PROTOCOL

PRODUCT NAME:	Varespladib-methyl
PROTOCOL NUMBER:	OPX-PR-01
IND NUMBER:	152097
NCT NUMBER:	04996264
CTRI NUMBER:	2021/07/045079 000062
DEVELOPMENT PHASE:	Phase 2
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 (BRAVO study - Broad-spectrum Rapid Antidote: Varespladib Oral for snakebite)
PROTOCOL DATE:	Version 3.0, 5 May 2022
SPONSORED BY:	Ophirex, Inc. 5643 Paradise Drive #2 Corte Madera, CA 94925 (415) 891-8682
CONTRACT RESEARCH ORGANIZATION:	[redacted]

1 APPROVAL SIGNATURES

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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

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

SIGNATURE	**DATE:**
[redacted]	5 May 2022
[redacted]	5 May 2022
[redacted]	5 May 2022
[redacted]	5 May 2022

2 PROTOCOL SUMMARY

2.1 Synopsis

Number of Subjects	Approximately 110 subjects (94 evaluable) enrolled
Population	Subjects ≥ 5 years of age and older
Investigational Product	Varespladib-methyl (LY333013), solid oral dosage forms
Study Objectives	
Primary	To evaluate the efficacy of a multiple-dose regimen of oral varespladib-methyl with standard of care (SOC) in subjects after venomous snakebite.
Study Endpoints	
Primary Efficacy	Change in the composite outcome of 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.
Secondary Efficacy	• AUC of the pulmonary, cardiovascular, hematologic symptoms, renal, and nervous system sections of the SSS from Baseline through Day 7 • Complete SSS from Baseline 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, creatine kinase (CK), from Baseline through Day 3 • Numeric Pain Rating Scale (NPRS) score in patients able to respond from Baseline through Day 28 • Kidney function markers from Baseline through Day 28 • Total differential antivenom requirement 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 • Clinical Global Impression-Improvement (CGI-I) from Baseline through Day 7 • Patient Global Impression of Change (PGIC) from Baseline through Day 7 • Patient-Specific Functional Scale (PSFS) total score from Baseline through Day 28

Exploratory Efficacy	• Change in the SSS from Baseline through Day 7 using compressed SSS scale • SSS from Baseline through Day 28 after first dose • 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 • Complete blood count (CBC) through all SSS evaluation days • Transfusion requirement from Baseline (Day 1) through Day 28 • C-reactive protein (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 patients 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
Pharmacokinetics	• PK parameters of varespladib-methyl in plasma from a subset of adult and pediatric subjects at specified timepoints on Days 1 and 3 followed by all subjects pre-dose on Day 7
Safety	• 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/Telephone Call at Day 28 • Number of subjects with a treatment-related SAE from beginning of treatment until last Follow-Up Visit/Telephone Call at Day 28 • Safety as assessed by – Vital signs – Clinical laboratory evaluations: 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
Investigational Product	<u>Varespladib-Methyl</u>: Tablet: Varespladib-methyl (LY333013) formulated as an immediate-release, white film-coated oval tablet (250 mg). Capsule: Varespladib-methyl (LY333013) formulated as an immediate-release capsule (50 mg).

Control Article	Placebo: Tablet: The oral placebo is supplied as a white film-coated oval tablet to match the LY333013 250 mg tablet for oral administration and contains a subset of the excipients: lactose monohydrate, microcrystalline cellulose, and magnesium stearate. Capsule: Placebo is supplied as an immediate-release capsule to match the 50 mg IP, and contains the excipients lactose monohydrate, microcrystalline cellulose, and magnesium stearate.
Route of Administration	Oral
Dose and Administration	Adult subjects will receive an initial loading dose of 500 mg (2 x 250 mg oral tablets) varespladib-methyl upon randomization and an additional dose of 250 mg (1 x 250 mg oral tablet) approximately 12 hours later, followed by dosing with 1 x 250 mg varespladib-methyl oral tablet twice daily (BID) for a total of 7 days from the first dose. Pediatric subjects (ages 5 to < 18) will be administered doses of varespladib-methyl determined by allometric scaling, provided as 50 mg capsules. Pediatric subjects will receive an initial loading dose of varespladib-methyl and an additional dose approximately 12 hours later (at the doses listed below), followed by the listed dose BID for the remainder of the 7-day treatment period. • Subjects 5 to < 11 years old will receive an initial loading dose of 200 mg varespladib-methyl, an additional dose of 100 mg approximately 12 hours later, followed by 100 mg BID • Subjects 11 to < 18 years old will receive a loading dose of 400 mg varespladib-methyl, an additional dose of 200 mg approximately 12 hours later, followed by 200 mg BID All patients will receive 14 doses total (*i.e.,* one oral loading dose and 13 additional oral doses).
Follow-Up	Subjects will be assessed on a regular schedule for a total of 28 days after administration of an initial dose of varespladib-methyl.

Eligibility	To be eligible to participate in the study an individual must meet all listed inclusion criteria and none of the exclusion criteria. The time between baseline and eligibility assessments, randomization, and IP administration should be minimized.
Inclusion Criteria	1. Is a male or female ≥ 5 years of age with venomous snakebite. 2. Index event (snakebite) must be symptomatic and symptom onset must have occurred within 10 hours of eligibility assessment. 3. Patients must meet one of two categories of inclusion criteria: **Category 1**: The patient has <u>not yet</u> completed first dose of antivenom: SSS inclusion score* of ≥2 in one system and ≥1 in another system (2+1) **OR** ≥3 in at least one system. OR **Category 2**: The patient <u>has</u> completed an initial dose of antivenom: SSS inclusion score* of ≥2 in one system and ≥1 in another system (2+1) OR ≥3 in at least one system **AND** CGI-I score of ≥5 (i.e., minimally worse, much worse, or very much worse). 4. Is willing (or legally authorized representative is willing) to provide informed consent prior to initiation of any study procedures. * Only local wound, pulmonary, cardiovascular, hematologic, or nervous system scores qualify for SSS inclusion criteria. GI and Renal scores are not used for inclusion. Hematologic score may be counted if available, but inclusion should not wait for laboratory results. Point of care tests (e.g., 20WBCT) may be used for enrollment, if used per site standard of care (see Appendix A).
Exclusion Criteria	1. Is considered by the Investigator to have a clinically significant upper GI bleed evidenced by hematemesis, "coffee-ground" emesis or nasogastric aspirate, or hematochezia thought to originate from upper GI tract. 2. Has history of cerebrovascular accident or intracranial bleeding of any kind, acute coronary syndrome, myocardial infarction, or severe pulmonary hypertension. 3. Has known history of inherited bleeding or coagulation disorder. 4. Is, at Screening Visit, using the following anticoagulants: warfarin/coumadin, argatroban, bilvalirudin, lepirudin, apixaban, dabigatran, clopidogrel, prasugrel, ticlodipine or another anticoagulant agent not specifically listed, or has used heparin, enoxaparin, fondaparinux, or other low molecular weight heparin or antiarrhythmic drugs within 14 days prior to treatment.

	5. Has a history of chronic liver disease such as chronic active viral hepatitis, alcohol-related liver disease, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hemochromatosis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis. 6. Reports or has known pre-existing renal impairment or chronic kidney disease. 7. Has a known allergy or significant adverse reaction to varespladib-methyl. 8. Is considered by the Investigator to be unable to comply with protocol requirements due to geographic considerations, psychiatric disorders, or other compliance concerns. 9. Is pregnant, has a positive urine or serum human chorionic gonadotropin (hCG) pregnancy test or not willing to use a highly effective method of contraception for 14 days after initial treatment, or is breast-feeding.
Safety Follow-up Assessments	Follow-up schedule: Day 14 and Day 28 after first dose of varespladib-methyl. If discharged before Day 7, follow-up will also be performed on Day 3 (if discharge prior to Day 3) and Day 7.
Study Duration	Approximately 12 months
Sample Size	The sample size for this study was determined by a formal power calculation. The total enrollment for this study will be approximately 110 subjects (94 evaluable). The assumptions used to determine sample size are as follows: • 2-sided alpha level 5% • Power 85% • Randomization Ratio 1:1. The randomization will be stratified by age group (5 to < 11 years, 11 to < 18 years, ≥ 18 years) 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 • Withdrawal rate of 15% • The sample size also assumes: A minimum difference of change in SSS average of the 6- and 9-hour scores of 1.1 and a standard deviation of 1.75
Statistical Analysis	Descriptive statistics (n, mean, median, standard deviation [SD], minimum, and maximum for continuous data; frequencies and percentages for categorical data) will be used to summarize study data and details of analysis are outlined in the study Statistical Analysis Plan.
Efficacy	All statistical testing for efficacy endpoints will be 2-sided and performed using a significance level of 0.05. All efficacy analyses will be performed on the analysis populations using descriptive statistics.

Safety	Safety and tolerability will be evaluated by examining the occurrence of AEs, including TEAEs. AEs leading to discontinuation from the study drug, causality and severity will be summarized by treatment group. AEs will also be presented in listings. Summary statistics of clinical laboratory measures, vital signs, and ECG will be presented by treatment group for each assessment. Number and percentage of subjects presenting at least one post-Baseline potentially clinically significant abnormality will be presented by treatment group for selected parameters. All safety analyses will be performed on the Safety Population set using descriptive statistics.

2.2 Schedule of Events

Table 1 Schedule of Events

Visit[a]	Baseline (Day 1)	Dosing (Day 1)	Day 1[c]					Day 2[d]	Day 3	Day 7	Day 14	Day 28 EOS Visit
Time After Dosing[e]	**Pre-dosing**	**0h**	**0.5–1h**	**3–4h**	**5–6h**	**8–10h**	**12h**	**2d**	**3d**	**7d ± 1d**	**14d ± 2d**	**28d ± 3d**
Informed consent	X											
Review inclusion / exclusion criteria	X											
Demographics	X[b]											
Medical history, including details of envenoming and treatments/interventions	X											
Body height/weight per institutional protocol	X[b]											X
Physical examination	X							X	X	X	X	X
Vital signs[f]	X			X	X	X		X	X	X	X	X
Randomization and IP assignment	X											
Snakebite Severity Scale (SSS) assessments: Individual Category Severity Assessments: Pulmonary, Cardiovascular, Local Wound, Gastrointestinal, Hematologic, Renal, Nervous Systems	X			X[g]	X[g]	X[g]		X	X	X	X	X
Head-Lift duration in inpatient participants (0 to 5 seconds)[h]	X			X	X	X		X	X	X	X	X
Numeric Pain Rating Scale (NPRS)	X			X	X	X		X	X	X	X	X
12-lead ECG	X[b]					X				X		X
Grip strength[i]	X			X	X	X		X	X	X	X	X
Laboratory assessments (see individual Laboratory Assessments Schedule of Events below)[j]	X			X	X	X		X	X	X	X	X
Patient Global Impression of Change (PGIC)[k]	X[b]			X	X	X		X	X	X	X	X
Clinical Global Impression-Improvement (CGI-I)[l]		X[l]			X	X		X	X	X	X	X
Patient-specific functional scale (PSFS)						X		X	X	X	X	X

Visit[a]	**Baseline (Day 1)**	**Dosing (Day 1)**	**Day 1**[c]					**Day 2**[d]	**Day 3**	**Day 7**	**Day 14**	**Day 28 EOS Visit**
Time After Dosing[e]	**Pre-dosing**	**0h**	**0.5–1h**	**3–4h**	**5–6h**	**8–10h**	**12h**	**2d**	**3d**	**7d ± 1d**	**14d ± 2d**	**28d ± 3d**
Columbia-Suicide Severity Rating Scale (C-SSRS)[m]	X[b]							X	X	X	X	X
IP administration (Oral loading dose followed by second dose approximately 12 hours later, then BID dosing for remainder of 7-day treatment period)		◄	―	―	―	―	―	―	―	►		
Standard of care (SOC)[n]	◄	―	―	―	―	―	―	―	―	―	―	►
Assess and record adverse events (AEs)	◄	―	―	―	―	―	―	―	―	―	―	►
Record concomitant medications/therapies/analgesic use, including sedatives and paralytics for intubated patients	◄	―	―	―	―	―	―	―	―	―	―	►
Additional assessments in intubated subjects[o]	◄	―	―	―	―	―	―	―	―	►		
Record pulmonary support interventions[p]	◄	―	―	―	―	―	―	―	―	―	―	►
Record hospitalization details	◄	―	―	―	―	―	―	―	―	―	―	►
Laboratory Assessments Schedule of Events												
Complete blood count (including WBCs with differential, hemoglobin/hematocrit, platelets)	X			X	X	X		X	X	X	X	X
Serum chemistry (including sodium, potassium, chloride, bicarbonate, BUN and creatinine with estimated GFR)	X			X	X	X		X	X	X	X	X
Serum pregnancy	X											X
Liver function tests (LFTs)	X				X			X	X	X		X
Hemolysis markers (hemolysis measured by plasma free hemoglobin, haptoglobin, LDH)	X			X	X	X		X	X			
PT, PTT, thrombin time, INR[q]	X			X	X	X		X	X	X	X	X
Absolute fibrinogen	X			X	X	X		X	X	X	X	X
Urinalysis, general[r]	X							X	X	X		X
Urine pregnancy	X											
Biomarkers: CRP, D-dimer	X					X		X	X	X	X	
Biomarker: creatine kinase (CK)	X			X	X	X		X	X			
$sPLA_2$ biomarker[s]	X		X	X	X	X		X	X	X		

Visit[a]	**Baseline (Day 1)**	**Dosing (Day 1)**	**Day 1**[c]					**Day 2**[d]	**Day 3**	**Day 7**	**Day 14**	**Day 28 EOS Visit**
Time After Dosing[e]	**Pre-dosing**	**0h**	**0.5–1h**	**3–4h**	**5–6h**	**8–10h**	**12h**	**2d**	**3d**	**7d ± 1d**	**14d ± 2d**	**28d ± 3d**
Pharmacokinetics sample[s,t]	X		X[s]						X	X		

Abbreviations: AE = adverse event; BID = twice daily; BUN = blood urea nitrogen; CGI-I = Clinical Global Impression-Improvement; CK = creatine kinase; CRP = C-reactive protein; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = End of Study; GFR = glomerular filtration rate; INR = international normalized ratio; IP = investigational product; LDH = lactate dehydrogenase; MIP = maximum inspiratory pressure; NIF = negative inspiratory force; NPRS = numeric pain rating scale; PGIC = patient global impression of change; PK = pharmacokinetic; PSFS = patient-specific functional scale; PT = prothrombin time; PTT = partial thromboplastin time; SOC = Standard of care; $sPLA_2$ = secretory phospholipase A_2; SSS = snakebite severity score; WBC = white blood cell

[a] Screening, enrollment, and Day 1 of the Treatment Period will take place on the same day.

[b] This noncritical assessment should be performed as early as possible, but may be performed after randomization and initiation of study drug or SOC if required due to patient condition

[c] Assessments (besides PK blood draws for each individual subject on Day 1) should be timed such that ≥ 90 minutes elapses between measurements.

[d] Assessments for each individual subject between hours 8 to 10 of Day 1 and the same measurements on Day 2 (except PK blood draws) should be timed such that at least 12 and not more than 18 hours elapse between measurements.

[e] Assessments for each individual subject between Day 2 and Day 3 should be timed such that approximately, but not more than, 24 hours elapse between measurements

[f] Vital signs will be assessed per institutional practice, but at a minimum of once per time point.

[g] The SSS measurements at each of the Day 1 timepoints (3 to 4 hours, 5 to 6 hours, and 8 to 10 hours post-dose) should be collected prior to administration of repeat doses of antivenom, if required.

[h] Head-lift will be evaluated from 0 to 5 seconds as described in Section 10.3.1.9.

[i] Grip strength should be performed as described in Section 10.3.1.8.

[j] Administration of treatment should **not** be delayed until laboratory test results are returned (e.g., eGFR, liver, renal, or serum pregnancy tests).

[k] The PGIC score is a rapid, qualitative assessment that should be performed prior to the PSFS score on Day 1

[l] Baseline CGI-I should be in comparison to previous clinical assessment. Additional CGI-I should be performed on Day 1 at 1, 2, and 3-4 hours post initial dose, then follow normal assessment schedule. All post-baseline CGI-I assessments should be compared to baseline CGI-I as described in Appendix C1.

[m] The C-SSRS will be evaluated at Baseline or at the earliest time point clinically allowable and then at every study visit through Day 28, with modifications to the scales at different study dates as described in Section 10.3.1.6.

[n] SOC (including antivenom as required) will continue to be administered throughout the subject's participation in the study according to the protocol and the judgment of the Investigator.

[o] For endotracheally intubated subjects, perform additional assessments as described in Section 10.3.1.7.

[p] Record the type of control of mechanical ventilation [e.g., volume control, pressure control, assist control, pressure-regulated volume control, synchronized intermittent mandatory ventilation, pressure support, adaptive support ventilation, airway pressure release ventilation or T piece, note NIF (MIP) values in eCRF as used per institutional practice].

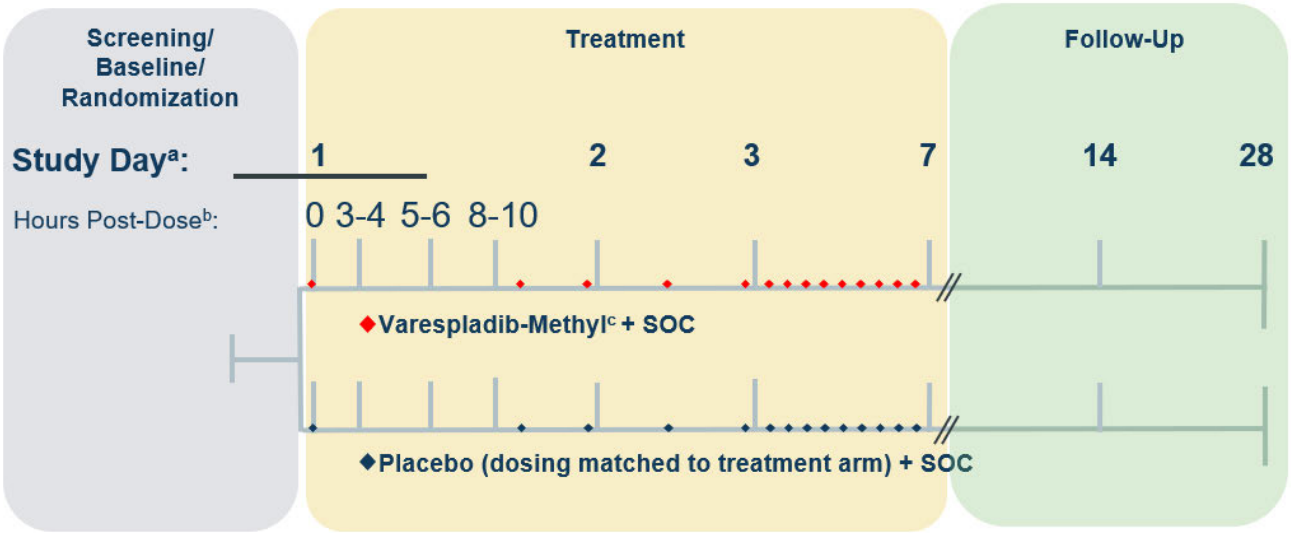
[q] Results of point of care testing (e.g., 20WBCT) will also be collected when performed per site standard of care.

[r] Urinalysis should not delay care and should not be obtained by catheter unless patient already being catheterized (e.g., Russell's viper). Urine from catheterized patients should not be collected from bag, but rather proximal port.

[s] $sPLA_2$ sampling will be performed for all subjects on Day 1 (pre-dose and 1, 3, 6, and 9 hours post-first dose), and on Day 2, Day 3, and Day 7 (pre-dose). $sPLA_2$ in serum and PK samples will be processed and analyzed in a central laboratory, not at individual sites.

[t] PK sampling will only be performed for a total of 20 adult and pediatric subjects on Days 1 and 3, and all subjects on Day 7. Once 20 subjects have provided PK samples for Days 1 and 3, sites will be notified by the sponsor to discontinue Day 1 and 3 PK sampling. Subjects will be enrolled for PK analysis as follows: Day 1 - 20 subjects, pre-dose and 0.5, 1, 2, 4, 6, 8, and 12 (pre-second dose) hours; Day 3 - 20 subjects, pre-dose and 0.5, 1, 2, 4, 6 hours; Day 7 - all subjects, pre-dose.

Figure 1 Study Schematic



a. Because snakebite subjects are considered critically ill and will arrive in an emergency department setting, Screening, Baseline evaluation, randomization, and treatment must all take place on Study Day 1

b. Assessments (see Schedule of Events) must be performed at the following times post-initial dose: 3 to 4 hours, 5 to 6 hours, 8 to 10 hours, 2 days (12 to 18 hours after last Day 1 measurements), 3 days (approximately 24 hours after Day 2 measurements), 7 days ± 1 day, 14 days ± 2 days, and 28 days ± 3 days

c. The varespladib-methyl dosing for adult subjects is a 500 mg loading dose, a 250 mg dose approximately 12 hours later, then 250 mg BID for the remainder of the study period; pediatric subjects (ages 5 to < 18) will be administered doses of varespladib-methyl determined by allometric scaling, provided as 50 mg capsules, depending on age (see Section 7.3). Abbreviations: BID = twice daily; SOC = standard of care; yr = years

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3.1 List of In-text Tables

3.2 List of In-text Figures

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ANCOVA	Analysis of covariance
AUC	Area under the curve
BUN	Blood urea nitrogen
CGI-I	Clinical Global Impression - Improvement
C-SSRS	Columbia-Suicide Severity Rating Scale
DDI	Drug-drug interaction
FDA	Food and Drug Administration
IC_{50}	Half-maximal inhibitory concentration
IND	Investigational New Drug application
INR	International normalized ratio
IV	Intravenous
LFT	Liver function test
MOF	Multiple organ failure
MIP	Maximum inspiratory pressure
NIF	Negative inspiratory force
PD	Pharmacodynamics
PK	Pharmacokinetics
PLA_2	Phospholipase A2
PSFS	Patient-Specific Functional Scale
PT	Prothrombin time
PTT	Partial thromboplastin time
PTSD	Post-traumatic stress disorder
Q12H	Once every 12 hours
QoL	Quality of life
RASS	Richmond Agitation Sedation Scale
SOC	Standard of care
$sPLA_2$	secreted phospholipase A_2
TEAE	Treatment-emergent adverse effect
ULN	Upper Limit of Normal
U.S.	United States
20WBCT	20 minute whole blood clotting time
WHO	World Health Organization

5 INTRODUCTION

5.1 Background and Rationale

The treatment of snakebite envenoming is an urgent, global unmet medical need. It is estimated that worldwide more than 5 million snakebite envenomings occur annually, causing significant morbidity (approximately 400,000 causing permanent deformities or amputation) and mortality (up to 138,000 causing death) (Gutierrez, et al., 2017; Longbottom, et al., 2018). Snakebite primarily affects poor, rural populations in tropical and sub-tropical regions of developing countries, where outcomes are adversely impacted by the snakebite victim's lack of proximity and/or access to healthcare, including access to currently available antivenom therapies (Longbottom, et al., 2018). Although comparatively unusual in the U.S., snakebite envenoming incurs significant morbidity and occasional mortality with bad outcomes primarily associated with delays in care, young age, neurological deficit, thrombocytopenia and coagulation abnormalities (Gerardo, et al., 2019).

Approximately 5.8 billion people live in regions that place them at risk for being bitten by a medically important snake (Longbottom, et al., 2018) and it is estimated that > 75% of deaths from snakebite occur outside the hospital setting before victims can reach medical care. While not all snakebites result in envenoming with morbidity and mortality, often by the time patients receive the appropriate medical care in a hospital setting it is far too late and the toxicities of snakebite envenoming have substantially progressed and are no longer amenable to effective treatment by antivenom therapy (Vaiyapuri, et al., 2013; Gerardo, et al., 2019). To underscore the urgency of the global public health crisis posed by snakebite envenoming, the World Health Organization (WHO) recently classified snakebite envenoming as a neglected tropical disease (Longbottom, et al., 2018). Furthermore, the WHO's Snakebite Envenoming Working Group stated that "accelerating preclinical and clinical testing of promising prehospital adjunctive treatments, such as the phospholipase A_2 inhibitor varespladib or varespladib-methyl, as part of the WHO snake bite envenoming research agenda may lead to early improvements in prehospital survival" (Williams, et al., 2019).

Even when the standard of care (SOC) antivenom therapies are available, their use is associated with a number of challenges and limitations, many of which could potentially be overcome with a small-molecule therapeutic (Bulfone, et al., 2018) (summarized in Section 5.3). Indeed, because snake venom secreted phospholipase A2 ($sPLA_2$) is involved in virtually every critical venom effect and exists as a major toxin in virtually all venomous snakes around the world (Tasoulis and Isbister, 2017), $sPLA_2$ has been identified as a desirable target for a toxin-specific approach to the treatment of snakebite (Williams, et al., 2019).

The objective of the development program by Ophirex is to advance varespladib, a high-potency small-molecule inhibitor of $sPLA_2$, and its oral prodrug formulation (varespladib-methyl) for the treatment of snakebite envenoming. Varespladib-methyl (LY333013) is rapidly hydrolyzed into varespladib (LY315920). LY315920 is a potent inhibitor of $sPLA_2$ (Snyder, et al., 1999). LY333013 is an orally bioavailable, methyl ester prodrug of the active $sPLA_2$ inhibitor LY315920, which is administered intravenously (IV).

Varespladib and varespladib-methyl were originally developed as $sPLA_2$ inhibitors for treating multiple diseases with an underlying inflammatory component (e.g., sepsis, rheumatoid arthritis, and cardiovascular disease) (Adis, 2011). These previous development efforts were terminated because of lack of efficacy or futility in diseases studied, but they have provided a substantial amount of clinical safety and bioavailability data, with > 4,600 subjects exposed to both varespladib and varespladib-methyl.

5.1.1 Scientific Rationale

$sPLA_2$ enzymes represent a family of enzymes implicated in the activation of the inflammatory process that produces multiple organ failure (MOF) in sepsis (Anderson, et al., 1994). In mammals, $sPLA_2$ originates from a variety of cells including macrophages, neutrophils, and inflamed synovial tissue. In snake venom it originates from modified salivary glands and is a key toxin not reliably neutralized by antibody-based products such as antivenom (Prasarnpun, et al., 2005). A defining characteristic of snakebite envenoming is that snake venom $sPLA_2$ proteins are injected in high concentrations directly into the victim with potentially rapid lethality or morbidity effects (Gutierrez, et al., 2017).

$sPLA_2$s are the most pharmacologically active component of snake venoms, and one of the components most responsible for lethality and long-term morbidity (Gutierrez, et al., 2017). Virtually all snake venoms—even those commonly associated with coagulopathy—may also have neurotoxic and blood pressure lowering effects because the primary purpose of the venom is to weaken and immobilize prey so that the snake can ingest it. While it is the $sPLA_2$-mediated neurotoxicity of snake venom that often causes rapid lethality in humans, snake venom $sPLA_2$ toxins are also responsible for hemolysis, coagulopathy, myonecrosis and kidney damage (Arce-Bejarano, et al., 2014; Gutierrez, et al., 2017; Bryan-Quiros, et al., 2019). Thus, inhibition of $sPLA_2$ could address several limitations of antivenom therapies that lead to adverse outcomes, including delays in care, the ability to reverse neurological effects not effectively mitigated by antivenom, and coagulation parameters and platelet dysfunction that can be severely provoked by venom $sPLA_2$ toxins (Bittenbinder, et al., 2018; Lewin, Gilliam, et al., 2018; Lewin, Gutierrez, et al., 2018; Alangode, et al., 2020; Albulescu, et al., 2020; Fontana Oliveira, et al., 2020; Gutierrez, et al., 2020; Xie, et al., 2020; Zinenko, et al., 2020; Kazandjian, et al., 2021).

In vitro, LY315920 and its prodrug LY333013 potently inhibit snake venom $sPLA_2$, with half-maximal inhibitory constant (IC_{50}) values in the nano- and sub-nanomolar range, including $sPLA_2$ enzymes from pit vipers such as copperhead, cottonmouth, several rattlesnakes and elapids including coral snake (Lewin, et al., 2016). As an example, *M. fulvius* (Eastern coral snake) has a well-characterized venom causing both neurotoxic and hemotoxic effects (Arce-Bejarano, et al., 2014) and the toxicity of coral snake venom, as for other elapids (snakes related to cobras and kraits) around the world, is mediated by $sPLA_2$ (Fernandez, et al., 2018). Several in vivo studies show that both the orally-administered LY333013 and IV-administered LY315920 rescue mice, rats and pigs from 100% lethal doses of coral snake venom, even when antivenom was no longer of benefit to the animals, returning platelet function to normal and reversing venom-induced hemolysis (Lewin, Gilliam, et al., 2018). The structural basis for LY315920 inhibition of snake venom $sPLA_2$ has recently been established, as well, through crystallographic study (Salvador, et al., 2019).

5.1.2 Epidemiology of Snakebites in Children

Children anywhere in the world are at great risk for severe snakebite because they are small, naturally curious, frequently play outdoors and often reach or step into areas blindly, such as when picking up rocks or gathering firewood. Their small size puts them at greater risk of severe bites because of the weight-based dosage effect of snake venom toxins (Gerardo, et al., 2019; Pach, et al., 2020). In many countries, older children are often bitten when participating in agricultural work or while playing or walking close to their homes. In sub-Saharan Africa, approximately 30% of envenomings occur in children (Chippaux, 2011). Pediatric cases are particularly challenging to manage clinically and too often the result of a bite is life-long complications from tissue damage, necrosis, neurological deficits, social and educational burdens (Sankar, et al., 2013; Gerardo, et al., 2019). Additionally, the long-term effects of amputations and post-traumatic stress disorder (PTSD) account for a significant part of the burden of snakebite envenoming in children (Halilu, et al., 2019).

Similar to the situation in low- and middle-income countries, snakebite envenoming in the United States (U.S.) is over-represented in pediatric population compared to percentage of the total population (Parrish, 1965; Seifert, et al., 2009). For example, in a series of 450 cases identified, 28.2% were children age 12 and under (Ruha, et al., 2017). In contrast, children aged 12 years or younger make up only about 16% of the U.S. population (U.S. Census Bureau, 2019). The U.S., the pediatric population is at a significant risk of hospitalizations, admissions to ICUs or death following snakebite envenoming (Schulte, et al., 2016). As with other places in the world, envenoming in the pediatric population is disproportionately more severe due to smaller body mass and higher concentration of venom delivered with young age being one of the main factors in snakebite severity (Gerardo, et al., 2019).

5.2 Clinical Experience

Multiple clinical studies have been performed by the previous sponsors for LY333013 (varespladib-methyl) and LY315920 (varespladib), Eli Lilly and Anthera, to characterize the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of LY315920 or LY333013. The inflammatory conditions studied clinically included sepsis, rheumatoid arthritis, ulcerative colitis, asthma, atherosclerosis, and acute chest syndrome in at-risk patients with sickle cell disease. Previous clinical studies have been summarized in the current version of the varespladib Investigator's Brochure (IB).

5.3 Summary of Potential Risks and Benefits

The potential benefits of study participation are that subjects suffering from snakebite envenoming may receive improved outcome in terms of snakebite severity and quality of life (QoL) assessments. Table 2 describes the limitations of current serum-based antivenoms, and the potential advantages of varespladib or varespladib-methyl.

Table 2 Comparison of Varespladib and Currently Available Serum-Based Antivenom Therapies

Challenge or Limitation	Limitations of Serum-Based Antivenom Therapy	Potential Advantages of Oral Varespladib
Ease of Use	Must be administered IV in a clinical setting: cannot be self-administered at the time of snakebite Intensive monitoring for antivenom induced complications required	In the clinic, oral and IV formulations can be administered in combination with antivenom therapies. If proven effective, an oral varespladib formulation could eventually be administered at the time of the snakebite—before reaching a hospital
Species Specificity	Generally specific to one species or closely related species of venomous snakes and $sPLA_2$ is poorly antigenic	Varespladib is a potent, broad-spectrum inhibitor of snake venom $sPLA_2$
Tissue Penetration	Large proteinaceous molecules with limited or no ability to penetrate tissues	Small molecules with the ability to penetrate tissues to neutralize or reverse $sPLA_2$-mediated venom toxicities
Potential for Allergenicity	High	Low (no documented allergies)
Cost to Manufacture	Higher	Lower
Requirement for Refrigeration	Yes (most formulations)	No refrigeration
Available Global Supply	Current and anticipated long-term global shortage (Williams, et al., 2019)	Potential for a comparably broader, more cost-effective, global distribution

Abbreviations: IV = intravenous; $sPLA_2$ = secreted phospholipase A2.

The proposed dosing of varespladib-methyl for adult subjects consists of an initial loading dose of 500 mg (2 × 250 mg oral tablet), an additional 250 mg dose (1 x 250 mg oral tablet) approximately 12 hours later, and then 250 mg (1 x 250 mg tablet) twice daily (BID) for the remainder of the study period. Pediatric subjects (ages 5 to < 18) will be administered doses of varespladib-methyl determined by allometric scaling, provided as 50 mg capsules (Section 7.3).

The doses proposed for this study are anticipated to be safe and tolerable for adult and pediatric subjects. The potential risks of study participation include those associated with varespladib, including adverse events (AEs) and serious adverse events (SAEs) as well as the risks of medical evaluation and treatment, including the minimal possibility of allergic reaction from the study drug. Across clinical studies, varespladib was tolerated well and generally did not induce AEs beyond those observed in placebo treatment groups, even in severely ill subjects. In a total of seven phase 1 and three phase 2 studies, IV varespladib was administered to 733 subjects. In a total of twelve phase 1 and five phase 2 studies oral varespladib-methyl was administered to a total of 3,679 subjects. Common AEs observed included rhinitis, nausea, and diarrhea. No clinically meaningful varespladib or varespladib-methyl treatment-related effects were noted for biochemical and hematologic parameters other than modest transient increases in liver enzymes that occurred in several subjects. Treatment with varespladib or varespladib-methyl was not

associated with changes in heart rate or blood pressure and there was no evidence of an effect on ventricular repolarization (QT interval prolongation). SAEs including cerebrovascular accident (CVA) and myocardial infarction (MI) have been observed in some acutely ill subjects in clinical studies for indications such as severe sepsis and acute coronary syndrome. Patients with conditions such as these are excluded from participation in this study.

In subjects receiving continuous IV varespladib (LY315920) infusion, plasma drug concentrations up to 800 ng/mL for 6 hours were tolerated well and treatment-related AEs were mild to moderate and were not clinically significant. No AEs were reported with short-term dosing with IV varespladib infusion, resulting in plasma concentrations of up to 1,200 ng/mL for 30 minutes; similarly, infusion of varespladib at doses up to 0.323 mg/kg/hour for 4 hours was well-tolerated with no treatment-emergent adverse events (TEAEs) observed. Multiple oral doses of varespladib-methyl tablets (LY333013) up to 500 mg once every 12 hours (Q12H) were tolerated well. Thus, short-term treatment with varespladib or varespladib-methyl (e.g., up to 1 hour) at doses exceeding 0.2 mg/kg/hr (IV) or 500 mg Q12H (oral) is not anticipated to induce AEs, TEAEs, or SAEs. In healthy subjects, dosing with varespladib or varespladib-methyl for up to 7 days and at doses up to 77 mg/kg or 500 mg Q12H, respectively, did not induce SAEs. In subjects with severe sepsis, continuous IV dosing with varespladib for up to 7 days at plasma concentrations of up to 800 ng/mL did not induce substantially more SAEs than were observed with placebo. Thus, oral dosing with 250 mg varespladib-methyl BID is not anticipated to induce AEs, even in severely ill subjects such as those with snakebite envenoming.

A summary of the pharmaceutical properties and known potential risks of varespladib or varespladib-methyl is provided in the current version of the Varespladib-Methyl IB. The Investigator must become familiar with all sections of the IB before the start of the study.

6 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Objective	**Primary Efficacy Endpoint**
• To evaluate the efficacy of a multi-dose regimen of oral varespladib-methyl with standard of care (SOC) in subjects after venomous snakebite	• Change in the composite outcome of pulmonary, cardiovascular, hematologic symptoms, 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.
Secondary Objectives	**Secondary Efficacy Endpoints**
• To evaluate efficacy of varespladib-methyl as treatment for $sPLA_2$-induced venom toxicities	• AUC of the pulmonary, cardiovascular, hematologic symptoms, renal, and nervous system sections of the SSS from Baseline through Day 7 • Complete SSS from Baseline 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, creatine kinase (CK), from Baseline through Day 3 • Numeric Pain Rating Scale (NPRS) score in patients able to respond from Baseline through Day 28 • Kidney function markers from Baseline through Day 28 • Total differential antivenom requirement 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 • Clinical Global Impression-Improvement (CGI-I) from Baseline through Day 7 • Patient Global Impression of Change (PGIC) from Baseline through Day 7 • Patient-Specific Functional Scale (PSFS) total score from Baseline through Day 28
Exploratory Objectives	**Exploratory Endpoints**
• To assess the efficacy of varespladib-methyl as evaluated by a compressed SSS scale	• Change in the SSS from Baseline through Day 7 using a compressed SSS scale
• To assess the efficacy of varespladib-methyl as evaluated by SSS	• SSS from Baseline through Day 28 after first dose

Objectives	Endpoints
• To assess the effect of varespladib-methyl on neurological function as evaluated by grip strength	• Grip strength pre-dosing through Day 28
• To assess the effect of varespladib-methyl on neurotoxicity	• SSS neurologic system subscore from Baseline through Day 7
• To assess the effect of varespladib-methyl on analgesic use	• Analgesic use from Baseline through Day 28
• To evaluate the effect of varespladib-methyl on clinician-based impression of improvement	• CGI-I from Baseline through Day 28
• To evaluate the effect of varespladib-methyl on the PGIC	• PGIC from Baseline through Day 28
• To assess the effect of varespladib-methyl on complete blood count (CBC)	• CBC through all SSS evaluation days
• To assess the effect of varespladib-methyl on transfusion requirement in patients with hemolysis	• Transfusion requirement from Baseline through Day 28
• To evaluate the effect of varespladib-methyl on the levels of C-reactive protein (CRP)	• CRP from Baseline through Day 14
• To assess the safety biomarker D-dimer	• D-dimer levels from Baseline through Day 14
• To assess the effect of varespladib-methyl on myonecrosis marker (CK) in subjects with and without tourniquets at enrollment	• Levels of CK in patients from Baseline through Day 3 in patients presenting with and without tourniquets at enrollment
• To evaluate the levels of secretory phospholipase A2 ($sPLA_2$) in serum	• $sPLA_2$ in serum at specified timepoints on Days 1 to 7 in all subjects
Pharmacokinetics Evaluation	
• To assess pharmacokinetics (PK) of varespladib-methyl in subjects with snakebite envenoming	• PK parameters of varespladib-methyl in plasma from a subset of adult and pediatric subjects at specified timepoints on Days 1 and 3 followed by all subjects pre-dose on Day 7
Safety	**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/Telephone call at Day 28 • Number of subjects with a treatment-related SAE from beginning of treatment until last Follow-Up

Objectives	Endpoints
	Visit/Telephone call at Day 28 • Safety as assessed by – Vital signs – Clinical laboratory evaluations: 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

7 STUDY DESIGN

7.1 Overall Study Design and Plan

This is a multicenter, 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.

- Approximately 110 male and female subjects (94 evaluable) will be randomized to receive active varespladib-methyl or placebo (in addition to SOC) in a 1:1 ratio. There will be no stratification by type of snakebite, though randomization will be 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.

Patients eligible for the study must be male or female ≥ 5 years of age with venomous snakebite. The index event (snakebite) must be symptomatic and symptom onset must have occurred within 10 hours of eligibility assessment and the patient must be willing (or legally authorized representative is willing) to provide informed consent prior to initiation of any study procedures.

Patients must meet one of two categories of inclusion criteria:

> **Category 1**: The patient has not yet completed first dose of antivenom:
>
> SSS inclusion score* of ≥2 in one system and ≥1 in another system (2+1) **OR** ≥3 in at least one system.
>
> OR
>
> **Category 2**: The patient has completed an initial dose of antivenom:
>
> SSS inclusion score* of ≥2 in one system and ≥1 in another system (2+1) OR ≥3 in at least one system **AND** CGI-I score of ≥5 (i.e., minimally worse, much worse, or very much worse).

* Only local wound, pulmonary, cardiovascular, hematologic, or nervous system scores qualify for SSS inclusion criteria. GI and Renal scores are not used for inclusion. Hematologic score may be counted if available, but inclusion should not wait for laboratory results. Point of care tests (e.g., 20WBCT) may be used for enrollment, if used per site standard of care (see Appendix A).

One group will be treated with the SOC plus placebo and the other treated with SOC plus varespladib-methyl. The time between baseline and eligibility assessments, randomization, and IP administration should be minimized.

There should be no delay in providing the SOC, nor should there be a delay in administration of study drug after randomization.

Primary efficacy outcome will be assessed by comparing the change in the combined pulmonary, cardiovascular, hematologic, renal, and nervous system subscores of the SSS from Baseline

(pre-dosing) to the average of the scores 6 and 9 hours post-Baseline for the treatment and control groups. Additional details will be provided in the SAP.

Safety and tolerability will be assessed by evaluating AEs, vital sign measurements, clinical laboratory test results, ECGs, physical examination findings, and concomitant medications and therapies.

All AEs observed by the study personnel or reported by the subject during the study (from the time of the signing of the informed consent and/or assent through the End of Study (EOS) visit) will be documented.

Pharmacokinetic sampling will be performed for a subset of subjects on Days 1 and 3 and on all subjects on Day 7.

7.2 Rationale and Discussion of Study Design

Snakebite envenoming represents a deadly and unmet global medical need. While antivenoms comprise the SOC for treatment of snakebites, they suffer from several limitations including specificity of each antivenom for specific species of snake, limited access to antivenom in rural areas, practical storage requirements, and delays in administration. Treatment of snakebite envenoming with the small-molecule drug varespladib-methyl, which targets $sPLA_2$ present in approximately 95% of snake venoms, has the potential to overcome several limitations of serum-based antivenoms that underpin traditional SOC.

The proposed study in the United States and India will provide coverage of a broad spectrum of venomous snake genera, including elapids, vipers, and pit vipers in differing geographies and differing $sPLA_2$ structures. Study sites will be selected based on demonstrated historical incidence of snake bites from species deemed relevant to this study, to ensure a broad range of envenoming toxins are expected to be encountered in potential study subjects.

This study was designed to exclude as few critically ill subjects as possible. The primary criteria for participation are that subjects must be ≥ 5 years of age, must present with an initial SSS of (A) 2 points in any SSS category other than GI or Renal and 1 or more additional point in any other SSS category other than GI or Renal or (B) an initial SSS score of ≥ 3 in any SSS category other than GI or Renal, must not be pregnant or breast-feeding, are not taking excluded medications, and have not been previously administered antivenom at another facility.

The study design allows for both treatment arms (varespladib-methyl and placebo) to receive SOC (e.g., antivenom) concurrently. Thus, critically ill adult and pediatric subjects may receive emergency treatment in a timely manner while being evaluated for the potential clinical benefit associated with inhibition of venom $sPLA_2$ by varespladib-methyl.

Because subjects with severe snakebites are admitted to emergency departments, this study was designed to screen, enroll, and administer treatment in a single visit at the hospital upon admission. Because varespladib-methyl is administered orally, subjects who demonstrate substantial improvement and are eligible for discharge from the hospital may continue investigational product (IP) treatment in an outpatient setting.

Risks associated with the control (placebo) arm of this study include the same risks associated with SOC (antivenom).

The efficacy endpoints for this study were selected to evaluate if varespladib-methyl plus SOC is superior to SOC alone. The primary endpoint was selected to evaluate clear clinical benefit based on SSS, whereas secondary and exploratory endpoints were selected to evaluate improvements in each subject's snakebite severity and QoL over the course of treatment. PK analysis will be performed at specified timepoints throughout the treatment period, including in pediatric subjects enrolled.

7.3 Selection of Doses in the Study

LY333013 (varespladib-methyl) is formulated in an immediate-release film-coated oval tablet at a unit dosage strength of 250 mg for oral administration. Ophirex is developing varespladib-methyl (LY333013) for oral administration for 7 days total for the treatment of venomous snakebites. LY333013 is a prodrug that is rapidly metabolized to LY315920; LY315920 is a potent inhibitor of $sPLA_2$ in vitro and in vivo.

This study evaluates the safety, tolerability, and efficacy of varespladib-methyl in subjects bitten by venomous snakes from diverse regions and snake genera, including (but not limited to) pit vipers (e.g., rattlesnake, copperhead), vipers (e.g., Russell's viper and saw-scaled viper), and elapids (e.g., coral snake, cobra, krait).

The proposed dosing of varespladib-methyl for adult subjects consists of 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, followed by BID dosing with 1 x 250 mg varespladib-methyl oral tablets for the remainder of the 7-day treatment period.

Pediatric subjects (ages 5 to < 18) will be administered doses of varespladib-methyl determined by allometric scaling, provided as 50 mg capsules, depending on age. Pediatric doses were determined based on the 250 mg BID adult dose. Median weights from the Centers for Disease Control (CDC) growth charts were used for the allometric scaling, with weights averaged for male and female pediatric subjects. Subjects 5 to < 11 years old will receive an initial loading dose of 200 mg varespladib-methyl, an additional dose of 100 mg approximately 12 hours later, followed by 100 mg BID. Subjects 11 to < 18 years old will receive a loading dose of 400 mg varespladib-methyl, an additional dose of 200 mg approximately 12 hours later, followed by 200 mg BID. Including the loading dose, subjects will receive a total of 14 doses of study medication. Dosing may occur on 7 or 8 calendar days, depending on whether the first dose of study medication is in the morning or the afternoon.

Initial loading dose may be taken with or without food to accommodate the need to provide treatment as soon as possible following enrollment. The status of food consumption at the time of administration of the initial loading dose should be recorded in the case report form (CRF). All scheduled doses following the initial dose should be taken with food for the remainder of the study's BID dosing period.

A summary of formulations and dosing for adult (age ≥ 18 years) and pediatric (ages ≥ 5 to < 18 years) subjects is provided in Table 3.

Table 3 Summary of Adult and Pediatric Dosing

	Age ≥ 18 yr (Adult)	**Age 11 to < 18 yr**	**Age 5 to < 11 yr**
Oral Formulation	Tablet	Capsule	Capsule
Loading Dose	500 mg (2 x 250 mg)	400 mg (8 x 50 mg)	200 mg (4 x 50 mg)
Second Dose (approximately 12 hours after loading dose)	250 mg (1 x 250 mg)	200 mg (4 x 50 mg)	100 mg (2 x 50 mg)
BID Dose (for remainder of 7-day treatment period)	250 mg (1 x 250 mg)	200 mg (4 x 50 mg)	100 mg (2 x 50 mg)

Abbreviations: BID = twice daily; yr = year

Serum $sPLA_2$ levels may exceed 3 µg/mL in patients with severe sepsis or septic shock (whereas normal levels of $sPLA_2$ are approximately 2 to 5 ng/mL), but 3 µg /mL can be rapidly exceeded with direct injection of snake venom. In vitro data suggest that complete inhibition of $sPLA_2$ by LY315920 may occur when the molar concentration of the inhibitor exceeds that of the enzyme by approximately 5- to 7-fold (Sorensen, et al., 1994; Uhl, et al., 1995). PK/PD models of envenoming suggest that a catastrophic snakebite injecting 200 mg total $sPLA_2$ (e.g., from the bite of an extremely large taipan with venom composed of > 80% $sPLA_2$) may result in plasma $sPLA_2$ concentrations up to almost 15 µg/mL in humans, whereas envenoming with a coral snake bite (i.e., 2.5 mg total $sPLA_2$) may result in $sPLA_2$ concentrations nearly 1000-fold lower (BSSA Modeling Report). According to these PK/PD calculations, a 500 mg loading dose and a subsequent 250 mg dose (total of 750 mg) on Day 1 of treatment, followed by 250 mg BID daily an additional 6 days, would be anticipated to result in clinically significant inhibition of $sPLA_2$ from most snakebite envenomings throughout the total venom exposure (including initial plasma $sPLA_2$ concentrations up to 200 mg total venom $sPLA_2$) (BSSA Modeling Report). In addition, the single 500 mg doses and 250 mg BID daily dosages used for adult subjects throughout the clinical development of LY333013 were safe and tolerated well. In sum, the proposed dose for adult subjects balances the predicted clinically significant inhibition of $sPLA_2$ in venom with the well documented safety profile of the 250 mg BID daily dosage.

Children often present with more severe effects of snakebite owing to their smaller size, weight-based dosage effect of snake venom toxins and lower volume of distribution relative to the mass of injected venom (Gerardo, et al., 2019; Pach, et al., 2020; Le Geyt, et al., 2021). The doses of antivenom used in children are the same as adult doses, as the volume of venom injected does not depend on the size of the victim (Le Geyt, et al., 2021), but small-molecule inhibitors whose venom binding is based on enzyme and drug concentrations are not subject to venom-antibody variability. Allometric scaling of adult doses of varespladib based on pediatric age-weight tables supports dosing in subjects 5 to < 11 years old and 11 to < 18 years old.

7.4 Study Sites

The study will take place at approximately 10 to 20 sites in the United States and India. Each site is anticipated to screen enough subjects to randomize approximately 5 to 20 subjects. No stratification or selection for type of snakebite will be made. Study site activation and enrollment periods will be planned to allow maximum enrollment during the most active seasonal snakebite months in each region. A study site with a high recruitment rate may be allowed to recruit more subjects if other sites have slow enrollment.

7.5 End of Study Definition

The EOS is the date when the last subject's last study visit occurs.

8 STUDY POPULATION

8.1 Selection of Study Population

Investigators or their designees will maintain a screening log of all candidates who are considered for participation in this study, including reasons for ineligibility or refusal to participate. Consent, screening, randomization, and dosing will occur on the same day. Subjects who do not meet all the eligibility criteria will not be enrolled. This study is estimated to enroll and randomize 110 male and female subjects equally into 2 groups. At least 94 evaluable subjects are expected to be available, allowing for up to 15% loss to follow-up.

8.2 Study Entry Criteria

8.2.1 Inclusion Criteria

A subject will be eligible for study participation if he or she meets all the following criteria:

1. Is a male or female ≥ 5 years of age with venomous snakebite.
2. Index event (snakebite) must be symptomatic and symptom onset must have occurred within 10 hours of eligibility assessment.
3. Patients must meet one of two categories of inclusion criteria:

   Category 1: The patient has not yet completed first dose of antivenom:

   SSS inclusion score* of ≥2 in one system and ≥1 in another system (2+1) **OR** ≥3 in at least one system.

   OR

   Category 2: The patient has completed an initial dose of antivenom:

   SSS inclusion score* of ≥2 in one system and ≥1 in another system (2+1) OR ≥3 in at least one system **AND** CGI-I score of ≥5 (i.e., minimally worse, much worse, or very much worse).

4. Is willing (or legally authorized representative is willing) to provide informed consent prior to initiation of any study procedures.

* Only local wound, pulmonary, cardiovascular, hematologic, or nervous system scores qualify for SSS inclusion criteria. GI and Renal scores are not used for inclusion. Hematologic score may be counted if available, but inclusion should not wait for laboratory results. Point of care tests (e.g., 20WBCT) may be used for enrollment, if used per site standard of care (see Appendix A).

8.2.2 Exclusion Criteria

A subject will be excluded from the study if he or she meets any of the following criteria:

1. Is considered by the Investigator to have a clinically significant upper GI bleed evidenced by significant hematemesis, "coffee-ground" emesis or nasogastric aspirate, hematochezia thought to originate from upper GI tract.
2. Has history of CVA or intracranial bleeding of any kind, acute coronary syndrome, MI, or severe pulmonary hypertension.
3. Has known history of inherited bleeding or coagulation disorder.
4. Is, at Screening Visit, using the following anticoagulants: warfarin/coumadin, argatroban, bilvalirudin, lepirudin, apixaban, dabigatran, clopidogrel, prasugrel, ticlodipine or another anticoagulant agent not specifically listed, or has used heparin, enoxaparin, fondaparinux, or other low molecular weight heparin or antiarrhythmic drugs within 14 days prior to treatment.
5. Has a history of chronic liver disease such as chronic active viral hepatitis, alcohol-related liver disease, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hemochromatosis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis.
6. Reports or has known pre-existing renal impairment or chronic kidney disease.
7. Has a known allergy or significant adverse reaction to varespladib-methyl.
8. Is considered by the Investigator to be unable to comply with protocol requirements due to geographic considerations, psychiatric disorders, or other compliance concerns.
9. Is pregnant, has a positive serum human chorionic gonadotropin (hCG) pregnancy test or not willing to use a highly effective method of contraception for 14 days after initial treatment, or is breast-feeding.

8.3 Early Subject Withdrawal

All subjects are free to withdraw from participation in this study at any time, for any reason. The Investigator should make every reasonable attempt to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to capture any AEs and determine whether a subject should be withdrawn. Every possible attempt should be made to collect and report AEs upon withdrawal, as described in Section 11.2.

The sponsor reserves the right to withdraw a subject due to protocol deviations or other reasons.

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of study discontinuation will be recorded on the appropriate page of the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time of withdrawal.

The reason for subject discontinuation from study medication or withdrawal from the study will be recorded on the eCRF. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, are randomized and receive the study intervention, and subsequently withdraw or are withdrawn or discontinued from the study will not be replaced.

8.4 Discontinuation of Study Intervention

An Investigator may discontinue a subject from study treatment for the following reasons:

- Pregnancy
- Significant study intervention or study procedure noncompliance
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject (if there is reasonable evidence of clinical benefit to justify continuation on the protocol, this must be discussed with the Ophirex medical monitor)
- If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

If a clinically significant finding is identified (including, but not limited to, changes from Baseline) after enrollment, the Investigator or qualified designee will determine if any change in subject management is needed. Specifically, this includes withdrawal of subjects who were initially enrolled but whose history of chronic liver disease, renal laboratory tests, or pregnancy tests suggest they are subject to exclusion criteria 6, 7, or 10.

Discontinuation from IP does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol.

Section 14.6 describes procedures in the event of suspension or termination of the study for all subjects.

8.5 Subject Replacement Criteria

Withdrawn subjects will not be replaced. If a substantial number of subjects are withdrawn from the study, the sponsor will evaluate the need for developing replacement criteria.

Randomized subjects withdrawn from the study may not reenter. The subject number for a withdrawn subject will not be reassigned to another subject.

9 TREATMENTS

9.1 Identification of Investigational Products or Placebo

The IP used in this study is varespladib-methyl along with matching placebo. Varespladib-methyl will be provided as an oral formulation.

- Varespladib-methyl
  - Varespladib-methyl (LY333013) is an immediate-release, oval, white, film-coated tablet at a dosage strength of 250 mg for oral administration.
  - Scaled pediatric doses of varespladib-methyl (LY333013) are supplied as 50 mg immediate-release capsules for oral administration.
- Placebo
  - The oral placebo is supplied as a white film-coated oval tablet to match the appearance of the LY333013 250 mg tablet and contains a subset of the excipients present in the active tablet formulation: lactose monohydrate, microcrystalline cellulose, and magnesium stearate.
  - Placebo for scaled pediatric dosing is supplied as an immediate-release capsule to match the LY333013 50 mg capsule, and contains the excipients lactose monohydrate, microcrystalline cellulose, and magnesium stearate.

9.2 Selection of Timing of Dose for Each Subject

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 x 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.
- Pediatric subjects (ages 5 to < 18) will be administered doses of varespladib-methyl determined by allometric scaling, provided as 50 mg capsules.

Tablets and age appropriate capsules may be administered via feeding tube (e.g. naso- or orogastric tubes) in patients requiring mechanical ventilation.

9.3 Dose Adjustment Criteria

Dose adjustment is not planned for this study.

9.4 Treatment Compliance

All hospitalized subjects will receive the IP or placebo at the study site under the surveillance of appropriate study personnel until discharged from the hospital. Tablet and capsule administration details will be recorded by the site. Subjects who are discharged during the 7-day treatment period will be asked to record the date and time of each dose.

9.5 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 will be computer generated using a permuted block algorithm and 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 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. 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 study contract research organization (CRO) before the start of the study. No subject will be randomized into this study more than once.

9.6 Blinding and Unblinding Treatment Assignment

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. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The Investigator will make this decision after consultation with the medical monitor.

9.7 Prohibited and Permitted Therapies

All concomitant medications (including over-the-counter medications and herbal supplements as well as sedatives and paralytics for intubated patients) and concomitant therapies used will be recorded in the source document and on the appropriate eCRF.

9.7.1 Prohibited Therapies

The prohibited therapies prior to enrollment are described in Section 8.2.2.

9.7.2 Permitted Therapies

All medications and therapies for snakebite envenoming, including SOC, are allowed after enrollment in this study. No other experimental therapies are permitted during participation in this study.

Initial inhibition/induction potential of varespladib towards major human CYP450 enzymes have been performed. Data suggest that the active form of varespladib-methyl does not inhibit or induce major CYP450 enzymes. Although varespladib-methyl has been given to over 3,600 subjects with few AEs, limited *in vitro* data exists regarding the potential of varespladib to act as an inducer for P450-mediated metabolism or impact major human transporters. Therefore, the sponsor recommends avoiding use of CYP450 inducers and substrates or inhibitors of major human transporters (but their use is not prohibited) during the period of IP administration based on the Investigator assessment of risk. A list of transporters is included on the FDA.gov Drug Development and Drug Interactions website in Table 5-1 and 5-2 of the Table of Substrates, Inhibitors and Inducers document (FDA, 2020):

- Table 3-3, "Examples of clinical inducers for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (12/03/2019)"
- Table 5-1, "Examples of clinical substrates for transporters (for use in clinical drug-drug interaction [DDI] studies and/or drug labeling) (12/03/2019)"
- Table 5-2, "Examples of clinical inhibitors for transporters (for use in clinical drug-drug interaction [DDI] studies and drug labeling) (9/26/2016)."

9.8 Treatment After End of Study

After the end of the study, each subject will be treated according to standard clinical practice.

9.9 Dispensing and Storage

The IP and placebo supplied by Ophirex is to be used exclusively in the clinical study according to the instructions in this protocol. The Investigator is responsible for dispensing the IP and placebo according to the dosage scheme and for ensuring proper storage of the products.

Until the IP is dispensed to the subjects, it must be stored in a securely locked area that is not generally accessible. The oral IP and placebo may be stored at room temperature. The key to the storage area is to be kept by the Investigator or designee responsible for the IP. The store will be accessible only to those persons authorized by the Investigator to dispense the products.

Detailed instructions for selecting and dispensing each dose of IP and placebo are in the study manual.

9.10 Drug Accountability

The Investigator or designee must confirm the receipt of the IP with his or her signature. A copy of this receipt must be kept by the Investigator and another copy will be stored at Ophirex, Inc. or designee.

The Investigator or designee must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IP, including the date, quantity, batch or code number, and identification of subjects who received the IPs. The Investigator will not supply the IP to any person except those named as sub-Investigators on the Food and Drug Administration (FDA) form 1572, designated study personnel, and subjects in this study. The Investigator will not dispense the IPs from any study sites other than those listed on the FDA Form 1572. IP may not be relabeled or reassigned for use by other subjects. If any of the IP is not dispensed, or is lost, stolen, spilled, unusable, or received in a damaged container, this information must be documented and reported to the sponsor and appropriate regulatory agencies, as required.

Upon completion of the study, the IP (partly used, unused, and empty packaging, e.g., vials and tablet bottles) must be left in the original packaging and destroyed on site.

9.11 Labeling and Packaging

Labeling and packaging of IP and placebo will be performed by Alcami, Inc., 1726 North 23rd Str, Wilmington, NC 28405.

9.11.1 Labeling

Kits will have labels affixed that meet the applicable regulatory requirements and may include the kit or randomization number, IP, dosage strength, lot number, protocol number, volume or number of tablets/capsules, caution statement, storage, and sponsor identification.

10 STUDY PROCEDURES

Subjects who are able must provide written informed consent and/or assent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy. As snakebites may constitute life-threatening medical conditions that necessitate urgent intervention, a legally authorized representative may provide consent for subjects who are not able to provide informed consent because of the severity of their condition.

For the timing of assessments and procedures throughout the study, refer to the Schedule of Events (Section 2.2). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the Schedule of Events for each subject. If a subject misses a study visit for any reason, the visit should be rescheduled as soon as possible. In the event that subjects are unable to respond to study visit assessments (i.e., CGI-I, PGIC, PSFS, NPRS, C-SSRS), data from those study visits will be handled as described in Section 10.3.1.

10.1 Study Duration

The overall study duration is expected to be approximately 12 months.

The sequence and duration of the study periods will be as follows:

1. Screening/Enrollment/Treatment Duration: 7 days. As subjects are admitted to ED, screening, enrollment, and treatment will take place on the same day.
2. Follow-up: approximately 21 days (28 days after initial study intervention).

10.2 Study Periods and Visits

10.2.1 sPLA$_2$ and Pharmacokinetics Sample Timing

Note that the sPLA$_2$ and PK sample collection will be performed with a different timing than the other assessments, as described in the Schedule of Events (Table 1).

Specifically, PK sampling will only be performed for a subset of adult and pediatric subjects on Days 1 and 3 and all subjects on Day 7 as described in Section 10.3.2.1. Subjects will be enrolled for PK analysis as follows: Day 1 - 20 subjects, pre-dose and 0.5, 1, 2, 4, 6, 8, and 12 (pre-second dose) hours; Day 3 - 20 subjects, pre-dose and 0.5, 1, 2, 4, 6 hours; Day 7 - all subjects, pre-dose. Special attention should be paid to collection of PK samples on Day 1 of this protocol.

sPLA$_2$ sampling will be performed for all subjects on Day 1 (pre-dose and 1, 3, 6, and 9 hours post-first dose), and on Day 2, Day 3, and Day 7 (pre-dose).

10.2.2 Screening (Enrollment and Baseline)

Because patients are enrolled after a snakebite with envenoming, each subject must be screened, and treated within the first day (Day 1) of the study. Following completion of all assessments and confirmation of eligibility, the subject will be randomized via the IWRS.

The following critical assessments/procedures must be performed at enrollment, prior to initiation of IP treatment: informed consent, inclusion/exclusion criteria review, medical history, physical examination, vital signs, SSS, Head-Lift, NPRS, and pre-dose laboratory blood draws. The following noncritical assessments should be performed as early as possible, but may be performed after randomization and initiation of study drug and SOC if required due to patient condition: demographic information, height/body weight, 12-lead ECG, grip strength, PGIC, CGI-I, and C-SSRS.

The following procedures will be performed at Screening:

- Baseline:
  - Obtain informed consent, either from the subject or a legally authorized representative
  - Review inclusion/exclusion criteria
  - Record prehospital tourniquet use as a snakebite treatment
  - Record hospitalization details
  - Record pulmonary support interventions
  - Perform physical examination
  - Measure vital signs per institutional practice
  - Perform individual assessments pertaining to the SSS (A scoring sheet for use by study personnel is provided in Appendix A; clinical evaluation of the overall SSS [Appendix B] will be performed after completion of the study):
    i. Local wound severity
    ii. Pulmonary severity
    iii. Cardiovascular severity
    iv. Gastrointestinal severity
    v. Hematologic severity (do not wait for laboratory results)
    vi. Renal severity (do not wait for laboratory results)
    vii. Nervous system severity
  - Measure Head-Lift duration (0 to 5 seconds)
  - Perform NPRS
  - Collect blood and urine for the following laboratory assessments:
    i. CBC

ii. Serum chemistry
iii. CK
iv. LFTs
v. eGFR
vi. Hemolysis (Free hemoglobin, haptoglobin, lactate dehydrogenase [LDH])
vii. Prothrombin time (PT), partial thromboplastin time (PTT), thrombin time, INR
viii. Absolute fibrinogen
ix. Urinalysis
x. $sPLA_2$ (see Section 10.2.1)
xi. Urine pregnancy
xii. Serum pregnancy test (subjects of childbearing potential only)
xiii. Biomarkers (C-reactive protein [CRP], and D-dimer)

- Collect samples for PK analysis from subset of subjects (see Section 10.3.2.1)
- Confirm and record details of snakebite envenoming. Obtain photographic documentation where feasible
- Assess and record demographic information (may be performed after randomization treatment should not be delayed)
- Assess and record medical history, including time of bite, current medications (e.g., prescription and nonprescription medications) and therapies including antivenom use and analgesics (may be performed after randomization, treatment should not be delayed)
- Measure weight and height (may be performed after randomization treatment should not be delayed)
- 12-lead ECG (may be performed after randomization treatment should not be delayed)
- Measure grip strength (may be performed after randomization, treatment should not be delayed)
- Perform PGIC (may be performed after randomization, treatment should not be delayed)
- Perform C-SSRS (Baseline/Screening Form; if subject is unable to respond, perform C-SSRS as early as clinically possible on Day 1, screening and randomization should not be delayed for C-SSRS performance)
- In sedated, endotracheally intubated subjects, perform additional assessments according to instructions in Section 10.3.1.7.
- Perform baseline CGI-I. Baseline CGI-I should be assessed compared to patient's previous clinical status.
- Randomize subjects and assign IP to treatment and placebo arms

Procedures for rescreening prospective subjects who initially fail to meet study entry criteria are described in Section 14.3.

10.2.3 Treatment Period

The treatment period is defined as the time of first dose on Day 1 through Day 7. Treatment should be initiated as soon as possible after snakebite envenoming.

The following procedures will be performed on Day 1 of the Treatment Period:

10.2.3.1 Day 1 (Dosing, 0 Hours)

- Administer IP (oral loading dose) (Day 1, 0 Hours) in treatment and placebo arms
- Record time to SOC and IP intervention
- Record details (type, brand, number of vials) of antivenom use from the point of the index snakebite through the completion of all antivenom use for this patient
- Record hospitalization details
- Record pulmonary support interventions
- Record any concomitant therapy
- Assess and record any AEs

10.2.3.2 Day 1 (1 Hour)

- Perform CGI-I (assess compared to Baseline CGI-I)

10.2.3.3 Day 1 (2 Hours)

- Perform CGI-I (assess compared to Baseline CGI-I)

10.2.3.4 Day 1 (3 to 4 Hours)

- Perform CGI-I (assess compared to Baseline GGI-I)
- Measure vital signs per institutional practice
- Perform individual assessments pertaining the SSS, prior to administration of repeat doses of antivenom, if required (clinical evaluation of the actual SSS point score will be performed after completion of the study):
  - Local wound severity

- Pulmonary severity
- Cardiovascular severity
- Gastrointestinal severity
- Hematologic severity
- Renal severity
- Nervous system severity

- Measure Head-Lift duration (0 to 5 seconds)
- Perform NPRS
- Measure grip strength
- Collect blood and urine for the following laboratory assessments:
  - CBC
  - Serum chemistry
  - Hemolysis (Free hemoglobin, haptoglobin, LDH)
  - PT, PTT, thrombin time, INR
  - Absolute fibrinogen
  - CK
  - $sPLA_2$ levels at 3 hours post-dose as described in Section 10.2.1
- Record concomitant medications and therapies (e.g., prescription and nonprescription medications, pain medications)
- Perform PGIC
- In sedated, endotracheally intubated subjects, perform additional assessments according to instructions in Section 10.3.1.7.
- Collect PK samples from subset of subjects as described in Section 10.3.2.1
- Record SOC treatment
- Record hospitalization details
- Record pulmonary support interventions
- Assess and Record AEs

10.2.3.5 Day 1 (5 to 6 Hours)

- Measure vital signs per institutional practice

- Perform individual assessments pertaining the SSS, prior to administration of repeat doses of antivenom, if required (clinical evaluation of the actual SSS point score will be performed after completion of the study):
  - Local wound severity
  - Pulmonary severity
  - Cardiovascular severity
  - Gastrointestinal severity
  - Hematologic severity
  - Renal severity
  - Nervous system severity
- Measure Head-Lift duration (0 to 5 seconds)
- Perform NPRS
- Measure grip strength
- Collect blood and urine for the following laboratory assessments:
  - CBC
  - Serum chemistry
  - LFTs
  - Hemolysis (Free hemoglobin, haptoglobin, LDH)
  - PT, PTT, thrombin time, INR
  - Absolute fibrinogen
  - CK
  - $sPLA_2$ levels at 6 hours post-dose as described in Section 10.2.1
- Record concomitant medications and therapies (e.g., prescription and nonprescription medications, pain medications)
- Perform CGI-I
- Perform PGIC
- In sedated, endotracheally intubated subjects, perform additional assessments according to instructions in Section 10.3.1.7.
- Collect PK samples from subset of subjects as described in Section 10.3.2.1
- Continue SOC treatment
- Record hospitalization details

- Record pulmonary support interventions
- Assess and record AEs

10.2.3.6 Day 1 (8 to 10 Hours)

- Measure vital signs per institutional practice
- Perform individual assessments pertaining the SSS, prior to administration of repeat doses of antivenom, if required (clinical evaluation of the actual SSS point score will be performed after completion of the study):
  - Local wound severity
  - Pulmonary severity
  - Cardiovascular severity
  - Gastrointestinal severity
  - Hematologic severity
  - Renal severity
  - Nervous system severity
- Measure Head-Lift duration (0 to 5 seconds)
- Perform NPRS
- 12-lead ECG
- Measure grip strength
- Collect blood and urine for the following laboratory assessments:
  - CBC
  - Serum chemistry
  - Hemolysis (Free hemoglobin, haptoglobin, LDH)
  - PT, PTT, thrombin time, INR
  - Absolute fibrinogen
  - CK
  - $sPLA_2$ levels as described in Section 10.2.1
  - Biomarkers (CRP, and D-dimer)
- Perform CGI-I
- Perform PGIC

- In sedated, endotracheally intubated subjects, perform additional assessments according to instructions in Section 10.3.1.7.
- Perform PSFS
- Collect PK samples from subset of subjects as described in Section 10.3.2.1
- Record concomitant medications and therapies (e.g., prescription and nonprescription medications, pain medications)
- Continue SOC treatment
- Record hospitalization details
- Record pulmonary support interventions
- Assess and record AEs

10.2.3.7 Day 2

- Continue BID oral treatment with the IP
- Perform physical examination
- Measure vital signs per institutional practice
- Perform individual assessments pertaining the SSS (clinical evaluation of the actual SSS point score will be performed after completion of the study):
  - Local wound severity
  - Pulmonary severity
  - Cardiovascular severity
  - Gastrointestinal severity
  - Hematologic severity
  - Renal severity
  - Nervous system severity
- Measure Head-Lift duration (0 to 5 seconds)
- Perform NPRS
- Measure grip strength
- Collect blood and urine for the following laboratory assessments:
  - CBC
  - Serum chemistry

- LFTs
- Hemolysis (Free hemoglobin, haptoglobin, LDH)
- PT, PTT, thrombin time, INR
- Absolute fibrinogen
- CK
- Urinalysis
- $sPLA_2$ levels as described in Section 10.2.1
- Biomarkers (CRP, and D-dimer)

- Perform CGI-I
- Perform PGIC
- Perform PSFS
- Assess C-SSRS (Frequent Screening Form)
- In sedated, endotracheally intubated subjects, perform additional assessments according to instructions in Section 10.3.1.7
- Record concomitant medications and therapies (e.g., prescription and nonprescription medications, pain medications)
- Continue SOC treatment
- Record hospitalization details
- Record pulmonary support interventions
- Assess and Record AEs

10.2.3.8 Day 3

- Continue BID oral treatment with the IP
- Perform physical examination
- Measure vital signs per institutional practice
- Perform individual assessments pertaining the SSS (clinical evaluation of the actual SSS point score will be performed after completion of the study):
  - Local wound severity
  - Pulmonary severity
  - Cardiovascular severity

  - Gastrointestinal severity
  - Hematologic severity
  - Renal severity
  - Nervous system severity
- Measure Head-Lift duration (0 to 5 seconds)
- Perform NPRS
- Measure grip strength
- Collect blood and urine for the following laboratory assessments:
  - CBC
  - Serum chemistry
  - LFTs
  - CK
  - Hemolysis (Free hemoglobin, haptoglobin, LDH)
  - PT, PTT, thrombin time, INR
  - Absolute fibrinogen
  - Urinalysis
  - $sPLA_2$ levels as described in Section 10.2.1
  - Biomarkers (CRP, and D-dimer)
- Collect PK samples from subset of subjects as described in Section 10.3.2.1
- Perform CGI-I
- Perform PGIC
- Perform PSFS
- Assess C-SSRS (Frequent Screening Form)
- In sedated, endotracheally intubated subjects, perform additional assessments according to instructions in Section 10.3.1.7
- Record concomitant medication and therapies (e.g., prescription and nonprescription medications, pain medications)
- Continue SOC treatment
- Record hospitalization details
- Record pulmonary support interventions

- Assess and Record AEs

10.2.3.9 Day 7 (7 Days ± 1 Day)

- Continue BID oral treatment with the IP
- Perform physical examination
- Measure vital signs per institutional practice
- Perform individual assessments pertaining the SSS (clinical evaluation of the actual SSS point score will be performed after completion of the study):
  - Local wound severity
  - Pulmonary severity
  - Cardiovascular severity
  - Gastrointestinal severity
  - Hematologic severity
  - Renal severity
  - Nervous system severity
- Measure Head-Lift duration (0 to 5 seconds)
- Perform NPRS
- 12-lead ECG
- Measure grip strength
- Collect blood and urine for the following laboratory assessments:
  - CBC
  - Serum chemistry
  - LFTs
  - PT, PTT, thrombin time, INR
  - Absolute fibrinogen
  - Urinalysis
  - $sPLA_2$ levels as described in Section 10.2.1
  - Biomarkers (CRP, and D-dimer)
- Collect PK samples from all subjects as described in Section 10.3.2.1
- Perform CGI-I

- Perform PGIC
- Perform PSFS
- Assess C-SSRS (Since Last Visit Form)
- In sedated, endotracheally intubated subjects, perform additional assessments according to instructions in Section 10.3.1.7
- Record concomitant medications and therapies (e.g., prescription and nonprescription medications, pain medications)
- Continue SOC treatment
- Record hospitalization details
- Record pulmonary support interventions
- Assess and Record AEs

10.2.3.10 Day 14 (14 Days ± 2 Days)

- Perform physical examination
- Measure vital signs per institutional practice
- Perform individual assessments pertaining the SSS (clinical evaluation of the actual SSS point score will be performed after completion of the study):
  - Local wound severity
  - Pulmonary severity
  - Cardiovascular severity
  - Gastrointestinal severity
  - Hematologic severity
  - Renal severity
  - Nervous system severity
- Measure Head-Lift duration (0 to 5 seconds)
- Perform NPRS
- Measure grip strength
- Collect blood and urine for the following laboratory assessments:
  - CBC
  - Serum chemistry

- PT, PTT, thrombin time, INR
- Absolute fibrinogen
- Biomarkers (CRP, and D-dimer)

- Perform CGI-I
- Perform PGIC
- Perform PSFS
- Assess C-SSRS (Since Last Visit Form)
- Record medical history, including current medications and therapies (e.g., prescription and nonprescription medications, pain medications)
- Continue SOC treatment
- Record hospitalization details
- Record pulmonary support interventions
- Assess and Record AEs

10.2.3.11 Day 28 (End of Study Visit)

- Perform physical examination
- Measure vital signs per institutional practice
- Measure body weight
- Perform individual assessments pertaining the SSS (clinical evaluation of the actual SSS point score will be performed after completion of the study):
  - Local wound severity
  - Pulmonary severity
  - Cardiovascular severity
  - Gastrointestinal severity
  - Hematologic severity
  - Renal severity
  - Nervous system severity
- Measure Head-Lift duration (0 to 5 seconds)
- Perform NPRS
- 12-lead ECG

- Measure grip strength
- Collect blood and urine for the following laboratory assessments:
  - CBC
  - PT, PTT, thrombin time, INR
  - Absolute fibrinogen
  - Serum chemistry
  - LFTs
  - Urinalysis
  - Serum pregnancy test (subjects of childbearing potential only)
- Perform CGI-I
- Perform PGIC
- Perform PSFS
- Assess C-SSRS (Since Last Visit Form)
- Record concomitant medications and therapies (e.g., prescription and nonprescription medications, pain medications)
- Continue SOC treatment
- Record hospitalization details
- Record pulmonary support interventions
- Assess and Record AEs

10.3 Assessments

10.3.1 Efficacy Assessments

Assessments used in this protocol include additional bedside assessments for endotracheally intubated subjects, the SSS, the CGI-I, the PGIC, the PSFS, the NPRS, grip strength, Head-Lift duration, and analgesic use. Each study subject will be evaluated using the PGIC, PSFS, grip strength, or NPRS at the timepoints indicated in the Schedule of Events (Table 1). The SSS evaluation is provided as a checklist in Appendix A and B; all other forms and assessments are provided in Appendix C.

Acute changes in a patient's clinical status that occur during the first 24 hours, including the period between enrollment and administration of IP, but outside of a "Scheduled Assessment" timepoint should be recorded as "Unscheduled Visit" in ePRO or EDC systems, as appropriate.

Individuals that cannot respond to 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

Missing measurements of the SSS at 6 or at 9 hours won't be replaced for the purpose of calculating the primary outcome. If the SSS at one of these timepoints is missing, the average SSS will be based solely on the SSS recorded for the other time point.

10.3.1.1 Composite Snakebite Severity Scale

The SSS (Dart RC et al., 1996) is a tool that was developed to measure the severity of envenoming based on 6 body system categories. The composite SSS score to be used, herein, is based on 7 categories and includes respiratory paralysis, acute renal failure, major thrombotic events, and death.

The renal system category will be used to characterize the severity of acute renal injury (scoring provided in appendix B). The baseline value for serum creatinine will be defined as the most recent serum creatinine in the past year, if one is available, or as the normal expected value for the patient.

Severe weakness or paralysis, including respiratory paralysis, will be scored a 3 in the nervous system section. Major thrombotic events will be scored in the appropriate SSS category as clinically presented. Death will be scored as the maximum score in each section.

The seven body systems are included as follows:

- Local wound (e.g., pain, swelling and ecchymosis)
- Pulmonary
- Cardiovascular
- Gastrointestinal
- Hematologic
- Nervous system
- Renal

Each of these 7 categories are graded at levels from Grade 0 to Grade 3 (pulmonary, cardiovascular, gastrointestinal, nervous, and renal systems) or Grade 0 to Grade 4 (local wound and hematologic symptoms). A higher score indicates worse signs or symptoms. SSS scores will be performed by study personnel using the scoring sheet provided in Appendix B. At each assessment timepoint, each of the 7 SSS subscores should be recorded and a justification for each score should be provided.

10.3.1.2 Clinical Global Impression-Improvement

The CGI-I provides a clinician-based overall rating of the patient's condition (i.e., severity, distress, impairment and impact on functioning) in comparison to previous clinical status. The CGI-I should be determined using all available information, such as interviews with patients and family members, reports from other providers (including prehospital and transfer reports), medical records, and prior laboratory data (Busner and Targum, 2007) (Appendix C1). Baseline rating should be in comparison to previous patient status. Additional CGI-I should be performed on Day 1 at 1, 2, and 3 hours post initial dose, then follow normal assessment schedule as provided in the Schedule of Events. All post-baseline CGI-I assessments should be compared to baseline CGI-I.

The CGI-I is defined as a selection of one of the following at each assessment period:

1 = very much improved since the initiation of treatment
2 = much improved
3 = minimally improved
4 = no change from baseline (the initiation of treatment)
5 = minimally worse
6 = much worse
7 = very much worse since the initiation of treatment

10.3.1.3 Patient Global Impression of Change Scale

The PGIC (Appendix C2) is a short, widely used, qualitative metric to evaluate a subject's belief regarding the efficacy of treatment. This metric consists of a question asking the subject to score their overall change in symptoms, followed by a question regarding the degree of change.

10.3.1.4 Patient-Specific Functional Scale

The PSFS (Appendix C3) is a questionnaire that can be used to quantify activity limitation and measure functional outcome for patients. The clinician asks each subject to identify up to 3 activities that they are unable to perform due to their medical condition, and asks the subject to rate their ability to perform that activity on a scale from 0 (unable to perform) to 10 (able to perform to the same ability as before the medical condition).

10.3.1.5 Numeric Pain Rating Scale

The NPRS is a numerical metric that is used by patients to evaluate pain they are experiencing. The NPRS may be adapted or replaced as necessary for pediatric subjects (Appendix C4).

10.3.1.6 Columbia-Suicide Severity Rating Scale

The C-SSRS is a short questionnaire, available in 114 languages, that is designed to provide suicide risk assessment. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale and patients indicating ideation of self-harm at any point in the study should be evaluated and treated per institutional practice.

Generally, the C-SSRS should be administered at Baseline, or at the earliest time point clinically allowable (ideally on Day 1) and then at every study visit through Day 28. For the sake of this clinical study, modified versions of the C-SSRS will be administered at different study visits to minimize burden on study subjects. The modified C-SSRS forms are provided in Appendix C5 as the "C-SSRS Baseline/Screening Form" and the "C-SSRS Since Last Visit Form." These modified C-SSRS forms should be administered to subjects as follows:

- The C-SSRS Baseline/Screening Form should be administered at Baseline (on Day 1) or as early as clinically allowable, performance should not delay care,
- The C-SSRS Since Last Visit Form should be administered for the remaining visits on Days 2, 3, 7, 14, and 28.

10.3.1.7 Additional Assessments on Endotracheally Intubated Subjects

For SSS nervous system examination in endotracheally intubated patients:

1. Record current mechanical ventilation modes and all relevant ventilator settings; e.g. control mode ventilation, weaning mode ventilation, or independent breathing without any support. Commonly used ventilatory modes are listed in Appendix C7.
2. Remove sedation (*and* if applicable, paralytics) sufficiently early for awake examination (e.g. until patient is sufficiently awake to follow commands) per institutional practice
3. In subjects able to respond and follow commands
    a. Once subject is sufficiently alert, record time from removal of sedation to examination and describe the level of alertness/sedation per institutional practice. If a sedation score is typically used, it should be recorded and the scoring system used should be specified.
    b. Measure Head-Lift duration in the same manner as for non-intubated subjects. With the patient supine on a flat bed, ask the subject to raise head approximately

8 cm off the bed. Record the duration of time that the subject can lift and hold head approximately 8 cm off the bed, up to a maximum of 5 seconds.

c. Perform and record the SSS.

4. In subjects who are unable to achieve an acceptable level of alertness 60 minutes after discontinuation of sedation (*and* if applicable, paralytics), record SSS and Head-Lift duration.

5. In subjects who meet institutional weaning criteria, record mode and settings of mechanical ventilation as listed in Appendix C7 to indicate the level of support/independence to which they have progressed.

6. In subjects who meet institutional criteria for immediate extubation but deferred or postponed as per institutional practice (e.g., meets criteria for extubation at night but not extubated until the next day), note patient status and record mode and settings of mechanical ventilation (see Appendix C7).

7. If used per institutional practice, record negative inspiratory force (NIF)/maximum inspiratory pressure (MIP).

10.3.1.8 Grip Strength

Grip strength will be evaluated using a dynamometer, as a measure of the severity of the neurological effects of snakebite. Grip strength should be measured in affected hand if the bite occurred in upper extremity or the dominant hand if bite occurred elsewhere.

10.3.1.9 Head-Lift duration

Patient should be supine on flat bed. Ask patient to lift their head approximately 8 cm off of bed. Measure the duration in seconds that the patient can hold their head approximately 8 cm off of the bed. Stop after 5 seconds (i.e. maximum duration is 5 seconds).

10.3.1.10 Analgesic Use

For each assessment time point, the patient's current analgesic use will be characterized by the clinical research team based on the strongest category of analgesic taken to treat snakebite-related pain.

10.3.2 Pharmacokinetics

10.3.2.1 Pharmacokinetic Analysis Methods

The concentration of varespladib-methyl in plasma will be evaluated in a subset of both adult and pediatric subjects on Days 1 and 3 and in all subjects on Day 7. PK sampling will only be performed for a total of 20 adult and pediatric subjects on Days 1 and 3, and all subjects on Day 7. Once 20 subjects have provided PK samples for Days 1 and 3, sites will be notified by the

sponsor to discontinue Day 1 and 3 PK sampling. Efforts will be made to include at least 4 pediatric subjects from each age tier (5 to < 11, 11 to < 18 years old) in the PK analysis. PK samples will be collected on Days 1 and 3 as follows:

- Day 1 (20 adult and pediatric subjects): pre-dose and 0.5, 1, 2, 4, 6, 8, and 12 (pre-second dose) hours post-dose.
- Day 3 (20 adult and pediatric subjects): pre-dose and 0.5, 1, 2, 4, and 6 hours post-dose.
- Day 7 (all 110 subjects): pre-dose.

The PK characterization of drug concentrations for each dose to be profiled will use noncompartmental analysis (NCA). Additional details of the parameters and their calculation and evaluation is included in the Statistical Analysis Plan (SAP).

10.3.2.2 Pharmacokinetic Parameters

Standard PK parameters assessed will include measures of the extent of absorption using estimates of the area under the curve (AUC), maximum plasma concentration and rate-of-absorption using the maximum concentration (C_{max}), and the time of C_{max} (T_{max}), respectively.

10.3.2.3 Sample Collection

Samples will be collected at the time points specified in Section 10.3.2.1 and the Schedule of Events (Section 2.2).

Blood

The total amount of blood to be collected will include samples for CBC, renal function tests, liver function test, coagulation profile, and biomarkers, $sPLA_2$ levels, and plasma drug levels. Blood volumes should be adjusted as necessary for pediatric subjects.

Urine

Mid-stream or catheter urine collected for dipstick urinalysis. Urinalysis should not delay care and should not be obtained by catheter unless patient already being catheterized. Urine should not be collected from a bag, but rather from proximal port.

10.3.3 Safety Variables

Safety will be assessed by evaluating AEs, vital sign measurements, clinical laboratory test results, 12-lead ECGs, physical examination findings, and concomitant medications and therapies.

10.3.3.1 Clinical Laboratory Safety Assessments

10.3.3.1.1 Clinical Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points indicated in the Schedule of Events (Table 1).

Complete blood count (CBC):	White blood cell count including differential, hemoglobin/hematocrit, platelets
Liver function:	Albumin, total and indirect bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, LDH
Serum chemistry:	Sodium, potassium, chloride, bicarbonate, creatinine, BUN, eGFR
Hemolysis	Free hemoglobin, haptoglobin, LDH
Myonecrosis	CK
Coagulation:	PT, PTT, absolute fibrinogen, INR
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones
Other:	$sPLA_2$ and biomarkers (CRP, D-dimer)
Serum pregnancy test:	evaluated for subjects of childbearing potential only

Routine laboratory specimens will be analyzed at local laboratories, as specified in the study laboratory manual. A central laboratory will be used for nonstandard assays.

10.3.3.1.2 Evaluation of Clinical Laboratory Values

Each local laboratory will provide the normal ranges of values for the clinical laboratory assessments in this study, and the local ranges will be regarded as the reference ranges on which decisions will be made by each Investigator.

If a laboratory value is out of the reference range, it is not necessarily clinically relevant. The Investigator must evaluate the out-of-range values and record his or her assessment of the clinical relevance in the appropriate eCRF.

All clinical laboratory values that in the Investigator's opinion show clinically relevant or pathological changes during or after termination of treatment must be reported as AEs and followed, as described in Section 11.2.5.

10.3.3.2 Clinical Examinations

10.3.3.2.1 Vital Signs

Vital signs will be assessed and recorded at the timepoints indicated in the Schedule of Events (Table 1) per institutional practice. In addition, body temperature will be measured and recorded every 4 to 8 hours during hospitalization.

10.3.3.2.2 Twelve-lead Electrocardiogram

A standard 12-lead ECG will be performed at the timepoints indicated in the Schedule of Events (Table 1) per institutional practice. All ECG recordings will be identified with the subject identification, date, and time of the recording and will be attached to the subject's eCRF.

10.3.3.2.3 Physical Examination

A physical examination will be performed at the timepoints indicated in the Schedule of Events (Table 1) per institutional practice.

10.3.3.2.4 Neurological Assessment

For sedated, endotracheally intubated subjects, a separate neurological assessment will be performed according to Section 10.3.1.7.

10.3.3.3 Adverse Events

The definitions and management of AEs, and any special considerations for AEs, are provided in Section 11.

11 ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered an IP that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether related to the medicinal product, or not.

Pre-existing diseases or conditions will **not** be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. Worsening of a pre-existing condition is considered an AE. Abnormal laboratory values related to liver and renal function that are deemed clinically significant by the investigator will always be considered as AEs if they have worsened from baseline. Any other laboratory values that are judged by the site investigator to be wholly caused by the snakebite envenoming will be regarded as AEs at the discretion of the investigator.

Events that occur in subjects treated with control product (SOC), or during treatment-free periods of the study, are also considered AEs.

11.1.2 Unexpected Adverse Event

An expected AE is one for which the nature or severity is consistent with the known AE profile of the product. For a pre-approval test product, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected adverse event (UAE) is one for which the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved IP or package insert/summary of product characteristics for an approved product). For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events. Examples would be (a) acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis (interstitial nephritis would be unexpected) and (b) hepatitis with a first occurrence of fulminant hepatitis (fulminant hepatitis would be unexpected.)

11.1.3 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
  An elective hospital admission to treat a condition present before exposure to the IP, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly
  NOTE: A congenital anomaly in an infant born to a mother who was exposed to the IP during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received an IP is not considered an SAE unless it is suspected that the IP(s) interacted with a contraceptive method and led to the pregnancy.
- Is an important medical event
  NOTE: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, development of drug dependency, or drug abuse.

11.1.4 Treatment-Emergent Adverse Events

An AE is defined as treatment-emergent if the first onset or worsening is during or after the first administration of IP and not more than 30 days after the last administration of IP.

11.2 Event Assessment and Follow-Up of Adverse Events

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution or stabilization.

Any medical condition that is present at the time that the subject is screened will be considered as Baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE, or an AE that is intermittent, will be documented as separate AEs to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Site staff will record all reportable AEs with start dates occurring any time after informed consent is obtained until 28 days after the last day of study participation. At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit.

11.2.1 Assessment

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The Investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

11.2.2 Evaluation

11.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as:

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.3.

11.2.2.2 Seriousness

The Investigator is to evaluate whether the AE meets serious criteria, as described in Section 11.1.3.

11.2.2.3 Action(s) Taken

Action(s) taken may consist of:

IP interrupted	IP schedule was modified by temporarily terminating the prescribed regimen of IP.
IP withdrawn	IP schedule was modified through termination of IP.
Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.

11.2.2.4 Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*Fatal should only be selected as an outcome when the AE results in death. If more than one AE is judged to be possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.2.2.5 Adverse Event Relationship to Investigational Product

The Investigator must assess each AE's relationship to the IP. The Investigator must carefully consider possible manifestations of snakebite when assigning a relationship of specific AEs to study drug. The categories for classifying the Investigator's opinion of the relationship are as follows:

Definitely	A definite probability exists of a relationship between the AE and IP.
Probably	A reasonable probability exists of a relationship between the AE and IP.
Possibly	A possibility exists of a relationship between the AE and IP.
Unrelated	No reasonable possibility exists of a relationship between the AE and IP.

11.2.3 Documentation

All AEs that occur within the period of observation for the study must be documented in the CRF with the following information, where appropriate. (The period of observation for the study is described in Section 11.2.)

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to the IP

11.2.4 Treatment of Adverse Events

AEs that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the decision about whether the subject may continue in the study will be made by the sponsor after consultation with the Investigator and/or medical monitor.

If AEs occur in a subject that are not tolerable, the Investigator must decide whether to stop the subject's involvement in the study and/or treat the subject. Special procedures may be recommended for the specific IP, such as the collection of a serum sample for determining blood concentrations of IP, specific tapering procedures, or treatment regimens, as appropriate.

For double-blinded studies, it is not necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 9.6 for a description of the unblinding procedures.

11.2.5 Follow-Up

Any AE will be followed (up to a maximum of 30 days after the last dose of IP) to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the eCRF page.

11.2.6 Reporting

11.2.6.1 Serious Adverse Events

The Investigator or designee must report all SAEs promptly to the study CRO within 24 hours of first becoming aware of the event by completing, signing and dating the SAE Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE form to the study CRO. SAEs from North America should be sent to: [redacted] SAEs from the rest of the world should be sent to: [redacted] This written report should be submitted on the SAE form provided for this purpose. At the time of first notification, the Investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and Investigator)
- Subject's study number
- Subject's year of birth
- Subject's sex
- Date of first dose of IP(s)
- Date of last dose of IP(s), if applicable
- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to IP(s) ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")
- Whether and when the Investigator was unblinded as to the subject's treatment assignment

Any missing or additional relevant follow-up information concerning the SAE should be sent to the sponsor/sponsor representative via the same contact details above as soon as possible on a follow-up SAE Report Form, together with the following minimal information (initial report,

AEs, date of occurrence, subject identification (ID), study ID, IP, and site number); this will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by the study CRO using a follow-up request form or via email communication.

The Investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his or her health authorities, institutional review board (IRB), principal and coordinating Investigators, study Investigators, and institutions. Each Investigator is obligated to learn about the reporting requirements for Investigators in his/her country. The study monitor can assist with this.

11.3 Special Considerations

11.3.1 Adverse Events of Special Interest

Investigators should specifically monitor several AEs associated with varespladib treatment, including cerebrovascular accident (CVA; stroke), MI, and malignant cardiac arrhythmias. However, these AEs may also be associated with many snakebites.

11.3.2 Pregnancy

All subjects of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during treatment. Subjects should be instructed to contact the Investigator or study staff immediately if pregnancy occurs or is suspected.

Participants of reproductive potential must agree to use a highly effective method of contraception from the time of consent and for 14 days following his or her last dose of IP. Highly effective methods of contraception are as follows:

- combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
- intrauterine device, intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence
- double-barrier method (condoms, sponge, diaphragm, with spermicidal jellies, or cream).

Pregnancy testing will be conducted prior to administration of the IP on every subject of childbearing potential. A subject who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

A subject who becomes pregnant during IP treatment will be immediately discontinued from receiving the study drug. The Investigator must report the pregnancy within 72 hours of learning of the pregnancy, to the study CRO pharmacovigilance team using the Pregnancy Data Collection Form via the same fax number and/or email address as for SAE reporting. The Investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on a pregnancy form provided by the sponsor or its designee.

The Investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on a pregnancy form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

11.3.3 Overdosage

As with any overdose, patients should be monitored closely and observed for expected and unexpected clinical and laboratory effects.

No specific antidote to varespladib or varespladib-methyl exists, so treatment should be directed at supportive care.

In the presence of normal hepatic and renal function, blood levels of varespladib would be expected to rapidly diminish. Clinical and laboratory effects of varespladib overdose, however, may be delayed and patients should be monitored until all such effects have resolved.

Based on preclinical toxicology studies, acute renal failure may result from high plasma levels of varespladib. Renal toxicity studies performed in rats suggest that forced diuresis may diminish the extent of renal injury following bolus administration of varespladib-methyl. No data in humans are available to support forced diuresis as a potential therapy. However, as the toxicity of many potential nephrotoxins can be diminished by increased urine flow rates, fluid or mannitol administration to promote diuresis may be reasonable in the setting of a varespladib-methyl overdose. In circulation, varespladib is highly (approximately 90%) protein bound. Studies to determine if hemodialysis or hemoperfusion would be of benefit in patients with varespladib-methyl overdose have not been performed.

12 DATA SAFETY MONITORING BOARD

The data safety monitoring board (DSMB) will operate under a charter that will be finalized prior to the start of the study. The DSMB will evaluate the safety data, including summaries by group, 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 in a particular dose group. If toxicity is observed, the treatment assignment for the subject(s) involved may be unblinded by the DSMB at its discretion.

13 STATISTICS

13.1 Statistical Analysis

This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

Descriptive statistical methods will be used to summarize the data from this study with confidence intervals calculated for the primary and secondary efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to the number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum for continuous data; and frequencies and proportions for categorical data. All data collected during the study will be included in data listings.

P-values of less than 0.05 will be considered statistically significant based on a 2-sided test unless otherwise specified.

All statistical analyses will be conducted with the SAS® System, version 9.3 or higher.

13.1.1 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 analysis.
- **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.

13.1.2 Study Subjects and Demographics

13.1.2.1 Disposition and Withdrawals

The numbers of subjects randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number of subjects in each analysis population will be reported.

13.1.2.2 Protocol Deviations

Protocol deviations will be identified and classified as minor or major for statistical analysis purposes before unblinding and will be summarized or listed as appropriate. Key protocol deviations will be used to exclude subjects from the PP population. Due to the Coronavirus Disease 2019 (COVID-19) global health crisis, study visits and protocol-defined procedures may be impacted; COVID-19-related protocol deviations are discussed in Appendix D.

13.1.2.3 Demographics and Other Baseline Characteristics

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

Demographic variables will include age, sex, height, and weight. Information on race and ethnicity will be collected for any eventual analysis of differences in response to the IP, in accordance with local regulatory requirements. Baseline subject characteristics will include medical history and physical examination findings.

Prior and concomitant medications will be summarized by treatment group, by the number and percentage of subjects taking each medication, classified using World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical classes and preferred terms.

13.1.3 Exposure and Compliance

IP exposure and dosing information including the number of doses and amount of IP received will be listed for each subject.

13.1.4 Efficacy Analysis

13.1.4.1 Primary Efficacy Endpoints

Statistical analysis of efficacy will be assessed by an improvement in the composite SSS (See SAP for SSS scale; Individual Category Severity Assessments: Pulmonary, Cardiovascular, Hematologic Symptoms, Renal, and Nervous Systems) from Baseline (pre-dosing) to 6 and 9 hours after first dose, where the average of the 6- and 9-hour scores are used as the post treatment value: Change = (Baseline – [6hr + 9hr]/2). Subjects that die before recording a 6 or 9 hour SSS measurement will be assigned the worst possible score when analyzing the primary endpoint. Missing measurements of the SSS at 6 or at 9 hours won't be replaced for the purpose of calculating the primary outcome. If the SSS at one of these timepoints is missing, the average SSS will be based solely on the SSS recorded for the other time point.

13.1.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are to evaluate the:

- AUC of the pulmonary, cardiovascular, hematologic symptoms, renal, and nervous system sections of the SSS from Baseline through Day 7
- Complete SSS from Baseline 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, creatine kinase (CK), from Baseline through Day 3
- Numeric Pain Rating Scale (NPRS) score in patients able to respond from Baseline through Day 28
- Kidney function markers from Baseline through Day 28
- Total differential antivenom requirement 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
- Clinical Global Impression-Improvement (CGI-I) from Baseline through Day 7
- Patient Global Impression of Change (PGIC) from Baseline through Day 7
- Patient-Specific Functional Scale (PSFS) total score from Baseline through Day 28

13.1.4.3 Exploratory Endpoints

The exploratory efficacy endpoints are to evaluate the:

- Change in the SSS from Baseline through Day 7 using compressed SSS scale
- SSS from Baseline through Day 28 after first dose
- 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
- Complete blood count (CBC) through all SSS evaluation days
- Transfusion requirement from Baseline (Day 1) through Day 28
- C-reactive protein (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 patients 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

13.1.4.4 Primary Analysis

The ITT and PP analysis populations will be used to analyze the primary efficacy endpoint. The ITT population will be the primary population for the efficacy analyses.

Descriptive statistics for the SSS score will be tabulated by treatment group. A detailed scoring algorithm of the SSS score will be given in the SAP.

The SSS score will be compared between treatment groups within an analysis of covariance model (ANCOVA) with the baseline SSS score, age group (5 to < 18 and ≥ 18 years), neurological system score ≥2 (Yes or No), and completion of the initial dose of antivenom prior to initiation of study drug (Yes or No) as covariates. The comparison of varespladib-methyl to placebo (varespladib-methyl vs placebo) will be tested at 5% two-sided significance level, the corresponding 95% two-sided confidence intervals will be presented. The null hypothesis for the ANCOVA model is given below.

- H_0: There is no difference in the change from baseline SSS (based on the Pulmonary, Cardiovascular, Hematologic, Renal and Nervous System subscores) to the SSS (based on those same 5 subscores) average at the 6- and 9-hour timepoints for subjects receiving SOC plus varespladib-methyl vs subjects receiving SOC plus placebo.

Summary statistics and ANCOVA model results will also be presented separately within pediatric (5 to < 18 years) and adult (≥ 18 years) subjects. Additional pediatric subgroups may be considered in a posthoc analysis depending on the total number of pediatric subjects that enroll in the study. For the subgroup analyses, age group will not be included as a covariate in the ANCOVA model. If an adequate number of pediatric subjects do not enroll in the study to fit an ANCOVA model, only summary statistics will be presented.

13.1.4.5 Secondary Analyses

Analysis of the secondary endpoints will be carried out for the ITT population.

All secondary endpoints will be summarized using frequencies and percentages for categorical endpoints, and numeric summary statistics for quantitative endpoints.

Additional ANCOVA or a repeated measures model (MMRM) analyses will be considered for quantitative secondary endpoints.

All-cause mortality will be analyzed using Kaplan-Meier methods.

PGI-C and CGI-I responders will be summarized by frequency and percentage at each visit within treatment group. The difference in treatment response will be analyzed using a logistic regression model at each visit with baseline SSS score, age group (5 to < 18 and ≥ 18 years), neurological system subscore ≥2 (Yes or No), and completion of the initial dose of antivenom prior to initiation of study drug (Yes or No) as covariates.

Additional details of the efficacy analyses will be given in the final SAP.

13.1.4.6 Exploratory, Corroborative, Sensitivity, and Other Analyses

Exploratory endpoint efficacy data will be summarized descriptively by visit within treatment groups.

Endpoints will also be analyzed in the subset of study participants who are enrolled prior to the completion of the first dose of antivenom and in the subset of study participants who are enrolled after the completion of the first dose of antivenom. Additional details will be provided in the SAP.

All $sPLA_2$ from beginning of IP dosing to discharge will be presented and used to calculate maximum concentrations in both treatment groups and compare concentration-time curves using a nonlinear regression to quantify a change in the half-maximal effective concentration (EC_{50}) and its confidence interval, and to compute a *p*-value that tests the null hypothesis that there is no difference between curves.

13.1.5 Clinical Pharmacology Analyses

13.1.5.1 Pharmacokinetics

For noncompartmental analysis, plasma concentrations will be listed and summarized at each time point using descriptive statistics; graphical representations will also be provided. The PK parameters will be summarized by dose using descriptive statistics. Testing of PK parameters will be outlined in the SAP.

13.1.6 Safety and Tolerability Analyses

All safety analyses will be performed on the Safety Population.

The variables for safety endpoints are TEAEs, vital signs, laboratory evaluations, 12-lead ECGs, physical examinations, and concomitant medications and therapies.

13.1.6.1 Adverse Events

Treatment-emergent AEs are defined as AEs that first occur or worsen in severity after the first dose of IP and prior to the 30 days after last administration of IP. AEs will be coded using the Medical Dictionary for Regulator Activities (MedDRA). For each treatment group, the number of TEAEs and incidence rates will be tabulated by preferred term and System Organ Class.

Treatment-emergent AEs will be summarized for each treatment group based on frequency, maximum severity, relationship to IP, SAEs, TEAEs leading to death, and TEAEs leading to discontinuation of IP.

13.1.6.2 Clinical Laboratory Evaluations

All serum chemistry, hematology, urinalysis, liver function tests, coagulation profile measurements, biomarker levels, and $sPLA_2$ levels will be summarized for each treatment group using descriptive statistics by visit for observed values and changes from Baseline.

Shift tables for measurements described above, summarizing the shifts from Baseline (high; normal; low) at each post-Baseline visit, will be presented.

13.1.6.3 Vital Signs

All vital signs will be summarized for each treatment group using descriptive statistics at each visit for raw numbers and change from Baseline.

13.1.6.4 12-lead Electrocardiograms

All ECG measurements will be summarized for each treatment group using descriptive statistics by visit for raw numbers and change from Baseline.

Additionally, frequencies and percentages of Investigator ECG interpretations by visit will be presented.

13.1.6.5 Physical Examination Findings

The number and percentage of subjects with normal and abnormal findings in the complete physical examination will be displayed for each treatment group.

13.1.6.6 Biomarkers

Observed values and changes from Baseline in biomarkers such as CK, CRP, D-dimer will be summarized using descriptive statistics by visit.

13.2 Sample Size Determination

- The planned approximate total enrollment is 110 patients (94 evaluable patients accounting for up to 15% loss to follow-up). The randomization scheme will be 1:1 with approximately one-half of subjects randomized to receive varespladib-methyl plus SOC and approximately one-half randomized to receive placebo plus SOC. The randomization will be stratified by age group (5 to < 11 years, 11 to < 18 years, ≥ 18 years) 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.

The determination of the effectiveness of varespladib-methyl versus placebo will be based on the primary efficacy endpoint. The sample size for this phase 2 study was determined by a formal power calculation. This study was powered at greater than 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
- Withdrawal rate of 15%
- A minimum difference in change from Baseline to the average of the 6- and 9-hour pulmonary, cardiovascular, hematologic, and nervous system subscores of the SSS of 1.1 points and a SD of 1.75.

14 STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study sites, review of protocol procedures with the Investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

14.1 Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 16). The sponsor reserves the right to withdraw a subject from the study (Section 8.3), to terminate participation of a study site at any time (Section 14.7), and/or to discontinue the study (Section 14.6).

Ophirex, Inc. agrees to provide the Investigator with sufficient material and support to permit the Investigator to conduct the study according to the study protocol.

14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 18.1), the Investigator indicates that he or she has read the protocol carefully, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The study will be conducted in accordance with ICH Good Clinical Practice (GCP) and applicable U.S. Code of Federal Regulations (CFR). The principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the IND or Investigational Device Exemption sponsor, funding agency and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the study subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP training.

Investigators should ensure that all persons who are delegated study-related responsibilities are adequately qualified and informed about the protocol, the IPs, and their specific duties within the context of the study. Investigators are responsible for providing Ophirex, Inc. with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The Investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.1.3 Confidentiality and Privacy

Subject confidentiality and privacy must be strictly held in trust by the participating Investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other

information generated must be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

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

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the study CRO. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and the study CRO will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

14.2 Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB or Ethics Committee approval for the protocol and the appropriate informed consent form (ICF).
2. All regulatory documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the Investigator, have participated in a study initiation meeting.

14.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

14.4 Study Documents

All documentation and material provided by Ophirex, Inc. for this study are to be retained in a secure location and treated as confidential material.

14.4.1 Informed Consent

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the subject, and written documentation of informed consent is required prior to starting intervention/administering study intervention. As snakebites may constitute life-threatening medical conditions that necessitate urgent intervention, a legally authorized representative may provide consent for subjects who are not able to provide informed consent because of the severity of their condition.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved and the subject will be asked to read and review the document. The Investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date) and the form signed before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.4.2 Investigator's Regulatory Documents

The regulatory documents are listed in the study plan.

The regulatory documents must be received from the Investigator and reviewed and approved by Ophirex, Inc. or its designee before the study site can initiate the study and before Ophirex, Inc. will authorize shipment of IP to the study site. Copies of the Investigator's regulatory documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the varespladib IB, eCRF completion guidelines, copies of regulatory references, copies of IRB correspondence, and IP accountability records should also be retained as part of the Investigator's regulatory documents. It is the Investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

14.4.3 Case Report Forms

By signing the Investigator's Agreement (Section 18.1), the Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

Electronic case report forms are considered confidential documents and should be protected accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the Investigator or a sub-Investigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.4.4 Source Documents

Information recorded in the EDC system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records. Source data permits not only reporting and analysis but also verification throughout the study for the purposes of confirmation, quality control, audit, or inspection. It is important that source data and the records that hold those data are:

- Accurate
- Legible
- Contemporaneous
- Original
- Attributable
- Complete
- Consistent
- Enduring
- Available when needed

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the study plan. Any protocol data that will be permitted to be entered directly into the eCRFs (i.e., with no prior written or electronic record of the data) will be specified.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described below.

14.5 Data Quality Control

Ophirex, Inc. and its designees will perform quality control checks on this clinical study.

14.5.1 Monitoring Procedures

Ophirex, Inc. and/or its designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the Investigator and study site at periodic intervals and maintain periodic communication. The Investigator agrees to allow the CRA(s) and other authorized Ophirex, Inc. personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff. While on site, the CRA(s) will review

- Regulatory documents, directly comparing entries in the EDC system with the source documents
- Consenting procedures
- AE procedures
- Storage and accountability of IP and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF are described in the study plan. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 18.1), the Investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the Investigator agrees to allow Ophirex, Inc. or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

For additional information, please refer to the clinical monitoring plan.

14.5.2 Data Management

Ophirex, Inc. or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and the study CRO's standard operating procedures. A comprehensive data management plan will be developed, including a data management overview, description of database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The Investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the study plan.

14.5.3 Quality Assurance/Audit

This study will be subject to audit by Ophirex, Inc. or its designee. Audits may be performed to check compliance with GCP guidelines and can include:

- site audits
- Trial Master File (TMF) audits
- database audits
- document audits (e.g., protocol and/or CSR)

Ophirex, Inc. or its designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB or regulatory authorities according to GCP guidelines. The Investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the Investigator that it intends to conduct an inspection, the Investigator shall notify Ophirex, Inc. immediately.

14.6 Study Termination

The study may be terminated at Ophirex, Inc.'s discretion at any time and for any reason.

14.6.1 Premature Study Termination

The study may be temporarily suspended or terminated prematurely at any time, for any reason, by Ophirex, Inc.

Written notification documenting the reason for study suspension or termination will be provided by the sponsor to Investigators, IRBs, and appropriate regulatory authorities. If the study is prematurely terminated or suspended, the Investigator will promptly inform study subjects. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Sponsor may terminate the study at any time for any reason.

Study sites may be asked to have all subjects currently participating in the study complete all the assessments for the Early Termination Visit.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or appropriate regulatory authority.

14.7 Study Site Closure

At the end of the study, all study sites will be closed. Ophirex, Inc. may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate subject enrollment

14.7.1 Record Retention

The Investigator shall retain and preserve 1 copy of all data generated during the study, specifically including, but not limited to, those defined by GCP as essential until:

- At least 3 years after the last marketing authorization for the IP has been approved or the sponsor has discontinued its research with the IP, or
- At least 3 years have elapsed since the formal discontinuation of clinical development of the IP.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the Investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor has 30 days to respond to the Investigator's notice, and the sponsor has further opportunity to retain such materials at the sponsor's expense.

14.8 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment by Ophirex, Inc. The protocol amendment must be signed by the Investigator and approved by the IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

14.9 Use of Information and Publication

All information concerning varespladib, varespladib-methyl, Ophirex, Inc.'s operations, patent applications, formula, manufacturing processes, basic scientific data, and formulation information supplied by Ophirex, Inc. or its designee to the Investigator, and not previously published, is considered confidential and remains the sole property of Ophirex, Inc.. Case report forms also remain the property of Ophirex, Inc. The Investigator agrees to use this information for purposes of study execution through finalization.

The information developed in this study will be used by Ophirex, Inc. in connection with the continued development of varespladib or varespladib-methyl and thus may be disclosed as required to other clinical Investigators or government regulatory agencies.

The information generated by this study is the property of Ophirex, Inc. Publication or other public presentation of varespladib or varespladib-methyl data resulting from this study requires prior review and written approval of Ophirex, Inc.. Abstracts, manuscripts, and presentation materials should be provided to Ophirex, Inc. for review at least 30 days prior to the relevant submission deadline.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the Investigator until Ophirex, Inc. has reviewed and commented on such a presentation or manuscript for publication. If applicable, this study will be registered at ClinicalTrials.gov, and results from this study will be submitted to ClinicalTrials.gov.

15 FINAL CLINICAL STUDY REPORT

Ophirex, Inc. will retain ownership of the data.

The final CSR will be written within 6 months of completion of the clinical part of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

The final CSR will be submitted to the regulatory authorities.

16 ETHICAL AND LEGAL CONSIDERATIONS

16.1 Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry GCP E6 (including archiving of essential study documents), the Integrated Addendum to ICH E6 (R2) of November 2016, and the applicable regulations of the country in which the study is conducted.

16.2 Subject Information and Informed Consent and/or Assent

A properly constituted, valid IRB or EC must review and approve the protocol, the Investigator's ICF, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the Investigator to ensure that written informed consent and/or assent is obtained from the subject before any activity or procedure is undertaken that is not part of routine care.

16.3 Approval by Institutional Review Board or Ethics Committee

For IND studies, the minimum standards of conduct and requirements for informed consent and/or assent are defined in the FDA regulations.

A valid IRB or EC must review and approve this protocol before study initiation. Written notification of approval is to be provided by the Investigator to the sponsor's designated contact before shipment of IP supplies, and will include the date of the committee's approval and the chairperson's signature.

Until written approval by the IRB or EC has been received by the Investigator, no subject may undergo any procedure not part of routine care for the subject's condition.

Protocol amendments must also be reviewed and approved by the IRB or EC. Written approval from the IRB or EC or a designee must be received by Ophirex, Inc. before implementation.

16.4 Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the Investigator and the sponsor.

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Guidance Documents:

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18 ATTACHMENTS

18.1 Investigator's Agreement

PROTOCOL NUMBER:	OPX-PR-01
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
FINAL PROTOCOL:	Version 3.0, 5 May 2022

I have read this protocol and agree to conduct this clinical study as outlined herein. I will ensure that all sub-Investigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Ophirex, Inc. during the study. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical studies on an IP during and after study completion.

Principal Investigator:

Printed Name:

_____

Signature:

_____

Date:

_____

APPENDICES

APPENDIX A SCORING SHEET FOR SNAKEBITE SEVERITY INCLUSION CRITERIA

The inclusion criteria for this study require that each subject is hospitalized with a suspected or confirmed venomous snakebite. Regardless of previous antivenom administration, subjects should only be included if they present at the time of eligibility assessment with 2 points in any of the system scores shown below and 1 or more additional points in any other category below OR a 3 or greater in any category below. Subjects that have completed the initial dose of antivenom must also have a CGI-I score of ≥ 5 (*i.e.,* minimally worse, much worse, or very much worse). This inclusion criteria scoring should not wait until hematologic laboratories are evaluated. Point of care testing (e.g., 20WBCT) may be used for enrollment determinations for the Hematologic system, if performed per site standard of care. Severe abnormalities of other coagulation parameter laboratory values, including 20WBCT, should be scored as a 4 in the Hematologic system subscore for purposes of enrollment.

Local wound	
No signs/symptoms	0
Pain, swelling, or ecchymosis within 5–7.5 cm of bite site	1
Pain, swelling, or ecchymosis involving less than half the extremity (7.5–50 cm from bite site)	2
Pain, swelling, or ecchymosis involving half to all of extremity (50–100 cm from bite site)	3
Pain, swelling, or ecchymosis extending beyond affected extremity (more than 100 cm of bite site)	4
Pulmonary symptoms	
No signs/symptoms	0
Dyspnea, minimal chest tightness, mild/vague discomfort, respirations of 20–25 breaths per minute	1
Moderate respiratory distress, 26–40 bpm	2
Cyanosis, air hunger, extreme tachypnea, or respiratory insufficiency/failure	3
Cardiovascular system	
No signs/symptoms	0
HR 100–125 BPM, palpitations, generalized weakness, benign dysrhythmia, or hypotension	1
HR 126–175 BPM, or hypotension with SBP > 100 mmHg	2
HR > 175 BPM, or hypotension with SBP < 100 mmHg, malignant dysrhythmia, or cardiac arrest	3
Hematologic symptoms	
No signs/symptoms	0
Coagulation parameters slightly abnormal: PT ULN–20 secs, PTT ULN–50 secs, platelets 100–150K/mL, or fibrinogen 100–150 mcg/mL	1
Coagulation parameters abnormal: PT 20–50 secs, PTT 50–75 secs, platelets 50–100K/mL, or fibrinogen 50–100 mcg/mL	2
Coagulation parameters abnormal: PT 50–100 secs, PTT 75–100 secs, platelets 20–50K/mL, or fibrinogen < 50 mcg/mL	3
Coagulation parameters markedly abnormal, with serious bleeding or the threat of spontaneous bleeding; unmeasurable PT or PTT, platelets < 20 K/mL, undetectable fibrinogen, severe abnormalities of other laboratory values also fall into this category	4
Nervous system	
No signs/symptoms	0
Minimal apprehension, headache, weakness, dizziness, chills, or paresthesia	1
Moderate apprehension, headache, weakness, dizziness, chills, paresthesia, confusion, fasciculation in area of bite site, ptosis, or dysphagia	2
Severe confusion, lethargy, weakness, paralysis, seizures, coma, psychosis, or generalized fasciculation	3
TOTAL	

APPENDIX B COMPOSITE SNAKEBITE SEVERITY SCORE FOR EFFICACY ENDPOINTS

Local wound	
No signs/symptoms	0
Pain, swelling, or ecchymosis within 5–7.5 cm of bite site	1
Pain, swelling, or ecchymosis involving less than half the extremity (7.5–50 cm from bite site)	2
Pain, swelling, or ecchymosis involving half to all of extremity (50–100 cm from bite site)	3
Pain, swelling, or ecchymosis extending beyond affected extremity (more than 100 cm of bite site)	4
Pulmonary symptoms	
No signs/symptoms	0
Dyspnea, minimal chest tightness, mild/vague discomfort, respirations of 20–25 breaths per minute	1
Moderate respiratory distress, 26–40 bpm	2
Cyanosis, air hunger, extreme tachypnea, or respiratory insufficiency/failure	3
Cardiovascular system	
No signs/symptoms	0
HR 100–125 BPM, palpitations, generalized weakness, benign dysrhythmia, or hypotension	1
HR 126–175 BPM, or hypotension with SBP > 100 mmHg	2
HR > 175 BPM, or hypotension with SBP < 100 mmHg, malignant dysrhythmia, or cardiac arrest	3
Gastrointestinal system	
No signs/symptoms	0
Pain, tenesmus, or nausea	1
Vomiting or diarrhea	2
Repeated vomiting, diarrhea, hematemesis, or hematochezia	3
Hematologic symptoms*	
No signs/symptoms	0
Coagulation parameters slightly abnormal: PT ULN–20 secs, PTT ULN–50 secs, platelets 100–150K/mL, or fibrinogen 100–150 mcg/mL	1
Coagulation parameters abnormal: PT 20–50 secs, PTT 50–75 secs, platelets 50–100K/mL, or fibrinogen 50–100 mcg/mL	2
Coagulation parameters abnormal: PT 50–100 secs, PTT 75–100 secs, platelets 20–50K/mL, or fibrinogen < 50 mcg/mL	3
Coagulation parameters markedly abnormal, with serious bleeding or the threat of spontaneous bleeding; unmeasurable PT or PTT, platelets < 20 K/mL, undetectable fibrinogen, severe abnormalities of other laboratory values also fall into this category	4
Nervous system	
No signs/symptoms	0
Minimal apprehension, headache, weakness, dizziness, chills, or paresthesia	1
Moderate apprehension, headache, weakness, dizziness, chills, paresthesia, confusion, fasciculation in area of bite site, ptosis, or dysphagia	2
Severe confusion, lethargy, weakness, paralysis, seizures, coma, psychosis, or generalized fasciculation	3
Renal system*	
Normal creatinine and urine output	0
Creatinine 1.5 to 1.9 times baseline, increase in creatinine ≥0.3mg/dl (≥26.5 µmol/L) from baseline, or urine output <0.5 ml/kg/h for >6 h	1
Creatinine 2 to 2.9 times baseline or urine output <0.5 ml/kg/h for >12 h	2
Creatinine ≥3.0 times baseline, increase in creatinine to ≥4.0 mg/dl (≥353.6 µmol/L), urine output <0.3 ml/kg/h for ≥24 h or anuria ≥12 h, or initiation of renal replacement therapy	3
TOTAL	

*Where applicable, confirmatory laboratory test results will be used to score the SSS for efficacy endpoints.

APPENDIX C STUDY-SPECIFIC REQUIREMENTS

Protocol Appendix	Assessment Tool
C1	Clinical Global Impression – Improvement (CGI-I)
C2	Patient Global Impression of Change (PGIC)
C3	Patient-Specific Functional Scale (PSFS)
C4	Numeric Pain Rating Scale (NPRS)
C5	Columbia-Suicide Severity Rating Scales
C6	Neurological evaluation (Grip Strength)
C7	Modes of Mechanical Ventilation
C8	Head-Lift Assessment
C9	Analgesic Use

Appendix C1:Clinical Global Impression-Improvement (CGI-I) Form

Baseline CGI-I rating should be in comparison to previous clinical assessments. Additional CGI-I should be performed on Day 1 at 1, 2, and 3-4 hours post initial dose, then follow normal assessment schedule as provided in the Schedule of Events. All post-baseline CGI-I assessments should be compared to baseline CGI-I.

Patient Name: Date:

Clinician Name:

Clinical Global Impression – Global Improvement (CGI –I) Scale

Rate total improvement whether or not, in your clinical judgment, it is due entirely to drug treatment.

Compared to his/her condition at baseline, how much has he/she changed?

- ☐ 0 = Not assessed
- ☐ 1 = Very much improved
- ☐ 2 = Much improved
- ☐ 3 = Minimally improved
- ☐ 4 = No change
- ☐ 5 = Minimally worse
- ☐ 6 = Much worse
- ☐ 7 = Very much worse

Appendix C2: Patient Global Impression of Change Scale

Patients' Global Impression of Change (PGIC) scale.

Name:_____ **Date:**_____ **DOB:**_____

Chief Complaint:_____

Since beginning treatment at this clinic, how would you describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS and OVERALL QUALITY OF LIFE, related to your painful condition? (tick ONE box).

No change (or condition has gotten worse)	☐ 1
Almost the same, hardly any change at all	☐ 2
A little better, but no noticeable change	☐ 3
Somewhat better, but the change has not made any real difference	☐ 4
Moderately better, and a slight but noticeable change	☐ 5
Better, and a definite improvement that has made a real and worthwhile difference	☐ 6
A great deal better, and a considerable improvement that has made all the difference	☐ 7

In a similar way, please circle the number below, that matches your degree of change since beginning care at this clinic:

Much Better					No Change					Much Worse
0	1	2	3	4	5	6	7	8	9	10

Protocol OPX-PR-01 Subject ID: ___ ___ ___ - ___ ___ ___ Date of Visit: ____/_____/_____ DD / MMM / YYYY	Subject Signature_____ Date_____

Reference: Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther 2004; 27:26-35.

Appendix C3: Patient-Specific Functional Scale

The PSFS is a 3-item instrument that is administered verbally. Completion takes approximately 2 minutes.

On the initial assessment, the question is: "I am going to ask you to identify 3 important activities that you are unable to do or are having difficulty with as a result of your snake bite. Today, are there any activities that you are unable to do or having difficulty with because of your snake bite?"

The patient then provides 3 activities. The patient then provides a rating for each item on an 11-item ordinal scale, where 0 is "unable to perform activity" and 10 is "able to perform activity at the same level as before injury or problem." The range of possible single activity scores is 0 to 10 and the range of possible total score is 0 to 10.

For all follow-up assessments, the question is: "When I assessed you on [state previous assessment date], you told me that you had difficulty with [read all activities from the list]. Today, do you still have difficulty with [read and have patient score each item on the list]?"

References:

Westaway MD, Stratford PW, Binkley JM. The patient-specific functional scale: validation of its use in persons with neck dysfunction. *J Orthop Sports Phys Ther* 1998; 27(5): 331-338.

Stratford P, Gill C, Westaway M, Binkley J. Assessing disability and change on individual patients: a report of a patient specific measure. *Physiotherap Canada* 1995; 47(4): 258-63.

Horn KK, Jennings S. Richardson G, van Vliet D, Hefford C, Abbott JH. The Patient-Specific Functional Scale: psychometrics, clinimetrics, and applications as a clinical outcome measure. J Orthop Sports *Phys Ther* 2012; 42(1):30-42.

Instrument: None

A sample PSFS assessment form is attached below.

The Patient Specific Functional Scale

This useful questionnaire can be used to quantify activity limitation and measure functional outcome for patients with any orthopaedic condition.

Clinician to read and fill in below: Complete at the end of the history and prior to physical examination.

Initial Assessment:

I am going to ask you to identify three important activities that you are unable to do or are having difficulty with as a result of your _____ problem. Today, are there any activities that you are unable to do or having difficulty with because of your problem?
(**Clinician:** Show scale to patient and have the patient rate each activity.)

Follow-up Assessments:

When I assessed you on (state previous assessment date), you told me that you had difficulty with (read all activities from list at a time). Today, do you still have difficulty with: (read and have patient score each item in the list)?

Patient-specific Activity Scoring Scheme (point to one number):

0	1	2	3	4	5	6	7	8	9	10
Unable to perform activity										Able to perform activity at the same level as before injury or problem

(Date and Score)

Activity	Initial										
1.											
2.											
3.											

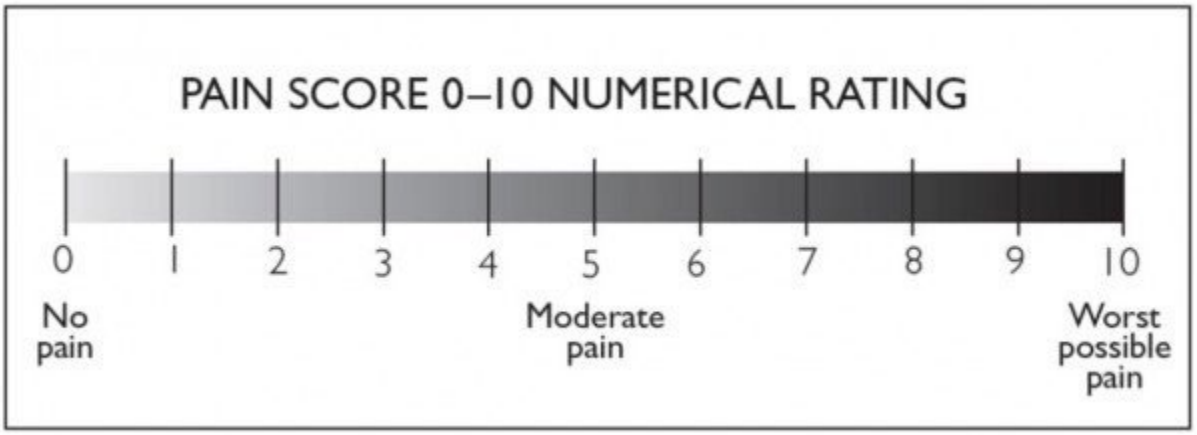
Total score = sum of the activity scores / number of activities
Minimum detectable change (90%CI) for average score = 2 Points
Minimum detectable change (90%CI) for single activity score = 3 points

PSFS developed by: Stratford, P., Gill, C., Westaway, M., & Binkley, J. (1995). "Assessing disability and change on individual patients: A report of a patient specific measure." *Physiotherapy Canada, 47:* 258-263.

Protocol OPX-PR-01
Subject ID: __ __ __ - __ __ __ Subject Signature: _____
Date of Visit: ____/____/_____ Date: _____
DD/MMM/YYYY

Appendix C4: NPRS Form

The numeric pain rating scale (NPRS) is an 11-point scale for patient self-reporting of pain. This scale is administered verbally by the clinical site staff and recorded by the administrator. An example NPRS is provided below.



Appendix C5: Columbia-Suicide Severity Rating Scale Forms

1. C-SSRS Baseline/Screening Form

2. C-SSRS Since Last Visit Form

1. C-SSRS Baseline/Screening Form

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

C-SSRS—Baseline/Screening (Version 1/14/09)
Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past _ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

2. C-SSRS Since Last Visit Form

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

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For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_eng-USori.doc

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:

Yes ☐ No ☐

2. Non-Specific Active Suicidal Thoughts
General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:

Yes ☐ No ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".*
Have you been thinking about how you might do this?
If yes, describe:

Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:

Yes ☐ No ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:

Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Appendix C6: Grip Strength

Grip strength will be evaluated using a dynamometer, as a measure of the severity of the neurological effects of snakebite. Grip strength should be measured in affected hand if the bite occurred in upper extremity or in the patient's dominant hand if the bite occurred elsewhere (i.e. not in an upper extremity).

The grip strength assessment is an objective measurement of hand function. The subject is asked to grip a dynamometer and squeeze with maximal force. The measurement is repeated for a total of 3 trials and the greatest value is recorded. Completion takes approximate 1 minute.

References:

Jones LA. The assessment of hand function: a critical review of techniques. J Hand Surg 1989; 14A:221-8.

Peters MJH, van Nes SI, Vanhoutte EK Bakkers M, van Doorn PA, Merkies ISJ, Faber CG, PeriNomS Study group. Revised normative values for grip strength with the Jamar dynamometer. J Periph Nervous Sys 2011; 16(1): 47-50.

Instrument: A standard dynamometer, such as the Jamar Hand Dynamometer, will be used according to the manufacturer's instructions.

Appendix C7: Modes of Mechanical Ventilation

Record the following in all endotracheally intubated patients. Modes of Ventilation will be collected in the CRF.

- Mechanical ventilation modes and ventilator settings
  - Control mode ventilation
    - Volume control
    - Pressure control
    - Assist control
    - Pressure-regulated volume control
  - Weaning mode ventilation
    - Synchronized intermittent mandatory ventilation
    - Pressure support
    - Adaptive support ventilation
    - Airway pressure release ventilation
    - T piece
  - Other
    (Since novel modes such as adaptive support ventilation and airway pressure release ventilation can be used during initiation, maintenance, or weaning phases of mechanical ventilation, clear documentation is warranted)
- Record NIF if collected per institutional practice

Appendix C8: Head-Lift Duration

The subject is asked to raise their head approximately 8 cm off the bed (enough to see clear separation from the head and the mattress). The duration of time that the patient can keep their head off the bed is measured for a maximum duration of 5 seconds (e.g. 1, 2, 3, 4, 5 seconds or if using timing device e.g. 4.25 seconds). Please note the duration of Head-Lift in seconds. Record up to 2 decimal places if using an electronic timing device (e.g. stop-watch).

References:

Heier T, Caldwell JE, Feiner JR, Liu L, Ward T, Wright PM. Relationship between normalized adductor pollicis train-of-four ratio and manifestations of residual neuromuscular block: a study using acceleromyography during near steady-state concentrations of mivacurium. *Anesthesiology.* 2010;113:825–832.

Lewin MR, Bickler P, Heier T, Feiner J, Montauk L, Mensh B. Reversal of experimental paralysis in a human by intranasal neostigmine aerosol suggests a novel approach to the early treatment of neurotoxic envenomation. *Clin Case Rep*. 2013;1(1):7-15. doi:10.1002/ccr3.3

Appendix C9: Analgesic Use

This analgesic use assessment is derived from data in the patient's medication history as collected through recording of concomitant medication usage, supplemented by focused questions if needed.

For each assessment time point, the patient's current analgesic use will be characterized by the clinical research team based on the strongest category of analgesic taken to treat snakebite-related pain, as follows:

Analgesic use category	Ordinal scale value
No analgesic	1
Nonprescription analgesic only	2
Prescription analgesic, non-opioid	3
Opioid analgesic (including tramadol, and opioid combination products)	4

The result is a 4-point ordinal scale with a range of possible values –4. Collection of these data should require less than 1 minute in addition to the time for overall medication use.

Reference: None

Instrument: None

APPENDIX D COVID-19 PROTOCOL DEVIATIONS

The impact of COVID-19 on this clinical study and study subjects will be extensively described in the SAP 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

APPENDIX E REGULATIONS AND GOOD CLINICAL PRACTICE GUIDELINES

1. Regulations

Refer to the following United States CFR:

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URLs:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf