Statistical Analysis Plan

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Sponsor	*Ophirex, Inc.*
Protocol Title:	*Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of a Multi-Dose Regimen of Oral Varespladib-Methyl in Subjects Bitten by Venomous Snakes*
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Document History

Version	Description
2.0	Added estimand statement, aligned with Protocol v3.0, specified how mortality factors into the primary analysis, and added baseline neurotoxicity as a pre-specified covariate.
3.0	- Added use of a fixed-sequence approach and specification of key (alpha-protected) secondary efficacy endpoints with details regarding analysis - Changed analyses of hospital durations from ANCOVA to Wilcoxon rank sum test. - Added clarification and details regarding handling of missing data; including the addition of multiple imputation used in primary and key secondary analyses. - Added additional subgroup analyses of the primary and key secondary outcomes, including analyses by country (United States, India), and by timing of bite or symptom onset to receipt of study drug (<5 hours, ≥5 hours) - Added SAS code for primary and key secondary endpoints. - Added clarification on the analysis of mortality regarding what will be done in the event of too few deaths for formal statistical models. - Fixing various typos from the prior version.
4.0	- Specified the use of FDA Medical Queries (FMQs) for safety endpoints. - Added SAS code for multiple imputation. - Specified sensitivity analysis for handling missing data. - Defined method for ensuring that SSS-AUC Day 7 uses 168 hours as duration of elapsed time for all patients. - Added country as a covariate for the analysis of the primary and key secondary efficacy endpoints. - Added a new key secondary endpoint: Numeric Pain Rating Score area under the curve from Baseline to Day 3. - Revised the analysis of one of the secondary outcomes: coagulation laboratory values. - Added graphical presentations for subscores of the Snakebite Severity Score.

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List of Abbreviations

Abbreviation	Definition
20WBCT	20-minute whole blood clotting test
AE	adverse event
ANCOVA	analysis of covariance
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASA	American Statistical Association
AST	aspartate aminotransferase
AUC	area under the curve
BID	bis in die (twice a day)
BUN	blood urea nitrogen
CGI-I	Clinical Global Impression - Improvement
CI	confidence interval
CNS	central nervous system
CRP	C-reactive protein
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form

Abbreviation	Definition
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	Food and Drug Administration
FMQ	FDA Medical Query
GGT	gamma-glutamyl transferase
HR	heart rate
ICH	International Council for Harmonisation
ICU	intensive care unit
IP	investigational product
ITT	intent-to-treat
IWRS	Interactive Web System Response
LDH	lactate dehydrogenase
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed model for repeated measurements
MPV	mean platelet volume
NPRS	Numeric Pain Rating Score
PD	protocol deviation

Abbreviation	Definition
PGIC	Patient Global Impression of Change
PK	pharmacokinetic
PLR	platelet to lymphocyte ratio
PSFS	Patient-Specific Functional Scale
QoL	quality of life
REML	restricted maximum likelihood
RSS	Royal Statistical Society
SAE	serious adverse event
SAF	safety population
SAP	Statistical Analysis Plan
SOC	standard of care
SOP	standard operating procedure
$sPLA_2$	secretory phospholipase A2
SSS	Snakebite Severity Score
TEAE	treatment-emergent adverse event
WHO-DD	World Health Organization Drug Dictionary

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Ophirex, Inc. protocol number OPX-PR-01 (Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of a Multi-Dose Regimen of Oral Varespladib-Methyl in Subjects Bitten by Venomous Snakes), dated 03 May 2022 version 3.0 (US) and version 3.1 (India). Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials (ICH, 1998). All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association (ASA, 2018) and the Royal Statistical Society (RSS, 2014), for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be approved before unblinding of any data pertaining to Ophirex, Inc.'s study OPX-PR-01.

2. Study Objective and Endpoints

2.1. Study Objective

The primary objective of the study is to evaluate the efficacy of a multi-dose regimen of oral varespladib-methyl alongside standard of care (SOC) compared to SOC alone in subjects after venomous snakebite.

The secondary objective is to evaluate efficacy of varespladib-methyl as treatment for $sPLA_2$-induced venom toxicities.

The exploratory objectives of the study are:

- To assess the efficacy of varespladib-methyl as evaluated by a compressed snakebite severity score (SSS) scale
- To assess the efficacy of varespladib-methyl as evaluated by SSS
- To assess the effect of varespladib-methyl on neurological function as evaluated by grip strength
- To assess the effect of varespladib-methyl on neurotoxicity
- To assess the effect of varespladib-methyl on analgesic use

- To evaluate the effect of varespladib-methyl on Clinical Global Impression-Improvement (CGI-I)
- To evaluate the effect of varespladib-methyl on the Patient Global Impression of Change (PGIC)
- To assess the effect of varespladib-methyl on complete blood count (CBC)
- To assess the effect of varespladib-methyl on transfusion requirement in subjects with hemolysis
- To evaluate the effect of varespladib-methyl on the levels of C-reactive protein (CRP)
- To assess the safety biomarker D-dimer
- To assess the effect of varespladib-methyl on myonecrosis markers in subjects with and without tourniquets at enrollment
- To evaluate the levels of secretory phospholipase A2 ($sPLA_2$) in serum

The pharmacokinetics (PK) of varespladib-methyl in subjects with snakebite envenoming will also be assessed.

2.2. Study Endpoints

2.2.1. Efficacy Endpoints

2.2.1.1. Primary Efficacy Endpoint

Change in the composite outcome of pulmonary, cardiovascular, hematologic symptoms, renal, and nervous system sections of the SSS from Baseline (pre-dosing) to the average of the scores from 6 and 9 hours after first dose.

The estimand for the primary efficacy endpoint of this study is defined here in accordance with the ICH E9 Addendum:

1) Population: The population targeted for the scientific questions is defined via the inclusion and exclusion criteria.
2) Variable (or endpoint): Change from Baseline to the average of 6 and 9 hours of the Double-blind Treatment Period in the composite outcome of pulmonary, cardiovascular, hematologic, renal, and nervous system sections of the SSS.
3) Intercurrent Events: The primary estimand will be based on a treatment policy analysis. All observed values will be used regardless of occurrence of an intercurrent event with the exception of mortality for which the worst possible SSS score will be assigned as described in Section 6.1.7.1.
4) Population level summary: The mean change of the composite outcome of pulmonary, cardiovascular, hematologic, renal, and nervous system sections of the SSS from Baseline to the average of hours 6 and 9 of the Double-blind Treatment Period will be analyzed using an analysis of covariance (ANCOVA) model. Additional details can be found in Section 8.1.

2.2.1.2. Key Secondary Efficacy Endpoints

Four key (alpha-protected) secondary outcomes have been selected for which formal hypothesis testing will be conducted. A fixed-sequence approach to controlling the type I error rate will be used. First, the primary endpoint above will be tested, followed by the four key secondary endpoints in the sequence with which they are presented below.

The efficacy of varespladib plus SOC vs. SOC alone will be assessed for these four outcomes. Details of this approach are described in section 8.1.2.

- Area under the curve (AUC) of the pulmonary, cardiovascular, local wound, hematologic symptoms, renal, and nervous system sections of the SSS from baseline through Day 7
- Total antivenom administration in vials from Baseline through Day 28
- AUC of the Numeric Pain Rating Score (NPRS) from baseline through Day 3
- Clinical Global Impression-Improvement (CGI-I) scale at Day 2

2.2.1.3. Other Secondary Endpoints

The study has the following other secondary efficacy endpoints:

- Complete SSS from baseline (pre-dosing) through Day 7
- SSS neurologic system subscore from Baseline through Day 3
- Coagulation abnormalities from Baseline through Day 7
- Hemolysis markers from baseline through Day 3
- Levels of the myonecrosis marker, creatinine kinase (CK), from Baseline through Day 3
- Numeric Pain Rating Scale (NPRS) score in subjects able to respond from Baseline through Day 28
- Kidney function markers from baseline through Day 28
- Head-Lift duration from Baseline through Day 7
- Total duration of ventilatory support from Baseline through Day 28
- Total duration of Intensive Care Unit (ICU) stay from Baseline through Day 28
- Total duration of hospitalization from Baseline through Day 28
- All-cause mortality from Baseline through Day 28
- CGI-I scale from Baseline through Day 7
- PGIC from Baseline through Day 7
- Patient-Specific Functional Scale (PSFS) total score from Baseline through Day 28

2.2.2. Safety and Tolerability Endpoints

The study has the following safety and tolerability endpoints:

- Incidence and severity of adverse events (AEs), serious AEs (SAEs), and AEs leading to discontinuation of Investigational Product (IP)
- Safety of varespladib-methyl as assessed by the number and rates of reported treatment-

emergent adverse events (TEAEs) from beginning of treatment until last Follow-Up Visit/Phone call at Day 28

- Treatment-related SAE from beginning of treatment until last Follow-up Visit/Phone call at Day 28
- Safety as assessed by
    - Vital signs
    - Clinical laboratory evaluations: complete blood count (CBC), urinalysis, liver function tests (LFTs), renal function tests (albumin, creatinine, blood urea nitrogen [BUN], estimated glomerular filtration rate [eGFR])
    - 12-lead electrocardiogram (ECG)
- Concomitant medications and therapies
- Columbia-Suicide Severity Rating Scale (C-SSRS) evaluated at Baseline or at the earliest time point clinically allowable (ideally Day 1) and then at every study visit through Day 28

Safety endpoints will be analyzed according to the following FDA Medical Queries (FMQs):

- Hepatic Injury (Narrow and Broad)
- Acute Kidney Injury (Narrow and Broad)
- Stroke and Transient Ischemic Attack [TIA] (Narrow and Broad)
- Myocardial Ischemia (Narrow)
- Arrythmia (Narrow)
- Cardiac Conduction Disturbance (Narrow)
- Hypersensitivity (Standard Narrow and Broad)

2.2.3. Pharmacokinetics

PK parameters of varespladib-methyl in plasma from a subset of adult and pediatric subjects at specified timepoints on Days 1 and 3 and from all subjects pre-dose on Day 7.

2.2.4. Exploratory Endpoints

The exploratory efficacy endpoints of this study include the following:

- Change in the SSS from Baseline through Day 7 using a compressed SSS scale.
- SSS from Baseline through Day 28
- Grip strength pre-dosing through Day 28
- SSS neurologic system subscore from Baseline through Day 7
- Analgesic use from Baseline through Day 28
- CGI-I from Baseline through Day 28
- PGIC from Baseline through Day 28
- CBC through all SSS evaluation days
- Transfusion requirement from Baseline through Day 28

- CRP from Baseline through Day 14
- D-dimer levels from Baseline through Day 14
- Levels of myonecrosis marker (CK) from Baseline through Day 3 in subjects presenting with and without tourniquets at enrollment
- Secretory phospholipase A_2 ($sPLA_2$) in serum at specified timepoints on Days 1 to 7 in all subjects

3. Overall Study Design and Plan

3.1. Overall Design

This is a multi-center, randomized, double-blind, placebo-controlled, phase 2 study designed to evaluate the safety, tolerability, and efficacy of varespladib-methyl, concurrently with SOC, in subjects bitten by venomous snakes. Subjects who have experienced a venomous snakebite with evidence of snakebite venom toxicity (see Study Population, Section 3.3, below) and who meet other inclusion criteria will be eligible for participation in the study. Consenting participants will be enrolled and randomized to receive study drug (active varespladib-methyl or placebo) in a 1:1 ratio. Study drug will be taken twice a day for a period of 7 days. Subjects in both arms of the trial will receive SOC. Outcomes will be assessed over a follow-up period of 28 days.

3.2. Sample Size and Power

The sample size for this phase 2 study was determined by a formal power calculation based on the primary efficacy endpoint. This study was powered at 85% to detect a statistically significant (2-sided alpha = 0.05) treatment effect. The assumptions are the following:

- 2-sided alpha level 5%
- Power 85%
- Randomization ratio 1:1
- A minimum difference in the change from Baseline to the average at 6- and 9-hour pulmonary, cardiovascular, hematologic, renal, and nervous system subscores of the SSS of 1.1 points and a standard deviation 1.75

A sample size of 94 patients will provide 85% power to identify a difference of 1.1 in the primary outcome (two-sided alpha = 0.05). The sample size has been calculated using nQuery 8.

The randomization scheme will be 1:1 stratified by age group (5 to < 11, 11 to < 18, and ≥ 18 years old) and by the presence or absence of neurotoxicity (SSS nervous system subscore of 0–1 or ≥ 2) at Baseline, resulting in 6 strata in total.

Because we anticipate up to 15% withdrawal through the end of the study, we requested permission to enroll up to 110 patients to ensure adequate power for secondary outcomes.

3.3. Study Population

The study population comprises subjects of both genders, aged ≥5 years, with venomous snakebite. The index event (snakebite) must be symptomatic and symptom onset must have

occurred within 10 hours of eligibility assessment and the subject must be willing (or legally authorized representative is willing) to provide informed consent prior to initiation of any study procedures.

Subjects must meet one of two categories of inclusion criteria:

1. Subjects who *have not yet* completed their initial dose of antivenom may be eligible if they have an SSS inclusion criteria score (excludes GI and renal subscores) of ≥3 points in any singe SSS category or a score of 2 in one category and at least 1 in any other category.
2. Subjects who *have* completed their initial dose of antivenom may be eligible if they have an SSS inclusion criteria score (excludes GI and renal subscores) of ≥2 points.

3.4. Treatments Administered

Varespladib-methyl or placebo will be administered, concurrently with institutional SOC, to subjects with suspected or confirmed snakebite envenoming:

- Adult subjects will receive an initial loading dose of 500 mg (2 × 250 mg oral tablet) varespladib-methyl upon randomization, followed by dosing with 250 mg varespladib-methyl (1 x 250 mg oral tablet) approximately 12 hours later, and subsequent BID dosing with 1 x 250 mg varespladib-methyl oral tablets for the remainder of the 7-day treatment period. Tablets may be administered via feeding tube (e.g., naso- or orogastric tubes) in subjects requiring mechanical ventilation.
- Pediatric subjects (ages 5 to < 18) will be administered doses of varespladib-methyl determined by allometric scaling, provided as 50 mg capsules. Age-appropriate capsules, as described in Section 7.3 of the protocol, may be administered via feeding tube (e.g., naso- or orogastric tubes) in subjects requiring mechanical ventilation.
- The timing of initial snakebite envenoming, and administration of SOC will be considered when determining study subject eligibility.

3.5. Method of Assigning Subjects to Treatment Groups

In this parallel-group randomized study, subjects who meet study entry criteria will be randomly assigned in a 1:1 ratio to varespladib-methyl or placebo. The randomization schedule, which will be computer generated using a permuted block algorithm, will randomly allocate IP to randomization numbers. The randomization numbers will be assigned sequentially through a central interactive web response system (IWRS) as subjects are entered into the study. The randomization schedule will be stratified by age group (5 to < 11 years, 11 to < 18 years, and ≥ 18 years) and by the presence or absence of moderate to severe neurotoxicity (SSS nervous system subscore of 0−1 or ≥ 2) at Baseline, resulting in 6 strata in total. Study center will not be a blocking factor in the randomization schedule. The block sizes will not be divulged to the Sponsor or the investigative team. No one involved in the study performance will have access to the randomization schedule before official unblinding of treatment assignment. The

randomization schedule will be prepared by the clinical research organization (CRO) before the start of the study. No subject will be randomized into this study more than once.

A subject will be considered randomized when the IWRS has given the treatment number to be allocated.

3.6. Blinding and Unblinding

All subjects, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment except for a specified unblinded statistician and programmer from the study CRO who will have access to the randomization code. The unblinded study personnel will not participate in study procedures or data analysis prior to unblinding of the study data to all study-related personnel upon database lock. If an interim analysis is conducted, then unblinded personnel who are not otherwise involved in the study will prepare the data for review.

Study personnel will make every effort to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

Unblinding should be discussed in advance with the medical monitor, if possible. For emergency unblinding, study personnel will use the IWRS. If the Investigator is not able to discuss treatment unblinding in advance, they must notify the medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment.

Unblinding for an individual subject will not result in unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised.

3.7. Schedule of Events

Please see Table 1 of the protocol for a detailed schedule of events.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will primarily use SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of

subjects who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment groups, unless otherwise specified.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Means will be reported to 1 degree of precision more than the observed data and measures of spread will be reported to 2 degrees of precision more than the observed data. Medians will be reported to the degree of precision measured.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and *P* values will be reported. Corresponding 95% confidence intervals (CIs) will be presented for statistical tests.

This study is considered a confirmatory study. Statistical tests will be regarded as formal tests of specific hypotheses.

4.2. Selection of Key Secondary Efficacy Endpoints.

The AUC of the pulmonary, cardiovascular, local wound, hematologic symptoms, renal, and nervous system sections of the SSS from baseline through Day 7 will provide a comprehensive measure of snakebite envenoming pathology through the first week. This outcome differs from the primary outcome because it includes the local wound score, which is an important component of snakebite envenoming pathology in both the U.S. and India. Also, by covering the 7-day period following randomization, it will enable the assessment of benefits of varespladib on the resolution of toxicity in different organ systems occurring at different time points within the first week.

Total antivenom administration from Baseline through Day 28 is an important secondary outcome. Administration of antivenom by clinicians is based on illness severity and clinical status over time: Patients who continue to manifest toxicity will typically receive additional doses. Antivenom has medical risks, including both hypersensitivity reactions and serum sickness. Moreover, antivenom is expensive and in many settings in both the U.S and India there is limited availability of antivenom (e.g., many small emergency departments in the U.S. do not stock antivenom). If $sPLA_2$ inhibition with varespladib reduces the need for antivenom, that would indicate a more rapid improvement in the patient's clinical condition, and be important to both patients and healthcare systems.

Pain is an important clinical manifestation of snakebite envenoming. While snakes use venom primarily for predation and defense, venom sPLA2 toxins directly affect or potentiate the action of other venom toxins to activate mammalian sensory neurons and cause enhanced pain (Kazandjian et al., 2021). In the U.S., bites from the common venomous snake species (*Agkistrokon spp*. and *Crotalus spp*.) often result in severe pain. Pain is not only a cause of immediate suffering, pain also correlates with tissue injury and short-term disability and predisposes patients to persistent symptoms and delays in return to work. Evidence that varespladib reduces pain symptoms in humans following snakebite envenoming would provide important evidence of efficacy that is distinct from the primary and other key secondary

endpoints.

The CGI-I provides a global summary of a patient's improvement from the clinician's perspective. This global summary has the potential to integrate information about improvements in multiple organ systems, which is valuable because of the complex and heterogenous pathology of snakebite envenoming. The investigators who are participating in the trial have extensive experience caring for patients bitten by venomous snakes and will be able to evaluate accurately what constitutes a meaningful improvement.

4.3. Interim Analysis and Data Monitoring

No interim efficacy analyses are planned.

The data safety monitoring board (DSMB) operates under a charter that was finalized prior to the start of the study. The DSMB evaluates the safety data at the intervals specified in the DSMB charter. In case of significant toxicity, the DSMB may choose to review the available safety data and recommend stopping recruitment. If toxicity is observed, the treatment assignment for the subject(s) involved may be unblinded by the DSMB at its discretion.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Safety Population (SAF):** The Safety Population includes all subjects who receive any amount of IP. Subjects who are members of the SAF population will be analyzed according to the treatment received. This population will be used for analysis of demographics, baseline characteristics, and all safety analyses.
- **Intent-To-Treat Population (ITT):** The ITT population includes all subjects who have been randomized. Subjects included in the ITT population will be analyzed as randomized. The ITT population will be used for analysis of demographics, baseline characteristics, and all efficacy analyses.*
- **Per-Protocol Population (PP):** The PP population includes all subjects in the ITT without any significant protocol deviation. Subjects who are members of the PP population will be analyzed as randomized. This will be a secondary supporting population for the primary efficacy analyses.*
- **Pharmacokinetic Population (PK):** The PK Population includes all subjects in the SAF Population who provide at least 1 evaluable post-dose PK measurement. Subjects who are members of the PK population will be analyzed according to the treatment received.*

*Assignment of subjects to populations will be confirmed at a blinded data review meeting to be held before the study database is locked.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

Prior to analyses, lab values will be standardized to consistent units.

6.1.1. Baseline

Observations recorded before or immediately after the first dose of treatment will be used as the baseline observation for all calculations of change from baseline.

6.1.2. Adjustments for Covariates

The comparison of the primary and secondary efficacy endpoints between the varespladib-methyl and placebo groups for the primary efficacy analysis will be adjusted for four variables: (1) baseline SSS composed of the pulmonary, cardiovascular, hematologic, renal, and nervous system sections treated as a continuous variable; (2) age group treated as a dichotomous variable (age 5-17 vs. age ≥18 years); (3) baseline neurotoxicity (SSS neurological system subscore) treated as a dichotomous variable (0-1 vs. ≥2); and (4) Country (U.S. vs. India). Because we anticipate low numbers of patients in the two pediatric age group strata, we have collapsed these two strata into a single group (age 5-17) for the purpose of data analysis. A sensitivity analysis for the primary and key secondary endpoints will include a fourth covariate: completion of the initial dose of antivenom prior to initiation of study drug (Yes or No).

The mixed model for repeated measurements (MMRM) will be adjusted for baseline SSS, baseline neurotoxicity, age group, completion of the initial dose of antivenom prior to initiation of study drug, and scheduled timepoint of assessment. It will also include terms for treatment-by-time interaction and baseline score-by-time interaction.

The Cox model to estimate the hazard ratios for all-cause mortality will be adjusted for baseline SSS, baseline neurotoxicity, age group, and completion of the initial dose of antivenom prior to initiation of study drug.

6.1.3. Multiple Comparisons

A gatekeeping or fixed-sequence procedure will be used for testing the key secondary endpoints. See details in Section 8.1.2.

6.1.4. Handling of Dropouts or Missing Data

For the primary efficacy analysis, subjects with a missing SSS at either 6- or 9- hours will be given an "average" SSS at 6 and 9 hours equal to the single score that is available from this time period. For subjects with missing SSS's at both 6 and 9 hours, the site investigator will be asked to use all available contemporaneous clinical and laboratory data to determine the SSS at these time points. These scores will be obtained and finalized prior to database lock to ensure that investigators are blinded during this process. Finally, if missing data persists after the prior methods, then multiple imputation will be performed based on country, gender, baseline age, baseline SSS scores, treatment assignment, and available post-baseline SSS scores. Subscores

will be imputed and then the SSS score will be derived. More details on the multiple imputation process are provided in Section 6.1.4.1 below.

For the first key secondary endpoint, AUC of the SSS through Day 7, for any missing data, the site investigators will again be asked to use all available contemporaneous clinical and laboratory data to determine the SSS at these time points. If data are still missing, multiple imputation will be used to determine missing scores and subscores based on country, baseline age, gender, baseline SSS scores, treatment assignment, and available post-baseline SSS scores. More details on the multiple imputation process are provided in Section 6.1.4.1 below.

For the second key secondary endpoint, total antivenom administration, if the patient has complete data on antivenom administration through Day 3, then no change will be made to the total antivenom administered. This decision reflects the fact that in clinical practice in the U.S. and India, antivenom administration after 48 hours is uncommon. If the patient is missing data prior to Day 3, then the treatment of missing data will depend on the reason for missingness. If the patient has been discharged from the hospital, then no changes will be made to the available total amount of antivenom administered. If the patient has missing data prior to Day 3 and has not been discharged from the hospital or is transferred to another hospital, we will review each case and based on the patient's SSS will determine if the patient met criteria of additional antivenom. If the patient did meet criteria for additional antivenom, then we will assume a single additional dose was given to the patient, with the number of vials in this dose corresponding to the standard treatment dose in the region where the patient is receiving care.

For the third key secondary endpoint, AUC of the NPRS through Day 3, multiple imputation will be used to replace missing scores based on country, baseline age, gender, baseline NPRS scores, treatment assignment, and available post-baseline NPRS scores. More details on the multiple imputation process are provided in Section 6.1.4.1 below.

For the fourth key secondary endpoint, CGI-I at Day 2, multiple imputation will be used to model missing values; with more details in Section 6.1.4.1 below.

Individuals who cannot respond to patient-reported assessments due to severity of snakebite envenoming will be given a score corresponding to the worst score available in the assessment. Specific assessments and unable to respond scores are:

- PSFS = 0 (Unable to perform activity)
- PGIC =10 (Feel much worse)
- Grip Strength = 0

A tipping point analysis will be conducted as a sensitivity analysis to handle missing data for the primary efficacy endpoint. More details are provided in Section 6.1.4.3 below.

For the key secondary efficacy endpoints, a sensitivity analysis to handle missing data will be conducted only if results cannot be calculated for more than 10 study participants. In this case, the nature of the sensitivity analysis will be determined on review of the data.

6.1.4.1. Multiple Imputation

The multiple imputation (MI) procedures for the primary and key secondary endpoints are described below.

For the primary analysis, missing data not due to mortality, and not addressed by the averaging rules above, will be imputed using the following regression-based multiple imputation model.

The following imputation algorithm will be applied to each SSS subscore separately, then the primary outcome SSS score will be derived.

1. The first step is to understand the pattern of missingness. In order to perform the multiple imputation, a monotone missing pattern must be achieved. For example, if there exist values for baseline and Day 2 visits, but missing values for the Day 1 (8-10h) visit, Markov-Chain Monte-Carlo (MCMC) method will be used to impute the small amount of missing data that may be missing at the intermediate visits that is required to make the missing data pattern monotone before applying the multiple imputation algorithm. This method uses a non-informative Jeffreys prior to derive the posterior mode from the expectation-maximization (EM) algorithm as the starting values for the MCMC method. This MCMC method will use seed of 432832. To avoid values that could not be observed in practice, imputed values will be constrained to be integers in the range of 0 to 3 or 0 to 4 by convention to align with the scale of the questionnaire. A total of 10 imputations will be done in the MCMC step.
2. Once the monotone pattern is achieved, the next step is to implement the imputation algorithm. For this, the Predictive Mean Matching method (PMM) will be used. This method is particularly helpful if the normality assumption is violated. For subjects with complete data up to a particular visit, a PMM model will be fit that includes the outcome at that visit as the dependent variable; and as independent variables gender, treatment assignment, study site, and non-missing scores using a seed of 931428. This process will be repeated 15 times, resulting in a total of 150 complete analysis datasets.
3. For each completed dataset, any necessary derived variables will be computed. Then the ANCOVA model will be performed for the 6 and 9 hour average SSS score. The results will be combined into one MI inference (LS mean, associated 95% CI, and p-value) using `PROC MIANALZE` as illustrated (Ratitch et al., 2013).

The first key secondary analysis on AUC will use the same process above, except in step 3 the AUC will be derived for each subject in each imputed dataset, then analyzed and aggregated as above using `PROC MIANALZE` (Ratitch et al., 2013).

The secondary key secondary analysis on antivenom amounts will not use multiple imputation.

The third key secondary analysis on NPRS AUC will use the same process above, except in step 3 the NPRS-AUC will be derived for each subject in each imputed dataset, then analyzed and aggregated as above using `PROC MIANALZE` (Ratitch et al., 2013).

The fourth key secondary analysis on CGI-I will use the same MI method described above, except using baseline and post-baseline CGI-I scores.

6.1.4.2. SAS Code for Multiple Imputation

See below for SAS code describing the multiple imputation approach.

```
Step 1:
proc mi data=&base._tr out=&base._mcmc seed=432832 nimpute=10
minimum=0 maximum=&maxval. round=1;
   mcmc impute=monotone prior=jeffreys;
   em maxiter = 300;
   var visit1-visitN;
run;

Step 2:
proc mi data=&base._mcmc seed=931428 nimpute=15  out=&base._pmm
minimum=0 maximum=&maxval. round=1;
  by _imputation1_;
  class sexn trt01pn countryn;
  monotone regpmm(visit1-visitN) ;
  var  sexn age trt01pn countryn visit1-visitN;
run;
```

6.1.4.3. Tipping Point Analysis

A sensitivity analysis for the primary endpoint will be performed by creating a table in which each patient who is missing primary outcome data is represented. For each of these patients, all possible values for the primary outcome that go towards the null hypothesis (i.e., decreasing SSS score for Placebo subjects and increasing SSS scores for Varespladib-Methyl subjects) will be examined and the p-value for the primary efficacy endpoint will be recalculated. This analysis will show the range of outcomes for which the results of the primary analysis shift from significant (i.e., $\alpha \leq 0.05$) to non-significant (i.e., $\alpha > 0.05$).

6.1.5. Analysis Visit Windows

Statistical analyses will be based on the assessment schedule described in the protocol.

6.1.6. Pooling of Sites

The question of pooling of sites does not arise since study sites will not be taken into account in the analyses.

6.1.7. Derived Variables

6.1.7.1. Primary Endpoint: Change in SSS from Baseline to Average at 6 and 9 hours

The primary endpoint SSS will be calculated from responses to the pulmonary, cardiovascular, hematologic, renal, and nervous system sections of the SSS. The sum of the values of the 5 subsections will be the total SSS used to calculate the primary endpoint. The primary endpoint will be the change from baseline to the average of the 6 hr and 9 hr scores: Change = (Baseline - [6hr + 9hr]/2). As such, a negative score will indicate an increase in severity from baseline (subject has gotten worse), and a positive score will indicate a decrease in severity from baseline (subject has gotten better). A subject who dies *before* 6 hours will receive the worst possible score (score = 16) to represent the SSS at 6 and 9 hrs. A subject who dies *between* the 6 and 9-hour period will receive the worst possible score (score = 16) at 9 hours, and this value will be averaged with the score at 6 hours for calculating the primary endpoint.

6.1.7.2. SSS-AUC7d

The AUC calculation includes the pulmonary, cardiovascular, local wound, hematologic, renal, and nervous system sections of the SSS assessment up to 7±1 days. The calculation will include the baseline assessment. All assessments within baseline and baseline + 8 days will be included in the calculation. This endpoint will be analyzed according to the missing data procedures described in Section 6.1.4 above.

In order to standardize the duration of time for each SSS-AUC_{7d} calculation, the "Day 7" SSS will be set at exactly 168 hours regardless of when it was actually assessed for this endpoint, with two exceptions:

1) For patients whose "Day 7" score was assessed prior to Day 7 (prior to 144 hours) and whose score is higher at the "Day 14" assessment than at the "Day 7" assessment, we will linearly interpolate between the "Day 7" and "Day 14" scores to impute the score at 168 hours.

2) For patients whose "Day 7" occurs on Day 10 or later (240 hours), we will linearly interpolate between "Day 3" and "Day 7" to impute the score at 168 hours.

The AUC will be calculated using the trapezoidal rule: average the SSS scores between two adjacent timepoints, multiply by the difference in time points in hours, repeating this across all time points and summing the results to obtain the total AUC across a fixed range of time. Thus the AUC at a particular timepoint j is calculated as follows.

$$\text{AUC}_j = \frac{1}{2}\left(SSS_j + SSS_{j-1}\right)\left(t_j - t_{j-1}\right)$$

where t is measured in hours; $j = 1, \ldots, J$; and J is the total number of timepoints at which SSS is measured. $J = 6$ if all planned SSS assessments are performed. Thus the total AUC for subject i from baseline to Day 7 is as follows.

$$\text{AUC}_{i,\text{BL to Day 7}} = \frac{1}{2}\sum_{j=1}^{J}\left(\text{SSS}_{i,j} + \text{SSS}_{i,j-1}\right)\left(t_{i,j} - t_{i,j-1}\right)$$

Thus AUC is calculated for each subject with baseline and post-baseline SSS scores, subject to the constraints on missingness described above. An example of this applied in SAS is provided at lexjansen.com/wuss/2004/posters/c_post_the_sas_calcuations_.pdf

- where:The SSS assessments SSS_0, SSS_1, … , SSS_J are made at times $t_0, \ldots, t_J$
- t_0 is the time of the initiation of the IV infusion
- SSS_0 is the SSS assessment at baseline
- t_j is the j^{th} timepoint at which SSS is assessed such that $t_J - t_0 \leq 7$ day

6.1.7.3. NPRS-AUC3d

The calculation will include all assessments from baseline to Day 3. The procedures for dealing with missing data are described in Section 6.1.4. See section 6.1.7.14 for definitions of Day 1, Day 2, and Day 3.

In order to standardize the duration of time for each NPRS-AUC_{3d} calculation, the "Day 3" NPRS will be set at exactly 48 hours regardless of when it was actually assessed for this endpoint, with two exceptions:

1) For patients whose "Day 3" score was assessed prior to Day 3 (prior to 36 hours) and whose score is higher at the "Day 7" assessment than at the "Day 3" assessment, we will linearly interpolate between the "Day 3" and "Day 7" scores to impute the score at 48 hours.

2) For patients whose "Day 3" occurs more than 12 hours after 48 hours (60 hours), we will linearly interpolate between "Day 2" and "Day 3" to impute the score at 48 hours.

The AUC will be calculated using the trapezoidal rule: average the NPRS scores between two adjacent timepoints, multiply by the difference in time points in hours, repeating this across all time points and summing the results to obtain the total AUC across a fixed range of time. Thus the AUC at a particular timepoint j is calculated as follows.

$$\text{AUC}_j = \frac{1}{2}\left(\text{NPRS}_j + \text{NPRS}_{j-1}\right)\left(t_j - t_{j-1}\right)$$

where t is measured in hours; $j = 1, \ldots, J$; and J is the total number of timepoints at which NPRS is measured. $J = 5$ if all planned NPRS assessments are performed. Thus the total AUC for subject i from baseline to Day 3 is as follows.

$$\text{AUC}_{i,\text{BL to Day 3}} = \frac{1}{2}\sum_{j=1}^{J}\left(\text{NPRS}_{i,j} + \text{NPRS}_{i,j-1}\right)\left(t_{i,j} - t_{i,j-1}\right)$$

Thus AUC is calculated for each subject with baseline and post-baseline NPRS scores, subject to the constraints on missingness described above.

6.1.7.4. Complete SSS

The complete SSS will be calculated from responses to all system sections of the SSS. The sum of the values of the 7 subsections will be the total SSS used to calculate the total complete SSS score.

6.1.7.5. Coagulation Abnormalities

Coagulation laboratory values (PT, PTT, platelets, and fibrinogen) will each be analyzed separately. For these analyses, each value at each time point will be categorized following the criteria established in the Snakebite Severity Score (Dart et al., 1996). Additional details are provided in Section 8.2.3.

6.1.7.6. Hemolysis

The assessment of hemolysis will be based on free hemoglobin concentration (mg/dL), which will be treated as a continuous variable.

6.1.7.7. Antivenom Administered

The amount of antivenom administered will be categorized into three groups: low, medium, and high. The relevant value for these categorizations will be the total vials of antivenom given to the patient for which the treatment was initiated after the receipt of study drug. (Antivenom given to patients before the receipt of study drug will not be included in this total.) The categorizations are defined below, separately for each of the major types of antivenom:

India Polyvalent Antivenom (includes all antivenom given to participants in India)
Low: 0 vials
Med: >0 to 10 vials
High: >10 vials

CroFab
Low: 0 vials
Med: >0 to 6 vials
High: >6 vials

ANAVIP
Low: 0 vials
Med: >0 to 10 vials

High: >10 vials

6.1.7.8. Time from Initiation of Ventilatory Support to Initiation of Weaning

The total time from initiation of ventilatory support to initiation of weaning will be calculated in hours. Subsequent re-intubations will not be included in this calculation.

6.1.7.9. Duration of Ventilatory Support

The duration (hours) of ventilatory support for primary neurotoxic envenoming will be calculated as the total duration of mechanical (ventilator) or manual (bag valve mask) methods used to assist or replace spontaneous respiration. If a subject is reintubated one or more times, these additional periods of ventilatory support (from initiation of ventilatory support to extubation or removal or ventilatory support) will be included as part of the total time.

$$\sum_{for\ each\ ventilation} (time\ of\ removal\ of\ support - time\ of\ initiation\ of\ support)$$

6.1.7.10. Duration of ICU Stay

The length of ICU stay from baseline to Day 28 will be calculated using the following duration in hours

$$\sum_{for\ each\ episode} (ICU\ discharge\ date\ and\ time - ICU\ admission\ date\ and\ time)$$

The duration of ICU stay will be truncated at Day 28. If a discharge date and time is after Day 28, it will be replaced by Day 28.

6.1.7.11. Duration of hospitalization

The length of hospital stay from baseline to Day 28 will be calculated using the following duration in hours

$$\sum_{for\ each\ admission} (discharge\ date\ and\ time - admission\ date\ and\ time)$$

The duration of hospitalization will be truncated at Day 28. If a discharge date and time is after Day 28, it will be replaced by Day 28.

6.1.7.12. Treatment-Emergent Adverse Event

Treatment-emergent AEs are defined as AEs that first occur or worsen in severity after the first dose of IP and prior to 30 days after last administration of IP.

Where an AE start date/time or end date/time is partially or fully missing, and it is unclear as to

whether the AE is a TEAE, it will be assumed that it is TEAE.

6.1.7.13. Percent of Study Medication Compliance

The percent of study medication compliance will be calculated as follows:

$$100 * \sum_{i=2}^{last\ visit} \frac{\text{Number of oral doses dispended at visit } (i-1) - \text{Number of oral doses returned at visit } i}{\text{Number of oral doses that the subject was instructed to take from visit } (i-1) \text{ to visit } i}$$

where the denominator is greater than zero.

6.1.7.14. SSS Score using Compressed SSS Scale

The compressed SSS will be calculated by first subtracting 1 from non-zero responses to the pulmonary, cardiovascular, hematologic, renal, and nervous system sections of the SSS. The sum of the adjusted values of the 5 subsections will be the total SSS used to calculate the compressed score. The endpoint will be the change from baseline through Day 7 compressed scores: Change = Baseline – Score (at each time).

6.1.7.15. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

Day 1 will refer to activities that occurred at baseline through the first 12 hours after the patient receives the study drug (regardless of whether the calendar day has changed). Day 2 assessments will occur at least 12 hours and not more than 18 hours after the 8-10 hour assessment on Day 1. Thereafter, Day will refer to calendar day following the initiation of treatment (e.g., Day 28 will occur 27 days after the day on which the patient received their first dose of study drug).

P values will be displayed with two significant figures if the value is greater than or equal to 0.01 (eg., 0.XX) and with one significant figure is less than 0.01 (eg., 0.00X). If a *P* value less than 0.0001 occurs, it will be shown in tables as < 0.0001.

Adverse events will be coded using the latest MedDRA version thesaurus.

6.1.8. COVID-19

The potential impact of COVID-19 on this clinical trial and trial participants will be described in listings and in the CSR.

The following aspects will be summarized when protocol deviations are due to COVID-19 infection or restriction:

- Changes to treatment dispensation
- Changes to treatment administration
- Changes to visit windows to accommodate delays for some assessments

- Missing efficacy endpoints
- Missing visits

7. Study Subjects and Demographics

7.1. Disposition of Subjects and Withdrawals

Disposition will include tabulations by treatment group and overall:

- the number of subjects randomized into each treatment group
- the number of subjects who received treatment
- the number of subjects who received the entire course of treatment
- the number of subjects completing the study
- tabulated reasons for discontinuation from the study
- and number of subjects in each analysis population.

The total number of (1) screening failures and (2) withdrawals prior to receipt of study drug and the reasons for screen failure and withdrawals prior to receipt of study drug will be presented in separate tables.

7.2. Protocol Violations and Deviations

A by-subject listing of protocol deviations will be presented. Protocol deviations will also be reported by major vs. minor status. Protocol deviations classified as important will be re-classified as major; protocol deviations classified as non-important will be re-classified as minor.

7.3. Demographics and Other Baseline Characteristics

These analyses will be conducted for the ITT and SAF populations.

Summary statistics for age, gender, race, ethnicity, height, and weight will be presented by treatment group.

The envenoming history, including the anatomic location of envenoming, initial swelling, snake identification, key toxicities as measured in Baseline SSS subscores, and tourniquet use will be summarized by treatment group. If obtained, results of the 20WBCT will also be summarized by treatment group.

The number and percent of subjects reporting various medical histories, grouped by MedDRA system organ class and preferred term, will be tabulated by treatment group.

7.4. Exposure and Compliance

IP exposure and dosing information including the number of doses per subjects and amount of IP received will be tabulated by treatment arm and age group.

For each treatment, IP compliance will be summarized by compliance category (≤ 80%, 80-120%, ≥ 120%) and the number of subjects in each compliance category. Study medication compliance will also be summarized as a continuous variable using descriptive statistics. This

analysis will be conducted for the SAF population.

8. Efficacy Analysis

8.1. Primary Efficacy Analysis

8.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change in the composite outcome of the pulmonary, cardiovascular, hematologic, renal, and nervous system sections of the snakebite severity score (SSS) from Baseline (pre-dosing) to the average of the scores from 6 and 9 hours after first dose: Change = (Baseline – [6hr + 9hr]/2).

The ITT population will be used to analyze the primary efficacy endpoint. For completeness the analyses will be repeated for the PP population.

Descriptive statistics for the SSS as well as the 6hr and 9hr mean scores will be tabulated by treatment group.

The primary analysis will use ANCOVA. A sensitivity analysis will use rank-regression applying the same adjustment covariates as specified in the ANCOVA. To better understand the appropriateness of applying a parametric vs. nonparametric approach, the CSR will include diagnostics plots of ANCOVA residuals.

The change from baseline to the average of the 6hr and 9hr scores will be compared between treatment groups using an ANCOVA with the baseline SSS score, subject age group, the presence or absence of baseline neurotoxic symptoms, and country as covariates. The varespladib-methyl to placebo (varespladib-methyl vs. placebo) will be compared at the 5% two-sided significance level; corresponding 95% two-sided confidence interval for the difference will be presented.

Six sets of subgroup analyses will be performed: (1) patient age, (2) baseline neurotoxic symptoms, (3) prior receipt of antivenom, (4) country, (5) snake type, and (6) timing of receipt of study drug. The following paragraphs describe these six sets of subgroup analyses.

1. *Patient age.* Summary statistics, including baseline SSS and least square means from the ANCOVA, will be presented separately for pediatric (5 to 17 years) and adult (≥18 years) subjects. If the study includes too few children to fit an ANCOVA, only summary statistics will be presented.

2. *Baseline neurotoxic symptoms*. The treatment effect will be estimated in subjects with and without moderate or severe neurotoxic symptoms at baseline (SSS nervous system score of 0-1 vs. 2-3). These analyses will be analogous to those described for the pediatric and adult subgroup analyses, except that the ANCOVA will include age group, but not neurotoxicity.

3. *Prior receipt of antivenom*. The treatment effect will be estimated separately in subjects who have and have not completed an initial dose of antivenom prior to initiation of study drug. These analyses will be analogous to those described for the pediatric and adult subgroup analyses, except that the ANCOVA will include age group but not receipt of antivenom prior to initiation of study

drug.

4. *Country*. The treatment effect will be estimated in separately in subjects enrolled in the U.S. and those enrolled in India. These analyses will be analogous to those described for the pediatric and adult subgroup analyses, except that the ANCOVA will include age group but not country.

5. *Snake type.* The treatment effect will be estimated separately in subjects bitten by vipers, elapids, and unknow snake types. These analyses will be analogous to those described for the pediatric and adult subgroup analyses, except that the ANCOVA will include age group.

6. *Timing of receipt of study drug.* The treatment effect will be estimated separately in subjects for whom the time from bite or symptom onset to receipt of study drug was <5 hours and >5 hours. These analyses will be analogous to those described for the pediatric and adult subgroup analyses, except that the ANCOVA will include age group.

There will be several sensitivity analyses.

Sensitivity analysis will be conducted for the primary efficacy analysis (1) adding completion of the initial dose of antivenom prior to the initiation of study drug as a covariate and (2) using a compressed SSS as the outcome and applying the same analytic methods as described above. A separate set of analyses will estimate the effect of treatment on individual component subscores of the SSS.

Other sensitivity analyses will estimate the treatment effect on the primary endpoint excluding data from one site at a time. For this analysis, data from sites that enrolled 10 patients or fewer will be combined and excluded as a single group. The purpose of this sensitivity analysis is to assess whether data from any single site has an outsized effect on the estimated treatment effect of the primary endpoint.

Another sensitivity analysis will apply the tipping point approach described in Section 6.1.4.3.

Sensitivity and subgroups analyses of the primary and key secondary endpoints will not be part of the gatekeeping procedure for hierarchical testing of endpoints.

8.1.2. Key Secondary Efficacy Endpoints

The ITT population will be used to analyze the secondary efficacy endpoints. All secondary endpoints will be analyzed using the prespecified assessment timepoints according to the protocol. All statistical models for change from baseline in a particular endpoint will include covariates for baseline value of the particular endpoint, baseline SSS, baseline neurotoxicity (Yes, No; based on the SSS neurological system subscore), age group (5-17, 18+), and country (U.S. vs. India). Key secondary endpoints will be tested sequentially using a fixed-sequence gatekeeping procedure for the hierarchical testing of multiple endpoints. The significance of the treatment effect for the primary endpoint (i.e., change in SSS from baseline to average at 6 and 9 hours) will be the first hypothesis tested, using a significance level of 0.05. If the null hypothesis for the primary endpoint is rejected, then the first key secondary endpoint (i.e., AUC of SSS through Day 7) will be tested, also with a significance level of 0.05. If the null hypothesis for this test is rejected, the second key secondary endpoint (total antivenom use) will be tested (α=0.05).

If the null hypothesis for this test is rejected, the third key secondary endpoint (AUC of NPRS through Day 3) will be tested (α=0.05). If the null hypothesis for this test is rejected, the fourth key secondary endpoint (CGI-I at Day 2) will be tested (α=0.05). Sensitivity and subgroups analyses of the primary and key secondary endpoints will not be part of the gatekeeping procedure for hierarchical testing of endpoints.

8.1.2.1. AUC of the Pulmonary, Cardiovascular, Local Wound, Hematologic Symptoms, Renal, and Nervous System Sections of the SSS from Baseline Through Day 7

The SSS-AUC$_{7d}$ will be compared between treatment groups within an ANCOVA model with the baseline SSS score, age group (5 to 17 years, ≥ 18 years), baseline neurotoxicity, and country as covariates. The comparison of varespladib-methyl to placebo (varespladib-methyl vs. placebo) will be tested at a 5% two-sided significance level; the corresponding 95% two-sided confidence intervals will be presented. The AUC will be calculated according to Section 6.1.7.2. Also note that this SSS score is calculated only using the pulmonary, cardiovascular, local wound, hematologic, renal, and nervous system subscores. A reduction in SSS-AUC (i.e., negative parameter estimate) will represent a faster improvement in snake bite symptoms on average. Individual subscore AUCs by treatment group will also be summarized using descriptive statistics. Subgroup analyses will estimate the treatment effect separately for pediatric and adult patients, for patients with and without clinically significant neurotoxicity, for patient who have and have not completed an initial dose of antivenom prior to randomization, for the U.S. and for India, for each snake type (viper, elapid, and unknown), and for patients for whom the time from bite or symptom onset to receipt of study drug was <5 hours and ≥5 hours.

8.1.2.2. Total Differential Antivenom Requirement from Baseline through Day 28

The total number of vials of antivenom administered will be analyzed using a proportional odds logistic regression with three ordered categories. For each type of antivenom administered, the number of vials of antivenom from baseline through Day 28 will be categorized as low, medium, or high. Cutoffs for these categories are based on recommendations regarding treatment for each antivenom type as well as a review of available blinded data.

<u>India Polyvalent Antivenom (all antivenom administered in India)</u>

- Low: 0 vials
- Medium: > 0 to 10 vials
- High: > 10 vials

<u>CroFab</u>

- Low: 0 vials
- Medium: > 0 to 6 vials
- High: > 6 vials

ANAVIP

- Low: 0 vials
- Medium: > 0 to 10 vials
- High: > 10 vials

This model will use the following covariates: baseline SSS score, age group (5 to 17 years, ≥ 18 years), baseline neurotoxicity, receipt of antivenom prior to baseline (Yes, No), and country. The treatment effect will be summarized with an estimated odds ratio. The comparison of varespladib-methyl to placebo (varespladib-methyl vs. placebo) will be tested at a 5% two-sided significance level; the corresponding 95% two-sided confidence intervals will be presented. Subgroup analyses will estimate the treatment effect separately for pediatric and adult patients, for patients with and without clinically significant neurotoxicity, for patient who have and have not completed an initial dose of antivenom prior to randomization, for the U.S. and for India, for each snake type (viper, elapid, and unknown), and for patients for whom the time from bite or symptom onset to receipt of study drug was <5 hours and ≥5 hours.

As an analysis of model fit, the assumption of proportional odds will be tested. An exploratory analysis will calculate a binomial logistic regression model collapsing the medium and high antivenom categories into a single category. The dependent variable will be either "low" or "medium or high" antivenom use. The model will use the same set of covariates described above.

8.1.2.3. AUC of the NPRS from Baseline Through Day 3

An ANOCVA will be used to compare the NPRS-AUC_{3d} for the two treatment groups with baseline NPRS score, age group (5 to 17 years, ≥ 18 years), baseline neurotoxicity, and country as covariates. The comparison of varespladib-methyl to placebo (varespladib-methyl vs. placebo) will be tested at a 5% two-sided significance level; the corresponding 95% two-sided confidence interval will be presented. The AUC will be calculated according to Section 6.1.7.3. A reduction in NPRS-AUC (i.e., negative parameter estimate) will represent a faster average improvement in pain symptoms. Subgroup analyses will estimate the treatment effect separately for pediatric and adult patients, for patients with and without clinically significant neurotoxicity, for patient who have and have not completed an initial dose of antivenom prior to randomization, for the U.S. and for India, for each snake type (viper, elapid, and unknown), and for patients for whom the time from bite or symptom onset to receipt of study drug was <5 hours and ≥5 hours.

8.1.2.4. Clinical Global Impression – Improvement (CGI-I) at Day 2

CGI-I (1-7 scale) at Day 2 will be treated as a continuous variable with scores compared using ANCOVA, with treatment as the variable of interest, and with baseline SSS, age group, baseline CGI-I score, baseline neurotoxicity, and country as covariates. The model will be used to estimate the effect of treatment on CGI-I scores at Day 2. The comparison of varespladib-methyl to placebo (varespladib-methyl vs. placebo) will be tested at a 5% two-sided significance level;

the corresponding p-value and 95% two-sided confidence intervals will be presented.

A sensitivity analysis will add completion of initial dose of antivenom prior to initiation of study drug as a covariate. Subgroup analyses will estimate the treatment effect separately for pediatric and adult patients, for patients with and without clinically significant neurotoxicity, for patient who have and have not completed an initial dose of antivenom prior to randomization, for the U.S. and for India, for each snake type (viper, elapid, and unknown), and for patients for whom the time from bite or symptom onset to receipt of study drug was <5 hours and ≥5 hours.

8.1.3. SAS Code for Primary and Key Secondary Efficacy Endpoints

Sample SAS code is provided below for these analyses using standard ADaM terminology; where TRT01PN is a numeric treatment group variable (0,1), AGEGR2BL is the two-group age strata (5 to 11 years, 12 to 17 years), NEUROBL is the indicator variable for baseline neurotoxicity (No, Yes), and ANTIVBLG is a three-group categorical variable for type of antivenom prior to baseline (Indian Polyvalents, CroFab, and ANAVIP). Note that PROC MIXED reduces to ANCOVA when no REPEATED statement is used. The LSMEANS option within will provide the treatment effect estimates of interest.

Primary Efficacy Endpoint

```
Proc univariate data=ADEFF;  /*visually inspect distribution*/
  Where PARAM="Primary Outcome SSS Score";
  Class AVISIT;
  Var CHG;
  Histogram;
  Run;

Proc mixed data=ADMI plots=studentpanel alpha=0.05;
  By _imputation_;
  Where PARAM="Primary Outcome SSS Score" and AVISIT="Average of 6 and
     9 hours";
  Class TRT01PN(ref='0') AGEGR2BL(ref='5 to 11 years')
     NEUROBL(ref='No') COUNTRY(ref='India');
  model CHG = BASE TRT01PN AGEGR2BL NEUROBL COUNTRY;
  lsmeans TRT01PN / cl pdiff;
  run;
proc mianalyze data=Estimates alpha=0.05;
  modeleffects estimate;
  stderr StdErr;
  run;
/*code for sensitivity analyses using initial antivenom dose as a
covariate, compressed SSS score, and component subscores are similar*/
```

Key Secondary Efficacy Endpoint #1, SSS-AUC

```
Proc mixed data=ADMI alpha=0.05;
  By _imputation_;
  Where PARAM="Primary Outcome SSS-AUC through Day 7" and AVISIT="Day
    7";
```

```
  Class TRT01PN(ref='0') AGEGR2BL(ref='5 to 11
    years')  NEUROBL(ref='No') COUNTRY(ref='India');
  model AVAL = TRT01PN SSSBL AGEGR2BL NEUROBL COUNTRY;
  lsmeans TRT01PN / cl pdiff;
  run;
proc mianalyze data=Estimates alpha=0.05;
  modeleffects estimate;
  stderr StdErr;
  run;
```

Key Secondary Efficacy Endpoint #2, Antivenom

```
proc logistic data = adeff descending;
    where paramcd = 'ANTIVG';
    class TRT01PN(ref = '2') AGEGR2BL(ref = '5 to 17 years')
        NEUROBL(ref = 'N') ANTIVBL(ref = 'N') COUNTRY(ref='India')
        /param = ref;
    model AVALC = TRT01PN SSSBL AGEGR2BL NEUROBL ANTIVBL COUNTRY /
link = clogit aggregate scale = none;
run;
```

Key Secondary Efficay Endpoint #3, NPRS-AUC

```
Proc mixed data=ADMI alpha=0.05;
  By _imputation_;
  Where PARAM=" NPRS-AUC through Day 3 - MI" and AVISIT="Day 3";
  Class TRT01PN(ref='0') AGEGR2BL(ref='5 to 11
    years')  NEUROBL(ref='No') COUNTRY(ref='India');
  model AVAL = TRT01PN SSSBL AGEGR2BL NEUROBL COUNTRY;
  lsmeans TRT01PN / cl pdiff;
  run;
proc mianalyze data=Estimates alpha=0.05;
  modeleffects estimate;
  stderr StdErr;
  run;
```

Key Secondary Efficay Endpoint #4, CGI-I

```
Proc mixed data=ADMI alpha=0.05;
  Where PARAM="CGI-I Score" and AVISIT="Day 2";
  Class TRT01PN(ref='0') AGEGR2BL(ref='5 to 11 years')
     NEUROBL(ref='No') COUNTRY(ref='India');
  Model AVAL = TRT01PN SSSBL AGEGR2BL NEUROBL COUNTRY;
  lsmeans TRT01PN / cl pdiff;
  run;
proc mianalyze data=Estimates alpha=0.05;
  modeleffects estimate;
  stderr StdErr;
  run;
```

8.2. Other Secondary Efficacy Analyses

The other secondary efficacy analyses will be interpreted as exploratory analyses. All secondary endpoints will be analyzed according to the prespecified assessment timepoints listed in the protocol. Statistical models will include covariates for baseline SSS, baseline neurotoxicity (Yes, No; based on the SSS neurological system subscore), age group (5-17, 18+), and, when available, the baseline value of the particular endpoint unless otherwise specified below. A sensitivity analysis will include as a covariate yes/no completion of an initial dose of antivenom prior to randomization. The methods described here are what is currently planned. However, for each analysis, we will examine the distribution of the strata pooled over treatment and placebo. If the data are unlikely to support the planned analysis or if the model fails to converge, removal of covariates and different estimation routines will be attempted and described in the CSR.

8.2.1. Complete SSS from Baseline through Day 7

The complete SSS (all sub-sections including pulmonary, cardiovascular, hematologic, renal, nervous system, gastrointestinal, and local wound) from baseline through Day 7 after first dose will be summarized using descriptive statistics of observed values and changes from baseline.

The post baseline complete SSS scores at each time point will be analyzed, without replacement of missing values, using a restricted maximum likelihood (REML) based repeated measures approach (MMRM). Analyses will include a random intercept and the fixed effects of treatment, baseline total SSS, age group (5-17 years, ≥ 18 years), baseline neurotoxicity, and visit (categorical) as covariates. The model will include a treatment-by-time interaction. An unstructured covariance model will be used to model the within-subject errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. If this analysis fails to converge, simpler structures (e.g., first-order compound symmetry and then autoregressive order-1 structures) will be tested in a model without treatment effect; the covariance structure and the degree of freedom approximation converging to the best fit, as determined by Akaike's Information Criterion, will be used in the full model. A description of all tested models and results from these models will be provided as an appendix in the CSR. Within this model, the estimate of interest is the effect of treatment at each time point, performed at significance level of 5%. The corresponding 95% two-sided confidence intervals will be presented at each time point of assessment.

8.2.2. SSS Neurologic System Subscore from Baseline through Day 3

The SSS neurologic system subscore from baseline through Day 3 after first dose will be summarized using descriptive statistics of observed values and changes from baseline. The SSS neurologic system subscore will be analyzed with a similar MMRM as the one described in Section 8.2.1. The MMRM will be used to assess the treatment effect on change in SSS neurologic system subscore through Day 3. The MMRM will include treatment as fixed effect as the variable of interest, with visit and visit by treatment interaction as covariates. The model will be used to estimate the effect of treatment on SSS neurologic subscore at each assessment time

point through Day 3. Treatment effect will be summarized via LS means, p-values, and 95% two-sided confidence intervals.

This analysis will be conducted in two groups of patients: (1) subjects with a baseline SSS neurologic system subscore ≥1; and (2) subjects with a baseline SSS neurologic system subscore ≥2.

Note: The effect of varespladib on neurotoxicity is supported by the observation that varespladib prevents, reverses, or delays lethality from venom neurotoxicity in animals experimentally envenomed with Mojave rattlesnake, coral snake, krait, and taipan venoms even when administered at a point when weakness is refractory to antivenom reversal (e.g., Prasarnpun 2005; Anil et al. 2010; Lewin et al. 2018a, 2018b; and Gutierrez et al. 2021). Neurologic outcomes were not selected as the focus of the primary or key secondary efficacy endpoints because of the unexpectedly small number of severely neurotoxic patients enrolled in the trial.

8.2.3. Coagulation Abnormalities from Baseline through Day 7

Each of the four coagulation lab values (PT, PTT, platelets, and fibrinogen) will be analyzed using a proportional odds logistic regression with five ordered categories. Categories for the lab values in each of these analyses will use those defined by the Snakebite Severity Score (Dart et al. 1996), with normal lab values receiving a score of 0 and abnormal lab values receiving a score of 1 to 4 based on the following published cutoffs.

Coagulation Parameter	0	1	2	3	4	Units
Prothrombin Time	Lab validated reference range	Above lab ref range to 20 sec	>20 to 50 sec	>50 to 100 sec	Unmeasureable or above 100 sec	Sec
Partial Thromboplastin Time	Lab validated reference range	Above lab ref range to 50 sec	>50 to 75 sec	>75 to 100 sec	Unmeasureable or above 100 sec	Sec
Platelet count	Lab validated reference range	100,000 to ref	50,000 to <100,000K	20,000 to <50,000	Less than 20,000	/mL
Fibrinogen	Lab validated reference range	100 to ref	50 to <100	Less than 50	Undetectable	mg/dL

Analysis for each of the four coagulation parameters will be run separately for each time point from Day 1 3 hours to Day 7. The models will use the following covariates: baseline SSS score, age group (5 to 17 years, ≥ 18 years), baseline neurotoxicity, receipt of antivenom prior to baseline (Yes, No), and country. The treatment effect will be summarized with an estimated odds ratio and tested at a 5% two-sided significance level; the corresponding 95% two-sided confidence intervals will be presented. These analysis will only include subjects with lab value-specific coagulation abnormalities (hematology subscore ≥1 as derived from the relevant coagulation lab value) at baseline.

8.2.4. Hemolysis Markers at Baseline through Day 3

Concentrations of free hemoglobin through Day 3 will be presented using graphs and summary statistics by treatment arm and time points.

An MMRM approach as described in Section 8.2.1 will be used to assess the treatment effect on change in free hemoglobin (continuous variable) through Day 3. The MMRM will include treatment as fixed effect, baseline SSS, age group, baseline free hemoglobin, baseline neurotoxicity, visit, and visit by treatment interaction as covariates. The model will be used to estimate the effect of treatment on hemolysis at each assessment time point through Day 3. Treatment effect will be summarized by LS means, p-values, and 95% two-sided confidence intervals.

Only subjects with hemolysis at baseline (free hemoglobin ≥ 15 mg/dL) will be included in this analysis. Additional analyses will examine the effect of treatment on other indicators of hemolysis including LDH and haptoglobin.

8.2.5. Levels of the Myonecrosis Marker (CK) from Baseline Through Day 3

Absolute value and change from baseline of creatine kinase (U/L) will be presented in graphs and summarized descriptively by treatment at baseline through Day 3.

An MMRM approach as described in Section 8.2.1 will be used to assess the effect of treatment on change in CK through Day 3. The MMRM will include treatment as a fixed effect as the variable of interest, with baseline CK, baseline neurotoxicity, age group, visit, and visit by treatment interaction as covariates. The model will be used to estimate the effect of treatment on myonecrosis at each assessment time point through Day 3. Treatment effect will be summarized by LS means, p-values, and 95% two-sided confidence intervals.

Only subjects with CK ≥ 2x institutional reference range at baseline will be included in this analysis.

8.2.6. NPRS Score in Subjects Able to Respond from Baseline through Day 28

The absolute values and change of NPRS will be tabulated by treatment arm and visit. An MMRM approach as described in Section 8.2.1 will be used to assess the treatment effect on NPRS scores through Day 28. The MMRM will include the fixed effect of treatment as the variable of interest, with the baseline NPRS, baseline SSS, age group, baseline neurotoxicity, and visit, and visit by treatment interaction as covariates.

8.2.7. Kidney Function Markers from Baseline through Day 28

Descriptive summaries of absolute value and change from the baseline of kidney function markers (i.e., creatine) will be tabulated by treatment group and visit. The mean change from baseline through Day 28 will be compared between treatment arm using an MMRM. The MMRM will include treatment as fixed effect as the variable of interest, with the baseline SSS, baseline kidney function measure, age group, baseline neurotoxicity, and visit, and visit by treatment interaction as covariates. The model will be used to estimate the effect of treatment on kidney function at each assessment time point through Day 28. Treatment effect will be summarized by LS means, p-values, and 95% two-sided confidence intervals.

Only subjects with a creatinine $\geq$ 2x the upper limit of normal at baseline will be included in the analysis.

8.2.8. Head-Lift Duration through Day 7

The number and proportion of subjects who are able to hold their head up for 5 seconds will be tabulated by treatment arm and visit.

A logistic generalized linear mixed model will be used to analyze the change from baseline to Day 7. Analyses will include the fixed effect of treatment as the covariate of interest, with baseline head-lift duration, age group, baseline neurotoxicity, visit (categorical), and visit by treatment interaction as covariates. The model will be used to estimate the effect of treatment on head-lift duration at each assessment time point through Day 7. LS means at each assessment time point will be calculated and tabulated from the model.

Only subjects with an SSS nervous system subscore $\geq$ 2 at baseline will be included in the analysis.

8.2.9. Total Duration of Ventilatory Support from Baseline through Day 28

The number and percent of subjects who need ventilatory support and the duration of time from initiation of ventilatory support to initiation of weaning will be tabulated by treatment arm. The time from initiation of ventilatory support to initiation of weaning will be compared using the Wilcoxon Rank Sum Test.

If the number of patients receiving ventilatory support is less than 5, this outcome will be reported descriptively.

8.2.10. Total Duration of ICU Stay from Baseline through Day 28

Duration of ICU stay through 28 days post-baseline will be summarized by treatment arm. Duration will be measured in days.

The duration of ICU stay will be compared between treatment groups using the Wilcoxon Rank Sum Test.

If fewer than five patients report ICU stay, this outcome will be reported descriptively.

8.2.11. Total Duration of Hospitalization from Baseline through Day 28

Duration of hospitalization through 28 days post-baseline will be summarized by treatment arm separately for the United States and India, recognizing the anticipated differences in the typical duration of hospital stay for patients experience snakebite envenoming in the two countries. Duration will be measured in days.

For patients enrolled in the United States, the duration of hospitalization will be compared between treatment groups using ANCOVA with baseline SSS, age group, and baseline neurotoxicity as covariates.

For patients enrolled in India, the duration of hospitalization will be compared using the Wilcoxon Rank Sum Test. A non-parametric test will be used for the data from India because the data are anticipated to exhibit rightward skew, with a few patients having a much longer duration of hospitalization than most.

Only hospitalization stays from baseline through Day 28 will be included in this analysis.

8.2.12. All-Cause Mortality from Baseline through Day 28

All-cause mortality will be analyzed using a time-to-event approach. Summaries will include the number of subjects experiencing the event (death) and the number of subjects censored; the median, lower quartile and upper quartile estimate of time-to-event; and point estimates for the mortality rates.

A Kaplan-Meier graph of mortality by treatment group will be presented.

The null hypothesis of no difference between varespladib-methyl and placebo will be tested using a Cox proportional hazard regression model with a categorical variable for the treatment arm as independent variable and adjusted for baseline SSS, age group, baseline neurotoxicity, and completion of initial dose of antivenom prior to initiation of study drug which will be presented together with two-sided 95% confidence intervals, as well as the corresponding P value.

All-cause mortality will be censored at Day 28.

If fewer than 5 subjects die, this analysis will not be performed. All deaths will be listed.

8.2.13. Clinical Global Impression–Improvement (CGI-I) from Baseline through Day 7

CGI-I (1-7 scale) will be treated as a continuous variable and summary statistics will be reported at each visit and depicted graphically showing mean scores for each treatment group over time. CGI-I scores from baseline through day 7 will be compared using MMRM, with treatment as the variable of interest, with baseline SSS, age group, baseline CGI-I score, and baseline neurotoxicity as covariates. The model will be used to estimate the effect of treatment on CGI-I scores at each assessment time point through Day 7.

Secondarily, CGI-C will be dichotomized into subjects who are responders (score of either 1 – very much improved; 2 – much improved) vs. non-responders (scores of 3-7). The proportion of responders within each treatment group will be compared with logistic regression including the same covariates described above.

8.2.14. Patient Global Impression of Change (PGI-C) from Baseline through Day 7

PGI-C (0-10 scale) will be treated as a continuous variable. Means and standard deviations will be tabulated at each visit and graphically for each treatment group over time. PGI-C scores from baseline through day 7 will be compared using MMRM, with treatment as the variable of interest, and baseline SSS, age group, baseline PGI-C score, baseline neurotoxicity, and visit, and treatment by visit interaction as covariates. The MMRM approach will be similar to the model described in Section 8.2.1. LS means and changes after baseline will be calculated from the model at Day 7. Logistic regression will also be used to compare PGI-C responders by treatment group at each visit through Day 7. A responder is defined as a PGI-C score of 3 or lower.

8.2.15. Patient-Specific Functional Scale (PSFS) Total Score through Day 28

PSFS (0-10 scale) will be treated as a continuous variable. The means and standard deviations will be tabulated at each visit and depicted graphically for each treatment group over time. PSFS scores through day 28 will be compared using MMRM, with treatment as the variable of interest, and baseline SSS, age group, baseline neurotoxicity, and visit, and visit by treatment interaction as covariates. The MMRM approach will be similar to the model described in Section 8.2.1. The model will be used to estimate the effect of treatment on PSFS scores at each assessment time point through Day 28.

8.3. Exploratory Efficacy Analysis

The ITT population will be used for the exploratory analyses.

8.3.1. Change in the SSS from Baseline through Day 7 Using Compressed SSS Scale

The compressed SSS as well as the 6hr and 9hr mean scores will be calculated by first subtracting 1 from non-zero responses to the pulmonary, cardiovascular, hematologic, renal, and nervous system sections of the SSS. The sum of the adjusted values of the 5 subsections will be the total SSS used to calculate the compressed score. The endpoint will be the change from baseline through Day 7 compressed scores: Change = Baseline – Score (at each time).

Descriptive statistics for the compressed SSS scores will be tabulated by treatment group.

The change from baseline to the average of the 6hr and 9hr of the compressed SSS will be presented by treatment group within an analysis of covariance model (ANCOVA) with the baseline SSS score, age group, the presence or absence of baseline neurotoxic symptoms as covariates.

8.3.2. SSS from Baseline through Day 28 After First Dose

The SSS from baseline through Day 28 post-initial dose will be summarized using descriptive statistics of absolute values and change from baseline at each time point and depicted graphically.

When more than one SSS assessment falls within the same time window, then only the SSS assessment closest to the middle point of the time window will be assigned to the time point. In case of values that are equidistant to the middle point, the latest assessment only will be assigned to the time point.

8.3.3. Grip Strength Pre-Dosing through Day 28

Descriptive summaries of absolute value and change from the baseline of grip strength will tabulated by treatment group and visit and depicted graphically.

8.3.4. SSS Neurologic System Subscore from Baseline through Day 7

Descriptive summaries of absolute value and change from the baseline for the SSS neurologic system subscore will be tabulated by treatment group and visit from baseline through Day 7 and depicted graphically.

8.3.5. Analgesic Use through Day 28

The number and proportion of subjects reporting (1) any analgesic and (2) any opioid use will be tabulated by treatment group and time point.

8.3.6. Clinical Global Impression – Improvement (CGI-I) from Baseline through Day 28

Descriptive summaries of absolute value and change from baseline of CGI-I will be tabulated by treatment group and visit and depicted graphically.

8.3.7. Patient Global Impression of Change (PGIC) from Baseline through Day 28

Descriptive summaries of absolute value and change from baseline of PGIC will be tabulated by treatment group and visit and depicted graphically.

8.3.8. Complete Blood Count (CBC) Laboratory Tests through All SSS Evaluation Days

The number of subjects with CBC laboratory values below, within, or above the normal range by visit and in relation to baseline will be tabulated for key clinical CBC laboratory analytes: white blood cell count, hemoglobin level, platelet count (shift table). Denominator of the percentages will be the number of subjects in the ITT Population.

8.3.9. Transfusion Requirement from Baseline through Day 28

The transfusion requirement will be assessed using the following indicators.

- Time to Hb stabilization
- Patients having transfusion event
- Time to first transfusion
- Total number of transfusions per subject
- Total blood units administered

Number and percentage of subject with a transfusion event will be described in summary tables by treatment arm and visit. Summary statistics of the total number of transfusions and the total blood units required will be presented in tables by treatment arm and visit for subject having a transfusion event.

Time to hemoglobin (Hb) stabilization and time to first transfusion will be analyzed using a descriptive time-to-event approach. Summaries will include the number of subjects experiencing the event and the number of subjects censored; the median, lower quartile and upper quartile estimate of time-to-event.

8.3.10. C-reactive Protein (CRP) from Baseline through Day 14

The absolute values and change from baseline of CRP test results will be tabulated by treatment arm and visit.

8.3.11. D-dimer Levels from Baseline through Day 14

D-dimer test results will be displayed in the data listings. Values outside the normal range will be

flagged, along with corresponding normal ranges.

8.3.12. Levels of Myonecrosis Marker (CK) from Baseline through Day 3 in Subjects Presenting with and without Tourniquets at Enrollment

The analysis described in Section 8.2.5 will be repeated for subjects:

- with tourniquets at enrollment
- without tourniquets at enrollment

Only subjects with CK ≥ 2x institutional reference range at baseline will be included in the analysis.

8.3.13. Secretory Phospholipase A2 (sPLA2) in Serum at Specified Timepoints on Days 1 to 7 in All Subjects

Descriptive summaries of absolute values and change from the baseline of $sPLA_2$ levels will be tabulated by treatment group and visit and depicted graphically.

All $sPLA_2$ from pre-dosing to Day 7 will be presented and used to (1) calculate maximum concentrations in both treatment groups, (2) compare concentration-time curves using a nonlinear regression to quantify a change in the half-maximal effective concentration (EC50) and its confidence interval, and (3) to compute a *p*-value that tests the null hypothesis that there is no difference between curves.

$sPLA_2$ analysis will be performed by a third-party central lab. The analysis of $sPLA_2$ will focus on enzyme activity. If available, another analysis will examine $sPLA_2$ mass.

8.4. Subgroup Analyses of Efficacy Variables

The primary efficacy endpoint and the three key secondary efficacy endpoints will be analyzed by doing separate subgroup analyses for the following subgroups: (1) pediatric (age 5 to 17 years) and adult (≥18 years) subgroups, (2) among subjects with and without neurotoxic symptoms at baseline as described in section 8.1, (3) among subjects who did and did not complete an initial dose of antivenom prior to randomization, (4) among subjects enrolled in the U.S. and India, (5) among patients bitten by vipers, elapids, and unknown snake types, and (6) among patients for whom the time from bite or symptom onset to receipt of study drug was <5 hours and ≥5 hours.

9. Safety and Tolerability Analysis

Safety will be evaluated from reported TEAEs, changes in clinical laboratory values, changes in vital signs, and electrocardiogram (ECG) results, and concomitant medications and therapies.

All safety analyses will be performed on the SAF Population. No inferential statistical tests are planned.

9.1. Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA thesaurus.

A summary table will present the number and percentage of subjects for each treatment group reporting:

- AEs
- TEAEs
- TEAEs related to IP
- Moderate TEAEs
- Severe TEAEs
- Serious TEAEs
- Serious TEAEs related to IP
- TEAEs resulting in death.

Summaries of the incidence (number and percentage of subjects reporting the TEAE and the number of TEAEs) of TEAEs will be displayed for each treatment group by:

- System organ class, and preferred term
- Maximum severity by system organ class, and preferred term
- Strongest relationship to IP by system organ class, and preferred term.

In the case of multiple occurrences of the same TEAE within the same subject, each subject will only be counted once for each preferred term. However, all multiple occurrences will be included in the number of events. The number of subjects experiencing anaphylaxis or acute hypersensitivity reactions will also be summarized by treatment group. This comparison will be conducted regardless of the determination of causal relationship to the study drug.

In the summaries showing severity and relationship to IP, the event with the maximum severity or strongest relationship will be reported. If a particular event is missing the severity and/or relationship, then the strongest possible severity or relationship will be assumed for analysis.

By-subject AE data listings with all AEs will be displayed.

9.1.1. Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of IP, by treatment group, system organ class, and preferred term will be prepared for the SAF Population.

A data listing of AEs leading to withdrawal of IP will also be provided, displaying details of the event(s) captured on the eCRF.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed. Moreover, all-cause mortality will be analyzed as described in Section 8.2.12.

Serious adverse events will be listed and tabulated by system organ class and preferred term and presented by treatment.

9.1.3. FDA Medical Queries

The number and percentage of subjects experiencing the following FMQs will be reported by treatment group. Construction of each item will be based on the PTs specified at https://www.regulations.gov/docket/FDA-2022-N-1961/document.

- Hepatic Injury (Narrow and Broad)
- Acute Kidney Injury (Narrow and Broad)
- Stroke and TIA (Narrow and Broad
- Myocardial Ischemia (Narrow)
- Arrythmia (Narrow)
- Cardiac Conduction Disturbance (Narrow)
- Hypersensitivity (Standard Narrow and Broad)

9.2. Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for all vital signs including systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature.

9.3. Clinical Laboratory Evaluations

The number of subjects with clinical laboratory values (chemistry, hematology, urinalysis) below, within, or above the normal range by visit and in relation to baseline will be tabulated for each clinical laboratory analyte (shift table). Continuous summaries of observed values and changes from baseline will also be reported. Denominators of the percentages will be the number of subjects in the SAF Population.

All laboratory test results, including coagulation and hematological function tests, will be displayed in by-subject listings and those that are outside the normal range will be flagged, along with corresponding normal ranges.

By-subject pregnancy test results will be listed.

9.4. Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for all vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature).

9.5. Electrocardiograms

The number and percentage of subjects with normal and abnormal ECG results will be summarized for the SAF Population by treatment group. Summaries of observed values and change from baseline will also be reported.

9.6. Physical Examination

The number and percentage of subjects with normal, abnormal clinically significant, and abnormal not clinically significant physical examination results by body system will be summarized for the SAF Population by treatment group.

9.7. Concomitant Medication

Prior and concomitant medications by Anatomical Therapeutic Chemical (ATC) level 3 will be summarized descriptively by treatment group using counts and percentages.

Prior medications will be presented separately from concomitant medications. Medications that started before the first drug use will be considered prior medications whether or not they were stopped before the first IP. Any medications continuing or starting after the first drug use will be concomitant. If a medication starts before the first drug use and continues after the first drug use it will be considered both prior and concomitant. Where a medication start date or end date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

Concomitant use of analgesics will also be summarized and presented separately.

Medications will be coded using the latest WHO-DD version.

9.8. Columbia-Suicide Severity Rating Scale

The C-SSRS items will be tabulated by treatment group and visit.

10. Changes from Planned Analysis

Several changes have occurred since version 1.0 of the SAP. For example, multiple imputation and fixed-sequence testing were added in SAP v3.0; and the FMQs and additional sensitivity analysis on the primary endpoint were added in SAP v4.0. More details are provided in the Document History section above. All changes were made while the study team was blind to treatment assignment and prior to database lock.

11. Other Planned Analysis

11.1. Pharmacokinetic Analysis

Descriptive summaries of the concentration level of varespladib-methyl in plasma and $sPLA_2$ activity at specified timepoints will be tabulated by treatment group.

By-subject concentrations of varespladib-methyl in plasma will also be presented.

The pharmacokinetic characterization of drug concentrations for each dose to be profiled will be performed using noncompartmental analysis (NCA).

The PK parameter estimates will be completed using Phoenix WinNonlin (Pharsight Corporation) software using the actual elapsed times from dose administration to sample collection. For plasma concentration data, all values below the limit of quantification (BLQ) will be set to 0 for summary statistics and graphs. For the PK parameter calculation, BLQ plasma concentrations occurring before Tmax will be set to 0, with the exception of a BLQ value occurring between two measurable concentrations, in which case it will be set to missing.

Standard PK parameters assessed will include measures of the extent of absorption using estimates of the area under the plasma concentration-time curve from time 0 to the time of the last quantifiable plasma concentration (AUC0-t), Area under the plasma concentration-time curve from time 0 to infinity (if data permits) (AUC0-inf) and rate of absorption using the maximum serum plasma concentration (Cmax), the time of Cmax (Tmax), apparent first order terminal elimination half-life (t1/2), apparent terminal phase rate constant (λz) (if data permits). Any subject for whom the portion of the AUC extrapolated to infinity exceeds 20% of the total AUC0-inf will be excluded from the calculation of the descriptive statistics for AUC0-inf.

Other PK parameters may be derived, where appropriate, and as data permit.

For noncompartmental analysis, plasma concentrations will be listed and summarized at each time point using descriptive statistics. Descriptive statistics reported will include the arithmetic mean, SD, CV%, geometric mean, minimum, maximum, and median. Only the range and the median will be reported for Tmax and Tlast, as these are categorical parameters. The PK parameters will also be summarized by treatment using descriptive statistics.

Individual plasma concentration plots and mean data graphs will be produced using both linear and semi-logarithmic scales. Mean data graphs will show plasma concentration profiles by treatment group. Pharmacokinetic parameter estimates and summaries will be completed for the subjects in the PK population.

Exploratory analysis to correlate PK endpoints with $sPLA_2$ activity may be conducted and documented in a separate analysis plan.

The PK analyses will be performed by a third-party central lab.

11.2. Pharmacoeconomic Analysis

Pharmacoeconomic analyses will be conducted to estimate the effect of varespladib treatment on the cost of care. These analyses will include, but are not limited to, the amount of antivenom given to the patient and the duration of hospital stay.

12. References

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13. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (CRF page or listing number).

The following are planned summary tables for protocol number OPX-PR-01. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

13.1. Demographic Data Summary Tables and Figures

Table 1: Demographic Data Summary Tables and Figures

Table Title / Summary
Table 14.1.1 Study Populations and Subject Disposition All Subjects
Table 14.1.2 Demographics and Baseline Characteristics Safety Population
Table 14.1.3 Summary of Envenoming History Safety Population
Table 14.1.4 Medical History by System Organ Class and Preferred Term Safety Population
Table 14.1.5 Prior Medications by ATC level 3 Safety Population
Table 14.1.6 Overall Study Drug Exposure and Compliance
Table 14.1.7 List of AEs Pertaining to Anaphylaxis or Acute Hypersensitivity Reactions

13.2. Efficacy Data

Table 2: Efficacy Data

Table Title / Summary
Table 14.2.1.0 Primary Outcome Change from Baseline to Average of 6 and 9 hour SS Scores Overall and by Prespecified Subgroup ITT Population
Table 14.2.1.1 Summary of Observed SSS Scores ITT Population
Table 14.2.1.2 Summary of Observed SSS Scores PP Population
Table 14.2.1.3 Summary of Observed SSS Scores by Age Group ITT Population
Table 14.2.1.4 Summary of Observed SSS Scores by Age Group PP Population
Table 14.2.1.5 Statistical Analysis of Mean 6 and 9 hour Primary Outcome SSS Scores: ANCOVA ITT Population
Table 14.2.1.6 Statistical Analysis of Mean 6 and 9 hour SSS Scores: ANCOVA PP Population
Table 14.2.1.7 Statistical Analysis of Mean 6 and 9 hour SSS Scores: ANCOVA by Age Group ITT Population
Table 14.2.1.8 Statistical Analysis of Mean 6 and 9 hour SSS Scores: ANCOVA by Baseline Neurotoxicity Status ITT Population
Table 14.2.1.9 Statistical Analysis of Mean 6 and 9 hour SSS Scores: ANCOVA by Antivenom Status prior to Baseline ITT Population
Table 14.2.1.10 Statistical Analysis of Mean 6 and 9 hour SSS Scores: ANCOVA by Country (US and India) ITT Population
Table 14.2.1.11 Statistical Analysis of Mean 6 and 9 hour SSS Scores: ANCOVA by Snake Type (Viper, Elapid, and Unknown) ITT Population

Table Title / Summary
Table 14.2.1.12 Statistical Analysis of Mean 6 and 9 hour SSS Scores: ANCOVA by Time from Bite or Symptom Onset to Receipt of Study Drug (<5 hours and ≥5 hours) ITT Population
Table 14.2.1.13 Sensitivity Analysis of Mean 6 and 9 hour SSS Scores: ANCOVA ITT Population
Table 14.2.1.14 Sensitivity Analysis of Mean 6 and 9 hour SSS Scores: Rank Regression ITT Population
Table 14.2.1.15 Sensitivity Analysis of Mean 6 and 9 hour SSS Scores: ANCOVA Iteratively Removing Sites ITT Population
Table 14.2.1.16 Sensitivity Analysis of Mean 6 and 9 hour SSS Scores: ANCOVA Tipping Point Analysis ITT Population
Table 14.2.2.0 Key Secondary Outcome: SSS-AUC through Day 7 Overall and by Prespecified Subgroups ITT Population
Table 14.2.2.1 Statistical Analysis of SSS-AUC through Day 7: ANCOVA ITT Population
Table 14.2.2.2 Statistical Analysis of SSS-AUC through Day 7: ANCOVA by Age Group ITT Population
Table 14.2.2.3 Statistical Analysis of SSS-AUC through Day 7: ANCOVA by Country (US, India) ITT Population
Table 14.2.2.4 Statistical Analysis of SSS-AUC through Day 7: ANCOVA by Snake Type (Viper, Elapid, and Unknown) ITT Population
Table 14.2.2.5 Statistical Analysis of SSS-AUC through Day 7: ANCOVA by Time from Bite or Symptom Onset to Receipt of Study Drug (<5 hours and ≥5 hours) ITT Population
Table 14.2.2.6 Statistical Analysis of SSS-AUC through Day 7: ANCOVA by Antivenom Status Prior to Baseline ITT Population
Table 14.2.2.7 Statistical Analysis of SSS-AUC through Day 7: ANCOVA by Baseline Neurotoxicity Status ITT Population
Table 14.2.2.8 Summary of SSS Subscore AUCs through Day 7 ITT Population
Table 14.2.3.0 Key Secondary Outcome: Antivenom Administration Overall and by Prespecified Subgroups ITT Population
Table 14.2.3.1 Statistical Analysis of Antivenom Categories: Proportional Odds Logistic Regression ITT Population
Table 14.2.3.2 Statistical Analysis of Antivenom Categories: Proportional Odds Logistic Regression by Country (US, India) ITT Population
Table 14.2.3.3 Statistical Analysis of Antivenom Categories: Proportional Odds Logistic Regression by Snake Type (Viper, Elapid, Unknown) ITT Population
Table 14.2.3.4 Statistical Analysis of Antivenom Categories: Proportional Odds Logistic Regression by Time from Bite or Symptom Onset to Receipt of Study Drug (<5 hours, ≥5 hours) ITT Population
Table 14.2.3.5 Statistical Analysis of Antivenom Categories: Proportional Odds Logistic Regression by Age Group ITT Population
Table 14.2.3.6 Statistical Analysis of Antivenom Categories: Proportional Odds Logistic Regression by Antivenom Status Prior to Baseline ITT Population
Table 14.2.3.7 Statistical Analysis of Antivenom Categories: Proportional Odds Logistic Regression by Baseline Neurotoxicity Status ITT Population
Table 14.2.3.8 Statistical Analysis of Antivenom Requirement through Day 28: ANCOVA ITT Population

Table 14.2.3.9 Sensitivity Analysis of Antivenom Categories: Binomial Logistic Regression ITT Population
Table 14.2.3.2.1 Statistical Analysis of NPRS-AUC through Day 7: ANCOVA ITT Population
Table 14.2.3.2.2 Statistical Analysis of NPRS-AUC through Day 7: ANCOVA by Age Group ITT Population
Table 14.2.3.2.3 Statistical Analysis of NPRS-AUC through Day 7: ANCOVA by Country (US, India) ITT Population
Table 14.2.3.2.4 Statistical Analysis of NPRS-AUC through Day 7: ANCOVA by Snake Type (Viper, Elapid, and Unknown) ITT Population
Table 14.2.3.2.5 Statistical Analysis of NPRS-AUC through Day 7: ANCOVA by Time from Bite or Symptom Onset to Receipt of Study Drug (<5 hours and ≥5 hours) ITT Population
Table 14.2.3.2.6 Statistical Analysis of NPRS-AUC through Day 7: ANCOVA by Antivenom Status Prior to Baseline ITT Population
Table 14.2.3.2.7 Statistical Analysis of NPRS-AUC through Day 7: ANCOVA by Baseline Neurotoxicity Status ITT Population
Table 14.2.4.0 Key Secondary Outcome: CGI-I Scores at Day 2 Overall and Prespecified Subgroups ITT Population
Table 14.2.4.1 Statistical Analysis of CGI-I Scores at Day 2: ANCOVA ITT Population
Table 14.2.4.2 Statistical Analysis of CGI-I Scores at Day 2: ANCOVA by Country (US, India) ITT Population
Table 14.2.4.3 Statistical Analysis of CGI-I Scores at Day 2: ANCOVA by Snake Type (Viper, Elapid, Unknown) ITT Population
Table 14.2.4.4 Statistical Analysis of CGI-I Scores at Day 2: ANCOVA by Time from Bite or Symptom Onset to Receipt of Study Drug (<5 hours and ≥5 hours) ITT Population
Table 14.2.4.5 Statistical Analysis of CGI-I Scores at Day 2: ANCOVA by Age Group ITT Population
Table 14.2.4.6 Statistical Analysis of CGI-I Scores at Day 2: ANCOVA by Antivenom Status Prior to Baseline ITT Population
Table 14.2.4.7 Sensitivity Analysis of CGI-I Scores at Day 2: ANCOVA ITT Population
Table 14.2.5.1 Statistical Analysis of SSS Total Scores through Day 7: MMRM ITT Population
Table 14.2.5.2 Statistical Analysis of Neurologic Subscore through Day 3 in Patients with Baseline Neurologic Subscore ≥1: MMRM ITT Population
Table 14.2.5.3 Statistical Analysis of Neurologic Subscore through Day 3 in Patients with Baseline Neurologic Subscore ≥2: MMRM ITT Population
Table 14.2.6.1 Summary of Coagulation Abnormalities in Patients with Hematology Score ≥ 1 from Baseline through Day 7 ITT Population
Table 14.2.6.2 Statistical Analysis of Coagulation Abnormalities in Patients with Hematology Score ≥ 1 from Baseline through Day 7: Proportional Odds Logistic Regression ITT Population
Table 14.2.7.1 Statistical Analysis of Hemolysis Markers in Subjects with Hemolysis at Baseline (free hemoglobin >=15 mg/dL) through Day 3: MMRM ITT Population
Table 14.2.8.1 Statistical Analysis of Creatinine Kinase (CK) in Subjects with CK >=2X Reference Range at Baseline through Day 3: MMRM ITT Population
Table 14.2.9.1 Statistical Analysis of Kidney Function Markers from Baseline through Day 28: MMRM ITT Population

Table Title / Summary
Table 14.2.10.1 Statistical Analysis of NPRS in Subjects Able to Respond through Day 28: MMRM ITT Population
Table 14.2.11.1 Summary of Head Lift Duration through Day 7 ITT Population
Table 14.2.11.2 Statistical Analysis of Head Lift Duration through Day 7 in Subjects with SSS Nervous System Subscore ≥2 at Baseline: Logistic MMRM ITT Population
Table 14.2.12.1 Statistical Analysis of Ventilatory Support, ICU Stay, and Hospitalization Durations through Day 28: Wilcoxon Rank Sum Test ITT Population
Table 14.2.12.2 Statistical Analysis of Ventilatory Support, ICU Stay, and Hospitalization Durations through Day 28: Wilcoxon Rank Sum Test by Age Group ITT Population
Table 14.2.12.3 Statistical Analysis of Ventilatory Support, ICU Stay, and Hospitalization Durations through Day 28: Wilcoxon Rank Sum Test by Neurotoxicity Status ITT Population
Table 14.2.12.4 Statistical Analysis of Ventilatory Support, ICU Stay, and Hospitalization Durations through Day 28: Wilcoxon Rank Sum Test by Antivenom Prior to Baseline ITT Population
Table 14.2.12.5 Statistical Analysis of Ventilatory Support, ICU Stay, and Hospitalization Durations through Day 28: Wilcoxon Rank Sum Test by Country ITT Population
Table 14.2.13 Statistical Analysis of All-cause Mortality through Day 28: Kaplan-Meier and Cox Model Results ITT Population
Table 14.2.14.1 Statistical Analysis of PGIC from Baseline through Day 7: MMRM ITT Population
Table 14.2.14.2 Statistical Analysis of PGIC from Baseline through Day 7: MMRM by Age Group ITT Population
Table 14.2.14.3 Statistical Analysis of PGIC from Baseline through Day 7: MMRM by Neurotoxicity Status ITT Population
Table 14.2.14.4 Statistical Analysis of PGIC from Baseline through Day 7: MMRM by Antivenom Status ITT Population
Table 14.2.15.1 Statistical Analysis of PSFS from Baseline through Day 28: MMRM ITT Population
Table 14.2.16.1 Statistical Analysis of CGI-I from Baseline through Day 7: MMRM ITT Population
Table 14.2.16.2 Statistical Analysis of CGI-I from Baseline through Day 7: MMRM by Age Group ITT Population
Table 14.2.16.3 Statistical Analysis of CGI-I from Baseline through Day 7: MMRM by Neurotoxicity Status ITT Population
Table 14.2.17 Exploratory Analysis of SSS Scores through Day 28 ITT Population
Table 14.2.18 Exploratory Analysis of Compressed SSS Scores through Day 28 ITT Population
Table 14.2.19 Exploratory Analysis of Grip Strength through Day 28PE ITT Population
Table 14.2.20 Exploratory Analysis of SSS Neurologic System Subscore through Day 7 ITT Population
Table 14.2.21 Exploratory Analysis of Analgesics Usage through Day 28 ITT Population
Table 14.2.22 Exploratory Analysis of PGIC from Baseline through Day 28 ITT Population

Table Title / Summary
Table 14.2.23 Exploratory Analysis of CGI-I from Baseline through Day 28 ITT Population
Table 14.2.24 Exploratory Analysis of Complete Blood Count Laboratory Tests through Day 28 ITT Population
Table 14.2.25 Exploratory Analysis of Transfusion Requirement in Subjects with Hemolysis through Day 28 ITT Population
Table 14.2.26 Exploratory Analysis of C-Reactive Protein through Day 14 ITT Population
Table 14.2.27 Exploratory Analysis of D-dimer levels through Day 14 ITT Population
Table 14.2.28 Exploratory Analysis of Levels of Myonecrosis Marker (CK) through Day 3 by Tourniquet Status at Enrollment: MMRM ITT Population

13.3. Safety Data

Table 3: Safety Data

Table Number	Population	Table Title / Summary
14.3.1 Displays of Adverse Events		
Table 14.3.1.1	Summary of All Adverse Events	Safety Population
Table 14.3.1.2	Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.3	Incidence of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term	Safety Population
Table 14.3.1.4	Incidence of Treatment-Emergent Adverse Events by Strongest Relationship to IP, System Organ Class, and Preferred Term	Safety Population
Table 14.3.1.5	Subjects with Safety Topics of Interest by FDA Medical Query and Preferred Term	Safety Population
14.3.2 Summary of Deaths, Other Serious and Significant Adverse Events		
Table 14.3.2.1	Serious Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.2	Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term	Safety Population
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events		
Table 14.3.3.1	Listing of Adverse Events Leading to Death	Safety Population
14.3.4 Abnormal Laboratory Values		
Table 14.3.4.1	Summary of Clinically Significant Abnormal Laboratory Values	Safety Population
14.3.5 Laboratory Data Summary Tables		
Table 14.3.5.1	Summary of Clinical Chemistry Results	Safety Population

Table Number	Population	Table Title / Summary
Table 14.3.5.2 Shift Tables of Clinical Chemistry Results Safety Population		
Table 14.3.5.3 Summary of Hematology Laboratory Results Safety Population		
Table 14.3.5.4 Shift Table of Hematology Results Safety Population		
Table 14.3.5.5 Summary of Urinalysis Results Safety Population		
Table 14.3.5.6 Shift Table of Urinalysis Results Safety Population		
14.3.6 Other Safety Data Summary Tables		
Table 14.3.6.1 Summary of Vital Signs Safety Population		
Table 14.3.6.2 Summary of ECG Findings Safety Population		
Table 14.3.6.3 Summary of Physical Examination Results Safety Population		
Table 14.3.6.4 Concomitant Medications by ATC Level 3 Safety Population		

13.4. Pharmacokinetic/Pharmacodynamic Data

Pharmacokinetic analysis results will be provided by a third-party central lab.

13.5. Other Data Summary Tables

Table 4: Other Data Summary Tables

Table Number	Population	Table Title / Summary
14.5 Other Data Summary Tables		
Table 14.4.1 Summary of Columbia-Suicide Severity Rating Scale (C-SSRS) Safety Population		

13.6. Planned Listing Descriptions

The following are planned data and subject data listings for protocol number OPX-PR-01.

In general, one listing will be produced per CRF domain. All listings will be sorted by treatment, site, and subject number. All calculated variables will be included in the listings.

In all listings a blank line will be placed between each subject. Within a data listing, if an item appears line after line (eg, repetition of subject number), then only the first occurrence will be displayed.

In data listings, the information for one subject will be kept on one page if at all possible, rather than splitting a subject's information across pages.

Table 5: Planned Listings

Data Listing Number	Population	Data Listing Title / Summary
16.2 Subject Data Listings		
16.2.1 Subject Discontinuations/Completions		
Data Listing 16.2.1.1	All subjects	Study Populations and Subject Disposition
Data Listing 16.2.1.2	Safety	Visit Dates
16.2.2 Protocol Deviations		
Data Listing 16.2.2	ITT	Protocol Deviations
16.2.3 Subjects Excluded from the Efficacy Analyses		
Data Listing 16.2.3	All subjects	Subjects Excluded from the PP Population (including reasons)
16.2.4 Demographic Data and Other Baseline Characteristics		
Data Listing 16.2.4.1	Safety	Demographics and Baseline Characteristics
Data Listing 16.2.4.2	Safety	Envenoming History
Data Listing 16.2.4.3	Safety	Medical History

Data Listing Number	Population	Data Listing Title / Summary
16.2 Subject Data Listings		
Data Listing 16.2.4.4	Safety	Prior Medications
16.2.5 Compliance and/or Drug Concentration Data		
Data Listing 16.2.5.1	Safety	Study Drug Exposure and Compliance
16.2.6 Individual Efficacy Response Data		
Data Listing 16.2.6.1	ITT	SSS Scores (including Total score, age group, and neurotoxicity)
Data Listing 16.2.6.2	ITT	SSS-AUC through Day 7
Data Listing 16.2.6.3	ITT	Coagulation Abnormalities
Data Listing 16.2.6.4	ITT	Hemolysis Markers and Creatinine Kinase
Data Listing 16.2.6.6	ITT	Antivenom Requirements
Data Listing 16.2.6.6	ITT	Duration of Ventilatory Support
Data Listing 16.2.6.7	ITT	Hospitalizations and ICU Stays
Data Listing 16.2.6.8	ITT	All-cause Mortality
Data Listing 16.2.6.9	ITT	Patient Global Impression of Change
Data Listing 16.2.6.10	ITT	Patient-Specific Functional Scale
Data Listing 16.2.6.11	ITT	Grip Strength and Head-Lift Duration
Data Listing 16.2.6.12	ITT	Clinical Global Impression - Improvement
Data Listing 16.2.6.13	ITT	Numeric Pain Rating Scores
Data Listing 16.2.6.14	ITT	Analgesics Usage
Data Listing 16.2.6.15	ITT	Kidney Function Markers
Data Listing 16.2.6.16	ITT	Complete Blood Count Laboratory Results
Data Listing 16.2.6.17	ITT	Transfusion Requirements
Data Listing 16.2.6.18	ITT	C-reactive protein
Data Listing 16.2.6.19	ITT	D-dimer
16.2.7 Adverse Event Listings (by Subject)		
Data Listing 16.2.7.1	SAF	Adverse Events for Each Subject
Data Listing 16.2.7.2	SAF	Serious Adverse Events
Data Listing 16.2.7.3	SAF	Listing of Deaths
Data Listing 16.2.7.4	SAF	Adverse Events Leading to Study Drug Discontinuation
Data Listing 16.2.7.5	SAF	FDA Medical Query Results by Subject
16.2.8 Laboratory Values (by Subject)		

Data Listing Number	Population	Data Listing Title / Summary
16.2 Subject Data Listings		
Data Listing 16.2.8.1	SAF	Hematology Laboratory Evaluations
Data Listing 16.2.8.2	SAF	Clinical Chemistry Laboratory Evaluations
Data Listing 16.2.8.3	SAF	Urinalysis Laboratory Evaluations
Data Listing 16.2.8.4	SAF	Pregnancy Test Results
Data Listing 16.2.8.5	SAF	Biomarker Test Results
16.2.9 Other Clinical Observations and Measurements (by Subject)		
Data Listing 16.2.9.1	SAF	Concomitant Medications
Data Listing 16.2.9.2	SAF	Vital Signs Measurements
Data Listing 16.2.9.3	SAF	ECG Results
Data Listing 16.2.9.4	SAF	Physical Examination Results
16.2.10 Other Study Measurements or Assessments (by Subject)		
Data Listing 16.2.10.1	SAF	Columbia-Suicide Severity Rating Scale

13.7. Planned Figure Descriptions

The following are planned summary figures for protocol number OPX-PR-01. The figure numbers and page numbers are place holders only and will be determined when the figures are produced.

Table 6: Planned Figures

Figure Number	Population	Figure Title/Summary
14.6.1.1	ITT	Primary Outcome Snakebite Severity Score by Treatment Arm and Visit over Time
14.6.1.2	ITT	Histograms of Change from Baseline to 6/9 Hour Average in Primary Outcome Snakebite Severity Score by Treatment Arm
14.6.1.3	ITT	Total SSS Score by Treatment Arm and Visit
14.6.1.4	ITT	Histograms of Total Snakebite Severity Score Area Under the Curve by Treatment Arm
14.6.1.5	ITT Subset	Neuro Snakebite Severity Subscore by Treatment Arm and Visit, in Subjects with Subscore ≥1 at Baseline, through Day 28
14.6.1.6	ITT Subset	Pulmonary Snakebite Severity Subscore by Treatment Arm and Visit, in Subjects with Subscore ≥1 at Baseline, through Day 28
14.6.1.7	ITT Subset	Cardiovascular Snakebite Severity Subscore by Treatment Arm and Visit, in Subjects with Subscore ≥1 at Baseline, through Day 28

14.6.1.8	ITT Subset	Hematological Snakebite Severity Subscore by Treatment Arm and Visit, in Subjects with Subscore ≥1 at Baseline, through Day 28
14.6.1.9	ITT Subset	Renal Snakebite Severity Subscore by Treatment Arm and Visit, in Subjects with Subscore ≥1 at Baseline, through Day 28
14.6.1.10	ITT Subset	Local Wound Snakebite Severity Subscore by Treatment Arm and Visit, in Subjects with Subscore ≥1 at Baseline, through Day 28
14.6.1.11	ITT Subset	Gastrointestinal Snakebite Severity Subscore by Treatment Arm and Visit, in Subjects with Subscore ≥1 at Baseline, through Day 28
14.6.2.1	ITT	Primary Outcome Snakebite Severity Score by Treatment Arm
14.6.3.1	ITT	Partial Thromboplastin Time by Treatment Arm and Visit
14.6.3.2	ITT	Prothrombin Time by Treatment Arm and Visit
14.6.3.3	ITT	Thrombin Time by Treatment Arm and Visit
14.6.3.4	ITT	Coagulation Abnormalities by Treatment Arm and Visit
14.6.4.1	ITT	Free Hemoglobin Concentration by Treatment Arm and Visit
14.6.4.2	ITT	Lactate Dehydrogenase by Treatment Arm and Visit
14.6.4.3	ITT	Haptoglobin by Treatment Arm and Visit
14.6.4.4	ITT	Abnormal Lactate Dehydrogenase by Treatment Arm and Visit
14.6.5	ITT	Myonecrosis Marker (CK) by Treatment Arm and Visit
14.6.6	ITT	Kaplan Meier Graph of All-cause Mortality
14.6.7	ITT	PGI-C by Treatment Arm and Visit
14.6.8	ITT	CGI-I by Treatment Arm and Visit
14.6.9	ITT	PSFS by Treatment Arm and Visit
14.6.10	PK	Varespladib Plasma Concentrations

14. Table, Figure, and Listing Shells

This SAP is intended for submission to regulatory authority and TLF shells have not been included.