Results

Not Applicable

8.2.2 Exploratory Assessments

Not Applicable

8.3 In-Patient and Follow up Procedures

The following assessments will be performed during the In-patient Treatment Period for evaluating the Safety and PK objectives of the study. (See also the SOA Section 1.2). Authorized clinicians, who are licensed to make medical diagnoses and listed on the Form FDA 1572, will be responsible for all study-related medical decisions.

8.3.1 Clinical Procedures and Evaluations

- **Medical History (MH):** After start of study drug dosing, any worsening of pre-dosing MH or new symptoms, including orthostatic symptoms, will be evaluated and reported as TEAEs.

  An interim MH will be obtained by interview of participants for evaluation of TEAEs from Day 1 to the last study visit, and any changes since the previous clinic visit or telephone call after discharge from the CTU will be noted. The interim MH should include an assessment for new medical conditions and symptoms suggestive of Medically- Attended AEs (MAAEs) (see Section 8.5.3) and protocol specified adverse events of special interest (AESIs) (See Section 8.5.9).

- **Assessment of TEAEs and SAEs**: Unsolicited AEs will be evaluated from the time of initial dosing to the last study visit (Day 28 ±2 days) (See Section 8.5). During the Inpatient treatment period, (Day 1 to Day 9), the participants will be monitored as inpatients and complete scheduled assessments. Following discharge on Day 9, CTU staff will contact the participants by phone on Days 15 (±2 days), 21(±2 days), and 28 (±2 days) and inquire about their well-being, the emergence of any AEs since the last visit and the use of any ConMeds. Based on the information collected, participants will be asked to return to the CTU for evaluation.

- **Concomitant Medications (ConMeds):** 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. (See Section 6.5 for prohibited medications during the study).

- **Physical Examination (PE):**

  - **A symptom-directed (focused) PE** may be performed for evaluation of new symptoms reported from the time of admission on Day -1 to before the first dose on Day 1 and assessment of TEAEs at any time after dosing on Day 1 to the last study visit, focusing on orthostatic vital signs and symptoms.

  - **A complete PE** will be performed on Day 9 prior to discharge from the CTU. (See Section 8.1.1)

  Any abnormal finding on a PE performed after dosing on Day 1 must be assessed as Not Clinically Significant (NCS) or Clinically Significant (CS) by the investigator (PI, sub-

investigator, or authorized clinician) listed on Form FDA 1572 and recorded in the source document and eCRF.

- **Vital Signs (VS) inclusive of orthostatic blood pressure and heart rate:** Include body temperature (oral), BP (resting more than 5 min), RR, and HR. Heart rate and BP will be measured at rest with the participant supine for at least 5 minutes. VS will be measured twice daily within 30 min before and 2h (± 10 min) after each dose on Days 1 to 7, once daily in the morning on Days 8 and 9, or at ET. Abnormal VS may also be measured at unscheduled visits as needed for follow up of AEs. Repeat measurements with the participant supine may be allowed if the first measurement is abnormal (See Section 8.3.3).[1]

  Note 1: Orthostatic blood pressure and heart rate will be obtained and recorded after the supine VS, while the participant is in the standing position with measurements taken at 1 minute ± 15 seconds and 3 minutes ± 15 seconds after standing.

- **ECG:** A standard 12-lead ECG will be recorded, within 30 min before the morning dose on Day 4, on Day 8 before the 12h blood (plasma) PK collection after the evening dose on Day 7, or ET. Additional ECGs may be recorded as needed for the evaluation of TEAEs. The participant should be in a supine position and should have an approximate 10-minute rest period prior to ECG recordings.

  A physician (PI or coinvestigator) or clinician who is licensed to make diagnoses (listed on Form FDA 1572) will evaluate the ECG for any abnormalities in ECG intervals including QT/QTcF, and any morphologic abnormalities for clinical significance. If a question regarding ECG interpretation arises, the study investigators will have the ECG reviewed by a cardiologist.

8.3.2 Laboratory Evaluations

- **Clinical Laboratory Assessments:**
  - Blood for HEM, CHEM, and COAG will be collected before the morning dose on Days 2, 4, and 6, and on Day 8, or ET for the evaluation of the same tests listed in Section 8.1.2. Clinical lab tests may also be performed at unscheduled visits as needed for follow up of AEs. Participants must be fasting at least for 4 h before any blood draw for clinical laboratory assessments.
  - UA will be collected before the morning dose on Day 4 and on Day 8, or ET (See Section 8.1.2)

8.3.3 Procedures to be Followed in the Event of Abnormal Clinical Laboratory Test Values or Abnormal Clinical Findings During Conduct of the Trial

All abnormal clinical findings or abnormal clinical laboratory test values post treatment will be considered AEs and followed up as AEs. If a physiologic parameter, e.g., VS or clinical laboratory value, is outside of the protocol-specified range, then the measurement may be repeated if, in the judgment of the participating site PI or appropriate licensed sub-investigator or clinician, the

abnormality is the result of an acute, short-term, rapidly reversible condition (e.g., stress, anxiety or "white coat syndrome") or other source of error (e.g., a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (i.e., inappropriate-sized BP cuff), or error in collecting or processing the clinical laboratory sample. If the repeat measure is within normal range, the most accurate value will be used. Any abnormal parameters will be recorded in the medical record.

Once dosed with study product, lab results that are above the upper limit of normal or below the lower limit of normal for the baseline reference ranges but are less than Grade 1 in the toxicity table, will not be graded and reported as outside the normal range. Lab results that were acceptable for enrollment within the Grade 1 toxicity range of the FDA toxicity tables will be graded as AEs if the on-study values are higher or lower than the baseline value and fall within the range of AEs with "increased" or "decreased" values.

Procedure followed for Abnormal Supine Vital Signs (Post Dosing On Days 1 through 9, or ET):

- Any time after the start of the oral dose administration, any abnormalities in supine VS that occur either due to technical or procedural error or the result of an acute, short-term condition as assessed by the PI (e.g., stress, anxiety, white coat syndrome) may be repeated twice more at rest, while the participant is in the supine position and at least 5 min of each other.
- If the second VS is abnormal, then the highest severity grade between the first and second measurements will be used for assessment of TEAE per Appendix A.
- If the second VS is normal, then a third repeat is to be taken at least 5 min of the previous measurement.
- If the third value is abnormal, the highest grade of severity between the first and third measurements will be used for assessment of TEAE per Appendix A.

8.3.4 Blood sampling for Plasma SLV213 Assay during the In-patient Period and Serum for Future Research

A validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) bioanalytical assay method for the quantitation of total SLV213 in plasma will be performed at the bioanalytical lab, KCAS.

Blood (plasma) will be drawn at the following timepoints to measure the concentration of study drug 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 timepoint is the same as the predose timepoint (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 timepoint 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 (t=0) and at 12h (±15 min) after the morning and evening doses on each day. (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 (t=0), and 12h (±15 min) after the morning dose. (The 12h timepoint is the same as the predose timepoint (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.

Blood (serum) will be drawn at the same timepoints as PK samples for storage for secondary future research if the subject consented to the collection and storage.

Blood samples will be obtained promptly after each corresponding VS assessment before each dose on Days 1 to 7, and on Days 8 and 9.

Sample collections will be scheduled for the nominal time point and actual collection times recorded.

Approximately 6 mL of peripheral blood will be drawn into prelabeled K2-EDTA plasma separator tubes for measurement of plasma concentration of SLV213 (PK samples) and 3.5 mL in serum separator tubes for secondary future research (if the participant has given consent) at each PK sampling timepoint. Details regarding the specimen preparation, handling, and storage of plasma PK bioanalytical samples and samples for secondary future research will be described in the protocol-specific MOP.

Specimen Shipment

Specimen shipment will occur at intervals during the trial following all applicable International Air Transport Association requirements and according to the specifics for storage temperature and documentation as detailed in the central clinical laboratory manual and protocol-specific MOP, as appropriate.

All specimens for clinical screening and safety laboratory evaluations will be transported from the CTU to the local clinical laboratory.

Primary and Back-up aliquots of plasma PK samples for storage will be shipped from the CTU to DMID CMS at:

Fisher BioServices

c/o DMID Clinical Materials Services (DMID CMS)
20439 Seneca Meadows Parkway
Germantown, MD 20876
Phone: 240-477-1350
Fax: 240-477-1360
Email: DMID.CMS@thermofisher.com

In order to perform bioanalytical assays of PK samples within the LTS period, aliquots of plasma PK samples designated by the SDCC (Emmes) picklist will be shipped to the bioanalytical lab, KCAS, Inc., from the DMID CMS at -70°C, and assays will be performed within the LTS timeframe. Further information will be provided in the study-specific MOP**.**

8.3.5 Total Blood Volume Drawn

The estimated blood volume drawn for tests at Screening and Day-1 is 38.9 mL, and for tests on Day 1 to Day 9 it is 325.8 mL (for safety lab tests, 60.8 mL; for plasma PK samples, 160 mL; and for serum for future research, if consent was provided, 105 mL). The total cumulative estimated blood volume drawn during the entire study is 384.7 mL.

Venipuncture schedule and blood volumes for screening and safety lab tests and for the PK and future research samples are provided in Appendix B, Table 3.

8.3.6 Disposition of Plasma Samples

Blood (plasma or serum) samples are collected for clinical laboratory testing, PK assays and, if consent was provided, for storage for future research. No genetic testing will be done on collected blood samples.

Clinical laboratory samples will be destroyed after tests are completed and results are reviewed according to standard practices of the Site Clinical Lab.

Plasma samples used for measurement of the concentration of study drug at the bioanalytical lab will be disposed of per sponsor (DMID) guidance.

Residual plasma PK samples and additional serum samples stored at the DMID CMS (Fisher) may be used for secondary research if the participant provided consent to store and use these samples for this purpose. (See Section 10.1.4 for further information.)

8.4 Study Drug Administration

Participants will receive daily dosing Q12h (morning and evening) for 7 days, with the first dose of the study drug administered in the morning on Day 1 and the last dose in the evening of Day 7. The study product will be administered orally with at least 240 mL (8 fluid ounces) or more of tap or bottled water.

All participants are required to fast for the indicated periods before and after dosing as follows:

- Day 1, Morning dose: at least 8h before and 4h after the morning dose
- Day 1, Evening dose: at least 2h before and 1h after the evening dose

- Days 2-6, Both morning and evening doses: at least 2h before and 1h after each dose
- Day 7, Morning dose: at least 2h before and 1h after the morning dose
- Day 7, Evening dose: at least 8h before and 4h after the evening dose

Fluids will be allowed during fasting except for at least 1h before and 1h after each scheduled dose.

The meal schedule will be structured to restrict meals before and after each dose as required. Standard meals will be provided at appropriate times before and after each drug administration and the time the last meal was consumed before and after each dose on Days 1 to 7 will be recorded.

8.5 Adverse Events and Serious Adverse Events

8.5.1 Definition of Adverse Events (AE)

An AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product.

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

Symptoms that increase in severity or frequency will be considered as AE's and processed accordingly.

Any medical condition that is present at the time the participant is screened will be considered as baseline and not reported as an AE. However, if the severity (i.e., grade) of any pre-existing medical condition increases, it should be recorded as an AE.

Adverse events can be further divided into solicited AEs and unsolicited AEs:

- Solicited AEs are those for which the study team will specifically query the participant whether they occurred. **Solicited AEs are not collected in this study**.
- Unsolicited events are all AEs spontaneously reported by the participant and/or in response to an open question from study personnel or revealed by observation, PE or other procedures. **All AEs collected in this study are unsolicited events.**

8.5.2 Definition of Serious Adverse Events (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes (21 CFR 312.32 (a)):

- Death

- A life-threatening adverse event*
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, convulsions that do not result in inpatient hospitalization, etc.

* An adverse event is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include grade 4 severity unless the adverse event might have caused death.

8.5.3 Definition of Medically-Attended Adverse Events (MAAE)

MAAEs are defined as AEs with medically attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. Adverse events (e.g., abnormal vitals) identified at a routine study visit will not be considered MAAEs.

8.5.4 Classification of an Adverse Event

The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment.

Severity of Event

All AEs or SAEs will be assessed for severity, according to the FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, available at https://www.fda.gov/media/73679/download, and supplemental grading parameters are included in Appendix A. If the severity of any AE changes, the highest severity should be recorded.

Relationship to Study Intervention

For each reported adverse event or reaction, the PI or designee must assess the relationship of the event to the study product using the following guideline:

Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE. For scale of relatedness, "possibly related", "probably related", and "definitely related" map to "related". Adverse Events when alternative etiology is not identified will be assessed as "related" to the study product.

Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.5.5 Time Period and Frequency for Event Assessment and Follow up

For this study:

- Unsolicited AEs will be collected from Study Day 1 through the end of the study.
- SAEs will be collected from Study Day 1 through the end of the study.
- All SAEs will be followed through resolution or until the site investigator deems the event to be chronic or stable.
- AEs will be followed through resolution or until the site investigator deems the event to be chronic or stable or has returned to baseline.

8.5.6 Adverse Event Reporting

Investigator Reporting of AEs

All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis or AE term, if available. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome. AEs characterized as intermittent require documentation of onset and duration of each episode.

All AEs occurring during the study, whether or not they are related to the study drug, must be recorded on the appropriate eCRF. Information to be collected for AEs includes event term or description, date of onset, assessment of severity, relationship to study product and alternate etiology (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as an investigator), date of resolution, seriousness, and outcome. AEs occurring during the trial collection and reporting period will be documented appropriately regardless of relationship.

Laboratory AEs Evaluation and Reporting

Once dosed with study product, lab results that are above the upper limit of normal or below the lower limit of normal for the baseline reference ranges, but are less than Grade 1 in the toxicity table, will not be graded and reported as outside the normal range.

Laboratory values that meet the post dosing grading criteria but did not preclude the subject from enrolling will be entered as AEs only if the value worsens in severity.

8.5.7 Serious Adverse Event Reporting

Investigator Reporting of SAEs

All SAEs will be recorded on the appropriate SAE form and sent to DMID Pharmacovigilance Group (PVG). The SAE form will collect all relevant data concerning the SAE, including event term or description, date of study product administration, date of onset, duration or date of resolution, severity, seriousness, outcome, any action taken with the study product, and relationship to each study product or an alternate etiology as assessed by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 (PI, co-investigator, licensed clinicians). In addition, the investigator should provide relevant MH, ConMeds, laboratory or diagnostic results, details of any treatment for the SAE, and a narrative including all other pertinent medical information.

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID PVG via fax or email. SAEs reported via the SAE Hot Line must be followed with a fax or email submission:

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20817, USA
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)
SAE FAX Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)
SAE Email Address: PVG@dmidcroms.com

In addition to the SAE form, select SAE data fields must also be entered into the SDCC system. Please see the protocol-specific MOP for details regarding this procedure.

Other supporting documentation of the event may be requested by the DMID PVG and should be provided as soon as possible.

At any time after completion of the study, if the site PI or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to study product, the site PI or appropriate sub-investigator will report the event to the DMID PVG.

Regulatory Reporting of SUSARs

The sponsor will report any Suspected Unexpected Serious Adverse Reactions (SUSAR) to the FDA in an IND safety report. DMID will report an AE as a suspected unexpected adverse event only if there is evidence to suggest a causal relationship between the study intervention and the AE.

The Sponsor must ensure the event meets all three of the definitions:

1. Suspected adverse reaction.
2. Serious.
3. Unexpected.

Both seriousness and unexpectedness are important, but the event will be reported only if there is evidence to suggest a **causal relationship between the drug and the adverse event**, such as:

A. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure.

B. One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug.

C. On review as an aggregate analysis when the occurrence is higher than the historical control.

DMID will report to the FDA any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. If the event is not fatal or life-threatening the IND safety report will be submitted within 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to the FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request. The DMID MM is responsible for determining whether a SAE is a SUSAR based on the nature, severity, or frequency of the event.

DMID will submit an IND safety report to the FDA and will notify all participating site PIs (i.e., all PIs to whom the sponsor is providing drug under its IND(s) or under any PI's IND(s) of potential serious risks from clinical studies or any other source, as soon as possible.

SAEs that are not SUSARs will be reported to the FDA at least annually in a summary format which includes all SAEs.

8.5.8 Reporting Events to Participants

Participants have the right to be informed of any new findings of AEs or SAEs that may affect their safety or influence their choice to participate or continue participating in the study. Any information provided to the participant will be blinded with respect to study treatment.

8.5.9 Adverse Events of Special Interest (AESI)

Definition of AESI

An AESI (serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor may be appropriate. Such clinically significant events may require further investigation in order to characterize and understand them and will be collected as AESIs, discussed by the SMC, and expanded narratives of each written as indicated.

Protocol-defined AESIs are:

- All clinically significant cardiovascular Grade 3 of higher AEs including symptomatic cardiac arrhythmias and ECG abnormalities
- All clinically significant Grade 3 or higher gastrointestinal AEs
- Hepatic toxicity assessed by severe (Grade 3 or higher) based on values of liver function tests (LFTs

All AESIs will be collected through study Day 28 and will be included in the safety analysis.

All AESIs are assessed for severity and relatedness to investigational product, recorded, and followed as described above under AEs and SAEs.

Reporting of AESI

All AESIs, whether serious or non-serious, also require additional reporting to the DMID PVG within 24 hours of site awareness for serious AESI or within 72 hours of site awareness for non-serious AESI. AESIs are reported on the appropriate CRF with additional reporting to DMID PVG using the protocol-approved SAE form. Submit AESI as follows:

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20817, USA
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)
SAE FAX Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)
SAE Email Address: PVG@dmidcroms.com

8.5.10 Reporting of Pregnancy

Pregnancy is not an AE. However, any pregnancy that occurs during study participation (through study Day 28 should be reported to the sponsor on the appropriate CRF. Pregnancy should be followed to outcome. This follow-up will include pregnancy outcome (termination, pre-term birth, term birth) and newborn outcome (live birth, fetal demise, stillbirth; presence of any congenital anomalies). No in-person visits will be required for pregnancy outcome determination.

8.6 Unanticipated Problems

8.6.1 Definition of Unanticipated Problems

The Department of Health and Human Services Office for Human Research Protections (DHHS-OHRP) considers **unanticipated problems** involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research

protocol and informed consent document; and (b) the characteristics of the participant population being studied; **and**

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); **and**
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Incidents arising from noncompliance with study procedures should be reported as protocol deviations (see Section 10.1.10). An incident that qualifies as both a unanticipated problems and a protocol deviation should be reported as both.

8.6.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems to the study sponsor (DMID), the reviewing IRB and to the SDCC. The unanticipated problems report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are SAEs will be reported to the IRB and to the SDCC/study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB and to the SDCC/study sponsor within a timeline defined according to the relevant policies.
- Unanticipated problems, whether they are SAEs or not, will be collected from Day 1 through the end of the study.

8.6.3 Reporting Unanticipated Problems to Participants

Participants will be informed of any unanticipated problems that will potentially influence their participation in this trial.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

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.

9.2 Sample Size Determination

The sample size chosen of a total of 36 is considered to be sufficient for evaluation of safety, tolerability, and PK data of each cohort; the sample size was not based on statistical power considerations.

9.3 Statistical Analyses

9.3.1 General Methodology

A Statistical Analysis Plan (SAP) will be developed and approved by the study biostatistician and investigative team before unblinding, and the database is locked. The SAP will present the detailed statistical methodology to analyze the safety, tolerability, and pharmacokinetic data from this trial. The SAP will also provide details for handling missing data and possible confounding variables.

The safety set will be the primary population for safety data analysis. Analysis of primary and secondary endpoints will be done for each dose of SLV213 and compared with a pooled placebo group from all cohorts. The primary endpoint is the proportion of participants experiencing any TEAEs judged related to study drug vs. placebo. Frequencies and percentages of these events will be presented by treatment group. We will also estimate the event risks by treatment group and risk differences with 95% exact confidence intervals. Risk differences will be estimated for each dose level as compared against the pooled placebo group.

Secondary endpoints:

Binary endpoints will be analyzed using the same methods as described above for the primary endpoint.

9.3.2 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.

A formal SAP, which will elaborate on the analyses described here and describe any changes to the planned analyses, will be developed and finalized before performing any of these analyses (with the exception of SRC/SMC reviews of descriptive safety analyses).

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 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.

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.

9.3.3 Populations for Analyses

The following analysis sets will be used in the analysis.

Full Analysis Set: All randomized participants and analyzed according to the treatment as randomized. This population is analogous to an intent-to-treat population.

Modified Intent-To-Treat (mITT): All randomized participants who meet eligibility criteria and receive at least 1 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.

Safety Set: All randomized participants who received at least 1 dose of any study treatment, and analysis will be performed according to the treatment actually received.

PK Analysis Set: All randomized 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.

9.3.4 Baseline Characteristics and Participant Disposition

Details of baseline characteristics and participant disposition will be addressed in the SAP.

9.3.5 Efficacy Analyses

Analysis of the Primary Efficacy Endpoint(s)

Not Applicable.

Analysis of the Secondary Efficacy Endpoint(s)

Not Applicable.

Analysis of the Exploratory Efficacy Endpoint(s)

Not Applicable.

9.3.6 Safety Analyses

AEs will be presented in listings and TEAEs will be 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.

AEs, including abnormal laboratory values, will be graded according to the protocol Toxicity Tables in Appendix A. PE findings will be presented in data listings.

All AEs occurring after study drug dosing 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, or severe).
- 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 subject summarization in reporting the incidence of TEAEs, a subject will be counted once if the subject 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.

Additional Safety Analyses:

Descriptive summary statistics (mean, standard deviation [SD], median, minimum, and maximum) for all clinical laboratory data, 12-lead standard ECG parameters, and VS at admission and each applicable post-dosing visit, including changes from baseline values, will be calculated and presented by treatment cohort. Baseline values will be the last values recorded before initiating administration of study drug. For change-from-baseline summaries, participants with an undefined change from baseline, due to missing data, will be excluded. Clinical significance of abnormalities,

as assessed by the study PI or authorized study clinicians, will be indicated. The number and percentage of participants who meet toxicity criteria for clinical laboratory, VS and 12-lead ECG investigations will be listed and tabulated by treatment cohort.

Tolerability Assessment:

Tolerability to study product will be summarized by dose cohort and include number and proportion of participants with early study withdrawal or termination experiencing any AEs assessed as related to study drug vs. placebo as follows: (A) 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 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 VS measurements at least once post-dose; and (5) Meet Grade 3 criteria for safety ECG parameters at least once post-dose, and (B) Number and percentage of oral medication doses completed.

9.3.7 Pharmacokinetic Analysis

Plasma concentrations of SLV213 on Day 1 and Day 7 will be summarized using descriptive statistics (n, mean, SD, CV%, median, minimum, and maximum) for each treatment cohort, study day and nominal timepoint. Plasma study drug concentrations observed after each morning and evening dose of study drug from Day 1 through Day 7 (trough concentrations) will be summarized similarly for each treatment cohort and study day.

Plasma PK parameters will be estimated by noncompartmental analysis methods using Phoenix® WinNonlin® version 8.0 or higher and presented by treatment cohort. PK parameters and linearity index and dose-normalized exposure parameters ($AUC_{(0\text{-}tau)}$/Dose and C_{max}/Dose) after the first dose on Day 1 and after the last dose on Day 7 will be analyzed and presented.

Graphical presentations of plasma concentration vs. time profiles will be provided for SLV213 and will include individual subject and mean concentration profiles. Semi-log concentration profiles will be provided for individual participants. Graphical presentation of mean and individual trough study drug concentrations and study drug concentrations collected 12 h after each morning and evening dose administered on Day 1 through Day 7 will be displayed.

Plasma PK parameters:

The study population and methodology used to evaluate PK parameters after first dose on Day 1 and multiple doses on Day 7 will be described in detail in the PK Plan and is reviewed briefly below.

The following single-dose plasma PK parameters will be computed (if estimable) from the plasma total concentration-time data over the 12-hour following the morning dose of study drug on Day 1 in each cohort::

- C_{max}: Observed maximum concentration
- T_{max}: Time of maximum concentration (h)

- C_{min}: Observed minimum concentration at the end of the dosing interval
- $AUC_{(0-t)}$: Area under the plasma concentration -time curve 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 time 0 to 12h 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
- $AUC_{(0-tau)}$: Area under the plasma concentration - time curve from time 0 to the end of the dosing interval
- $t_{1/2}$: Terminal half-life
- CLT: Total clearance
- K_e: terminal phase elimination rate constant
- V_d: Volume of distribution
- Dose-normalized exposure parameters ($AUC_{(0-tau)}$/Dose and C_{max}/Dose)

The following multiple-dose plasma PK parameters will be computed (if estimable) from the drug total concentration-time data over the 48h dosing interval following the morning dose of study drug on Day 7 in each cohort.

- $C_{max,ss}$: observed maximum concentration at steady state
- $C_{min,ss}$: 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 time 0 to 48h after dosing
- $AUC_{(0-tau),ss}$: Area under the plasma concentration - time curve to the end of the dosing interval at steady state
- $t_{1/2}$: Terminal half-life (Day 7 only)
- CLT: Total clearance
- $V_{d,ss}$: Volume of distribution at steady state
- Linearity Index: $AUC_{(0-tau),ss}$ (Day 7) / AUC(0-∞) (Day 1)

- RAUC: Accumulation ratio for AUC estimated as $AUC_{(0\text{-}tau)}$ (Day 7) / $AUC_{(0\text{-}tau)}$ (Day 1)
- RC_{max}: Accumulation ratio for C_{max} estimated as C_{max} (Day 7) / C_{max} (Day 1).
- Dose-normalized exposure parameters ($AUC_{(0\text{-}tau)}$/Dose and C_{max}/Dose)

Trough plasma concentrations of total SLV213 at 12h after each morning and evening dose from Day 1 through Day 7 will be summarized in a tabular form and presented graphically.

9.3.8 Missing Values and Outliers

All attempts will be made to collect all data per protocol. No imputation will be performed for missing values. Rules for identifying outliers will be described in the SAP. Outliers will not be excluded from the primary analyses. Outliers identified during the PK analysis will be discussed in the analysis report.

9.3.9 Multiple Comparisons / Multiplicity

This is a small Phase 1 Study with multiple endpoints. Because analyses of endpoints are descriptive rather than hypothesis tests, no adjustments for multiplicity testing are planned.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

This study will be conducted in conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; April 18, 1979), and the federal policy for the Protection of Human Subjects codified in 45 CFR Part 46, 21 CFR Part 50 (Protection of Human Subjects), and the ICH E6(R2).

An OHRP-registered IRB will review and approve this protocol, associated informed consent documents, recruitment materials, and handouts or surveys intended for the participants, prior to the recruitment, screening, and enrollment of participants. Review shall be in accordance with 45 CFR 46 and 21 CFR 50, 21 CFR 56 (IRBs), and other federal, state, and local regulations and policies, as applicable. Investigator(s) will obtain IRB approval for this protocol and any amendments to be conducted at his/her research site(s). Any amendments to the protocol or informed consent documents will be approved by the IRB before they are implemented. DMID must receive documentation of IRB approval prior to the recruitment, screening, and enrollment of participants under any IRB approvals for continuing review.

Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and approval will occur at least annually throughout the enrollment and follow-up of participants, according to applicable regulations and the IRB/IEC. The investigator will notify the IRB/IEC of events such as deviations, SAEs, etc. as applicable to the IRB/IEC policy.

Each institution engaged in this research will hold a current Federalwide Assurance (FWA) issued by the DHHS-OHRP for federally funded research and provide the FWA number to DMID.

10.1.1 Informed Consent Process

For the following, "informed consent" applies to participant assent. Where appropriate, these will be obtained and documented for all study participants.

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, informed consent will be obtained and documented. Participants will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. Key information will include the purpose of the study, the procedures and experimental aspects of the study, study interventions/products, probability for random assignment to treatment groups, risks and discomforts, the expected duration of the participant's participation in the trial, any expected benefits to the participant, and alternative treatments and procedures that may be available to the participant. The explanation will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

Participants will receive an explanation as to what happens if injury occurs, including whether any compensation and any medical treatments are available, and, if so, what they consist of, or where further information may be obtained. Participants are informed of the anticipated financial expenses, if any. They will be informed of whom to contact (e.g., the investigator) for answers to any questions relating to the research project. Information will also include the foreseeable circumstances and/or reasons under which the participant's participation in the trial may be terminated. The participants will be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the participant is otherwise entitled.

Participants will be informed that records identifying the participant will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the participant's identity will remain confidential. Participants will be informed whether private information collected from this research and/or specimens will be used for additional research, even if identifiers are removed.

Participants will be informed that the monitor(s), auditors(s), IRB, NIAID, and regulatory authority(ies) will be granted direct access to the participant's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations, and that, by signing a written informed consent form, the participant is authorizing such access.

Participants will be allowed sufficient time to consider participation in this research trial and have the opportunity to discuss this trial with their family, friends, or legally authorized representative, or think about it prior to agreeing to participate.

Informed consent forms will be IRB-approved, and participants will be asked to read and review the consent form. Participants will complete an informed consent form prior to starting any study procedures being done specifically for this trial. Once signed, a copy of the informed consent form will be given to the participant(s).

New information will be communicated by the site PI to participants who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated, and participants consented per IRB requirements, if necessary.

Requirements for Permission by Parents/Guardians and Assent by Children (in case of a minor)

Not Applicable.

Other Informed Consent Procedures

No human genetic testing will be conducted in this study.

10.1.2 Study Termination and Closure

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or ET of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a significant change in the known risk/benefit profile for the drug, such that the risk is no longer acceptable for participants participating in the study.
- Significant violation of GCP guidelines that compromises the ability to achieve the primary study objectives or compromises participant safety.
- Study-specific criteria for terminating the study:
- Participants in more than one cohort have met Cohort Stopping Criteria (see Section 7.1.1).

The study may be terminated early prior to full attainment of these criteria if warranted by safety data from the other participants dosed in the study to that point.

Section 7 describes the temporary halting of the study.

This study may be prematurely terminated if there is sufficient reasonable cause, including but not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Halting criteria met and it is deemed unsafe to proceed with further dosing
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Regulatory authorities' determination

- Sponsor's determination

If the study is prematurely terminated, the PI will promptly inform study participants and the IRB and regulatory authorities as applicable. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule. The PI will assure appropriate follow-up for the participants, as necessary.

The sponsor will notify regulatory authorities as applicable.

10.1.3 Confidentiality and Privacy

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover clinical information relating to participants, test results of biological samples and genetic tests, and all other information generated during participation in the study. No identifiable information concerning participants will be released to any unauthorized third party. Participant confidentiality will be maintained when study results are published or discussed in conferences.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

All source records including electronic data will be stored in secured systems in accordance with institutional policies and federal regulations.

All study data and research specimens that leave the site (including any electronic transmission of data) will be coded.

As this research is funded by the National Institutes of Health (NIH), it is covered by NIH policy which effectively issues the research a Certificate of Confidentiality. By this policy, researchers cannot be forced to disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects, like this study, or for information that must be released in order to meet the requirements of the FDA.

A Certificate of Confidentiality does not prevent the participant from voluntarily releasing information about themselves or their involvement in this research. If any person or agency obtains a written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not cover matters that must be legally reported, including child and elder abuse, sexual abuse, wanting to harm themselves or others, and certain infectious diseases that meet the criteria for reporting. In these cases, researchers may report information that would identify a participant without the participant's consent.

The release of individual private information or specimens for other research will only occur if consent was obtained from the individual to whom the information, document, or biospecimen pertains, *or* for the purposes of other research that the release is in compliance with applicable Federal regulations governing the protection of human subjects in research.

10.1.4 Secondary Use of Stored Specimens and Data

Secondary Human Participant Research is the re-use of identifiable data or identifiable biospecimens that were collected from some other "primary" or "initial" activity, such as the data and samples collected in this protocol. Participants will be informed and consent obtained if the participant agrees to collection of additional blood (3.5 mL per sample for 30 times) for the purpose of preparing and storing serum in the DMID CMS for use in other research not specified at this time. The "additional" samples may be released during this study or at completion of all lab analyses.

Residual Research Sample:

Remaining samples not utilized for PK analyses and stored in the DMID CMS repository will be reserved for future research with the participant's consent.

Data and residual samples from this study may be used for secondary research. All of the individual participant data and residual samples collected during the trial will be made available to Selva Therapeutics, Inc. to conduct additional research in support of their product's development to include the measurement of SLV213 metabolites, the PD of SLV213, and the analysis of cytokines to understand the host response to SLV213. Samples and data will be coded so that the data from this study may be linked to an individual's results in secondary research, however, no personal identifying information will be linked to the data or samples that could identify a participant. No genetic testing will be conducted.

10.1.5 Key Roles and Study Governance

The PI is listed on the cover page. Other study team members and roles are listed in the study-specific MOP.

10.1.6 Safety Oversight

Safety Monitoring Committee (SMC)

Safety oversight will be conducted by a SMC, a group of experts that monitors participant safety, reviews accumulated trial data, and advises DMID on trial safety. SMC members will be separate and independent of study personnel participating in this trial and should not have scientific, financial, or other conflict of interest related to this trial. The SMC will operate under a DMID-approved charter or safety monitoring plan in which the procedures for review will be defined. The SMC will review safety data at *ad hoc* meetings if halting criteria for dose escalation were

met in the review by the SRC, at the conclusion of the trial when data are available, and as needed during this trial.

The SMC will conduct the following reviews:

- *Ad hoc* meetings:
  - When trial-level halting criteria are met
  - At the request of DMID to review a potential safety concern identified by either the PI, DMID MM, DMID MO, or the Pharmaceutical (Selva) MO.
- A final review meeting to review the cumulative unblinded safety, tolerability and trial progress and final PK data and provide recommendation for the dose to be used in a Phase 2 trial.

Additional reviews may be requested by the SMC to evaluate interim data if there are immediate concerns regarding participant safety observed during the course of the trial. The SMC will receive blinded data and may request the treatment assignment be unblinded if required for safety assessment. The SMC members will review grouped and unblinded data in the closed session only. The SMC will make a recommendation as to the advisability of proceeding with study interventions (as applicable), and to continue, modify, or terminate this trial.

Safety Review Committee (SRC)

A SRC will consist of a DMID MM, the DMID MO, the clinical site PI and the Pharmaceutical (Selva) MO. The SRC will review combined safety data to Day 15 after each cohort and recommend dose escalation if halting criteria are not met.

The DMID MM is empowered to stop enrollment and study product administration if AEs that meet the halting criteria are reported.

10.1.7 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable. Clinical Monitoring also ensures conduct of the trial is in compliance with the currently approved protocol / amendment(s), ICH, GCP, and with applicable regulatory requirement(s) and sponsor requirements. Clinical monitoring will also verify any critical study procedures are completed following specific instructions in the MOP.

10.1.8 Quality Assurance and Quality Control

Each site participating in the conduct of a DMID-funded study is responsible for integrating quality checks throughout the lifecycle of the protocol by developing, implementing, and evaluating a Clinical Quality Management Plan (CQMP). Quality activities are essential to the safety of participants, and the reliability of study data. Quality management planning should be risk-based, commensurate with the risks associated with the research.

The CQMP will describe:

- Routine internal quality control (QC) and quality assurance (QA) activities
    - for the purposes of measuring, documenting, and reporting study conduct, protocol adherence, human subjects' protections, and reliability of the protocol-driven data collected;
    - independent of sponsor site monitoring.
- A process for addressing data quality issues (i.e., collecting, recording, and reporting findings in a timely manner); systemic issues (i.e., protocol conduct, non-compliance, human participant protections), and implementation and evaluation of Corrective and Preventative Action Plan (CAPA) procedures.

10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data collection is the responsibility of the study staff at the participating site under the supervision of the participating site PI. The participating site PI must maintain complete and accurate source documentation. The site PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Clinical research data from source documentation, including, but not limited to AEs/SAEs, ConMeds, MH, PE, ECG, and clinical laboratory data, will be entered by the participating site into eCRFs via a 21 CFR Part 11-compliant internet data entry system provided by the SDCC.

The IND sponsor is responsible for review of data collection tools and processes, and review of data and reports.

At the end of the study, a copy of all datasets, including annotated CRFs and data dictionary, will be provided to DMID per the requirements of the funding mechanism and agreements.

10.1.9.2 Statistical and Data Coordinating Center (SDCC)/ Biostatistician Responsibilities

The SDCC for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

Adverse events and MH will be coded according to the MedDRA dictionary.

ConMeds will be coded according to the WHODrug dictionary.

At the end of the study, a copy of all datasets including annotated CRFs, and data dictionary will be provided to DMID.

10.1.9.3 Source Records

Source data are all information, original records of clinical findings, observations, or other activities documented in a clinical trial necessary for the reconstruction and evaluation of the trial. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP, regulatory, and institutional requirements. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

For this trial, the electronic subject record utilized by the participating site is considered source data.

10.1.9.4 Data Capture Methods

Data will be captured in the subject's electronic source record and entered manually into the eCRF in the SDCC database. Clinical research data (including, but not limited to, AE/SAEs, ConMeds, MH, PE, VS and clinical laboratory data will be extracted from the source documentation and/or collected on source document worksheet by study personnel and then entered into eCRFs via a 21 CFR Part 11-compliant internet data entry system provided by the SDCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. (See study-specific MOP and eCRF Guidelines for details.)

10.1.9.5 Study Record Retention

Study related records, including the regulatory file, study product accountability records, consent forms, participant source documents and electronic records should be maintained for a minimum period of 2 years following the date a marketing application is approved for the investigational product for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 3 years after the investigation is discontinued and FDA is notified. These documents should be retained for a longer period, however, if required by local policies or regulations. No records will be destroyed without the written consent of DMID. Consent forms with specimen retention linked to identifiable specimens will be maintained for as long as the specimens remain in identifiable format, and a minimum of three years after use of the identifiable specimens in nonexempt human subject research.

10.1.10 Protocol Deviations

A protocol deviation is any noncompliance that impacts the safety of the subject or scientific validity with the clinical trial protocol, any process that is noted in the protocol and refers to details in the MOP, or GCP requirements.

The noncompliance may be either on the part of the participant, the investigator, or the study site staff. Following a deviation(s), corrective actions should be developed by the site and implemented promptly. All individual protocol deviations will be addressed in participant study records.

It is the responsibility of the site PI and personnel to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five

working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID per the protocol deviation reporting procedures. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site PI and personnel are responsible for knowing and adhering to their IRB requirements. A completed copy of the DMID Protocol Deviation Form must be maintained in the Regulatory File, as well as in the participant's chart if the deviation is participant specific.

10.1.11 Publication and Data Sharing Policy

Data Sharing Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

- The NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

As of January 2018, all clinical trials supported by the NIH must be registered on ClinicalTrials.gov, no later than 21 days after the enrollment of the first participant. Results of all clinical trials supported by the NIH, generally, need to be submitted no later than 12 months following the primary completion date. As part of the result posting, a copy of this protocol and a copy of the Statistical Analysis Plan (if applicable) will be posted on ClinicalTrials.gov.

10.1.12 Conflict of Interest Policy

Investigators will file appropriate financial disclosures prior to their involvement in this study. The study will adhere to relevant policies with regard to conflicts of interest.

10.2 Additional Considerations

10.2.1 Research Related Injuries

For any potential research related injury, the site PI or sub-investigator or licensed clinician listed in FDA Form 1572 will assess the participant. The site PI should then determine if an injury occurred as a direct result of the tests or treatments that are done for this trial. As needed, referrals to appropriate health care facilities will be provided to the participant.

No financial compensation will be provided by the NIAID, NIH, or the US Federal Government to the participant, for any injury suffered due to participation in this trial.

Public Readiness and Emergency Preparedness Act (PREP Act)

The study treatment(s) and the efforts for this clinical trial are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) and the Declaration issued by the Secretary of the U.S. Department of Health and Human Services under that Act. Under the PREP Act and the Declaration, covered persons (such as manufacturers, distributers, program planners, and other qualified persons who prescribe, administer, or dispense study product) are immune from liability

from the administration, or use of a covered countermeasure, such as for SLV213. The PREP Act provides immunity for covered persons from liability unless the injury was caused by willful misconduct. The Declaration invoking the PREP Act for COVID-19 covered countermeasures was made on March 20, 2020.

The PREP Act also established the Countermeasures Injury Compensation Program (CICP) to provide compensation for serious injuries or death that occur as the direct result of the administration or use of certain countermeasures. Any requests for compensation must be filed within one year of the administration or use of the covered countermeasure. Requests for Benefits must be made to the Health Resources and Services Administration's (HRSA) CICP (http://www.hrsa.gov/cicp/) by filing a Request for Benefits Form and all required medical records and supporting documentation. Additional information on filing a Request for Benefits is available on the CICP's website at http://www.hrsa.gov/cicp/. Compensation may then be available for reasonable and necessary medical benefits, lost wages and/or death benefits to eligible individuals for certain injuries in accordance with regulations published by the Secretary of HHS (found at 42 CFR Part 110).

If an individual suffers a serious physical injury or death from the administration or use of a covered countermeasure in this study, the individual, the individual's legal or personal representative, the administrator/executor of a deceased individual's estate, or certain survivors may request benefits from the CICP. A serious physical injury means an injury that warranted hospitalization (whether or not the person was actually hospitalized) or that led to a significant loss of function or disability. The CICP is the payer of last resort. This means that it only covers expenses or provides benefits that other third-party payers (such as health insurance, the Department of Veterans Affairs, or Workers' Compensation programs) do not have an obligation to pay.

If the Secretary of HHS does not make a final determination on the individual's request within 240 days, or if the individual decides not to accept the compensation, the injured individual or his representative may pursue a tort claim in the US District Court for the District of Columbia, but only if the claim involves willful misconduct and meets the other requirements for suit under the PREP Act. Any award is reduced by any public or private insurance or worker's compensation available to the injured individual. Awards for non-economic damages, such as pain, suffering, physical impairment, mental anguish, and loss of consortium are also limited. If the individual accepts compensation, or if there is no willful misconduct, then the individual does not have a tort claim that can be filed in a US Federal or a State court.

10.3 Abbreviations

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase

Abbreviation	Definition
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration – Time Curve
BID	Twice Daily
BMI	Body mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CHEM	Chemistries
CFR	Code of Federal Regulations
COAG	Coagulation
CICP	Countermeasures Injury Compensation Program
CMS	Clinical Materials Services
ConMed(s)	Concomitant Medication(s)
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CS	Clinically Significant
CTU	Clinical Trial Unit
DHHS	Department of Health and Human Services
DLT	Dose-limiting Toxicity
DMID	Division of Microbiology and Infectious Diseases
DVC	DynPort Vaccine Company, LLC
ECG	Electrocardiogram – Also Electrocardiographic
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
GDIT	General Dynamics Information Technology
GLP	Good Laboratory Practice
h	Hour or Hours
HBsAg	Hepatitis B virus surface antigen
HCG	Human Chorionic Gonadotropin
HDPE	high density polyethylene
HEM	Hematology
HR	Heart rate
HRSA	Health Resources and Services Administration
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure

Abbreviation	Definition
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational New Drug Application
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IV	Intravenous
LFT	Liver Function Tests
LTS	Long-Term Stability
MAAE	Medically-Attended Adverse Events
MAD	Multiple Ascending Dose
mg	Milligram(s)
MH	Medical History
min	minutes
mITT	Modified Intent-To-Treat
MM	Medical Monitor
MO	Medical Officer
MOP	Manual of Procedures
MTD	Maximum Tolerated Dose
NCS	Not Clinically Significant
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OTC	Over the Counter
PD	Pharmacodynamic(s)
PI	Principal Investigator
PK	Pharmacokinetic(s)
PO	Per os (orally)
PREP ACT	Public Readiness and Emergency Preparedness Act
PVG	Pharmacovigilance Group
QD	Daily
RBC	Red Blood Cell
RR	Respiratory rate
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SARS-COV-2	Severe Acute Respiratory Syndrome-Related Coronavirus 2
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOA	Schedule of Assessments

Abbreviation	Definition
SOC	System Organ Class
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Adverse Reactions
T	Temperature
TEAE	Treatment-Emergent Adverse Event
Q12h	Every 12 hours
VS	Vital Signs
UDS	Urine Drug Screen
US(A)	United States of America

10.4 Protocol Amendment History

Version/Date	Section # and Name	Description of Change	Brief Rationale
2.0/18 December 2023	Section 1.2, Schedule of Assessments	• Added PK sampling timepoints after morning dose on Day 1 (Footnote u) • Added column for Unscheduled visits (Footnote w) – See also Sections 8.3.1 and 8.3.2	• Correction • Additional information for clarification
	Section 4.1, Overall Design Section 5, Study Population Section 7.2.2, Participant Replacement	A randomized participant will be replaced with a participant who will receive the same treatment and, if possible, of the same gender	• Clarification
	Section 5.1, Inclusion Criteria Section 5.2, Exclusion Criteria	• Edited inclusion criteria (IC) 2, 4, 7 and 9 • Edited exclusion criteria (EC) 8 and 16	• To meet CDISC requirement for 200 characters including spaces in text of IC and EC excluding Notes. Notes added as needed
	Section 6.1.1, Study Product Description	Updated study product information	• To match latest edition of the IB
	Section 6.2.5, Preparation	Staff delegated to administer DP under supervision of licensed PI, investigator and clinicians listed on FDA Form 1572	• Clarification
	Section 6.5, Concomitant Therapy	Edited format of prohibited medications and exceptions	• Clarification
	Section 7.1.1, Study Halting Criteria Section 7.1.2, Individual Halting Criteria	• Updated Cohort halting criteria • Updated individual halting criteria	• Clarification
	Section 7.2, Participant Withdrawal from the Study and Replacement	Created separate Sections 7.2.1 (for withdrawal reasons) and 7.2.2 (for replacements) and updated text	• Clarification

Version/Date	Section # and Name	Description of Change	Brief Rationale
	Section 8.1.2, Laboratory Evaluations	HIV and hepatitis serology only at Screening and rapid FDA approved molecular diagnostic for SARS-CoV- test on Day-1 to replace PCR	• Clarification
	Section 8.3.4, Blood sampling for Plasma SLV213 Assay and Serum for Future Research	Changed volume of blood drawn for plasma PK and serum for future secondary research	• Updated information
	Section 8.4, Study Drug Administration	• Updated duration of fasting before and after each dose on Days 1-7; and • Entered duration of fasting before clinical labs on Days 2, 4 and 6.	• Correction • Additional information
	Section 8.5.3, Definition of Medically-Attended Adverse Events (MAEE)	Added new subsection for the definition of MAAEs	• MAAEs will be assessed and reported throughout the study, not part of AESI's
	Section 8.5.9, Adverse Events of Special Interest (AESI)	Updated section; retained only protocol specific AESIs. MAAEs moved to Section 8.5.3. New-Onset Chronic Medical Conditions (NOCMCs) and Potentially Immune-Mediated Medical Conditions (PIMMCs) deleted.	• Clarification
	Appendix A, Table 4, Toxicity Grading Tables – LABORATORY AEs	Updated clinical reference ranges for most recent Lab manual and edited corresponding lab toxicity scales.	• To ensure lab data reported match lab reference ranges and linked toxicity grads in the protocol.
	Appendix Table 6, Laboratory Samples and Estimated Total Blood Volume (mL)	Updated total volume of blood drawn for PK and future use samples	• Due to decreased volume of blood drawn for plasma PK samples
3.0/22 February 2024	Section 1.2 Schedule of Assessments	• Removed focused PE from Day 9 • Additions to footnotes "f" and "g"	• Complete PE is performed on the same day • Clarifications
	Section 5.1 Inclusion Criteria	Updated inclusion criteria	• Updated in response to non-hold questions received from the FDA.
	Section 5.2 Exclusion Criteria	• Updated exclusion criteria • Added "sinus" to bradycardia	• Updated in response to non-hold questions received from the FDA.

Version/Date	Section # and Name	Description of Change	Brief Rationale
			• Clarification
	Section 5.4 Lifestyle Considerations	Added "or 5 half-lives of the drug, whichever is longer"	• Clarification
	Section 6.2.5, Preparation	Updated administration of dose that after Dose 1 (Morning dose on Day 1), each subsequent dose will be administered 12 h (+/- 15 min) after previous dose.	• Clarification
	Section 6.5 Concomitant Therapy	• Deleted contraceptives. • Added 5 half-lives or whichever is longer	• Updated in response to non-hold questions received from the FDA.
	Section 7.1.1, Study Halting Criteria, Cohort Halting Rules	• Added an additional bullet to the cohort halting rules for one participant experiences a treatment-related Grade 3 or higher adverse event • Revised fold increase above upper limit of normal for ALT and/or AST in first 2 bullets	• Added at the request of FDA • To align with wording in FDA 2009 Guidance for Hepatic Toxicity
	Section 7.1.2 Individual Halting Criteria	Updated criteria for discontinuation from dosing	• Updated in response to non-hold questions received from the FDA.
	Section 8.1.1 Clinical Procedures and Evaluation	• Updated Medical History, Physical Exam, and Vital signs to add orthostatic evaluation • Deleted 2nd paragraph from PE and placed in under Vital Signs • Described conditions for measuring resting VS as well as orthostatic BP and HR	• Updated in response to non-hold questions received from the FDA. • Correction made • Clarification for supine VS assessments precede orthostatic
	Section 8.1.4, Procedures to be Followed in the Event of Abnormal Clinical Laboratory Test Values or Abnormal Clinical Findings During Screening	• Added "supine" • Revised repeat vital signs at least 5 min of each other	• Clarification • Clarification
	Section 8.3.1, Clinical Procedures and Evaluations, Physical Examinations	• Medical History: Added orthostatic • Physical Examination: Added assessment of not clinically significant or clinically significant • Vital Signs: Added orthostatic • Described conditions for measuring resting VS as well as orthostatic BP and HR	• Updated in response to non-hold questions received from the FDA • Additional information • Updated in response to non-hold questions received from the FDA

Version/Date	Section # and Name	Description of Change	Brief Rationale
			• Clarification for supine VS assessments precede orthostatic
	Section 8.3.3, Procedures to be Followed in the Event of Abnormal Clinical Laboratory Test Values or Abnormal Clinical Findings During Conduct of the Trial	• Added information regarding reference ranges • Added "supine" to sub-title • Revised repeat vital signs at least 5 min of each other • Described reporting of abnormal labs that are outside reference range, but below limits of Grade 1 • Added "supine" to subtitle for VS	• Updated in response to non-hold questions received from the FDA • Clarification • Clarification • Clarification • Clarification
	Section 8.3.5, Total Blood Volume Drawn	Updated total blood volume drawn	• Correction
	Section 8.5.4 Classification of an Adverse Event	Revised to add the use of the September 2007 FDA Guidance: Toxicity Grading Scales for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials	Updated in response to non-hold questions received from the FDA
	Section 8.5.6 Adverse Event Reporting	• Section added to address Laboratory AE Evaluation and Reporting • Described reporting of abnormal labs that are outside reference range, but below limits of Grade 1	• Added in response to non-hold questions received from the FDA • Clarification
	Section 8.5.9 Adverse Events of Special Interest	Added "or higher" to Grade 3 AEs	Added in response to non-hold questions received from the FDA
	Appendix A: Adverse Events Toxicity Grading Criteria	• Deleted toxicity tables and replaced with a link to the FDA Toxicity Grading Scales for Healthy Volunteers • Added Supplemental Toxicity Tables to be used when needed • Added a footnote under Supplemental Vital Signs	• Revised in response to non-hold questions received from the FDA • Revised in response to non-hold questions received from the FDA • To provided information on coding of vital sign AEs with or without associated systemic symptoms
4.0/27 March 2024	Section 1.2 Schedule of Assessments	• Added ± 15 seconds to 1 minute and 3 minutes for orthostatic vital signs	• Clarifications to add a range
	Section 5.1 Inclusion Criteria	• Updated inclusion criterion #4 to include exceptions	• Clarification to add exceptions to clinical laboratory tests within normal range

Version/Date	Section # and Name	Description of Change	Brief Rationale
	Section 8.1.1, Clinical Procedures and Evaluation	• Added ± 15 seconds to 1 minute and 3 minutes for orthostatic vital signs	• Clarifications to add a range
	Section 8.1.2, Laboratory Evaluations	• Deleted reference to "Appendix A" under Clinical Laboratory Assessments • Added a paragraph to state laboratory normal reference ranges are included in the MOP	• There are no exceptions included in Appendix A • Clarification
	Section 8.3.1, Clinical Procedures and Evaluations, Physical Examinations	• Added ± 15 seconds to 1 minute and to 3 minutes for orthostatic vital signs	• Clarifications to add a range
	Section 8.3.3, Procedures to be Followed in the Event of Abnormal Clinical Laboratory Test Values or Abnormal Clinical Findings During Conduct of the Trial	• Added text regarding grading the severity of lab AEs in subjects whose allowable baselines were in the FDA Grade 1 range	• Clarification
	Appendix A: Adverse Events Toxicity Grading Criteria	• Deleted red blood cell from supplemental tox table as it is included in the FDA toxicity table • Added "dipstick" for nitrites as these are tested by dipstick • Revised grading for bacteria (microscopic)	• Deleted as not necessary, included in FDA toxicity table • Clarification • Clarification

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12. APPENDICES

APPENDIX A: ADVERSE EVENTS TOXICITY GRADING CRITERIA

The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials will be used in this protocol, available at the following link: https://www.fda.gov/media/73679/download.

Supplemental Toxicity Tables

Vital Signs

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Sinus Bradycardia – when baseline HR <60 bpm[1]	45 – 49 bpm	40 – 44 bpm	<40 bpm	Life-threatening consequences, urgent intervention indicated

[1]Use clinical judgement when characterizing bradycardia among some healthy subject 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.

Laboratory Parameters

Hematology	Grade 1	Grade 2	Grade 3	Grade 4
Monocytes increase, All ages – $x10^3/\mu L$	1.01 – 2.00	2.01 – 3.00	>3.00	Intervention indicated
Basophils increase, All ages – $x10^3/\mu L$	0.16 – 0.50	0.51 – 0.80	>0.80	Intervention indicated
Carbon dioxide increase, All ages – mEq/L	32.1 – 36.0	36.1 – 40.0	>40.0	Intervention indicated
Carbon dioxide decrease, All ages – mEq/L	17.0 – 21.9	14.0 – 16.9	<14.0	Metabolic acidosis Invention indicated

ECG Parameters

ECG interval abnormality	Grade 1	Grade 2	Grade 3	Grade 4
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

Urine Microscopy

Urine Microscopy	Grade 1	Grade 2	Grade 3	Grade 4
Nitrite (dipstick)	1+	2+	>2+	
White blood cells (WBC) per HPF	0 – 10	11 – 50	>50 or gross	Hospitalization of intervention

Urine Microscopy	Grade 1	Grade 2	Grade 3	Grade 4
Bacteria (microscopic)	Few	Moderate	Many	Hospitalization or intervention

Estimating Severity Grade for Parameters Not Identified in the Grading Table

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.

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

APPENDIX B: BLOOD VOLUME WITHDRAWN DURING THE TRIAL

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 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.

APPENDIX C: STRONG INHIBITORS, INDUCERS, AND SENSITIVE SUBSTRATES OF CYP3A4 AND CYP2D6

CLASSIFICATION	CYP3A4	CYP2D6
STRONG INHIBITORS[1]	• ceritinib • clarithromycin • cobicistat • elvitegravir and ritonavir • idelalisib • indinavir and ritonavir • itraconazole • ketoconazole • lopinavir and ritonavir • nefazodone • nelfinavir • paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) • posaconazole • ritonavir • saquinavir and ritonavir • telithromycin • tipranavir and ritonavir • voriconazole	• bupropion • fluoxetine • paroxetine • quinidine • terbinafine
STRONG INDUCERS[2]	• apalutamide • carbamazepine • enzalutamide • ivosidenib • lumacaftor and ivacaftor • mitotane • phenytoin • rifampin • St. John's wort	• None
SENSITIVE SUBSTRATES[3]	• alfentanil • avanafil • budesonide • buspirone • conivaptan	• atomoxetine • desipramine • dextromethorphan • eliglustat • nebivolol

CLASSIFICATION	CYP3A4	CYP2D6
	• darifenacin • darunavir6 • dasatinib • dronedarone • eletriptan • eplerenone • everolimus • felodipine • ibrutinib • indinavir • isavuconazole • ivabradine • lemborexant • lomitapide • lovastatin • lurasidone • maraviroc • midazolam • mobocertinib • naloxegol • nisoldipine • quetiapine • saquinavir • sildenafil • simvastatin • sirolimus • tacrolimus • ticagrelor • tipranavir • tolvaptan • triazolam • vardenafil • venetoclax	• nortriptyline • perphenazine • R-venlafaxine • tolterodine

Source: For Healthcare Professionals: FDA's Examples of Drugs that Interact with CYP Enzymes and Transporter Systems | FDA. Accessed at www.fda.gov.
[1]Drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold.
[2]Drugs that decrease the AUC of sensitive substrates of a given metabolic pathway by ≥80%.
[3]Drugs that demonstrate an increase in AUC of ≥5-fold with strong inhibitors of a given metabolic pathway.