CLINICAL STUDY PROTOCOL AMENDMENT 2
IND 69,019

A POST MARKETING STUDY OF THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF TPOXX® IN ADULT SUBJECTS WEIGHING MORE THAN 120 KG

Post Marketing Commitment: 3417-4

SIGA-246-022

Sponsor:	SIGA Technologies, Inc. 4575 SW Research Way, Suite 110 Corvallis, OR 97333
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]
Version of Protocol:	Final 3.0
Date of Protocol:	02 August 2019

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation Guideline E6(R2): Good Clinical Practice.

SIGNATURE PAGE

PROTOCOL TITLE: A Post Marketing Study of the Safety, Tolerability, and Pharmacokinetics of TPOXX® in Adult Subjects Weighing More Than 120 kg

PROTOCOL NUMBER: SIGA-246-022

Dennis E. Hruby, PhD
Chief Scientific Officer
SIGA Technologies, Inc.

Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree to conduct the study as outlined in the protocol titled "A Post Marketing Study of the Safety, Tolerability, and Pharmacokinetics of TPOXX® in Adult Subjects Weighing More Than 120 kg" in accordance with the guidelines and all applicable government regulations, including US Title 21 of the Code of Federal Regulations Part 54. I have read and understand all sections of the protocol.

[redacted]

Date

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PROTOCOL SYNOPSIS

PROTOCOL NO.: SIGA-246-022

TITLE: A Post Marketing Study of the Safety, Tolerability, and Pharmacokinetics of TPOXX® in Adult Subjects Weighing More Than 120 kg

STUDY PHASE: 4 Post Marketing Study

STUDY SITE: PPD Phase I Clinic, 7551 Metro Center Drive, Suite 200, Austin, TX 78744, USA.

OBJECTIVES:

Primary:

The primary objective of this study is to determine the pharmacokinetic (PK) profile of 600 mg oral TPOXX (3 × 200-mg capsules) administered twice daily (BID) for 7 days in adult subjects weighing more than 120 kg to determine if a change in dosing regimen would be needed in these patients.

Secondary:

The secondary objective of this study is to evaluate the safety and tolerability of 600 mg oral TPOXX administered BID for 7 days in healthy adult subjects weighing more than 120 kg.

STUDY DESIGN AND METHODOLOGY:

This is an open-label, multiple-dose study to assess the safety, tolerability, and PK of TPOXX 600 mg BID when administered orally for 7 days to adult subjects weighing more than 120 kg. A total of 36 subjects, ages 18 to 50, inclusive, will be enrolled. The study will consist of a screening period (Day –28 to Day –2), a treatment and confinement period (Days –1 to 9), a follow-up telephone call or visit (Day 14 [+2 days]), and a follow-up telephone call (Day 37 [+2 days]).

Subjects will undergo screening evaluations to determine eligibility within 28 days before study drug administration. Subjects will be admitted to the study site on Day –1 to complete baseline assessments; results of these assessments must be reviewed by the investigator before dosing. Starting in the morning of Day 1, subjects will receive 600 mg oral TPOXX BID for 7 days (Days 1 through 7).

All subjects will be provided meals (consisting of approximately 600 calories and 25 g fat) 30 minutes prior to study drug administration and subjects must fast for 2 hours after taking study drug. Subjects should eat this meal within 30 minutes or less of taking study drug. Study drug and meals must be taken with water only, and no other beverage except water should be ingested within 3 hours before or 3 hours after study drug administration.

Subjects will remain confined to the study site for collection of PK samples and will be carefully monitored for safety and tolerability until discharge on Day 9. Subjects who have abnormal physical examination findings or an ongoing adverse event (AE)/serious adverse event (SAE) on Day 9 that is deemed related to study drug or per investigator or SIGA discretion will return to the study site on Day 14 (+2 days) for a follow-up visit. All other subjects will have the Day 14 (+2 days) follow-up via telephone. All subjects will have a

follow-up telephone call 30 days after administration of the last dose of study drug (Day 37 [+2 days]) to report any SAEs. At the time of discharge from the clinical research unit, subjects will be instructed to notify the investigator of any SAEs that occur within 30 days after administration of the last dose of study drug. Serious AEs will be followed until the SAE is stable or until resolution as determined by the investigator and/or medical monitor.

The total duration of the study for each subject, including the screening period, treatment period, and the Day 37 (+2 days) follow-up telephone call, will be approximately 65 days.

STUDY POPULATION:

Inclusion Criteria:

Each subject must meet all the following criteria to be enrolled in this study:

1. Subject is male or female between 18 and 50 years of age, inclusive.
2. Subject has a body weight >120 kg at screening, at check-in on Day -1, and prior to dosing on Day 1.
3. Women of childbearing potential, have a negative β human chorionic gonadotropin pregnancy test (serum) at the screening visit and a confirmatory negative serum pregnancy test on Day –1 before receipt of study drug, and meet 1 of the following criteria:
    a. The subject or their partner has undergone surgical sterilization
    b. The subject is postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause and has a documented plasma follicle-stimulating hormone level >40 IU/mL
    c. The subject agrees to be abstinent (ie, heterosexually inactive or women in a religious order)
    d. The subject agrees to consistently use 1 of the following methods of contraception from the beginning of screening (which they had been consistently using for at least 30 days before the first dose of study drug) through 30 days after the last dose of study drug:
        i. Condoms, male or female, with a spermicide

            NOTE: For male subjects, condoms must be used for 90 days after the last dose of study drug.
        ii. Diaphragm or cervical cap with spermicide
        iii. Intrauterine device with spermicide
        iv. Oral contraceptives or other hormonal methods

            NOTE: Subject must agree to use an additional nonhormonal method of contraception in conjunction with oral contraceptives.
        v. Male sexual partner who had undergone a vasectomy at least 3 months before screening
4. Male subjects must agree to not donate sperm from the first dose of study drug through 90 days after the last dose of study drug.

5. Subject is considered by the investigator to be in good general health as determined by medical history (no hospitalizations for chronic medical conditions in the previous 2 years), clinical laboratory results, vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings at screening.
6. Subject agrees to comply with all protocol requirements.
7. Subject is able to provide written informed consent.
8. Subject agrees to comply with the dietary requirements.
9. Subject does not intend to lose weight (diet or weight loss) from the screening visit and throughout the study.

EXCLUSION CRITERIA:
Subjects meeting any of the following criteria will be excluded from the study:

1. Subject is a female who is pregnant or breastfeeding or planning to become pregnant within 3 months after the last dose of study drug.
2. Subject has a history of any clinically significant conditions including:
   - Asthma treated with oral systemic steroids within the past 6 months
   - Diabetes mellitus (type 1 or 2), with the exception of gestational diabetes
   - Thyroidectomy or thyroid disease that required medication within the past 12 months
   - Serious angioedema episodes within the previous 3 years or requiring medication in the previous 2 years
   - Head trauma resulting in a diagnosis of traumatic brain injury other than concussion
   - Frequent episodes of headache.
3. Subject has received treatment in another clinical study of an investigational drug (or medical device) within 30 days or 5 half-lives (whichever is longer) before the first dose of study drug.
4. Subject has been previously enrolled in any clinical study involving TPOXX (tecovirimat).
5. Subject has a history of relevant drug and/or food allergies (ie, allergy to tecovirimat or excipients, or any significant food allergy that could preclude a standard diet in the study site).
6. Subject has any condition possibly affecting drug absorption (eg, previous surgery on the gastrointestinal tract, including removal of parts of the stomach, bowel, liver, gallbladder, or pancreas, with the exception of appendectomy).
7. Subject has evidence or history of clinically significant allergic (except for untreated, asymptomatic, seasonal allergies at time of the first dose of study drug), hematological, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, or neurological disease. Exceptions to these criteria (eg, stable, mild joint disease unassociated with collagen vascular disease) may be made following discussions with the medical monitor.

8. Subject has a history of cardiac disease, symptomatic or asymptomatic arrhythmias, syncopal episodes, or risk factors for torsades de pointes (eg, heart failure, hypokalemia).
9. Subject has a family history of sudden cardiac death, not clearly due to acute myocardial infarction.
10. Subject has a seizure disorder or history of seizures (does not include childhood febrile seizures) or a past history that increases seizure risks such as significant head injury that caused loss of consciousness or other changes in the subject's daily function, concussion, stroke, central nervous system infection or disease, or alcohol or drug abuse or family history of idiopathic seizures.
11. Subject has a history of a peptic ulcer or significant gastrointestinal bleed.
12. Subject has a bleeding disorder diagnosed by a doctor (eg, factor deficiency, coagulopathy, or platelet disorder requiring special precautions) or significant bruising or bleeding difficulties with blood draws.
13. Subject has a malignancy that is active, or treated malignancy for which there is not reasonable assurance of sustained cure, or malignancy that is likely to recur during the period of the study (subject should be in complete remission for at least 5 years).
14. Subject has neutropenia or other blood dyscrasia determined to be clinically significant by the investigator.
15. Subject has used any of the following prohibited medications from within 7 days (or 5 half-lives, whichever is longer) before the first dose of study drug: antidiabetic medication; anticoagulants; anticonvulsants; substrates of the breast cancer resistance protein transporter including methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, and topotecan; substrates of CYP2C8 including repaglinide, paclitaxel, Montelukast, pioglitazone, rosiglitazone; and substrates of CYP2C19 including S-mephenytoin, clobazam, diazepam, rabeprazole, voriconazole, lansoprazole, and omeprazole. Medications not listed here that are known (or thought) to be CYP3A4 substrates may be allowed at the investigator's discretion, after consultation with the medical monitor, if administration poses little to no risk to the subject.
16. Subject has a history of drug or alcohol abuse or dependency within the last year before screening.
17. Subject has a history of an eating disorder.
18. Subject has a current or recent (<30 days before screening) history of clinically significant bacterial, fungal, or mycobacterial infection.
19. Subject has a current clinically significant viral infection.
20. Subject has a known clinically significant chronic viral infection (eg, human T cell lymphotropic virus I or II).
21. Subject has consumed grapefruit or grapefruit juice, Seville orange or Seville orange-containing products (eg, marmalade), or caffeine- or xanthine-containing products within 48 hours before the first dose of study drug or throughout the study.
22. Subject has used any prescription (excluding hormonal birth control) or over-the-counter medication (including herbal or nutritional supplements) within 14 days before the first dose of study drug.

23. Subject demonstrates long-term use (≥14 consecutive days) of glucocorticoids including oral or parenteral prednisone or equivalent (>20 mg total dose per day) or high-dose inhaled steroids (>800 mcg/day of beclomethasone dipropionate or equivalent) within the preceding 1 month (low-dose [≤800 mcg/day of beclomethasone dipropionate or equivalent] inhaled and topical steroids are allowed).
24. Subject has donated >450 mL blood or blood components within 30 days before the first dose of study drug. The investigator should instruct subjects who participate in this study to not donate blood or blood components for 4 weeks after the completion of the study.
25. Subject is a smoker or has used nicotine or nicotine-containing products (eg, cigarettes, electronic vapor cigarettes, cigars, chewing tobacco, snuff, nicotine patches, or nicotine gum) within 6 months before the first dose of study drug.
26. Subject has consumed pomegranate or pomegranate juice, pomelo fruits or pomelo juice, or alcohol within 72 hours before the first dose of study drug.
27. Subject reports participation in strenuous activity or contact sports within 24 hours before the first dose of study drug.
28. Subject has known hepatitis B or C infection or positive test for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus type 1 or 2 antibodies at screening.
29. Subject has a positive test result for amphetamines (including methamphetamines and ecstasy/methylenedioxymethamphetamine), barbiturates, benzodiazepines, cannabinoids (including tetrahydrocannabinol), cocaine metabolites, opiates (including heroin, codeine, and oxycodone), or alcohol at screening or check-in.
30. Subject has any of the following laboratory test results within 28 days before the first dose of study drug:
    - Estimated serum creatinine clearance (Cockcroft-Gault) <90 mL/min
    - Creatinine in males >1.7 mg/dL and in females >1.4 mg/dL (1.3 times the upper central laboratory reference range)
    - Hemoglobin ≤10% of the lower central laboratory reference range
    - White blood cell count not within the central laboratory reference range
    - Absolute neutrophil count <1000 cells/mm^3
    - Platelets not within ±10% of central laboratory reference range
    - Alanine aminotransferase >1.5 times above the upper central laboratory reference range
    - Aspartate aminotransferase >1.5 times above the upper central laboratory reference range
    - Alkaline phosphatase >20% above the upper central laboratory reference range
    - Hemoglobin A1c ≥7.0%
    - Cholesterol ≥300 mg/dL and low-density lipoprotein ≥190 mg/dL.
31. Subject has a blood pressure considered to be clinically significant by the investigator. Blood pressure may be retested twice in the sitting position at 5-minute intervals.

32. Subject has a resting heart rate of <40 beats per minute or >100 beats per minute at screening.
33. Subject has an abnormal ECG at screening that is determined by the investigator to be clinically significant.
34. Male subject has a QTcF >450 ms or female subject has a QTcF >470 ms at screening or Day –1.
35. In the opinion of the investigator, the subject is not suitable for entry into the study.

EVALUATION PROCEDURES:

Pharmacokinetic Assessments:

Blood samples for PK analysis of TPOXX will be collected from all subjects on Day 1 before study drug administration (0 hour), at 0.5, 1, 2, 4, 6, 8, 12 (before the PM dose), 14, 16, 18, 20, and 24 hours (before the AM dose on Day 2), on Day 6 (before the AM dose and 4 hours after the AM dose), on Day 7 before the AM dose (0 hour), at 0.5, 1, 2, 4, 6, 8, 12 (before the PM dose), 14, 16, 18, 20, and 24 hours (Day 8, 24 hours after the AM dose on Day 7), and on Day 9 (48 hours after the AM dose on Day 7).

For PK samples, the acceptable window for collection from the scheduled collection time point will be as follows: ±5 minutes for the time points from 1 to 8 hours and ±15 minutes for the 12- to 48-hour time points.

The following plasma PK parameters will be calculated for TPOXX using actual sampling times rather than scheduled sampling times and will include but are not limited to:

- Area under the plasma concentration-time curve (AUC) from time 0 to the last quantifiable measurement (AUC_{0-t})
- AUC from time 0 extrapolated to infinity ($AUC_{0-\infty}$)
- AUC from time 0 to 24 hours (AUC_{0-24})
- AUC during the first dosing interval (tau = 12 hours) (AUC_{0-tau})
- Maximum drug concentration in plasma (C_{max})
- Time to C_{max} (T_{max})
- Apparent volume of distribution (V_d/F)
- Apparent total body clearance (CL/F)
- Concentration observed prior to the next dose administration (C_{trough})
- Terminal elimination half-life ($t_{1/2}$)
- Terminal elimination rate constant (λ_z)
- Percentage of $AUC_{0-\infty}$ extrapolated from the last quantifiable measurement to infinity ($\%AUC_{extrap}$).

Safety Assessments:
Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory test results (hematology, serum chemistry, pregnancy, and urinalysis), vital sign measurements (systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature), 12-lead ECG results, and physical examination findings.

STUDY DRUG, DOSAGE, AND ROUTE OF ADMINISTRATION:
TPOXX, 600 mg (3 × 200-mg capsules), will be administered orally twice daily, approximately 12 hours (±30 minutes) apart, on Days 1 through 7.

STATISTICAL METHODS:
Complete, detailed statistical methods will be described in the statistical analysis plan.

Sample Size:
The sample size (N = 36 [to allow at least 32 enrolled subjects to complete]) for this study is based on clinical and practical considerations and not on a formal statistical power calculation. The sample size is considered sufficient to effectively assess the PK and safety profiles of TPOXX.

Analysis Populations:
- The Safety Population will include all subjects who receive at least 1 dose of study drug.
- The PK Population will include subjects who receive study drug and have sufficient concentration data to facilitate the calculation of PK variables.

Pharmacokinetic Analyses:
Individual plasma concentration and time deviation data will be presented in a data listing. Plasma concentration data will be listed and summarized using the following descriptive statistics: number of subjects, arithmetic mean, standard deviation (SD), coefficient of variation (CV), geometric mean, geometric CV, median, minimum, and maximum. Individual and mean plasma concentration versus time profiles will be presented in figures on both linear and semilogarithmic scales.

The PK parameters of TPOXX will be analyzed based on the actual sampling times. All parameters will be determined using noncompartmental methods using Phoenix® WinNonlin® Version 8.0 or higher (Certara, L.P., Princeton, New Jersey) or SAS® Version 9.4 or higher (SAS Institute Inc., Cary, North Carolina).

The individual PK parameters and weight-normalized PK parameters will be presented in data listings and summarized using the following descriptive statistics: number of subjects, arithmetic mean, SD, CV, median, minimum, maximum, geometric mean, geometric SD, and geometric CV.

Safety Analyses:
Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities and summarized overall. All AE data will be presented in a data listing. Treatment-emergent AEs will be summarized overall, as well as by severity and relationship to study drug. Serious AEs and AEs leading to

discontinuation of study drug will also be presented in the data listings and summarized overall.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results. Clinical laboratory data, vital sign measurements, 12-lead ECG results, and physical examination findings will be presented in data listings.

DATE OF PROTOCOL: 02 August 2019

1. INTRODUCTION

1.1 BACKGROUND

Historically, variola virus (VARV), the etiologic agent of smallpox, has been one of the more important human pathogens. Smallpox is highly communicable and carries exceptionally high morbidity. Secondary attack rates from 30% to 80% have been reported among unvaccinated members of households.[1] Mortality rates range from 1% for variola minor to 30% for variola major.[1] With the advent of biowarfare as an instrument of terrorism, smallpox can no longer be thought of as a disease only of historic impact.

In July 2018, the FDA approved the oral formulation of TPOXX for the treatment of patients with human smallpox disease caused by VARV.

1.2 RATIONALE FOR STUDY

This study is being conducted as an FDA post marketing commitment to the approved New Drug Application for TPOXX. SIGA is required to conduct a study to determine the pharmacokinetic (PK) profile of TPOXX in subjects with a body weight greater than 120 kilograms (>120 kg) to determine if a change in dosing regimen would be needed in these patients.

1.3 POTENTIAL RISKS AND BENEFITS

1.3.1 Potential Risks

The effect of TPOXX on a fetus or nursing baby is not yet known; therefore, women of childbearing potential participating in this study will be required to agree to use an acceptable means of birth control from 30 days before the first dose of study drug and continuing through 30 days after the last dose of study drug. Pregnancy testing will be performed at the screening visit and checked by the investigator for negative pregnancy before administration of study drug on Day –1. Women who are pregnant or lactating or plan to become pregnant within 3 months after study drug administration will be excluded from the study; if a female subject becomes pregnant during study participation, study drug dosing will be discontinued, and the subject will be withdrawn from the study (Section 6.2.1.9).

As with all drugs, there is potential risk of an allergic reaction. At this time, there is no definitive information on the allergic activity of TPOXX. Headache and nausea have been the most common AEs in clinical studies completed to date. There may be other side effects

of TPOXX that are not yet known. Full details can be found in the TPOXX full prescribing information.[2]

1.3.2 Known Potential Benefits

As this study will be conducted in subjects free from smallpox, no direct health benefits from taking the study drug are expected. Study subjects may benefit from receiving the laboratory testing, ECGs, and physical examinations. Others may benefit from knowledge gained in this study that may aid in the development of a drug for the treatment of smallpox.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to determine the PK profile of 600 mg oral TPOXX (3 × 200-mg capsules) administered twice daily (BID) for 7 days in adult subjects weighing more than 120 kg to determine if a change in dosing regimen would be needed in these patients.

2.2 SECONDARY OBJECTIVE

The secondary objective of this study is to evaluate the safety and tolerability of 600 mg oral TPOXX administered BID for 7 days in adult subjects weighing more than 120 kg.

3. STUDY POPULATION

Approximately 36 male and female subjects will be enrolled at a single center in the United States to achieve at least 32 evaluable enrolled subjects.

3.1 INCLUSION CRITERIA

Each subject must meet all the following criteria to be enrolled in this study:

1. Subject is male or female between 18 and 50 years of age, inclusive.
2. Subject has a body weight >120 kg at screening, at check-in on Day -1, and prior to dosing on Day 1.
3. Women of childbearing potential, have a negative β human chorionic gonadotropin pregnancy test (serum) at the screening visit and a confirmatory negative serum

pregnancy test on Day –1 before receipt of study drug, and meet 1 of the following criteria:

a. The subject or their partner has undergone surgical sterilization
b. The subject is postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause and has a documented plasma follicle-stimulating hormone level >40 IU/mL
c. The subject agrees to be abstinent (ie, heterosexually inactive or women in a religious order)
d. The subject agrees to consistently use 1 of the following methods of contraception from the beginning of screening (which they had been consistently using for at least 30 days before the first dose of study drug) through 30 days after the last dose of study drug:
    i. Condoms, male or female, with a spermicide

       NOTE: For male subjects, condoms must be used for 90 days after the last dose of study drug.
    ii. Diaphragm or cervical cap with spermicide
    iii. Intrauterine device with spermicide
    iv. Oral contraceptives or other hormonal methods

       NOTE: Subject must agree to use an additional nonhormonal method of contraception in conjunction with oral contraceptives.
    v. Male sexual partner who had undergone a vasectomy at least 3 months before screening.

4. Male subjects must agree to not donate sperm from the first dose of study drug through 90 days after the last dose of study drug.
5. Subject is considered by the investigator to be in good general health as determined by medical history (no hospitalizations for chronic medical conditions in the previous 2 years), clinical laboratory results, vital sign measurements, 12-lead ECG results, and physical examination findings at screening.
6. Subject agrees to comply with all protocol requirements.
7. Subject is able to provide written informed consent.
8. Subject agrees to comply with the dietary requirements.

9. Subject does not intend to lose weight (diet or weight loss) from the screening visit and throughout the study.

3.2 EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded from the study:

1. Subject is a female who is pregnant or breastfeeding or planning to become pregnant within 3 months after the last dose of study drug.
2. Subject has a history of any clinically significant conditions including:
   - Asthma treated with oral systemic steroids within the past 6 months
   - Diabetes mellitus (type 1 or 2), with the exception of gestational diabetes
   - Thyroidectomy or thyroid disease that required medication within the past 12 months
   - Serious angioedema episodes within the previous 3 years or requiring medication in the previous 2 years
   - Head trauma resulting in a diagnosis of traumatic brain injury other than concussion
   - Frequent episodes of headache.
3. Subject has received treatment in another clinical study of an investigational drug (or medical device) within 30 days or 5 half-lives (whichever is longer) before the first dose of study drug.
4. Subject has been previously enrolled in any clinical study involving TPOXX (tecovirimat).
5. Subject has a history of relevant drug and/or food allergies (ie, allergy to tecovirimat or excipients, or any significant food allergy that could preclude a standard diet in the study site).
6. Subject has any condition possibly affecting drug absorption (eg, previous surgery on the gastrointestinal tract, including removal of parts of the stomach, bowel, liver, gallbladder, or pancreas, with the exception of appendectomy).
7. Subject has evidence or history of clinically significant allergic (except for untreated, asymptomatic, seasonal allergies at time of the first dose of study drug), hematological, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, or neurological disease. Exceptions to these criteria (eg, stable, mild

joint disease unassociated with collagen vascular disease) may be made following discussions with the medical monitor.

8. Subject has a history of cardiac disease, symptomatic or asymptomatic arrhythmias, syncopal episodes, or risk factors for torsades de pointes (eg, heart failure, hypokalemia).
9. Subject has a family history of sudden cardiac death not clearly due to acute myocardial infarction.
10. Subject has a seizure disorder or history of seizures (does not include childhood febrile seizures) or a past history that increases seizure risks such as significant head injury that caused loss of consciousness or other changes in the subject's daily function, concussion, stroke, central nervous system infection or disease, or alcohol or drug abuse or family history of idiopathic seizures.
11. Subject has a history of a peptic ulcer or significant gastrointestinal bleed.
12. Subject has a bleeding disorder diagnosed by a doctor (eg, factor deficiency, coagulopathy, or platelet disorder requiring special precautions) or significant bruising or bleeding difficulties with blood draws.
13. Subject has a malignancy that is active, or treated malignancy for which there is not reasonable assurance of sustained cure, or malignancy that is likely to recur during the period of the study (subject should be in complete remission for at least 5 years).
14. Subject has neutropenia or other blood dyscrasia determined to be clinically significant by the investigator.
15. Subject has used any of the following prohibited medications from within 7 days (or 5 half-lives, whichever is longer) before the first dose of study drug: antidiabetic medication; anticoagulants; anticonvulsants; substrates of the BCRP transporter including methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, and topotecan; substrates of CYP2C8 including repaglinide, paclitaxel, Montelukast, pioglitazone, rosiglitazone; and substrates of CYP2C19 including S-mephenytoin, clobazam, diazepam, rabeprazole, voriconazole, lansoprazole, and omeprazole. Medications not listed here that are known (or thought) to be CYP3A4 substrates may be allowed at the investigator's discretion, after consultation with the medical monitor, if administration poses little to no risk to the subject.

16. Subject has a history of drug or alcohol abuse or dependency within the last year before screening.
17. Subject has a history of an eating disorder.
18. Subject has a current or recent (<30 days before screening) history of clinically significant bacterial, fungal, or mycobacterial infection.
19. Subject has a current clinically significant viral infection.
20. Subject has a known clinically significant chronic viral infection (eg, human T cell lymphotropic virus I or II).
21. Subject has consumed grapefruit or grapefruit juice, Seville orange or Seville orange-containing products (eg, marmalade), or caffeine- or xanthine-containing products within 48 hours before the first dose of study drug or throughout the study.
22. Subject has used any prescription (excluding hormonal birth control) or over-the-counter medication (including herbal or nutritional supplements) within 14 days before the first dose of study drug.
23. Subject demonstrates long-term use (≥14 consecutive days) of glucocorticoids including oral or parenteral prednisone or equivalent (>20 mg total dose per day) or high-dose inhaled steroids (>800 mcg/day of beclomethasone dipropionate or equivalent) within the preceding 1 month (low-dose [≤800 mcg/day of beclomethasone dipropionate or equivalent] inhaled and topical steroids are allowed).
24. Subject has donated >450 mL blood or blood components within 30 days before the first dose of study drug. The investigator should instruct subjects who participate in this study to not donate blood or blood components for 4 weeks after the completion of the study.
25. Subject is a smoker or has used nicotine or nicotine-containing products (eg, cigarettes, electronic vapor cigarettes, cigars, chewing tobacco, snuff, nicotine patches, or nicotine gum) within 6 months before the first dose of study drug.
26. Subject has consumed pomegranate or pomegranate juice, pomelo fruits or pomelo juice, or alcohol within 72 hours before the first dose of study drug.
27. Subject reports participation in strenuous activity or contact sports within 24 hours before the first dose of study drug.

28. Subject has known hepatitis B or C infection or positive test for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus type 1 or 2 antibodies at screening.
29. Subject has a positive test result for amphetamines (including methamphetamines and ecstasy/methylenedioxymethamphetamine), barbiturates, benzodiazepines, cannabinoids (including tetrahydrocannabinol), cocaine metabolites, opiates (including heroin, codeine, and oxycodone), or alcohol at screening or check-in.
30. Subject has any of the following laboratory test results within 28 days before the first dose of study drug:
    - Estimated serum creatinine clearance (Cockcroft-Gault) <90 mL/min
    - Creatinine in males >1.7 mg/dL and in females >1.4 mg/dL (1.3 times the upper central laboratory reference range)
    - Hemoglobin ≤10% of the lower central laboratory reference range
    - White blood cell count not within the central laboratory reference range
    - Absolute neutrophil count <1000 cells/mm^3
    - Platelets not within ±10% of central laboratory reference range
    - Alanine aminotransferase >1.5 times above the upper central laboratory reference range
    - Aspartate aminotransferase >1.5 times above the upper central laboratory reference range
    - Alkaline phosphatase >20% above the upper central laboratory reference range
    - Hemoglobin A1c ≥7.0%
    - Cholesterol ≥300 mg/dL and low-density lipoprotein ≥190 mg/dL.
31. Subject has a blood pressure considered to be clinically significant by the investigator. Blood pressure may be retested twice in the sitting position at 5-minute intervals.
32. Subject has a resting heart rate of <40 beats per minute or >100 beats per minute at screening.
33. Subject has an abnormal ECG at screening that is determined by the investigator to be clinically significant.
34. Male subject has a QTcF >450 ms or female subject has a QTcF >470 ms at screening or Day –1.
35. In the opinion of the investigator, the subject is not suitable for entry into the study.

3.3 OTHER SCREENING CONSIDERATIONS

3.3.1 Subject Restrictions During the Study

- Subjects must be willing to remain confined at the study site from check-in (Day –1) until safety assessments are completed on Day 9.
- Subjects who have abnormal physical examination findings or an ongoing AE/SAE on Day 9 that is deemed related to study drug or per investigator or SIGA discretion will return to the study site on Day 14 (+2 days) for a follow-up visit.

3.4 WITHDRAWAL OF SUBJECTS FROM THE STUDY

3.4.1 Reasons for Withdrawal

Subjects can withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment.

The investigator may withdraw a subject from the study for any of the following:

- The subject is in violation of the protocol.
- The subject experiences a serious or intolerable AE.
- The subject becomes pregnant.
- The subject is noncompliant.
- The subject has laboratory abnormalities for assessments listed in Sections 4.1 or 4.2 that meet Grade 3 or Grade 4 on the Division of Acquired Immune Deficiency Syndrome (DAIDS) AE Grading Table Version 2.1 July 2017, any other Grade 3 or Grade 4 AE; or a Grade 2 or higher rash considered by the investigator to be possibly, probably, or definitely related to study drug.
- The subject develops, during the course of the study, symptoms or conditions listed in the exclusion criteria.
- The subject requires a medication prohibited by the protocol.
- The subject requests an early discontinuation for any reason.
- The subject′s primary care provider requests that the subject be withdrawn.

- The independent safety monitor (ISM), SIGA, or the FDA requests subject withdrawal based on study safety findings.

The investigator can also withdraw a subject upon the request of SIGA or if SIGA terminates the study. Upon occurrence of a SAE or intolerable AE, the investigator will confer with SIGA. If a subject is discontinued because of an AE, the event will be followed until it is resolved or stabilized as determined by the investigator and/or the medical monitor.

3.4.2 Handling of Withdrawals

Subjects are free to withdraw from the study at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of SIGA.

When a subject withdraws from the study, the reason(s) for withdrawal will be recorded by the investigator in the electronic case report form (eCRF). Whenever possible, any subject who withdraws from the study prematurely will undergo all Day 9/early discontinuation assessments (Table 9-1). Any subject who fails to return for final assessments will be contacted by the study site personnel in an attempt to have them comply with the protocol. The status of subjects who fail to complete final assessments will be documented in the eCRF.

3.4.3 Halting Rules

The medical monitor, investigator, SIGA, and ISM will review all AEs. All AEs determined by the investigator to be severe and possibly, probably, or definitely related to study drug, as well as all clinical assessments, laboratory test results, ECG results, or vital sign measurements that meet Grade 3 criteria on the DAIDS AE Grading Table will be assessed by the medical monitor, who will make a recommendation as to whether or not halting of the study should occur. At the discretion of the medical monitor, depending on the assessment of the severity of the event, the recommendation to halt the study may be made after consultation with the investigator, SIGA, and the ISM.

The study will be temporarily halted (no new enrollments and no further study drug administration) by the investigator and the medical monitor, SIGA, and the ISM will be promptly notified according to the following criteria:

- One subject experiences a Grade 4 AE assessed as possibly, probably, or definitely related to study drug.

- There is a subject death assessed as possibly, probably, or definitely related to study drug.
- One subject experiences a seizure assessed as possibly, probably, or definitely related to study drug.
- Two or more subjects experience the same or similar SAEs that are possibly, probably, or definitely related to the study drug.
- Three or more subjects experience the same or similar AEs that are Grade 3 or above and are possibly, probably, or definitely related to the study drug.

Study enrollment and study drug administration would resume if review of the AEs that caused the halt resulted in a recommendation to permit further continuation. In such an instance, SIGA, with participation by the investigator and the medical monitor, would consult with the ISM to conduct the review of all AEs that meet the criteria for halting the study. The study would remain suspended until the events were reviewed by the ISM and a recommendation was made as to whether the study should be continued or stopped. This constitutes a minimum criterion, and the decision to halt the study may be made based on any other criteria that, in the judgment of the investigator, with agreement of the medical monitor and ISM, indicate a potentially serious safety concern. The investigator will advise SIGA immediately if any of the halting rules are met.

4. STUDY DESIGN

This is an open-label, multiple-dose study to assess the safety, tolerability, and PK of TPOXX 600 mg BID when administered orally for 7 days to adult subjects weighing more than 120 kg. A total of 36 subjects, ages 18 to 50, inclusive, will be enrolled. The study will consist of a screening period (Day –28 to Day –2), a treatment and confinement period (Days –1 to 9), a follow-up telephone call or visit (Day 14 [+2 days]), and a follow-up telephone call (Day 37 [+2 days]).

Subjects will undergo screening evaluations to determine eligibility within 28 days before study drug administration. Subjects will be admitted to the study site on Day –1 to complete baseline assessments; results of these assessments must be reviewed by the investigator before dosing. Starting in the morning of Day 1, subjects will receive 600 mg oral TPOXX BID for 7 days (Days 1 through 7).

All subjects will be provided meals (consisting of approximately 600 calories and 25 g fat) 30 minutes prior to study drug administration and subjects must fast for 2 hours after taking

study drug. Subjects should eat this meal within 30 minutes or less of taking study drug. Study drug and meals must be taken with water only, and no other beverage except water should be ingested within 3 hours before or 3 hours after study drug administration.

Subjects will remain confined to the study site for collection of PK samples and will be carefully monitored for safety and tolerability until discharge on Day 9. Subjects who have abnormal physical examination findings or an ongoing adverse event (AE)/serious adverse event (SAE) on Day 9 that is deemed related to study drug or per investigator or SIGA discretion will return to the study site on Day 14 (+2 days) for a follow-up visit. All other subjects will have the Day 14 (+2 days) follow-up via telephone. All subjects will have a follow-up telephone call 30 days after administration of the last dose of study drug (Day 37 [+2 days]) to report any SAEs. At the time of discharge from the clinical research unit, subjects will be instructed to notify the investigator of any SAEs that occur within 30 days after administration of the last dose of study drug. Serious AEs will be followed until the SAE is stable or until resolution as determined by the investigator and/or medical monitor.

The total duration of the study for each subject, including the screening period, treatment period, and the Day 37 (+2 days) follow-up telephone call, will be approximately 65 days.

4.1.1 Replacements

At the discretion of the investigator, and after consultation with the medical monitor, any subject who withdraws before completing the study may be replaced to retain the target of 32 evaluable enrolled subjects.

5. STUDY TREATMENT

5.1 TREATMENT ADMINISTERED

On Days 1 to 7, all subjects will receive an oral dose of TPOXX 600 mg (3 × 200-mg capsules) BID, approximately 12 hours (±30 minutes) apart, for 7 days.

All subjects will be provided meals consisting of approximately 600 calories and 25 g fat, 30 minutes before study drug administration. Subjects should eat this meal within 30 minutes or less of taking study drug. Study drug will be administered approximately 30 minutes after the start of the meal. All doses of study drug will be administered to subjects by study site personnel with approximately 240 mL of water. Subjects must fast 2 hours after taking study

drug. Study drug and meals must be taken with water only, and no other beverage except water should be ingested within 3 hours before or 3 hours after study drug administration.

5.2 STUDY DRUG

TPOXX will be supplied as 200-mg capsules containing tecovirimat monohydrate as the active pharmaceutical ingredient. The TPOXX capsules are immediate release, size 0, orange and black, hard gelatin capsules containing white to off white powder. All inactive ingredients/excipients are generally recognized as safe and are United States Pharmacopeia/National Formulary grade. The TPOXX excipients are shown in Table 5-1.

Table 5-1 Excipients of TPOXX Capsules

Component	Quality Designation
Microcrystalline cellulose	NF[a]
Lactose monohydrate	NF
Croscarmellose sodium	NF[a]
Colloidal silicon dioxide	NF
Hydroxypropyl methylcellulose	USP
Sodium lauryl sulfate	NF
Purified water[b]	USP
Magnesium stearate	NF

Abbreviations: NF, National Formulary; USP, United States Pharmacopeia.

[a] Microcrystalline cellulose and croscarmellose sodium are added as intragranular and extragranular excipients.

[b] Removed during processing.

Compendial components are tested and released in accordance with full compendial methods and specifications before their use in clinical formulations. TPOXX 200-mg capsules are manufactured and analyzed for clinical use in accordance with Current Good Manufacturing Practices.

TPOXX capsules are manufactured by:
Catalent Pharma Solutions
1100 Enterprise Drive
Winchester, KY 40391.

Further information on TPOXX can be found in the TPOXX full prescribing information.[2]

5.2.1 Study Drug Packaging and Storage

TPOXX capsules are packaged, labeled, distributed, and placed on stability testing in accordance with Current Good Manufacturing Practice and International Council for Harmonisation (ICH) guidelines.

The 200-mg TPOXX capsules are supplied in 75-mL high density polyethylene bottles fitted with a heat induction seal and child-resistant screw cap closure system. Each bottle of study drug will contain 42 capsules and will be labeled with the drug name, SIGA's name, a space to fill in the protocol number, and a space to fill in the bottle number.

SIGA (or designee) will provide the investigator and study site with adequate quantities of TPOXX.

All study drug must be stored in a secure area (eg, a locked cabinet), protected from moisture and light, and stored at 15°C to 30°C (59°F to 86°F). Study drug should not be refrigerated or used beyond the expiration dates provided by the manufacturer. The study site will be required to keep a temperature log to establish a record of compliance with these study drug storage conditions. All study drug will be kept in a secure cabinet or room with access restricted to necessary study site personnel.

5.2.2 Study Drug Accountability

The investigator will maintain accurate records of receipt of all study drug, including dates of receipt. Accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. Study drug accountability will be recorded in the subject source documentation, entered into the eCRF, and should be reviewed by the monitor during each monitoring visit. On a regular basis and at the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable regulations.

5.3 TREATMENT COMPLIANCE

All doses of the study drug will be administered in the study site under direct observation of study site personnel and recorded in the eCRF. Per standard clinic procedure, study site personnel will perform a mouth check and inspect all dose containers to ensure that the entire dose was administered. Following completion of dosing procedures and return of dosing containers to the pharmacy by team members, pharmacy staff will follow standard clinic

procedures for study drug reconciliation. SIGA will provide information to PPD for destruction of returned used and unused study drug and study drug bottles.

The date and time of study drug dosing will be captured and recorded on the appropriate page of the eCRF. If a subject is not administered study drug, the reason for the missed dose will be recorded.

5.3.1 Prior and Concomitant Medications

Restrictions for prior and concomitant medications and therapies are provided in Sections 4.1 and 4.2. Prior and concomitant medications and therapies will be coded using the latest version of the World Health Organization Drug Dictionary.

5.3.1.1 Prior Medications

Information regarding prior medications taken by the subject within the 30 days before signing the informed consent form (ICF) will be recorded in the subject's eCRF.

5.3.1.2 Concomitant Medications

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. If a concomitant medication listed in Section 4.2 is taken it will be documented as a protocol deviation and a joint decision will be made by the investigator and SIGA to continue or discontinue the subject based on the time the medication was administered, its pharmacology and PK, and whether the use of the medication will compromise the safety of the subject or the interpretation of the data. The investigator is responsible for ensuring that details regarding the medication are adequately recorded in both the subject's source document and the eCRF.

6. STUDY PROCEDURES

Before performing any study procedures, all potential subjects will sign an ICF as outlined in Section 9.3.2.3. Subjects will undergo study procedures at the time points specified in the schedule of events (Table 9-1).

The total amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

6.1 PHARMACOKINETIC ASSESSMENTS AND ENDPOINTS

Blood samples for PK analysis of TPOXX will be collected from all subjects Day 1 before study drug administration (0 hour), at 0.5, 1, 2, 4, 6, 8, 12 (before the PM dose), 14, 16, 18, 20, and 24 hours (before the AM dose on Day 2), on Day 6 (before the AM dose and 4 hours after the AM dose), on Day 7 before the AM dose (0 hour), at 0.5, 1, 2, 4, 6, 8, 12 (before the PM dose), 14, 16, 18, 20, and 24 hours (Day 8, 24 hours after the AM dose on Day 7), and on Day 9 (48 hours after the AM dose on Day 7).

For PK samples, the acceptable window for collection from the scheduled collection time point will be as follows: ±5 minutes for the time points from 1 to 8 hours and ±15 minutes for the 12- to 48-hour time points.

The following plasma PK parameters will be calculated for TPOXX using actual sampling times rather than scheduled sampling times and will include but are not limited to:

- Area under the plasma concentration-time curve (AUC) from time 0 to the last quantifiable measurement (AUC_{0-t})
- AUC from time 0 extrapolated to infinity ($AUC_{0-\infty}$)
- AUC from time 0 to 24 hour (AUC_{0-24})
- AUC during the first dosing interval (tau = 12 hours) (AUC_{0-tau})
- Maximum drug concentration in plasma (C_{max})
- Time to C_{max} (T_{max})
- Apparent volume of distribution (V_d/F)
- Apparent total body clearance (CL/F)
- Concentration observed prior to the next dose administration (C_{trough})
- Terminal elimination half-life ($t_{1/2}$)
- Terminal elimination rate constant (λ_z)
- Percentage of $AUC_{0-\infty}$ extrapolated from the last quantifiable measurement to infinity ($\%AUC_{extrap}$).

6.1.1 Pharmacokinetic Sample Collection, Shipping, and Storage

Blood samples (approximately 5 mL) for the determination of plasma concentrations of TPOXX will be collected in 5-mL lavender-topped K_3EDTA Vacutainer® tubes using a 21 gauge or larger needle, or from an indwelling intravenous catheter using a vacutainer tube. Blood samples should be placed on wet ice or equivalent (approximately 4°C to 8°C) and kept at this temperature until processed to separate plasma.

The exact time and date of sample collection will be recorded for each sample by the investigator or designee on the subject's eCRF, the vacutainer and cryovial labels, and the specimen shipping log. In addition, the time of study drug administration before PK sampling will be recorded on the subject's eCRF. Labels will be created by the site and should contain the protocol number, matrix (plasma), subject number, date, and time drawn. For information that is not preprinted on the label, a fine tipped indelible marking pen is to be used to complete the entry.

The 5-mL blood sample will be centrifuged in a refrigerated centrifuge immediately, if possible, or within 60 minutes of collection at 1000 to 1200 × *g* (2000 to 3000 rpm) for 10 minutes to separate plasma. Each plasma sample should be transferred via pipette into 2 cryovials labeled as described previously and should be capped tightly. The second tube will be a duplicate and retained at the site as a backup sample. If red blood cells are inadvertently drawn into the plasma, the sample should be re-centrifuged as soon as possible. Adequate space between the solution and the tube cap should be allowed for expansion during freezing.

Cryovial tubes containing plasma samples must be frozen at –70°C or below until shipment in a freezer equipped with a temperature monitor and temperature-activated alarm. Uncentrifuged specimens should not be frozen.

The study site will batch ship sets of frozen plasma samples. A log sheet listing the samples being shipped will be included in each shipment. The samples will be sent on dry ice via courier to Alturas Analytics (Moscow, ID). The back-up sets will remain at the site until confirmation that the first sets have been received. After receipt confirmation is received from Alturas Analytics, the back-up sets should be shipped. The site will contact Alturas Analytics and coordinate the shipment prior to sending the samples. Shipments before weekends or holidays must be avoided.

The samples will be shipped for analysis to:

Alturas Analytics
1324 Alturas Drive
Moscow, ID 83843

The bioanalytical laboratory will store all plasma samples at –70°C until analysis for tecovirimat is complete. SIGA will advise Alturas to destroy any remaining plasma samples after regulatory review is complete or the samples have met their applicable length of stability, whichever comes sooner.

6.1.2 Pharmacokinetic Sample Analysis

Pharmacokinetic samples will be analyzed by Alturas Analytics using a validated liquid chromatography coupled with tandem mass spectrometry assay for tecovirimat in human plasma method in accordance with the US FDA Guidance for Industry on Bioanalytical Method Validation.[3]

6.2 SAFETY ASSESSMENTS AND ENDPOINTS

Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory test results (hematology, serum chemistry, pregnancy, and urinalysis), vital sign measurements (systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature), 12-lead ECG results, and physical examination findings. Adverse events will be assessed from the time of the first dose of study drug until the follow-up telephone call on Day 37 (+2 days).

6.2.1 Adverse Events

6.2.1.1 Adverse Event Definitions

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

An AE is any event or other untoward medical occurrence, including those AEs that result from dosing errors, which may present during administration of a study drug or during a reasonable follow-up period and which does not necessarily have a causal relationship with this treatment. An AE is any unfavorable and unintended sign (eg, a clinically significant

abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered to be related to the medicinal product. All AEs will be followed until the AE is resolved or stabilized as determined by the investigator and/or the medical monitor.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure to study drug.

An adverse reaction is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there are reasons to conclude that the drug caused the event.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the study drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a study drug.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the TPOXX full prescribing information or at the specificity or severity that has been observed with the study drug being tested. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the TPOXX full prescribing information referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the TPOXX full prescribing information listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the TPOXX full prescribing information as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

An AE or suspected adverse reaction is considered an SAE if, in the view of either the investigator or SIGA, it results in any of the following outcomes:

- Results in death.
- Is life threatening (subject is at immediate risk of death at the time of the event).
- Requires inpatient hospitalization or prolongation of existing hospitalization, other than elective hospitalization, during the period of protocol defined surveillance.

- Results in congenital anomaly or birth defect.
- Results in a persistent or significant disability/incapacity.
- Any other important medical event that may not result in death, be life threatening, or requires hospitalization may be considered an SAE when, based on appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition or is otherwise considered to be medically significant.

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

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or SIGA, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious AEs will be followed until the SAE is stable or until resolution as determined by the investigator and/or the medical monitor.

6.2.1.2 Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to SIGA by PPD. Adverse events and SAEs will be assessed from the first dose of study drug through the telephone call on Day 37 (+2 days).

At every study visit or assessment, subjects will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to subject observations, AEs will be documented from any data collected on the AE page of the eCRF (eg, laboratory values, physical examination findings, and ECG changes) or other documents that are relevant to subject safety.

6.2.1.3 Reporting Adverse Events

All AEs reported or observed from the first dose of study drug through the follow-up telephone call on Day 37 (+2 days) will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, type of event, date and time of onset, investigator-specified assessment of severity and relationship to study drug, date and time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported.

All AEs will be followed until they are resolved or stabilized as determined by the investigator and/or medical monitor. These data will be reviewed on an ongoing basis by the study coordinator, the investigator, the medical monitor, and the ISM. This requirement indicates that for some events, follow-up may be required after the subject has completed study participation. These events will be reported by SIGA, as required, to the FDA.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE. Prior to this, medical conditions reported by subjects are considered medical history.

6.2.1.4 Reporting of Serious Adverse Events

Any AE considered serious by the investigator or which meets SAE criteria (Section 6.2.1.1), or any other event or condition regardless of grade, which in their judgment represents a reportable event, must be reported to the medical monitor and SIGA as soon as the investigator becomes aware of the event. In addition, the event must be reported to PPD via the SAE hotline. The PPD SAE Report Form must be submitted within 24 hours of knowledge of the event. SIGA (or designee) will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in US Title 21 Code of Federal Regulations (CFR) Parts 312 and 320. The investigator is responsible for notifying the institutional review board (IRB) directly.

In addition, the investigator (or designee) must report any Grade 3 (severe) AE that they deem possibly, probably, or definitely related to study drug to the medical monitor and SIGA within 24 hours after becoming aware of the event.

After notification from the investigator, SIGA will report all study drug-related and unexpected SAEs (those not listed in the TPOXX full prescribing information) to the FDA within 15 calendar days of first knowledge. Fatalities or life-threatening events assessed as related and unexpected will be reported to the FDA within 7 calendar days of first knowledge. The ISM will also receive these reports.

The following contact information is to be used for SAE reporting:

[redacted]

The collection and monitoring period for SAEs is 30 days after administration of the last dose of study drug. At the time of discharge or early termination from the study site, the subject will be instructed to notify the investigator of any SAEs that occur within 30 days after the last dose of study drug.

All subjects will have a follow-up telephone call 30 days after administration of the last dose of study drug (Day 37 [+2 days]) to report any SAEs.

6.2.1.5 Assessment of Severity

All AEs will be graded for intensity according to the current DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1 July 2017.

Any laboratory or clinical AE that is not listed on the DAIDS Table will be assessed for severity and classified into 1 of 5 clearly defined categories as follows:

- Grade 1 (Mild): Events require minimal or no treatment and do not interfere with the subject's daily activities.
- Grade 2 (Moderate): Events result in a low level of inconvenience or concern with the therapeutic measures and may cause some interference with normal functioning.

- Grade 3 (Severe): Events interrupt a subject's usual daily activity, may require systemic drug therapy or other treatment, and are usually incapacitating.

- Grade 4 (Life-threatening): Event that, in the opinion of the investigator, places the subject at immediate risk of death from the reaction as it occurred (ie, it does not include a reaction that, had it occurred in a more severe form, might have caused death).

- Grade 5 (Death).

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterized as intermittent requires documentation of onset and duration of each episode.

6.2.1.6 Assessment of Causality

Any occurrence of an AE will be assessed for relationship to the study drug. A causal relationship means that the study drug caused (or is reasonably likely to have caused) the AE. This usually implies a relationship in time between the drug and the AE; for example, the AE occurred shortly after the subject received the study drug.

The investigator who examines and evaluates the subject will determine AE causality based on the temporal relationship to administration of the study drug, the pharmacology of the study drug, and their clinical judgment. Terms used to describe the degree of causality between a study drug and an AE are definitely related, probably related, possibly related, unlikely related, or not related.

The best estimate at the time of reporting of an event and the degree of certainty about the causal relationship between the study drug administration and the AE will be graded as follows:

<u>Associated</u>

- Definitely Related: The AE and administration of study drug are related in time, and a direct association can be demonstrated (eg, the event disappears or decreases with reduction in dose or cessation of study drug and recurs with re-exposure).

- Probably Related: The AE and administration of study drug are reasonably related in time and/or follow a known pattern of response, and the AE is more likely explained by study drug than other causes.

- Possibly Related: The AE and administration of study drug are reasonably related in time and/or follow a known pattern of response, but the AE can be explained equally well by causes other than study drug (eg, could readily have been produced by the subject's clinical state or could have been due to environmental or other interventions).

Not Associated

- Unlikely Related: A potential relationship between study drug and the AE could exist (ie, the possibility cannot be excluded), but the AE is most likely explained by causes other than the study drug (eg, could readily have been produced by the subject's clinical state or could have been due to environmental or other interventions).

- Not Related: The AE is clearly due to extraneous causes (eg, underlying disease, environment) or exposure to the study drug has not occurred. Such events MUST have an alternative, definitive etiology documented in the subject's medical record.

6.2.1.7 Follow-up of Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed until they are resolved or stabilized as determined by the investigator and/or medical monitor.

6.2.1.8 Reactogenicity

At this time, there is no definitive information on allergic activity of TPOXX. Reactogenicity will be monitored in subjects during the study treatment period.

6.2.1.9 Reporting of Pregnancy

Pregnant women are not eligible to participate in the study. Subjects must be counseled regarding prevention of pregnancy and encouraged to make every effort to avoid pregnancy during study participation. If a female subject becomes pregnant during study participation, study drug dosing will be discontinued, and the subject will be withdrawn from the study. The pregnancy itself is not considered an SAE. However, the investigator must complete the pregnancy report form and fax it to PPD Pharmacovigilance within 24 hours of knowledge of the pregnancy. After delivery or termination of pregnancy, the follow-up pregnancy report form should be completed and submitted via fax to PPD Pharmacovigilance. Spontaneous abortions should always be reported as SAEs. Pregnancy data will be captured and followed by PPD. All pregnancies and outcomes will be tracked. The case will not be closed until after the child is followed for 3 months.

If there are complications during the pregnancy, the complications will be recorded as AEs in the usual manner. The subject will be asked to report the outcome of the pregnancy. If there is a congenital anomaly in the infant, this will be recorded as an SAE in the data forms for the mother (ie, the study subject).

If a subject becomes pregnant during the study after receiving the study drug, all safety evaluations will be collected as per protocol. In addition, at the time that the pregnancy is reported, consent will be requested to contact the subject and her physician in the postpartum period to assess delivery and health status of the neonate.

If the partner of a male subject becomes pregnant, the partner will be asked for consent to allow her treating physician to provide SIGA or its designee with follow-up information regarding the pregnancy and its outcome.

6.2.2 Clinical Laboratory Testing

Clinical laboratory tests will be performed by the PPD Central Laboratory. Blood samples will be collected at the time points indicated in the schedule of events (Table 9-1) and will be prepared using standard procedures.

Repeat clinical laboratory tests may be performed at the discretion of the investigator, if necessary, to evaluate inclusion and exclusion criteria or clinical laboratory abnormalities. PPD central laboratory will provide the reference ranges for all clinical laboratory safety parameters.

The following clinical laboratory assessments will be performed:

Hematology	Hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, total and differential leukocyte count (basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume, platelet count, red blood cell count, and red cell distribution width
Serum Chemistry	Alanine aminotransferase, albumin, alkaline phosphatase, anion gap, aspartate aminotransferase, bilirubin (total), blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine clearance (calculated[a]), gamma-glutamyltransferase, globulin, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total protein, and uric acid

Urinalysis	Appearance, bilirubin, blood, color, glucose, ketones, leukocytes, microscopy (performed if dipstick is ≥1+; includes bacteria, cast, crystals, epithelial cells, red blood cells, and white blood cells), nitrates, pH, protein, specific gravity, turbidity, and urobilinogen

[a] Creatinine clearance (CLcr) will be calculated using the Cockcroft-Gault formula:

$$CLcr\ (mL/min) = \frac{[140 - age(years)] \times weight\ (kg)}{72\ \times serum\ creatinine\ (mg/dL)}\{\times 0.85\ if\ female\}$$

Glycosylated hemoglobin A1c and a fasting lipid panel including cholesterol (total, high-density lipoprotein, calculated low-density lipoprotein, and triglycerides) will be performed at screening.

Serum pregnancy test (β human chorionic gonadotropin) for women of childbearing potential will be performed at screening and on Day –1.

A serum follicle-stimulating hormone test for postmenopausal women will be performed at screening.

Human immunodeficiency virus (type 1 and 2) antibodies, hepatitis B surface antigen, and hepatitis C virus antibody will be assessed at screening only.

A urine drug screen for alcohol, amphetamines (including methamphetamines and ecstasy/methylenedioxymethamphetamine), barbiturates, benzodiazepines, cannabinoids (including tetrahydrocannabinol), cocaine metabolites, and opiates (including heroin, codeine, and oxycodone) will be performed at screening and on Day –1.

Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference ranges for each laboratory parameter. The investigator will determine whether any of the abnormally high or low results are clinically significant or not clinically significant. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If a clinically significant change from the screening value is noted, the clinically significant value and reason for clinical significance will be documented on the AE page of the eCRF. The investigator will continue to monitor the subject with additional assessments until the values have reached the reference range or the values at screening or until the investigator determines that follow-up is no longer medically necessary.

6.2.3 Medical History

A complete medical history will be obtained, including a review of systems, recreational and prescription drug use, over-the-counter drug use, nicotine and alcohol use, and past hospitalizations.

6.2.4 Vital Sign Measurements

Vital signs will be measured after the subject has been seated for at least 5 minutes at the time points indicated in the schedule of events (Table 9-1).

Vital sign measurements will include systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature.

When procedures are overlapping and occurring at the same time point, the order of procedures should be ECG, vital sign measurements, and then blood collection, with the blood collection scheduled to occur at the nominal time point, unless dictated by other study events happening at that time, such as dosing requirements.

The investigator will determine whether any of the vital sign measurements are clinically significant or not clinically significant. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If a clinically significant change from the screening values is noted, the clinically significant value and reason for clinical significance will be documented on the AE page of the subject's eCRF. The investigator will continue to monitor the subject with additional assessments until the value has reached the reference range or the value at screening or until the investigator determines that follow up is no longer medically necessary.

6.2.5 Electrocardiograms

A 12-lead ECG will be obtained after the subject has been in the supine position for at least 10 minutes at the time points indicated in the schedule of events (Table 9-1). On Days 1, 4, and 7, an ECG will be recorded 4 hours after the AM study drug administration. The acceptable window for collection from the scheduled collection time point will ±15 minutes.

Electrocardiogram assessments will include comments on whether the tracings are normal or abnormal, rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST segment, T wave, and U wave abnormalities. In addition, the

following parameters will be measured and reported: heart rate; PR, RR, and QT intervals; QTcF; QT interval corrected using Bazett's formula; and QRS duration. All ECGs must be performed by an experienced ECG technician.

The investigator will determine whether any of the 12-lead ECG results are clinically significant or not clinically significant. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If a clinically significant change from screening is noted, the clinically significant value and reason for clinical significance will be documented on the AE page of the subject's eCRF. The investigator will continue to monitor the subject with additional assessments until either the values have reached reference range or the values at screening or until the investigator determines that follow-up is no longer medically necessary.

6.2.6 Physical Examinations

A full physical examination will be performed at the time points indicated in the schedule of events (Table 9-1) and will include assessment of the following body systems: head, ears, eyes, nose, and throat; cardiac (including auscultation of heart); pulmonary (chest) auscultation of lungs; abdomen; skin; musculoskeletal system; lymphatic system; and neurologic system (cranial nerves, sensation, motor function, coordination, reflexes, and mental status).

A symptom-directed physical examination will be performed at the time points indicated in the schedule of events (Table 9-1) (for those subjects who require it), and at unscheduled visits as necessary. This examination will include an assessment of the heart, lungs, abdomen, a neurologic review, and a review of symptoms for assessments and/or follow-up of reported or potential AEs.

Weight will be measured without shoes and in light clothing at screening and without shoes and in hospital gowns at all other time points indicated in the schedule of events (Table 9-1). The scales should be calibrated, and the same weight scale should be used throughout the study starting with Screening through Day 9. Weight measurements will be rounded to one decimal place.

Height will be measured at Check-in on Day -1.

6.2.7 Unscheduled Visits

Subjects will be provided with the contact information for the study site personnel. Subjects are free to contact study site personnel at any time, and the site may require an unscheduled visit for the purpose of physical examinations, laboratory tests, etc. Unscheduled visits will be documented by the site personnel in the source documents. Unscheduled procedures and laboratory tests and results will also be recorded in the eCRF.

7. STATISTICAL ANALYSIS PLANS

7.1 SAMPLE SIZE CALCULATIONS

The sample size (N = 36 [to allow at least 32 enrolled subjects to complete]) for this study is based on clinical and practical considerations and not on a formal statistical power calculation. The sample size is considered sufficient to effectively assess the PK and safety profiles of TPOXX.

7.2 ANALYSIS POPULATIONS

The Safety Population will include all subjects who receive at least 1 dose of study drug.

The PK Population will include subjects who receive study drug and have sufficient concentration data to facilitate the calculation of PK variables.

7.3 STATISTICAL ANALYSIS

Details of all statistical analyses will be described in a statistical analysis plan. All data collected will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings, but not included in the calculation of summary statistics.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation [SD], minimum, and maximum).

Baseline demographic and background variables will be summarized overall for all subjects. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. Frequency and percentage of subjects who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

7.3.1 Pharmacokinetic Analyses

Individual plasma concentration and time deviation data will be presented in a data listing. Plasma concentration data will be listed and summarized using the following descriptive statistics: number of subjects, arithmetic mean, SD, coefficient of variation (CV), geometric mean, geometric CV, median, minimum, and maximum. Individual and mean plasma concentration versus time profiles will be presented in figures on both linear and semilogarithmic scales.

The PK parameters of TPOXX will be analyzed based on the actual sampling times. All parameters will be determined using noncompartmental methods using Phoenix® WinNonlin® Version 8.0 or higher (Certara, L.P., Princeton, New Jersey) or SAS® Version 9.4 or higher (SAS Institute Inc., Cary, North Carolina).

The individual PK parameters and body weight-normalized PK parameters will be presented in data listings and summarized using the following descriptive statistics: number of subjects, arithmetic mean, SD, CV, median, minimum, maximum, geometric mean, geometric SD, and geometric CV.

7.3.2 Safety Analyses

Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities and summarized overall. All AE data will be presented in a data listing. Treatment-emergent AEs will be summarized overall, as well as by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be presented in the data listings and summarized overall.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results. Clinical laboratory data, vital sign measurements, 12-lead ECG results, and physical examination findings will be presented in data listings.

7.4 HANDLING OF BELOW THE LIMIT OF QUANTIFICATION AND MISSING DATA

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero for descriptive statistics. Geometric mean values will not be calculated or displayed when zero is the minimal value. Mean BLQ concentrations will be presented as BLQ, and the SD and CV will be reported as not applicable. Missing concentrations will be excluded from the calculations.

7.5 INTERIM ANALYSES

No formal interim safety analyses will be performed in this study.

8. REFERENCE LIST

1. Breman JG, Henderson DA. Diagnosis and management of smallpox. N Engl J Med. 2002;346(17):1300-8.

2. TPOXX (tecovirimat) [full prescribing information]. SIGA Technologies, Inc. Corvallis (OR); 2018. 18 p.

3. Department of Health and Human Services, Food and Drug Administration (US). Guidance for Industry. Bioanalytical Method Validation. May 2018. Available from: https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf.

9. APPENDICES

9.1 APPENDIX 1: LIST OF ABBREVIATIONS

Abbreviation	Term
$\%AUC_{extrap}$	percentage of $AUC_{0-\infty}$ extrapolated from the last quantifiable measurement to infinity
λ_z	terminal elimination rate constant
AE	adverse event
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from time 0 to 24 hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 extrapolated to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time 0 to the last quantifiable measurement
AUC_{0-tau}	area under the plasma concentration-time curve during the first dosing interval
BCRP	breast cancer resistance protein
BID	twice daily
BLQ	below the limit of quantification
CFR	Code of Federal Regulations
CL/F	apparent total body clearance
C_{max}	maximum drug concentration in plasma
C_{trough}	concentration observed prior to the next dose administration
CRA	clinical research associate
CV	coefficient of variation
CYP	cytochrome P450
DAIDS	Division of Acquired Immune Deficiency Syndrome
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
ISM	independent safety monitor
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic(s)
QTcF	QT interval corrected using Fridericia's formula
SAE	serious adverse event
SD	standard deviation
SOP	standard operating procedures
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event

Abbreviation	Term
T_{max}	time to maximum drug concentration in plasma
UGT	uridine diphosphate-glucuronosyltransferase
VARV	variola virus
V_d/F	apparent volume of distribution

9.2 APPENDIX 2: SCHEDULE OF EVENTS

Table 9-1 Schedule of Events

	Screening	Check-in	Treatment Period									Telephone Call or Follow-up Visit[a]	Follow-up Telephone Call[b]
Procedure[c] Day	**–28 to –2**	**–1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 or Early Discontinuation**	**14 (+2)**	**37 (+2)**
Admission to clinic		X											
Discharge from clinic[d]											X		
Informed consent	X												
Inclusion/exclusion criteria	X	X											
Medical history[e]	X	X											
Complete physical examination[f]	X	X							X		X		
Weight[g]	X	X	X[h]								X		
Height		X											
Vital sign measurements[i]	X	X	X[j]			X[j]			X[j]	X	X	X[k]	
Glycosylated hemoglobin (HbA1c)	X												
Fasting lipid panel[l]	X												
Clinical laboratory testing[m]	X[n]	X				X				X[o]	X[n]		
Serum follicle-stimulating hormone[p]	X												
Serum pregnancy test[q]	X	X											
Urine drug/alcohol screen[r]	X	X											
Serology (HBsAg, HCV, and HIV)	X												
12-Lead ECG[s]	X	X	X			X			X		X		
TPOXX administration[t]			X	X	X	X	X	X	X				
Pharmacokinetic sampling[u]			X	X				X	X	X	X		
Symptom-directed physical examination[v]				X	X	X	X	X				X[k]	
Adverse events			◄	———	———	———	———	———	———	———	X	———	►
Prior/concomitant medications	◄	———	———	———	———	———	———	———	X	———	———	———	►

Abbreviations: AE, adverse event; ECG, electrocardiogram; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PK, pharmacokinetic; SAE, serious adverse event.

Notes:

[a] The follow-up visit or telephone call will occur on Day 14 (+2 days), 7 days after the last dose of study drug. Subjects who have abnormal physical examination findings or an ongoing AE/SAE on Day 9 that is deemed related to study drug or per investigator or SIGA discretion will return to the study site on Day 14 (+2 days) for a follow-up visit. All other subjects will have the Day 14 (+2 days) follow-up via telephone.

[b] The follow-up telephone call will be made 30 days after the last dose of study drug (Day 37 [+2 days]).

[c] When procedures are overlapping and occurring at the same time point, the order of procedures should be ECG, vital sign measurements, and then blood collection, with the blood collection scheduled to occur at the nominal time point, unless dictated by other study events happening at that time, such as dosing requirements.

[d] Discharge following collection of all safety assessments.

[e] Including a review of systems; recreational, prescription, and over-the-counter drug use; nicotine and alcohol use; and past hospitalizations.

[f] Including assessment of the following body systems: head, ears, eyes, nose, and throat; cardiac (including auscultation of heart); pulmonary (chest) auscultation of lungs; abdomen; skin; musculoskeletal system; lymphatic system; and neurologic system (cranial nerves, sensation, motor function, coordination, reflexes, and mental status).

[g] Weight will be measured without shoes and in light clothing at screening and without shoes and in hospital gowns at all other time points. The scales should be calibrated and the same weight scale should be used throughout the study starting with Screening through Day 9. Weight measurements will be rounded to one decimal place.

[h] Weight will be collected prior to dosing.

[i] Vital sign measurements will include systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. Vital signs will be measured after the subject has been seated for at least 5 minutes.

[j] Vital sign measurements will be performed before dosing and 4 hours after the AM study drug administration on Days 1 and 7 and 4 hours after the AM study drug administration on Day 4. The acceptable window for collection from the scheduled collection time point is ±15 minutes.

[k] Collected only if subjects are required to return to the study site on Day 14 (+2 days) for a follow-up visit.

[l] Including cholesterol (total, high-density lipoprotein, calculated low-density lipoprotein, and triglycerides).

[m] Clinical laboratory testing will include hematology and serum chemistry.

[n] Clinical laboratory testing at screening and at Day 9 or early discontinuation will include hematology, serum chemistry, and urinalysis.

[o] Collect 12 hours after the PM study drug administration on Day 7.

[p] For postmenopausal women, a serum follicle-stimulating hormone test will be performed at screening.

[q] Women of childbearing potential only.

[r] Includes alcohol, amphetamines (including methamphetamines and ecstasy/methylenedioxymethamphetamine), barbiturates, benzodiazepines, cannabinoids (including tetrahydrocannabinol), cocaine metabolites, and opiates (including heroin, codeine, and oxycodone).

[s] A 12-lead ECG will be collected after the subject has been in the supine position for at least 10 minutes. On Days 1, 4, and 7, an ECG will be recorded 4 hours after the AM study drug administration. The acceptable window for collection from the scheduled collection time point is ±15 minutes.

[t] TPOXX, 600 mg (3 × 200-mg capsules) will be administered orally twice daily, approximately 12 hours (± 30 minutes) apart on Days 1 through 7. All subjects will be provided meals consisting of approximately 600 calories and 25 g fat, which will start 30 minutes before study drug administration. Subjects should eat this meal within 30 minutes or less of taking study drug. Study drug will be administered approximately 30 minutes after the start of the meal. All doses of study drug will be administered to subjects by study site personnel with approximately 240 mL of water. Subjects must fast 2 hours after taking study drug. Study drug and meals must be taken with water only, and no other beverage except water should be ingested within 3 hours before or 3 hours after study drug administration.

[u] Blood samples for PK analysis of TPOXX will be collected from all subjects at the following tome points: on Day 1 before study drug administration (0 hour), at 0.5, 1, 2, 4, 6, 8, 12 (before the PM dose), 14, 16, 18, 20, and 24 hours (before the AM dose on Day 2), on Day 6 (before the AM dose and 4 hours after the AM dose), on Day 7 before the AM dose (0 hour), at 0.5, 1, 2, 4, 6, 8, 12 (before the PM dose), 14, 16, 18, 20, and 24 hours (Day 8, 24 hours after the AM dose on Day 7), and on Day 9 (48 hours after the AM dose on Day 7). For PK blood samples, the acceptable window for collection from the scheduled collection time point will be as follows: ±5 minutes for the time points from 1 to 8 hours and ±15 minutes for the 12- to 48-hour time points.

[v] Including assessment of heart, lungs, abdomen, a neurologic review, and a review of symptoms for assessment and/or follow-up of reported or potential adverse events.

9.3 APPENDIX 3: STUDY GOVERNANCE

9.3.1 Data Quality Assurance

This study will be conducted using the quality processes described in applicable procedural documents. The quality management approach to be implemented will be documented and will comply with current ICH guidance on quality and risk management. All aspects of the study will be monitored for compliance with applicable government regulatory requirements, current Good Clinical Practice, the protocol, and standard operating procedures (SOPs). The monitor 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. Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

Steps to be taken to ensure the accuracy and reliability of data include, but are not limited to: selection of qualified investigator and appropriate study center, protocol training and review of protocol procedures with the investigator and study site personnel before the start of the study, site initiation and periodic interim monitoring visits by SIGA or PPD, and direct transmission of safety laboratory data into the PPD study database for all clinical safety laboratory tests performed. The eCRF will be reviewed for accuracy and completeness by PPD Clinical research associate (CRA) remotely and during on-site monitoring visits. Discrepancies will be resolved with the investigator or designees, as appropriate. The data will be entered into the clinical study database and validated for accuracy. During on-site monitoring visits, 100% of the data will be verified using source documentation. SIGA or Biomedical Advanced Research and Development Authority representatives may accompany the PPD CRA on any scheduled site visit. The investigator will be informed in advance of any visitors to the study site in addition to the PPD CRA.

Representatives of SIGA’s Quality Assurance department (or designee) may visit the site to carry out an audit of the study in compliance with regulatory guidelines and PPD policy. Such audits will require access to all study records, including source documents, for inspection and source document verification with the eCRF. Subject privacy must, however, be respected. Sufficient prior notice will be provided to allow the investigator to prepare properly for the audit. Similar auditing procedures may also be conducted by any regulatory body reviewing the results of this study in support of a Licensing Application. The

investigator will immediately notify SIGA if they are contacted by a regulatory agency requesting a site inspection.

9.3.2 Investigator Obligations

The following administrative items are meant to guide the investigator in the conduct of the study and may be subject to change based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

9.3.2.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Subjects will not be identified by name in any reports in this study. All records will be kept confidential to the extent provided by federal, state, and local law. Medical records are made available for review when required by the FDA or other authorized users only under the guidelines set by the Federal Privacy Act. Direct access, as defined in the Federal Privacy Act, includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform the subjects that these representatives may review their study-related records without violating the confidentiality of the subjects. The requirement to maintain subject confidentiality is included in the study informed consent document.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from SIGA or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.3.2.2 Institutional Review

Federal regulations and ICH guidelines require that approval be obtained from an IRB before participation of human subjects in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject’s legal guardian must be approved by the IRB. Documentation of all IRB approvals and of the IRB

compliance with the ICH harmonised tripartite guideline E6(R2): Good Clinical Practice will be maintained by the site and will be available for review by SIGA or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

9.3.2.3 Subject Consent

Written documentation of informed consent in compliance with US Title 21 CFR Part 50 shall be obtained from each subject before any study-related procedures are performed and study drug is administered. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by SIGA or its designee or both before IRB submission. Once reviewed, the investigator will submit the ICF to the IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised ICF.

Before recruitment and enrollment, each prospective subject or his/her legal guardian will be given a full explanation of the study and will be asked to read and review the approved ICF. Once the investigator is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give his or her consent to participate in the study by signing the ICF. A copy of the ICF will be provided to the subject/legal guardian.

9.3.2.4 Exclusion of Children

Effort will be made to include women and minorities in proportions similar to that of the community from which they are recruited. Because this study is designed to establish safety of the study drug in adults, enrollment will be limited to persons at least 18 years of age, and no older than 50 years. Children are excluded from participation in this clinical study because it does not meet the Department of Health and Human Services' guidelines (45 CFR 46, Subpart D, 401-409) for inclusion of children in research. These guidelines provide guidance for the protection of children in research. Generally, healthy children can be studied when the research is considered as "not greater than minimal risk." Children can be involved in research with greater than minimal risk only when it presents the prospect of direct benefit to the individual child or is likely to yield generalizable knowledge about the child's disorder or condition.

9.3.2.5 Study Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the time line and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate.

9.3.2.6 Financial Disclosure and Obligations

The investigator is required to provide financial disclosure information to allow SIGA to submit the complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54. In addition, the investigator must provide to SIGA a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither SIGA nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither SIGA nor PPD is financially responsible for further treatment of the disease under study.

9.3.2.7 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) Section 8.2 and US Title 21 of the CFR by providing essential documents, including but not limited to, the following:

- IRB approval.
- An original investigator-signed investigator agreement page of the protocol.
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572.
- Curriculum vitae for the principal investigator and each subinvestigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. Curriculum vitae will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current.
- Financial disclosure information to allow SIGA to submit complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54. In addition, the investigators must provide to SIGA a commitment to promptly update this

information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

- An IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information about this study that is to be provided to the subject or legal guardians.

- Laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with US Title 42 CFR Part 493.

9.3.2.8 Study Conduct

The investigator agrees to perform all aspects of this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH E6(R2): Good Clinical Practice; the protocol; and all national, state, and local laws or regulations.

9.3.2.9 Case Report Forms and Source Documents

Site personnel will maintain source documentation, enter subject data into the eCRF as accurately as possible, and will rapidly respond to any reported discrepancies.

Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and any subsequent investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be an internal quality review audit of the data and additional reviews by PPD's CRA.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new subjects, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed and signed by the investigator. This system provides site personnel, PPD CRAs, and reviewers with access to hardcopy audits, discrepancy reviews, and investigator comment information.

9.3.2.10 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol, in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.3.2.11 Reporting Adverse Events

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate. The investigator also agrees to provide SIGA with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

9.3.2.12 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome and SIGA and regulatory authorities with any reports required.

9.3.2.13 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with SIGA. SIGA is responsible for informing the investigator/institution when these documents no longer need to be retained.

9.3.2.14 Publications

All information concerning TPOXX, SIGA operations, patent application, formulas, manufacturing processes, basic scientific data, and formula information, supplied by SIGA to the investigator and not previously published, is considered confidential and remains the sole property of SIGA. The investigator agrees to use this information only to accomplish this study and will not use it for other purposes without SIGA's written consent. The investigator understands that the information developed in the clinical study will be used by SIGA, in connection with the continued development of TPOXX, and thus may be disclosed as required to other clinical investigators or government regulatory agencies. To permit the

information derived from the clinical studies to be used, the investigator is obligated to provide SIGA with all data obtained in the study. Any publication or other public presentation of results from this study, including manuscripts and materials for presentation at scientific meetings, should be provided to SIGA at least 30 working days before abstract or other relevant submission deadlines. Authorship of publications resulting from this study will be determined at the discretion of SIGA.

9.3.3 Study Management

9.3.3.1 Monitoring

9.3.3.1.1 Monitoring of the Study

Site monitoring for safety is conducted to ensure that human subject protection, study procedures, and laboratory, study drug dosing, and data collection processes are of high quality and meet SIGA, GCP/ICH, and regulatory guidelines. PPD CRA(s) will conduct site monitoring visits as detailed in the monitoring plan.

Site investigators will allow the CRA(s), the designated IRB, SIGA or its designee and the FDA to review, audit, and inspect study documents (eg, ICFs, drug accountability and distribution forms, eCRF), pertinent hospital and site records, and source documentation for verification of the study data.

Clinical research associates will conduct site visits in accordance with PPD SOPs to monitor the following: study operations, the quality of data collected in the research records, the accuracy and timeliness of data entered in the database, and to determine that all process and regulatory requirements are met. Study monitoring visits will occur at initiation of the study site, at intervals determined by SIGA during conduct of the study, and at completion of the study.

The CRA 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. During the routine monitoring visits, the CRA will perform a 100% source document verification of all subject data entered into the eCRF. Discrepancies, if any, will be clarified with the study site coordinator and investigator, and corrected at the site by the study coordinator. Any questions or required data clarifications will be sent to the study site electronically.

9.3.4 Safety Monitoring Plan

Close cooperation between the designated members of the study team will occur to evaluate and respond to individual AEs in a timely manner. Designated team members (investigator, subinvestigators, study coordinator, and other designated study clinicians) will review the subject safety information and data (laboratory test results, ECGs, AEs, and concomitant medications) and update the PPD project team and the ISM on the status of all enrolled subjects at their site on a weekly basis (or more frequently if required because of an unexpected safety issue) through completion of each subject's final study visit.

9.3.5 Medical Monitor

The medical monitor, or their qualified designee, will receive reports within 24 hours of study site awareness of all SAEs and within 7 days of study site awareness of all other AEs. The safety monitors will review all safety data and alert the medical monitor of SAEs and AEs of interest. The medical monitor may make a request for data to the investigator as necessary for safety evaluations.

The medical monitor will review each significant AE in a timely fashion and ensure that appropriate management is initiated and completed. Drug safety representatives and the medical monitor will have direct contact with the investigators and follow all significant events as needed.

9.3.6 Safety Oversite (Independent Safety Monitor)

In addition to the investigator's ongoing review of the safety data, the ISM will review the protocol for any major concerns and will be involved in data review in coordination with the investigator. The primary role of the ISM will be to evaluate the study safety and tolerability data. The ISM will provide independent safety monitoring in a timely fashion, which will include reviewing individual SAE reports and a review of periodic cumulative AE reports. Clinical safety and laboratory data, clinical records, and other safety study-related records will be made available for the ISM to review. Based on review of this data, the ISM may make recommendations regarding the safe continuation of the study. Specific details will be outlined in the Safety and Medical Management Plan.

9.3.6.1 Inspection of Records

The investigator and study site involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records.

In the event of an audit, the investigator agrees to allow SIGA, their representatives, the FDA, or other regulatory agencies access to all study records.

The investigator should promptly notify SIGA and study site of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to SIGA.

9.3.6.2 Management of Protocol Amendments and Deviations

9.3.6.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent immediate hazard to the subject, must be reviewed and approved by SIGA or designee. Amendments to the protocol must be submitted in writing to the IRB for approval before subjects are enrolled into an amended protocol.

9.3.6.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study subjects without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to SIGA for agreement, and to the regulatory authorities, if required.

A *protocol deviation* is any change, divergence, or departure from the study design or procedures defined in the protocol. An *important protocol deviation* (sometimes referred to as a protocol violation or a major protocol deviation) is a subset of protocol deviations that might significantly affect the reliability of the study data or that might significantly affect a subject's safety. An important deviation can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH E6(R2) guidelines.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations, if appropriate, in a timely manner.

9.3.6.3 Study Termination

Although SIGA has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

An initiative for closure of the clinical investigative site or termination of the study can be taken at any time either by SIGA, PPD, or the investigator provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for such action include, but are not limited to:

- Study site closure
    - Inadequate site recruitment/enrollment of subjects
    - Failure of an investigator to comply with the protocol, PPD SOPs, GCP guidelines, or applicable federal regulations
- Termination of enrollment
    - Enrollment of the required estimated number of subjects for the study
- Study termination
    - Completion of the study
    - Safety concerns

In addition, the ISM and FDA have the prerogative to delay or terminate the study.

The end of the study is defined as the date on which the last subject completes the last visit (includes the follow-up visit and the follow-up telephone call). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be reported through an amendment to the clinical study report.

9.3.6.4 Final Report

Whether the study is completed or prematurely terminated, SIGA will ensure that clinical study reports are prepared and provided to regulatory agency(ies) as required by the applicable regulatory requirement(s). SIGA will also ensure that clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Upon completion of the clinical study report, the investigator will be provided with the final approved clinical study report, as appropriate.

9.4 APPENDIX 4: CHANGE HISTORY

9.4.1 Protocol Amendment 1

Protocol Amendment 1 was issued to clarify the weight requirements for qualified subjects on Day -1 and Day 1, clarify that the same scale will be used in Screening and how rounding procedures will be used, update Reference 3 to cite the current FDA Guidance, remove the ±2 day window for the Day 9 / Early Discontinuation visit, and remove symptom-directed physical examination from Day 7. The changes to Protocol Amendment 1 are outlined as follows:

Protocol Section	Change	Rationale
Synopsis and Section 3.1 Inclusion Criteria	Clarified subjects need to weigh >120 kg at check-in on Day -1, and prior to dosing on Day 1, in addition to weighing >120 kg at Screening.	In order to obtain accurate pharmacokinetic data in subjects weighing >120 kg, subjects participating in this study need to meet the weight requirement during dosing.
Section 6.2.6 Physical Examinations and Section 9.2 Appendix 2: Schedule of Events	Clarified the scale should be used throughout the entire study including Screening. Clarified rounding should occur by adding the following text: *Weight measurements will be rounded to one decimal place.*	The same scale should be used for the screening of subjects as will be used in the study to ensure weight measurement consistency. Scales at the site measure weight to two decimal places.
Section 8 Reference List	Updated reference 3 to cite the May 2018 Bioanalytical Method Validation Guidance for Industry	An updated Guidance was published in May of 2018.
Section 9.2 Appendix 2: Schedule of Events	Removal of (±2) from Day 9 or Early Discontinuation visit header	The ±2 day visit window was included in error. Subjects will check out on day 9 or will undergo Early Discontinuation Procedures on the day they discontinue. There is no window for these visits.
Section 9.2 Appendix 2: Schedule of Events	Removal of Day 7 symptom-directed physical examination from schedule.	A complete physical exam is already being conducted on Day 7.

9.4.2 Protocol Amendment 2

Protocol Amendment 2 was issued to revise Exclusion Criteria 31; to remove redundant Exclusion Criteria; to add the measurement of height to the Day -1 Check-in procedures; and to remove the one hour observation period for allergic reaction following dosing. The changes to Protocol Amendment 2 are outlined as follows:

Protocol Section	Change	Rationale
Synopsis and Section 3.2 Exclusion Criteria	Removed bullet point 3 from Exclusion Criteria 2, which stated: *Hypertension that is poorly controlled (repeat readings >140 mm Hg systolic and/or >90 mm Hg diastolic)* and revised Exclusion Criteria 31 from *Subject has a sustained sitting systolic blood pressure >140 mm Hg or <100 mm Hg or a diastolic blood pressure >90 mm Hg at screening. Blood pressure may be retested twice in the sitting position at 5-minute intervals. The pressure elevation is considered sustained if either the systolic or the diastolic pressure exceeds the stated limits on all 3 assessments* to *Subject has a blood pressure considered to be clinically significant by the investigator. Blood pressure may be retested twice in the sitting position at 5-minute intervals.*	Bullet point 3 was removed as it was redundant with Exclusion Criteria 31. Exclusion Criteria 31 was revised to allow the investigator to determine clinical significance of blood pressure for study inclusion or exclusion.
Section 6.2.6 Physical Examinations and Section 9.2 Appendix 2: Schedule of Events	Added height to Day -1 Check-in procedures	This measurement was previously unintentionally omitted from the study assessments.
Section 6.2.1.8 Reactogenicity and Section 9.2 Appendix 2: Schedule of Events	Removed specific mention of a one hour observation period for allergic reaction following dosing from Section 6.2.1.8 and removed reactogenicity from the Schedule of Events.	Subjects are required to stay at the clinical site throughout the entire dosing period and are continually under observation by site staff.