A POSTMARKETING OPEN-LABEL, 5-PERIOD CROSSOVER, DRUG-DRUG INTERACTION STUDY OF ORALLY ADMINISTERED TPOXX® WHEN COADMINISTERED WITH 4 DIFFERENT PHOSPHATE BINDERS IN HEALTHY ADULT SUBJECTS

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CLINICAL STUDY PROTOCOL
AMENDMENT 1

IND 69,019

A POSTMARKETING OPEN-LABEL, 5-PERIOD CROSSOVER, DRUG-DRUG INTERACTION STUDY OF ORALLY ADMINISTERED TPOXX® WHEN COADMINISTERED WITH 4 DIFFERENT PHOSPHATE BINDERS IN HEALTHY ADULT SUBJECTS

Postmarketing Commitment: 3417-5

SIGA-246-023

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:	27 January 2022, 2.0
Previous Date(s) and Version(s)	06 March 2020, 1.0

CONFIDENTIAL

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

SIGNATURE PAGE

PROTOCOL TITLE: A Postmarketing Open-Label, 5-Period Crossover, Drug-Drug Interaction Study of Orally Administered TPOXX® when Coadministered With 4 Different Phosphate Binders in Healthy Adult Subjects

PROTOCOL NUMBER: SIGA-246-023

[redacted]

[redacted]
Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree to conduct the study as outlined in the protocol titled "A Postmarketing Open-Label, 5-Period Crossover, Drug-Drug Interaction Study of Orally Administered TPOXX® when Coadministered With 4 Different Phosphate Binders in Healthy 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-246-023

TITLE: A Postmarketing Open-Label, 5-Period Crossover, Drug-Drug Interaction Study of Orally Administered TPOXX® when Coadministered With 4 Different Phosphate Binders in Healthy Adult Subjects

STUDY PHASE: 4 Postmarketing Study

STUDY SITE: [redacted]

OBJECTIVES:

Primary:

The primary objective of this study is to evaluate potential drug-drug interaction as measured by the effect of coadministration of 4 separate phosphate binders on the pharmacokinetics (PK) of orally administered TPOXX in healthy adult subjects.

Secondary:

The secondary objective of this study is to evaluate the safety and tolerability of 600 mg oral TPOXX administered with 4 different phosphate binders in healthy adult subjects.

STUDY DESIGN AND METHODOLOGY:

This is a postmarketing, open-label, 5-period crossover drug interaction study designed to evaluate the potential effects of coadministration of 4 different phosphate binders on the PK of orally administered TPOXX in healthy adult subjects. A total of 44 subjects, ages 18 to 50, inclusive, will be enrolled and randomly assigned to 1 of 4 treatment sequences. The study will consist of a screening period (Day –28 to Day –2), 5 treatment periods (Day –1 to Day 31), an end-of-study visit (Day 36 [+2 days]), and a follow-up telephone call (Day 59 [+4 days]). The treatment sequences and periods will be as follows:

Treatment Sequence	Period 1 Treatment	Period 2 Treatment	Period 3 Treatment	Period 4 Treatment	Period 5 Treatment
ABCDE	A	B	C	D	E
ACEBD	A	C	E	B	D
ADBEC	A	D	B	E	C
AEDCB	A	E	D	C	B

- Treatment A: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX.
- Treatment B: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 1600 mg (2 × 800 mg tablets) sevelamer carbonate (Renvela® or generic equivalent).
- Treatment C: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 500 mg sucroferric oxyhydroxide (Velphoro®) chewable tablet.

- Treatment D: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 1334 mg (2 × 667 mg capsules) calcium acetate (PhosLo® generic equivalent).
- Treatment E: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 500 mg lanthanum carbonate (Fosrenol® or generic equivalent) chewable tablet.

There will be a washout period of 7 days between dosing in each treatment period. All subjects will be provided a meal (consisting of approximately 600 calories and 25 g fat). The meal should be completed within 30 minutes. 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 study drug administration. Study drug and meals must be taken with water only, and no other beverage except water should be ingested within 3 hours before or 3 hours after study drug administration. Water is allowed at all times throughout the study. Subjects must fast for 2 hours after taking study drug as further food consumption may affect drug absorption.

Subjects will report to the study site on Day –1 and remain confined to the study site until 48 hours after dosing in Period 5 (Day 31). Subjects will be monitored for safety and tolerability. Serial blood samples for PK analysis of TPOXX will be collected before dosing (0 hour) and up to 48 hours after administration of the study drug(s).

All subjects will have a follow-up telephone call 30 days after administration of the last dose of study drug (Day 59 [+4 days]) to report any serious adverse events (SAEs). At the time of discharge from the clinical research unit, subjects will be instructed to notify the investigator of any SAEs that occur within 30 days after administration of the last dose of study drug. Serious AEs will be followed until the SAE is stable or until resolution as determined by the investigator and/or medical monitor.

The total duration of the study for each subject, including the screening period, treatment period, the Day 36 (+2 days) end-of-study visit, and the Day 59 (+4 days) follow-up telephone call, will be approximately 87 days.

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 18 to 50 years of age, inclusive.
2. Blood phosphorus levels within normal laboratory reference range.
3. Women of childbearing potential have a negative β human chorionic gonadotropin pregnancy test (serum) at the screening visit and a confirmatory negative serum pregnancy test on Day –1 before receipt of study drug, and meet one of the following criteria:
    a. The subject or their partner has undergone surgical sterilization
    b. The subject is postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause and has a documented plasma follicle-stimulating hormone level >40 IU/mL

c. The subject agrees to be abstinent (ie, heterosexually inactive or women in a religious order)

d. The subject agrees to consistently use 1 of the following methods of contraception from the beginning of screening (which they had been consistently using for at least 30 days before the first dose of study drug) through 30 days after the last dose of study drug:

   i. Condoms, male or female, with a spermicide

      NOTE: For male subjects, condoms must be used for 90 days after last dose of study drug

   ii. Diaphragm or cervical cap with spermicide

   iii. Intrauterine device with spermicide

   iv. Oral contraceptives or other hormonal methods

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

   v. Male sexual partner who has undergone a vasectomy at least 3 months before screening.

4. Male subjects must agree to not donate sperm from the first dose of study drug through 90 days after the last dose of study drug.
5. Subject is considered by the investigator to be in good general health as determined by medical history, clinical laboratory test results, vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings at screening.
6. Subject agrees to comply with the dietary requirements.
7. Subject agrees to comply with all protocol requirements.
8. Subject is able 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
   - Hypertension that is poorly controlled (repeat readings >140 mm Hg systolic and/or >90 mm Hg diastolic)
   - Thyroidectomy or thyroid disease that required medication within the past 12 months
   - Serious angioedema episodes within the previous 3 years or requiring medication in the previous 2 years

- Head trauma resulting in a diagnosis of traumatic brain injury other than concussion
- Frequent episodes of headache.

3. Subject has received treatment in another clinical study of an investigational drug (or medical device) within 30 days or 5 half-lives (whichever is longer) before the first dose of study drug.
4. Subject has a history of relevant drug and/or food allergies (ie, allergy to TPOXX or excipients, or any significant food allergy that could preclude a standard diet in the study site).
5. Subject has any condition possibly affecting drug absorption (eg, previous surgery on the gastrointestinal tract, including removal of parts of the stomach, bowel, liver, gallbladder, or pancreas, with the exception of appendectomy).
6. Subject has evidence or history of clinically significant allergic (except for untreated, asymptomatic, seasonal allergies at time of the first dose of study drug), hematological, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, or neurological disease. Exceptions to these criteria (eg, stable, mild joint disease unassociated with collagen vascular disease) may be made following discussions with the medical monitor.
7. Subject has a history of cardiac disease, symptomatic or asymptomatic arrhythmias, syncopal episodes, or risk factors for torsades de pointes (eg, heart failure, hypokalemia).
8. Subject has a family history of sudden cardiac death not clearly due to acute myocardial infarction.
9. 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.
10. Subject has a history of a peptic ulcer or significant gastrointestinal bleeding.
11. Subject has a bleeding disorder diagnosed by a doctor (eg, factor deficiency, coagulopathy, or platelet disorder requiring special precautions) or significant bruising or bleeding difficulties with blood draws.
12. 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).
13. Subject has neutropenia or other blood dyscrasia determined to be clinically significant by the investigator.
14. Subject has used any of the following prohibited medications from within 7 days (or 5 half-lives, whichever is longer) before the first dose of study drug: antidiabetic medication; anticoagulants; anticonvulsants; substrates of the breast cancer resistance protein transporter including methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, and topotecan; substrates of CYP2C8 including repaglinide, paclitaxel, Montelukast, pioglitazone, rosiglitazone; and substrates of CYP2C19

including S-mephenytoin, clobazam, diazepam, rabeprazole, voriconazole, lansoprazole, and omeprazole. Medications not listed here that are known (or thought) to be CYP3A4 substrates may be allowed at the investigator's discretion, after consultation with the medical monitor, if administration poses little to no risk to the subject.

15. Subject has a history of drug or alcohol abuse or dependency within the last year before screening.
16. Subject has a current or recent (<30 days before screening) history of clinically significant bacterial, fungal, or mycobacterial infection.
17. Subject has a current clinically significant viral infection.
18. Subject has a known clinically significant chronic viral infection (eg, human T cell lymphotropic virus I or II).
19. Subject has consumed grapefruit or grapefruit juice, Seville orange or Seville orange-containing products (eg, marmalade), or caffeine- or xanthine-containing products within 48 hours before the first dose of study drug.
20. Subject has used any prescription (excluding hormonal birth control) or over-the-counter medication (including herbal or nutritional supplements) within 14 days before the first dose of study drug.
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 is a smoker or has used nicotine or nicotine-containing products (eg, cigarettes, electronic vapor cigarettes, cigars, chewing tobacco, snuff, nicotine patches, or nicotine gum) within 6 months before the first dose of study drug.
24. Subject has consumed pomegranate or pomegranate juice, pomelo fruits or pomelo juice, or alcohol within 72 hours before the first dose of study drug.
25. Subject reports participation in strenuous activity or contact sports within 24 hours before the first dose of study drug.
26. 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.
27. Subject has a positive test result for amphetamines (including methamphetamines and ecstasy/methylenedioxymethamphetamine), barbiturates, benzodiazepines, cannabinoids (including tetrahydrocannabinol), cocaine metabolites, opiates (including heroin, codeine, and oxycodone), or alcohol at screening or check-in.

28. 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 count 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 >2.0 times above the upper laboratory reference range
    - Aspartate aminotransferase >2.0 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.
29. Subject has a blood pressure considered to be clinically significant by the investigator. Blood pressure may be retested twice in the sitting position at 5-minute intervals.
30. Subject has a resting heart rate of <40 beats per minute or >110 beats per minute at screening.
31. Subject has an abnormal ECG at screening that is determined by the investigator to be clinically significant.
32. 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.
33. In the opinion of the investigator, the subject is not suitable for entry into the study.

EVALUATION PROCEDURES:

Pharmacokinetic Assessments:

Blood samples for PK analysis of TPOXX will be collected from all subjects at the following time points: within 60 minutes before dosing (0 hour) and at 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours after administration of study drug in each period. For PK blood samples, the acceptable window for collection from the scheduled collection time point will be as follows: ±5 minutes for the time points from 0.5 through 8 hours and ±15 minutes for the time points from 12 through 48 hours.

The following plasma PK parameters will be calculated for TPOXX to the extent that data permit:

- Area under the plasma concentration versus time curve (AUC) from time 0 to 24 hours (AUC_{0-24})
- AUC from time 0 to 48 hours (AUC_{0-48})

- AUC from time 0 to infinity ($AUC_{0\text{-}inf}$)
- AUC from time 0 to the last quantifiable concentration ($AUC_{0\text{-}t}$)
- Maximum drug concentration in plasma (C_{max})
- Time to C_{max} (T_{max}).

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

STUDY DRUG, DOSAGE, AND ROUTE OF ADMINISTRATION:
Single oral dose of 600 mg (3 × 200-mg capsules) TPOXX, administered under fed conditions.

Single oral dose of 1600 mg (2 × 800-mg) sevelamer carbonate (Renvela® or generic equivalent) tablet coadministered with TPOXX under fed conditions.

Single oral dose of 500 mg sucroferric oxyhydroxide (Velphoro®) chewable tablet coadministered with TPOXX under fed conditions. Note: Velphoro must be chewed and not swallowed whole.

Single oral dose of 1334 mg (2 × 667-mg) calcium acetate (PhosLo® generic equivalent) capsule coadministered with TPOXX under fed conditions.

Single oral dose of 500 mg lanthanum carbonate (Fosrenol® or generic equivalent) chewable tablet coadministered with TPOXX under fed conditions. Note: Fosrenol or generic equivalent must be chewed and not swallowed whole.

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

Sample Size:
The sample size (N = 44 [to allow at least 36 enrolled subjects to complete]) for this study is based on clinical and practical considerations and not on a formal statistical power calculation. The sample size is considered sufficient for the objectives of the study.

Prior estimates of within-subject variability (CV_w) of a single dose of 600 mg TPOXX were obtained from Study SIGA-246-018, which evaluated the single-dose PK of TPOXX in a similar population. The CV_w% for C_{max}, $AUC_{0\text{-}24}$, and $AUC_{0\text{-}inf}$ ranged from 11.39% to 12.62%, 9.38% to 18.12%, and 15.70% to 18.02%, respectively.

For a sensitivity analysis, a range for CV_w of 10%, 15%, and 20% across point estimates of 0.9, 1.0, and 1.1 will be explored.

For the sensitivity analysis, assuming a range of CV_w, a sample size of 36 evaluable subjects, it is estimated that the precision (ie, half-width of the 90% confidence interval [CI] on the log and ratio scale), and CI with tolerance probability of 80% on the original scale for each point estimate will be:

CV_w (%)	Half-Width (log scale)	Half-Width (original scale)	Point Estimate	90% Confidence Interval
10	0.043	0.044	0.9	(0.862, 0.94)
			1.0	(0.958, 1.044)
			1.1	(1.054, 1.148)
15	0.065	0.067	0.9	(0.843, 0.96)
			1.0	(0.937, 1.067)
			1.1	(1.031, 1.174)
20	0.086	0.090	0.9	(0.826, 0.981)
			1.0	(0.918, 1.09)
			1.1	(1.009, 1.199)

Abbreviation: CV_w, within-subject variability.

Analysis Populations:

- The PK population will include subjects who receive at least 1 dose of TPOXX and have sufficient concentration data to support accurate estimation of at least 1 PK parameter.
- The safety population will include all subjects who receive any amount of study drug.

Pharmacokinetic Analyses:

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

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 treatment using the following descriptive statistics: number of subjects, mean, SD, CV, geometric mean, geometric SD, geometric CV, minimum, median, and maximum. Geometric means will be included for AUC_{0-24} and C_{max}.

A linear mixed model with sequence, treatment, and period as fixed effects and subject within sequence as a random effect will be performed on the natural log-transformed values of AUC_{0-24} and C_{max} to assess the effect of phosphate binders on the PK of TPOXX. The geometric least squares means and corresponding 90% CIs will be computed for AUC_{0-24} and C_{max} of TPOXX + phosphate binder versus TPOXX alone by taking the antilog of the least squares means from the linear mixed-effect model on the natural logarithms of the corresponding PK parameters. A 90% CI for the ratio will be constructed as the antilog of the confidence limits of the mean difference. No adjustment will be made for multiplicity. The geometric mean ratios and corresponding 90% CIs for AUC_{0-24} and C_{max} for TPOXX will be summarized in forest plots for overall assessment of the drug-drug interaction.

It will be concluded that there is no relevant interaction of phosphate binders on TPOXX if the 90% CIs for AUC_{0-24} and C_{max} ratios (TPOXX + phosphate binder/TPOXX alone) are completely contained within the [80%, 125%] interval.

Non-parametric methods will be used to examine median differences in T_{max} for TPOXX.

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

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment 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.

DATE OF PROTOCOL: 27 January 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] 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 the oral formulation of TPOXX for the treatment of patients with human smallpox disease caused by variola virus. In November 2021, Health Canada approved the oral formulation of TPOXX for the same indication. In January 2022, the European Medicines Agency (EMA) approved the oral formulation for the treatment of patients with smallpox, monkeypox, cowpox, and complications due to replication of vaccinia virus following vaccination against smallpox.

1.2 RATIONALE FOR STUDY

This study is being conducted as an FDA postmarketing commitment ([redacted]) to the approved New Drug Application for TPOXX. SIGA is required to conduct a drug-drug interaction (DDI) study to evaluation the potential effects of coadministration of 4 different phosphate binders on the pharmacokinetics (PK) of orally administered TPOXX. This study is in accordance with the FDA Guidance for Industry, Clinical Drug Interaction Studies—Study Design, Data Analysis, and Clinical Implications.[2]

1.3 RATIONALE FOR DOSE SELECTION

A single dose of 600 mg (3 × 200 mg capsules) TPOXX was chosen as this is the recommended dose for TPOXX.

Sevelamer carbonate, sucroferric oxyhydroxide, calcium acetate, and lanthanum carbonate were chosen for this study because they are common phospate binders that patients prescribed TPOXX may be concurrently taking. The planned doses for each of these drugs were selected based on the FDA Guidance “Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications”, which states the maximum dose and the shortest dosing interval should be used.[2]

Any potential DDI will be determined based on an analysis of TPOXX PK in the presence of phosphate-binding drugs. The planned doses of TPOXX and the 4 phosphate binders are expected to be sufficiently high to quantify an effect on TPOXX plasma exposure levels.

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. Pregnancy testing will be performed at the screening visit and checked by the investigator for negative pregnancy on Day –1 of each period before administration of study drug. Women who are pregnant or lactating or plan to become pregnant within 3 months after study drug administration will be excluded from the study; if a female subject becomes pregnant during study participation, study drug dosing will be discontinued, and the subject will be withdrawn from the study (Section 6.2.1.8).

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.[3]

A single dose of the phosphate binders should not lead to any major AEs, but there may be an increased risk of hypercalcemia (specifically with calcium acetate). Other potential AEs include diarrhea, dyspepsia, nausea, vomiting, abdominal pain, flatulence, and hypotension (specifically with sucroferric oxyhydroxide).

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 knowledge gained in this study which may aid in the use of TPOXX for the treatment of smallpox in patients taking phosphate binders.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to evaluate potential DDI as measured by the effect of coadministration of 4 separate phosphate binders on the PK of orally administered TPOXX in healthy adult subjects.

2.2 SECONDARY OBJECTIVE

The secondary objective of this study is to evaluate the safety and tolerability of 600 mg oral TPOXX administered with 4 different phosphate binders in healthy adult subjects.

3. STUDY DESIGN AND METHODOLOGY

This is a postmarketing, open-label, 5-period crossover drug interaction study designed to evaluate the potential effects of coadministration of 4 different phosphate binders on the PK of orally administered TPOXX in healthy adult subjects. A total of 44 subjects, ages 18 to 50, inclusive, will be enrolled and be randomly assigned to 1 of 4 treatment sequences. The study will consist of a screening period (Day –28 to Day –2), 5 treatment periods (Day –1 to Day 31), an end-of-study visit (Day 36 [+2 days]), and a follow-up telephone call (Day 59 [+4 days]). The treatment sequences and periods will be as follows:

Treatment Sequence	Period 1 Treatment	Period 2 Treatment	Period 3 Treatment	Period 4 Treatment	Period 5 Treatment
ABCDE	A	B	C	D	E
ACEBD	A	C	E	B	D
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AEDCB	A	E	D	C	B

- Treatment A: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX.
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- Treatment C: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 500 mg sucroferric oxyhydroxide (Velphoro®) chewable tablet.

- Treatment D: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 1334 mg (2 × 667 mg capsules) calcium acetate (PhosLo® generic equivalent).

- Treatment E: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 500 mg lanthanum carbonate (Fosrenol® or generic equivalent) chewable tablet.

There will be a washout period of 7 days between dosing in each treatment period. All subjects will be provided a meal (consisting of approximately 600 calories and 25 g fat). The meal should be completed within 30 minutes. 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 study drug administration. Study drug and meals must be taken with water only, and no other beverage except water should be ingested within 3 hours before or 3 hours after study drug administration. Water is allowed at all times throughout the study. Subjects must fast for 2 hours after taking study drug as further food consumption may affect drug absorption.

In each period, subjects will report to the study site on Day –1 and remain confined to the study site until 48 hours after dosing in Period 5 (Day 31). Subjects will be monitored for safety and tolerability. Serial blood samples for PK analysis of TPOXX will be collected before dosing (0 hour) and up to 48 hours after administration of the study drug(s).

All subjects will have a follow-up telephone call 30 days after administration of the last dose of study drug (Day 59 [+4 days]) to report any serious AEs (SAEs). At the time of discharge from the clinical research unit, subjects will be instructed to notify the investigator of any SAEs that occur within 30 days after administration of the last dose of study drug. Serious AEs will be followed until the SAE is stable or until resolution as determined by the investigator and/or medical monitor.

The total duration of the study for each subject, including the screening period, treatment period, the Day 36 (+2 days) end-of-study visit, and the Day 59 (+4 days) follow-up telephone call, will be approximately 87 days.

4. STUDY POPULATION

Approximately 44 healthy male and female subjects will be enrolled at a single center in the United States to achieve at least 36 evaluable subjects.

4.1 INCLUSION CRITERIA

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

1. The subject is male or female 18 to 50 years of age, inclusive.

2. Blood phosphorus levels within normal laboratory reference range.

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

    a. The subject or their partner has undergone surgical sterilization

    b. The subject is postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause and has a documented plasma follicle-stimulating hormone level >40 IU/mL

    c. The subject agrees to be abstinent (ie, heterosexually inactive or women in a religious order)

    d. The subject agrees to consistently use 1 of the following methods of contraception from the beginning of screening (which they had been consistently using for at least 30 days before the first dose of study drug) through 30 days after the last dose of study drug:

        i. Condoms, male or female, with a spermicide

            NOTE: For male subjects, condoms must be used for 90 days after last dose of study drug

        ii. Diaphragm or cervical cap with spermicide

        iii. Intrauterine device with spermicide

        iv. Oral contraceptives or other hormonal methods

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

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

4. Male subjects must agree to not donate sperm from the first dose of study drug through 90 days after the last dose of study drug.

5. The subject is considered by the investigator to be in good general health as determined by medical history, clinical laboratory test results, vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings at screening.

6. The subject agrees to comply with the dietary requirements.

7. The subject agrees to comply with all protocol requirements.

8. The subject is able 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
- Hypertension that is poorly controlled (repeat readings >140 mm Hg systolic and/or >90 mm Hg diastolic)
- Thyroidectomy or thyroid disease that required medication within the past 12 months
- Serious angioedema episodes within the previous 3 years or requiring medication in the previous 2 years
- Head trauma resulting in a diagnosis of traumatic brain injury other than concussion
- Frequent episodes of headache.

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

4. Subject has a history of relevant drug and/or food allergies (ie, allergy to TPOXX or excipients, or any significant food allergy that could preclude a standard diet in the study site).

5. Subject has any condition possibly affecting drug absorption (eg, previous surgery on the gastrointestinal tract, including removal of parts of the stomach, bowel, liver, gallbladder, or pancreas, with the exception of appendectomy).

6. Subject has evidence or history of clinically significant allergic (except for untreated, asymptomatic, seasonal allergies at time of the first dose of study drug), hematological, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, or neurological disease. Exceptions to these criteria (eg, stable, mild joint disease unassociated with collagen vascular disease) may be made following discussions with the medical monitor.

7. Subject has a history of cardiac disease, symptomatic or asymptomatic arrhythmias, syncopal episodes, or risk factors for torsades de pointes (eg, heart failure, hypokalemia).

8. Subject has a family history of sudden cardiac death not clearly due to acute myocardial infarction.

9. 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.

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

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

12. 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).

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

14. Subject has used any of the following prohibited medications from within 7 days (or 5 half-lives, whichever is longer) before the first dose of study drug: antidiabetic medication; anticoagulants; anticonvulsants; substrates of the breast cancer resistance protein transporter including methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, and topotecan; substrates of CYP2C8 including repaglinide, paclitaxel, Montelukast, pioglitazone, rosiglitazone; and substrates of CYP2C19 including S-mephenytoin, clobazam, diazepam, rabeprazole, voriconazole, lansoprazole, and omeprazole. Medications not listed here that are known (or thought) to be CYP3A4 substrates may be allowed at the investigator's discretion, after consultation with the medical monitor, if administration poses little to no risk to the subject.

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

16. Subject has a current or recent (<30 days before screening) history of clinically significant bacterial, fungal, or mycobacterial infection.

17. Subject has a current clinically significant viral infection.

18. Subject has a known clinically significant chronic viral infection (eg, human T cell lymphotropic virus I or II).

19. Subject has consumed grapefruit or grapefruit juice, Seville orange or Seville orange-containing products (eg, marmalade), or caffeine- or xanthine-containing products within 48 hours before the first dose of study drug.

20. Subject has used any prescription (excluding hormonal birth control) or over-the-counter medication (including herbal or nutritional supplements) within 14 days before the first dose of study drug.

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 is a smoker or has used nicotine or nicotine-containing products (eg, cigarettes, electronic vapor cigarettes, cigars, chewing tobacco, snuff, nicotine patches, or nicotine gum) within 6 months before the first dose of study drug.

24. Subject has consumed pomegranate or pomegranate juice, pomelo fruits or pomelo juice, or alcohol within 72 hours before the first dose of study drug.

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

26. 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.

27. Subject has a positive test result for amphetamines (including methamphetamines and ecstasy/methylenedioxymethamphetamine), barbiturates, benzodiazepines, cannabinoids (including tetrahydrocannabinol), cocaine metabolites, opiates (including heroin, codeine, and oxycodone), or alcohol at screening or check-in.

28. 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 count 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 >2.0 times above the upper laboratory reference range

- Aspartate aminotransferase >2.0 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.

29. Subject has a blood pressure considered to be clinically significant by the investigator. Blood pressure may be retested twice in the sitting position at 5-minute intervals.

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

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

32. 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.

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

4.3 OTHER SCREENING CONSIDERATIONS

- Subjects must be willing to be confined to the study site until Day 31 (5 separate dosing periods).
- Subjects must be willing and agree to return for the end-of-study visit on Day 36 (+2 days) and answer a follow-up telephone call on Day 59 (+4 days).

4.4 WITHDRAWAL OF SUBJECTS FROM THE STUDY

4.4.1 Reasons for Withdrawal

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

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

- The subject is in violation of the protocol.

- The subject experiences a serious or intolerable AE.
- The subject becomes pregnant.
- The subject is noncompliant.
- The subject has laboratory abnormalities for assessments listed in Section 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 Version 2.1 July 2017 any other Grade 3 or Grade 4 AE; or a Grade 2 or higher rash considered by the investigator to be possibly, probably, or definitely related to study drug.
- The subject develops, during the course of the study, symptoms or conditions listed in the exclusion criteria.
- The subject requires a medication prohibited by the protocol.
- The subject requests an early discontinuation for any reason.
- The subject's primary care provider requests that the subject be withdrawn.
- The independent safety monitor (ISM), SIGA, or the FDA requests subject withdrawal based on study safety findings.

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

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 shall be recorded by the investigator in the electronic case report form (eCRF). Whenever possible, any subject who withdraws from the study prematurely will undergo all Day 36/early discontinuation visit assessments (+2 days) (Table 9-2). 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

The medical monitor, investigator, SIGA, and ISM will review all AEs. All AEs determined by the investigator to be severe and possibly, probably, or definitely related to study drug, as well as all clinical assessments, laboratory test results, ECG results, or vital sign measurements that meet Grade 3 criteria on the DAIDS AE Grading Table[5] will be assessed by the medical monitor, who will make a recommendation as to whether or not halting of the study should occur. At the discretion of the medical monitor, depending on the assessment of the severity of the event, the recommendation to halt the study may be made after consultation with the investigator, SIGA, and the ISM.

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

- One subject experiences a Grade 4 AE assessed as possibly, probably, or definitely related to study drug.
- There is a subject death assessed as possibly, probably, or definitely related to study drug.
- One subject experiences a seizure assessed as possibly, probably, or definitely related to study drug.
- Two or more subjects experience the same or similar SAEs that are possibly, probably, or definitely related to the study drug.
- Three or more subjects experience the same or similar AEs that are Grade 3 or above and are possibly, probably, or definitely related to the study drug.

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

and ISM, indicate a potentially serious safety concern. The investigator will advise SIGA immediately if any of the halting rules are met.

4.4.4 Replacements

At the discretion of the investigator, and after consultation with the medical monitor, any subject who withdraws before completing the study may be replaced to retain the target of 36 evaluable enrolled subjects.

5. STUDY TREATMENTS

5.1 TREATMENTS ADMINISTERED

All subjects will receive the following study treatments as follows:

- Treatment A: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX.
- Treatment B: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 1600 mg (2 × 800 mg tablets) sevelamer carbonate (Renvela® or generic equivalent).
- Treatment C: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 500 mg sucroferric oxyhydroxide (Velphoro®) chewable tablet.
- Treatment D: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 1334 mg (2 × 667 mg capsules) calcium acetate (PhosLo® or generic equivalent).
- Treatment E: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 500 mg lanthanum carbonate (Fosrenol® or generic equivalent) chewable tablet.

There will be a washout period of 7 days between dosing in each treatment period.

All subjects will be provided a meal (consisting of approximately 600 calories and 25 g fat). The meal should be completed within 30 minutes. 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 study drug administration. All study drug will be administered to subjects by the study site personnel with approximately 240 mL of water.

Study drug and meals must be taken with water only, and no other beverage except water should be ingested within 3 hours before or 3 hours after study drug administration. Water is allowed at all times throughout the study. Subjects must fast for 2 hours after taking study drug as further food consumption may affect drug absorption. Subjects should receive standardized meals that are scheduled at the same time in each period of the study.

5.2 INVESTIGATIONAL PRODUCTS

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

Table 5-1 Excipients of TPOXX Capsules

Component	Quality Designation
[redacted]	[redacted]

Abbreviations: EP, European Pharmacopoeia; JP, Japanese Pharmacopoeia; 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 prescribing information.[3]

The phosphate binder study drugs that will be used in this study are as follows:

Product	Supplied Formulation
Sevelamer carbonate (Renvela® or generic equivalent)	800 mg tablet
Sucroferric oxyhydroxide (Velphoro®)	500 mg chewable tablet
Calcium acetate (PhosLo® generic equivalent)	667 mg tablet or capsule
Lanthanum carbonate (Fosrenol® or generic equivalent)	500 mg chewable tablet

5.2.1 Study Drug Packaging and Storage

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

The 200-mg TPOXX capsules are supplied in 75-mL high-density polyethylene bottles fitted with a heat induction seal and child-resistant screw cap closure system. Each bottle of study drug will contain 42 capsules and will be labeled with, at a minimum, the study number, bottle content, direction for distribution, storage conditions, and cautionary statement.

SIGA will provide the investigator and study site with adequate quantities of TPOXX.

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

The phosphate binders will be supplied by the study site. The study site pharmacy will prepare the study treatments for each subject according to the schedule of events (Table 9-1 and Table 9-2).

All study drugs must be stored according to the labeled instructions in a secure cabinet or room with access restricted to necessary clinic personnel. The study site will be required to keep a temperature log to establish a record of compliance with storage conditions.

5.2.2 Study Drug Accountability

The investigator 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. Study drug accountability will be recorded in the subject source documentation, entered into the eCRF, and should be reviewed by the monitor during each monitoring visit. On a regular basis and at the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained or destroyed according to applicable regulations.

5.3 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

Randomization will occur according to the randomization schedule before study drug administration on Day 1 of Period 1 after it has been confirmed that the subject fulfills all eligibility criteria. Subjects will be randomly assigned to receive study drug in 1 of 4 treatment sequences (ABCDE, ACEBD, ADBEC, and AEDCB) in 1:1:1:1 ratio.

5.4 BLINDING

This is an open-label study.

5.5 TREATMENT COMPLIANCE

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

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

5.5.1 Prior and Concomitant Medications

Restrictions for prior and concomitant medications and therapies are provided in Section 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.

5.5.1.1 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.

5.5.1.2 Concomitant Medications

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

6. STUDY PROCEDURES

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

Blood samples for PK analysis of TPOXX will be collected from all subjects at the following time points: within 60 minutes before dosing (0 hour) and at 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours after administration of study drug in each period.

For PK blood samples, the acceptable window for collection from the scheduled collection time point will be as follows: ±5 minutes for the time points from 0.5 through 8 hours and ±15 minutes for the time points from 12 through 48 hours.

The following plasma PK parameters will be calculated for TPOXX to extent that data permit using actual sampling times rather than scheduled sampling times:

- Area under the plasma concentration versus time curve (AUC) from time 0 to 24 hours (AUC_{0-24})
- AUC from time 0 to 48 hours (AUC_{0-48})
- AUC from time 0 to infinity (AUC_{0-inf})
- AUC from time 0 to the last quantifiable concentration (AUC_{0-t})
- Maximum drug concentration in plasma (C_{max})
- Time to C_{max} (T_{max}).

6.1.1 Pharmacokinetic Sample Collection

Blood samples (approximately 5 mL) for the determination of plasma concentrations of TPOXX will be collected in 5-mL lavender-topped K_3EDTA Vacutainer® tubes using a 20 gauge or larger needle, or from an indwelling intravenous catheter using a vacutainer tube. Blood samples should be placed on wet ice (approximately 4°C to 8°C) immediately after collection and kept at this temperature until processed to separate plasma.

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

Plasma Sample Processing

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

Adequate space between the solution and the tube cap should be allowed for expansion during freezing.

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

Plasma samples for bioanalytical analysis will be split upon collection at the site. The study site will batch ship sets of frozen plasma samples. A log sheet listing the samples being shipped will be included in each shipment. The samples will be sent on dry ice via courier to Alturas Analytics (Moscow, ID USA). The back-up sets will remain at the study site until further notice from SIGA. The study site will contact Alturas Analytics and coordinate the shipment prior to sending the samples. Shipments before weekends or holidays must be avoided.

The samples will be shipped for analysis to:

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

Alturas Analytics will store all plasma samples at –70°C until analysis for TPOXX is complete at which time SIGA will advise Alturas Analytics 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 assay for TPOXX in human plasma method in accordance with the US FDA Guidance for Industry on Bioanalytical Method Validation.[6]

6.2 SAFETY ASSESSMENTS AND ENDPOINTS

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

be assessed from the time of the first dose of study drug in Period 1 until the follow-up telephone call on Day 59 (+4 days).

For all safety assessments, the investigator will determine whether results are clinically significant or not clinically significant. Clinical significance is defined as any variation in a result that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If a clinical significance change from baseline is noted, the result and reason for significance will be documented and an AE reported on the AE page in the subject's eCRF. The investigator will continue to 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.

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.

6.2.1 Adverse Events

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

6.2.1.1 Adverse Event Definitions

An AE is defined as any untoward medical occurrence, including those AEs that result from dosing errors, which may present during administration of a study drug or during a reasonable follow-up period and which does not necessarily have a causal relationship with the study drug(s). An AE is any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered to be related to the medicinal product. All AEs will be followed until the AE is resolved or stabilized as determined by the investigator and/or the medical monitor. Subjects will be instructed to contact the investigator at any time after randomization 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 to the study drug.

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.

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, which means any AE caused by a study drug.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the TPOXX full prescribing information[3] or if it occurs with specificity or severity that has not 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 TPOXX full prescribing information referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the TPOXX full prescribing information listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the TPOXX full prescribing information as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

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

- Results in death.
- Is life-threatening (subject is at immediate risk of death at the time of the event).
- Requires inpatient hospitalization or prolongation of existing hospitalization, other than elective hospitalization, during the period of protocol defined surveillance.
- Results in congenital anomaly or birth defect.
- Results in a persistent or significant disability/incapacity.
- Any other important medical event that may not result in death, be life-threatening, or requires hospitalization may be considered an SAE when, based on appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical

intervention to prevent one of the outcomes listed in this definition or is otherwise considered to be medically significant.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical 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 or SIGA, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

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

6.2.1.2 Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to SIGA by PPD. Adverse events and SAEs will be assessed from the first dose of study drug in Period 1 through the telephone call on Day 59 (+4 days).

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

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

6.2.1.3 Reporting Adverse Events

All AEs reported or observed from the first dose of study drug in Period 1 through the follow-up telephone call on Day 59 (+4 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,

dosage, 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.

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

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

6.2.1.4 Reporting of Serious Adverse Events

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

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

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

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

Medical Monitor: [redacted]

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

All subjects will have a follow-up telephone call 30 days after administration of the last dose of study drug (Day 59 [+4 days]) to report any SAEs.

6.2.1.5 Assessment of Severity

All AEs will be graded for intensity according to the current DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1 July 2017.[5]

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

- Grade 1 (Mild): Events require minimal or no treatment and do not interfere with the subject's daily activities.
- Grade 2 (Moderate): Events result in a low level of inconvenience or concern with the therapeutic measures and may cause some interference with normal functioning.
- Grade 3 (Severe): Events interrupt a subject's usual daily activity, may require systemic drug therapy or other treatment, and are usually incapacitating.
- Grade 4 (Life-threatening): Event that, in the opinion of the investigator, places the subject at immediate risk of death from the reaction as it occurred (ie, it does not include a reaction that, had it occurred in a more severe form, might have caused death).
- Grade 5 (Death).

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

The investigator who examines and evaluates the subject will determine AE causality based on the temporal relationship to administration of the study drug, the pharmacology of the study drug, and their clinical judgment. Terms used to describe the degree of causality between each 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 (eg, the event disappears or decreases with reduction in dose or cessation of study drug and recurs with re-exposure).

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

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

Not Associated

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

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

6.2.1.7 Follow-up of Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed until they are resolved or stabilized as determined by the investigator and/or 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 female subject becomes pregnant during study participation, study drug dosing will be discontinued, and the subject will be withdrawn from the study. The pregnancy itself is not considered an SAE. However, the investigator must complete the pregnancy report form and fax it to PPD Pharmacovigilance within 24 hours of knowledge of the pregnancy. After delivery or termination of pregnancy, the follow-up pregnancy report form should be completed and submitted via fax to PPD Pharmacovigilance. Spontaneous abortions should always be reported as SAEs. Pregnancy data will be captured and followed by PPD. All pregnancies and outcomes will be tracked. The case will not be closed until after the child is followed for 3 months.

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

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

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

6.2.2 Clinical Laboratory Testing

Clinical laboratory testing will be performed by the PPD Central Laboratory. Blood and urine samples will be collected at the time points indicated in the schedule of events (Table 9-1 and Table 9-2) and will be prepared using standard procedures.

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

The following clinical laboratory assessments will be performed:

Hematology	Hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, total and differential leukocyte count (basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume, platelet count, red blood cell count, and red cell distribution width
Serum Chemistry	Alanine aminotransferase, albumin, alkaline phosphatase, anion gap, aspartate aminotransferase, bilirubin (total), blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine clearance (calculated[a]), gamma-glutamyltransferase, globulin, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total protein, and uric acid
Urinalysis	Appearance, bilirubin, blood, color, glucose, ketones, 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, turbidity, 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 A1c and a fasting lipid panel including cholesterol (total, high-density lipoprotein, calculated low-density lipoprotein, and triglycerides) will be performed at screening.

Serum pregnancy test (β human chorionic gonadotropin) for women of childbearing potential will be performed at screening. A urine pregnancy test will be performed at check-in on Day –1). A positive urine pregnancy test will be verified with a follow-up serum pregnancy test.

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

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

A urine drug screen for alcohol, 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. At check-in on Day –1., 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 study site.

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

6.2.3 Medical History

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

6.2.4 Vital Sign Measurements

Vital signs will be measured after the subject has been in a seated position for at least 5 minutes at the time points indicated in the schedule 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 12-lead ECG will be obtained after the subject has been in a supine position for at least 10 minutes at the time points indicated in the schedule of events (Table 9-1 and Table 9-2).

On Day 1 of each period, an ECG will be recorded 4 hours after study drug administration. The acceptable window for collection from the scheduled collection time point is ±15 minutes.

Electrocardiogram assessments will include comments on whether the tracings are normal or abnormal, rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST-segment, T-wave, and U-wave abnormalities. In addition, measurements of the following intervals will be measured and reported: heart rate; PR, RR, and QT interval; QTcF, QT interval corrected using Fridericia's formula; and QRS duration. All ECGs must be performed by an experienced ECG technician.

The investigator will determine whether any of the 12-lead ECG results are clinically significant or not clinically significant.

6.2.6 Physical Examinations

A full physical examination will be performed at the time points indicated in the schedule of events (Table 9-1 and 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 at the time points indicated in the schedule of events (Table 9-1 and Table 9-2) (for those subjects who require it), and at unscheduled visits as necessary. This examination will include an assessment of the heart, lungs, abdomen, a neurologic review, and a review of symptoms for assessments and/or follow-up of reported or potential AEs.

Height and weight and will be measured at screening only.

6.2.7 Unscheduled Visits

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

7. STATISTICAL ANALYSIS PLAN

7.1 SAMPLE SIZE CALCULATIONS

The sample size (N = 44 [to allow at least 36 enrolled subjects to complete]) for this study is based on clinical and practical considerations and not on a formal statistical power calculation. The sample size is considered sufficient for the objectives of the study.

Prior estimates of within-subject variability (CV_w) of a single dose of 600 mg TPOXX were obtained from Study SIGA-246-018, which evaluated the single-dose PK of TPOXX in a similar population. The CV_w% for C_{max}, AUC_{0-24} and AUC_{0-inf} ranged from 11.39% to 12.62%, 9.38% to 18.12%, and 15.70% to 18.02%, respectively.

For a sensitivity analysis, a range for CV_w of 10%, 15%, and 20% across point estimates of 0.9, 1.0, and 1.1 will be explored.

For the sensitivity analysis, assuming a range of CV_w, a sample size of 36 evaluable subjects, it is estimated that the precision (ie, half-width of the 90% confidence interval [CI] on the log and ratio scale), and CI with tolerance probability of 80% on the original scale for each point estimate will be:

CVw (%)	Half-Width (log scale)	Half-Width (original scale)	Point Estimate	90% Confidence Interval
10	0.043	0.044	0.9	(0.862, 0.94)
			1.0	(0.958, 1.044)
			1.1	(1.054, 1.148)
15	0.065	0.067	0.9	(0.843, 0.96)
			1.0	(0.937, 1.067)
			1.1	(1.031, 1.174)
20	0.086	0.090	0.9	(0.826, 0.981)
			1.0	(0.918, 1.09)
			1.1	(1.009, 1.199)

Abbreviation: CV_w, within-subject variability.

7.2 ANALYSIS SETS

The analysis populations are as follows:

- The PK population will include subjects who receive at least 1 dose of TPOXX and have sufficient concentration data to support accurate estimation of at least 1 PK parameter.
- The safety population will include all subjects who receive any amount of study drug.

7.3 STATISTICAL ANALYSIS

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

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

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

7.3.1 Pharmacokinetic Analyses

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

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 treatment using the following descriptive statistics: number of subjects, mean, SD, CV, geometric mean, geometric SD, geometric CV, minimum, median, and maximum. Geometric means will be included for $AUC_{0\text{-}24}$ and C_{max}.

A linear mixed model with sequence, treatment, and period as fixed effects and subject within sequence as a random effect will be performed on the natural log-transformed values of $AUC_{0\text{-}24}$ and C_{max} to assess the effect of phosphate binders on the PK of TPOXX. The geometric least squares means and corresponding 90% CIs will be computed for $AUC_{0\text{-}24}$ and C_{max} of TPOXX + phosphate binder versus TPOXX alone by taking the antilog of the least squares means from the linear mixed-effect model on the natural logarithms of the corresponding PK parameters. A 90% CI for the ratio will be constructed as the antilog of the

confidence limits of the mean difference. No adjustment will be made for multiplicity. The geometric mean ratios and corresponding 90% CIs for AUC_{0-24} and C_{max} for TPOXX will be summarized in forest plots for overall assessment of the DDI.

It will be concluded that there is no relevant interaction of phosphate binders on TPOXX if the 90% CIs for AUC_{0-24} and C_{max} ratios (TPOXX + phosphate binder/TPOXX alone) are completely contained within the [80%, 125%] interval.

Non-parametric methods will be used to examine median differences in T_{max} for TPOXX.

7.3.2 Safety Analyses

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

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment 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.

7.4 HANDLING OF BELOW THE LIMIT OF QUANTIFICATION AND MISSING DATA

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

8. REFERENCE LIST

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6. Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research (US). Guidance for Industry. Bioanalytical Method Validation. May 2018 [cited 24 Jan 2022]. Available from: https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf.

9. APPENDICES

9.1 APPENDIX 1: LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AUC	area under the plasma concentration versus time curve
AUC_{0-24}	area under the plasma concentration versus time curve from time 0 to 24 hours
BLQ	below the limit of quantification
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum drug concentration in plasma
CRA	clinical research associate
CV	coefficient of variation
CV_w	within-subject variability
DAIDS	Division of Acquired Immune Deficiency Syndrome
DDI	drug-drug interaction
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
ISM	independent safety monitor
PK	pharmacokinetic(s)
QTcF	QT interval corrected using Fridericia's formula
SAE	serious adverse event
SD	standard deviation
SOP	standard operating procedures
T_{max}	time to maximum drug concentration in plasma

9.2 APPENDIX 2: SCHEDULE OF EVENTS

Table 9-1 Schedule of Events: Period 1 through Period 3

Procedure[a]	Phase	Screening	Check-in	Treatment Period 1						Treatment Period 2							Treatment Period 3						
	Day	–28 to –2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	Day									–1	1	2	3	4	5	6	–1	1	2	3	4	5	6
Admission to clinic			X																				
Domiciled at clinic				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Informed consent		X																					
Inclusion/exclusion criteria		X	X																				
Medical history[b]		X	X																				
Physical examination[c]		X	X																				
Demographics		X																					
Height and weight		X																					
Vital sign measurements[d]		X	X	X	X	X				X	X	X	X				X	X	X	X			
Glycosylated hemoglobin (HbA1c)		X																					
Fasting lipid panel[e]		X																					
Clinical laboratory testing[f]		X[g]	X		X					X		X					X		X				
Serum follicle-stimulating hormone[h]		X																					
Serum pregnancy test[i]		X																					
Urine pregnancy test[i]			X																				
Urine drug/alcohol screen[j]		X	X																				
Serology (HBsAg, HCV, and HIV)		X																					
Randomization[k]			X																				
12-lead electrocardiogram[l]		X	X	X							X							X					
Administration of study drug(s)[m]				X							X							X					
Pharmacokinetic sample collection[n]				X	X	X					X	X	X					X	X	X			
Adverse events				◄ X ►																			
Prior/concomitant medications		◄ X ►																					

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

Notes:

[a] When procedures overlap or occur at the same time point, all blood draws should follow vital signs or ECGs, and PK sampling should be timed to occur last and as close to the scheduled time window as possible.

[b] Medical history will include a review of systems; recreational, prescription, and over-the-counter drug use; nicotine and alcohol use; and past hospitalizations.

[c] 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). Symptom-directed physical examination will include an assessment of the heart, lungs, abdomen, a neurologic review, and a review of symptoms for assessment and/or follow-up of reported or potential adverse events.

[d] Vital sign measurements will include systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. Vital signs will be measured at screening, and in each period, at check-in; within 60 minutes prior to dosing; and at 4, 8, 12, 24, and 48 hours following dosing in each period after the subject has been in a seated position for at least 5 minutes.

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

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

[g] Clinical laboratory testing at screening will include hematology, serum chemistry, and urinalysis.

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

[i] Women of childbearing potential only.

[j] 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.

[k] Randomization will occur according to the randomization schedule before study drug administration on Day 1 of Period 1 after it has been confirmed that the subject fulfills all eligibility criteria. Subjects will be randomly assigned to receive study drug in 1 of 4 treatment sequences (ABCDE, ACEBD, ADBEC, and AEDCB) in 1:1:1:1 ratio.

[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 of each period, an ECG will be recorded 4 hours after study drug administration. The acceptable window for collection from the scheduled collection time point is ±15 minutes.

[m] All subjects will be provided a meal (consisting of approximately 600 calories and 25 g fat). The meal should be completed within 30 minutes. Subjects should be administered study drug(s) as soon as possible following completion of the meal but no more than 30 minutes should elapse between meal completion and study drug administration. Study drug and meals must be taken with water only, and no other beverage except water should be ingested within 3 hours before or 3 hours after study drug administration. Subjects must fast for 2 hours after taking study drug. The time of study drug dosing will be called "0" hour in each period.
Treatment A: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX
Treatment B: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 1600 mg (2 × 800 mg tablets) sevelamer carbonate (Renvela® or generic equivalent)
Treatment C: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 500 mg sucroferric oxyhydroxide (Velphoro®) chewable tablet.
Treatment D: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 1334 mg (2 × 667 mg capsules) calcium acetate (PhosLo® generic equivalent).
Treatment E: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 500 mg lanthanum carbonate (Fosrenol® or generic equivalent) chewable tablet.

[n] Blood samples for PK analysis of TPOXX will be collected from all subjects at the following time points: within 60 minutes before dosing (0 hour) and at 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours after administration of study drug in each period. For PK blood samples, the acceptable window for collection from the scheduled collection time point will be as follows: ±5 minutes for the time points from 0.5 through 8 hours and ±15 minutes for the time points from 12 through 48 hours.

Table 9-2 Schedule of Events: Period 4 and Period 5

Procedure[a]	Phase	Treatment Period 4							Treatment Period 5				End of Study Visit or Early Termination[b]	Follow-up Telephone Call[c]
	Day	21	22	23	24	25	26	27	28	29	30	31	36 (+2)	59 (+4)
	Day	–1	1	2	3	4	5	6	–1	1	2	3		
Domiciled at clinic		X	X	X	X	X	X	X	X	X	X			
Discharge from clinic												X		
Outpatient visit													X	X
Physical examination[d]													X	
Vital sign measurements[e]		X	X	X	X				X	X	X	X	X	
Clinical laboratory testing[f]		X		X					X		X		X[g]	
12-lead electrocardiogram[h]			X							X			X	
Administration of study drug(s)[i]			X							X				
Pharmacokinetic sample collection[j]			X	X	X					X	X	X		
Adverse events		◄							X				►	
Serious adverse events		◄								X				►
Prior/concomitant medications		◄								X				►

Abbreviations: ECG, electrocardiogram; PK, pharmacokinetic.

Notes:

[a] When procedures overlap or occur at the same time point, all blood draws should follow vital signs or ECGs, and PK sampling should be timed to occur last and as close to the scheduled time window as possible.

[b] The end-of-study visit will occur 7 days after the last dose of study drug.

[c] The follow-up telephone call will be made 30 days after the last dose of study drug (Day 59 [+4 days]). Discharge will follow all safety assessments and PK sample collections.

[d] Symptom-directed physical examination will include an assessment of the heart, lungs, abdomen, a neurologic review, and a review of symptoms for assessment and/or follow-up of reported or potential adverse events.

[e] Vital sign measurements will include systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. Vital signs will be measured after the subject has been seated for at least 5 minutes. Vital signs will be measured at screening, and in each period, vital sign measurements will be measured at check-in; within 60 minutes prior to dosing; and at 4, 8, 12, 24, and 48 hours after the study drug administration.

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

[g] Clinical laboratory testing at end of study or early discontinuation will include hematology, serum chemistry, and urinalysis.

[h] A single 12-lead ECG will be collected after the subject has been in the supine position for at least 10 minutes. In each period, an ECG will be recorded 4 hours after the study drug administration. The acceptable window for collection from the scheduled collection time point is ±15 minutes.

[i] All subjects will be provided a meal (consisting of approximately 600 calories and 25 g fat). The meal should be completed within 30 minutes. Subjects should be administered study drug(s) as soon as possible following completion of the meal but no more than 30 minutes should elapse between meal completion and study drug administration. Study drug and meals must be taken with water only, and no other beverage except water should be ingested within

3 hours before or 3 hours after study drug administration. Subjects must fast for 2 hours after taking study drug. The time of study drug dosing will be called "0" hour in each period.
Treatment A: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX
Treatment B: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 1600 mg (2 × 800 mg tablets) sevelamer carbonate (Renvela® or generic equivalent)
Treatment C: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 500 mg sucroferric oxyhydroxide (Velphoro®) chewable tablet.
Treatment D: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 1334 mg (2 × 667 mg capsules) calcium acetate (PhosLo® generic equivalent).
Treatment E: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 500 mg lanthanum carbonate (Fosrenol® or generic equivalent) chewable tablet.

(j) Blood samples for PK analysis of TPOXX will be collected from all subjects at the following time points: within 60 minutes before dosing (0 hour) and at 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours after administration of study drug in each period. For PK blood samples, the acceptable window for collection from the scheduled collection time point will be as follows: ±5 minutes for the time points from 0.5 through 8 hours and ±15 minutes for the time points from 12 through 48 hours.

9.3 APPENDIX 3: STUDY GOVERNANCE

9.3.1 Data Quality Assurance

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

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

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

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

9.3.2 Investigator Obligations

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

9.3.2.1 Confidentiality

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

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

9.3.2.2 Institutional Review

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

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

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

9.3.2.3 Subject Consent

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

Before recruitment and enrollment, each prospective subject or his/her legal guardian will be given a full explanation of the study and will be 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 his or her consent to participate in the study by signing the ICF. A copy of the ICF will be provided to the subject/legal guardian.

9.3.2.4 Exclusion of Children

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

9.3.2.5 Study Reporting Requirements

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

9.3.2.6 Financial Disclosure and Obligations

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

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

9.3.2.7 Investigator Documentation

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

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

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

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

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

9.3.2.8 Study Conduct

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

9.3.2.9 Case Report Forms and Source Documents

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

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

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

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

9.3.2.10 Adherence to Protocol

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

9.3.2.11 Reporting Adverse Events

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate. The investigator also agrees to provide the sponsor 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 the sponsor and regulatory authorities with any reports required.

9.3.2.13 Records Retention

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

9.3.2.14 Publications

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

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

9.3.3 Study Management

9.3.3.1 Monitoring

9.3.3.1.1 Monitoring of the Study

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

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

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

The CRA will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. During the routine monitoring visits, the CRA will perform a 100% source document verification of all subject data entered into the eCRF. Discrepancies, if any, will be clarified with the study site coordinator and investigator, and corrected at the site by the study coordinator. Any questions or required data clarifications will be sent to the study site electronically.

9.3.4 Safety Monitoring Plan

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

9.3.5 Medical Monitor

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

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

9.3.6 Safety Oversight (Independent Safety Monitor)

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

9.3.6.1.1 Inspection of Records

The investigator and institution 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 the sponsor, their representatives, the FDA, or other regulatory agencies access to all study records.

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

9.3.6.2 Management of Protocol Amendments and Deviations

9.3.6.2.1 Modification of the Protocol

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

9.3.6.2.2 Protocol Deviations

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

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

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

9.3.6.3 Study Termination

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

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

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

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

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

9.3.6.4 Final Report

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

9.4 APPENDIX 4: CHANGE HISTORY

Protocol Amendment 1 dated January 27, 2022 was issued to update the medical monitor and update the study design per request from the clinic to keep subjects domiciled at the study site for the duration of the study (Day –1 to Day 31) versus subjects checking out 48 hours after each dose in each period.

Protocol Section	**Change**
Title page and Section 6.2.1.4 Reporting for Serious Adverse Events	PPD Medical Monitor information was updated.
Synopsis and Section 2.1 Primary Objective	Primary objective was updated to "The primary objective of this study is to evaluate potential drug-drug interaction as measured by the effect of coadministration of 4 separate phosphate binders on the PK of orally administered TPOXX in healthy adult subjects."
Synopsis and Section 3 Study Design and Methodology	Removed "check-in and" and updated treatment period to (Day –1 to Day 31). The study will consist of a screening period (Day -28 to Day –2), 5 ~~check in and~~ treatment periods (Day –1 to Day 31), an end-of-study visit (Day 36 [+2 days]), and a follow-up telephone call (Day 59 [+4 days]).
Synopsis and Section 3 Study Design and Methodology	Added "in Period 5 (Day 31)" In each period, subjects will report to the study site on Day –1 and remain confined to the study site until 48 hours after dosing **in Period 5 (Day 31).**
Synopsis and Section 4.2 Exclusion Criteria	"Day 1 of each period" was changed to "the first dose of study drug" in exclusion criteria 19 and 24
Section 4.3 Other Screening Considerations	Clarified that subjects will be confined to the study site until Day 31 (5 separate periods).
Section 5.2 Investigational Product	Reference to the prescribing information was added.
Section 6.1.1 Pharmacokinetic Sample Collection	Updated Alturas Analytics address and instructions for back-up samples.
Section 6.2.2 Clinical Laboratory Testing	• "on Day –1 of each period" was updated to "at check-in (Day –1)". • Removed serum pregnancy test and added a urine pregnancy test at Check-in on Day -1. • Added clarification that urine drug screen at Check-in on Day -1 will be performed and read locally and that blood alcohol will be tested using a breathalyzer device at the study site.

Section 8 Reference List	• Additional information for the TPOXX full prescribing reference was added. • Added reference for DAIDS grading and citation was added to Section 4.2.3 and Section 6.2.1.5. • Updated version, year, and page number of the tecovirimat IB.
Appendix 2 Schedule of Events Table 9-1	• "X" was removed from Day –1 for admission to clinic in treatment period 2 and 3. • Line for domiciled at clinic was added. • Discharge from clinic line and corresponding footnote (b) were removed. • "X" was removed from Day –1 for serum pregnancy test and urine drug/alcohol screen in treatment period 2 and 3. • Line for urine pregnancy was added. • "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" was added to the end of footnote (j).
Appendix 2 Schedule of Events Table 9-2	• Line for domiciled at clinic was added. • "X" was removed from Day 3 for discharge from the clinic in treatment period 4. • Line for serum pregnancy test and corresponding footnote (h) and urine drug/alcohol screen and corresponding footnote (i) were removed in treatment period 4 and 5. • Line for adverse events was added. Adverse events will be collected through Day 36 (end of study visit or early termination).
Throughout the protocol	Minor administrative changes were made.

SIGA Technologies, Inc.

Protocol: SIGA-246-023

A POSTMARKETING OPEN-LABEL, 5-PERIOD CROSSOVER, DRUG-DRUG INTERACTION STUDY OF ORALLY ADMINISTERED TPOXX® WHEN COADMINISTERED WITH 4 DIFFERENT PHOSPHATE BINDERS IN HEALTHY ADULT SUBJECTS

28JUN2023

Draft Statistical Analysis Plan

Version 2.0

Prepared by:

PPD
3900 Paramount Parkway
Morrisville, NC 27560 USA

Date: _____

Date: _____

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List of Abbreviations

AE	Adverse event
AUC	area under the curve
$AUC_{0\text{-}inf}$	area under the curve from time 0 extrapolated to infinity
AUC_t	area under the curve from time 0 to the last measurable observed concentration
BLQ	below the limit of quantification
BMI	body mass index
CI	confidence interval
CL/F	apparent total body clearance
C_{max}	maximum observed concentration
CSR	clinical study report
CTMS	Clinical Trial Management System
CV	coefficient of variation
DDI	drug-drug Interaction
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
FDA	Food and Drug Administration
g	grams
ICF	Informed Consent Form
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
PD	pharmacodynamic
PK	pharmacokinetic
PT	preferred term
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
$t_{1/2}$	apparent terminal elimination half-life
TLFs	tables, listings and figures
T_{max}	time of maximum observed concentration
V_z/F	apparent volume of distribution during the terminal phase

1. Introduction

A single dose of 600 mg (3 × 200 mg capsules) TPOXX was chosen as this is the recommended dose for TPOXX. Sevelamer carbonate, sucroferric oxyhydroxide, calcium acetate, and lanthanum carbonate were chosen for this study because they are common phosphate binders that patients prescribed TPOXX may be concurrently taking. The planned doses for each of these drugs were selected based on the FDA Guidance "Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications", which states the maximum dose and the shortest dosing interval should be used.[2] Any potential drug-drug interaction (DDI) will be determined based on an analysis of TPOXX PK in the presence of phosphate-binding drugs, compared to TPOXX PK in the absence of these phosphate binders. The planned doses of TPOXX and the 4 phosphate binders are expected to be sufficiently high to quantify an effect on TPOXX plasma exposure levels.

The purpose of this statistical analysis plan (SAP) is to define the planned statistical analysis of the study data consistent with the study objectives. This SAP is written based on Protocol: SIGA-246-023, version 2.0, dated 27 January 2022.

2. Study Objectives

2.1 Primary Objective

The primary objective of this study is to evaluate potential DDI as measured by the effect of coadministration of 4 separate phosphate binders on the PK of orally administered TPOXX in healthy adult subjects.

2.2 Secondary Objective

The secondary objective of this study is to evaluate the safety and tolerability of 600 mg oral TPOXX administered with 4 different phosphate binders in healthy adult subjects.

3. Study Design

This is a postmarketing, open-label, 5-period crossover drug interaction study designed to evaluate the potential effects of coadministration of 4 different phosphate binders on the PK of orally administered TPOXX in healthy adult subjects. A total of 44 subjects, ages 18 to 50, inclusive, will be enrolled and randomly assigned to 1 of 4 treatment sequences. The study will consist of a screening period (Day –28 to Day –2), 5 treatment periods (Day –1 to Day 31), an end-of-study visit (Day 36 [+2 days]), and a follow-up telephone call (Day 59 [+4 days]). The treatment sequences and periods will be as follows:

Treatment Sequence	Period 1 Treatment	Period 2 Treatment	Period 3 Treatment	Period 4 Treatment	Period 5 Treatment
ABCDE	A	B	C	D	E
ACEBD	A	C	E	B	D
ADBEC	A	D	B	E	C
AEDCB	A	E	D	C	B

- Treatment A: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX.
- Treatment B: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 1600 mg (2 × 800 mg tablets) sevelamer carbonate (Renvela® or generic equivalent).
- Treatment C: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 500 mg sucroferric oxyhydroxide (Velphoro®) chewable tablet.
- TPOXX + Calcium Acetate: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 1334 mg (2 × 667 mg capsules) calcium acetate (PhosLo® generic equivalent).
- Treatment E: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 500 mg lanthanum carbonate (Fosrenol® or generic equivalent) chewable tablet.

There will be a washout period of 7 days between dosing in each treatment period. All subjects will be provided a meal (consisting of approximately 600 calories and 25 g fat). The meal should be completed within 30 minutes. 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 study drug administration. Study drug and meals must be taken with water only, and no other beverage except water should be ingested within 3 hours before or 3 hours after study drug administration. Water is allowed at all times throughout the study. Subjects must refrain from taking food for 2 hours after taking study drug as further food consumption may affect drug absorption.

In each period, subjects will report to the study site on Day –1 and remain confined to the study site until 48 hours after dosing in Period 5 (Day 31). Subjects will be monitored for safety and tolerability. Serial blood samples for PK analysis of TPOXX will be collected before dosing (0 hour) and up to 48 hours after administration of the study drug(s).

All subjects will have a follow-up telephone call 30 days after administration of the last dose of study drug (Day 59 [+4 days]) to report any serious adverse events (SAEs). At the time of discharge from the clinical research unit, subjects will be instructed to notify the investigator of any SAEs that occur within 30 days after administration of the last dose of study drug. Serious AEs will be followed until the SAE is stable or until resolution as determined by the investigator and/or medical monitor.

The total duration of the study for each subject, including the screening period, treatment period, the Day 36 (+2 days) end-of-study visit, and the Day 59 (+4 days) follow-up telephone call, will be approximately 87 days.

Schedules of assessments can be found in Section 13.

4. General Statistical Considerations

All statistical analyses will be conducted using statistical analysis system SAS® Version 9.4 (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.

General study descriptors, as in subject disposition, demographics, protocol deviations, and enrollment characteristics, will be summarized for all randomized subjects, regardless of treatment sequence. Otherwise, safety outcomes, as in adverse events, lab values, vital signs, and electrocardiogram measures, will be summarized by treatment. The treatments below will be used for such presentation:

- TPOXX
- TPOXX + Sevelamer Carbonate
- TPOXX + Sucroferric Oxyhydroxide
- TPOXX + Calcium Acetate
- TPOXX + Lanthanum Carbonate

All data listings will be sorted by treatment and subject number.

No algorithm for imputation of missing data will be employed. Missing data will be treated as missing. If partial data exists for concomitant medications, the start dates will be imputed to the first of the month (for missing day) or first of the year (for missing day and month) for purposes of assigning a prior mediation flag.

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

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 day the subject checks in (Day -1) 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. Sample Size

The sample size (N = 44 [to allow at least 36 enrolled subjects to complete]) for this study is based on clinical and practical considerations and not on a formal statistical power calculation. The sample size is considered sufficient for the objectives of the study.

Prior estimates of within-subject variability (CVw) of a single dose of 600 mg TPOXX were obtained from Study SIGA-246-018, which evaluated the single-dose PK of TPOXX in a similar population. The CVw% for Cmax, AUC_{0-24} and AUC_{0-inf} ranged from 11.39% to 12.62%, 9.38% to 18.12%, and 15.70% to 18.02%, respectively.

For a sensitivity analysis, a range for CVw of 10%, 15%, and 20% across point estimates of 0.9, 1.0, and 1.1 will be explored. For the sensitivity analysis, assuming a range of CVw, a sample size of 36 evaluable subjects, it is estimated that the precision (ie, half-width of the 90% confidence interval [CI] on the log and ratio scale), and CI with tolerance probability of 80% on the original scale for each point estimate will be:

CVw (%)	Half-Width (log scale)	Half-Width (original scale)	Point Estimate	90% Confidence Interval
10	0.043	0.044	0.9	(0.862, 0.94)
			1.0	(0.958, 1.044)
			1.1	(1.054, 1.148)
15	0.065	0.067	0.9	(0.843, 0.96)
			1.0	(0.937, 1.067)
			1.1	(1.031, 1.174)
20	0.086	0.090	0.9	(0.826, 0.981)
			1.0	(0.918, 1.09)
			1.1	(1.009, 1.199)

4.2. Randomization, Stratification, and Blinding

PPD statistician will generate the randomization schedule. Eligible subjects who meet all inclusion and none of the exclusion criteria will be randomly assigned. Randomization numbers will be assigned before the first dose of investigational drug is administered at the Baseline Visit.

Eligible subjects will be randomly assigned to one of the 4 aforementioned sequences in 1:1:1:1 ratio based on the randomization schedule prepared before the study by PPD randomization statistician.

This is an open label study and no stratification will be used.

4.3. Analysis Population

The analysis populations are as follows:

- The PK Population will include subjects who receive at least 1 dose of TPOXX and have sufficient concentration data to support accurate estimation of at least 1 PK parameter.

- The Safety Population will include all subjects who receive any amount of study drug.

5. Subject Disposition

5.1 Disposition

The following will be summarized for the safety population, by treatment sequence and overall for all subjects:

- The number of subjects who received each treatment sequence
- 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 data will be presented in a data listing.

5.2 Protocol Deviations

Protocol deviations will be collected during monitoring visits. All protocol deviations are to be recorded in CTMS (Clinical Trial Management System) with the indication of whether these are important. These data will be listed including the assignment of not important or important. A *protocol deviation* is any change, divergence, or departure from the study design or procedures defined in the protocol. An *important protocol deviation* (sometimes referred to as a protocol violation or a major protocol deviation) is a subset of protocol deviations that might significantly affect the reliability of the study data or that might significantly affect a subject's safety.

Important protocol deviations will be summarized overall. All protocol deviations will be presented in a data listing, including the categorization of the deviation as important or not important.

5.3 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria deviations will be presented in a data listing.

5.4 Treatment Compliance

All doses of the study drugs will be administered in the study site under direct observation of study site personnel and recorded in the eCRF. Per standard clinic procedure, study site personnel will perform a mouth check and inspect all dose containers to ensure that the entire dose was administered. Following completion of dosing procedures and return of dosing containers to the pharmacy by team members, pharmacy staff will follow standard clinic procedures for study drug reconciliation. SIGA will provide information to PPD for destruction of returned used and unused TPOXX study drug and study drug bottles.

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

Treatment compliance, defined as the percentage of capsules consumed, will be summarized by treatment using statistics for continuous variables as well as presented in a listing.

6. Demographics and Baseline Characteristics

6.1 Demographics

Demographic information collected at screening will be presented in a data listing.
Descriptive statistics will be calculated for the following continuous demographic characteristics:

- Age (years)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2)

Frequency counts and percentages will be tabulated for the categorical variables:

- Sex
- Race
- Ethnicity

The summaries will be presented overall for the safety population.

6.2 Medical History

The medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version to be delineated in the clinical study report [CSR]) and presented in a data listing.

7. Treatments and Medications

7.1 Prior and Concomitant Medications

Medications taken within 30 days prior to the signing of the informed consent form (ICF) up until the first dose of study drug will be classified as prior medications. Medications that start on or after the first dose of study drug will be classified as concomitant.

If a prohibited concomitant medication listed in Section 4.2 of the protocol is taken, it will be documented as a protocol deviation and a joint decision will be made by the investigator and SIGA to continue or discontinue the subject based on the time the medication was administered, its pharmacology and PK, and whether the use of the medication will compromise the safety of the subject or the interpretation of the data.

The investigator is responsible for ensuring that details regarding the medication are adequately recorded in both the subject's source document and the eCRF.

All prior and concomitant medications will be coded according to the World Health Organization Drug Dictionary (version to be delineated in the CSR) and will be summarized by treatment.

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 study drug administration and drug accountability data as collected on eCRF will be presented in the data listings, including but not limited to the treatment sequence, time point and date, study dose, and reason for adjustment if any.

8. Pharmacokinetics

Individual TPOXX plasma concentration and time data will be presented in a data listing and individual plots based on the safety population, and all summaries and analyses of the PK data of TPOXX will be based on the PK population as defined in Section 4.3.

8.1 Data Handling

The following procedures will be used for plasma concentrations data of TPOXX below the lower limit of quantification (LLOQ) and missing values:

- Concentration values that are below limit of quantification (BLQ) will be reported as provided by the bioanalytical data in the PK data listings.
- For the calculation of concentration summary statistics, BLQ values will be replaced with zero at individual timepoints.
- If the mean concentration value is less than the lower limit of quantitation (LLOQ) value, then the mean concentration value will be set to BLQ in tables with other summary statistics reported as not applicable (NA) except for median, minimum and maximum, where BLQ were reported. The mean concentration plotted as zero in linear scale graphics and missing in semi-logarithmic scale graphics.
- For calculation of PK parameters, BLQ concentration values prior to the first measurable concentration will be set to zero. Post-dose BLQ values after the first quantifiable time point that are followed by measurable concentrations will be set to half the value of LLOQ. Post-dose BLQ value after first quantifiable time point that are not followed by measurable concentrations will be replaced by zero.
- Missing concentration values will not be imputed and will be excluded from the calculations.
- Default significant figures used for reporting in text, tables, and summary statistics of the study report is three significant figures, except for N (number of subjects in the group) and n (number of subjects in the group with reported data), where integer will be presented.

8.2 Pharmacokinetic Concentrations

Blood samples for PK analysis of TPOXX will be collected from all subjects at the following time points: within 60 minutes before dosing (0 hour) and at 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours after administration of study drug in each period.

For PK blood samples, the acceptable window for collection from the scheduled collection time point will be as follows: ±5 minutes for the time points from 0.5 through 8 hours and ±15 minutes for the time points from 12 through 48 hours.

Individual plasma concentration and time deviation data will be presented in a data listing. Plasma concentration data will be summarized by time point for each treatment using the

following descriptive statistics: number of subjects, arithmetic mean, SD, coefficient of variation (CV), geometric mean, geometric CV, geometric SD, minimum, median, and maximum.

Individual and mean plasma concentration versus scheduled time profiles will be presented in figures on both linear and semilogarithmic scales.

8.3 Plasma Pharmacokinetic Parameters

Plasma concentration-time data will be analyzed by non-compartmental analysis using Phoenix® WinNonlin® Version 8.3 (Certara USA, Inc., Princeton, NJ). The following plasma PK parameters will be calculated for TPOXX to the extent that data permit using actual sampling times rather than scheduled sampling times:

C_{max}	Maximum drug concentration in plasma
T_{max}	Time of maximum 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 up log down rule
AUC_{0-48}	AUC from time 0 to 48 hours, calculated using the linear up log down rule
AUC_{0-t}	AUC from time 0 to the last quantifiable concentration, calculated using the linear up log down rule
AUC_{0-inf}	AUC from time 0 extrapolated to infinity, calculated using the linear up log down rule

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:

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
$t_{1/2}$	Apparent terminal elimination half-life, calculated as: ln (2) / λ_z
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
λ_z lower	Lower bound used for the estimation of λ_z
λ_z upper	Upper bound used for the estimation of λ_z
Span	Number of elapsed half-lives over which λ_z is estimated, calculated as (λ_z upper – λ_z lower) / $t_{½}$
Rsq	r^2, the coefficient of determination (goodness of fit statistic); λ_z and all associated parameters will only be reported where $r^2 \geq 0.80$.

The individual PK parameters will be presented in data listings and summarized by treatment using the following descriptive statistics: number of subjects, mean, SD, CV, geometric mean, geometric SD, geometric CV, minimum, median, and maximum. T_{max} will be summarized using number of observations, median, minimum, and maximum only.

8.4 Pharmacokinetic Statistical Analysis

A linear mixed model with sequence, treatment, and period as fixed effects and subject within sequence as a random effect will be performed on the natural log-transformed values of AUCs (AUC_{0-24}, AUC_{0-48}, AUC_{0-t}, and AUC_{0-inf}) and C_{max} to assess the effect of phosphate binders on the PK of TPOXX. The geometric least square means and corresponding 90% CIs will be computed for AUCs and C_{max} of TPOXX + phosphate binder versus TPOXX alone by taking the anti-log of the least squares means from the linear mixed-effect model on the natural logarithms of the corresponding PK parameters. A 90% CI for the ratio will be constructed as the anti-log of the confidence limits of the mean difference. No adjustment will be made for multiplicity.

It will be concluded that there is no relevant interaction of phosphate binders on TPOXX if the 90% CIs for AUCs and C_{max} ratios (TPOXX + phosphate binder/TPOXX alone) are completely contained within the (80%, 125%) interval.

Non-parametric methods will be used to examine median differences in T_{max} for TPOXX.

The geometric mean ratios and corresponding 90% CIs for AUCs and C_{max} for TPOXX will be presented in forest plots for overall assessment of the DDI.

9. Safety Analysis

All safety summaries and analyses will be based upon the safety population.

9.1 Adverse Events

An AE is defined as any untoward medical occurrence, including those AEs that result from dosing errors, which may present during administration of a study drug or during a reasonable follow-up period and which does not necessarily have a causal relationship with the study drug(s). All AEs reported or observed from the first dose of study drug in Period 1 through the Day 36 End of Study Visit will be recorded on the AE page in the eCRF.

All AEs will be followed until the AE is resolved or stabilized as determined by the investigator and/or the medical monitor. Subjects will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A serious AE (SAE) is defined as any AE that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a congenital anomaly or birth defect, a persistent or significant incapacity or substantial disruption of the ability to conduct normal activities of daily living. 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. All SAEs reported or observed from the first dose of study drug in Period 1 through follow-up telephone call on Day 59 (+4 days) will be recorded on the AE page in the eCRF.

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.

The AE's relationship to study treatment will be evaluated by the investigator. The following relationships will be collected on eCRF: definitely related, probably related, possibly related, unlikely related, or not related.

The AEs that are evaluated as definitely, probably, or possibly related will be considered treatment-related AEs for summary purpose.

The severity of AEs will be classified by the investigator as mild, moderate, severe, life threatening, or death.

An overall AE summary will be generated presenting the frequency and percentage of subjects and the number of AEs for the following:

- Any AE
- Any treatment-related AE
- Any moderate AE
- Any treatment-related moderate AE
- Any treatment-related severe AE
- Any SAE
- Any treatment-related SAE
- Any AE leading to early discontinuation
- Any death

All AEs will be coded using MedDRA (version to be delineated in the CSR). The AEs will also be summarized by system organ class (SOC), preferred term (PT), by severity and relationship to study treatment.

The AE summary tables will be sorted by SOC and PT. System organ class will be displayed in descending order of overall frequency then alphabetically. Preferred term will be displayed in descending order of overall frequency and then alphabetically within SOC. A subject with 2 or more events within the same level of summarization will be counted only once in that level using the most severe incident or most related incident. Percentages will be based on the number of subjects in the safety population.

In summaries of AEs by treatment, AEs will be summarized according to the most recent treatment received prior to the AE onset. For example, an AE that occurred on or after

administration of the study drug on Day 1 of Period 1 but before the administration of study drug on Day 1 of Period 2 will be summarized for study drug administered in Period 1.
All AEs will be presented in a data listing. Separate data listings will be generated for treatment-related AEs, SAEs, and AEs leading to study discontinuation.

9.2 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 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, turbidity, 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 timepoints indicated in the schedule of assessments (schedules of assessments can be found in Section 13). Glycosylated hemoglobin A1c and a fasting lipid panel including cholesterol (total, high-density lipoprotein, calculated low-density lipoprotein, and triglycerides) will be performed at screening.

Note: All lab parameters will be graded according to the Division of Acquired Immune Deficiency Syndrome (DAIDS)[3] toxicity grading scale and will be adjusted according to local laboratory reference ranges.

Serum pregnancy test (β human chorionic gonadotropin) for women of childbearing potential will be performed at screening. A urine pregnancy test will be performed at check-in on Day –1. A positive urine pregnancy test will be verified with a follow-up serum pregnancy test.

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

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

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 population. 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. Abnormal laboratory values for hematology, serum chemistry and urinalysis, defined as any laboratory value with a toxicity grade of 1 or above, will be presented in a listing.

9.3 Vital Sign Measurements

Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature, and will be measured at the timepoints indicated in the schedule of assessments (schedules of assessments can be found in Section 13).

All vital sign, body weight, and height measurements will be presented in a data listing. The actual values and change from baseline values at each time point will be summarized for the safety population.

9.4 Physical Examination

A full physical examination will include, at minimum, assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. A brief physical examination will include, at minimum, assessment of skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Full physical examinations will be performed at Screening (Visit 1), and abbreviated physical examinations will be performed at the timepoints indicated in the schedule of assessments (schedules of assessments can be found in Section 13).

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

All physical examination results will be presented in a data listing.

9.5 Electrocardiograms

Single 12-lead ECGs will be obtained after the subject has been in the supine position for at least 10 minutes. A single repeat measurement is permitted at screening for eligibility determination. Electrocardiogram assessments will include comments on whether the tracings are normal or abnormal, rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST-segment, T-wave, and U-wave abnormalities.

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

Single 12-lead ECG will be performed at the timepoints indicated in the schedule of assessments (schedules of assessments can be found in Section 13).

Actual values at baseline for numeric ECG data will be summarized by visit and treatment for subjects in the safety population.

All ECG data will be presented in a data listing.

10. Interim Analysis

No formal interim analyses will be performed in this study.

11. Changes in the Planned Analysis

Any changes from this statistical analysis plan will be documented in the CSR for this study.

12. References

1. Breman JG, Henderson DA. Diagnosis and management of smallpox. N Engl J Med. 2002;346(17):1300-8.
2. Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research, Center for Drug Evaluation and Research. Guidance for Industry: Clinical Drug Interaction Studies—Cytochrome P450 Enzyme-and Transporter-Mediated Dug Interactions. January 2020 [cited 24 Jan 2022]. Available from: https://www.fda.gov/media/134581/download.
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.

13. Schedule of Events

Schedule of Events: Period 1 through Period 3

Procedure[a] / Phase	Screening	Check-in	Treatment Period 1						Treatment Period 2							Treatment Period 3						
Day	–28 to –2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Day									–1	1	2	3	4	5	6	–1	1	2	3	4	5	6
Admission to clinic		X																				
Domiciled at clinic			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Informed consent	X																					
Inclusion/exclusion criteria	X	X																				
Medical history[b]	X	X																				
Physical examination[c]	X	X																				
Demographics	X																					
Height and weight	X																					
Vital sign measurements[d]	X	X	X	X	X				X	X	X	X				X	X	X	X			
Glycosylated hemoglobin (HbA1c)	X																					
Fasting lipid panel[e]	X																					
Clinical laboratory testing[f]	X[g]	X		X					X		X					X		X				
Serum follicle-stimulating hormone[h]	X																					
Serum pregnancy test[i]	X																					
Urine pregnancy test[i]		X																				
Urine drug/alcohol screen[j]	X	X																				
Serology (HBsAg, HCV, and HIV)	X																					
Randomization[j]		X																				
12-lead electrocardiogram[l]	X	X	X							X							X					
Administration of study drug(s)[m]			X							X							X					
Pharmacokinetic sample collection[n]			X	X	X					X	X	X					X	X	X			
Adverse events			◄——— X ———►																			
Prior/concomitant medications	◄——— X ———►																					

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

Notes:

(a) When procedures overlapped or occurred at the same time point, all blood draws followed vital signs or ECGs, and PK sampling was timed to occur last and as close to the scheduled time window as possible.

(b) Medical history included a review of systems; recreational, prescription, and over-the-counter drug use; nicotine and alcohol use; and past hospitalizations.

(c) A full physical examination included, 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). Symptom-directed physical examination included an assessment of the heart, lungs, abdomen, a neurologic review, and a review of symptoms for assessment and/or follow-up of reported or potential adverse events.

(d) Vital sign measurements included systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. Vital signs were measured at screening, and in each period, on Day –1; within 60 minutes prior to dosing; and at 4, 8, 12, 24, and 48 hours following dosing in each period after the subject has been in a seated position for at least 5 minutes.

(e) Fasting lipid panel included cholesterol (total, high-density lipoprotein, calculated low-density lipoprotein, and triglycerides).

(f) Clinical laboratory testing included hematology and serum chemistry.

(g) Clinical laboratory testing at screening included hematology, serum chemistry, and urinalysis.

(h) For postmenopausal women, a serum follicle-stimulating hormone test was performed at screening.

(i) Women of childbearing potential only.

(j) Included 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 was collected and sent to the central laboratory at the screening visit. A urine drug screen and alcohol breath test using a breathalyzer was performed and read locally on Day –1.

(k) Randomization occurred according to the randomization schedule before study drug administration on Day 1 of Period 1 after it has been confirmed that the subject fulfilled all eligibility criteria. Subjects were randomly assigned to receive study drug in 1 of 4 treatment sequences (ABCDE, ACEBD, ADBEC, and AEDCB) in 1:1:1:1 ratio.

(l) A single 12-lead ECG was obtained after the subject had been in the supine position for at least 10 minutes. On Day 1 of each period, an ECG was recorded 4 hours after study drug administration. The acceptable window for collection from the scheduled collection time point was ±15 minutes.

(m) All subjects were provided a meal (consisting of approximately 600 calories and 25 g fat). The meal was completed within 30 minutes. Subjects were administered study drug(s) as soon as possible following completion of the meal but no more than 30 minutes elapsed between meal completion and study drug administration. Study drug and meals were taken with water only, and no other beverage except water was ingested within 3 hours before or 3 hours after study drug administration. Subjects fasted for 2 hours after taking study drug. The time of study drug dosing was called “0” hour in each period.
Treatment A: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX.
Treatment B: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 1600 mg (2 × 800 mg tablets) sevelamer carbonate (Renvela® or generic equivalent).
Treatment C: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 500 mg sucroferric oxyhydroxide (Velphoro®) chewable tablet.

TPOXX + Calcium Acetate: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 1334 mg (2 × 667 mg capsules) calcium acetate (PhosLo® generic equivalent).
Treatment E: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 500 mg lanthanum carbonate (Fosrenol® or generic equivalent) chewable tablet.

(n) Blood samples for PK analysis of TPOXX were collected from all subjects at the following time points: within 60 minutes before dosing (0 hour) and at 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours after administration of study drug in each period. For PK blood samples, the acceptable window for collection from the scheduled collection time point was as follows: ±5 minutes for the time points from 0.5 through 8 hours and ±15 minutes for the time points from 12 through 48 hours.

Schedule of Events: Period 4 and Period 5

Phase	Treatment Period 4							Treatment Period 5				End of Study Visit or Early Termination[b]	Follow-up Telephone Call[c]
Procedure[0] **Day**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**36 (+2)**	**59 (+4)**
Day	**–1**	**1**	**2**	**3**	**4**	**5**	**6**	**–1**	**1**	**2**	**3**		
Domiciled at clinic	X	X	X	X	X	X	X	X	X	X			
Discharge from clinic											X		
Outpatient visit												X	X
Physical examination[d]												X	
Vital sign measurements[e]	X	X	X	X				X	X	X	X	X	
Clinical laboratory testing[f]	X		X					X		X		X[g]	
12-lead electrocardiogram[h]		X							X			X	
Administration of study drug(s)[i]		X							X				
Pharmacokinetic sample collection[Error! Reference source not found.]		X	X	X					X	X	X		
Adverse events	←							X				→	
Serious adverse events	←							X					→
Prior/concomitant medications	←							X					→

Abbreviations: ECG, electrocardiogram; PK, pharmacokinetic.

Notes:

[a] When procedures overlapped or occurred at the same time point, all blood draws followed vital signs or ECGs, and PK sampling was timed to occur last and as close to the scheduled time window as possible.

[b] The end-of-study visit occurred 7 days after the last dose of study drug.

[c] The follow-up telephone call was made 30 days after the last dose of study drug (Day 59 [+4 days]). Discharge followed all safety assessments and PK sample collections.

[d] Symptom-directed physical examination included an assessment of the heart, lungs, abdomen, a neurologic review, and a review of symptoms for assessment and/or follow-up of reported or potential adverse events.

[e] Vital sign measurements included systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. Vital signs were measured after the subject has been seated for at least 5 minutes. Vital signs were measured at screening, and in each period, vital sign measurements were measured at check-in; within 60 minutes prior to dosing; and at 4, 8, 12, 24, and 48 hours after the study drug administration.

[f] Clinical laboratory testing included hematology and serum chemistry.

[g] Clinical laboratory testing at end of study or early discontinuation included hematology, serum chemistry, and urinalysis.

[h] A single 12-lead ECG was collected after the subject had been in the supine position for at least 10 minutes. In each period, an ECG was recorded 4 hours after the study drug administration. The acceptable window for collection from the scheduled collection time point was ±15 minutes.

(i) All subjects were provided a meal (consisting of approximately 600 calories and 25 g fat). The meal was completed within 30 minutes. Subjects were administered study drug(s) as soon as possible following completion of the meal but no more than 30 minutes elapsed between meal completion and study drug administration. Study drug and meals were taken with water only, and no other beverage except water was ingested within 3 hours before or 3 hours after study drug administration. Subjects fasted for 2 hours after taking study drug. The time of study drug dosing was called "0" hour in each period.
Treatment A: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX.
Treatment B: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 1600 mg (2 × 800 mg tablets) sevelamer carbonate (Renvela® or generic equivalent).
Treatment C: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 500 mg sucroferric oxyhydroxide (Velphoro®) chewable tablet.
TPOXX + Calcium Acetate: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 1334 mg (2 × 667 mg capsules) calcium acetate (PhosLo® generic equivalent).
Treatment E: A single oral dose of 600 mg (3 × 200 mg capsules) TPOXX coadministered with a single oral dose of 500 mg lanthanum carbonate (Fosrenol® or generic equivalent) chewable tablet.

(j) Blood samples for PK analysis of TPOXX was collected from all subjects at the following time points: within 60 minutes before dosing (0 hour) and at 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours after administration of study drug in each period. For PK blood samples, the acceptable window for collection from the scheduled collection time point was as follows: ±5 minutes for the time points from 0.5 through 8 hours and ±15 minutes for the time points from 12 through 48 hours.

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16. Appendix

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Albumin, Low (g/dL; g/L)	3.0 to < LLN 30 to < LLN	⩾ 2.0 to < 3.0 ⩾ 20 to < 30	⩾ 2.0 to < 3.0 ⩾ 20 to < 30	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
ALT or SGPT, High *Report only one	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
AST or SGOT, High *Report only one	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
Bilirubin				
Direct Bilirubin[1], High > 28 days of age	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	ULN with lifethreatening consequences (e.g., signs and symptoms of liver failure)
Total Bilirubin[1], High > 28 days of age	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	⩾ 5.0 x 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
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

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
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
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
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
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	⩾ 20 x ULN
Creatinine, High *Report only one	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	⩾ 3.5 x ULN OR Increase of ⩾ 2.0 x participant's baseline
Creatinine Clearance [2] **or eGFR, Low** *Report only one	NA	< 90 to 60 ml/min or ml/min/1.73 m2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m2 OR ⩾ 50% decrease from participant's baseline or dialysis needed
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

Hemoglobin[3], Low (g/dL; mmol/L) [17] ⩾ 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
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
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
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
Urate (umol/L), High (umol/L; µmol/L)	>1 x ULN >1 x ULN	NA	NA	NA
Eosinophils (10^9/L; /mm3)	>1 x ULN >1 x baseval	NA	NA	NA
Hemoglobin[3], Low (g/dL; mmol/L) [4] ⩾ 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

Absolute Lymphocyte Count, Low (cell/mm3; cells/L) > 5 years of age (not HIV infected)	600 to < 650 0.600 x 109 to < 0.650 x 109	500 to < 600 0.500 x 109 to < 0.600 x 109	350 to < 500 0.350 x 109 to < 0.500 x 109	< 350 < 0.350 x 109
Absolute Neutrophil Count (ANC), Low (cells/mm3; cells/L) > 7 days of age	800 to 1,000 0.800 x 109 to 1.000 x 109	600 to 799 0.600 x 109 to 0.799 x 109	400 to 599 0.400 x 109 to 0.599 x 109	< 400 < 0.400 x 109
Neutrophils/Leukocytes (%)				
Platelets, Decreased (cells/mm3; cells/L)	100,000 to < 125,000 100.000 x 109 to < 125.000 x 109	50,000 to < 100,000 50.000 x 109 to < 100.000 x 109	25,000 to < 50,000 25.000 x 109 to < 50.000 x 109	< 25,000 < 25.000 x 109
Leukocytes, white blood cell decreased (10^9/L; /mm3)	<LLN - 3.0 x 10^9 /L <LLN - 3000/mm3	<3.0 - 2.0 x 10^9 /L <3000 - 2000/mm3	<2.0 - 1.0 x 10^9 /L <2000 - 1000/mm3	<1.0 x 10^9 /L <1000/mm3
Leukocytes, Leukocytosis (10^9/L; /mm3)	NA	NA	>100 x 10^9/L >100000/mm3	NA
Urobilinogen (umol/dL)				

[1] 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.
[2] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.
[3] 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).
[4] 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.