A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF TPOXX® WHEN ADMINISTERED ORALLY FOR 28 DAYS IN ADULT SUBJECTS

NCT: 04971109

PROTOCOL: 01AUG2022

SAP: 16APR2023

CLINICAL STUDY PROTOCOL
AMENDMENT 1

IND 69,019

A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF TPOXX® WHEN ADMINISTERED ORALLY FOR 28 DAYS IN ADULT SUBJECTS

SIGA-246-024

Sponsor:	SIGA Technologies, Inc. 4575 SW Research Way, Suite 110 Corvallis, OR 97333
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]
Version of Protocol:	2.0
Date of Protocol:	01 August 2022
Previous Version(s) and Date(s):	1.0 dated 04 November 2021

CONFIDENTIAL

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

SIGNATURE PAGE

PROTOCOL TITLE: A Double-Blind, Randomized, Placebo-Controlled, Multicenter Trial to Assess the Safety, Tolerability, and Pharmacokinetics of TPOXX® When Administered Orally for 28 Days in Adult Subjects

PROTOCOL NUMBER: SIGA-246-024

[redacted]

Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree to conduct the study as outlined in the protocol titled "A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety, Tolerability, and Pharmacokinetics of TPOXX® When Administered Orally for 28 Days in Adult Subjects" 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-246-024

TITLE: A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety, Tolerability, and Pharmacokinetics of TPOXX® When Administered Orally for 28 Days in Adult Subjects

STUDY PHASE: 3

STUDY SITES: [redacted]

OBJECTIVES:

Primary:

The primary objective of this study is to determine the safety and tolerability of TPOXX when administered orally for 28 days in adult subjects.

Secondary:

The secondary objective of this study is to describe the pharmacokinetic (PK) profile of TPOXX when administered orally for 28 days in adult subjects.

STUDY DESIGN AND METHODOLOGY:

This is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study to assess the safety, tolerability, and PK of oral TPOXX 600 mg when administered orally for 28 days in adult subjects.

A total of at least 445 subjects (includes a PK subset of 40 subjects), ages 18 to 80, inclusive, will be enrolled and randomly assigned within stratified age groups (18 to 30 years, 31 to 45 years, 46 to 64 years, and 65 to 80 years) to 1 of 2 treatment groups in an overall randomization of 4:1 (approximately 356 subjects will receive TPOXX and 89 subjects will receive TPOXX matching placebo). There will be 2 dosing regimens based on the subject's body weight: subjects with a body weight of 120 kg or less will be administered either TPOXX 600 mg or placebo two times a day (BID), 12 hours apart (±30 minutes); and subjects with a body weight more than 120 kg will be administered either TPOXX 600 mg or placebo three times a day (TID), 8 hours apart (±30 minutes). The enrollment goal for the study is to randomly assign a sufficient number of subjects to ensure that at least 300 subjects receive at least 92% of the oral TPOXX 600 mg BID or TID dosing regimen over the 28-day treatment period. Overall, across all clinical investigative sites, a goal of approximately 20% of subjects (i.e., 89 subjects) or more will be enrolled and randomly assigned in each age group to ensure a respective investigation of TPOXX safety and PK across age groups. The treatment groups will be as follows:

- Treatment Group 1: An oral dose of 600 mg (3 × 200-mg capsules) TPOXX BID (every 12 hours [±30 minutes]) for subjects with a body weight of 120 kg or less or TID (every 8 hours [±30 minutes]) for subjects with a body weight more than 120 kg for 28 days (Day 1 to Day 28).

- Treatment Group 2: An oral dose of placebo (3 capsules identical to TPOXX) BID (every 12 hours [±30 minutes]) for subjects with a body weight of 120 kg or less or TID (every 8 hours [±30 minutes]) for subjects with a body weight more than 120 kg for 28 days (Day 1 to Day 28).

When study drug is administered at the clinical investigative site, all subjects will be provided a meal (consisting of approximately 600 calories and 25 g of fat). The meal should be consumed within 30 minutes and prior to the administration of study drug (TPOXX or matching placebo). Subjects should be administered study drug as soon as possible following completion of the meal but no more than 30 minutes should elapse between meal completion and administration of study drug. Subjects should take study drug with 8 oz. (240 mL) of water. Subjects will be instructed at the screening visit and prior to check-in to the clinical investigative site on either Day –1 or Day 1 that other than water, no beverages may be ingested within 3 hours before or 3 hours after study drug administration.

When study drug (TPOXX or matching placebo) is administered at home, subjects will be instructed to take it within 30 minutes after the completion of a meal consisting of approximately 600 calories and 25 g of fat and with 8 oz. (240 mL) of water. Other than water, no beverages may be ingested within 3 hours before or 3 hours after taking study drug, excluding a beverage that is being consumed as a part of the required meal.

Clinical investigative sites will provide subjects with instructions and dietary information in order to help them meet the study requirement for eating meals with an appropriate caloric and fat content before study drug dosing.

Clinical investigative sites will provide subjects with a subject diary and instructions to record the time that they completed their last meal before taking study drug in the subject diary. Subjects will be instructed to record that they have met the required caloric and fat intake of eating a meal containing approximately 600 calories and 25 g of fat before each dose of study drug.

Clinical investigative sites will instruct subjects to record the time that they take study drug in their subject diary. Subjects will follow a dosing regimen of study drug appropriate for their weight for 28 days and will be instructed to take their study drug at the same time of the day each day.

Safety assessments will include clinical laboratory test results (hematology, serum chemistry, and urinalysis), monitoring of adverse events (AEs) including serious AEs (SAEs), vital sign measurements (systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature), electrocardiogram (ECG) results, and physical examination findings.

All subjects will have a follow-up telephone call 14 and 30 days after the last dose of study drug (Day 42 [+2 days] and Day 58 [+2 days], respectively) to report any AEs and SAEs. All AEs, SAEs, and clinically significant laboratory abnormalities will be followed until resolution or until stability of the abnormality has been demonstrated as determined by the investigator and/or medical monitor.

The study will consist of a screening period (Day –28 to Day –2), 1 check-in, on-site visits (Day 7, Day 14, and Day 21), a dosing complete/early termination (ET) visit (Day 29), and 2 follow-up telephone calls (Day 42 [+2 days] and Day 58 [+2 days]).

The total duration of the study for each subject, including screening, treatment, and follow-up telephone calls, will be approximately 86 days.

Non-PK Study Subjects:

Those subjects not participating in the PK subset will check into the clinical investigative site in the morning of Day 1 and will remain at the clinical investigative site until after the first dose on Day 1 and all safety assessments have been completed.

With the exception of the first dose of study drug administered at the clinical investigative site on Day 1, subjects will administer study drug at home for all remaining doses through Day 28.

PK Subset Study Subjects:

Those subjects participating in the PK subset will follow the same general schedule with the addition of several overnight stays. Specifically, the PK subset will consist of a screening period (Day –28 to Day –2), 3 check-in and in-house periods (Day –1 to Day 2; Day 13 to Day 14; and Day 27 to Day 31), a dosing complete/ET visit (Day 29), and 2 follow-up telephone calls (Day 42 [+2 days] and Day 58 [+2 days]).

Subjects in the PK subset will check into the clinical investigative site on Day –1, Day 13, and Day 27 and be discharged from the clinical investigative site on Day 2, Day 14, and Day 31. Subjects will check into the clinical investigative site early enough to eat the required meal and then be administered the final dose for that day on Day 13 and Day 27.

When the study drug is not administered at the clinical investigative site, subjects will administer study drug at home.

Serial blood samples for PK analysis of TPOXX will be collected before the first dose of study drug (0 hour) on Days 1, 14, and 28 and up to 24 hours after study drug administration on Day 1 and up to 72 hours after the first dose of study drug on Day 28.

STUDY POPULATION:

Inclusion Criteria:

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

1. Subject is male or female between 18 and 80 years of age, inclusive.
2. Subject is available for clinical follow-up for the duration of the study.
3. Women of childbearing potential have a negative β-human chorionic gonadotropin pregnancy test (serum) at the screening visit and a negative urine pregnancy test on Day 1 or Day –1 (PK subset) before receipt of study drug, and meet one of the following criteria:

a. Subject or their partner has undergone surgical sterilization.
b. Male sexual partner who has undergone a vasectomy at least 3 months before screening.
c. 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.
d. Subject agrees to be abstinent (i.e., heterosexually inactive) for the duration of the study.
e. 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. Male and female condoms should not be used together, as this can reduce their effectiveness.
    ii. Diaphragm or cervical cap with spermicide
    iii. Intrauterine device with spermicide
    iv. Oral contraceptives or other hormonal methods

       NOTE: Another nonhormonal method of contraception must be used in conjunction with oral contraceptives.

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 test results, vital sign measurements, 12-lead ECG results, and physical examination findings at screening.
6. Subject agrees not to use nicotine products, including electronic vapor cigarettes, nicotine patches, or nicotine gum, for at least 30 days before the Day 1 randomization visit through completion of the Day 29 dosing complete/ET visit.
7. Subject agrees to comply with the study dietary requirements throughout the study drug dosing period.
8. Subject agrees not to consume caffeine- or xanthine-containing products during all study visits, including overnight stays (PK subset); sodas, coffee, and tea designated as caffeine-free or noncaffeinated may be consumed on study days; caffeine may be consumed while at home and between study visits.
9. Subject agrees to comply with all protocol requirements.
10. Subject has adequate venous access if participating in the PK subset.
11. Subject is able and willing to provide written informed consent.

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
   - History of head trauma resulting in a diagnosis of traumatic brain injury other than concussion
   - Frequent episodes of headache
3. Subject has received any vaccination within 28 days prior to Day 1 or plans to receive a vaccination at any time during the treatment period or within 28 days after study Day 28.
4. Subject has received treatment in another clinical study of an investigational drug (or medical device) or investigational vaccine within 30 days or 5 half-lives (whichever is longer) before the first dose of study drug.
5. Subject has a history of relevant drug and/or food allergies (i.e., allergy to TPOXX or excipients, or any significant food allergy that could preclude a standard diet in the clinical investigative site).
6. Subject has any condition possibly affecting drug absorption (e.g., 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 reaction (excluding seasonal allergies); or has evidence or history of clinically significant disease, including hematological, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, or neurological disease. Exceptions to these disease criteria (e.g., 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, chest pain (that is diagnosed as cardiac related) or trouble breathing on exertion, or risk factors for torsades de pointes (e.g., heart failure, hypokalemia).
9. Subject has a family history of an immediate family member (father, mother, brother, or sister) who has had an onset of ischemic heart disease before the age of 50 years.
10. Subject is 20 years of age or older and has a ≥30% risk of developing a myocardial infarction or coronary death within the next 10 years using the National Cholesterol Education Program's Risk Assessment Tool: https://www.mcw.edu/calculators/ldl-cholesterol-goal-level.

11. 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.
12. Subject has a history of a peptic ulcer or significant gastrointestinal bleeding.
13. Subject has a bleeding disorder diagnosed by a doctor (e.g., factor deficiency, coagulopathy, or platelet disorder requiring special precautions) or significant bruising or bleeding difficulties with blood draws.
14. 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).
15. Subject has neutropenia or other blood dyscrasia determined to be clinically significant by the investigator.
16. 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 cytochromes (CYP)2C8 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.
17. Subject has a history of drug or alcohol abuse or dependency within the last year before screening.
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 (e.g., human T cell lymphotropic virus I or II).
21. 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).
22. 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.
23. Subject reports participation in strenuous activity or contact sports within 24 hours before the first dose of study drug.

24. 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.
25. 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), cotinine, or alcohol at screening or check-in.
26. 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) <70 mL/min
    - Creatinine in males >1.7 mg/dL and in females >1.4 mg/dL (1.3 times the upper laboratory reference range)
    - Hemoglobin ≤10% of the lower laboratory reference range
    - White blood cell counts considered to be clinically significant by the investigator
    - Absolute neutrophil count <1000 cells/mm^3
    - Platelets not within ±10% of laboratory reference range
    - Alanine aminotransferase >2 times above the upper laboratory reference range
    - Aspartate aminotransferase >2 times above the upper laboratory reference range
    - Alkaline phosphatase >20% above the upper laboratory reference range
    - Hemoglobin A1c ≥7.0%
    - Cholesterol ≥300 mg/dL and low-density lipoprotein ≥190 mg/dL
27. Subject has hypertension that is poorly controlled (repeat reading >140 mm Hg systolic and/or >90 mm Hg diastolic) or blood pressure considered to be clinically significant by the investigator. Blood pressure may be retested twice in the sitting position at 5-minute intervals.
28. Subject has a resting heart rate of <40 beats per minute or >110 beats per minute at screening.
29. Subject has an abnormal ECG at screening that is determined by the investigator to be clinically significant.
30. Male subject has a QT interval corrected using Fridericia's formula (QTcF) >450 ms or female subject has a QTcF >470 ms at screening or Day 1 or Day –1 (PK subset).
31. Subject has used any prescription antiviral drugs with the intention of coronavirus disease (COVID-19) treatment or prophylaxis, including those that are thought to be effective for prevention of COVID-19 but have or have not been licensed for this indication, within 1 month prior to study entry or during the study.
32. In the opinion of the investigator, the subject is not suitable for entry into the study.
33. Subject is a member or family member of the investigator or study site personnel.
34. Subject has previously participated in this clinical trial.

EVALUATION CRITERIA:
Pharmacokinetic Assessments and Endpoints (PK Subset)
BID Dosing: Subjects weighing 120 kg or less:

Blood samples for PK analysis of TPOXX in plasma will be collected on Day 1 before the first dose (0 hour) and at 2, 4, 6, 8, 10, 12 (before the second dose), 14, 16, 18, 20, 22, and 24 hours (before the first dose on Day 2); on Day 14 (before the first dose); and on Day 28 (before the first dose) and at 2, 4, 6, 8, 10, 12 (before the second dose on Day 28), 14, 16, 18, 20, 22, 24 (Day 29, AM), 48 (Day 30, AM), and 72 (Day 31, AM) hours after the first dose on Day 28.

TID Dosing: Subjects weighing more than 120 kg:

Blood samples for PK analysis of TPOXX in plasma will be collected on Day 1 before the first dose (0 hour) and at 2, 4, 6, 8 (before the second dose), 10, 12, 14, 16 (before the third dose), 18, 20, 22, and 24 hours (before the first dose on Day 2); on Day 14 (before the first dose); and on Day 28 (before the first dose) and at 2, 4, 6, 8 (before the second dose), 10, 12, 14, 16 (before the third dose), 18, 20, 22, 24 (Day 29, AM), 48 (Day 30, AM), and 72 (Day 31, AM) hours after the first dose on Day 28.

For PK blood samples, the acceptable window for collection from the scheduled collection time point will be as follows: ±15 minutes from 0 to 24 hours (except where samples are collected predose) and ±60 minutes from 48 to 72 hours.

The following plasma PK parameters will be calculated separately for BID and TID dosing as endpoints for TPOXX to the extent that data permit using actual sampling times rather than scheduled sampling times and will include, but are not limited to the following:

Day 1:

- Maximum observed plasma concentration (C_{max}), reported separately for each dose
- Time to reach C_{max} (T_{max}), reported separately for each dose
- Area under the plasma concentration-time curve (AUC) from time zero to 24 hours (AUC_{0-24})
- AUC from time zero to tau where tau is the 8-hour or 12-hour dosing interval following the first dose (AUC_{tau})

Day 28:

- C_{max}
- Average steady-state plasma concentration (C_{avg})
- Trough plasma concentration (C_{trough})
- Minimum observed plasma concentration (C_{min})
- T_{max}
- AUC_{0-24}
- AUC from time zero to tau where tau is the 8-hour or 12-hour dosing interval (AUC_{tau})
- AUC from time zero to the last measurable sample (AUC_{0-last})

- AUC from time zero to infinity ($AUC_{0-\infty}$)
- Observed elimination rate constant (λ_z)
- Terminal elimination half-life ($t_{1/2}$)
- Apparent clearance (CL_{ss}/F)
- Apparent volume of distribution (V_z/F)
- Accumulation ratio (Rac)
- %Fluctuation

Safety Assessments:
Safety and tolerability will be assessed by the following endpoints: monitoring and recording of AEs; clinical laboratory test results (hematology, serum chemistry, and urinalysis); pregnancy testing; vital sign measurements (systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature); 12-lead ECG results; and physical examination findings. A blood sample will be collected for all subjects who discontinue from the study for TPOXX plasma concentration *if the ET visit occurs within 30 hours after the subject's last dose of TPOXX/matching placebo* in order to collect information about the relationship between TPOXX blood level and ET from the study.

STUDY DRUG, DOSAGE, AND ROUTE OF ADMINISTRATION:
Subjects Weighing 120 kg or Less:

- An oral dose of 600 mg (3 × 200-mg capsules) TPOXX BID (every 12 hours [±30 minutes]) for 28 days
- An oral dose of placebo (3 capsules identical to TPOXX) BID (every 12 hours [±30 minutes]) for 28 days

Subjects Weighing More Than 120 kg:

- An oral dose of 600 mg (3 × 200-mg capsules) TPOXX TID (every 8 hours [±30 minutes]) for 28 days
- An oral dose of placebo (3 capsules identical to TPOXX) TID (every 8 hours [±30 minutes]) for 28 days

STATISTICAL CONSIDERATIONS:
A summary of statistical considerations is provided below. More specific descriptions of the statistical methods to be used will be described in the statistical analysis plan (SAP).

Sample Size:
There is no formal sample size calculation for this study. Although the sample size is not based on statistical power considerations, administration of TPOXX 600 mg to 300 subjects provides approximately 95% probability of observing at least 1 occurrence of any AE if the incidence of AEs in the study population is 1% and is considered adequate to provide a reasonable assessment of safety and tolerability. A sufficient number of subjects will be randomly assigned to ensure that at least 300 subjects receive at least 92% of the doses of the BID or TID dosing regimen of oral TPOXX 600 mg over the 28-day treatment period.

Study Population:
Adult subjects from 18 to 80 years old, inclusive, are eligible for this study. A total of at least 445 subjects will be enrolled and randomly assigned into stratified age groups (18 to 30 years, 31 to 45 years, 46 to 64 years, and 65 to 80 years). Approximately 356 subjects will be randomly assigned to receive active drug (TPOXX 600 mg) and 89 subjects will be randomly assigned to receive placebo. Overall, across all clinical investigative sites, a goal of approximately 20% of subjects (i.e., 89 subjects) or more will be enrolled and randomly assigned in each age group to ensure a representative investigation of the safety and PK across age groups.

Analysis Populations:
All populations will be identified and finalized before the database lock. All subjects who are randomly assigned are considered study subjects. Study populations are defined as the following:

- The Intent-to-Treat Population will include all subjects who were randomly assigned to the study (i.e., a randomization number and randomization date are present in the database).
- The Safety Population will include all subjects who received at least 1 dose of study drug (TPOXX or matching placebo).
- The Per-Protocol (PP) Safety Population will include all subjects who received at least 92% of the 600 mg BID or TID dosing regimen of TPOXX or matching placebo.
- The PK Population will include all subjects in the PK subset who have taken at least 92% of the 600 mg BID or TID dosing regimen of TPOXX, have sufficient drug concentrations in plasma, and have no protocol deviations or other circumstances that would exclude the subject from analysis.

Pharmacokinetic Analyses:
The PK Population will be used for the preparation of PK summaries and analyses.

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

The PK parameters of TPOXX will be analyzed using noncompartmental methods based on the actual sampling times. The individual PK parameters will be presented in data listings and summarized by study day and study drug dosing regimen using the following descriptive statistics: number of subjects, arithmetic mean, SD, CV, geometric mean, geometric SD, geometric CV, minimum, median, and maximum.

Safety Analyses:
The safety and tolerability data summaries will be presented separately for the Safety Population and the PP Safety Population and will also be presented by BID or TID study drug dosing regimen.

Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities. All AE data will be presented in a data listing. Treatment-emergent AEs will be summarized by treatment, BID and TID study drug dosing regimen, and overall, as well as by severity and relationship to study drug for the Safety Population and PP Safety Population. For any subject who discontinues the study for any reason, data will be summarized by treatment group, reason for discontinuation, if the drug concentration was collected, and the result of the bioanalysis. In addition, SAEs and AEs leading to subject study discontinuation will be presented in the data listings and summarized by treatment, dosing regimen, and overall.

The overall AE rate will be defined as the percentage of subjects in the Safety Population and PP Safety Population who report at least 1 postdose AE. The overall AE rate will be compared between treatment groups using Mantel-Haenszel test stratified for age group (18 to 30, 31 to 45, 46 to 64, and 65 to 80 years). If expected cell counts are less than 5, then Fisher's exact test will be applied. An exact unadjusted 95% confidence interval (CI), calculated using the Clopper-Pearson method, will be presented for each treatment group. For the difference in overall AE rates between treatment groups, a continuity corrected exact 95% CI around the difference will be calculated. In addition, the Mantel-Haenszel adjusted odds ratio and 95% CIs from the stratified analysis will be presented. The relationship of treatment group, age, clinical investigative site, and their interactions on overall AE rate will also be investigated using a logistic regression model; CIs for the odds ratios associated with each factor in the model will be presented. Further details will be included in the SAP.

Time from the first dose to the first AE or to discontinuation from study for any reason will be analyzed using Kaplan-Meier quartile estimates along with 2-sided 95% CIs. Treatment groups will be compared using the log rank test stratified by age group and site. If a subject does not experience any AE or does not discontinue from study, the time to first AE or time to discontinuation will be censored at the date of study completion.

Toxicity grades for laboratory tests will be determined according to the Division of Acquired Immune Deficiency Syndrome (DAIDS) AE Grading Table. The maximum postbaseline grade increase from baseline grade will be summarized by treatment group and BID and TID study drug dosing regimen and overall for the Safety Population and PP Safety Population using frequency and percentage of subjects with increase to grade 1, 2, 3, 4, 1 to 4, 2 to 4, and 3 to 4, respectively.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment group and BID and TID study drug dosing regimen at each time point using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). Shift tables will be generated for clinical laboratory test results. Physical examination findings will be presented in a data listing.

Narratives will be presented for all deaths, subjects who reported SAEs, subjects withdrawn because of AEs, and grade 3 AEs deemed by the investigator to be possibly, probably, or definitely related to study drug.

DATE OF PROTOCOL: 01 August 2022

1. INTRODUCTION

1.1 BACKGROUND

Historically, variola virus, 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] Smallpox is defined by 2 clinical forms, variola major and variola minor. 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 US Food and Drug Administration (FDA) approved oral TPOXX® for the treatment of human smallpox disease in adults and pediatric patients weighing at least 13 kilograms.

1.2 RATIONALE FOR STUDY

Treatment with TPOXX following exposure to variola virus and prior to the onset of clinically diagnosed smallpox disease would constitute postexposure prophylaxis treatment. For human smallpox, the asymptomatic incubation period following exposure to the variola virus may range from 7 to 19 days (most commonly 12 to 14 days) postexposure. This approximately 2-week asymptomatic incubation period (with variability in duration) in humans before the development of secondary viremia, symptoms, and the generation of neutralizing antibody responses, necessitates the need for a longer treatment duration of TPOXX as a prophylactic. Humoral immune responses in the form of hemagglutination inhibition, complement fixing, and virus-neutralizing antibodies are detectable within approximately 5 days after the appearance of the rash and therefore approximately 12 to 24 days postexposure. To ensure the proper development of a neutralizing antibody response to the variola virus and to avoid a post-treatment virologic rebound, SIGA proposes the administration of TPOXX 600 mg for 28 days to support a postexposure prophylaxis treatment claim.

1.3 RATIONALE FOR DOSE SELECTION

TPOXX 600 mg (3 × 200-mg capsules) two times a day (BID) is the approved dose of TPOXX for the treatment of smallpox in patients weighing between 13 kg and 120 kg, inclusive. The FDA and SIGA have agreed that TPOXX dosing for patients weighing 120 kg

or more should be adjusted to 600 mg TPOXX *three* times a day (TID).[2] The 28-day TPOXX treatment duration, rather than the 14-day duration, was chosen for the postexposure prophylaxis indication as a longer treatment period may be necessary to provide protection from smallpox from the time of initial exposure to variola virus until the development of protective neutralizing antibodies. This accounts for the 7- to 17-day, asymptomatic stage; the subsequent 2- to 3-day, prodromal stage; and finally, the development of neutralizing antibodies, which are evident from about the sixth day following the onset of clinical symptoms and increase in antibody titer thereafter.

1.4 POTENTIAL RISKS AND BENEFITS

1.4.1 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 signing of the informed consent form (ICF) and continuing through 30 days after the last dose of study drug. For all women of childbearing potential, serum pregnancy testing will be performed and checked by the investigator to confirm a negative test result at the screening visit. For women of childbearing potential in the pharmacokinetic (PK) subset, a urine pregnancy test will be performed at check-in on Day –1 and must be confirmed as negative by the investigator prior to randomization and before receipt of the first dose of study drug on Day 1. Additional serum pregnancy testing will be performed on Days 7, 13, 21, and on Day 29 dosing complete/early termination (ET) visit. For women of childbearing potential not in the PK subset, a urine pregnancy test will be performed at check-in on Day 1 and must be verified as negative by the investigator prior to randomization and before receipt of the first dose of study drug. Additional serum pregnancy testing will be performed on Days 7, 14, 21, and on Day 29 dosing complete/ET visit. Women who are pregnant or breastfeeding 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 6.2.1.8).

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 adverse events (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]

1.4.2 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, electrocardiograms (ECGs), and physical examinations. Others may benefit from knowledge gained in this study that may aid in the use of TPOXX for the treatment of smallpox.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to determine the safety and tolerability of TPOXX when administered orally for 28 days in adult subjects.

2.2 SECONDARY OBJECTIVE

The secondary objective of this study is to describe the PK profile of TPOXX when administered orally for 28 days in adult subjects.

3. STUDY DESIGN

This is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study to assess the safety, tolerability, and PK of oral TPOXX 600 mg when administered for 28 days in adult subjects.

A total of at least 445 subjects (includes a PK subset of 40 subjects), ages 18 to 80, inclusive, will be enrolled and randomly assigned within stratified age groups (18 to 30 years, 31 to 45 years, 46 to 64 years, and 65 to 80 years) to 1 of 2 treatment groups in an overall randomization of 4:1 (approximately 356 subjects will receive TPOXX and 89 subjects will receive TPOXX matching placebo). There will be 2 dosing regimens based on the subjects body weight: subjects with a body weight of 120 kg or less will be administered either TPOXX 600 mg or placebo BID, 12 hours apart (±30 minutes); and subjects with a body weight of more than 120 kg will be administered TPOXX 600 mg or placebo TID, 8 hours apart (±30 minutes). The enrollment goal for the study is to randomly assign a sufficient number of subjects to ensure that at least 300 subjects receive at least 92% of the oral TPOXX 600 mg BID or TID dosing regimen over the 28-day treatment period. Overall, across all clinical investigative sites, a goal of approximately 20% of subjects (i.e., 89 subjects) or more will be enrolled and randomly assigned in each age group to ensure a

representative investigation of TPOXX safety and PK across age groups. The treatment groups will be as follows:

- Treatment Group 1: An oral dose of 600 mg (3 × 200-mg capsules) TPOXX BID (every 12 hours [±30 minutes]) for subjects with a body weight of 120 kg or less or TID (every 8 hours [±30 minutes]) for subjects with a body weight more than 120 kg for 28 days (Day 1 to Day 28).

- Treatment Group 2: An oral dose of placebo (3 capsules identical to TPOXX) BID (every 12 hours [±30 minutes]) for subjects with a body weight of 120 kg or less or TID (every 8 hours [±30 minutes]) for subjects with a body weight more than 120 kg for 28 days (Day 1 to Day 28).

When study drug is administered at the clinical investigative site, all subjects will be provided a meal (consisting of approximately 600 calories and 25 g of fat). The meal should be consumed within 30 minutes and prior to the administration of study drug (TPOXX or matching placebo). Subjects should be administered study drug as soon as possible following completion of the meal but no more than 30 minutes should elapse between meal completion and administration of study drug. Subjects should take study drug with 8 oz. (240 mL) of water. Subjects will be instructed at the screening visit and prior to check-in to the clinical investigative site on either Day –1 or Day 1 that other than water, no beverages may be ingested within 3 hours before or 3 hours after study drug administration.

When study drug (TPOXX or matching placebo) is administered at home, subjects will be instructed to take it within 30 minutes after the completion of a meal consisting of approximately 600 calories and 25 g of fat and with 8 oz. (240 mL) of water. Other than water, no beverages may be ingested within 3 hours before or 3 hours after taking study drug excluding a beverage that is being consumed as a part of the required meal.

Clinical investigative sites will provide subjects with instructions and dietary information in order to help them meet the study requirement for eating meals with an appropriate caloric and fat content before study drug dosing.

Clinical investigative sites will provide subjects with a subject diary and instructions to record the time that they completed their last meal before taking study drug in the subject diary. Subjects will be instructed to record that they have met the required caloric and fat intake of eating a meal containing approximately 600 calories and 25 g of fat before each dose of study drug.

Clinical investigative sites will instruct subjects to record the time that they take study drug in their subject diary. Subjects will follow a dosing regimen of study drug appropriate for their weight for 28 days and will be instructed to take their study drug at the same time of the day each day.

Safety assessments will include clinical laboratory test results (hematology, serum chemistry, and urinalysis), monitoring of AEs including serious AEs (SAEs), vital sign measurements (systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature), ECG results, and physical examination findings.

All subjects will have a follow-up telephone call 14 and 30 days after the last dose of study drug (Day 42 [+2 days] and Day 58 [+2 days], respectively) to report any AEs and SAEs. All AEs, SAEs, and clinically significant laboratory abnormalities will be followed until resolution or until stability of the abnormality has been demonstrated as determined by the investigator and/or medical monitor.

The study will consist of a screening period (Day –28 to Day –2), 1 check-in, on-site visits (Day 7, Day 14, and Day 21), a dosing complete/ET visit (Day 29), and 2 follow-up telephone calls (Day 42 [+2 days] and Day 58 [+2 days]).

The total duration of the study for each subject, including screening, treatment, and follow-up telephone calls, will be approximately 86 days.

Non-PK Study Subjects:

Those subjects not participating in the PK subset will check into the clinical investigative site in the morning of Day 1 and will remain at the clinical investigative site until after the first dose on Day 1 and all safety assessments have been completed.

With the exception of the first dose of study drug administered at the clinical investigative site on Day 1, subjects will administer study drug at home for all remaining doses through Day 28.

PK Subset Safety Subjects:

Those subjects participating in the PK subset will follow the same general schedule with the addition of several overnight stays. Specifically, the PK subset will consist of a screening period (Day –28 to Day –2), 3 check-in and in house periods (Day –1 to Day 2; Day 13 to Day 14; and Day 27 to Day 31), a dosing complete/ET visit (Day 29), and 2 follow-up telephone calls (Day 42 [+2 days] and Day 58 [+2 days]).

Subjects in the PK subset will check into the clinical investigative site on Day –1, Day 13, and Day 27 and be discharged from the clinical investigative site on Day 2, Day 14, and Day 31. Subjects will check into the clinical investigative site early enough to eat the required meal and then be administered the final dose for that day on Day 13 and Day 27.

When the study drug is not administered at the clinical investigative site, subjects will administer study drug at home.

Serial blood samples for PK analysis of TPOXX will be collected before the first dose (0 hour) on Days 1, 14, and 28 and up to 24 hours after study drug administration on Day 1 and up to 72 hours after study drug administration on Day 28.

4. STUDY POPULATION

A total of at least 445 adult male and female subjects will be enrolled at approximately 12 clinical investigative sites in the United States.

4.1 INCLUSION CRITERIA

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

1. Subject is male or female between 18 and 80 years of age, inclusive.

2. Subject is available for clinical follow-up for the duration of the study.

3. Women of childbearing potential have a negative β-human chorionic gonadotropin pregnancy test (serum) at the screening visit and a negative urine pregnancy test on Day 1 or Day –1 (PK subset) before receipt of study drug, and meet one of the following criteria:

    a. Subject or their partner has undergone surgical sterilization.

b. Male sexual partner who had undergone a vasectomy at least 3 months before screening

c. 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.

d. Subject agrees to be abstinent (i.e., heterosexually inactive) for the duration of the study.

e. 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. Male and female condoms should not be used together, as this can reduce their effectiveness.

   ii. Diaphragm or cervical cap with spermicide

   iii. Intrauterine device with spermicide

   iv. Oral contraceptives or other hormonal methods

      NOTE: Another nonhormonal method of contraception must be used in conjunction with oral contraceptives.

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 test results, vital sign measurements, 12-lead ECG results, and physical examination findings at screening.

6. Subject agrees not to use nicotine products, including electronic vapor cigarettes, nicotine patches, or nicotine gum, for at least 30 days before the Day 1 randomization visit through completion of the Day 29 dosing complete/ET visit.

7. Subject agrees to comply with the study dietary requirements throughout the study drug dosing period.

8. Subject agrees not to consume caffeine- or xanthine-containing products during all study visits, including overnight stays (PK subset); sodas, coffee, and tea designated as caffeine-free or noncaffeinated may be consumed on study days; caffeine may be consumed while at home and between study visits.

9. Subject agrees to comply with all protocol requirements.

10. Subject has adequate venous access if participating in the PK subset.

11. Subject is able and willing to provide written informed consent.

4.2 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
   - History of head trauma resulting in a diagnosis of traumatic brain injury other than concussion
   - Frequent episodes of headache

3. Subject has received any vaccination within 28 days prior to Day 1 or plans to receive a vaccination at any time during the treatment period or within 28 days after study Day 28.

4. Subject has received treatment in another clinical study of an investigational drug (or medical device) or investigational vaccine within 30 days or 5 half-lives (whichever is longer) before the first dose of study drug.

5. Subject has a history of relevant drug and/or food allergies (i.e., allergy to TPOXX or excipients, or any significant food allergy that could preclude a standard diet in the clinical investigative site).

6. Subject has any condition possibly affecting drug absorption (e.g., 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 reaction(s) (excluding seasonal allergies); or has evidence or history of clinically significant disease, including hematological, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, or neurological disease. Exceptions to these disease criteria (e.g., 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, chest pain (that is diagnosed as cardiac related) or trouble breathing on exertion, or risk factors for torsades de pointes (e.g., heart failure, hypokalemia).

9. Subject has a family history of an immediate family member (father, mother, brother, or sister) who parents and/or siblings) who has had an onset of ischemic heart disease before the age of 50 years.

10. Subject is 20 years of age or older and has a ≥30% risk of developing a myocardial infarction or coronary death within the next 10 years using the National Cholesterol Education Program's Risk Assessment Tool: https://www.mcw.edu/calculators/ldl-cholesterol-goal-level.

11. 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.

12. Subject has a history of a peptic ulcer or significant gastrointestinal bleeding.

13. Subject has a bleeding disorder diagnosed by a doctor (e.g., factor deficiency, coagulopathy, or platelet disorder requiring special precautions) or significant bruising or bleeding difficulties with blood draws.

14. 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).

15. Subject has neutropenia or other blood dyscrasia determined to be clinically significant by the investigator.

16. 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 cytochromes (CYP)2C8 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.

17. Subject has a history of drug or alcohol abuse or dependency within the last year before screening.

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 (e.g., human T cell lymphotropic virus I or II).

21. 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).

22. 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.

23. Subject reports participation in strenuous activity or contact sports within 24 hours before the first dose of study drug.

24. 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.

25. 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), cotinine, or alcohol at screening or check-in.

26. 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) <70 mL/min
    - Creatinine in males >1.7 mg/dL and in females >1.4 mg/dL (1.3 times the upper laboratory reference range)
    - Hemoglobin ≤10% of the lower laboratory reference range
    - White blood cell counts considered to be clinically significant by the investigator
    - Absolute neutrophil count <1000 cells/mm^3
    - Platelets not within ±10% of laboratory reference range
    - Alanine aminotransferase >2 times above the upper laboratory reference range
    - Aspartate aminotransferase >2 times above the upper laboratory reference range
    - Alkaline phosphatase >20% above the upper laboratory reference range
    - Hemoglobin A1c ≥7.0%
    - Cholesterol ≥300 mg/dL and low-density lipoprotein ≥190 mg/dL

27. Subject has hypertension that is poorly controlled (repeat readings >140 mm Hg systolic and/or >90 mm Hg diastolic) or blood pressure considered to be clinically significant by the investigator. Blood pressure may be retested twice in the sitting position at 5-minute intervals.

28. Subject has a resting heart rate of <40 beats per minute or >110 beats per minute at screening.

29. Subject has an abnormal ECG at screening that is determined by the investigator to be clinically significant.

30. Male subject has a QT interval corrected using Fridericia's formula (QTcF) >450 ms or female subject has a QTcF >470 ms at screening or Day 1, or Day –1 (PK subset).

31. Subject has used any prescription antiviral drugs with the intention of coronavirus disease (COVID-19) treatment or prophylaxis, including those that are thought to be effective for prevention of COVID-19 but have or have not been licensed for this indication, within 1 month prior to study entry or during the study.

32. In the opinion of the investigator, the subject is not suitable for entry into the study.

33. Subject is a member or family member of the investigator or study site personnel.

34. Subject has previously participated in this clinical trial.

4.3 OTHER SCREENING CONSIDERATIONS

- Subjects not enrolled in the PK subset must be willing and agree to return to the clinical investigative site for follow-up visits on Day 7, Day 14, and Day 21 (+1 day), a dosing complete visit on Day 29 or ET visit, and answer follow-up telephone calls on Day 42 (+2 days) and on Day 58 (+2 days).

- Subjects in the PK subset must be willing and agree to return to the clinical investigative site for 3 separate dosing and PK periods, for follow-up visits on Day 7 and Day 21, and answer follow-up telephone calls on Day 42 (+2 days) and on Day 58 (+2 days).

- Subjects must be willing to fast for 8 hours prior to specimen collection of the fasting lipid panel that will be performed at screening.

- Subjects must be willing to take study drug within 30 minutes after eating a meal containing approximately 600 calories and 25 g of fat.
- Subjects must be willing to take study drug at home for 28 days and record the date and time in a subject diary.
- Subjects must be willing to record information related to TPOXX or matching TPOXX placebo, concomitant medications, AEs, and meal compliance in their subject diary.

4.4 WITHDRAWAL OF SUBJECTS FROM THE STUDY

4.4.1 Reasons for Withdrawal

Under certain circumstances, a subject may be terminated from participating in the study based on the opinion of the investigator, SIGA, FDA, and/or the Data Safety Monitoring Board (DSMB). Subjects will be withdrawn from the study if they do not meet the study inclusion and exclusion criteria before dosing of the study drug.

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:

- Subject is in violation of the protocol.
- Subject experiences a serious or intolerable AE that in the investigator's opinion requires withdrawal from the study.
- Subject becomes pregnant.
- Subject is noncompliant.
- Subject has laboratory abnormalities for assessments listed in Sections 4.1 or Section 4.2 that meet grade 3 or grade 4 on the Division of Acquired Immune Deficiency Syndrome AE Grading Table[3]; 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.
- Subject develops, during the course of the study, symptoms or conditions listed in the exclusion criteria.

- Subject develops during the course of the study, laboratory abnormalities listed in the exclusion criteria.
- Subject requires a medication prohibited by the protocol.
- Subject requests an early discontinuation for any reason.
- Subject's primary care provider requests that the subject be withdrawn.
- The FDA, SIGA, or the DSMB 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 an SAE or intolerable AE, the investigator will confer with the medical monitor and 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.

4.4.2 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 ET visit assessments (Table 9-1 and Table 9-2). A blood sample will be collected for all subjects who discontinue from the study for TPOXX plasma concentration analysis *if the ET visit occurs within 30 hours after the subject's last dose of TPOXX/matching placebo* in order to collect information about the relationship between TPOXX blood level and ET from the study. Any subject who fails to return for final assessments will be contacted by the site 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.

4.4.3 Halting Rules

Safety evaluations will include: medical history, body weight, physical assessments, vital sign measurements, routine laboratory test results, ECG results, and AEs reported by

subjects. Symptom-directed or targeted physical examinations may be performed if indicated by interim complaints or laboratory findings.

The medical monitor and investigator will closely monitor and analyze study data as they become available and will make determinations regarding the presence and level of AEs. The medical monitor will provide an independent review of the AEs that have a bearing on study stopping. 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 temporary halting of the study should occur.

The study will be temporarily halted (no new enrollments and no further study drug dosing) by the medical monitor or designee by promptly notifying the investigators and the DSMB (as outlined in the DSMB charter) 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 that is assessed as possibly, probably, or definitely related to study drug.
- One subject experiences a seizure that is 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 DAIDS grade 3 or above and are possibly, probably, or definitely related to the study drug.
- Three or more subjects have clinically significant laboratory abnormalities that meet DAIDS grade 3 or above criteria.

Investigators will advise SIGA immediately if any of the halting rules are met and SIGA will notify the FDA immediately.

Study enrollment and study drug dosing 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 DSMB and review all AEs that meet the criteria for halting the study. The study would remain suspended until the events were reviewed by the DSMB and recommendation was made as to

whether the study would 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, indicate a potentially serious safety concern. Investigators will advise SIGA immediately if any of the halting rules are met. Safety oversight for this study is discussed in Section 9.3.3.1.4.

4.4.4 Replacements

At the discretion of the investigator, and after consultation with the medical monitor and SIGA, any subject who withdraws before completing the study may be replaced. Any replacement subject will be assigned to the same treatment as the subject they are replacing.

5. STUDY TREATMENTS

5.1 TREATMENTS ADMINISTERED

Subjects will be randomly assigned to 1 of 2 treatment groups. The treatment groups will be as follows:

- Treatment Group 1: An oral dose of 600 mg (3 × 200-mg capsules) TPOXX BID (every 12 hours [±30 minutes]) for subjects with a body weight of 120 kg or less or TID (every 8 hours [±30 minutes]) for subjects with a body weight more than 120 kg for 28 days (Day 1 to Day 28).

- Treatment Group 2: An oral dose of placebo (3 capsules identical to TPOXX) BID (every 12 hours [±30 minutes]) for subjects with a body weight of 120 kg or less or TID (every 8 hours [±30 minutes]) for subjects with a body weight more than 120 kg for 28 days (Day 1 to Day 28).

5.2 STUDY DRUG

TPOXX will be supplied as 200-mg capsules containing tecovirimat monohydrate as the active pharmaceutical ingredient. The matching TPOXX placebo will be identical in appearance and have the same excipient ingredients but will not include the active compound. 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 and Matching TPOXX Placebo Capsules

Component	Quality Designation
[redacted]	[redacted]

Abbreviations: EP, European Pharmacopeia; JP, Japanese Pharmacopeia; 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:

[redacted]

Further information on TPOXX can be found in the TPOXX Investigator Brochure[4] and Full Prescribing Information.[2]

5.2.1 Study Drug Packaging, Preparation, Administration, and Storage

SIGA will be responsible for providing the investigator and clinical investigative sites with adequate quantities of TPOXX and TPOXX matching placebo.

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

Packaging of bulk TPOXX:

[redacted]

Packaging of bulk matching placebo:

[redacted]

Labeling, storage, and distribution of TPOXX and matching placebo:

[redacted]

The 28-day supply of 200-mg TPOXX capsules and matching placebo 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 TPOXX and matching placebo will contain 42 capsules and will be labeled with at a minimum, the study number, bottle content, direction for distribution, storage conditions, and cautionary statement. The study drug will be provided to subjects in either 4 bottles (subjects weighing 120 kg or less) or 6 bottles (subjects weighing more than 120 kg) containing 42 capsules each. Each daily dose is 3 capsules taken orally either BID or TID depending on the subject's weight, for a total of 6 capsules (1200 mg) or 9 capsules (1800 mg) per day.

TPOXX and matching placebo must be stored in a secure area (e.g., a locked cabinet), out of reach of children and pets, protected from moisture and light, and stored at room temperature (15°C to 30°C or 59°F to 86°F).

TPOXX and matching placebo should not be refrigerated or used beyond the expiration dates provided by the manufacturer.

Clinical investigative sites will be required to keep temperature logs to establish a record of compliance for study drug storage conditions for TPOXX and matching TPOXX placebo.

5.2.2 Study Drug Accountability

The clinical investigative sites will maintain accurate records of receipt of all study drugs, 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. At the completion of the study, and to satisfy regulatory requirements regarding study drug accountability, all study drug will be reconciled and returned for destruction according to the instructions provided by SIGA.

Each clinical investigative site will maintain a study drug accountability log of all study drug dispensed and returned. Subjects will be instructed to bring the subject diary and all study drug bottles (including empty bottles) and unused study drug (in study drug bottles) with them to every study visit. Study drug for each subject will be inventoried and accounted for by the designated study personnel throughout the study. Study drug accountability will be recorded in the subject's source documentation, entered in the eCRF, and reviewed by the monitor during monitoring visits. On a regular basis and after study completion or termination of the study, the monitor will prepare used and unused study drug bottles for return and destruction.

5.3 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

Randomization will be performed using an interactive web response system (IWRS). The randomization will be balanced by using permuted blocks of an appropriate size and be stratified by age group (18 to 30 years, 31 to 45 years, 46 to 64 years, and 65 to 80 years). In the event of the withdrawal of a clinical investigative site, no adjustments to the randomization scheme will be implemented because site will not be used as a stratification factor. After a randomization number has been assigned, it will not be reused.

The PK subset of 40 subjects will be enrolled at up to 2 sites with at least 32 subjects who will receive TPOXX and at least 8 subjects who will receive placebo. Of the remaining subjects who are not enrolled in the PK subset, at least 324 subjects will be randomly assigned to receive TPOXX and 81 subjects to receive placebo. The IWRS will facilitate the random assignment of treatment for subjects in the study. Randomization will occur before study drug administration on Day 1, after it has been confirmed that the subject fulfills all eligibility criteria. The IWRS will assign a randomization number that is used to link the subject to 1 of the 2 treatment groups using a 4:1 ratio based on a computer-generated central randomization schedule prepared before enrollment. The IWRS will also specify the study

drug bottle numbers to be assigned to the subject where the study drug bottle numbers match the treatment group assigned by the randomization list. The assigned study drug bottles will be dispensed to the subject by the clinical investigative site. The randomization code will not be broken or made available to study subjects or their families, investigators, clinical personnel, or site managers until all subjects have completed the double-blind phase of the study and the database has been closed in accordance with the clinical investigative sites standard operating procedures (SOPs).

5.4 BLINDING

5.4.1 Blinding Procedures

This study will be performed as a double-blind study. All parties involved in the study except for the medical monitor (in the event of a suspected unexpected serious adverse reaction) and the unblinded statistician for DSMB Closed Session meetings, will remain blinded to the treatment until study completion. Under routine circumstances, the blind will not be broken.

TPOXX and matching placebo capsules are indistinguishable and all study drug bottles will be packaged the same way. Study drug bottle labeling will include all required identifying information except for the identity of the study treatment.

5.4.2 Breaking the Blind

The medical monitor will be responsible for maintaining the blind throughout the study. If a subject becomes seriously ill or pregnant during the study, the blind will be broken only if knowledge of the administered study drug will affect that subject's available treatment options. In the event of a medical emergency requiring identification of the study drug administered to an individual subject, the investigator will make every attempt to contact the medical monitor to explain the need for opening the code within 24 hours of unblinding the subject's randomization assignment. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved. All unblinding activities will be tracked via an audit trail in IWRS. Requests for unblinding of a subject's randomization assignment will be made through the IWRS after consultation with the medical monitor. Subject code breaks by the investigator will result in withdrawal of the subject from the study. The date, time, and reason for the unblinding must be documented on the appropriate page in the eCRF, and SIGA must be informed as soon as possible. The treatment assignment of subjects will remain blinded until all clinical evaluations have been completed. Unblinding at the end of the study will occur only by written request from the

lead statistician to the unblinded randomization statistician and the unblinded IWRS team after database lock and confirmation of protocol deviations. The DSMB may request to unblind the treatment assignment of a subject or the study at any time.

5.5 TREATMENT COMPLIANCE

On Day 1, study site personnel will document assessment of subject compliance to include: direct observation of TPOXX or matching placebo dosing with 8 oz. (240 mL) of water, time of completion of last meal before study drug dosing, and time of study drug dosing/observation in the source document and eCRF.

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

5.5.1 Subject Diary

Clinical investigative sites will provide subjects with a subject diary and instructions on its completion. On days when study drug dosing does not occur at the clinical investigative site, subjects will be required to record the following information in their subject diary: the date and time they completed their meals (or the last time they ate), whether or not the meal they ate was the required meal of approximately 600 calories and 25 g of fat, the date and time of their study drug doses, whether or not they took 3 capsules of study drug at dosing, and a comments for any missed capsules or dose. Subjects will also enter into the diary any new or changed concomitant medications (including over-the-counter medications taken, such as vitamin, supplemental, and herbal preparations), with the start and stop date of the medication, the reason for use, and any symptoms or problems (illness or injuries) that subjects may have experienced.

Subjects will be instructed to record all AEs in the subject diary. Instructions will be provided by the clinical investigative sites advising subjects to record the start and stop dates that they experience AEs. Subjects will be instructed to bring the subject diary with them to all study visits. The subject diary will be reviewed by study site personnel with the subject at study visits.

5.5.2 Prior and Concomitant Medications

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

5.5.2.1 Prior Medications

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

5.5.2.2 Concomitant Medications

Concomitant medications taken by subjects will be recorded at each study visit up to the follow-up telephone call on Day 42. Concomitant medications related to SAEs will be collected and recorded at the Day 58 follow-up telephone call.

Subjects will be instructed to record concomitant medications in the subject diary. 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 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 schedules of events (Table 9-1 and Table 9-2).

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 SUBSET ASSESSMENTS AND ENDPOINTS

Blood samples for PK analysis of TPOXX in plasma will be collected at the time points specified in the schedule of events (Table 9-1).

The following plasma PK parameters will be calculated separately for BID or TID dosing as endpoints for TPOXX to the extent that data permit using actual sampling times rather than scheduled sampling times and will include, but are not limited to the following:

Day 1:

- Maximum observed plasma concentration (C_{max}), reported separately for each dose
- Time to reach C_{max} (T_{max}), reported separately for each dose
- Area under the plasma concentration-time curve (AUC) from time zero to 24 hours (AUC_{0-24})
- AUC from time zero to tau where tau is the 8-hour or 12-hour dosing interval following the first dose (AUC_{tau})

Day 28:

- C_{max}
- Average steady-state plasma concentration (C_{avg})
- Trough plasma concentration (C_{trough})
- Minimum observed plasma concentration (C_{min})
- T_{max}
- AUC_{0-24h}
- AUC from time zero to tau where tau is the 8-hour or 12-hour dosing interval (AUC_{tau})
- AUC from time zero to the last measurable sample (AUC_{0-last})
- AUC from time zero to infinity ($AUC_{0-\infty}$)

- Observed elimination rate constant (λ_z)
- Terminal elimination half-life ($t_{1/2}$)
- Apparent clearance (CL_{ss}/F)
- Apparent volume of distribution (V_z/F)
- Accumulation ratio (Rac)
- %Fluctuation

6.1.1 Pharmacokinetic Sample Collection

Blood samples (approximately 5 mL) for the determination of plasma concentrations of TPOXX will be collected in lavender-topped K_3EDTA Vacutainer® tubes using a 20 gauge or larger needle, or from an in-dwelling intravenous catheter using a vacutainer tube.

Note: Refer to the investigative clinical site SOPs regarding flushing of peripherally inserted in-dwelling intravenous catheters and/or if a heparin lock is used, 1 cc of blood should be withdrawn and discarded before sample collection to assure that the heparin solution used to maintain catheter patency does not dilute the sample.

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 their designee in the subject's eCRF, on the vacutainer and cryovial labels, and the Specimen Shipping Log. In addition, the time of study drug administration before PK sampling will be recorded in the subject's eCRF. Labels will 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.

Pharmacokinetic Sample Processing

The blood sample must be centrifuged immediately, if possible, or within less than or equal to 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 above and should be capped tightly. The second tube will be a duplicate and retained at the site as a back-up plasma 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. Sample processing and storage should be as follows:

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 freezer should be equipped with a temperature monitor and should be checked on the weekend if it is not equipped with a temperature-activated alarm.

The clinical investigative sites will batch ship sets (primary and back-up plasma samples) of frozen plasma samples using frozen shippers and dry ice. A log sheet listing the samples being shipped will be included in each shipment. Plasma samples will be shipped on dry ice via courier to Alturas Analytics (Moscow, ID USA). Back-up plasma samples will remain at the clinical investigative site until further notice from SIGA. Shipments before weekends or holidays must be avoided.

The samples will be shipped for analysis to:

Alturas Analytics, Inc.
1917 South Main Street
Moscow, ID 83843, USA

Alturas Analytics will store all plasma samples at –70°C until analysis for TPOXX is complete. SIGA will advise Alturas Analytics when to destroy any remaining plasma samples.

6.1.2 Pharmacokinetic Sample Analysis

Pharmacokinetic samples will be analyzed by Alturas Analytics using a validated high-performance liquid chromatography and liquid chromatography-tandem mass spectrometry analysis for TPOXX in human plasma method in accordance with the US FDA Guidance for Industry on Bioanalytical Method Validation.[5]

6.2 SAFETY ASSESSMENTS AND ENDPOINTS

Safety and tolerability will be assessed by the following endpoints: monitoring and recording of AEs; clinical laboratory test results (hematology, serum chemistry, and urinalysis); pregnancy testing; vital sign measurements (systolic and diastolic blood pressures, heart rate,

respiratory rate, and body temperature); 12-lead ECG results; and physical examination findings. A blood sample will be collected for all subjects who discontinue from the study for TPOXX plasma concentration analysis *if the ET visit occurs within 30 hours after the subject's last dose of TPOXX/matching placebo* in order to collect information about the relationship between TPOXX blood level and ET from the study.

For all safety assessments, the investigator will determine whether results are clinically significant, which is defined as any variation in a result that has medical relevance and may result in an alteration in medical care (e.g., active observation, diagnostic measures, or therapeutic measures). If clinical significance is noted, the result and reason for significance will be documented and an AE will be reported on the AE page in the subject's eCRF. The investigator will monitor the subject until the result has reached the reference range or the result at screening, or until the investigator determines that follow-up is no longer medically necessary.

6.2.1 Adverse Events

Adverse events will be assessed from the time of the first dose of study drug until Day 42. Serious AEs will be collected up to Day 58. All AEs, SAEs, and clinically significant laboratory abnormalities should be followed until they are resolved or until stability of the abnormality has been demonstrated as determined by the investigator and/or the medical monitor.

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to SIGA, 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.

6.2.1.1 Adverse Event Definitions

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Subjects will be instructed to contact the investigator at any time after start of study drug dosing if any symptoms develop.

A treatment-emergent AE 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.

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 investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between

the study drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

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

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Full Prescribing Information[2] or if it occurs with specificity or severity that has been previously observed with the study drug being tested. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the 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 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 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, medical monitor, or SIGA, it results in any of the following outcomes:

- Results in death.
- Is life-threatening (subject 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 events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon 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 judgment, 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, medical monitor, 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. All AEs, SAEs, and clinically significant laboratory abnormalities will be followed until resolution or until stability of the abnormality has been demonstrated as determined by the investigator and/or medical monitor.

6.2.1.2 Eliciting and Documenting Adverse Events

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 and AEs recorded in subject diaries, AEs will be documented from any data collected on the AE page in the eCRF (e.g., 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, observed, or recorded in the subject diary from the first dose of study drug through the follow-up telephone call on Day 42 (+2 days) will be recorded on the AE page in 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, any required treatment or evaluations, and outcome. Any AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. The Medical Dictionary of Regulatory Activities will be used to code all AEs. 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 following the administration of study drug on Day 1, 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 that is 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 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 DSMB will also receive these reports (refer to Section 9.3.3.1.4).

For this study, the following contact information will be used for SAE reporting:

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 ET from the clinical study, 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 58 [+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 AE Grading Table.[3]

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): These events require minimal or no treatment and do not interfere with the subject's daily activities.
- Grade 2 (Moderate): These events result in a low level of inconvenience or require minor therapeutic measures and may cause some interference with normal functioning.
- Grade 3 (Severe): These events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Grade 4 (Life-threatening): Events that, in the opinion of the investigator, place the subject at immediate risk of death from the reaction as it occurred (i.e., 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 the 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 study drug and the AE; for example, the AE occurred shortly after the subject took 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:

Associated

- Definitely Related: The AE and administration of study drug are related in time, and a direct association can be demonstrated (e.g., 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 (e.g., 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 (i.e., the possibility cannot be excluded), but the AE is most likely explained by causes other than the study drug (e.g., 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 (e.g., 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/source document.

6.2.1.7 Follow-Up of Adverse Events

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

6.2.1.8 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 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 abortion should always be reported as an SAE. Pregnancy data will be captured and followed by PPD. All pregnancies and outcomes will be tracked by PPD Pharmacovigilance. A pregnancy 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, this will be recorded as an SAE in the data forms for the mother (i.e., 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

Blood and urine samples will be collected at the time points indicated in the schedules of events (Table 9-1 and Table 9-2) and will be prepared using standard procedures. Samples for safety testing will be shipped via courier to PPD Central Lab where they will be analyzed. The central laboratory for the study will receive, test, and store laboratory safety samples at the following location:

[redacted]

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 Lab will provide the reference ranges for all clinical laboratory safety parameters.

The following clinical laboratory assessments will be performed by the PPD Central Lab:

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, 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, leukocyte esterase, microscopy (performed if dipstick is ≥1+; includes bacteria, casts, crystals, epithelial cells, red blood cells, and white blood cells), nitrites, pH, protein, specific gravity, and urobilinogen

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

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

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

screening. Subjects will fast for 8 hours prior to specimen collection of the fasting lipid panel.

For women of childbearing potential, serum pregnancy test will be performed at the screening visit and on Days 7, 14, 21, and 29 and analyzed by PPD Central Lab as indicated in the schedule of events tables (Table 9-1 and Table 9-2). A urine pregnancy test will be performed and read locally at check-in on Day -1 (PK subset) or predose on Day 1 (Non-PK subset). All positive urine tests will be verified using a serum β-human chorionic gonadotropin test.

For postmenopausal women, a serum follicle-stimulating hormone test 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.

Drug/Alcohol/Cotinine Testing

Screening:

A urine drug screen for alcohol, cotinine, 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 sent to the central lab.

Day –1 (Check-in - PK Subset, Table 9-1) or Day 1 (Predose - Non-PK Subset Table 9-2):

A urine drug screen for cotinine, amphetamines (including methamphetamines and ecstasy/methylenedioxymethamphetamine), barbiturates, benzodiazepines, cannabinoids (including tetrahydrocannabinol), cocaine metabolites, and opiates (including heroin, codeine, and oxycodone) will be performed and read locally. Blood alcohol will be tested using a breathalyzer device at the clinical investigative site.

Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference range for each laboratory parameter. The investigator will determine whether any of the abnormally high or low results are clinically significant or not clinically significant.

6.2.3 Medical History

Review of medical history will be performed prior to the first dose of study drug and if determined by the investigator based on medical history/symptomology and will include a review of systems; recreational, prescription, and over-the-counter drug use; nicotine and alcohol use; and past hospitalizations at the time points indicated in the schedules of events (Table 9-1 and Table 9-2).

6.2.4 Vital Sign Measurements

Vital signs will be measured after the subject has been in the seated position for at least 5 minutes at the time points indicated in the schedules of events (Table 9-1 and Table 9-2).

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

6.2.5 Electrocardiograms

A single 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 schedules of events (Table 9-1 and Table 9-2). The acceptable window for collection from the scheduled collection time point is ±15 minutes.

The investigator will review the 12-lead ECGs and determine if they are normal or abnormal. Electrocardiogram assessments will include comments on whether the tracings are normal or abnormal (clinically significant or not clinically significant), rhythm, the presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST-segment, T-wave, and U-wave abnormalities. In addition, measurements of the following intervals will be measured and reported: heart rate; PR, RR, and QT interval; QTcF; and QRS duration. The investigator will determine if any abnormal 12-lead ECG results are clinically significant or not clinically significant prior to study drug dosing and throughout the study to confirm that the subject can remain in the study.

All ECGs must be performed by an experienced ECG technician.

6.2.6 Physical Examinations

Full physical examinations will be performed at the time points indicated in the schedules of events (Table 9-1 and Table 9-2) and will include, at minimum, 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 on Day 31 (PK subset only) as well as unscheduled physical exams at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

Height and weight will be measured at screening only.

6.2.7 Unscheduled Visits

Clinical investigative sites will provide subjects 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 study site personnel in the source document. Unscheduled procedures and laboratory tests and results will also be recorded in the eCRF.

7. STATISTICAL ANALYSIS PLANS

7.1 SAMPLE SIZE CALCULATIONS

There is no formal sample size calculation for this study. Although the sample size is not based on statistical power considerations, administration of TPOXX 600 mg to 300 subjects provides approximately 95% probability of observing at least 1 occurrence of any AE if the incidence of AEs in the study population is 1% and is considered adequate to provide a reasonable assessment of safety and tolerability. A sufficient number of subjects will be randomly assigned to ensure that at least 300 subjects receive at least 92% of the doses of the BID or TID dosing regimen of oral TPOXX 600 mg over the 28-day treatment period.

7.2 ANALYSIS SETS

All populations will be identified and finalized before the database lock. All subjects who are randomly assigned are considered study subjects. Study populations are defined as the following:

- The Intent-to-Treat (ITT) Population will include all subjects who were randomly assigned to the study (i.e., a randomization number and randomization date are present in the database).

- The Safety Population will include all subjects who received at least 1 dose of TPOXX or matching placebo.

- The Per-Protocol (PP) Safety Population will include all subjects who received at least 92% of the doses of TPOXX or matching placebo 600 mg BID or TID dosing regimen over the 28 day treatment period.

- The PK Population will include all subjects in the PK subset who have taken at least 92% of the doses of the 600 mg BID or TID dosing regimen of TPOXX, have sufficient drug concentrations in plasma, and have no protocol deviations or other circumstances that would exclude the subject from analysis.

7.3 STATISTICAL ANALYSIS

Details of all statistical analyses will be described in a statistical analysis plan (SAP). 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, SD, minimum, and maximum).

Baseline demographic and background variables will be summarized by treatment for the ITT, Safety, PP Safety, and PK Populations. The demographics table will also be summarized overall and by age group as per the stratification used in randomization. For treatment-related tables and listings, the data will be summarized by BID or TID study drug dosing regimen. 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

The PK Population will be used for the preparation of PK summaries and analyses.

Individual plasma concentration and time deviation data will be presented in a data listing. Plasma concentration data will be summarized by study day, time point, and study drug dosing regimen using the following descriptive statistics: number of subjects, arithmetic

mean, SD, coefficient of variation (CV), minimum, median, and maximum. Individual and mean plasma concentration versus scheduled time profiles will be presented in figures on both linear and semilogarithmic scales. Mean concentration versus scheduled time profiles will be presented by study drug dosing regimen.

The PK parameters of TPOXX will be analyzed using noncompartmental methods based on the actual sampling times. The individual PK parameters will be presented in data listings and summarized by study day and study drug dosing regimen using the following descriptive statistics: number of subjects, arithmetic mean, SD, CV, geometric mean, geometric SD, geometric CV, minimum, median, and maximum.

7.3.2 Safety Analyses

The safety and tolerability data summaries will be presented separately for the Safety Population and the PP Safety Population and will also be presented by BID and TID TPOXX/matching placebo dosing regimen.

Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities. All AE data will be presented in a data listing. Treatment-emergent AEs will be summarized by treatment, BID and TID study drug dosing regimen, and overall, as well as by severity and relationship to study drug for the Safety Population and the PP Safety Population. For any subject who discontinues the study for any reason, data will be summarized by treatment group, reason for discontinuation, if the drug concentration was collected, and the result of the bioanalysis. In addition, SAEs and AEs leading to subject study discontinuation will be presented in the data listings and summarized by treatment, dosing regimen, and overall.

The overall AE rate will be defined as the percentage of subjects in the Safety Population and PP Safety Population who report at least 1 postdose AE. The overall AE rate will be compared between treatment groups using Mantel-Haenszel test stratified for age group (18 to 30, 31 to 45, 46 to 64, and 65 to 80 years). If expected cell counts are less than 5, then Fisher’s exact test will be applied. An exact unadjusted 95% confidence interval (CI), calculated using the Clopper-Pearson method, will be presented for each treatment group. For the difference in overall AE rates between treatment groups, a continuity corrected exact 95% CI around the difference will be calculated. In addition, the Mantel-Haenszel adjusted odds ratio and 95% CIs from the stratified analysis will be presented. The relationship of treatment group, age, clinical investigative site, and their interactions on overall AE rate will also be

investigated using a logistic regression model; CIs for the odds ratios associated with each factor in the model will be presented. Further details will be included in the SAP.

Time from the first dose to the first AE or to discontinuation from study for any reason will be analyzed using Kaplan-Meier quartile estimates along with 2-sided 95% CIs. Treatment groups will be compared using the log rank test stratified by age group and site. If a subject does not experience any AE or does not discontinue from study, the time to first AE or time to discontinuation will be censored at the date of study completion.

Toxicity grades for laboratory tests will be determined according to the DAIDS AE Grading Table. The maximum postbaseline grade increase from baseline grade will be summarized by treatment group and BID and TID study drug dosing regimen and overall for the Safety Population and PP Safety Population using frequency and percentage of subjects with increase to grade 1, 2, 3, 4, 1 to 4, 2 to 4, and 3 to 4, respectively.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment group and BID and TID study drug dosing regimen 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. Physical examination findings will be presented in a data listing.

Narratives will be presented for all deaths, subjects who reported SAEs, subjects withdrawn because of AEs, and grade 3 AEs deemed by the investigator to be possibly, probably, or definitely related to study drug.

7.4 HANDLING OF MISSING DATA

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero for descriptive statistics. 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.

For the PK analysis, BLQ values will be treated as zero with the exception that a BLQ value between 2 quantifiable concentrations will be set as missing. Missing concentrations will be treated as missing from the PK parameter calculations. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing.

7.5 INTERIM ANALYSES

No formal interim analyses are planned for 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); 2022.

3. Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events. July 2017 [cited 2020 Aug 18]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

4. SIGA Technologies, Inc. TPOXX (tecovirimat). Investigator's Brochure, 17th ed. Corvallis (OR); 2021. 125 p.

5. Department of Health and Human Services (DHHS), Food and Drug Administration Center for Drug Evaluation and Research (US). Guidance for Industry: Bioanalytical Method Validation. May 2018 [cited 2020 Aug 18]. Available from: https://www.fda.gov/media/70858/download.

9. APPENDICES

9.1 APPENDIX 1: LIST OF ABBREVIATIONS

Abbreviation	Term
λ_z	the observed 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 zero to 24 hours
AUC_{0-tau}	area under the plasma concentration-time curve during the first dosing interval
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
BID	two times a day
BLQ	below the limit of quantification
C_{avg}	average steady-state plasma concentration
CFR	Code of Federal Regulations
CI	confidence interval
CL_{ss}/F	apparent clearance
C_{min}	minimum observed plasma concentration
C_{max}	maximum observed plasma concentration
CRA	clinical research associate
CRF	case report form
C_{trough}	trough plasma concentration
CV	coefficient of variation
CYP	cytochromes
DAIDS	Division of Acquired Immune Deficiency Syndrome
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
ITT	intent to treat
IWRS	interactive web response system
PK	pharmacokinetic(s)
PP	per protocol
QTcF	QT interval corrected using Fridericia's formula
Rac	accumulation ratio
SAE	serious adverse event

Abbreviation	Term
SAP	statistical analysis plan
SOP	standard operating procedure
$t_{1/2}$	terminal elimination half-life
TID	three times a day
T_{max}	time to reach maximum observed plasma concentration
V_z/F	apparent volume of distribution

9.2 APPENDIX 2: SCHEDULE OF EVENTS

Table 9-1 Schedule of Events: Pharmacokinetic Subset Study Subjects

Period	Screening	Check-in	Treatment												PK Sampling			Follow-up	
Procedure[a] Day	–28 to –2	–1	1	2	3 to 6	7	8 to 12	13	14	15 to 20	21	22 to 26	27	28	Dosing Complete /ET Visit 29	30	31	Telephone Call 42 (+2 days)	SAE Telephone Call 58 (+2 days)
Admission to clinic		X						X					X						
Discharge from clinic[b]				X					X								X		
Informed consent	X																		
Inclusion/exclusion criteria	X	X[c]																	
Medical history	X	X[d]																	
Physical examination[e]	X	X				X			X		X				X		X		
Demographics	X																		
Height and weight	X																		
Serology (HBsAg, HCV, and HIV)	X																		
Vital sign measurements[f]	X	X	X[g]			X			X[g]		X				X		X		
Drug/alcohol/cotinine screen[h]	X	X																	
Glycosylated hemoglobin (HbA1c)	X																		
Fasting lipid panel[i]	X																		
Clinical laboratory testing[j]	X	X				X		X			X				X				
Serum pregnancy test[k]	X					X		X			X				X				

Period	Screening	Check-in	Treatment												PK Sampling			Follow-up	
Procedure[a] Day	–28 to –2	–1	1	2	3 to 6	7	8 to 12	13	14	15 to 20	21	22 to 26	27	28	Dosing Complete /ET Visit 29	30	31	Telephone Call 42 (+2 days)	SAE Telephone Call 58 (+2 days)
Urine pregnancy test[k]		X																	
Serum follicle-stimulating hormone[l]	X																		
12-lead ECG[m]	X	X	X			X			X		X				X				
Randomization			X																
Meal[n]			X	X				X	X				X	X					
Administration of study drug[o]			X	X	X	X	X	X	X	X	X	X	X	X					
Dispense study drug				X															
Collect study drug								X					X						
Study drug instructions				X															
Pharmacokinetic sampling[p]			X	X					X					X	X[q]	X	X		
Subject diary dispensing[r]				X															
Subject diary review						X		X			X		X						
Subject diary collection													X						
AEs/SAEs[s]			X															X	X
Prior/concomitant medications[t]	X		X															X	X

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

[a] 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.

[b] Discharge from the clinical investigative site will follow collection of all safety assessments.

[c] Review of inclusion/exclusion criteria will be performed prior to the first dose of study drug.

(d) Review of medical history will be performed prior to the first dose of study drug and if determined by the investigator based on medical history/symptomology and will include a review of systems; recreational, prescription, and over-the-counter drug use; nicotine and alcohol use; and past hospitalizations.

(e) A full physical examination will include, at minimum, 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 on Day 31 at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

(f) Vital signs will be measured after the subject has been in the seated position for at least 5 minutes and will include systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. Day 31 vital signs only need to be collected in the event that a symptom-directed physical examination is performed.

(g) Vital signs will be measured within 60 minutes prior to the first dose of the day and 4 hours following the first dose of the day. The acceptable window for collection is ±15 minutes from the scheduled time point.

(h) Includes alcohol, cotinine, amphetamines (including methamphetamines and ecstasy/methylenedioxymethamphetamine), barbiturates, benzodiazepines, cannabinoids (including tetrahydrocannabinol), cocaine metabolites, and opiates (including heroin, codeine, and oxycodone). A urine drug screen including alcohol and cotinine will be collected and sent to the central laboratory at the screening visit. A urine drug screen and alcohol breath test using a breathalyzer will be performed and read locally on Day –1.

(i) Fasting lipid panel will include cholesterol (total, high-density lipoprotein, calculated low-density lipoprotein, and triglycerides). Fasting shall occur for 8 hours prior specimen collection.

(j) Clinical laboratory testing will include hematology, serum chemistry, and urinalysis. Clinical laboratory testing from screening will be used to determine eligibility.

(k) Women of childbearing potential only. A urine pregnancy test will be performed and read locally on Day –1. All other pregnancy tests, including screening, are by serum and read by the Central Lab.

(l) For postmenopausal women.

(m) A single 12-lead ECG will be obtained after the subject has been in the supine position for at least 10 minutes. On Day 1 and Day 14, an ECG will be recorded within 60 minutes prior to the first dose of the day and 4 hours after the first dose of the day. The acceptable window for collection from the scheduled collection time point is ±15 minutes.

(n) When study drug is administered at the clinical investigative site, all subjects will be provided a meal (consisting of approximately 600 calories and 25 g of fat). The meal should be consumed within 30 minutes and prior to the administration of study drug (TPOXX or matching placebo). Subjects should be administered study drug as soon as possible following completion of the meal but no more than 30 minutes should elapse between meal completion and administration of study drug. Subjects should take study drug with 8 oz. (240 mL) of water.

(o) The time of study drug dosing will be called “0” hour. Study drug will be administered to subjects by study site personnel when subjects are in house and subjects will self-administer study drug when at home.

(p) **Two times a day dosing: Subjects weighing 120 kg or less:**
Blood samples for PK analysis of TPOXX in plasma will be collected on Day 1 before the first dose (0 hour) and at 2, 4, 6, 8, 10, 12 (before the second dose), 14, 16, 18, 20, 22, and 24 hours (before the first dose on Day 2); on Day 14 (before the first dose); and on Day 28 (before the first dose) and at 2, 4, 6, 8, 10, 12 (before the second dose on Day 28), 14, 16, 18, 20, 22, 24 (Day 29, AM), 48 (Day 30, AM), and 72 (Day 31, AM) hours after the first dose on Day 28.
Three times a day dosing: Subjects weighing more than 120 kg:
Blood samples for PK analysis of TPOXX in plasma will be collected on Day 1 before the first dose (0 hour) and at 2, 4, 6, 8 (before the second dose), 10, 12, 14, 16 (before the third dose), 18, 20, 22, and 24 hours (before the first dose on Day 2); on Day 14 (before the first dose); and on Day 28 (before the first dose) and at 2, 4, 6, 8 (before the second dose), 10, 12, 14, 16 (before the third dose), 18, 20, 22, 24 (Day 29, AM), 48 (Day 30, AM), and 72 (Day 31, AM) hours after the first dose on Day 28.
For PK blood samples, the acceptable window for collection from the scheduled collection time point will be as follows: ±15 minutes from 0 to 24 hours (except where samples are collected predose) and ±60 minutes from 48 to 72 hours.

(q) If the subject is completing the ET visit, a blood sample for TPOXX concentration analysis should be collected within 30 hours after the last dose of study drug from subjects who discontinue. If the visit occurs more than 30 hours following the subject's last dose of study drug, no sample needs to be collected.

(r) One diary will be dispensed to record TPOXX or matching placebo administration, completion of required meals before and after dosing, all concomitant medications, and all AEs.

(s) Adverse events will be collected from first dose of study drug until Day 42. Serious AEs will be collected up to Day 58. All AEs, SAEs, and clinically significant laboratory abnormalities will be followed until resolution or until stability of the abnormality has been demonstrated as determined by the investigator and/or medical monitor.

(t) Concomitant medication information will only be collected at the Day 58 follow-up telephone call if it is related to an SAE.

Table 9-2 Schedule of Events: Non-Pharmacokinetic Subset Safety Subjects

Procedure[a]	Screening (Day –28 to -1)	Baseline Day 1 Predose (AM)	Day 1 Postdose	Day 7 Follow-up	Day 14 Follow-up	Day 21 Follow-up	Day 29 Dosing Complete/ET Visit	Follow-up Telephone Call Day 42 (+2 days)	SAE Follow-up Telephone Call Day 58 (+2 days)
Admission to clinic		X							
Discharge from clinic[b]			X						
Informed consent	X								
Inclusion/exclusion criteria	X	X[c]							
Medical history	X	X[d]							
Physical examination[e]	X			X	X	X	X		
Demographics	X								
Height and weight	X								
Serology (HBsAg, HCV, and HIV)	X								
Vital sign measurements[f]	X	X	X[g]	X	X	X	X		
Urine drug/alcohol/cotinine screen[h]	X	X							
Glycosylated hemoglobin (HbA1c)	X								
Fasting lipid panel[i]	X								
Clinical laboratory testing[j]	X	X		X	X	X	X		
Serum pregnancy test[k]	X			X	X	X	X		
Urine pregnancy test[k]		X							
Serum follicle-stimulating hormone[l]	X								
12-lead ECG[m]	X	X	X	X	X	X	X		
Randomization		X							
Meal[n]		X							
Administration of study drug[o]		X							
Dispense study drug			X						
Collect study drug							X		
Study drug instructions			X						
Subject diary dispensing[p]			X						
Subject diary review				X	X	X			
Subject diary collection							X		
TPOXX concentration sampling							X[q]		

Procedure[a]	Screening (Day –28 to -1)	Baseline Day 1 Predose (AM)	Day 1 Postdose	Day 7 Follow-up	Day 14 Follow-up	Day 21 Follow-up	Day 29 Dosing Complete/ET Visit	Follow-up Telephone Call Day 42 (+2 days)	SAE Follow-up Telephone Call Day 58 (+2 days)
AEs/SAEs[r]			X					X	X
Prior/concomitant medications[s]	X	X	X					X	X

Abbreviations: AE, adverse events; ECG, electrocardiogram; ET, early termination; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SAE, serious adverse event.

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

[b] Discharge from the clinical investigative site will follow collection of all safety assessments.

[c] Review of inclusion/exclusion criteria will be performed prior to the first dose of study drug.

[d] Review of medical history will be performed prior to the first dose of study drug and if determined by the investigator based on medical history/symptomology and will include a review of systems; recreational, prescription, and over-the-counter drug use; nicotine and alcohol use; and past hospitalizations.

[e] A full physical examination will include, at minimum, 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). Interim, unscheduled, symptom-directed physical examination will be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

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

[g] Vital signs will be measured within 60 minutes prior to the first dose of the day and 4 hours following the first dose of the day. The acceptable window for collection is ±15 minutes from the scheduled time point

[h] Includes alcohol, cotinine, amphetamines (including methamphetamines and ecstasy/methylenedioxymethamphetamine), barbiturates, benzodiazepines, cannabinoids (including tetrahydrocannabinol), cocaine metabolites, and opiates (including heroin, codeine, and oxycodone). A urine drug screen including alcohol and cotinine will be collected and sent to the central laboratory at the screening visit. A urine drug screen and alcohol breath test using a breathalyzer will be performed and read locally on Day 1.

[i] Fasting lipid panel will include cholesterol (total, high-density lipoprotein, calculated low-density lipoprotein, and triglycerides). Fasting shall occur for 8 hours prior specimen collection.

[j] Clinical laboratory testing will include hematology, serum chemistry, and urinalysis. Clinical laboratory testing from screening will be used to determine eligibility.

[k] Women of childbearing potential only.. A urine pregnancy test will be performed and read locally on Day 1 Predose. All other pregnancy tests, including screening, are by serum and read by the Central Lab.

[l] For postmenopausal women.

[m] A single 12-lead ECG will be obtained after the subject has been in the supine position for at least 10 minutes. On Day 1, an ECG will be recorded prior to the first dose of the day and after the first dose of the day.

(n) When study drug is administered at the clinical investigative site, all subjects will be provided a meal (consisting of approximately 600 calories and 25 g of fat). The meal should be consumed within 30 minutes and prior to the administration of study drug (TPOXX or matching placebo). Subjects should be administered study drug as soon as possible following completion of the meal but no more than 30 minutes should elapse between meal completion and administration of study drug. Subjects should take study drug with 8 oz. (240 mL) of water.

(o) The time of study drug dosing will be called "0" hour. Study drug will be administered to subjects by study site personnel for the first dose on Day 1 and subjects will self-administer study drug when at home. Subjects will be instructed at the screening visit and prior to check-in to the clinical investigative site on Day 1 that other than water, no beverages may be ingested within 3 hours before or 3 hours after study drug administration, excluding a beverage that is being consumed as a part of the required meal.

(p) One diary will be dispensed to record TPOXX or matching placebo administration, completion of required meals before and after dosing, all concomitant medications (dose and frequency), and all AEs.

(q) If the subject is completing the ET visit, a blood sample for TPOXX concentration analysis should be collected within 30 hours after the last dose of study drug from subjects who discontinue. If the visit occurs more than 30 hours following the subject's last dose of study drug, no sample needs to be collected.

(r) Adverse events will be collected from first dose of study drug until Day 42. Serious AEs will be collected up to Day 58. All AEs, SAEs, and clinically significant laboratory abnormalities will be followed until resolution or until stability of the abnormality has been demonstrated as determined by the investigator and/or medical monitor.

(s) Concomitant medication information will only be collected at the Day 58 follow-up telephone call if it is related to an SAE.

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 (GCP), the protocol, and 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 case report forms (eCRFs) 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 investigators and appropriate clinical investigative sites, protocol training and review of protocol procedures with the investigators and study site personnel before the start of the study, site initiation and periodic interim monitoring visits by 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 a PPD clinical research associate (CRA) during on-site monitoring visits. Discrepancies will be resolved with the investigators or designees, as appropriate. The data will be entered into the clinical study database and validated for accuracy. During on-site monitoring visits, 100% source documentation verification will be performed. SIGA or the Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense representatives may accompany the PPD CRA on any scheduled site visit. Investigators will be informed in advance of any visitors to the clinical investigative 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. Investigators are 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 ICF.

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 that is to be provided to the subject or the subject’s legal guardian must be approved by a central IRB.

ADVARRA IRB
6940 Columbia Gateway Drive, Suite 110
Columbia, MD 21046
Telephone: 410-884-2900

Documentation of all IRB approvals and of the IRB compliance with the ICH harmonised tripartite guideline E6(R2): GCP will be maintained by the clinical investigative 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 administrated. 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 their legal guardian will be given a full explanation of the study and will be allowed 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 their 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 80 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 timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to the central IRB.

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 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): GCP; the protocol; and all national, state, and local laws or regulations.

9.3.2.9 Case Report Forms and Source Documents

Study 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 CRAs.

Each eCRF is presented as an electronic copy, allowing data entry by study 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 study site personnel, 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 the central IRB. 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, patient applications, 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. Clinical research associates will conduct site monitoring visits as detailed in the monitoring plan.

Site investigators will allow the CRA(s), the central IRB, SIGA or its designee, and the FDA to review, audit, and inspect study documents (e.g., 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 clinical investigative 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 clinical investigative site electronically.

9.3.3.1.2 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/SIGA project team 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.

9.3.3.1.3 Medical Monitor

The medical monitor, or their qualified designee, will receive reports within 24 hours of clinical investigative site awareness of all SAEs and within 7 days of clinical investigative site awareness of all other AEs. The safety monitors will review all safety data and alert the medical monitor of SAEs. 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.

9.3.3.1.4 Safety Oversight

In addition to the investigator's ongoing review of the safety data, an independent DSMB will be established to review the protocol for any major concerns and will be involved in data review in coordination with the investigators and the medical monitor. The primary role of the committee will be to evaluate the study safety and tolerability data.

The 3-member independent DSMB will establish a charter for the committee with procedures for reviewing the safety information during the study and intends to meet at least 4 times throughout the study as follows:

- At the beginning of the study (before first subject randomized).
- At the completion of 112 subjects (approximately 25% of subjects) receiving their first dose of study drug.
- After the last subject receives the final dose of study drug.
- At the completion of all subjects in the study, including the final follow-up safety visits.
- At any time during the study as deemed necessary by the committee and/or SIGA.

Before initiation of the study, the DSMB will review the study design, the methods for safety assessments, and the rules for halting this study. As part of their responsibility, DSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study subjects. The DSMB will also assess the performance of overall study operations and any other relevant issues, as necessary. The DSMB will remain blinded to study treatment assignments unless the need to unblind treatment assignment(s) is deemed necessary by the committee. PPD will provide access to the randomization codes through the unblinded statistician who will be available for DSMB meetings and as requested to provide unblinding information when needed.

Immediate notification will be provided to DSMB of specific events, including the following:

- All events meeting the criteria for an SAE.
- Withdrawal of subjects because of an AE possibly, probably, or definitely related to study drug.
- DAIDS grade 4 laboratory abnormalities that are considered clinically significant by the investigator (may require additional testing or treatment beyond protocol-specific assessments).
- Any death of a subject.

A summary of safety results will be provided to the DSMB for review and discussion at scheduled and ad-hoc meetings. The specific reporting requirements will be outlined in the DSMB Charter, but are anticipated to be based on data collected up to and including the follow-up period and will include the following: demographics, study accountability, subjects withdrawn, summaries and listings of SAEs/AEs coded by the Medical Dictionary for Regulatory Activities, summary of abnormal clinical laboratory results, summary of ECG results, and protocol deviations. Narrative summaries for subjects with withdrawals because of AEs determined by the investigator to be possibly, probably, or definitely related to the study drug; AEs that are grade 3 and higher; SAEs; or special cases of particular interest will be provided to the DSMB per the reporting requirements of the DSMB Charter.

The study can be temporarily halted in 2 capacities based on the observations in a summary review: immediate halt (no new enrollments and no further study drug dosing) or enrollment halt (no new enrollments but further study drug dosing of enrolled subjects may continue), with PPD providing notification to the investigators.

9.3.3.1.5 Inspection of Records

The investigators and institutions 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.

Investigators should promptly notify PPD and SIGA of inspections scheduled by any regulatory authorities and promptly forward copies of any inspection forms or other documentation received to SIGA.

9.3.3.1.6 General COVID-19 Precautions at Clinical Investigative Sites

Clinical investigative sites participating in this study will have processes in place locally for following recommendations of the local public health authorities for the management of COVID-19. Subjects will be asked to follow good hygiene and safe physical distancing measures such as wearing a face mask on-site, frequent hand hygiene, and maintaining a physical distance of 2 meters (or 6 feet) from others, except during procedures where staff must come into close proximity of subjects (e.g., blood draws, collecting vital sign measurements).

Staff at the clinical investigative sites will also follow the same good hygiene and safe physical distancing measures as the subjects at the clinical investigative site. In addition, the study site staff will be responsible for disinfecting materials and/or areas between each use by subjects and study site staff. All study site staff involved with on-site procedures will have a back-up member who is qualified to perform the same duties/responsibilities in the event that a member of the study site staff is infected with SARS-CoV-2 or comes into contact with an individual known to have COVID-19 and is restricted to self-isolation and following the recommendations of the local public health authorities for the management of COVID-19.

Subjects will be asked to inform the clinical investigative site if they have tested positive for COVID-19 and if they are following the actions (e.g., quarantine, re-testing) recommended by local public health authorities. Subjects will be asked to not visit the clinical investigative site until after they have fully recovered (i.e., no more clinical symptoms) and have completed all of the actions (e.g., quarantine, re-testing) recommended by local public health authorities. If the quarantine period for the subject overlaps with clinical investigative site visit and the visit window, then the procedures for that particular visit may be performed by trained medical staff, using reliable personal protective equipment, and following good hygiene, at the subject's home (or place of quarantine).

9.3.3.2 Management of Protocol Amendments and Deviations

9.3.3.2.1 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 central IRB and IRB approved before subjects are enrolled into an amended protocol.

9.3.3.2.2 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 major or significant deviation) is a subset of protocol deviations that leads to a subject being discontinued from the study, or significantly affects the subject's rights, safety, or well-being and/or completeness, accuracy, and reliability of the study data. 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 and shared with the PPD/SIGA team. 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.

9.3.3.3 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 by SIGA, PPD, or the FDA. Reasons for such action include, but are not limited to:

- Clinical investigative 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 FDA has 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 (including the follow-up telephone calls). 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.

9.3.3.4 Final Report

Regardless of 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.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review complete study results.

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

9.4 APPENDIX 4: DIVISION OF ACQUIRED IMMUNE DEFICIENCY SYNDROME (DAIDS)

Introduction

The DAIDS oversees more than 300 clinical trials domestically and internationally, which evaluate the safety and efficacy of therapeutic products, vaccines, and other preventive modalities. Adverse event data collected during these clinical trials form the basis for subsequent safety and efficacy analyses of pharmaceutical products and medical devices. Incorrect and inconsistent AE severity grading can lead to inaccurate data analyses and interpretation, which in turn can impact the safety and well-being of clinical trial participants and future patients using pharmaceutical products.

Over the years, DAIDS scientific knowledge and experience have expanded, necessitating revisions of the DAIDS grading table which serves as a guide for assessing the severity of AEs (including clinical and laboratory abnormalities) in participants enrolled in DAIDS-sponsored and -supported clinical trials. The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* updates and replaces version 2.1 (March 2017).

DAIDS is grateful to the DAIDS Grading Table Working Group, numerous government and non-government affiliated medical subject matter experts and reviewers who were instrumental in the revision of the DAIDS grading table.

Instructions for Use

General Considerations

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term “severe” is not the same as the term “serious” in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

Clinical sites are encouraged to report parameters in the DAIDS grading table as they are written to maintain data consistency across clinical trials. However, since some parameters can be reported with more specificity, clinical sites are encouraged to report parameters that convey additional clinical information. For example, diarrhea could be reported as neonatal diarrhea; seizures, as febrile seizures; and pain, as jaw pain.

The DAIDS grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death (Note: This grade is not specifically listed on each page of the grading table).

Other points to consider include:

- Use age and sex values as applicable.
- Unless noted, laboratory values are for term neonates.
- Where applicable, Standard International (SI) units are included in italics.

Selecting and Reporting a Primary AE Term

When selecting a primary AE term to report, sites should select the term that best describes what occurred to the participant. For example, a participant may present with itching, urticaria, flushing, angioedema of the face, and dyspnea. If the underlying diagnosis is determined to be an acute allergic reaction, sites should report "Acute Allergic Reaction" as the primary AE term.

Primary AE terms should be reported using the DAIDS Adverse Experience Reporting System (DAERS) only if they meet expedited reporting criteria. However, all primary AE terms should be reported using protocol-specific case report forms (CRFs). Because the reported information is stored in different databases (i.e., safety and clinical), sites should report primary AE terms using the same terminology for data consistency.

When reporting using DAERS, other clinically significant events associated with a primary AE term that more fully describe the nature, severity, or complications of the primary AE term should be entered in the "Other Events" section. However, the severity grade for these events must be lower than or equal to the severity grade of the primary AE term. In the

example above, dyspnea and angioedema of the face may be entered in the "Other Events" section, because they are more descriptive and provide additional information on the severity of the acute allergic reaction. However, their severity grades must be lower than or equal to the severity grade of the primary AE term of "Acute Allergic Reaction".

Differences exist in the reporting and recording of information (e.g., signs and symptoms, clinically significant events) in DAERS and CRFs. Therefore, sites should refer to their protocols and CRF requirements for further instructions.

Grading Adult and Pediatric Adverse Events

When a single parameter is not appropriate for grading an AE in both adult and pediatric populations, separate parameters with specified age ranges are provided. If no distinction between adult and pediatric populations has been made, the listed parameter should be used for grading an AE in both populations.

Reporting Pregnancy Outcomes

In the Pregnancy, Puerperium, and Perinatal section, all parameters are pregnancy outcomes and should be reported using the mother's participant ID. If an infant is not enrolled in the same study as the mother, any identified birth defects should be reported using the mother's participant ID. However, if an infant is enrolled in the same study as the mother or in another study, any identified birth defects should be reported using the infant's participant ID. Sites should refer to the applicable network standards for reporting abnormal pregnancy outcomes on the CRFs.

Determining Severity Grade for Parameters between Grades

If the severity of an AE could fall in either one of two grades (i.e., the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the two grades.

Using Addenda 1-3: Grading Tables Used in Microbicide Studies

In protocols involving topical application of products to the female and male genital tracts or rectum, strong consideration should be given to using Addenda 1 to 3 (see below) as the primary grading tables for these areas. Although these grading tables are used specifically in microbicide studies, they may be used in other protocols as adjuncts to the main grading table (i.e., the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0*). It should be clearly stated in a protocol which addendum is being used as the

primary grading table (and thus takes precedence over the main grading table) and which addendum is being used in a complementary fashion.

- Addendum 1 – Female Genital Grading Table for Use in Microbicide Studies http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables
- Addendum 2 – Male Genital Grading Table for Use in Microbicide Studies http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables
- Addendum 3 – Rectal Grading Table for Use in Microbicide Studies http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables

Estimating Severity Grade for Parameters Not Identified in the Grading Table

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

Table 9-3 Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event NOT identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death
Cardiovascular				
Arrhythmia (by ECG or physical examination) Specify type, if applicable	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Blood Pressure Abnormalities ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit) ≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one > 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[a]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline dysrhythmia)	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)
Dermatologic				
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[b] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar nonketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (a disorder characterized by fat loss in the face, extremities, and buttocks)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Endocrine and Metabolic				
Lipohypertrophy (characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Gastrointestinal				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Musculoskeletal				
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social &	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
		functional activities		
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[c] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[c] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age NA	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Neurologic				
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
	with ataxia detected on examination			
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on parttime basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a fulltime basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Seizures *New Onset Seizure* *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or preexisting febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA
Pregnancy, Puerperium, and Perinatal				
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[d] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA
Psychiatric				
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization Indicated	Suicide attempted
Respiratory				
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)
Sensory				
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< 12 years of age (based on a 1, 2, 3, 4,6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or panuveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
Systemic				
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cytokine Release Syndrome[e]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than Minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[f] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness[g]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[h] *> 5 to 19 years of age*	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	WHO Weight-for-height z-score < -1 to -2	WHO Weight-for-height z-score < -2 to -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life threatening consequences
< 2 years of age WHO	Weight-for-length z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary				
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences
Site Reactions to Injections and Infusions				
Injection Site Erythema or Redness[i] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
Laboratory Values - Chemistry				
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life threatening consequences	pH < 7.3 with life threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life threatening consequences	pH > 7.5 with life threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 × ULN	1.5 to < 3.0 × ULN	3.0 to < 5.0 × ULN	≥ 5.0 × ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin *Direct Bilirubin*[j], *High* *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity	> ULN with life threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 × ULN	1.6 to < 2.6 × ULN	2.6 to < 5.0 × ULN	≥ 5.0 × ULN
Calcium, High (mg/dL; *mmol/L*) *≥ 7 days of age*	10.6 to < 11.5 *2.65* to < *2.88*	11.5 to < 12.5 *2.88* to < *3.13*	12.5 to < 13.5 *3.13* to < *3.38*	≥ 13.5 *≥ 3.38*
< 7 days of age	11.5 to < 12.4 *2.88* to < *3.10*	12.4 to < 12.9 *3.10* to < *3.23*	12.9 to < 13.5 *3.23* to < *3.38*	≥ 13.5 *≥ 3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*
Calcium, Low (mg/dL; *mmol/L*) *≥ 7 days of age*	7.8 to < 8.4 *1.95* to < *2.10*	7.0 to < 7.8 *1.75* to < *1.95*	6.1 to < 7.0 *1.53* to < *1.75*	< 6.1 *< 1.53*
< 7 days of age	6.5 to < 7.5 *1.63* to < *1.88*	6.0 to < 6.5 *1.50* to < *1.63*	5.50 to < 6.0 *1.38* to < *1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 × ULN	6 to < 10 × ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High **Report only one (Choose the method that selects for the higher grade)*	1.1 to 1.3 × ULN	> 1.3 to 1.8 × ULN OR Increase to 1.3 to < 1.5 × participant's baseline	> 1.8 to < 3.5 × ULN OR Increase to 1.5 to < 2.0 × participant's baseline	≥ 3.5 × ULN OR Increase of ≥ 2.0 × participant's baseline
Creatinine Clearance[k] **or eGFR, Low** **Report only one (Choose the method that selects for the higher grade)*	NA	< 90 to 60 ml/min or mL/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or mL/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or mL/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Glucose, Low (mg/dL; *mmol/L*) *≥ 1 month of age*	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to < 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 × ULN without acidosis	≥ 2.0 × ULN without acidosis	Increased lactate with pH < 7.3 without life threatening consequences	Increased lactate with pH < 7.3 with life threatening consequences
Lipase, High	1.1 to < 1.5 × ULN	1.5 to < 3.0 × ULN	3.0 to < 5.0 × ULN	≥ 5.0 × ULN
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High*** *≥ 18 years of age*	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High *≥ 18 years of age*	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[l], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*) *> 14 years of age*	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*
Laboratory Values - Hematology				
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	600 to < 650 *0.600 × 10^9 to < 0.650 × 10^9*	500 to < 600 *0.500 × 10^9 to < 0.600 × 10^9*	350 to < 500 *0.350 × 10^9 to < 0.500 × 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count, Low (cells/mm^3; *cells/L*) *> 7 days of age*	800 to 1,000 *0.800 × 10^9 to 1.000 × 10^9*	600 to 799 *0.600 × 10^9 to 0.799 × 10^9*	400 to 599 *0.400 × 10^9 to 0.599 × 10^9*	< 400 *< 0.400 × 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 × 10^9 to 1.500 × 10^9*	1,000 to 1,249 *1.000 × 10^9 to 1.249 × 10^9*	750 to 999 *0.750 × 10^9 to 0.999 × 10^9*	< 750 *< 0.750 × 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 × $10^9$to 5.000 × 10^9*	3,000 to 3,999 *3.000 × 10^9 to 3.999 × 10^9*	1,500 to 2,999 *1.500 × 10^9 to 2.999 × 10^9*	< 1,500 *< 1.500 × 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 × LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 × LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 × LLN	< 50 *< 0.50* OR < 0.25 × LLN OR Associated with gross bleeding
Hemoglobin[m], Low (g/dL; *mmol/L*)[n] *≥ 13 years of age (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 × ULN	1.5 to < 2.0 × ULN	2.0 to < 3.0 × ULN	≥ 3.0 × ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 × ULN	1.66 to < 2.33 × ULN	2.33 to < 3.00 × ULN	≥ 3.00 × ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100.000 x 109 to < 125.000 × 10^9*	50,000 to < 100,000 *50.000 × 10^9 to < 100.000 × 10^9*	25,000 to < 50,000 *25.000 × 10^9 to < 50.000 × 10^9*	< 25,000 *< 25.000 × 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 × ULN	1.25 to < 1.50 × ULN	1.50 to < 3.00 × ULN	≥ 3.00 × ULN
WBC, Decreased (cells/mm^3; *cells/L*) *> 7 days of age*	2,000 to 2,499 *2.000 × 10^9 to 2.499 × 10^9*	1,500 to 1,999 *1.500 × 10^9 to 1.999 × 10^9*	1,000 to 1,499 *1.000 × 10^9 to 1.499 × 10^9*	< 1,000 *< 1.000 × 10^9*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≤ 7 days of age	5,500 to 6,999 *5.500 × 10^9 to 6.999 × 10^9*	4,000 to 5,499 *4.000 × 10^9 to 5.499 × 10^9*	2,500 to 3,999 *2.500 × 10^9 to 3.999 × 10^9*	< 2,500 *< 2.500 × 10^9*
Urinalysis				
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

a. As per Bazett's formula.
b. For pruritus associated with injections or infusions, see the Site Reactions to Injections and Infusions section.
c. BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.
d. A pregnancy loss occurring at < 20 weeks gestational age.
e. Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
f. For pain associated with injections or infusions, see the Site Reactions to Injections and Infusions section.
g. Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
h. WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.
i. Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.
j. Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.
k. Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m^2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.
l. To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.
m. Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).
n. The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

Source: DAIDS 2017.

9.5 APPENDIX 5: CHANGE HISTORY

9.5.1 Protocol Amendment 1

Protocol Amendment 1 was issued in order to make administrative changes, update exclusion criteria noted in the table, update references, remove preterm and term neonate information, and to provide clarification regarding meal consumption, fasting, vital signs collection, and pregnancy testing.

Protocol Section	**Change**	**Rationale**
Throughout the protocol	Minor administrative changes were made.	
Synopsis Study Design, 3. Study Design and 9.2 Appendix 2: Schedule of events	Clarification regarding beverage ingestion: …no beverages may be ingested within 3 hours before or 3 hours after study drug administration; excluding a beverage that is being consumed as a part of the required meal.	Clarification added that beverages other than water may be ingested during 3 hours before or 3 hours after taking study drug so long as they are being consumed as part of the required meal.
Synopsis Exclusion Criteria and 4.2 Exclusion Criteria	Amended Exclusion Criteria #7: Subject has evidence or history of clinically significant allergic reaction (excluding seasonal allergies); or has evidence or history of clinically significant disease, including hematological, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, or neurological disease. Exceptions to these disease criteria (e.g., stable, mild joint disease unassociated with collagen vascular disease) may be made following discussions with the medical monitor.	Clarification added to allow for subject inclusion for those that have evidence or history of seasonal allergies.

Protocol Section	Change	Rationale
Synopsis Exclusion Criteria and 4.2 Exclusion Criteria	Amended Exclusion Criteria #10: Subject is 20 years of age or older and has a ≥30% risk of developing a myocardial infarction or coronary death within the next 10 years using the National Cholesterol Education Program's Risk Assessment Tool: https://www.mcw.edu/calculators/ldl-cholesterol-goal-level.	The risk calculator was updated in order to prevent automatic elimination of males aged 70+ years with no other risk indicators. Cardiac and pulmonary function is adequately monitored using additional inclusion/exclusion criteria. Therefore, this criteria was amended from ≥10% risk to ≥30% risk.
Synopsis Exclusion Criteria and 4.2 Exclusion Criteria	Removed Exclusion Criteria #32: Subject is at a high risk of contracting SARS-CoV-2/COVID-19 infection, including, but not limited to, individuals with known close contact with: a. Anyone residing in, visiting, or working at a health care or long-term care institution (i.e., long-term care facilities, acute care hospitals, rehabilitation hospitals, mental health hospitals, emergency departments). b. Anyone with a known history of COVID-19 within 2 weeks prior to study entry. c. Anyone who traveled outside the United States or has recently traveled outside of the state in which they will be enrolled in the study and has returned from a state that is listed on a travel advisory list requiring quarantine for any duration within 30 days before study entry.	Because the majority of the population has been vaccinated for COVID-19 and the sites have their own guidelines in place regarding COVID-19, this exclusion criteria was removed.

Protocol Section	**Change**	**Rationale**
Synopsis Exclusion Criteria and 4.2 Exclusion Criteria	Amended Exclusion Criteria #34: Subject has previously participated in this clinical trial.	Clarification added to only prevent subject inclusion for those that have previously participated in this study. Other tecovirimat study enrollment is allowable so long as all other Inclusion/Exclusion criteria are met.
Section 4.3, Section 6.2.2 Clinical Laboratory Testing and 9.2 Appendix 2: Schedule of events	Clarification regarding fasting for fasting lipid panel: Fasting shall occur for 8 hours prior specimen collection.	Clarify amount of time subjects are required to fast prior to screening.
Section 5.2.2 Study Drug Accountability	Clarification regarding study visit requirements for study drug accountability: Subjects will be instructed to bring the subject diary and all study drug bottles (including empty bottles) and unused study drug (in study drug bottles) with them to every study visit.	Clarification for subjects to bring all bottles (including empty) and study drug to every study visit.
Section 6.2 Clinical Laboratory Testing	Clarification regarding clinical laboratory testing performed at the Central Laboratory: The following clinical laboratory assessments will be performed by the PPD Central Lab	Clarification added to clinical laboratory testing.
Section 6.2.2 Clinical Laboratory Testing	Clarification regarding pregnancy testing: All positive urine tests will be verified using a serum β-human chorionic gonadotropin test.	Clarification added to pregnancy serum and urine testing type.
Section 8 Reference List	Reference updated for the TPOXX full prescribing information.	TPOXX prescribing information was updated.
Section 8 Reference List	Reference updated for the TPOXX investigator brochure.	TPOXX investigator brochure was updated.

Protocol Section	**Change**	**Rationale**
9.2 Appendix 2: Schedule of events	Clarification regarding vital signs testing: Vital signs will be measured within 60 minutes prior to the first dose of the day and 4 hours following the first dose of the day.	Clarification added for predose vital signs.
9.2 Appendix 2: Schedule of events	Clarification regarding pregnancy testing: A urine pregnancy test will be performed and read locally on Day –1 (PK subset) or Day 1 Predose (Non-PK subset). All other pregnancy tests, including screening, are by serum and read by the Central Lab.	Clarification added to pregnancy serum and urine testing.
9.4 Appendix 4: Division of Acquired Immune Deficiency Syndrome (DAIDS)	Remove preterm and term neonate DAIDS information: - Preterm neonates should be assessed using local laboratory normal ranges. - Appendix A takes priority over the main grading table in all assessments of total bilirubin for term and preterm neonates. - See Appendix A. Total Bilirubin for Term and Preterm Neonates6	Reference to neonate grading and Appendix A is not applicable to this study and has therefore been removed.
Appendix 5	Added Protocol Change History.	First amendment.

SIGA Technologies, Inc.

Protocol: SIGA-246-024

A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF TPOXX®WHEN ADMINISTERED ORALLY FOR 28 DAYS IN ADULT SUBJECTS

16 APR 2023

Statistical Analysis Plan

Draft Version 2.0

Prepared by:

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Date: _____

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Date: _____

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List of Abbreviations

λ_z	the observed 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 zero to 24 hours
AUC_{0-tau}	area under the plasma concentration-time curve during the first dosing interval
BID	two times a day
BLQ	below the limit of quantification
C_{avg}	average steady-state plasma concentration
CFR	Code of Federal Regulations
CI	confidence interval
CL_{ss}/F	apparent clearance; total systemic clearance not corrected for bioavailability (F) after multiple dosing at steady state
C_{min}	minimum observed drug concentration in plasma
C_{max}	maximum observed drug concentration in plasma
CRA	clinical research associate
CRF	case report form
C_{trough}	trough plasma concentration
CV	coefficient of variation
CYP	cytochromes
DAIDS	Division of Acquired Immune Deficiency Syndrome
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
ITT	Intent-to treat
IWRS	interactive web response system
PK	pharmacokinetic(s)
PP	per protocol
PT	preferred term
QTcF	Fridericia-corrected QT interval

R_{ac}	accumulation ratio
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOP	standard operating procedure
TLFs	tables, listings and figures
t1/2	terminal elimination half-life
TID	three times a day
T_{max}	time to maximum observed plasma concentration
Vz/F	volume of distribution in the terminal elimination phase not corrected for bioavailability (F) after multiple dosing (D28)

1. Introduction

The purpose of this statistical analysis plan (SAP) is to define and ensure that the data listings, summary tables and figures that will be produced, and the statistical methods that will be used are complete and appropriate to allow valid conclusions consistent with the study objectives. This SAP V2 dated March XX, 2023 is written based on SIGA Protocol: SIGA-246-024, version 2.0, dated 01 August 2022.

TPOXX 600 mg (3 × 200-mg capsules) two times a day (BID) for 14 days is the approved dose of TPOXX for the treatment of smallpox in patients weighing between 13 kg and less than 120 kg,. TPOXX dosing for patients weighing 120 kg or more should be adjusted to 600 mg TPOXX three times a day (TID).[1] The 28-day TPOXX treatment duration, rather than the 14-day duration, was chosen for the postexposure prophylaxis indication as a longer treatment period may be necessary to provide protection from smallpox from the time of initial exposure to variola virus until the development of protective neutralizing antibodies. This accounts for the 7- to 17-day, asymptomatic stage; the subsequent 2- to 3-day, prodromal stage; and finally, the development of neutralizing antibodies, which are evident from about the sixth day following the onset of clinical symptoms and increase in antibody titer thereafter.

2. Study Objectives

2.1. Primary Objective

The primary objective of this study is to determine the safety and tolerability of TPOXX when administered orally for 28 days in adult subjects.

2.2. Secondary Objective

The secondary objective of this study is to describe the PK profile of TPOXX when administered orally for 28 days in adult subjects.

3. Study Design and Description

This is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study to assess the safety, tolerability, and PK of oral TPOXX 600 mg when administered for 28 days in adult subjects.

A total of at least 445 subjects (includes a PK subset of 40 subjects), ages 18 to 80, inclusive, will be enrolled and randomly assigned within stratified age groups (18 to 30 years, 31 to 45 years, 46 to 64 years, and 65 to 80 years) to 1 of 2 treatment groups in an overall randomization of 4:1 (approximately 356 subjects will receive TPOXX and 89 subjects will receive TPOXX matching placebo). There will be 2 dosing regimens based on the subject's body weight: subjects with a body weight of 120 kg or less will be administered either TPOXX 600 mg or placebo two times a day (BID), 12 hours apart (±30 minutes); and subjects with a body weight of more than 120 kg will be administered TPOXX 600 mg or placebo three times a day (TID), 8 hours apart (±30 minutes). The study will consist of a screening period (Day –28 to Day –2), 1 check-in, on-site visits (Day 7, Day 14, and Day 21), a dosing complete/ET visit (Day 29), and 2 follow-up telephone calls (Day 42 [+2 days] and Day 58 [+2 days]). The total duration of the study for each subject, including screening, treatment, and follow-up telephone calls will be approximately 86 days,

The enrollment goal for the study is to randomly assign a sufficient number of subjects to ensure that at least 300 subjects receive at least 92% of the oral TPOXX 600 mg BID or TID dosing regimen over the 28-day treatment period. Overall, across all clinical investigative sites, a goal of approximately 20% of subjects (i.e., 89 subjects) or more will be enrolled and randomly assigned in each age group to ensure a representative investigation of TPOXX safety and PK across age groups. The treatment groups will be as follows:

- Treatment Group 1: An oral dose of 600 mg (3 × 200-mg capsules) TPOXX BID (every 12 hours [±30 minutes]) for subjects with a body weight of 120 kg or less or TID (every 8 hours [±30 minutes]) for subjects with a body weight more than 120 kg for 28 days (Day 1 to Day 28).
- Treatment Group 2: An oral dose of placebo (3 capsules identical to TPOXX) BID (every 12 hours [±30 minutes]) for subjects with a body weight of 120 kg or less or TID (every 8 hours [±30 minutes]) for subjects with a body weight more than 120 kg for 28 days (Day 1 to Day 28).

Subjects that fail to meet any inclusion or meet one or more exclusion criteria prior to study drug administration will not be randomized into the study. Under certain circumstances, a subject may be terminated from participating in the study based on the opinion of the investigator, the medical monitor, the sponsor, the Food and Drug Administration (FDA), and/or the Data Safety Monitoring Board (DSMB).

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:

- Subject is in violation of the protocol.
- Subject experiences a serious or intolerable AE that in the investigator's opinion requires withdrawal from the study.
- Subject becomes pregnant.
- Subject is noncompliant.
- Subject has laboratory abnormalities for assessments listed in Sections 4.1 or Section 4.2 that meet grade 3 or grade 4 on the Division of Acquired Immune Deficiency Syndrome (DAIDS) AE Grading Table; 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.
- Subject develops, during the course of the study, symptoms or conditions listed in the exclusion criteria.
- Subject develops laboratory abnormalities listed in the exclusion criteria during the course of the study.
- Subject requires a medication prohibited by the protocol.
- Subject requests an early discontinuation for any reason.
- Subject's primary care provider requests that the subject be withdrawn.

The FDA, SIGA, or the DSMB may request 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 an SAE or intolerable AE, the investigator will confer with the medical monitor and 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.

3.1. Subject Selection

The study population will consist of male and female volunteers, aged 18 to 80 years inclusive.

3.1.1 Inclusion Criteria

As stated in Protocol Section 4.1.

3.1.2 Exclusion Criteria

As stated in Protocol Section 4.2.

4. General Statistical Considerations

All statistical analyses will be conducted using statistical analysis system SAS® Version 9.4 or higher (SAS Institute, Cary, NC).

Descriptive statistics for continuous variables will include number of subjects, mean, standard deviation (SD), median, minimum, and maximum, unless otherwise noted. For categorical variables, frequencies and percentages will be presented.

All tables, listings, and figures will be presented by treatment and weight. The treatments below will be used for presentations:

- TPOXX 600mg
- Matching TPOXX Placebo

Unless otherwise indicated, outputs which are summarized by treatment and weight will be summarized for each dose level for subjects on active study drug.

All data listings will be sorted by treatment (TPOXX or placebo), by treatment regimen (BID or TID dosing), and subject number.

Visit Windows

There are no plans to derive visit windows; visits will be used in the analyses as reported on the eCRF.

Pooling of Sites

Up to 10 sites in the USA will be used in this study. The PK subset will be enrolled at 1 Phase 1 unit. For the remaining sites, a maximum number of subjects will be agreed upon and enrollment

will be competitive. Thus major differences in subject enrollment numbers per site are not expected, and therefore there will be no inter-subject pooling of data.

Subgroups

The effects of age group (18 to 30 years, 31 to 45 years, 46 to 64 years, and 65 to 80 years) used for stratification at randomization and site will be investigated for AE and severe AE rates. Time to first AE or severe AE and time to withdrawal for any reason will be calculated.

Study day is relative to first dose of study drug. Study days are calculated with respect to the first dose date as below:

- If the assessment/observation date is on or after the first dose date, then Study Day = Assessment/Observation Date – First Dose Date + 1;
- Otherwise, Study Day = Assessment/Observation Date – First Dose Date.

Baseline will be defined as the last non-missing assessment (including repeated and unscheduled assessments) before the first dose of study drug administration, unless otherwise specified.

For summary of safety assessments, if there are repeated measurements at a time point, the first non-missing assessment at that time point will be used in the summary tables.

Unscheduled results will not be included in the summary tables, except for determining Baseline, but will be presented in data listings.

The methodology and data handling specifications for PK data are detailed in Section 8.

4.1. General Definitions

Age: Will be calculated as the integer part of the difference between birth date and the date of informed consent divided by 365.25. Birth date with missing day will be imputed as day 15 and birth data with missing day and month will be imputed as 30-June.

Adverse Event: any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug.

4.2. Sample Size

There is no formal sample size calculation for this study. Although the sample size is not based on statistical power considerations, administration of TPOXX 600 mg to 300 subjects provides approximately 95% probability of observing at least 1 occurrence of any AE if the incidence of AEs in the study population is 1% and is considered adequate to provide a reasonable assessment of safety and tolerability. A sufficient number of subjects will be randomly assigned to ensure that at least 300 subjects receive at least 92% of the doses of the BID or TID dosing regimen of oral TPOXX 600 mg over the 28-day treatment period.

4.3. Randomization, Stratification, and Blinding

Healthy subjects will be randomized to receive:

- Treatment Group 1: An oral dose of 600 mg (3 × 200-mg capsules) TPOXX BID (every 12 hours [±30 minutes]) for subjects with a body weight of 120 kg or less or TID (every 8 hours [±30 minutes]) for subjects with a body weight more than 120 kg for 28 days (Day 1 to Day 28).
- Treatment Group 2: An oral dose of placebo (3 capsules identical to TPOXX) BID (every 12 hours [±30 minutes]) for subjects with a body weight of 120 kg or less or TID (every 8 hours [±30 minutes]) for subjects with a body weight more than 120 kg for 28 days (Day 1 to Day 28).

Randomization will occur according to the randomization schedule and will happen before the study drug administration on Day 1 after informed consent has been obtained and after it has been confirmed that the subject fulfills all eligibility criteria. Subjects will be randomly assigned to 1 of 2 treatment groups using a 4:1 ratio so that 4 subjects will receive TPOXX and 1 subject will receive placebo. This will be based on a randomization schedule prepared by a PPD biostatistician before the study. The groups will be stratified by age groups (18 to 30 years, 31 to 45 years, 46 to 64 years, and 65 to 80 years).

This study will employ a double-blind study design. Treatment assignment will not be known to the subjects, the Sponsor, the investigator, or the staff who are involved in the clinical evaluation of the subjects and the analysis of data. The randomization schedule will be generated by an unblinded randomization statistician at PPD according to PPD's standard operating procedures.

The medical monitor will be responsible for maintaining the blind throughout the study. If a subject becomes seriously ill or pregnant during the study, the blind will be broken only if knowledge of the administered study drug will affect that subject's available treatment options. In the event of a medical emergency requiring identification of the study drug administered to an individual subject, the investigator will make every attempt to contact the medical monitor to explain the need for opening the code within 24 hours of unblinding the subject's randomization assignment. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved. All unblinding activities will be tracked via an audit trail in IWRS. Requests for unblinding of a subject's randomization assignment will be made through the IWRS after consultation with the medical monitor. Subject code breaks by the investigator will result in withdrawal of the subject from the study. The date, time, and reason for the unblinding must be documented on the appropriate page in the eCRF, and SIGA must be informed as soon as possible. The treatment assignment of subjects will remain blinded until all clinical evaluations have been completed. Unblinding at the end of the study will occur only by written request from the lead statistician to the unblinded randomization statistician and the unblinded IWRS team after database lock and confirmation of protocol deviations. The DSMB may request to unblind the treatment assignment of a subject or the study at any time.

4.4. Administration of Study Medication

Study Medication will be provided to subjects in 4 or 6 bottles (depending on weight which determines BID or TID daily dosing regimen), which is equivalent to 56 or 84 doses. Subjects will be randomly assigned to receive 4 or 6 bottles each containing 42 capsules of 200 mg TPOXX capsules or matching placebo. Each daily dose will be 3 capsules taken orally twice or three times a day for a total of 6 or 9 capsules per day depending upon subject weight.

4.5. Endpoints

4.5.1 Safety Endpoints

The primary outcome measure is the evaluation of the safety and tolerability of twice or three times daily oral dosing of TPOXX 600 mg for 28 days through adverse event (AE) findings, clinical laboratory tests, vital sign measurements, electrocardiogram (ECG) tests, and physical examinations. The primary endpoint is the AE rate. Other endpoints include severe AE rate, time to first AE and time to withdrawal for any reason.

4.5.2 Pharmacokinetic Endpoints

The plasma samples will be collected at specific time points before and after dosing to evaluate the appropriate pharmacokinetic (PK) endpoints for TPOXX after treatment with oral TPOXX 600 mg twice daily or three times daily in the PK subset. A validated bioanalytical method will be used to analyze plasma samples for quantification of TPOXX. For relevant PK timepoints, please refer to Section 8.2.

4.6. Analysis Sets

All populations will be identified and finalized before the database lock. All subjects who are randomly assigned are considered study subjects.

4.6.1 Intent to Treat (ITT) Population

The Intent-to-Treat (ITT) Population will include all subjects who were randomly assigned to the study (i.e., a randomization number and randomization date are present in the database).
This population will be used for summaries of subject disposition.

4.6.2 Safety Population

The Safety Population is defined as all subjects who received at least 1 dose of study drug (TPOXX or matching placebo).

The Safety Population will be used for all summary and analysis of safety endpoints.

4.6.3 Per-Protocol Safety Population

The Per-Protocol (PP) Safety Population will include all subjects who received at least 92% of the 600 mg BID or TID dosing regimen of TPOXX or matching placebo.

If a subject takes less than 92% of study drug, then they will be considered ‘Course Too Short’ but will be included in the safety analysis.

The Per-Protocol Safety Population will also be used for all summary and analyses of safety endpoints.

4.6.4 Pharmacokinetic (PK) Population

The PK Population will include all subjects in the Per-Protocol Safety Population who have taken at least 2 doses of study drug in sequence, have sufficient TPOXX plasma concentrations, and who have no protocol deviations or other circumstances that would exclude the subject from analysis.

Potential subject exclusions will be determined on a case-by-case basis before unblinding. For example, where subjects experience issues, which may affect exposure to study drug (e.g., emesis, dosing errors, etc.), data will be reviewed by the study pharmacokineticist and evaluated for exclusion from the PK population on a case-by-case basis. All subjects excluded from the PK population will be documented in the data listings.

All plasma drug concentrations by time profiles will be reviewed by the pharmacokineticist.

The PK Population will be used for the preparation of PK summaries and analysis.

5. Subject Disposition

5.1. Disposition

A disposition table will be provided by treatment for the number and percentage of subjects enrolled/randomized, completed, and discontinued together with the reasons for discontinuation. This table will also include the number and percentage of subjects recruited into each age group (randomization strata) and the number and percentage of subjects included in each analysis population will also be presented.

Informed consent, eligibility, and randomization details and protocol details will be listed for all enrolled subjects.

The following will be summarized for the overall population and by treatment for all subjects.

- The number of subjects who were enrolled
- The number of subjects who were randomized
- The number of subjects who received each treatment
- The number of subjects who completed the study treatment
- The number of subjects who did not complete the study treatment
- The number of subjects who completed the study
- The number of subjects who did not complete the study (both overall and according to reasons for discontinuation from the study)
- The number of subjects in each analysis population

Subject disposition will be summarized by dose level and overall based on ITT population using frequency distribution or descriptive statistics. Subjects who complete, withdraw consent, or are terminated early from the study and the associated reasons will be summarized using frequency distribution.

Baseline demographic and background variables will be summarized by treatment for the ITT, Safety, PP Safety, and PK Populations. The demographics table will also be summarized overall

and by age group as per the stratification used in randomization. For treatment-related tables and listings, the data will be summarized by BID or TID study drug dosing regimen.

5.2. Protocol Deviations

Protocol deviations will be collected during monitoring visits. All protocol deviations are to be recorded in the Clinical Trial Management System (CTMS) with the indication of whether these are major. These data will be listed including the assignment of minor or major. Major deviations are defined as those that may have an impact on subject safety or the validity of the study data (this should be noted in the Clinical Monitoring Plan). The assignment is finalized prior to unblinding.

Major protocol deviations will be summarized overall. All protocol deviations will be presented in a data listing, including the categorization of the deviation as major or minor.

5.3. Inclusion and Exclusion Criteria

All inclusion/exclusion criteria deviations recorded in the electronic case report form (eCRF) will be presented in a data listing.

6. Demographics and Other Baseline Characteristics

6.1. Demographics

The descriptive summaries of demographic and baseline characteristics will be presented for the Safety, PP Safety and PK Populations. The demographics table will also be summarized overall and by age category as per the stratification used in randomization.

For all ITT subjects, demographic data to be summarized include: age (years), gender, race, height (cm), and weight (kg) at screening, and ethnicity. A subject's age in years is calculated using the date of the informed consent and date of birth. Age (years) and baseline weight (kg) will be summarized using descriptive statistics. The number and percentage of subjects by race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White), ethnicity (Hispanic or Latino, Not Hispanic or Latino). Percentages will be based on the total number of subjects in the Safety Population.

Subject demographic and baseline characteristics will be presented in a data listing.

6.2. Medical History

Previous and concurrent diseases/conditions will be listed for all ITT subjects sorted by treatment group, subject, and start date. A complete medical history will be obtained, including recreational, prescription drug use, over-the-counter drug use, nicotine and alcohol use, and past hospitalizations.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version to be delineated in the clinical study report [CSR]).

Medical history will be presented in a data listing.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Medications taken are to be recorded for each subject from screening through day 42 or Day 58 for subjects with any SAEs. Medications that stop within 30 days of the first dose of study drug will be classified as prior medication. Medications that start on or after the first dose of study drug will be classified as concomitant. If a medication starts before the first dose of study drug and stops on or after the first dose of study drug, then the medication will be classified as both prior and concomitant.

Concomitant medications taken by subjects will be recorded at each study visit up to the follow-up telephone call on Day 42. Concomitant medications related to SAEs will be collected and recorded at the Day 58 follow-up telephone call. Subjects will be instructed to record concomitant medications in the subject diary. 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 that meets exclusion criteria is taken during the study, 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.

All medications will be listed for all safety subjects by treatment group and dosing regimen, subject and start date, and those taken between Day 1 post-dose through to Day 28, i.e., concomitant will be indicated. See SAP Section 4.0 which describes how to deal with partial dates when determining whether a medication is concomitant or prior. Any prior medication will be flagged in the listings. Prohibited medication are indicated in section 4.2 of the protocol. Any subject taking a prohibited medication will be considered a protocol deviator. Prohibited medications will also be flagged in the data listing.

Prior and concomitant medications will be summarized overall for all subjects by treatment.

Prior and concomitant medications and therapies will be coded using the latest version of the World Health Organization Drug Dictionary.

All prior and concomitant medications will be presented in a data listing.

7.2. Medical or Surgical Treatment Procedures

Medical or surgical treatment procedures will be presented in a data listing.

7.3. Study Treatment

The investigational drug administration and drug accountability data will be summarized by treatment and treatment regimen and presented in the data listings. Visit name, study treatment, date and time of administration, route of administration, actual dose, amount of drug dispensed and adjusted, as well as reason for adjustment, and TPOXX concentration will be recorded.

7.4. Meals

Subjects will receive a subject diary where they'll keep track of meal consumption. Meal data, which includes time of meal and whether or not the required meal was eaten will be summarized by treatment arm.

Meal data will be presented in a data listing.

8. Analysis of Pharmacokinetics

The ITT Population will be used for the presentation of subjects in all subject listings. The PK population will be used for the pharmacokinetic analysis. Pharmacokinetic tables, mean figures, and all statistical analyses will be presented using data from the PK population.

8.1. Collection Schedule

Serial blood samples will be collected at the following time points for PK assessment:

- BID Dosing (Subjects weighing 120 kg or less)
    - Day 1: Before the first dose (0 hour) and at 2, 4, 6, 8, 10, 12 (before the second dose), 14, 16, 18, 20, 22, and 24 hours (before the first dose on Day 2)
    - Day 14: Before the first dose (0 hour)
    - Day 28: Before the first dose (0 hour) and at 2, 4, 6, 8, 10, 12 (before the second dose on Day 28), 14, 16, 18, 20, 22, 24 (Day 29, AM), 48 (Day 30, AM), and 72 (Day 31, AM) hours after the first dose on Day 28
- TID Dosing (Subjects weighing more than 120 kg)
    - Day 1: Before the first dose (0 hour) and at 2, 4, 6, 8 (before the second dose), 10, 12, 14, 16 (before the third dose), 18, 20, 22, and 24 hours (before the first dose on Day 2)
    - Day 14: Before the first dose (0 hour)
    - Day 28: Before the first dose (0 hour) and at 2, 4, 6, 8 (before the second dose), 10, 12, 14, 16 (before the third dose), 18, 20, 22, 24 (Day 29, AM), 48 (Day 30, AM), and 72 (Day 31, AM) hours after the first dose on Day 28

For PK blood samples, the acceptable window for collection from the scheduled collection time point will be as follows: ±15 minutes from 0 to 24 hours (except where samples are collected predose) and ±60 minutes from 48 to 72 hours.

Individual plasma concentrations and time deviation data will be presented in data listings. Plasma concentration data will be summarized using descriptive statistics (number of observations, arithmetic mean, SD, CV, median, minimum, and maximum) by study day, time point, and study drug dosing regimen.

Individual plasma concentrations versus nominal time will be plotted on both linear and semi-logarithmic scales. Mean plasma concentrations versus scheduled time will be plotted by study day and study drug dosing regimen on both linear and semi-logarithmic scales.

8.2. Data Handling

Data rounding specifications for PK data are documented in the PK table, listing, and figure shells.

Plasma concentrations that are below the limit of quantification (BLQ) will be replaced by zero for calculation of concentration descriptive statistics. Mean BLQ concentrations will be presented as BLQ, and the SD and coefficient of variation (CV) will be reported as not applicable. Missing concentrations will be excluded from the calculations.

Non-compartmental PK parameters for TPOXX will be calculated. Actual sampling times will be used in the determination of the individual PK parameters.

Handling of Dropouts or Missing Data

Missing concentration data for all subjects who take scheduled study drug treatment will be considered as non-informative missing and will not be imputed.

The following rules will apply for the derivation of all kinds of AUCs:

- Concentration values that are BLQ for pre-dose samples will be treated as zero.
- The sampling time relative to dosing for pre-dose samples will also be treated as zero.
- Concentration values that are BLQ before the first quantifiable concentration will be treated as zero.
- Post-dose BLQ values after the first quantifiable time point that are flanked or followed by measurable concentrations will be set to half the value of BLQ.
- Post-dose BLQ value after first quantifiable time point that are not followed by measurable concentrations will be replaced by zero.

If the actual time of sampling is missing, the nominal time may be used.

No further imputation will be applied to any missing values.

8.3. Plasma Pharmacokinetic Parameters and Definitions

Plasma concentration-time data will be analyzed by non-compartmental analysis using Phoenix® WinNonlin® Version 8.0 or higher (Certara USA, Inc., Princeton, NJ). The following PK parameters will be calculated for TPOXX, where data permit:

C_{max}	Maximum observed drug concentration in plasma, reported separately for each dose.
C_{avg}	Average steady-state drug concentration in plasma, calculated as: AUC_{tau} / tau (Day 28 only)
C_{trough}	Trough plasma concentration (Day 28 only).
C_{min}	Minimum observed drug concentration in plasma (Day 28 only).
T_{max}	Time of maximum observed drug concentration in plasma.
AUC_{0-24}	Area under the plasma concentration-time curve (AUC) from time 0 to 24 hours, calculated using the linear trapezoidal rule.

AUC_{tau}	AUC from time zero to tau where tau is the 8-hour or 12-hour dosing interval following the first dose, calculated using the linear trapezoidal rule
$AUC_{(0\text{-last})}$	AUC from time 0 to the last measurable observed concentration (C_t), calculated using the linear trapezoidal rule (Day 28 only).
λ_z	Observed elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase. (Day 28 only).
$t_{1/2}$	Apparent terminal elimination half-life, calculated as: ln (2) / λ_z. (Day 28 only).
CL_{ss}/F	Apparent total body clearance, calculated as: Dose / AUC_{tau} (Day 28 only).
V_z/F	Apparent volume of distribution during the terminal phase, calculated as: Dose / [λ_z * AUC_{tau}] (Day 28 only).
$RacC_{max}$	Accumulation ratio based on C_{max}, calculated as: C_{max} (following first dose on Day 28) / C_{max} (following first daily dose on Day 1).
RacAUC	Accumulation ratio based on AUC, calculated as: AUC_{tau} (following first dose on Day 28) / AUC_{tau} (following first daily dose on Day 1).
Fluctuation	Calculated as: (C_{max} – C_{tau}) / C_{tau} * 100 (Day 28 only).

In addition to the above PK parameters, which will be listed and summarized, the following parameters will also be listed to document the selection of data points used to estimate $t_{1/2}$ using non-compartmental procedures:

Number points	Number of data points used to estimate λ_z; a minimum of 3 data points must be used, and C_{max} must not be included (Day 28 only).
λ_z lower	Lower bound used for the estimation of λ_z (Day 28 only).
λ_z upper	Upper bound used for the estimation of λ_z (Day 28 only).
Span	Number of elapsed half-lives over which λ_z is estimated, calculated as (λ_z upper – λ_z lower) / $t_{½}$. (Day 28 only)
Rsq	r^2, the coefficient of determination (goodness of fit statistic); λ_z and all associated parameters will only be reported where $r^2 \geq 0.80$. (Day 28 only)

Actual sampling times will be used for the estimation of all matrix PK parameters, and all concentrations will be included in the analysis (including concentrations collected outside predefined collection windows).

Plasma PK parameters will be presented in data listings and summarized separately using descriptive statistics (number of observations, arithmetic mean, SD, CV, geometric mean,

geometric SD, geometric CV, median, minimum, and maximum) by study day and study drug dosing regimen. T_{max} will be summarized using number of observations, median, minimum, and maximum only.

9. Safety Analysis

The Safety Population and the Per-Protocol Safety Population will be used for the safety data summaries and analysis. All safety data collected will be listed. The safety and tolerability data summaries will be presented separately for the Safety Population and the PP Safety Population and will also be presented by BID and TID TPOXX/matching placebo dosing regimen. Safety will be assessed on the basis of AE reports, clinical laboratory data, vital signs, ECG parameters and physical examinations.

For all subjects that discontinued, data will be summarized by treatment group and dosing regimen, and reason for discontinuation.

9.1. Extent of Exposure

All derived exposure variables and variables recorded on the eCRF will be listed by subject number.

9.2. Treatment Compliance

Compliance will be derived for each subject and listed with exposure data.

% Compliance= (Number of capsules dispensed- Sum of number of capsules returned and lost) /(Number of capsules dispensed)X 100

Percentage compliance will be summarized by treatment group and dosing regimen using statistics for continuous variables, and the number of percentages of subjects achieving at least 92% compliance will be summarized by treatment group and dosing regimen.

9.3. Adverse Events

The primary objective of this study is to determine the safety and tolerability of TPOXX when administered orally for 28 days in adult subjects. The overall AE rate in the Safety Population and the Per-Protocol Safety Population will be compared between treatment groups using a stratified Mantel-Haenszel test accounting for age (18 to 30 years, 31 to 45 years, 46 to 64 years, and 65 to 80 years). If expected cell counts are less than 5, then Fisher's extract test will be applied. The AE rate is the number of subjects who report at least 1 post-dose AE expressed as a proportion of the number of subjects in the Safety Population and the Per-Protocol Safety Population. An exact unadjusted 95% confidence interval (CI), calculated using the Clopper-Pearson method, will be given for each treatment group. For the difference in AE rates between the treatment groups, a continually corrected exact 95% CI around the difference will be calculated. In addition, the Mantel-Haenszel adjusted odds ratio and 95% Cis from the stratified analysis will be presented.

9.3.1 Time to First Adverse Event

Time to first AE is defined as the duration from start of the treatment to the first recorded post-dose AE. If the subject does not have an AE, time to first event will be censored at the date of the last adequate assessment; this is expected to be on the Day 42 (+2 day) Follow-up Telephone Call.

Time to First AE (days) = (Date of first AE – Date of first dose) +1

Time to first AE will be analyzed using Kaplan Meier (KM) quartile estimates along with 2 sided 95% CIs. Treatment groups will be compared using the log rank test stratified by age group and clinical investigative site. Statistical significance will be assessed at the 0.5 level. A summary table will be produced.

If a subject does not experience any AE during the study, the time to first AE will be censored at the date of study completion.

9.3.2 Time to Withdrawal for Any Reason

Time to Withdrawal for Any Reason is defined as the duration from start of treatment to study withdrawal for any reason. If the subject does not discontinue from the study, time to withdrawal for any reason will be censored at the date of study completion; this is expected to be the Day 42 (+ 2 days) Follow-up Telephone Call.

Time to Withdrawal for Any Reason (days) = (Date of study withdrawal – Date of first dose) + 1

Time to Withdrawal for Any Reason will be analyzed as described above for the time to first AE.

If a subject does not discontinue or withdraw from the study, the time to discontinuation will be censored at the date of study completion.

9.3.3 Adverse Event Summaries

An adverse event (AEs) will include any newly occurring event or previous condition that has increased in severity or frequency since administration of the first dose of study drug. If there are partial AE start date and times, an AE will be date/time of onset on or after the time of first dose of study medication on Day 1 to Day 42 (+2 day) Follow-up Telephone Call.

Adverse events will be coded by preferred term (PT) and system organ class (SOC) using MedDRA (version to be delineated in the CSR).

Each AE will be graded for severity and classified into one of five categories according to Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric AEs (protocol Appendix 4): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), and Grade 5 (death).

Each AE is assessed for relationship to study drug. Terms to describe the degree of causality between a study drug and an event are definitely, probably, possibly, unlikely related or not related. If relationship to study drug is missing, it will be regarded as definitely related for the purposes of data summaries.

Frequency of AEs will be calculated for each system organ class, by preferred term and treatment group for the number of subjects reporting the event for the Safety Population and the Per-Protocol Safety Population.

Each AE will be counted only once per subject at the preferred term level.

For summaries of AEs by system organ class, preferred term, maximum severity and treatment the rule is as follows: if a subject experiences more than one episode of an AE, the subject is counted only once by the maximum severity of the episode (preferred term). If a subject has more than one AE within a system organ class, the subject is counted only once in that system organ class. Similarly, when study drug relationship is presented, the strongest relationship to study drug is used for AEs mapping to the same preferred term, or within a system organ class.

Summaries will be ordered by descending frequency of SOC and then, within a SOC, by overall descending frequency of PT for the TPOXX group.

The following AE tables will be produced:

- An Overall summary of the number of events and number and percentage of subjects reporting the following:
    - All AES
    - Serious AEs
    - Treatment-related AEs
    - AEs leading to early study discontinuation and
    - AEs leading to death
- AEs overall by system organ class and preferred term
- AEs by maximum severity, overall and by system organ class and preferred term
- AEs by maximum relationship to study treatment, overall and by system organ class and preferred term
- Treatment-related AEs, overall and by system organ class and preferred term
- Serious AEs, overall and by system organ class and preferred term.

In general, all AE tables will show the number and percentage of subjects with an event. The number of events overall by treatment group and dosing regimen will also be included.

A listing of all AEs will provide details including system organ class, preferred term, verbatim term, whether treatment was emergent or not, severity, relationship to treatment, onset and resolution date and time, duration (in days for any AEs lasting longer than 24 hours, in hours otherwise, derived as stop date and time – start date and time), action and outcome. Similar listings will be presented for SAEs, AEs with Grade 3 or higher, AEs with a fatal outcome (or Grade 5) and AEs leading to early withdrawal.

Toxicity grades for laboratory tests will be determined according to the DAIDS AE Grading Table[2]. The maximum post-baseline grade increase from baseline grade will be summarized by treatment group and dosing regimen and overall for the safety population and PP safety population using frequency and percentage of subjects with increase to grade 1, 2, 3, 4, 1 to 4, 2 to 4, and 3 to 4, respectively.

All AEs will be presented in a data listing.

9.4. Clinical Laboratory Evaluations

The following laboratory tests 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, 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, leukocyte esterase, microscopy (performed if dipstick is ≥1+; includes bacteria, casts, crystals, epithelial cells, red blood cells, and white blood cells), nitrites, pH, protein, specific gravity, and urobilinogen.

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

$$\text{Creatinine clearance (mLmin /)} = \frac{[140 - age(years)]\ x\ weight(kg)}{72\ x\ serum\ creatine\ \left(\frac{mg}{dL}\right)}\{x\ 0.85\ if\ female\}$$

The hematology, serum chemistry, and urinalysis tests will be performed at the time points indicated in the schedule of assessments (schedules of assessments can be found in Section 13.

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

For women of childbearing potential, serum pregnancy test will be performed at the screening visit and analysed by PPD Central Lab. A urine pregnancy test will be performed and read locally at check-in on Day -1 (PK subset) or predose on Day 1 (Non-PK subset). Serum pregnancy tests will be read by PPD Central Lab at the time points indicated in the schedules of events (Section 13). All positive urine pregnancy tests will be verified using the ß-human chorionic gonadotropin test.

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

All clinical laboratory test results will be presented in the data listings. Laboratory values that are outside of the normal reference range will be flagged in the data listings.

Actual results and change from baseline for hematology, serum chemistry and urinalysis at each time point will be summarized for the Safety and PP Safety Populations by treatment group and dosing regimen at each time point using descriptive statistics. Shift from baseline in terms of low/normal/high for hematology and serum chemistry tests, and in terms of normal/abnormal for urinalysis tests will be summarized for the safety population.

A urine drug screen for alcohol, cotinine, 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 sent to the central lab.

Day –1 (Check-in - PK Subset or Day 1 (Predose - Non-PK Subset) (Section 13):

A urine drug screen for cotinine, amphetamines (including methamphetamines and ecstasy/methylenedioxymethamphetamine), barbiturates, benzodiazepines, cannabinoids (including tetrahydrocannabinol), cocaine metabolites, and opiates (including heroin, codeine, and oxycodone) will be performed and read locally. Blood alcohol will be tested using a breathalyzer device at the clinical investigative site.

Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference range for each laboratory parameter. The investigator will determine whether any of the abnormally high or low results are clinically significant or not clinically significant.

Toxicity grades for laboratory tests will be determined according to the DAIDS AE Grading Table[2].

Actual values and changes from baseline for clinical laboratory test results, will be summarized for Safety and PP Safety Populations and by treatment group and dosing regimen at each time point using descriptive statistics.

9.5. 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 (Section 13).

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

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 (e.g., 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.

Summary tables presenting observed values and changes from baseline will be summarized for Safety and PP Safety populations and by treatment group and dosing regimen at each time point using descriptive statistics.

All vital sign data will be presented in a data listing. All vital signs, body weight, and height measurements will be presented in a data listing.

9.6. Physical Examination

Full physical examinations will be performed at the time points indicated in the schedules of events (Section 13) and will include, at minimum, 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 on Day 31 (PK subset only) as well as unscheduled physical examinations at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

Height and weight will be measured at screening only.

Physical examination results will be presented in a data listing.

9.7. Electrocardiograms

A standard 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 (Section 13).

Electrocardiogram assessments will include comments on whether the tracings are normal, abnormal, indeterminate, not evaluable and unknown. The following parameters will be measured and reported: heart rate; PR interval, QT intervals; QT interval corrected using Fridericia's formula; QRS duration and RR interval. 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 (e.g., 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.

Summaries will be presented separately for the Safety Population and the PP Safety Population and will also be presented by treatment and dosing regimen. ECG tables presenting observed values and changes from baseline will be presented for numeric results. Changes from baseline to each scheduled post baseline visit will be presented.

All ECG data will be presented in a data listing.

9.8. Unscheduled Visits

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

10. Timing of Analyses

10.1. Final Analysis

The primary analysis of safety and pharmacokinetics is planned after all subjects complete the final study visit or terminate early from the study and the data base has been hard locked.

10.2. Data Safety Monitoring Board (DSMB) Analysis

An independent DSMB will review descriptive summaries of accumulating safety data at least 4 times during the course of the study as described in Protocol Section 9.3.3.1.4. Further description of the DSMB analyses can be found in the DSMB Charter. Data summaries for the DSMB will have dummy treatment and/or subject codes assigned to maintain the study blind.

Interim Analysis: No formal interim analysis is planned for this study.

11. Changes in the Planned Analysis

Protocol version 1.0, dated 04 NOV 2021, states that "the relationship of treatment group, age, clinical investigative site, and their interactions on overall AE rate will also be investigated using a logistic regression model…". This is an outcome that will not be presented in the TLFs.

Any further changes from this SAP and the protocol will be documented in the CSR for this study.

12. References

1. TPOXX (tecovirimat) capsules for oral use [full prescribing information]. SIGA Technologies, Inc. Corvallis (OR); 2022, 24 p.

2. Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events. July 2017 [cited 2020 Aug 18]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

3. SIGA Technologies, Inc. TPOXX (tecovirimat). Investigator's brochure, 18th ed. Corvallis (OR); 2022. 112 p.

4. Department of Health and Human Services (DHHS), Food and Drug Administration Center for Drug Evaluation and Research (US). Guidance for Industry: Bioanalytical Method Validation. May 2018 [cited 2020 Aug 18]. Available from: https://www.fda.gov/media/70858/download.

13. Schedule of Assessments

Table 13-1 Schedule of Events: Pharmacokinetic Subset Study Subjects

Period	Screening	Check-in	Treatment												PK Sampling			Follow-up	
Procedure[a] Day	–28 to –2	–1	1	2	3 to 6	7	8 to 12	13	14	15 to 20	21	22 to 26	27	28	Dosing Complete/ET Visit 29	30	31	Telephone Call 42 (+2 days)	SAE Telephone Call 58 (+2 days)
Admission to clinic		X						X					X						
Discharge from clinic[a]				X					X								X		
Informed consent	X																		
Inclusion/exclusion criteria	X	X[b]																	
Medical history	X	X[c]																	
Physical examination[d]	X	X				X			X		X				X		X		
Demographics	X																		
Height and weight	X																		
Serology (HBsAg, HCV, and HIV)	X																		
Vital sign measurements[e]	X	X	X[f]			X			X[f]		X				X		X		
Drug/alcohol/cotinine screen[g]	X	X																	
Glycosylated hemoglobin (HbA1c)	X																		
Fasting lipid panel[h]	X																		
Clinical laboratory testing[i]	X	X				X		X			X				X				
Serum or urine pregnancy test[j]	X	X				X		X			X				X				

Period	Screening	Check-in	Treatment												PK Sampling			Follow-up	
Procedure[a] Day	**–28 to –2**	**–1**	**1**	**2**	**3 to 6**	**7**	**8 to 12**	**13**	**14**	**15 to 20**	**21**	**22 to 26**	**27**	**28**	**Dosing Complete/ET Visit 29**	**30**	**31**	**Telephone Call 42 (+2 days)**	**SAE Telephone Call 58 (+2 days)**
Serum follicle-stimulating hormone[k]	X																		
12-lead ECG[l]	X	X	X			X			X		X				X				
Randomization			X																
Meal[m]			X	X				X	X				X	X					
Administration of study drug[n]			X	X	X	X	X	X	X	X	X	X	X	X					
Dispense study drug				X															
Collect study drug								X					X						
Study drug instructions				X															
Pharmacokinetic sampling[o]			X	X					X					X	X[p]	X	X		
Subject diary dispensing[q]				X															
Subject diary review						X		X			X		X						
Subject diary collection													X						
AEs/SAEs[r]			X															X	X
Prior/concomitant medications[s]	X		X															X	X

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

[a] 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.

[a] Discharge from the clinical investigative site will follow collection of all safety assessments.

[b] Review of inclusion/exclusion criteria will be performed prior to the first dose of study drug.

(c) Review of medical history will be performed prior to the first dose of study drug and if determined by the investigator based on medical history/symptomology and will include a review of systems; recreational, prescription, and over-the-counter drug use; nicotine and alcohol use; and past hospitalizations.

(d) A full physical examination will include, at minimum, 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 on Day 31 at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

(e) Vital signs will be measured after the subject has been in the seated position for at least 5 minutes and will include systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. Day 31 vital signs only need to be collected in the event that a symptom-directed physical examination is performed.

(f) Vital signs will be measured within 60 minutes of the first dose of the day and 4 hours following the first dose of the day. The acceptable window for collection is ±15 minutes from the scheduled time point.

(g) Includes alcohol, cotinine, amphetamines (including methamphetamines and ecstasy/methylenedioxymethamphetamine), barbiturates, benzodiazepines, cannabinoids (including tetrahydrocannabinol), cocaine metabolites, and opiates (including heroin, codeine, and oxycodone). A urine drug screen including alcohol and cotinine will be collected and sent to the central laboratory at the screening visit. A urine drug screen and alcohol breath test using a breathalyzer will be performed and read locally on Day –1.

(h) Fasting lipid panel will include cholesterol (total, high-density lipoprotein, calculated low-density lipoprotein, and triglycerides).

(i) Clinical laboratory testing will include hematology, serum chemistry, and urinalysis. Clinical laboratory testing from screening will be used to determine eligibility.

(j) Women of childbearing potential only. A urine pregnancy test will be performed and read locally on Day –1.

(k) For postmenopausal women.

(l) A single 12-lead ECG will be obtained after the subject has been in the supine position for at least 10 minutes. On Day 1 and Day 14, an ECG will be recorded within 60 minutes prior to the first dose of the day and 4 hours after the first dose of the day. The acceptable window for collection from the scheduled collection time point is ±15 minutes.

(m) When study drug is administered at the clinical investigative site, all subjects will be provided a meal (consisting of approximately 600 calories and 25 g of fat). The meal should be consumed within 30 minutes and prior to the administration of study drug (TPOXX or matching placebo). Subjects should be administered study drug as soon as possible following completion of the meal but no more than 30 minutes should elapse between meal completion and administration of study drug. Subjects should take study drug with 8 oz (240 mL) of water.

(n) The time of study drug dosing will be called “0” hour. Study drug will be administered to subjects by study site personnel when subjects are in house and subjects will self-administer study drug when at home.

(o) **Two times a day dosing: Subjects weighing 120 kg or less:**
Blood samples for PK analysis of TPOXX in plasma will be collected on Day 1 before the first dose (0 hour) and at 2, 4, 6, 8, 10, 12 (before the second dose), 14, 16, 18, 20, 22, and 24 hours (before the first dose on Day 2); on Day 14 (before the first dose); and on Day 28 (before the first dose) and at 2, 4, 6, 8, 10, 12 (before the second dose on Day 28), 14, 16, 18, 20, 22, 24 (Day 29, AM), 48 (Day 30, AM), and 72 (Day 31, AM) hours after the first dose on Day 28.
Three times a day dosing: Subjects weighing more than 120 kg:
Blood samples for PK analysis of TPOXX in plasma will be collected on Day 1 before the first dose (0 hour) and at 2, 4, 6, 8 (before the second dose), 10, 12, 14, 16 (before the third dose), 18, 20, 22, and 24 hours (before the first dose on Day 2); on Day 14 (before the first dose); and on Day 28 (before the first dose) and at 2, 4, 6, 8 (before the second dose), 10, 12, 14, 16 (before the third dose), 18, 20, 22, 24 (Day 29, AM), 48 (Day 30, AM), and 72 (Day 31, AM) hours after the first dose on Day 28.
For PK blood samples, the acceptable window for collection from the scheduled collection time point will be as follows: ±15 minutes from 0 to 24 hours (except where samples are collected predose) and ±60 minutes from 48 to 72 hours.

(p) If the subject is completing the ET visit, a blood sample for TPOXX concentration analysis should be collected within 30 hours after the last dose of study drug from subjects who discontinue. If the visit occurs more than 30 hours following the subject's last dose of study drug, no sample needs to be collected.

(q) One diary will be dispensed to record TPOXX or matching placebo administration, completion of required meals before and after dosing, all concomitant medications, and all AEs.

(r) Adverse events will be collected from first dose of study drug until Day 42. Serious AEs will be collected up to Day 58. All AEs, SAEs, and clinically significant laboratory abnormalities will be followed until resolution or until stability of the abnormality has been demonstrated as determined by the investigator and/or medical monitor.

(s) Concomitant medication information will only be collected at the Day 58 follow-up telephone call if it is related to an SAE.

Table 13-2 Schedule of Events: Non-Pharmacokinetic Subset Safety Subjects

Procedure[a]	Screening (Day –28 to -1)	Baseline Day 1 Predose (AM)	Day 1 Postdose	Day 7 Follow-up	Day 14 Follow-up	Day 21 Follow-up	Day 29 Dosing Complete/ET Visit	Follow-up Telephone Call Day 42 (+2 days)	SAE Follow-up Telephone Call Day 58 (+2 days)
Admission to clinic		X							
Discharge from clinic[b]			X						
Informed consent	X								
Inclusion/exclusion criteria	X	X[b]							
Medical history	X	X[c]							
Physical examination[d]	X			X	X	X	X		
Demographics	X								
Height and weight	X								
Serology (HBsAg, HCV, and HIV)	X								
Vital sign measurements[f]	X	X	X[g]	X	X	X	X		
Urine drug/alcohol/cotinine screen[g]	X	X							
Glycosylated hemoglobin (HbA1c)	X								
Fasting lipid panel[i]	X								
Clinical laboratory testing[i]	X	X		X	X	X	X		
Serum or urine pregnancy test[j]	X	X		X	X	X	X		
Serum follicle-stimulating hormone[l]	X								
12-lead ECG[l]	X	X	X	X	X	X	X		
Randomization		X							
Meal[n]		X							
Administration of study drug[n]		X							
Dispense study drug			X						
Collect study drug							X		
Study drug instructions			X						
Subject diary dispensing[p]			X						
Subject diary review				X	X	X			

Procedure[(a)]	Screening (Day –28 to -1)	Baseline Day 1 Predose (AM)	Day 1 Postdose	Day 7 Follow-up	Day 14 Follow-up	Day 21 Follow-up	Day 29 Dosing Complete/ET Visit	Follow-up Telephone Call Day 42 (+2 days)	SAE Follow-up Telephone Call Day 58 (+2 days)
Subject diary collection							X		
TPOXX concentration sampling							X[(q)]		
AEs/SAEs[(r)]			X					X	X
Prior/concomitant medications[0]	X	X	X					X	X

Abbreviations: AE, adverse events; ECG, electrocardiogram; ET, early termination; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SAE, serious adverse event.

(a) When procedures are overlapping and occurring at the same time point, the order of procedures should be ECG then vital sign measurements unless dictated by other study events happening at that time, such as dosing requirements.

(b) Discharge from the clinical investigative site will follow collection of all safety assessments.

(c) Review of inclusion/exclusion criteria will be performed prior to the first dose of study drug.

(d) Review of medical history will be performed prior to the first dose of study drug and if determined by the investigator based on medical history/symptomology and will include a review of systems; recreational, prescription, and over-the-counter drug use; nicotine and alcohol use; and past hospitalizations.

(e) A full physical examination will include, at minimum, 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). Interim, unscheduled, symptom-directed physical examination will be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

(f) Vital signs will be measured after the subject has been in the seated position for at least 5 minutes and will include systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature.

(g) Vital signs will be measured within 60 minutes of the first dose of the day and 4 hours following the first dose of the day. The acceptable window for collection is ±15 minutes from the scheduled time point

(h) Includes alcohol, cotinine, amphetamines (including methamphetamines and ecstasy/methylenedioxymethamphetamine), barbiturates, benzodiazepines, cannabinoids (including tetrahydrocannabinol), cocaine metabolites, and opiates (including heroin, codeine, and oxycodone). A urine drug screen including alcohol and cotinine will be collected and sent to the central laboratory at the screening visit. A urine drug screen and alcohol breath test using a breathalyzer will be performed and read locally on Day 1.

(i) Fasting lipid panel will include cholesterol (total, high-density lipoprotein, calculated low-density lipoprotein, and triglycerides).

(j) Clinical laboratory testing will include hematology, serum chemistry, and urinalysis. Clinical laboratory testing from screening will be used to determine eligibility.

(k) Women of childbearing potential only. A urine pregnancy test will be performed and read locally on Day 1 Predose.

(l) For postmenopausal women.

(m) A single 12-lead ECG will be obtained after the subject has been in the supine position for at least 10 minutes. On Day 1, an ECG will be recorded prior to the first dose of the day and after the first dose of the day.

(n) When study drug is administered at the clinical investigative site, all subjects will be provided a meal (consisting of approximately 600 calories and 25 g of fat). The meal should be consumed within 30 minutes and prior to the administration of study drug (TPOXX or matching placebo). Subjects should be administered study drug as soon as possible following completion of the meal but no more than 30 minutes should elapse between meal completion and administration of study drug. Subjects should take study drug with 8 oz (240 mL) of water.

(o) The time of study drug dosing will be called "0" hour. Study drug will be administered to subjects by study site personnel for the first dose on Day 1 and subjects will self-administer study drug when at home. Subjects will be instructed at the screening visit and prior to check-in to the clinical investigative site on Day 1 that other than water, no beverages may be ingested within 3 hours before or 3 hours after study drug administration.

(p) One diary will be dispensed to record TPOXX or matching placebo administration, completion of required meals before and after dosing, all concomitant medications (dose and frequency), and all AEs.

(q) If the subject is completing the ET visit, a blood sample for TPOXX concentration analysis should be collected within 30 hours after the last dose of study drug from subjects who discontinue. If the visit occurs more than 30 hours following the subject's last dose of study drug, no sample needs to be collected.

(r) Adverse events will be collected from first dose of study drug until Day 42. Serious AEs will be collected up to Day 58. All AEs, SAEs, and clinically significant laboratory abnormalities will be followed until resolution or until stability of the abnormality has been demonstrated as determined by the investigator and/or medical monitor.

Concomitant medication information will only be collected at the Day 58 follow-up telephone call if it is related to an SAE.

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