Combined Cross-Discipline Team Leader, Clinical, Clinical Pharmacology, and Division Director Review

Date	May 4, 2022
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Subject	Combined Cross-Discipline Team Leader, Clinical, Clinical Pharmacology, and Division Director Review
Application Type	New Drug Application (NDA)
NDA/BLA # and Supplement#	214518
Applicant	SIGA Technologies, Inc.
Date of Submission	April 30, 2021
PDUFA Goal Date	May 28, 2022
Proprietary Name	TPOXX®
Established or Proper Name	Tecovirimat
Dosage Form(s)	10 mg/mL injection
Applicant Proposed Indication(s)/Population(s)	Treatment of human smallpox disease caused by variola virus in adults and pediatric patients
Applicant Proposed Dosing Regimen(s)	Weight-based dosing (b) (4)  Patients weighing at least 13 kg should be switched to TPOXX Capsules to complete the 14 day treatment course as soon as oral therapy can be tolerated
Recommendation on Regulatory Action	Approval

<table>
<tr><td>Recommended Indication(s)/Population(s)</td><td>Treatment of human smallpox disease caused by variola virus in adults and pediatric patients weighing at least 3 kg</td></tr>
<tr><td>Recommended Dosing Regimen</td><td>Weight-based dosing
<table>
<tr><td>Body Weight</td><td>IV Tecovirimat Dosing</td></tr>
<tr><td>3 kg to less than 35 kg</td><td>6 mg/kg every 12 hours via 6-hour infusion</td></tr>
<tr><td>35 kg to less than 120 kg</td><td>200 mg every 12 hours via 6-hour infusion</td></tr>
<tr><td>120 kg and above</td><td>300 mg every 12 hours via 6-hour infusion</td></tr>
</table>
Patients weighing at least 13 kg should be switched to TPOXX Capsules to complete the 14 day treatment course as soon as oral therapy can be tolerated</td></tr>
<tr><td>Cross-Reference</td><td>NDA 208627 supplemental S-007 (letter date: April 18, 2022)</td></tr>
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1. Benefit-Risk Assessment

The Agency's benefit-risk assessment is summarized below.

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Smallpox is a serious and life-threatening disease caused by infection with variola virus, an orthopoxvirus. Historic mortality in variola major, the more common and serious form of smallpox, has been commonly cited at 30%. As a result of an intense global vaccination campaign, the disease was declared eradicated from the world in 1980. However, smallpox remains a high risk to national security and public health due to the bio-threat potential of variola virus. As routine smallpox vaccination in the U.S. ended in the 1970s, most of the U.S. population is susceptible to smallpox. Therefore, medical countermeasures, including antiviral therapies, are critically needed in the event of a smallpox outbreak. Tecovirimat was developed by the Applicant, SIGA Technologies, Inc., for the treatment of human smallpox.

The development of antiviral drugs for smallpox presents significant challenges. Because smallpox is a potentially serious and life-threatening disease but does not occur naturally, clinical efficacy trials are not feasible, and human challenge studies in healthy subjects are unethical. Therefore, tecovirimat was developed under the Animal Rule (21 CFR part 314, subpart I), which supports a regulatory approval pathway in which studies using suitable animal models contribute directly to drug approval.

The approval of oral tecovirimat in July 2018 constituted the first FDA-approved antiviral drug for smallpox. Oral tecovirimat is indicated for the treatment of adults and pediatric patients weighing at least 13 kg. Dosing recommendations for the oral formulation are constrained by the absence of an approved pediatric formulation of tecovirimat.

Based on the clinical data submitted in support of this New Drug Application (NDA) for an intravenous (IV) formulation of tecovirimat, the proposed dosage for IV tecovirimat achieves exposures within the desired target range for safety and efficacy.

IV tecovirimat has an acceptable safety profile for the indicated patient population. The major safety issue identified with IV tecovirimat was related to the potential for hydroxypropyl-β-cyclodextrin (HP-β-CD) accumulation, particularly in patients with renal impairment as well as in pediatric patients less than 2 years (due to renal immaturity in this pediatric age range). The following key steps were taken by the multidisciplinary review team and are reflected in labeling:

- The review team conducted modeling and simulation analyses and recommended an alternative dosing regimen to reduce the HP-β-CD amount in low body weight pediatric patients. The recommended dosing regimen also provides the benefit of a simplified dosing regimen with fewer body weight tiers.
- A Contraindication will provide wording that clearly describes the excipient HP-β-CD is eliminated through glomerular filtration and, therefore, IV tecovirimat is contraindicated in patients with severe renal impairment (defined as creatinine clearance below 30 mL/min).
- The Warnings and Precautions section will provide wording that clearly describes the risks of HP-β-CD accumulation in patients with renal insufficiency (mild, moderate, or severe) and in pediatric patients less than 2 years of age, and outlines risk mitigation strategies for health care providers to consider.

• Given the potential for HP-β-CD accumulation, labeling will outline that creatinine clearance should be determined in all patients prior to starting IV tecovirimat and monitored while receiving IV tecovirimat as clinically appropriate.
• Given the potential for drug accumulation due to renal immaturity in pediatric patients less than 2 years, monitoring of renal function after treatment is also recommended.

Most adverse events (AEs) were mild in severity. Infusion site pain, infusion site swelling, infusion site erythema, and infusion site extravasation occurred at similar or lower rates in the IV tecovirimat group compared to placebo.

The overall benefit-risk assessment of tecovirimat is favorable for the treatment of smallpox disease. The IV formulation allows for the administration of tecovirimat in adults and pediatric patients who are unable to take oral tecovirimat; it also extends the dosing down to pediatric patients weighing at least 3 kg.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Smallpox is a disease caused by infection with variola virus. The historic mortality rate for variola major, the more common and serious form of smallpox, was variable but commonly cited at 30%. • Because of an intense global vaccination campaign, no cases of human smallpox have occurred since 1978, and the disease was declared eradicated from the world in 1980. Routine smallpox vaccination in the U.S. ended in the 1970s. • Despite the eradication of naturally acquired smallpox, variola virus is categorized by the National Institute of Allergy and Infectious Diseases (NIAID) as a Category A priority pathogen.	Smallpox is a serious and life-threatening disease. Most of the U.S. population is immunologically susceptible to smallpox. Smallpox remains a high risk to national security and public health due to its bio-threat potential.
Current Treatment Options	• Currently there are two approved antiviral treatment regimens for patients with human smallpox disease caused by variola virus: o Tecovirimat (capsules), for adults and pediatric patients weighing at least 13 kg [approved in July 2018] o Brincidofovir (tablets; suspension), for adults and pediatric patients, including neonates [approved in June 2021] • No approved intravenous (IV) formulations are currently available.	Due to concerns regarding potential biothreat uses of variola virus, the availability of an alternative formulation for adults and pediatric patients who are unable to take oral treatment options for smallpox would be beneficial.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Tecovirimat was developed under the Animal Rule which supports a regulatory approval pathway in which studies using suitable animal models contribute directly to drug approval. • To support the original NDA approval of oral tecovirimat, the Applicant conducted pivotal efficacy studies of tecovirimat using two well-characterized, lethal animal models of non-variola, surrogate orthopoxviruses: non-human primates infected with monkeypox virus and rabbits infected with rabbitpox virus. • In this application, the proposed dosage for IV tecovirimat achieves exposures within the desired target range for safety and efficacy.	Because smallpox is a serious and life-threatening disease but does not occur naturally, clinical efficacy trials are not feasible, and human challenge studies in healthy subjects are unethical. Treatment efficacy was demonstrated using two lethal animal models of non-variola orthopoxvirus infection with disease characteristics relevant to human smallpox. This application provides the first approved IV formulation of an antiviral for treatment of smallpox. The IV formulation of tecovirimat extends the dosing down to pediatric patients weighing at least 3 kg. Of note, pediatric patients weighing 3 kg to < 13 kg would have to use the IV formulation for the entire 14-day treatment duration, due to the absence of an approved oral pediatric formulation of tecovirimat.
Risk and Risk Management	• The major risks associated with IV tecovirimat were related to the potential for hydroxypropyl-β-cyclodextrin (HP-β-CD) accumulation: o A Contraindication will be included to describe that the excipient HP-β-CD is eliminated through glomerular filtration and, therefore, IV tecovirimat is contraindicated in patients with severe renal impairment (defined as creatinine clearance below 30 mL/min). o Section 5 will include a warning to describe the risks of HP-β-CD accumulation in patients with renal insufficiency (mild, moderate, or severe) and in pediatric patients less than 2	IV tecovirimat has an acceptable safety profile for the indicated patient population. The major safety signal identified was the potential for HP-β-CD accumulation, particularly in patients with renal impairment as well as in pediatric patients less than 2 years (due to renal immaturity in this pediatric age range). Safety concerns associated with IV tecovirimat will be adequately addressed in product labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	years of age, and outline risk mitigation strategies for health care providers to consider. ○ Given the potential for HP-β-CD accumulation, the label will outline that creatinine clearance should be determined in all patients prior to starting IV tecovirimat and monitored while receiving IV tecovirimat as clinically appropriate. ○ Given the potential for drug accumulation due to renal immaturity in pediatric patients less than 2 years, monitoring of renal function after treatment is also recommended. ○ Label will also clarify that patients weighing at least 13 kg should be switched to TPOXX Capsules to complete the 14 day treatment course as soon as oral therapy can be tolerated. • Most adverse events (AEs) were mild in severity. • Infusion site pain, infusion site swelling, and infusion site erythema were the most common adverse drug reactions (ADRs) and occurred at similar or lower rates with IV tecovirimat compared to placebo. • Headache occurred at higher rates with IV tecovirimat compared to placebo.	

2. Background

Smallpox is caused by infection with variola virus, a member of the orthopoxvirus genus of viruses. Historic mortality in variola major, the more common and serious form of smallpox, was commonly cited at 30% but reported to vary widely among outbreaks, ranging from 5% to 40% or higher.(1)

Because of an intense global vaccination campaign, no cases of human smallpox have occurred since 1978, and the disease was declared eradicated from the world in 1980. Despite the eradication of naturally acquired smallpox, variola virus is categorized by the NIAID as a Category A priority pathogen.(2) Category A pathogens are those organisms/biological agents that pose the highest risk to national security and public health. Due to the discontinuation of routine vaccination in the U.S. in the 1970s, most of the U.S. population is now immunologically susceptible to smallpox. Therefore, medical countermeasures, including antiviral therapies, could be of critical importance in the event of a variola (smallpox) virus outbreak.

Because smallpox is a serious and life-threatening disease but does not occur naturally, clinical efficacy trials are not feasible, and human challenge studies in healthy subjects are unethical. Therefore, tecovirimat was developed under the Animal Rule (21 CFR part 314, subpart I), which supports a regulatory approval pathway in which studies using suitable animal models contribute directly to drug approval.(3)

The original Investigational New Drug Application (IND 69,019) for tecovirimat was submitted in 2005. Milestone regulatory events included the granting of Fast Track designation in 2005 (for the oral formulation) and for the intravenous (IV) formulation under IND 111,390 in 2012, Orphan Drug designation in 2006, an FDA Public Workshop in 2009, an Antiviral Drugs Advisory Committee meeting in 2011, and an Antiviral Drugs Advisory Committee meeting in 2018 during the original NDA review (NDA 208,627).(4-6) From the time of the IND submission, the Agency has worked closely with the Applicant to guide tecovirimat's development program.

Tecovirimat is an antiviral agent that interferes with critical steps in the replication cycle of variola virus. Approved in July 2018 under the Animal Rule, oral tecovirimat was the first FDA-approved antiviral drug for smallpox and was indicated for the treatment of adults and pediatric patients weighing at least 13 kg.(7) The 13 kg cut-off is due to the absence of an approved pediatric formulation of tecovirimat. The current NDA, submitted by SIGA on April 30, 2021, contains information to support the approval of an IV formulation of TPOXX® (tecovirimat) for the treatment of human smallpox disease caused by variola virus. The IV formulation

allows for the administration of tecovirimat in adults and pediatric patients who are unable to take oral tecovirimat; it also extends the dosing down to pediatric patients weighing at least 3 kg. This document presents the major findings and key issues of this review.

3. Product Quality

The Product Quality review team recommends approval of this NDA based on their review of the submitted data. Please refer to the Product Quality reviews for additional details. There are no unresolved product quality issues.

4. Nonclinical Pharmacology/Toxicology

Drs. David McMillan and L. Peyton Myers recommended approval of this NDA based on their review of the nonclinical safety information provided in the submission. Repeat-dose general toxicology studies were conducted in mice, rats, dogs, and monkeys. No adverse drug-related findings were noted in the 3-month studies in mice and monkeys at the highest exposure doses (exposures were 24 and 2.7 fold the human exposure, respectively). In the 12-day rat study findings were limited to the decreased body weight, food consumption, and mild liver toxicity consisting of increased liver weights in all treated animals, elevated bilirubin in the two highest dose groups and liver discoloration in the highest dose group. In two non-GLP 7-day toxicology studies in beagle dogs, neurotoxicity consisting of convulsions (tonic and clonic), tremors, ataxia, stereotypic walk, excessive blinking, face-twitching and jerky head movements were observed at an exposure multiple of 2.6 times that human dose. The exposure in dogs that led to neurotoxicity was considered in selecting the human dose in order to avoid human exposures at levels that were associated with neurotoxicity in dogs. Please refer to the Pharmacology/Toxicology review for additional details.

5. Clinical Pharmacology

As noted before, an oral tecovirimat capsule is approved by the FDA for the treatment of smallpox in adults and pediatric patients weighing ≥ 13 kg under NDA 208627. Clinical pharmacology information on tecovirimat's absorption, distribution, metabolism, and excretion (ADME) properties following oral administration; drug-drug interaction potential; and therapeutic individualization were assessed and summarized in the clinical pharmacology reviews of submissions under NDA 208627. In this submission, the Applicant proposes a new IV formulation for the same indication in adults and pediatric patients weighing ≥ 3 kg. In support of the proposed IV tecovirimat treatment, the Applicant has submitted clinical pharmacology study reports of two Phase 1 clinical studies that evaluated the IV tecovirimat formulation in healthy subjects: Study SIGA-246-IV-202 (Single dose comparative bioavailability (200 mg IV vs. 600 mg oral) and multiple dose PK study (240 mg IV BID for 7 days) and Study SIGA-246-IV-201 (Single ascending dose PK study, dose range: 37.5 -200 mg). In addition, population PK analyses reports have been submitted in support of the proposed tecovirimat IV

treatment. The selected key PK information for tecovirimat is summarized in Table 1 and detailed summary of these two studies and population PK analyses are provided in Appendix 2. Of note, the estimated absolute bioavailability following oral administration is 48% based on dose normalized AUC values following a single dose of 200 mg tecovirimat by IV infusion over 6 hours and a single dose of 600 mg tecovirimat orally (3 × 200-mg capsules) within 30 minutes after a meal consisting approximately 600 calories and 25 g fat. However, dose level was identified as a significant covariate on tecovirimat CL. See Section 3.3 Pharmacometrics Review for details.

Table 1. Pharmacokinetic Properties of Tecovirimat IV Injection

Drug exposure at steady state following 200 mg tecovirimat by 6-hr IV infusion every 12 hrs	Parameter	Geometric Mean (CV%)[a]
	$AUC_{0\text{-}24}$ (hour*ng/mL)	39405 (22.9)
	C_{max} (ng/mL)	2630 (21.5)
	C_{min} (ng/mL)	747 (29.3)
	T_{max} (hr)	6 (6-6.5)[b]
Distribution		
% Bound to human plasma proteins	77-82	
Blood-to-plasma ratio (drug or drug-related materials)	0.62-0.90	
Volume of distribution (Vz, L) (CV%)	383 (46%)[a]	
Metabolism		
Metabolic pathways[c]	Hydrolysis, UGT1A1d, UGT1A4	
Elimination		
Major route of elimination	Metabolism	
Clearance (CL, L/hr) (CV%)	13 (23%)[a]	
$t_{½}$ (h)[e] (CV%)	21 (45%)	

[a]Estimates from Study SIGA-246-IV-202 (n=22)
[b]For Tmax, median and range is reported
[c]Tecovirimat is metabolized by hydrolysis of the amide bond and glucuronidation. The following inactive metabolites were detected in plasma: M4, M5, and TFMBA (4 (trifluoromethyl) benzoic acid)
[d]Uridine diphosphate (UDP)-glucuronosyl transferase (UGT) enzymes
[e]$t_{½}$ value refers to mean terminal plasma half-life.

Of note, the Day 1 and steady-state tecovirimat exposures (i.e., AUC and Cmax estimates) reported in Study SIGA-246-IV-202 following 200 mg tecovirimat by IV infusion over 6 hours every 12 hours were observed to be 27-40% higher (Table 13) than the exposures reported previously from Study SIGA-246-008 that evaluated the currently approved tecovirimat oral dosing regimen (600 mg BID dosing regimen under fed conditions, Data source: previous clinical pharmacology review

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/208627Orig1s000ClinPharmR.pdf.). Such a difference was not observed in Day 1 exposures in Study SIGA-246-IV-202 (Figure 7). The rationale for this observation is not clear. See details in Appendix 2. Further comparison of tecovirimat exposures was pursued using simulations between the FDA recommended tecovirimat IV dosing regimen and the currently approved oral dosing regimen. See Section 5.1 for additional details.

5.1. Dosing and Therapeutic Individualization

Based on the collective findings from the abovementioned two Phase 1 studies and population PK modeling and simulation analyses, the Applicant proposed IV tecovirimat dosing regimen as noted in Table 2 for adults and pediatrics weighing ≥ 3 kg. The review team reviewed the submitted findings and performed independent analyses to evaluate the Applicant proposed dosing regimen. The review team's approach in evaluating the Applicant's proposed dosing regimen focused on the following two review questions:

1. Is the Applicant's proposed IV dosing regimen expected to be effective?
   - Approach: The simulated human tecovirimat exposures following proposed IV dosing regimen were compared to the exposures reported in pivotal non-human primate (NHP) efficacy studies following two effective dosing regimens: 3 mg/kg/day and 10 mg/kg/day.
2. Can the potential risk of hydroxypropyl-β-cyclodextrin (HP-β-CD) accumulation be reduced in pediatric patients with low body weight?
   - Approach: Each 20 ml vial of the proposed tecovirimat IV solution (10 mg/mL of tecovirimat) contains 40% HP-β-CD (8 g per vial), i.e., 40 mg HP-β-CD per 1 mg of tecovirimat dose. With the proposed dosing (Table 2), the HP-β-CD amounts for patients [redacted] (b) (4) (Table 2). These doses are higher than the amount in any FDA approved IV drug products for adults or pediatrics. Given that HP-β-CD exposures are associated with renal toxicities, the review team explored alternative weight-based dosing regimens as discussed below.

Table 2. The Applicant Proposed Pediatric and Adult Tecovirimat Dosage for IV Infusion

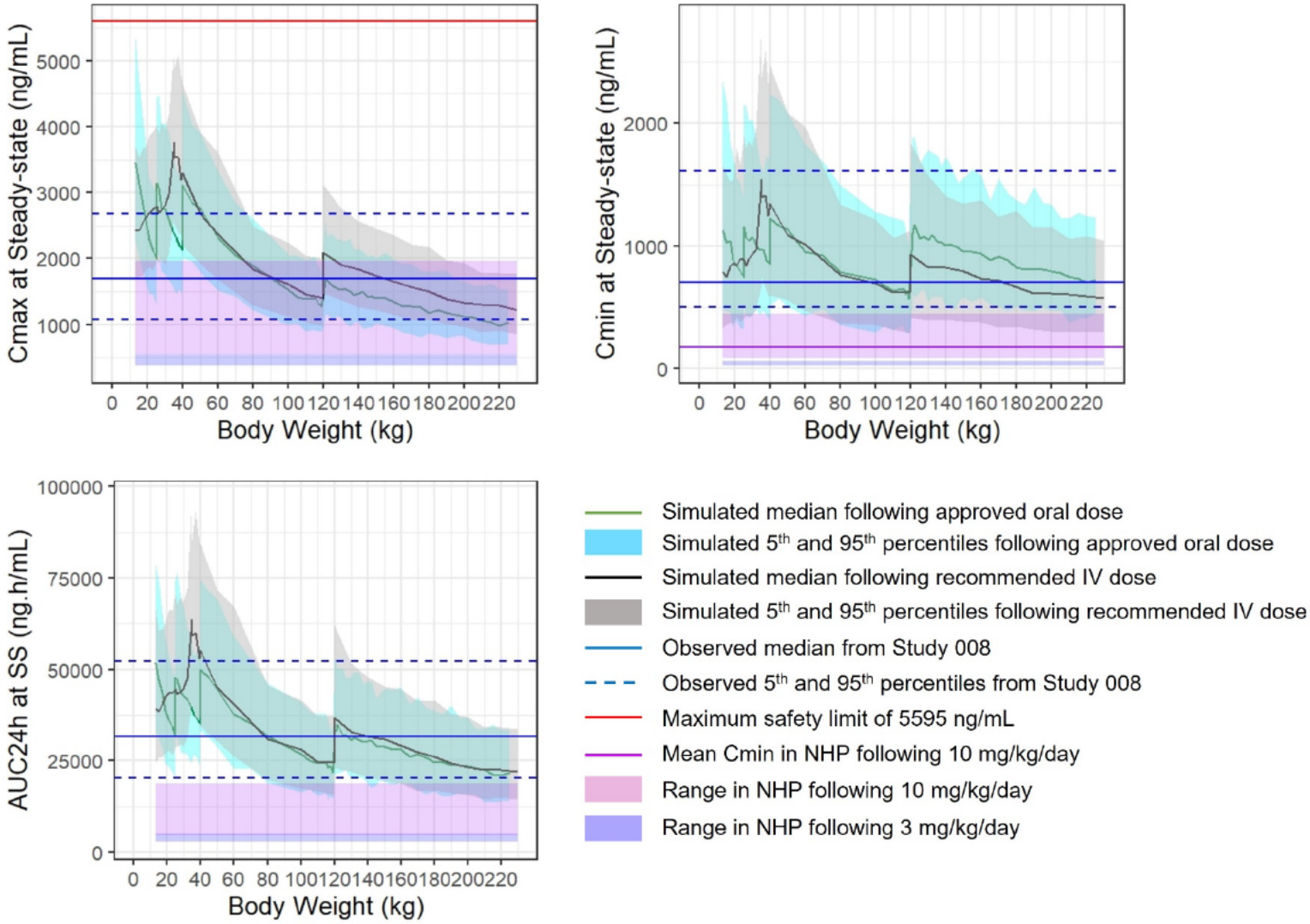
[redacted] (b) (4)

The review team performed additional modeling and simulation analyses (Refer to details in Appendix 2, Section 3.3 Pharmacometrics Review for details) and recommended a weight-based dosing regimen with a reduced number of weight bands as noted in Table 3. With the review team's proposed dosing regimen, tecovirimat exposures are expected to remain above or comparable to NHP exposures associated with survival (Figure 1), while reducing the maximum HP-β-CD dose amounts to 240 mg/kg unit dose and 480 mg/kg daily dose (Table 3). In addition, FDA proposed tecovirimat IV dosing regimen is expected to provide exposures that largely overlapped with exposures following the approved oral treatment. The revised dosing regimen and need for additional safety monitoring in labeling recommendations related to the potential HP-β-CD accumulation were discussed internally with the multidisciplinary review teams including the Office of Pediatric Therapeutics (OPT). See Section 8 for complete details. The revised dosing regimen and the safety monitoring recommendations were conveyed to the Applicant and the Applicant agreed.

Table 3. FDA Recommended Pediatric and Adult Tecovirimat Dosage for IV Infusion

Body Weight	Tecovirimat Dosage for up to 14 days	HP-β-CD Dosage Range for up to 14 days
3 kg to less than 35 kg	6 mg/kg every 12 hours 6-hr infusion	240 mg/kg twice daily
35 kg to less than 120 kg	200 mg every 12 hours 6-hr infusion	67-229 mg/kg twice daily
120 kg and above	300 mg every 12 hours 6-hr infusion	< 100 mg/kg

Figure 1: FDA simulated Cmax, AUC, and Cmin at steady-state following FDA recommended IV dose, and the comparison of exposures between FDA recommended IV dose versus approved oral dose



Source: FDA review team analysis, Study 008 (Study SIGA-246-008) was a multicenter, double-blind, randomized, placebo-controlled study that assessed the safety, tolerability, and PK of tecovirimat 600 mg BID for 14 days in healthy adult subjects. This study was the pivotal safety and PK study for the approval of tecovirimat oral formulation.

5.2. Missed Dose Instructions

In the original NDA submission for oral tecovirimat formulation, dosage instructions for a missed dose were not included in the proposed label. Subsequently, the Applicant proposed the following language based on the available tecovirimat PK information:

> **Missed Dose**
> If a dose of oral TPOXX is missed, the patient should take the dose as soon as possible and anytime up to 8 hours prior to the next scheduled dose. If less than 8 hours remain before the next scheduled dose, do not take the missed dose, and resume dosing at the next scheduled dose.

The Applicant's proposal is reasonable because, even though the proposal may lead to a potential risk of higher Cmax (for a brief period of time) in a subset of small patient population (approximately ≤ 5%) due to the reduced dosing interval of 8-hours (instead of 12-hours), this risk is outweighed by the potential benefit of taking the missed dose. Optimizing adherence is also important because there are several pathways to select for very high-level drug resistance to tecovirimat.

5.3. Formulation Switch Recommendations

In the DOSAGE AND ADMINISTRATION section, the Applicant originally proposed [redacted] (b) (4) Subsequently, following an information request from the review team, the Applicant proposed the following revised language on switching a patient between IV and oral formulations for patients weighing at least 13 kg:

- If IV treatment is necessary, patients weighing at least 13 kg should be switched to tecovirimat capsules to complete the 14 day treatment course as soon as patient is able to tolerate oral treatment.
- In patients receiving an IV infusion, the first dose of oral treatment should be given at the time of and in place of the next scheduled IV dosing.
- In patients receiving an oral treatment who subsequently require IV treatment, the first dose of IV infusion should be given at the time of and in place of the next scheduled oral dosing.

The Applicant submitted population PK modeling and simulation analyses in support of the abovementioned proposals based on their originally proposed dosing regimen (Table 2). The review team performed additional modeling and simulation analyses to evaluate the Applicant's proposals (See Appendix 2, Section 3.3 Pharmacometrics Review for the details). Based on the review of the Applicant provided information and the review team's independent analyses, the simulated concentration-time profiles in different scenarios were all within the target exposure range between the maximum safety limit of 5595 ng/mL and mean Cmin of 169 ng/mL associated with 10 mg/kg/day in NHP in all simulated scenarios regardless the timing of switching (switching on day 1 or day 4, from oral to IV, or from IV to oral). Thus, the review team concluded that the switch from IV to oral or oral to IV may occur prior to or at steady-state, and that such a switch can occur at the next scheduled dosing time.

6. Clinical Microbiology

No new virology data were submitted in this application. Please refer to the Clinical Virology review of the original NDA (208627).

7. Clinical/Statistical - Efficacy

No new animal efficacy data were submitted in this application. Please refer to the Clinical, Statistics, Clinical Virology, and Pharmacology/Toxicology reviews of the original NDA (208627).

8. Safety

The proposed adult human dosage for IV tecovirimat was based on achieving exposures within the desired target range for safety and efficacy. This section will provide a summary of safety focusing on SIGA-246-IV-202 (referred to as Study 202), the clinical safety and PK trial evaluating multiple doses of IV tecovirimat.

Adequacy of the safety database, Applicant's safety assessments, and submission quality

The safety database at the time of the NDA submission included 26 adult subjects from the healthy volunteer Study 202 who had been exposed to multiple doses of IV tecovirimat. It is important to note that the safety data for tecovirimat (oral [n=359] and IV [n=26]) were generated in healthy volunteers which supported the approval of tecovirimat. Overall, the safety for the majority of the weight bands is supported by the safety data for 359 healthy adults treated with oral tecovirimat. Although subjects weighing between 35 kg and 45 kg may have Cmax and AUC exposures higher than adults with the oral formulation, given the narrow weight range where IV exposures may be higher compared to the oral formulation, the overall safety profile is reasonable for the intended indication and patient population.

The Applicant provided a basic assessment of safety as a component of the NDA submission. No substantive issues with data integrity were identified.

Categorization of adverse events (AEs)
No issues were identified with respect to recording, coding, and categorizing AEs. The Applicant categorized AEs and SAEs in accordance with standard regulatory definitions. AEs were graded using the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, which is derived from the Division of AIDS (DAIDS) toxicity grading criteria.

Study design
Study 202 is a Phase 1, single center, three-period, crossover, pharmacokinetic (PK) comparison of single doses of IV tecovirimat versus oral tecovirimat, followed by a double-blind, randomized, placebo-controlled, multiple-dose period to determine the safety, tolerability, and PK of IV tecovirimat administered twice daily (approximately every 12 hours) for 7 days in adult subjects. The primary objectives of the study are to compare the PK of a single, 200 mg IV dose of tecovirimat to a single, 600 mg oral dose (in the fed state) of tecovirimat in healthy adults; to evaluate the safety and tolerability of 240 mg IV tecovirimat administered over 6 hours twice daily (BID) for 7 days in healthy adults; to establish the PK profile of 240 mg IV tecovirimat administered BID for 7 days in healthy adults; to determine the absolute bioavailability of the oral formulation, by comparing it to the IV formulation. IV tecovirimat consisted of tecovirimat monohydrate (200 mg per vial) in a 10-mg/mL stock solution containing 40% hydroxypropyl-β-cyclodextrin (8 g per vial) with water for injection (approximately 20 mL). Placebo consisted of a stock solution containing 40% hydroxypropyl-β-cyclodextrin with water for injection. The 7 day duration was assessed as sufficient to characterize the PK of multiple doses of IV tecovirimat.

Study 202 began on July 13, 2018 and was completed on January 29, 2019. Subjects were enrolled at one US site. Healthy male and non-pregnant/non-lactating female subjects, 18 – 64 years of age, weight 50 –120 kg, and with adequate venous access were eligible.

Exclusion criteria encompassed subjects with any clinically significant medical condition (active, recent [as defined in the protocol] or chronic); clinically significant electrocardiogram abnormality; estimated creatinine clearance (Cockcroft-Gault) <90 mL/min; creatinine 1.3x upper limit of normal (ULN); hemoglobin ≤10% of the lower limit of normal; white blood cell count not within the central laboratory reference range; absolute neutrophil count not within the central laboratory reference range; platelets not within ± 10% of central laboratory reference range; alanine aminotransferase (ALT) >1.5x ULN; aspartate aminotransferase (AST) >1.5x ULN; alkaline phosphatase >1.2x ULN; hemoglobin A1c ≥7.0%; cholesterol ≥300 mg/dL and low-density lipoprotein ≥90 mg/dL; greater than 20 mg prednisone or equivalent dose or any immunosuppressant or immunomodulatory medication within 1 month before

screening; any investigational medication/therapy within 30 days or 5 half-lives, whichever was longer, before the first dose of study drug; previously enrolled in any clinical study involving tecovirimat.

Subjects were also ineligible if they had been currently (as defined in the protocol) using any of the following medications: antidiabetic medication; anticoagulants; anticonvulsants; substrates of the breast cancer resistance protein transporter including methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, and topotecan; substrates of cytochrome P450 (CYP) 2C8 including repaglinide, paclitaxel, montelukast, pioglitazone, rosiglitazone; and substrates of CYP2C19 including S-mephenytoin, clobazam, diazepam, rabeprazole, voriconazole, lansoprazole, and omeprazole.

Routine clinical tests

Routine clinical evaluation and laboratory testing occurred at pre-specified intervals: Screening; Baseline; Days 1-13 (for the multi-dose cohort); Follow-Up on Day 37 (±2). The frequency and scope of this testing was deemed adequate. Safety assessments primarily included clinical evaluation of AEs, vital sign measurement, physical examinations, 12-lead ECGs, and standard laboratory safety tests. Additional testing occurred as indicated or deemed clinically necessary by the investigator during the trials.

Safety population; disposition; protocol violations/deviations

The safety population comprised all subjects who received at least one dose of study drug (n=32). In the multi-dose cohort, 26 subjects received IV tecovirimat and 6 subjects received placebo. Five subjects (16%) prematurely discontinued study treatment (IV tecovirimat [n=4]; placebo [n=1]). In the tecovirimat group, three subjects discontinued due to adverse events (AEs) and one subject discontinued due to subject withdrawal. In the placebo group, one subject discontinued due to physician decision.

A total of 19 important protocol deviations were reported: missing endpoint assessments (n=15), violations of withdrawal/termination criteria (n=3), violations of study treatment administration/dispensation (n=1). These protocol violations had no bearing on the interpretability of the trial results.

Reviewer Comment: Other than issues related to IV administration, the overall safety findings from Study 202 were similar to the safety data for 359 healthy adults treated with oral tecovirimat. Infusion related AEs were overall mild in severity.

Issues related to the hydroxypropyl-β-cyclodextrin (HP-β-CD) excipient in the IV formulation are discussed in the subsection on submission-specific safety issues.

Baseline demographics

Table 4 summarizes the baseline demographic characteristics.

Table 4. Baseline demographic characteristics, Full Analysis Set (FAS)

Demographic parameter	IV Tecovirimat (n=26)	IV Placebo (n=6)
Sex		
Male	15 (58%)	2 (33%)
Female	11 (42%)	4 (67%)
Age (years)		
Mean	41	32
Minimum, maximum	23, 62	20, 48
Race		
White	18 (69%)	4 (67%)
Black	6 (23%)	1 (17%)
Multiple	2 (8%)	0
American Indian or Alaskan	0	1 (17%)
Ethnicity: Hispanic/Latino		
Yes	11 (42%)	2 (33%)
No	15 (58%)	4 (67%)
Weight (kg)		
Mean	84	81
Minimum, maximum	58, 117	67, 106

Reviewer Comment: The two treatment groups are overall balanced with respect to race and ethnicity. The slight age imbalance in the tecovirimat group did not impact the safety findings in Study 202. The slight gender imbalance observed across Study 202 (i.e. more males received tecovirimat; more females received placebo) did not impact the safety findings. Given the small sample size in Study 202, safety analyses by demographic subgroups were not feasible.

Key safety results, including common adverse drug reactions, deaths, serious adverse events (SAEs), discontinuations due to AEs, significant adverse events and results of laboratory tests

An overall summary of safety events in Study 202 is presented in Table 5. The reviewer assessments and conclusions are similar to those of the Applicant.

Table 5. Overview of Adverse Events, FAS

Subjects Experiencing Event n (%)	IV Tecovirimat (n=26)	IV Placebo (n=6)
Any AE	22 (85%)	6 (100%)
Grade 2 AE	3 (12%)	0
Grade 3 or 4 AE	0	0

Related AE	22 (85%)	6 (100%)
Related Grade 2 AE	3 (12%)	0
Related Grade 3 or 4 AE	0	0
SAE	0	0
Discontinuation of study drug due to AE	3 (12%)	0
Death	0	0

Common adverse drug reactions (ADRs, i.e., adverse events assessed as reasonably associated with the use of the drug) that occurred in at least 4% of subjects are displayed in Table 6. Most of the adverse reactions reported were mild in severity.

Table 6. Treatment-emergent ADRs Reported in ≥ 4% of Subjects, All Grade, FAS

Dictionary Derived Term	IV Tecovirimat (n=26)	IV Placebo (n=6)
Infusion site pain	19 (73%)	4 (67%)
Infusion site swelling	10 (39%)	4 (67%)
Infusion site erythema	6 (23%)	4 (67%)
Infusion site extravasation	5 (19%)	3 (50%)
Headache	4 (15%)	0 (0%)
Total subjects with ADR	22 (85%)	6 (100%)

Note: 4% cut-off corresponds to displaying ADRs that occurred in more than one subject.
Reviewer Comment: The ADRs in the above table will be displayed in product labeling.

There were no deaths, no serious adverse events (SAEs), and no Grade 3/4 AEs.

Discontinuations due to AEs occurred in 3 subjects (12%) in the tecovirimat group and no subjects in the placebo group; these AEs were assessed by investigators as related to IV tecovirimat.

Table 7. Adverse Events Leading to Study Drug Discontinuation assessed as related to IV tecovirimat

ID	AE	Day, Start of AE	Day, End of AE	Last day of study drug	# of doses	SAE	Grade	Outcome
(b) (6)	Infusion site swelling	4	22	6	11	No	1	Resolved
	Infusion site pain	6	22	6	11	No	1	Resolved
	Infusion site extravasation	1	5	1	2	No	2	Resolved
	Infusion site extravasation	2	6	3	5	No	1	Resolved

Reviewer Comment: The narratives were reviewed and the FDA clinical reviewer agrees with the investigators' assessments.

Laboratory abnormalities were infrequent and are summarized below:
- There was one Grade 2 creatinine elevation (>1.3 to 1.8x ULN) in the tecovirimat group and none in the placebo group.
- There was one Grade 2 low glucose (40 to <50 mg/dL) in the tecovirimat group and none in the placebo group.
- There were nine Grade 1 non-fasting glucose elevations (116 to 160 mg/dL) in the tecovirimat group and three in the placebo group. There were three Grade 2 non-fasting glucose elevations (>160 to 250 mg/dL) in the tecovirimat group and none in the placebo group.
- There were no ALT or AST elevations in Study 202.
- There were no Grade 3 and 4 laboratory abnormalities in Study 202.

Reviewer Comment: No additional product labeling is warranted at this time for laboratory abnormalities.

Immunogenicity

Because tecovirimat is a small molecule and not a peptide, immunogenicity was not anticipated and therefore not specifically evaluated in clinical trials.

Submission-specific safety issues

Seizures

As previously noted in the original NDA (208627), non-clinical toxicology studies in dogs demonstrated neurological effects (e.g., tremors, seizures) at higher than anticipated clinical exposures of tecovirimat. No seizure events were reported. No subjects exceeded Cmax 5,575 ng/mL (maximum allowable exposure level for humans) with IV tecovirimat.

Potential for hydroxypropyl-β-cyclodextrin (HP-β-CD) accumulation

As outlined in European Medicines Agency (EMA) 2014 and 2017 reports on cyclodextrins[8,9]:
- HP-β-CD at high doses can cause vacuolation of the kidney tubular cells without loss of kidney function in animals.
- HP-β-CD is considered safe at relatively high doses; amounts of HP-β-CD 250 mg/kg/day have been assessed to be safe in humans older than 2 years when given for up to 21 days.
- Non-clinical findings for HP-β-CD include nephrotic changes in rats, rabbits and dogs and ototoxicity observed in cats and rats.
- Due to renal immaturity in pediatric patients less than 2 years, the major concern is the risk of osmotic nephrosis. Based on ontogeny the lower glomerular filtration rate in young infants can lead to higher blood levels of cyclodextrins, leading to an increase in extra-renal adverse effects. Cyclodextrins should be used in this population on a case-by-case basis.

In the Applicant's proposed dosing regimen for IV tecovirimat, the amount of HP-β-CD administered to low body weight pediatric patients is higher per body weight (b) (4) compared to the amount for adults and the amount from any of the current FDA approved drug products. This issue was assessed collaboratively by the clinical, clinical pharmacology, and pharmacology/toxicology reviewers, along with input from the Office of Pediatric Therapeutics (OPT) because pediatric patients weighing 3 kg to < 13 kg would have to use the IV formulation for the entire 14-day treatment duration due to the absence of an approved pediatric formulation of tecovirimat. Please refer to the pharmacology/toxicology review and OPT review (An Massaro, Gerri Baer, Dionna Green; DARRTS Reference ID: 4857632) for details.

The following key steps were taken by the multidisciplinary review team and are reflected in labeling:
• The review team conducted modeling and simulation analyses and recommended an alternative dosing regimen to reduce the HP-β-CD amount in low body weight pediatric patients and to simplify the dosing regimen with fewer body weight bands.
• A Contraindication was added to describe that the excipient HP-β-CD is eliminated through glomerular filtration and, therefore, IV tecovirimat is contraindicated in patients with severe renal impairment (defined as creatinine clearance below 30 mL/min).
• A Warnings and Precautions was added to provide wording that clearly describes the risks of HP-β-CD accumulation in patients with renal insufficiency (mild, moderate, or severe) and in pediatric patients less than 2 years of age, and outlines risk mitigation strategies for health care providers to consider.
• Given the potential for HP-β-CD accumulation, the review team recommends that creatinine clearance should be determined in all patients prior to starting IV tecovirimat and monitored while receiving IV tecovirimat as clinically appropriate.
• Given the potential for drug accumulation due to renal immaturity in pediatric patients less than 2 years, monitoring of renal function after treatment is also recommended.

9. Advisory Committee Meeting

An Advisory Committee meeting was not convened for this application because the acceptability of the animal models were discussed at the 2011 Antiviral Drugs Advisory Committee, the Applicant closely followed FDA's recommendations for developing tecovirimat under the Animal Rule, the results from two animal models demonstrated a statistically significant survival benefit, and the regulatory considerations, animal efficacy and pharmacokinetic data from these animal models, and human safety and pharmacokinetic data were previously discussed during the May 2018 Advisory Committee meeting convened for the original NDA (208627) application.[3-6]

10. Pediatrics

No pediatric trials were submitted in support of this NDA. Tecovirimat has orphan drug status and is therefore exempt from Pediatric Research Equity Act (PREA) requirements. Please refer to Section 5 (Clinical Pharmacology) for a discussion of pediatric dose selection based on modeling and simulation. As discussed in the original NDA (208627), due to the absence of an approved pediatric formulation of tecovirimat, the oral formulation can only be used in patients weighing at least 13 kg. The Applicant is currently developing a pediatric formulation of tecovirimat. In this NDA, the IV formulation extends the dosing down to pediatric patients weighing at least 3 kg. However, pediatric patients weighing 3 kg to < 13 kg would have to use the IV formulation for the entire 14-day treatment duration.

11. Other Relevant Regulatory Issues

- *Financial disclosures*

Financial disclosures were provided and reviewed for investigators involved in the relevant clinical trials. There were no financial disclosures of significant concern, individually or collectively. The financial disclosures do not impact the approvability of this application. Please refer to Appendix 1 for additional details.

- *Other Good Clinical Practice (GCP) issues*

The clinical trials discussed in this review were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Counsel (ICH) Good Clinical Practice (GCP) guidelines.

- *Office of Scientific Investigations (OSI) audits*

For this application for a new formulation with supporting PK data, no clinical inspections were warranted.

- *Office of Study Integrity and Surveillance (OSIS) audits*

OSIS inspected two sites that participated in evaluating the pharmacokinetics of IV tecovirimat in Study 202 and Study 201. Their inspection confirmed the data integrity of these studies. Please refer to OSIS' Consult Review for further details.

12. Labeling

Prescribing Information

The summary that follows reflects the major changes to the prescribing information (PI) that have been proposed by the Agency and accepted by the Applicant. Please refer to the individual FDA reviews from each of the review disciplines for additional details.

- INDICATIONS AND USAGE:
  - The indication for tecovirimat was expanded to encompass pediatric patients weighing at least 3 kg, consistent with the lowest weight allowed for by the IV formulation.

- DOSAGE AND ADMINISTRATION:
  - In the Applicant's proposed dosing regimen for IV tecovirimat, the amount of HP-β-CD administered to low body weight pediatric patients is higher per body weight (b) (4) compared to the amount for adults and the amount from any of the FDA approved drug products. Therefore, the review team conducted modeling and simulation analyses and recommended an alternative dosing regimen to reduce the HP-β-CD amount in low body weight pediatric patients and to simplify the dosing regimen with fewer body weight tiers. The Agency's simulation was based on the Applicant's originally submitted population PK model developed using the IV formulation only.

Body Weight	**IV Tecovirimat Dosage**
3 kg to less than 35 kg	6 mg/kg every 12 hours via 6-hour infusion
35 kg to less than 120 kg	200 mg every 12 hours via 6-hour infusion
120 kg and above	300 mg every 12 hours via 6-hour infusion

  - Using the above proposed IV dosing regimen, the review team conducted additional simulations to evaluate different formulation switch scenarios (IV to oral or oral to IV). Based on these results, the review team concluded that the switch from IV to oral or oral to IV may occur prior to or at steady-state, and that such a switch can occur at the next scheduled dosing time.

  - Given the potential for HP-β-CD accumulation, the review team recommends that creatinine clearance should be determined in all patients prior to starting IV tecovirimat and monitored while receiving IV tecovirimat as clinically appropriate.

  - Clarify that patients weighing at least 13 kg should be switched to TPOXX Capsules to complete the 14 day treatment course as soon as oral therapy can be tolerated.

- CONTRAINDICATIONS section:
  - A contraindication was added to describe that the excipient HP-β-CD is eliminated through glomerular filtration and, therefore, IV tecovirimat is contraindicated in patients with severe renal impairment (defined as creatinine clearance below 30 mL/min).

- WARNINGS AND PRECAUTIONS section:
  - A Warnings and Precautions was added to describe the risks of HP-β-CD in patients with renal insufficiency and in pediatric patients less than 2 years of age, and to provide risk mitigation strategies and recommendations for management when using IV tecovirimat.

- ADVERSE REACTIONS section:
  - Adverse reactions occurring in at least 4% of subjects with IV tecovirimat will be displayed.
  - Adverse reactions leading to discontinuation of IV tecovirimat will be displayed.

- USE IN SPECIFIC POPULATIONS section:
  - Section 8.2 (Lactation) was revised to clarify that, because of the potential for variola virus transmission through direct contact with the breastfed infant, breastfeeding is not recommended in patients with smallpox.
  - Section 8.4 (Pediatric Use) will describe that there are limited data regarding the use of HP-β-CD, an ingredient in IV tecovirimat, in pediatric patients less than 2 years of age. Given the potential for drug accumulation due to renal immaturity in pediatric patients less than 2 years, monitoring of renal function after treatment is recommended.

- CLINICAL PHARMACOLOGY section:
  - Section 12.3 will describe pharmacokinetic (PK) data for IV tecovirimat to allow comparison between oral and IV PK parameters.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Based on the overall safety profile of tecovirimat, a REMS is not recommended.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

To date, the Agency has determined that no PMRs and PMCs should be issued for this application.

14. References

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

2. NIAID Emerging Infectious Diseases/Pathogens. Available at: https://www.niaid.nih.gov/research/emerging-infectious-diseases-pathogens.

3. Guidance for Industry. Product Development Under the Animal Rule. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm399217.pdf.

4. Materials for the 2009 FDA Public Workshop are available at: https://www.federalregister.gov/documents/2009/08/18/E9-19781/development-of-antiviral-products-for-treatment-of-smallpox-and-related-poxvirus-infections-public.

5. Materials for the 2011 Antiviral Drugs Advisory Committee are available at: https://wayback.archive-it.org/7993/20170404145348/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/ucm247236.htm.

6. Materials for the 2018 Antiviral Drugs Advisory Committee are available at: 2018 Meeting Materials, Antimicrobial Drugs Advisory Committee (formerly known as the Anti-Infective Drugs Advisory Committee).

7. TPOXX® [package insert]. Corvallis, OR: SIGA Technologies Inc.; 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208627s006lbl.pdf.

8. European Medicines Agency, 2017. Cyclodextrins used as excipients. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-cyclodextrins-used-excipients-medicinal-products-human-use_en.pdf.

9. European Medicines Agency, 2014. Background review for cyclodextrins used as excipients. Available at: https://www.ema.europa.eu/en/documents/report/background-review-cyclodextrins-used-excipients-context-revision-guideline-excipients-label-package_en.pdf.

Appendix 1 – Financial Disclosure

There were no financial disclosures of significant concern, individually or collectively. The financial disclosures described below do not affect approvability of IV tecovirimat.

Covered Clinical Study (Name and/or Number): SIGA-246-IV-201, SIGA-246-IV-202

Was a list of clinical investigators provided:	Yes X	No __ (Request list from Applicant)
Total number of investigators identified: 17 Overall: 2 Principal Investigators, 15 Sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/ arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes	No __ (Request explanation from Applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes	No __ (Request explanation from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes	No __ (Request explanation from Applicant)

The Applicant adequately examined financial disclosure information from all clinical investigators for the covered clinical trials, as recommended in the *Guidance for Industry: Financial Disclosure by Clinical Investigators*. The Applicant certified in Form FDA 3454 that, as the sponsor of the submitted studies, the Applicant has not entered into any financial arrangement with the listed clinical investigators (list was included in the submission) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. The Applicant further certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Those investigators who are participating or have participated in the clinical trials and who have financial interest or arrangements as described in 21 CFR 54.4(a)(3) are noted in the above template. There are no investigators with a financial interest.

In conclusion, the likelihood that trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

Appendix 2 – Clinical Pharmacology: Additional Information and Assessment

Note: The following is the summary of individual study reports that support the Office of Clinical Pharmacology (OCP) review. The conclusions drawn by the Applicant are listed at the end of individual study summary. The Applicant's conclusions are found to be reasonable by the review team unless noted otherwise in a Reviewer's Assessment section.

1. Summary of Bioanalytical Method Validation and Performance

Plasma samples collected from studies SIGA-246-IV-202 and SIGA-246-IV-201 were analyzed to quantify tecovirimat, M4, M5, and TFMBA concentrations according to bioanalytical methods described in a validation report (AV15-ST246-03). Report AV15-ST246-03 has been reviewed previously as a part of NDA submissions related to oral tecovirimat formulation. Bioanalytical method performance reports for SIGA-246-IV-201 and SIGA-246-IV-202 are summarized in Table 8 below.

Table 8: Summary of Bioanalytical Performance

Method/Report	**Findings**	
Study: SIGA-246-IV-201		
Analyte/assessment	Tecovirimat, M4, M5, and TFMBA (4-trifluoromethyl benzoic acid)	
Method	HPLC/MS/MS	
Matrix	Human plasma (K_2EDTA/K_3EDTA) Note: Study samples were collected and stored with K_3EDTA as the anticoagulant. These samples were quantified against standard curves prepared in K_2EDTA. The report notes that this procedure was cross-validated as SOP AA-308. The Reviewer was not able to identify further information on SOP AA-308, however, cross-validation findings reported in Addendum 1 to AV15-ST246-03 appear to support the Applicant's approach.	
Performance reports	Performance reports provided: SIGA-246-IV-201/AD16-605	☒ Yes ☐ No
	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control (QC) samples' concentration range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No

	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
Inspection	Will an inspection for bioanalytical site be requested? Note: The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time as the same bio-analytical site was inspected in February 2018, which falls within the surveillance interval for Study SIGA-246-IV-201. OSIS recommended that the data (from other NDAs) be accepted. See OSIS memorandum dated 06/25/2021 under NDA214518 for additional details.	☒ Yes ☐ No
Method/Report	**Findings**	
Study: SIGA-246-IV-202		
Analyte/assessment	Tecovirimat	
Method	HPLC/MS/MS	
Matrix	Human plasma (K_2EDTA)	
Performance reports	Performance reports provided: SIGA-246-IV-202/AD18-840	☒ Yes ☐ No
	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control (QC) samples' range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
Inspection	Will an inspection for bioanalytical site be requested? Note: See Note Section for Study SIGA-246-IV-201	☒ Yes ☐ No

2. In Vitro Studies

The Applicant has not submitted any new clinical pharmacology related in vitro study findings.

3. Clinical Studies

3.1. Study SIGA-246-IV-201

Overview:

This was a double-blind, randomized, placebo-controlled, single ascending dose phase 1 study that evaluated the safety, tolerability, and PK of tecovirimat when administered by IV infusion over 6 hours as a single dose of 37.5, 75, 150, or 200 mg in healthy subjects.

In total, 32 subjects were enrolled and 18 (56%) were male, 25 (78%) were White, 6 (19%) were Black or African American, and 1 (3%) was Asian. Enrolled subjects were randomly assigned in 3:1 ratio (drug:placebo) to either tecovirimat (37.5, 75, 150, or 200 mg; n = 6 per cohort) or placebo (n = 2 per cohort). All 32 subjects completed the study and were included in the safety analysis, with 24 subjects included in PK analysis. The age and weight of enrolled subjects ranged (mean) between 18 to 50 (31) years and between 52 to 108 (84) kg, respectively.

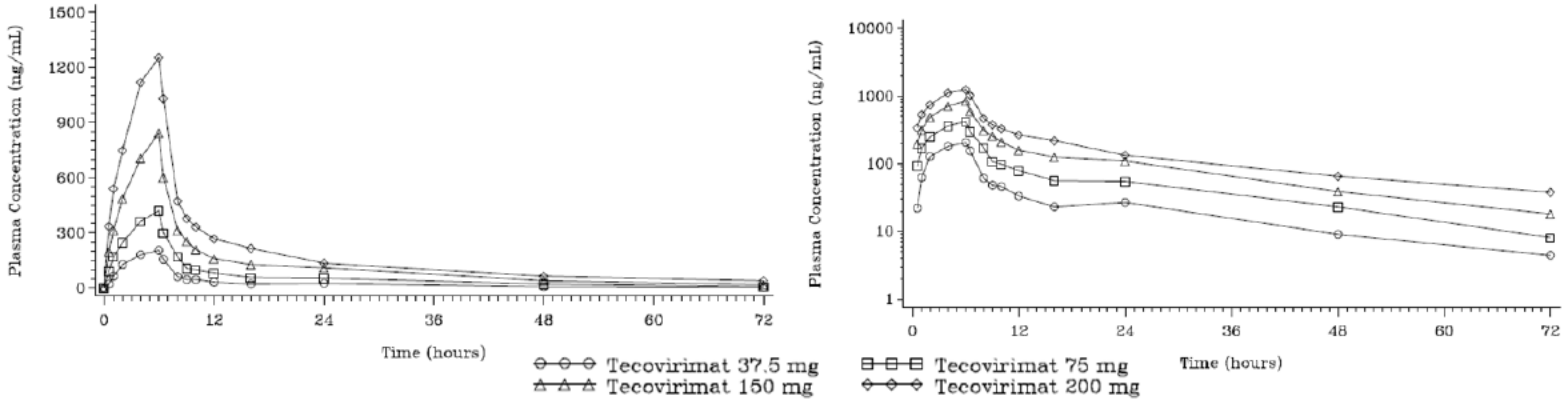
The subjects remained at the study site for PK sample collection until discharge at 72 hours post-dose. For PK assessments, 15 blood samples were collected between pre-dose to 72 hours post-dose. Tecovirimat and its metabolites' (M4, M5, and 4-trifluoromethyl-benzoic acid (TFMBA)) concentrations in plasma were measured using a validated LC-MS/MS method.

During the conduct of the study, there were two protocol deviations related to duration of infusion and corresponding end of infusion PK sample collection. These deviations were deemed (by the Applicant) unlikely to affect the results of the study or the integrity of the data.

Pharmacokinetic Results:

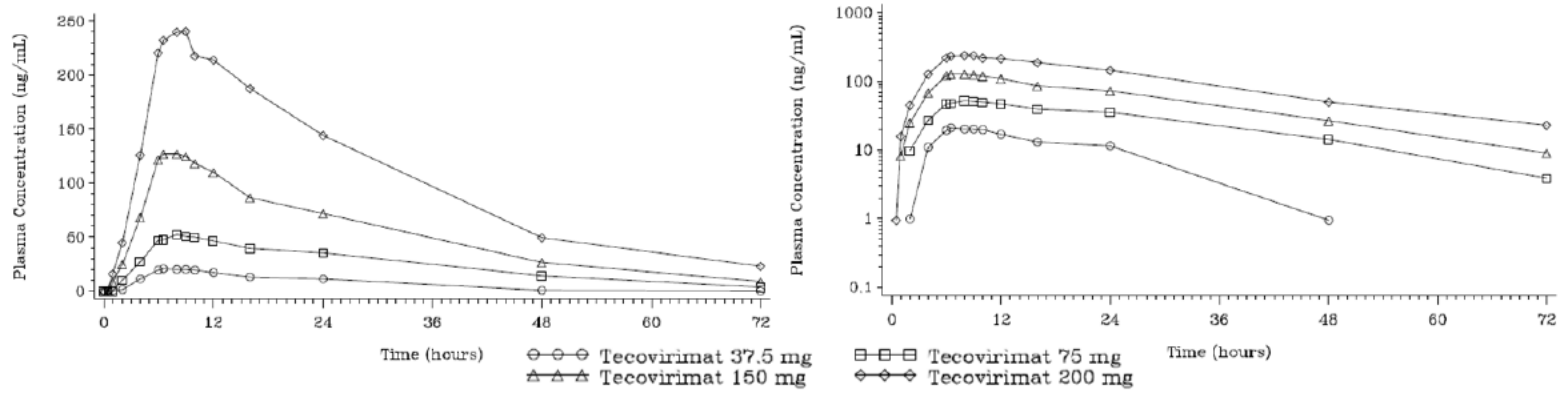
Mean plasma concentration-time profiles for tecovirimat and its metabolites are presented in Figure 2 to Figure 5. The plasma concentrations of tecovirimat and its metabolites were analyzed using noncompartmental analysis to derive PK parameter estimates reported in Table 9. Dose proportionality for tecovirimat was also evaluated and findings are reported in Figure 6.

Figure 2: Mean (±SD) Plasma Concentrations of Tecovirimat in Plasma (Left: linear scale, Right: semi-logarithmic scale)



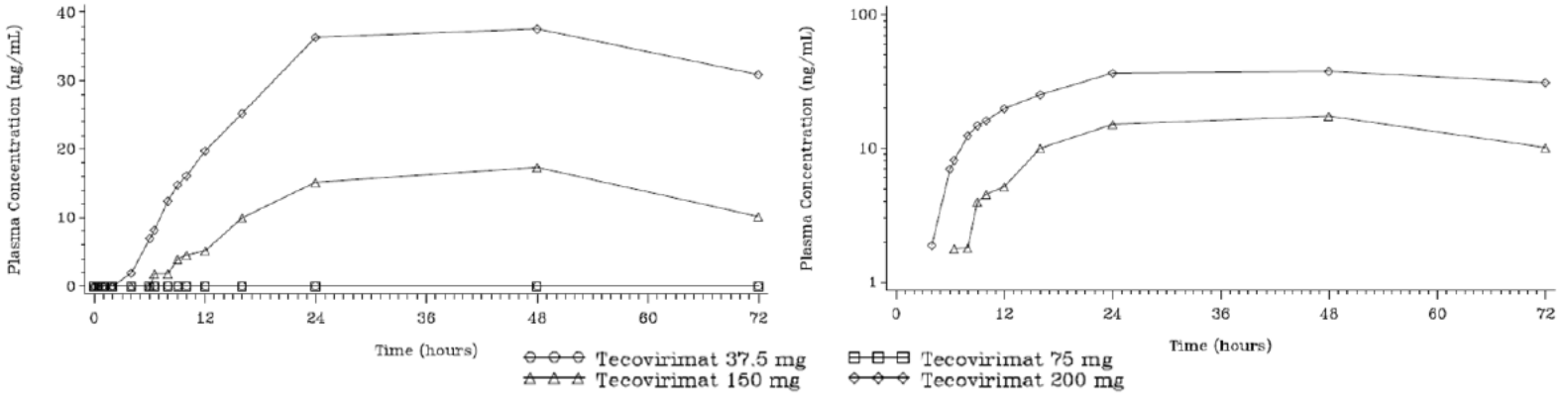
Source: Adapted from Study SIGA-246-IV-201 report

Figure 3: Mean (±SD) Plasma Concentrations of M4 in Plasma (Left: linear scale, Right: semi-logarithmic scale)



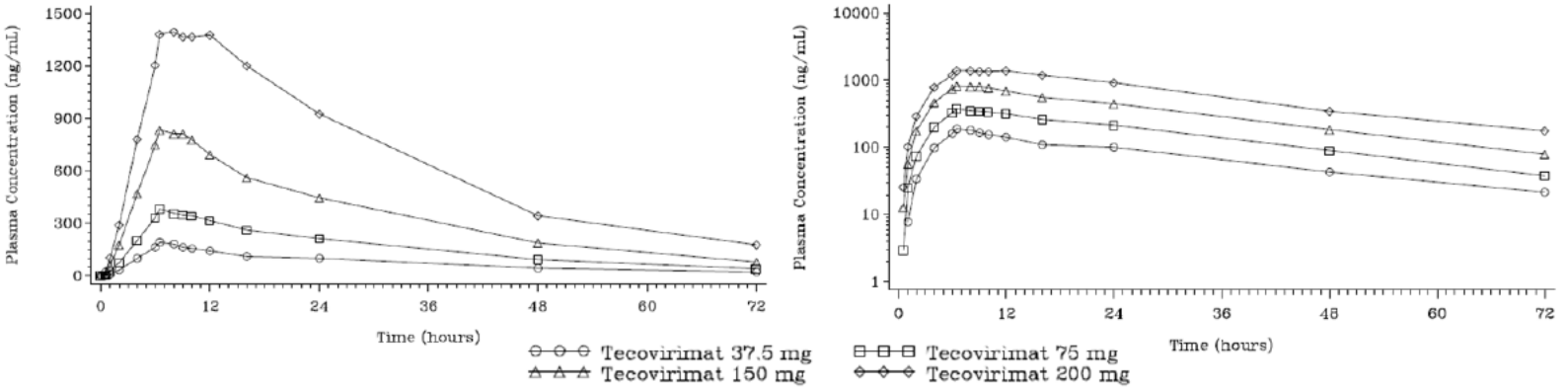
Source: Adapted from Study SIGA-246-IV-201 report

Figure 4: Mean (±SD) Plasma Concentrations of M5 in Plasma (Left: linear scale, Right: semi-logarithmic scale)



Source: Adapted from Study SIGA-246-IV-201 report

Figure 5: Mean (±SD) Plasma Concentrations of TFMBA in Plasma (Left: linear scale, Right: semi-logarithmic scale)



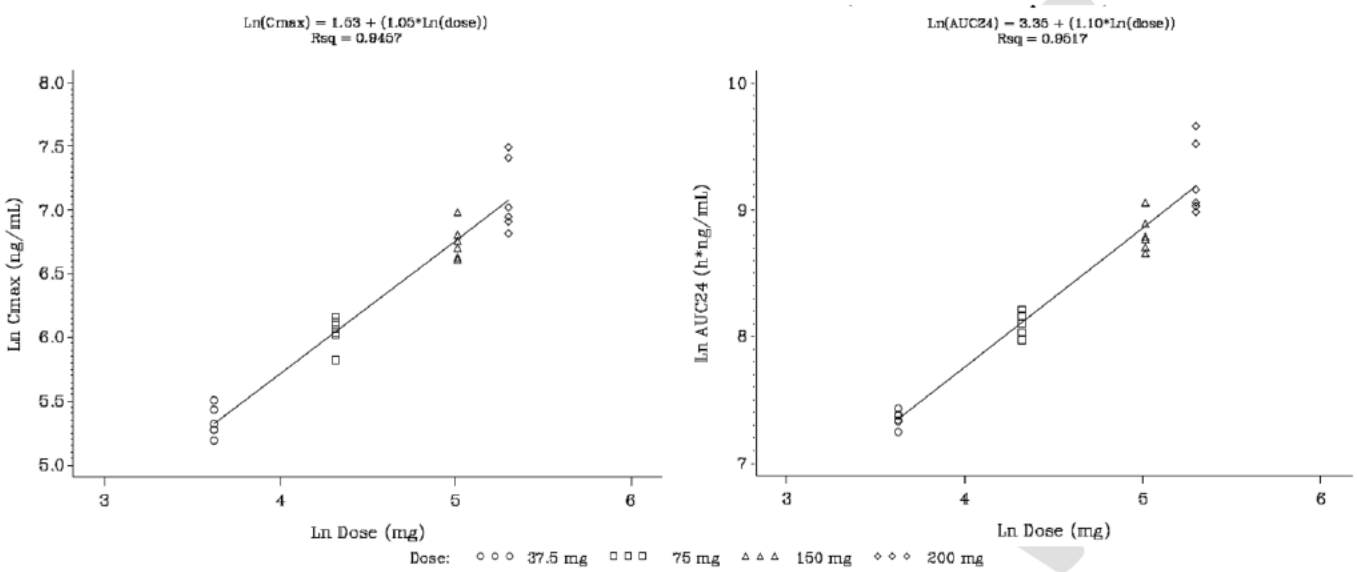
Source: Adapted from Study SIGA-246-IV-201 report

Table 9: Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for Tecovirimat and Metabolites

Dose	N	AUC_{0-24} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	T^{a}_{max}(h)	$T_{1/2}$(h)
Tecovirimat						
37.5 mg	6	1559.7 (6.4)	2400.9 (14.1)[b]	208 (11.7)	5.86 (4-6)	22.05 (23.8)[b]
75 mg	6	3363.7 (9.8)	4973.7 (22.7)	420 (11.1)	6 (6-6)	18.40 (41.5)
150 mg	6	6773.7 (15.2)	9808.5 (15.1)	861 (14.3)	6 (4-6)	19.91 (28.4)
200 mg	6	10648.5 (30.7)	15747.1 (26.9)	1250 (29.8)	6 (6-6)	26.00 (21)
M4						
37.5 mg	6	319.71 (14.8)	757.65 (NE)[c]	21.3 (18)	6.45 (6-10)	29.60 (NE)[c]
75 mg	6	888.09 (11.2)	1950.08 (17.6)[b]	55.4 (14.2)	9 (8-16)	19.57 (19.8)[b]
150 mg	6	2060.17 (13.2)	3933.58 (16.8)	132 (11.6)	8 (6-9)	17.37 (20.5)
200 mg	6	4054.67 (40.2)	7858.55 (41.8)	251 (42.4)	8.5 (6-10)	18.30 (14.0)
M5						
37.5 mg	6	NE	NE	NE	NE	NE
75 mg	6	NE	NE	NE	NE	NE
150 mg	6	150.96 (86)	NE	18.6 (36.7)	36 (24-48)	NE
200 mg	6	432.05 (94)	NE	40.9 (68.3)	36 (24-48)	NE
TFMBA						
37.5 mg	6	2751.9 (30.2)	5983.5 (48.8)	195 (22.2)	6.5 (6.27-10)	19.66 (32.2)
75 mg	6	6011.2 (11.9)	12340.7 (19)	398 (5.8)	6.5 (6.5-12)	19.78 (16.4)
150 mg	6	13262.5 (23.3)	26433.3 (29.4)	877 (17.8)	7.25 (6.5-10)	19.48 (19.1)
200 mg	6	25182.9 (28.9)	51818.7 (26.2)	1490 (33.5)	9.5 (6.5-12)	19.91 (7.7)

a: Median [Range], b: n=5, c: n=1, h: Hours, NE: not estimable
Source: Adapted from Study SIGA-246-IV-201 report

Figure 6: Relationship between Tecovirimat Dose and Exposures (Left: Cmax and Right:AUC24)



Source: Adapted from Study SIGA-246-IV-201 report

Applicant's Conclusions :

- Following a 6-hour IV infusion of tecovirimat, systemic exposure (Cmax and AUC) to tecovirimat increased with increasing doses over the 37.5 to 200 mg range and dose proportionality was demonstrated across the doses.
- Systemic exposures to M4, M5, and TFMBA increased with the increasing dose. Among the 3 metabolites, TFMBA showed the highest peak and total exposures at each dose level. Concentrations for M5 could only be detected at the higher doses of 150 and 200 mg.

Reviewer's comment: We agree with the Applicant's conclusions.

3.2. Study SIGA-246-IV-202

Overview:

This was a three-period, crossover, double-blind, randomized, placebo-controlled phase 1 study that evaluated the safety, tolerability, and PK of tecovirimat when administered by oral route and IV infusion (over 6 hours) in healthy subjects. Specifically, the study evaluated PK of tecovirimat following the administration of following three treatments:

- Period 1: 200 mg tecovirimat by IV infusion over 6 hours
- Period 2: 600 mg tecovirimat orally (3 × 200-mg capsules) within 30 minutes after a meal consisting approximately 600 calories and 25 g fat
- Period 3: 240 mg tecovirimat or placebo, by IV infusion over 6 hours BID (approximately 12 hours apart) for 7 days

Enrolled subjects received a single-dose treatment in periods 1 and 2 in a crossover manner with 7 days between dosing under each period. For Period 3, subjects were randomly assigned to treatment or placebo in the multiple-dose period after 12 weeks period.

In total, 49 subjects were enrolled in the study. In periods 1 and 2, 32 subjects were enrolled, 31 subjects (96.9%) completed, and 1 subject (3.1%) discontinued in Period 2 after withdrawal by subject. There were 15 subjects (46.9%) who completed Period 2 who were randomized in Period 3. Remainder of 17 subjects did not return for Period 3 and were replaced. In Period 3, total 32 subjects were randomly assigned to either placebo or active treatment with 26 subjects assigned to 240 mg tecovirimat IV BID for 7 days treatment and 6 subjects assigned to placebo IV BID for 7 days. From 26 subjects assigned to tecovirimat treatment, 22 (84.6%) completed Period 3. From 4 (15.4%) discontinued subjects, 3 subjects discontinued due to an AE and 1 subject withdrew from study. Overall, all 32 subjects (100.0%) were included in the PK population from periods 1 and 2. From Period 3, 22 subjects (84.6%) were included in the multiple dose PK population.

In total, 49 subjects were enrolled and 28 (57%) were male, 29 (59%) were White, 16 (33%) were Black or African American, and 4 (8%) were American Indian or Alaska Native or mixed. The age and weight of enrolled subjects ranged (mean) between 20 to 62 (39.2) years and between 58 to 117 (85) kg, respectively.

For periods 1 and 2, the subjects remained at the study site for PK sample collection until discharge on Day 4 post-dose. For PK assessments, 15 blood samples were collected between pre-dose to 72 hours post-dose during both the periods. For Period 3, 11 blood samples were collected following AM dose on days 1 and 7. Additional 10 samples were collected on days 1 and 7 following PM dose. After the final AM dose, 6 blood samples were collected between 24 hours and 144 hours post-dose. Samples collected from all periods were analyzed for tecovirimat and its metabolites' (M4, M5, and TFMBA) concentrations using a validated LC-MS/MS method.

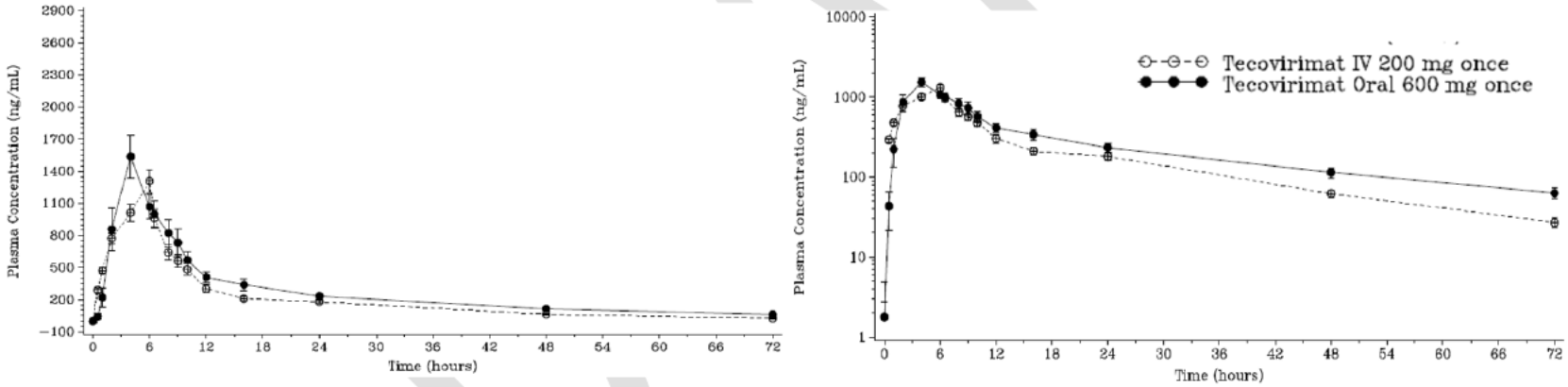
During the conduct of the study, there were major protocol deviations reported for 10 subjects. Other than early termination related deviations, none of the major deviations appear to be related to dosing or PK related assessment. These deviations were deemed (by the Applicant) unlikely to affect the results of the study or the integrity of the data.

Pharmacokinetic Results:

Periods 1 and 2

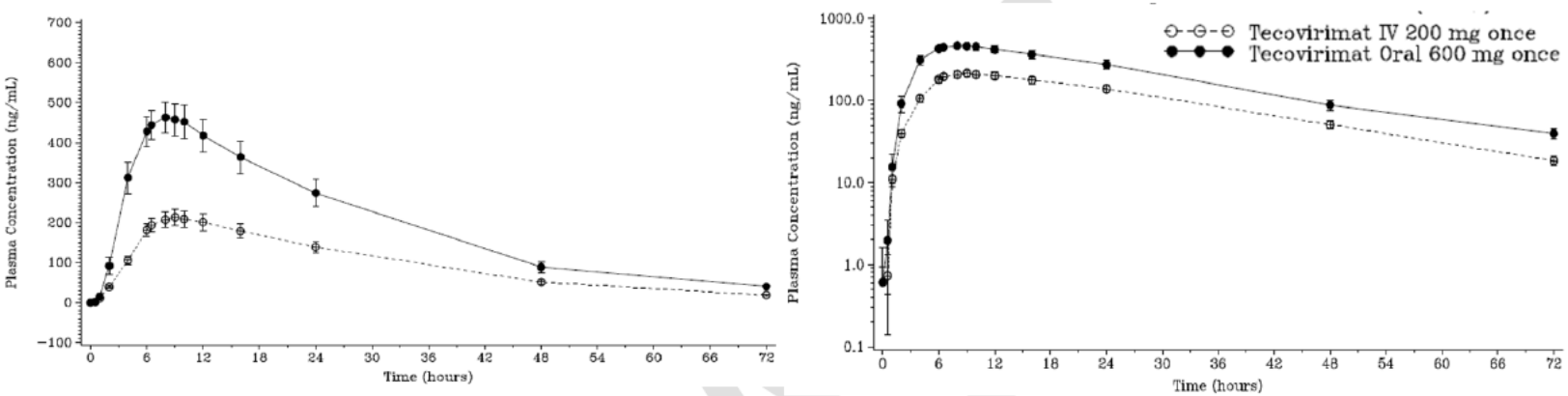
Mean plasma concentration-time profiles for tecovirimat and its metabolites are presented in Figure 7 to Figure 10. The plasma concentrations of tecovirimat and its metabolites were analyzed using noncompartmental analysis to derive PK parameter estimates reported in Table 10. The mean absolute oral bioavailability (F) of tecovirimat was determined using the arithmetic means of dose-normalized AUC0-∞ (DAUC0-∞) values and estimated to be 48%. Based on the geometric mean ratio, the estimated F value was 46%. Statistical analysis of tecovirimat exposure estimates is reported in Table 11.

Figure 7: Mean (±SD) Plasma Concentrations of Tecovirimat in Plasma (Left: linear scale, Right: semi-logarithmic scale)



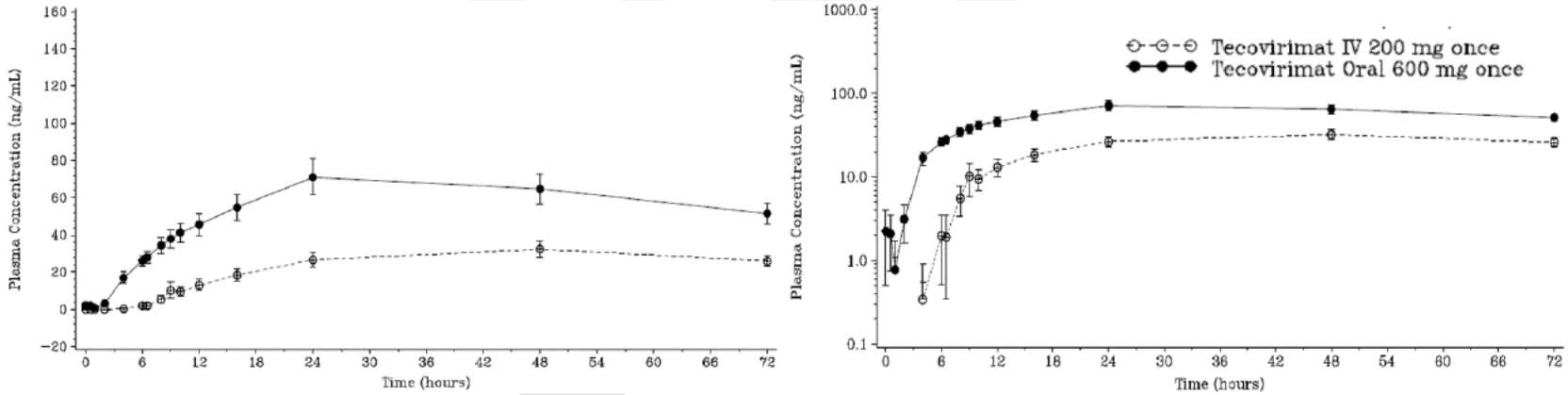
Source: Adapted from Study SIGA-246-IV-202 report

Figure 8: Mean (±SD) Plasma Concentrations of M4 in Plasma (Left: linear scale, Right: semi-logarithmic scale)



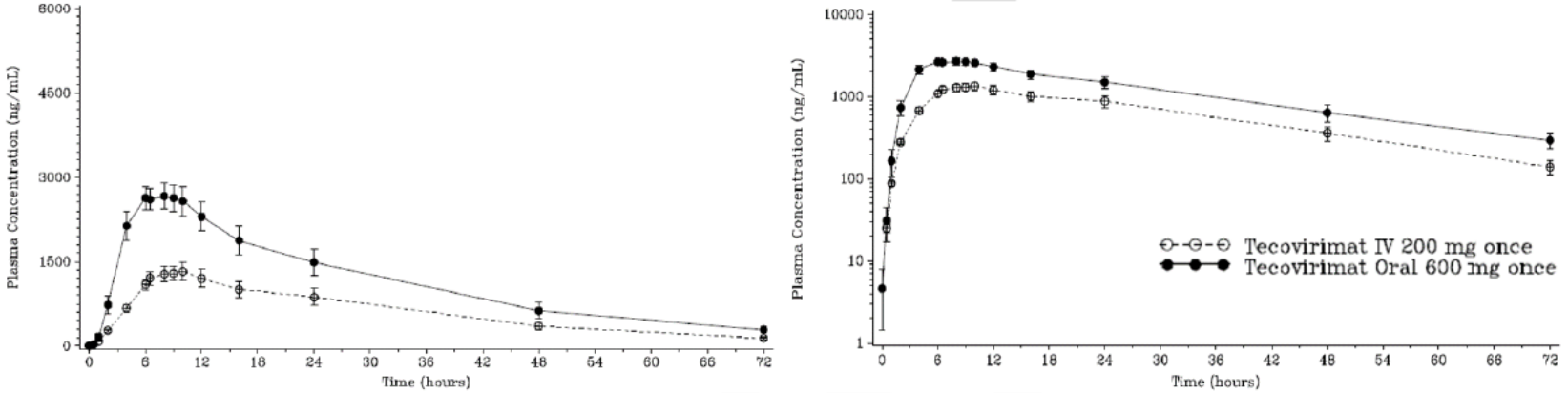
Source: Adapted from Study SIGA-246-IV-202 report

Figure 9: Mean (±SD) Plasma Concentrations of M5 in Plasma (Left: linear scale, Right: semi-logarithmic scale)



Source: Adapted from Study SIGA-246-IV-202 report

Figure 10: Mean (±SD) Plasma Concentrations of TFMBA in Plasma (Left: linear scale, Right: semi-logarithmic scale)



Source: Adapted from Study SIGA-246-IV-202 report

Table 10: Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for Tecovirimat and Metabolites (N=32)

Dose	AUC_{0-24} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	T^{a}_{max}(h)	$T_{1/2}$(h)
Tecovirimat					
200 mg IV	11262 (27.2)	16063 (27.3)	1308 (27.4)	6 (6-5)	18.97 (30.6)
600 mg oral	13808 (31.1)	22732 (31.8)	1671 (35.9)	4 (1-9)	29.79 (77.4)
M4					
200 mg IV	3717 (31.3)	7290 (32.5)	222 (31)	9 (6.5-12)	16.45 (18.6)
600 mg oral	7979 (29.4)	15356 (29.9)	497 (26.4)	8 (6-16)	18.24 (39.8)
M5					
200 mg IV	301 (58.6)	NE	34 (45)	48 (9-72)	NE
600 mg oral	971 (42.1)	NE	73 (41.4)	24 (4-72)	NE

Dose	AUC_{0-24} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	T^{a}_{max}(h)	$T_{1/2}$(h)
TFMBA					
200 mg IV	22451 (42.1)	46937 (52.2)	1396 (38.9)	9 (6.5-12)	17.94 (20.6)
600 mg oral	44633 (33.1)	92595 (46.2)	2902 (28)	6.5 (4-12)	21.49 (37.4)
a: Median [Range], h: Hours, NE: not estimable					
Source: Adapted from Study SIGA-246-IV-201 report					

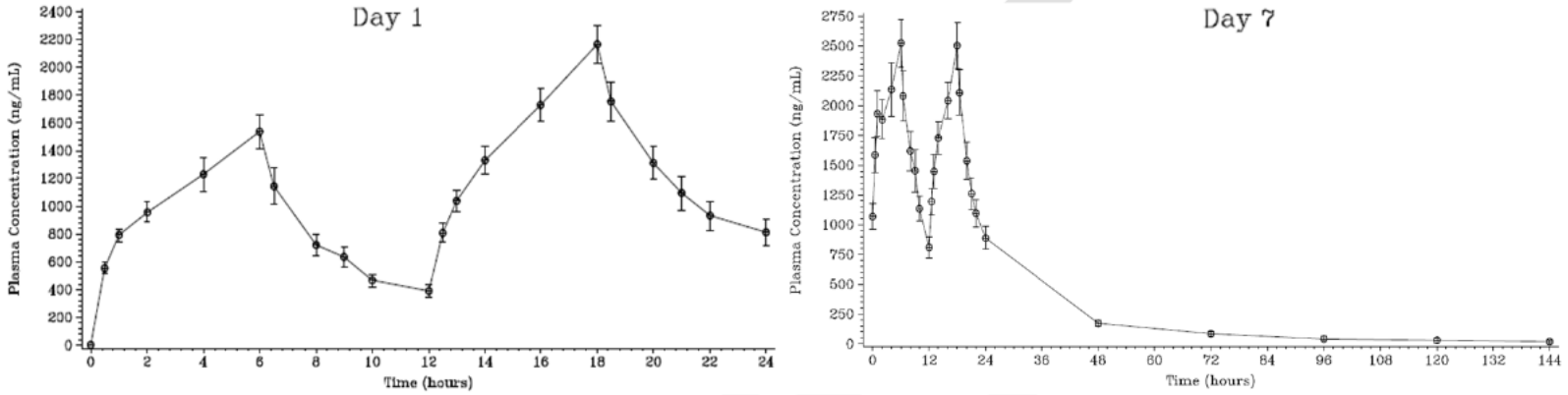
Table 11: Statistical Analysis of Plasma Pharmacokinetic Parameters of Tecovirimat

Parameter	Ratio (%) of Geometric LS Means (90% CI) (Oral/IV)
Dose normalized C_{max} (ng/mL)	0.41 (0.37, 0.46)
Dose normalized $AUC_{0-\infty}$ (h*ng/mL)	0.46 (0.43, 0.49)

Period 3

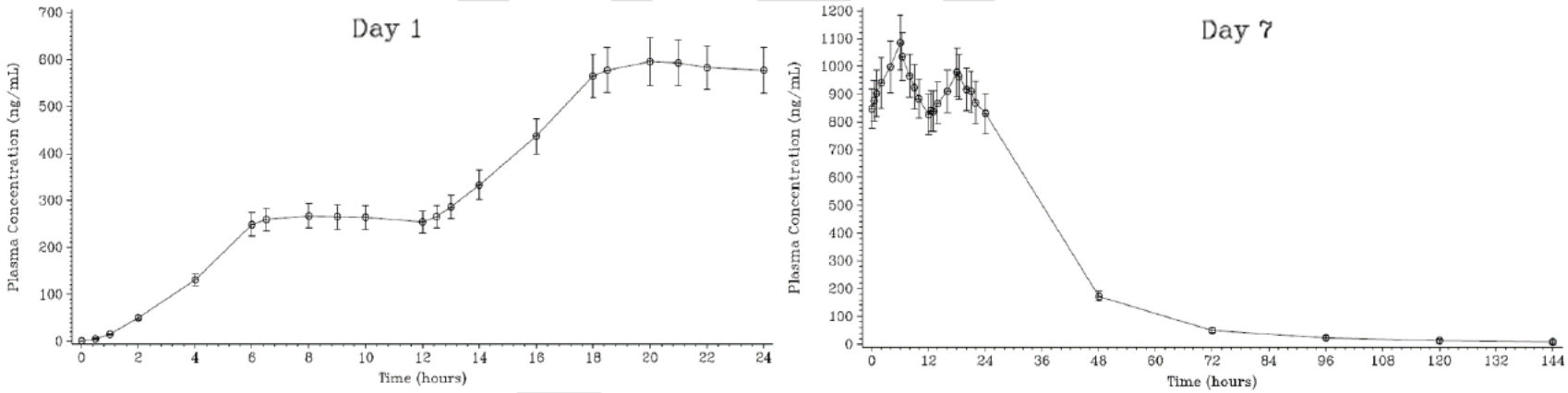
Mean plasma concentration-time profiles for tecovirimat and its metabolites on Day 1 and Day 7 are presented in Figure 11 to Figure 14. The plasma concentrations of tecovirimat and its metabolites were analyzed using noncompartmental analysis to derive PK parameter estimates reported in Table 12.

Figure 11: Mean (±SD) Plasma Concentrations of Tecovirimat in Plasma (Left: Day 1, Right: Day 7)



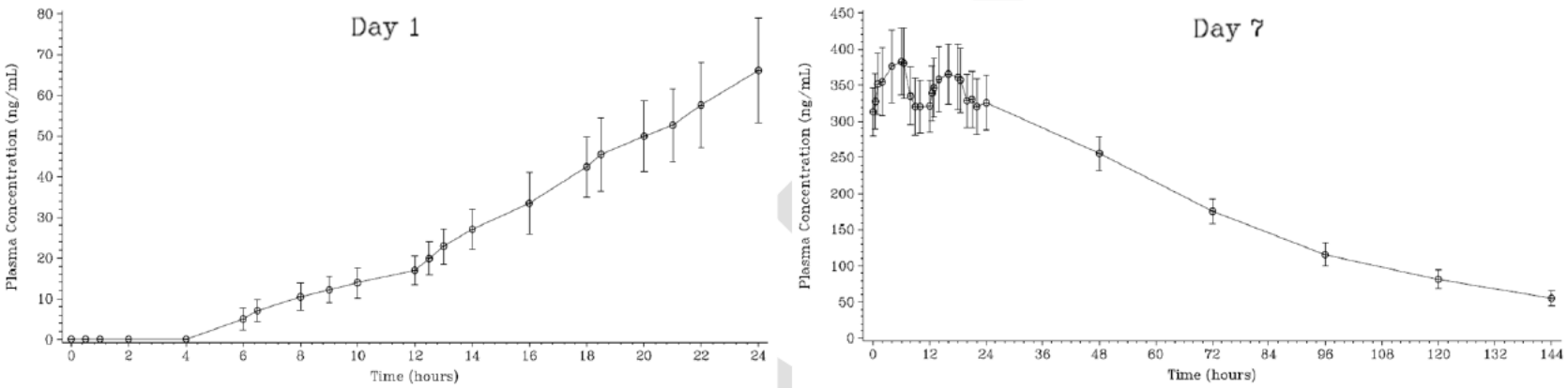
Source: Adapted from Study SIGA-246-IV-202 report

Figure 12: Mean (±SD) Plasma Concentrations of M4 in Plasma (Left: Day 1, Right: Day 7)



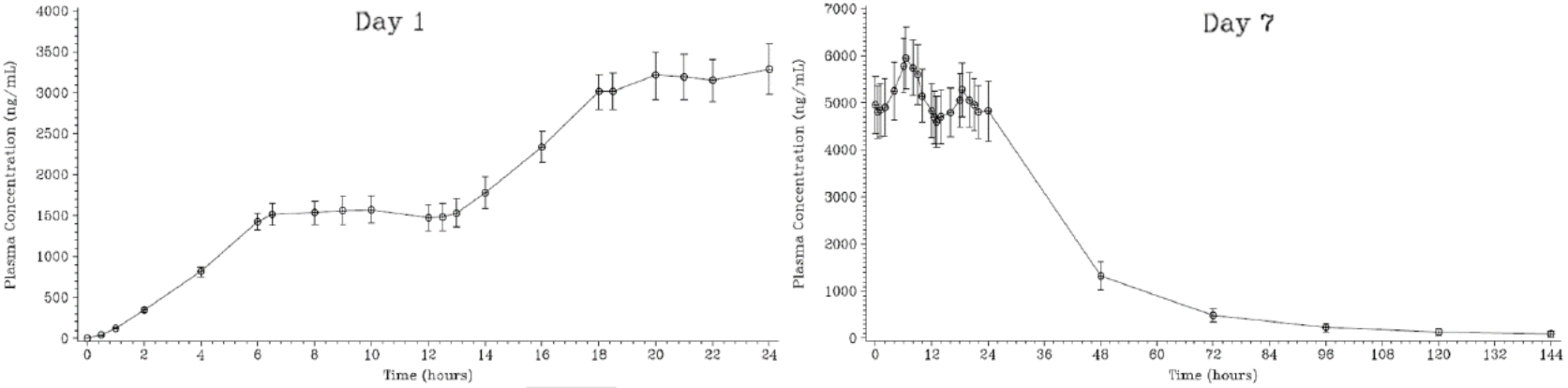
Source: Adapted from Study SIGA-246-IV-202 report

Figure 13: Mean (±SD) Plasma Concentrations of M5 in Plasma (Left: Day 1, Right: Day 7)



Source: Adapted from Study SIGA-246-IV-202 report

Figure 14: Mean (±SD) Plasma Concentrations of TFMBA in Plasma (Left: Day 1, Right: Day 7)



Source: Adapted from Study SIGA-246-IV-202 report

Table 12: Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for Tecovirimat and Metabolites (N=22)

Dose	AUC_{0-24} (ng·h/mL)	AUC_{0-12} (ng·h/mL)	C_{max} (ng/mL)	T^{a}_{max}(h)	$T_{1/2}$(h)
Tecovirimat					
Day 1	26547 (20.5)	10446 (22.4)	2166 (17.1)	18 (18-18)	-
Day 7	40370 (22.4)	20833 (23.8)	2688 (21.4)	11 (1-18.5)	21 (45.1)
M4					
Day 1	7932 (22.9)	2167 (25.4)	619 (23.7)	20 (18-24)	-
Day 7	22161 (22.9)	11410 (23.1)	1118 (23.8)	6 (2-18)	18.37 (53.3)
M5					
Day 1	576 (52.8)	78 (72.5)	67 (51.6)	24 (20-24)	-
Day 7	8329 (31.9)	4194 (32.2)	421 (34.5)	6 (0.5-18)	44.54 (42.1)
TFMBA					
Day 1	44015 (22.5)	12873 (23.9)	3498 (25.3)	22 (18-24)	-
Day 7	122229 (30.4)	63653 (30.1)	6181 (28.5)	7 (4-24)	21.28 (48.8)

a: Median [Range] values reported following the second dose at approximately 12 hour, h: Hours, NE: not estimable, Source: Adapted from Study SIGA-246-IV-202 report

Applicant's Conclusions:

- The mean absolute oral bioavailability (F) of tecovirimat determined using dose normalized $AUC_{0-\infty}$ ($DAUC_{0-\infty}$) was 48% of IV infusion.
- On Day 7, the geometric mean AUC_{0-24} of M4, M5, and TFMBA values were increased approximately 3-fold, 16-fold, and 3-fold, respectively, compared with those values on Day 1 indicating some accumulation of these metabolites due to repeat dosing of tecovirimat.

Reviewer's Assessments: *The Applicant's conclusions are reasonable. The systemic exposures to tecovirimat and its metabolites on Day 7 were compared by the Reviewer with the values reported for Day 14 following the administration of tecovirimat 600 mg BID*

dosing with the currently approved oral formulation under fed conditions. The exposures estimates were extracted from the previous clinical pharmacology review from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/208627Orig1s000ClinPharmR.pdf.

The comparison of steady-state exposures following the administration of proposed 200 mg tecovirimat BID 6-hr infusion dosing regimen and the currently approved tecovirimat 600 mg BID dosing regimen under fed conditions shows that mean tecovirimat exposures were 13-40% higher and its metabolites exposures were 4-27% lower (Table 13). Similar difference in Day 1 exposure was not observed in PK data from periods 1 and 2 (Figure 7 and Table 6). The rationale for this observation is not clear.

Table 13: Comparison of Exposure Following IV and Oral Administrations

Parameters		Mean Estimates (CV%)		
		Following 200 mg tecovirimat BID 6-hr IV Infusion on Day 7 (N=22)	Following 600 mg tecovirimat BID oral with food on Day 14 (N=48)	% Change from Oral Treatment
Tecovirimat				
	C_{max}	2166 (17.1)	1516 (32)	↑ 43%
Day 1	AUC_{0-24}	26547 (20.5)	20879 (35)	↑ 27%
	C_{min}	814 (31.9)	477 (65)	↑ 71%
	C_{max}	2688 (21.4)	2106 (33)	↑ 28%
Steady-State	AUC_{0-24}	40370 (22.4)	28791 (35)	↑ 40%
	C_{min}	778 (29.3)	689 (38)	↑ 13%
M4				
	C_{max}	1118 (23.8)	1230 (34)	↓ 9%
	AUC_{0-24}	22161 (22.9)	22969 (33)	↓ 4%
M5				
	C_{max}	421 (34.5)	578 (61)	↓ 27%
	AUC_{0-24}	8329 (31.9)	11260 (62)	↓ 26%
TFMBA				
	C_{max}	6181 (28.5)	7391 (39)	↓ 16%
	AUC_{0-24}	122229 (30.4)	142506 (41)	↓ 14%

Source: Collated PK data from Study SIGA-246-IV-202 and clinical pharmacology review from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/208627Orig1s000ClinPharmR.pdf.

3.3. Pharmacometrics Review

A Population Pharmacokinetics (popPK) model was developed by the Applicant to characterize the PK of tecovirimat in healthy adult subjects, and to characterize subjects intrinsic and extrinsic factors which influence the PK and PK variability of tecovirimat. Simulations were conducted to select the dosing regimen following IV formulation with the aim to match tecovirimat exposure within the target range derived from NHP pivotal studies to provide the efficacy margin, as well as from dog toxicology study to provide the safety limit. Further simulations were used to determine the dosage of both oral and IV formulation in the scenarios of starting with oral formulation and switching to IV formulation, and vice versa. In this review, the FDA review team evaluated the Applicant's popPK model and simulations, as well as conducted independent analyses to recommend the appropriate dosing regimen for IV infusion and formulation switching between IV and oral administration.

3.3.1 Population PK Analyses

The Applicant originally developed a popPK model based on two clinical studies, SIGA-246-IV-201 and SIGA-246-IV-202. In both studies, the adult healthy subjects received single or multiple doses of tecovirimat IV infusion. Of the 69 subjects included in this popPK analysis, 6 subjects (8.7%) received a single dose of 37.5, or 75, or 150 mg, 38 subjects (55.1%) received a single dose of 200 mg, and 13 subjects (18.8%) received 240 mg BID for 7 days. Effects of age, body weight, gender, race/ethnicity, and dose levels were tested in the popPK analysis. Only body weight and dose levels ($<$200 mg or $\geq$200 mg) were identified as significant covariates as shown in Table 14.

Table 14 Final popPK model parameters of tecovirimat (IV formulation)*

Pop PK Parameters	Dose (mg BID)	Population Estimates (CV%)		Between Subject Variability (η-Shrinkage)%
CL (L/h)	< 200	16.6 (8.1%)	x $[BWt/84]^{0.96}$	17.1 (7.5)%
	≥ 200	12.8 (8.1%) [a]		
CL2 (L/h)	37.5 - 240	17.5 (4.8%)	x $[BWt/84]^{1.32}$	32.5 (13.9)%
V (L)	37.5 - 240	52.3 (2.9%)	x $[BWt/84]^{0.49}$	19.1 (17.6)%
V2 (L)	< 200	250.8 (13.8%)	x $[BWt/84]^{0.87}$	29.6 (13.0)%
	≥ 200	147.4 (13.8%)[b]		
Error Model	37.5 - 240	Additive Error: 6.7 Proportional Error: 16.6%		-

[a]Approximately 23% less CL compared to < 200 mg BID
[b]Approximately 41% less V2 compared to < 200 mg BID
KEY: BID = twice daily; BWt = bodyweight; CL = central clearance; CL2 = peripheral clearance; PK = pharmacokinetic; Pop = population; V = central volume of distribution; V2 = peripheral volume of distribution

Source: Applicant's original popPK study report for IV formulation

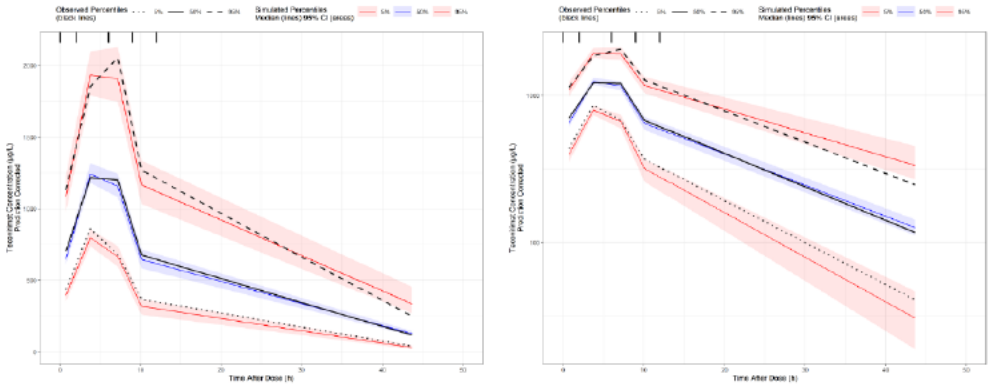
The Applicant claimed a linear PK observed from the subjects received tecovirimat IV infusion. However, dose level was identified as a significant covariate on CL. Population estimates of CL and V2 were respectively 23% and 41% lower in subjects received tecovirimat dose ≥200 mg BID compared to those received <200 mg BID dose. Based on the Applicant's response to FDA's information request (IR), the decrease of CL at higher doses was also observed in cynomolgus monkeys administered at single 4-h infusion doses of 1, 3, 10, 20, and 30 mg/kg and 6-h infusion doses of 20 and 30 mg/kg. Thus, FDA review team considered that the elimination of tecovirimat may not follow a linear manner.

To address the impact of dose dependency on model predictions, the Applicant conducted a sensitivity analysis on the popPK model. The goodness-of-fits and model predictions derived from the final model were compared to those derived with the model without dose effects on CL and V2 (base model). Based on visual predictive checks (VPCs), the final model showed slight improvement in prediction of the median concentration compared to the base model (Figure 15 and Figure 16). In addition, the tecovirimat exposure

(Cmin, Cmax and AUC0-24) were simulated from the two models and compared to the exposure levels obtained from observed concentrations. The Applicant concluded that the dose effects on CL and V2 did not have significant impact on the key exposure parameters used to support the dosing regimen (Figure 17).

Figure 15 Visual Predictive Check plots of popPK model with covariates (final model) -- linear and semi-log scales

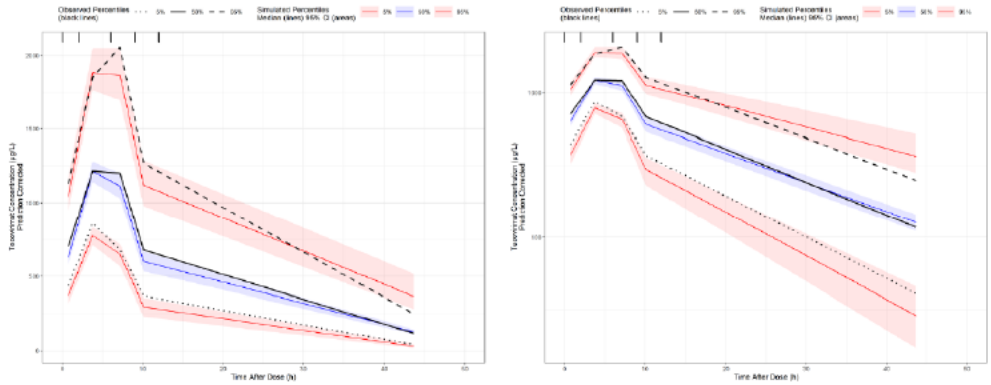
Linear Scale **Semi-Log Scale**



Source: Applicant response to FDA Clin Pharm IR sent on Sep 22, 2021

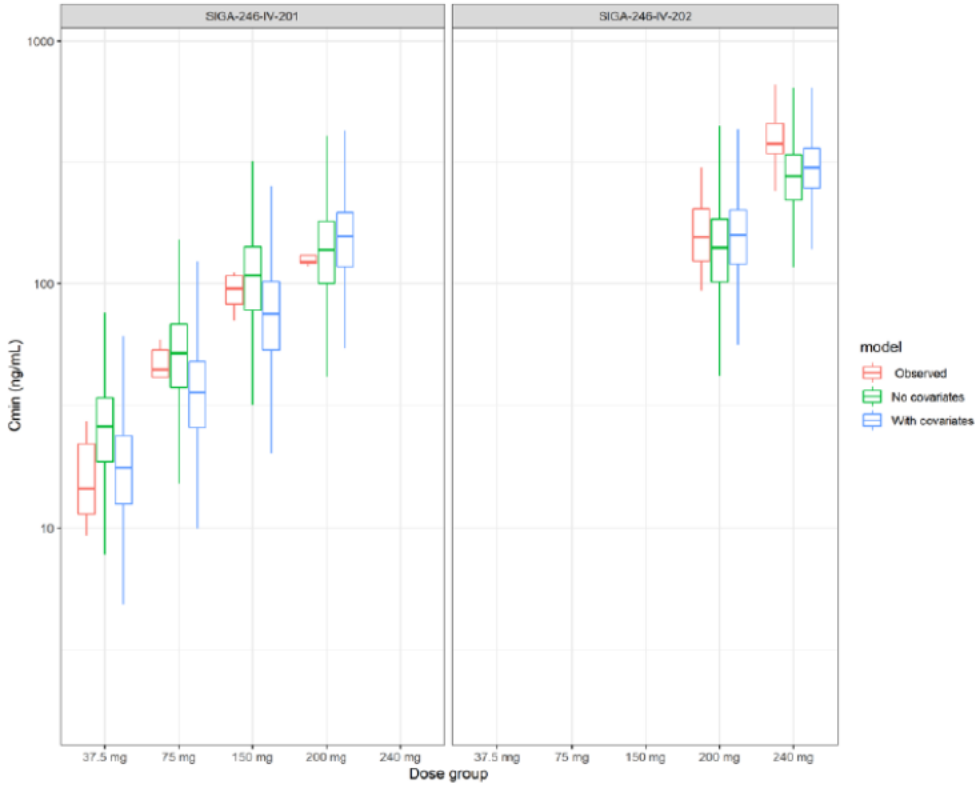
Figure 16 Visual Predictive Check Plots of Population PK Model Without Covariates (base model) -- linear and semi-log scales

Linear Scale **Semi-Log Scale**

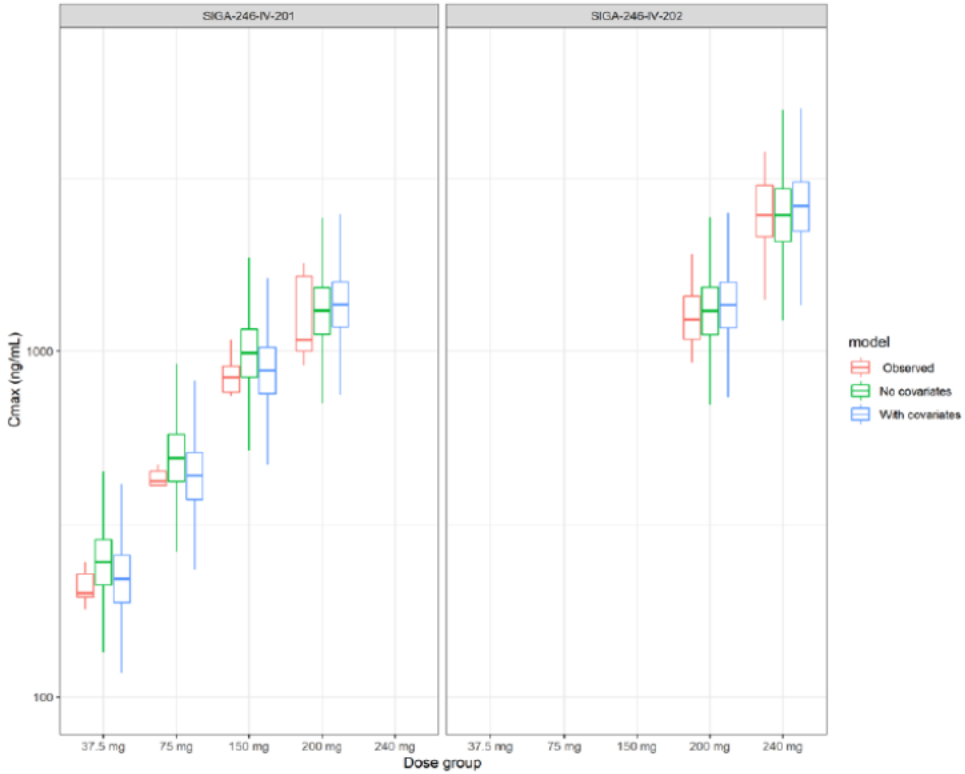


Source: Applicant response to FDA Clin Pharm IR sent on Sep 22, 2021

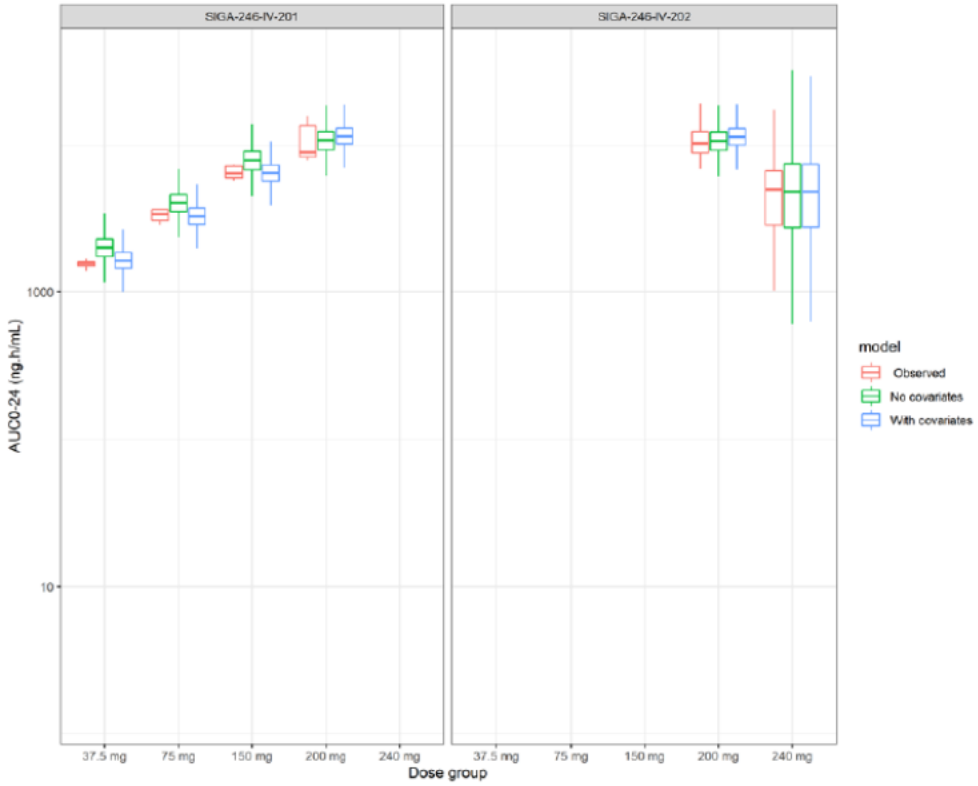
Figure 17 Distribution of Cmin, Cmax and AUC0-24 simulated with models with and without dose effects vs dose group, compared to observed Cmin, Cmax and AUC0-24, respectively.



KEY: C_{min} = minimum concentration of tecovirimat within 24 h



KEY: C_{max} = maximum concentration of tecovirimat within 24 h



KEY: $AUC_{0\text{-}24}$: area under concentration-time curve from times 0 to 24 h after dose

Source: Applicant response to FDA Clin Pharm IR sent on Sep 22, 2021

Generally, the simulated Cmin, Cmax and AUC0-24 based on the final model appeared to be closer to the observed exposure parameters, compared to the simulated exposure parameters obtained from the base model. The simulated exposure parameters obtained from the base model were slightly over predicted. Therefore, the current popPK model developed by the Applicant is considered acceptable to describe the PK of tecovirimat and further, to support the dose selection for pediatrics.

The Applicant conducted simulation by fixing the allometric scaling coefficients at 0.75 for CL and CL2, and 1 for V and V2, which were different from the model estimated allometric scaling coefficients (Table 14). Thus, FDA review team performed a sensitivity

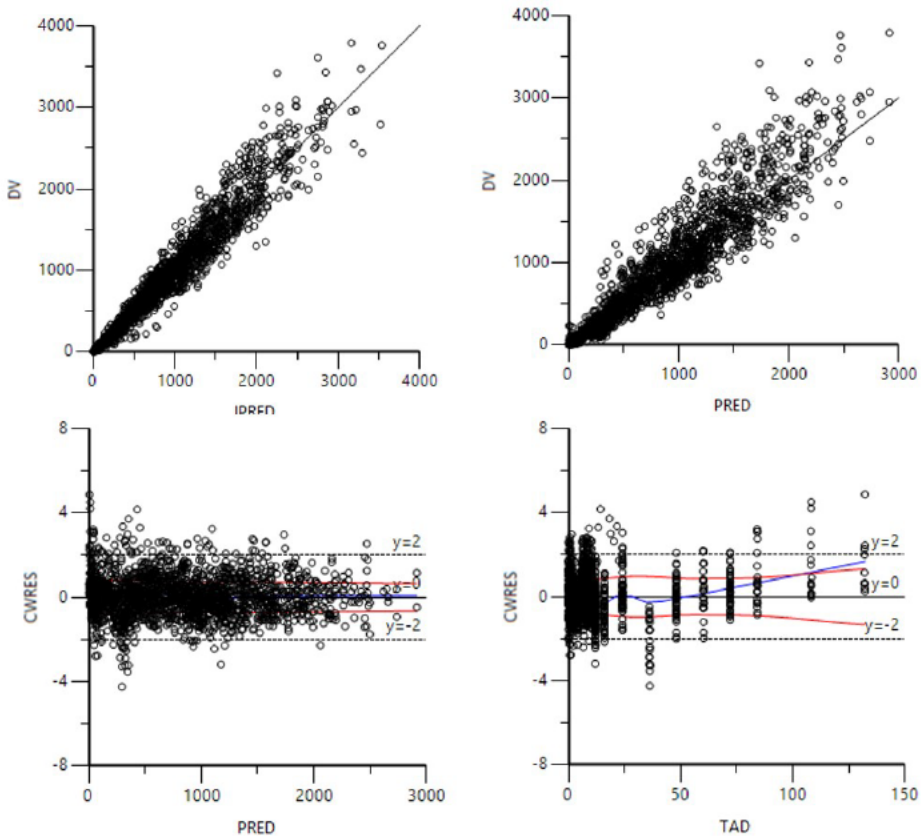
analysis by fitting the popPK model using the fixed allometric scaling coefficients at 0.75 for CL and CL2, and 1 for V and V2. The -2 × Log Likelihood (-2LL) and model estimated parameters are similar to those in the Applicant's final population PK model (Table 15). The goodness-of-fit plots of the popPK model in the sensitivity analysis are also similar to Applicant's final model (Figure 18).

Table 15 Comparison of PK parameters estimated by Applicant's final popPK model and sensitivity analysis popPK model

PK Parameter	Dose (mg BID)	Applicant Final PopPK Model		Sensitivity Analysis PopPK Model	
		Estimates (CV%)	BSV (η-Shrinkage) %	Estimates (CV%)	BSV (η-Shrinkage) %
CL (L/h)	< 200 ≥ 200	16.6 (8.1%) 12.8 (8.1%)	17.1 (7.5) %	16.7 (5.1%) 12.3 (5.1%)	17.7 (7.3) %
CL2 (L/h)	37.5 – 240	17.5 (4.8%)	32.5 (13.9) %	17.4 (5.1%)	34.9 (12.8) %
V (L)	37.5 – 240	52.3 (2.9%)	19.1 (17.6) %	52.5 (3.0%)	20.7 (15.0) %
V2 (L)	< 200 ≥ 200	250.8 (13.8%) 147.4 (13.8%)	29.6 (13.0) %	247.5 (6.9%) 121.0 (6.9%)	30.3 (12.7) %

Source: Applicant's popPK study report and Reviewer analyses

Figure 18 Goodness-of-fit plots for sensitivity analysis popPK model



Source: Reviewer analysis

To better characterize the PK of tecovirimat and facilitate simulations to evaluate the formulation switching scenarios, FDA review team requested the Applicant to update the popPK model by combining the data from all available oral formulation trials (e.g., Studies 022, 004, 008 and 018, as well as Period 2 in Study SIGA-246-IV-202) and the data from IV formulation trials (Studies SIGA-246-IV-201 and SIGA-246-IV-202). The tecovirimat dose ranges were 37.5-240 mg and 100-600 mg for IV and oral administrations,

respectively. The popPK analysis included 286 subjects with 6646 PK observations. All subjects receiving the oral dose were under fed conditions with the same formulation. The covariates are summarized in Table 16.

Table 16 Summary of continuous and categorical covariates at baseline by study

Covariate	Mean (CV%) Median [Minimum, Maximum] Geometric Mean (Geometric CV%)						
	246-004 (N=87)	246-008 (N=48)	246-018 (N=48)	SIGA-246-022 (N=34)	SIGA-246-IV-201 (N=24)	SIGA-246-IV-202 (N=45)	Overall (N=286)
Age (years)	42.4 (37.2) 42.0 [18.0, 73.0] 39.3 (42.0)	38.9 (42.1) 39.0 [18.0, 72.0] 35.7 (44.0)	31.2 (23.6) 31.0 [18.0, 45.0] 30.3 (25.3)	35.5 (23.4) 34.5 [20.0, 50.0] 34.5 (25.6)	31.1 (28.8) 27.5 [22.0, 50.0] 30.0 (27.7)	39.9 (30.3) 38.0 [20.0, 62.0] 38.1 (31.7)	37.8 (35.9) 36.0 [18.0, 73.0] 35.5 (36.8)
Weight (kg)	78.4 (20.4) 78.6 [42.7, 133] 76.8 (21.0)	85.2 (21.0) 85.3 [54.3, 145] 83.4 (20.7)	73.4 (19.0) 70.7 [42.3, 111] 72.1 (19.7)	138 (15.1) 131 [120, 220] 137 (13.6)	83.8 (15.9) 82.4 [51.7, 108] 82.7 (16.9)	85.2 (17.0) 85.5 [58.2, 117] 84.0 (17.2)	87.3 (28.7) 82.9 [42.3, 220] 84.2 (26.9)
Sex	N (%)						
Female	42 (48.3%)	24 (50.0%)	20 (41.7%)	23 (67.6%)	15 (62.5%)	27 (60.0%)	151 (52.8%)
Male	45 (51.7%)	24 (50.0%)	28 (58.3%)	11 (32.4%)	9 (37.5%)	18 (40.0%)	135 (47.2%)

KEY: CV= coefficient of variation; N= number of subjects

Dose Category	N (%)		
	Intravenous Administration	Oral Administration	Overall
Dose Category 1			
IV and Oral Dose < 200 mg	18 (26.1%)	12 (4.82%)	30 (9.43%)
IV Dose ≥ 200 mg	51 (73.9%)		51 (16.0%)
Oral Dose ≥ 200 mg		237 (95.2%)	237 (74.5%)
Dose Category 2			
IV Dose > 200 mg	26 (31.7%)		26 (7.85%)
IV Dose ≤ 200 mg	56 (68.3%)		56 (16.9%)
Oral Dose > 200 mg		225 (90.4%)	225 (68.0%)
Oral Dose ≤ 200 mg		24 (9.64%)	24 (7.25%)

KEY: IV= intravenous; N= number of subjects
NOTE: Subjects from the crossover study SIGA-246-IV-202 were assigned to multiple categories

Source: Applicant's response to an IR sent on September 22, 2021

The combined popPK model was a 2-compartment model with linear elimination. Oral absorption was described by a first-order process with lag time of absorption, and oral bioavailability was estimated relative to IV administration. The allometric scaling factors were fixed at 0.75 and 1 for clearances and volumes of distribution, respectively. The PK parameters estimated by the combined final popPK model are summarized in Table 17. The shrinkages of ETAs of the combined popPK model appears to be larger than that estimated by the original popPK model developed using IV formulation only. Thus, simulations for dosage following IV

administration based on the original popPK model may provide a more reliable result. Based on goodness-of-fit (GOF) plots (Figure 19), the combined popPK model developed by the Applicant is accepted to describe the PK of tecovirimat following oral or IV dosing in adult subjects. However, based on the combined model estimation, CL in subjects received ≥200 mg IV dose is higher than that in subjects received <200 mg IV dose, which was contrary to the existed popPK models based on IV or oral formulation only. In addition, the Applicant added dose effect on CL2, which was not identified in existed popPK models using IV data or oral data. Thus, FDA review team modified the Applicant's combined popPK model based on the existing popPK models developed using IV or oral data only. The details will be discussed in the section 3.3.4 (Reviewer's Analyses).

Table 17 Final model parameter estimates for tecovirimat PK based on the combined oral and *IV* data

Parameter	Typical Value		BSV		
	Estimate	RSE (%)	Estimate (%)	RSE (%)	Shrinkage (%)
Bioavailability	0.310	9.59	37.7	10.2	32.3
Lag (h)	0.612	37	63.8	64.1	27.1
Ka (1/h)	0.319	12.3	51.6	9.6	20.6
CL (L/h) IV and Oral dose < 200 mg	12.8 (Weight/82.9)$^{0.75}$	12.0	24.9	25.3	25.8
IV dose ≥ 200 mg	× 1.08 (13.9 L/h)	14.8	-	-	-
Oral dose ≥ 200 mg	× 0.864 (11.1 L/h)	11	-	-	-
Vc (L)	55.6 (Weight/82.9)	7.02	30.5	11.9	35.2
CL2 (L/h) IV dose > 200 mg	14.9 (Weight/82.9)$^{0.75}$	20.8	65.0	12.7	16.8
IV dose ≤ 200 mg	× 0.742 (11.1 L/h)	18.6	-	-	-
Oral dose > 200 mg	× 0.614 (9.15 L/h)	23.8	-	-	-
Oral dose ≤ 200 mg	× 0.561 (8.36 L/h)	22.9	-	-	-
V2 (L)	145 (Weight/82.9)	10.5	55.9	13.3	22.0
Multiplicative (log)	0.343	8.73	-	-	-

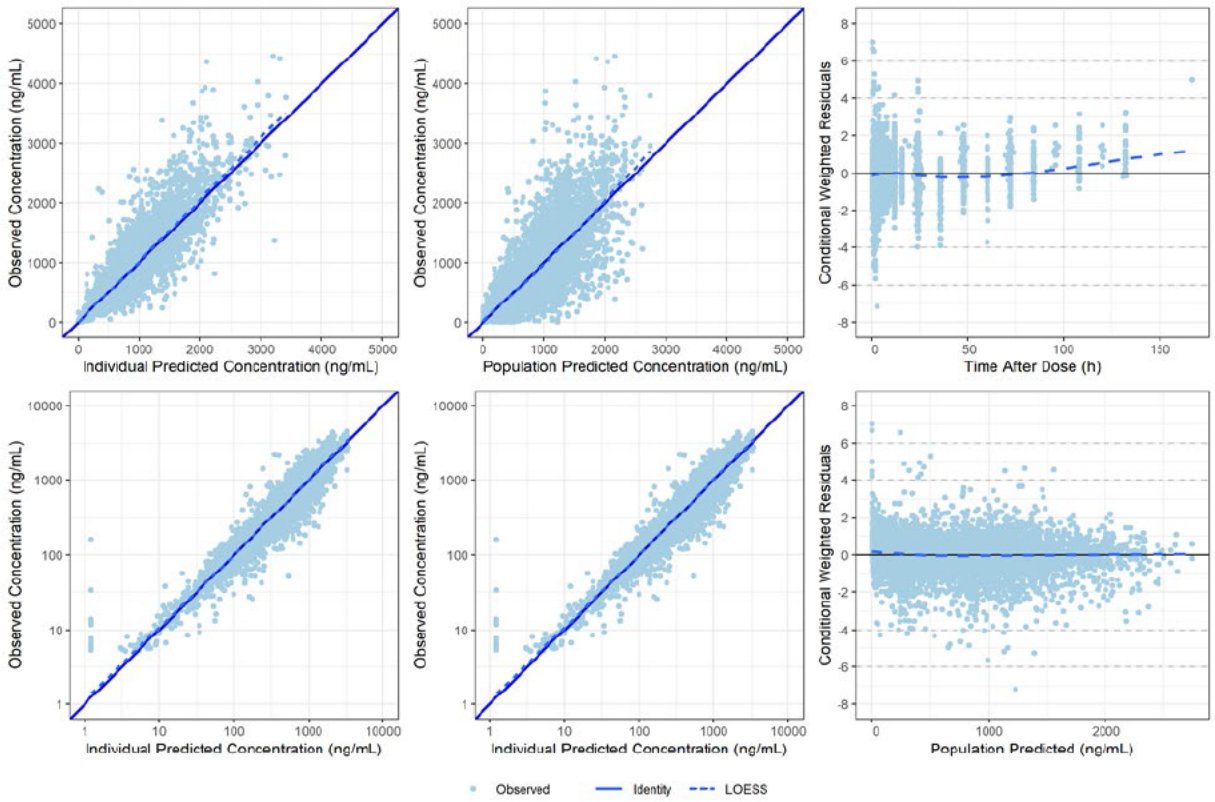
KEY: BSV= between subject variability; CI=confidence interval; CL=clearance; CL2 =inter-compartmental clearance; F=oral bioavailability; Ka=absorption rate constant; RSE= relative standard error; Vc= central volume of distribution; V2=peripheral volume of distribution

NOTE: The Phoenix settings for the base and final models are presented in the Appendix

NOTE: RSE was derived with bootstrap outputs

Source: Applicant's response to an IR sent on September 22, 2021

Figure 19 Goodness-of-fit plots for the updated final model based on the combined oral and *IV* data



KEY: CWRES=conditional weighted residuals; DV=dependent variable (usually observation); GOF=goodness-of-fit; IPRED=individual predictions; IV=intravenous; LOESS=locally weighted scatterplot smoothing; PRED=population predictions

Source: Applicant's response to an IR sent on September 22, 2021

3.3.2 Dosing Selection for Pediatric IV Infusion Based on Population PK Simulation

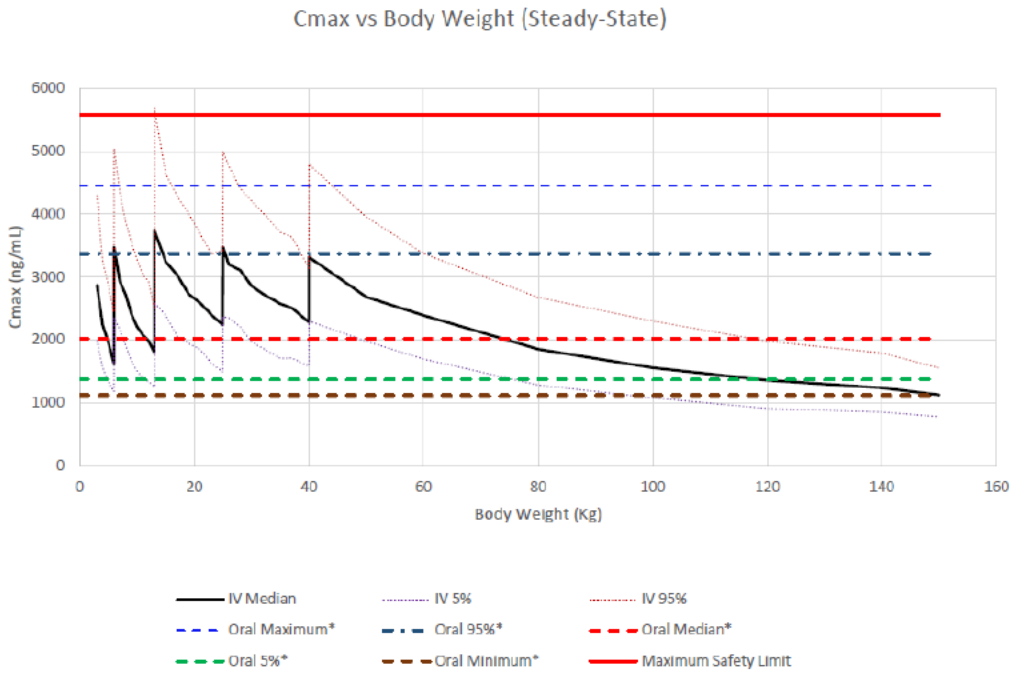
The Applicant simulated rich concentration-time profiles of tecovirimat for their proposed dosing regimen of IV infusion (Table 18) using the original popPK model developed based on IV data. They estimated individual PK parameters of tecovirimat, and derived the

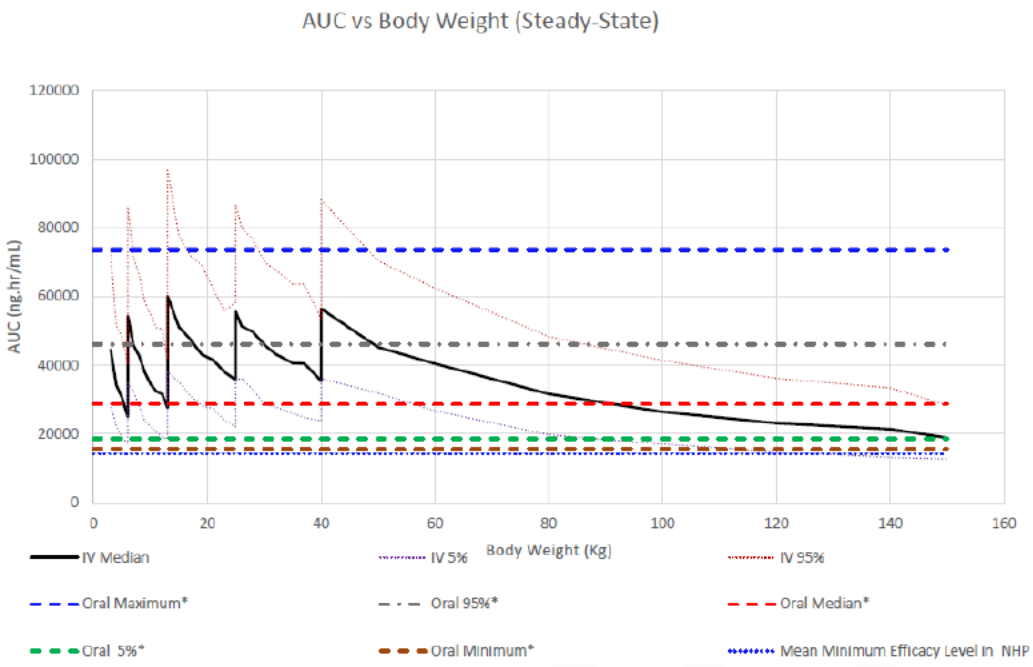
exposure metrics (Cmax, Cmin and AUC24h of Day 1 and steady-state) for each individual. The virtual population was constructed with the body weight range from 3 to 150 kg, which was divided into 5 body weight groups. The simulations were replicated (n=250) to generate a distribution of values for each body weight range. The proposed doses for different body weight groups in Table 18 were selected by the Applicants to provide comparable drug exposures to those observed in subjects administered with tecovirimat oral capsules at 600 mg BID (Study 008). The simulated tecovirimat exposures at steady state following the proposed dosing regimen are shown in Figure 20.

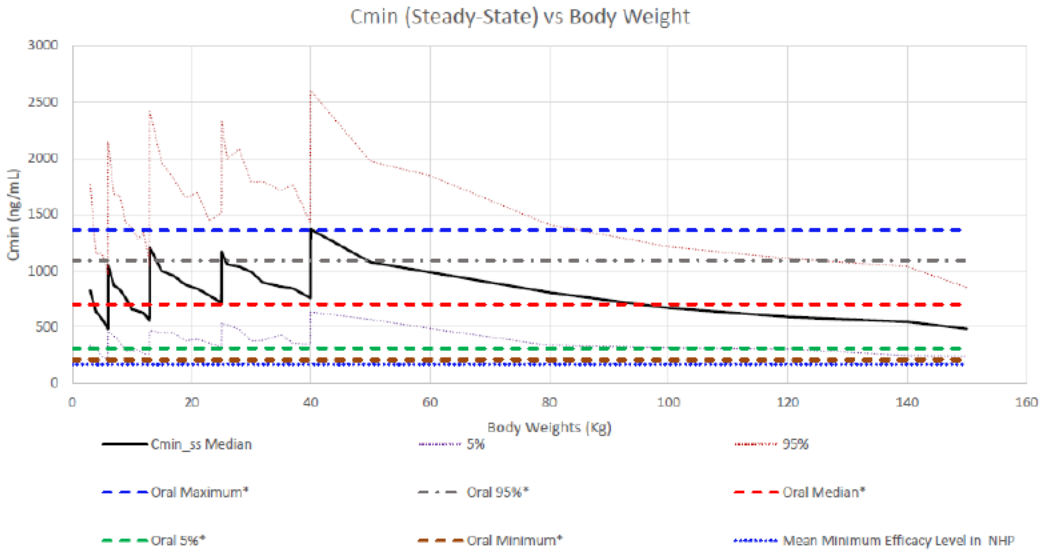
Table 18 Applicant proposed dosing regimens for different body weight groups following IV infusion

Source: Applicant popPK study report

Figure 20 Applicant simulated Cmax, AUC and Cmin at steady state for different body weight groups







Source: Applicant's popPK study report

As shown in Figure 20, 5% of the model simulated Cmax for subjects with body weight of approximately 13 kg will potentially exceed the safety limit from the dog toxicology study. In addition, following the Applicant proposed IV dosing regimen, the administered amount of β-cyclodextrin in lowest body weight pediatric subjects was considered high (b) (4) Furthermore, for subjects with high body weight (e.g., ≥ 120 kg), AUC and Cmin following 200 mg BID 6-hour IV infusion are predicted to be lower than the observed exposure following 600 mg BID oral formulation from Study 008, while the Applicant only simulated the exposure for subjects with body weight up to 150 kg. Thus, to avoid potential toxicity for subjects with low body weight pediatric subjects and to avoid the loss of efficacy for subjects with body weight ≥ 120 kg, alternative IV dosing regimens were evaluated by the FDA review team as discussed in section 3.3.4.

3.3.3 Switching Between Oral and IV Dosing Based on Population PK Simulation

During the treatment with tecovirimat, it is expected that some patients may need to switch from IV formulation to oral formulation or vice versa. Upon FDA's request, the Applicant simulated scenarios of switching to IV administration from oral formulation or vice versa. However, given the issues in the combined popPK model as discussed above, this review will not discuss about the Applicant's

simulation results. After refining the popPK model, the FDA review team performed independent simulations for the formulation switching scenarios. The details will be discussed in section 3.3.4 (Reviewer's Analyses)

3.3.4 Reviewer's Analyses

3.3.4.1 Dose selection for IV formulation

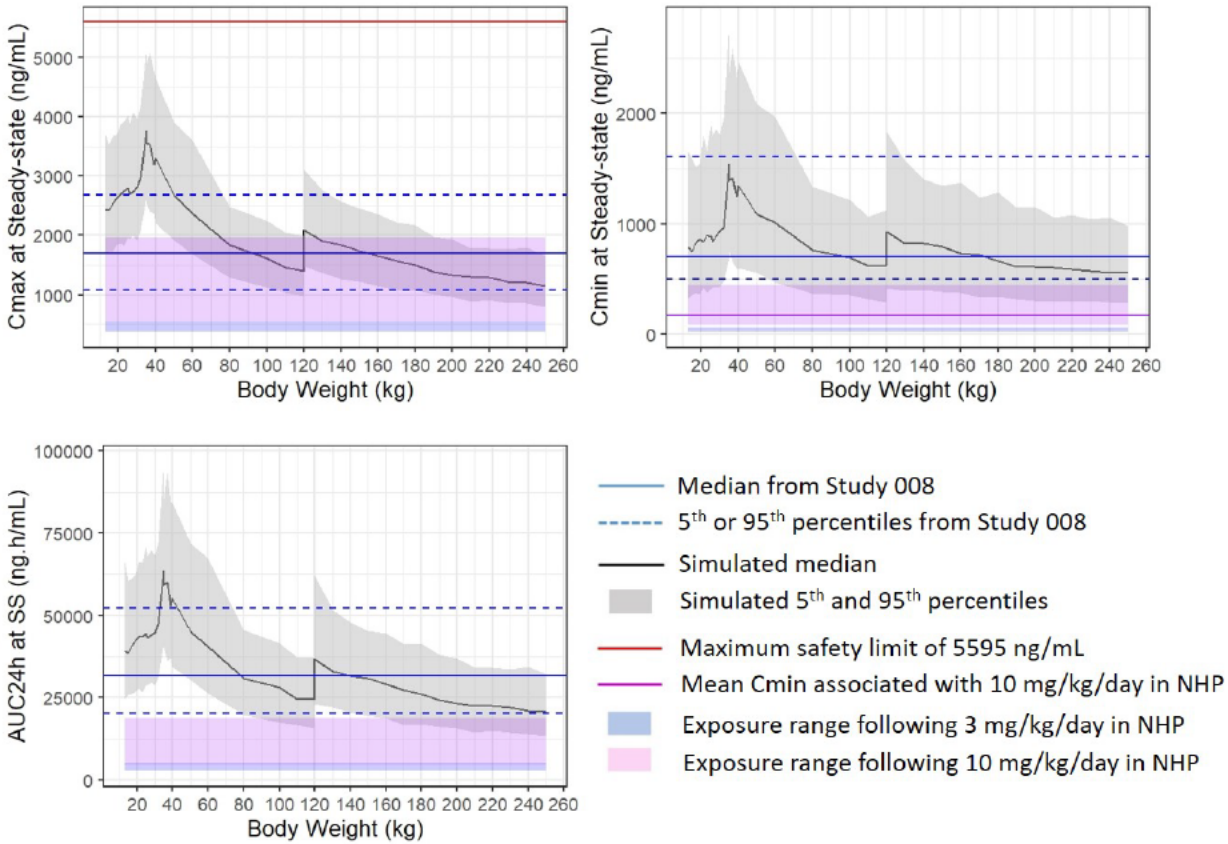
As discussed in section 3.3.2, following the Applicant proposed [redacted] (b) (4) may exceed the safety limit of 5595 ng/mL from dog toxicology study (Figure 20). In addition, the administered amount of β-cyclodextrin in subjects with the lowest body weight was considered high [redacted] (b) (4) Furthermore, based on Applicant simulation (Figure 20), the predicted AUC and Cmin in subjects with high body weight (120 to 150 kg) appeared to be lower than the observed range from Study 008. For subjects with body weight higher than 150 kg, the exposure in them is expected to be even lower.

To address these issues, FDA review team conducted independent analyses to explore alternative dosing regimens with the aim to keep exposure at steady-state across the body weight range within the target exposure range (between 169 ng/mL and 5595 ng/mL), as well as to lower the administered amount of β-cyclodextrin in pediatric subjects with the lowest body weight. The simulation method was consistent with the Applicant's [redacted] (b) (4) Based on the simulation results, the following dosing regimen was selected by the FDA review team to optimize benefit and risk profile across the intended population:

- 3 to <35 kg: 6 mg/kg 6-hr IV infusion BID
- 35 to <120 kg: 200 mg 6-hr IV infusion BID
- 120 kg and above: 300 mg 6-hr infusion BID

This newly selected dosing regimen could significantly lower the amount of β-cyclodextrin administered in lowest body weight pediatric subjects by using mg/kg dose in subjects weighing 3 to <35 kg, as well as avoid the potential loss of efficacy in high body weight subjects (120 kg and above) by increasing the dose level to 300 mg from the Applicant proposed [redacted] (b) (4) In addition, this new dosing regimen also simplified the body weight tiers. As shown in Figure 21, Cmax,ss across the body weight range following this newly selected IV infusion dosing regimen is expected to be fully below the safety limit of 5595 ng/mL, and the simulated Cmin,ss in the subjects across the body weight range is above the mean Cmin of 169 ng/mL associated with 10 mg/kg/day in NHP. Thus, FDA review team recommend this dosing regimen for tecovirimat IV infusion.

Figure 21 FDA simulated Cmax, AUC and Cmin at steady-state following 6 mg/kg, 200 mg, and 300 mg 6-hr infusion BID for body weight groups of 3 to <35 kg, 35 to <120 kg, and 120 kg and above, respectively



Source: Reviewer's analysis

3.3.4.2 Population PK Analysis using combined data from IV and oral formulations

As discussed above, the dose effect on CL in Applicant's combined popPK model was contrary to the existed popPK models developed using IV or oral data only. However, the results in two existed popPK models (IV or oral) were consistent. The FDA review team conducted independent analyses to refine the combined popPK model by removing the dose effect on CL2 regardless oral

or IV formulation; removing the dose effect on CL and Vc for oral formulation, while adding this dose effect on F; as well as adding the dose effect on V2 for IV formulation, to be consistent with the existed popPK models. In addition, the inter-individual variability on bioavailability and TLAG was removed. The PK parameters estimated from this modified combined popPK model are summarized in Table 19. Compared to the Applicant developed combined model, the FDA modified model provides closer estimates to the existed popPK model based on IV or oral data only. In addition, the η-shrinkage was also smaller, indicating that the simulation based on this modified model is more reliable.

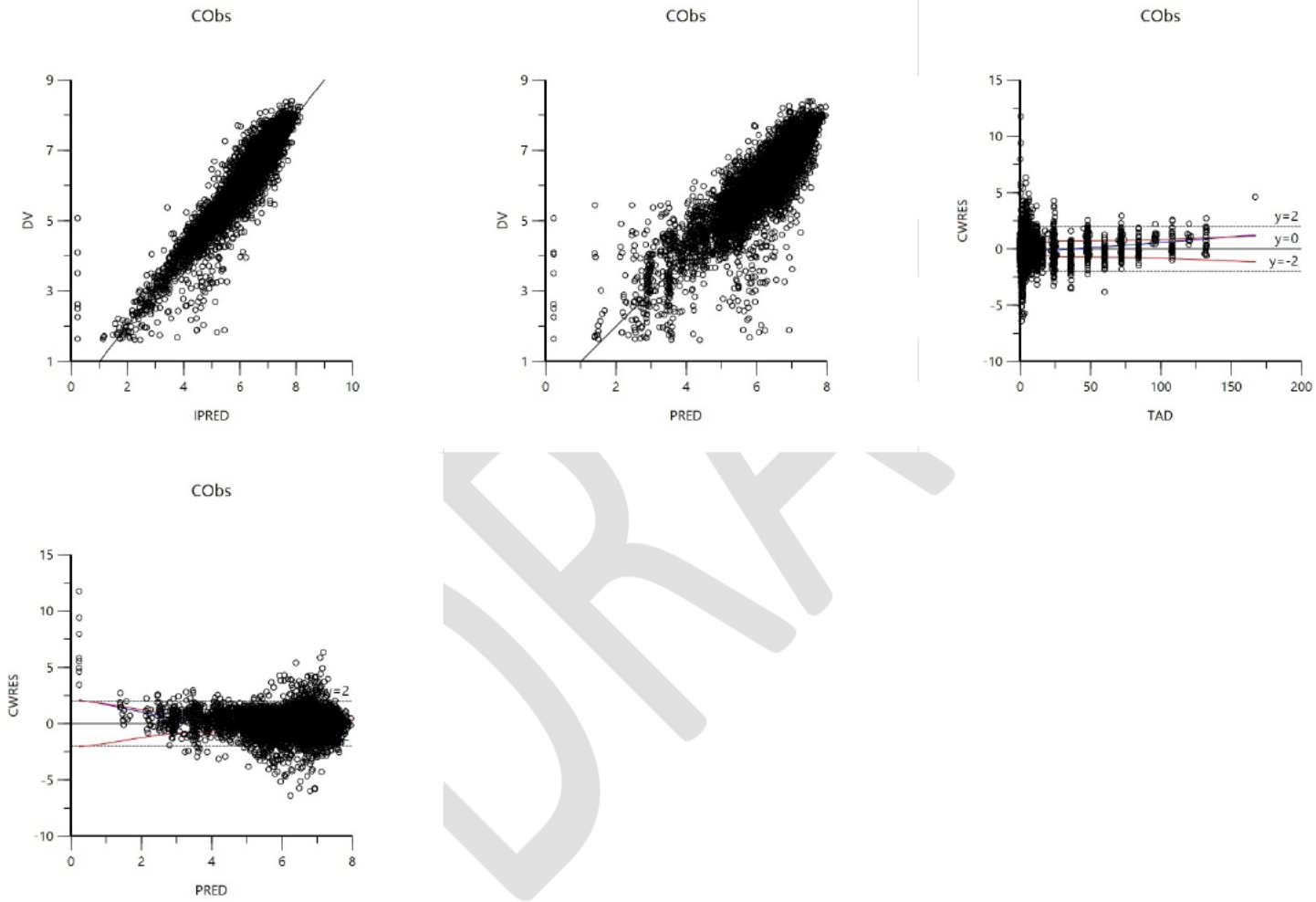
Table 19 PK parameters estimated by FDA review team updated popPK model based on combined data from IV and oral formulations

Population PK parameters		Population estimates	Inter-individual variability % (η-shrinkage)
Ka (h-1)		0.231	62.8% (14.9%)
TLAG (h)		0.467	-
CL (L/h)	<200 mg IV dose	$14.2*(Weight/82.9)^{0.75}$	29.4% (7.0%)
	≥200 mg IV dose	$13.3*(Weight/82.9)^{0.75}$	
V (L)		66.6*(Weight/82.9)	45.1% (16.1%)
CL2 (L/h)		$9.59*(Weight/82.9)^{0.75}$	73.1% (15.6%)
V2 (L)	<200 mg IV dose	173*(Weight/82.9)	54.2% (22.3%)
	≥200 mg IV dose	120*(Weight/82.9)	
F	<200 mg oral dose	0.438	-
	≥200 mg oral dose	0.373	-
Multiplicative (log)		0.412	-

Source: Reviewer's analysis

The GOF plots of this modified popPK model are shown in Figure 22. Overall, the fitting of the modified popPK model is acceptable to describe the PK of tecovirimat following IV or oral formulation in healthy adult subjects.

Figure 22 Goodness-of-fit for Reviewer modified popPK model using combined data from oral and IV formulation



Source: Reviewer's analysis

3.3.4.3 Switching between oral and IV formulations

Next, FDA's modified combined popPK model was used to conduct simulation to evaluate switching scenarios between oral and IV formulations, based on the approved dosing regimen for oral formulation and FDA's recommended dosing regimen for IV infusion. Multiple scenarios were simulated and evaluated as shown in Table 20.

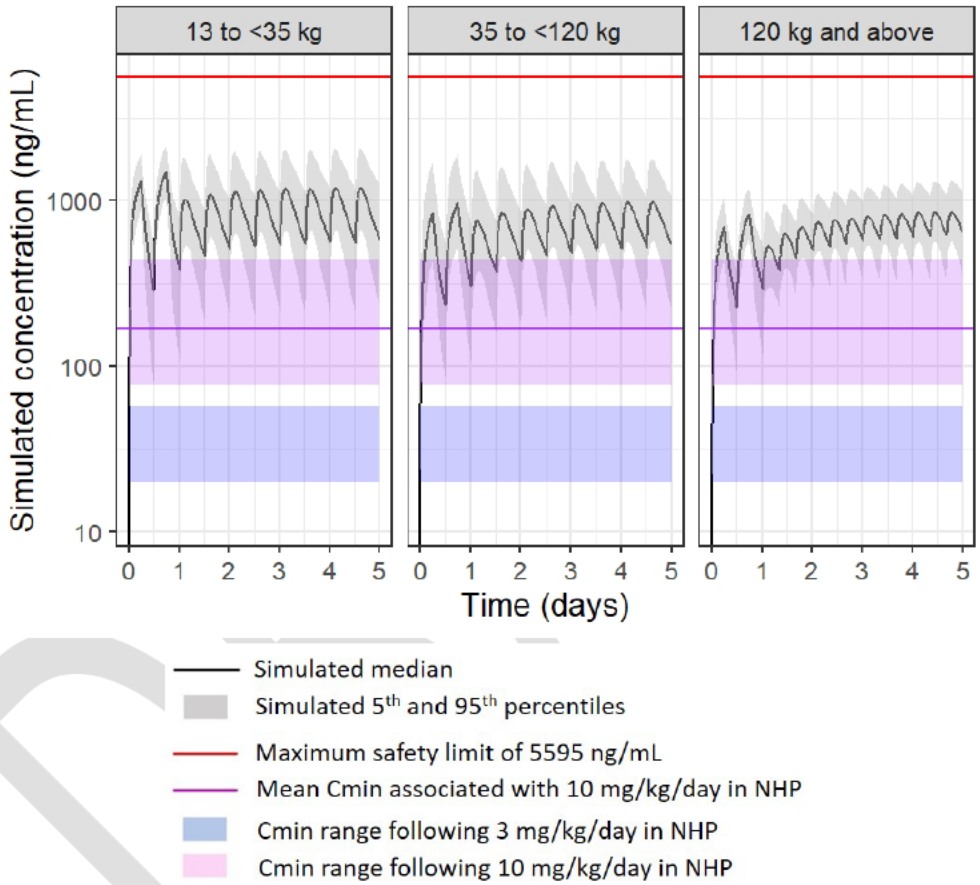
Table 20 Simulated scenarios for formulation switch

Scenario	13 kg to < 35 kg	35 kg to < 120 kg	120 kg and above
IV to oral switch after day 1	Day 1 • IV 6 mg/kg BID Day 2-5 • Oral 200 mg BID (13 to <25 kg) • Oral 400 mg BID (25 to <35 kg)	Day 1 • IV 200 mg BID Day 2-5 • Oral 400 mg BID (35 to <40 kg) • Oral 600 mg BID (40 to <120 kg)	Day 1 • IV 300 mg BID Day 2-5 • Oral 600 mg TID
IV to oral Switch after Day 4 (steady state)	Day 1-4 • IV 6 mg/kg BID Day 5-10 • Oral 200 mg BID (13 to <25 kg) • Oral 400 mg BID (25 to <35 kg)	Day 1-4 • IV 200 mg BID Day 5-10 • Oral 400 mg BID (35 to <40 kg) • Oral 600 mg BID (40 to <120 kg)	Day 1-4 • IV 300 mg BID Day 5-10 • Oral 600 mg TID
Oral to IV Switch after Day 1	Day 1 • Oral 200 mg BID (13 to <25 kg) • Oral 400 mg BID (25 to <35 kg) Day 2-5	Day 1 • Oral 400 mg BID (35 to <40 kg) • Oral 600 mg BID (40 to <120 kg) Day 2-5	Day 1 • Oral 600 mg TID Day 2-5 • IV 300 mg BID

	• IV 6 mg/kg BID	• IV 200 mg BID	
Oral to IV Switch after Day 4 (steady state)	Day 1-4 • Oral 200 mg BID (13 to <25 kg) • Oral 400 mg BID (25 to <35 kg) Day 5-10 • IV 6 mg/kg BID	Day 1-4 • Oral 400 mg BID (35 to <40 kg) • Oral 600 mg BID (40 to <120 kg) Day 5-10 • IV 200 mg BID	Day 1-4 • Oral 600 mg TID Day 5-10 • IV 300 mg BID

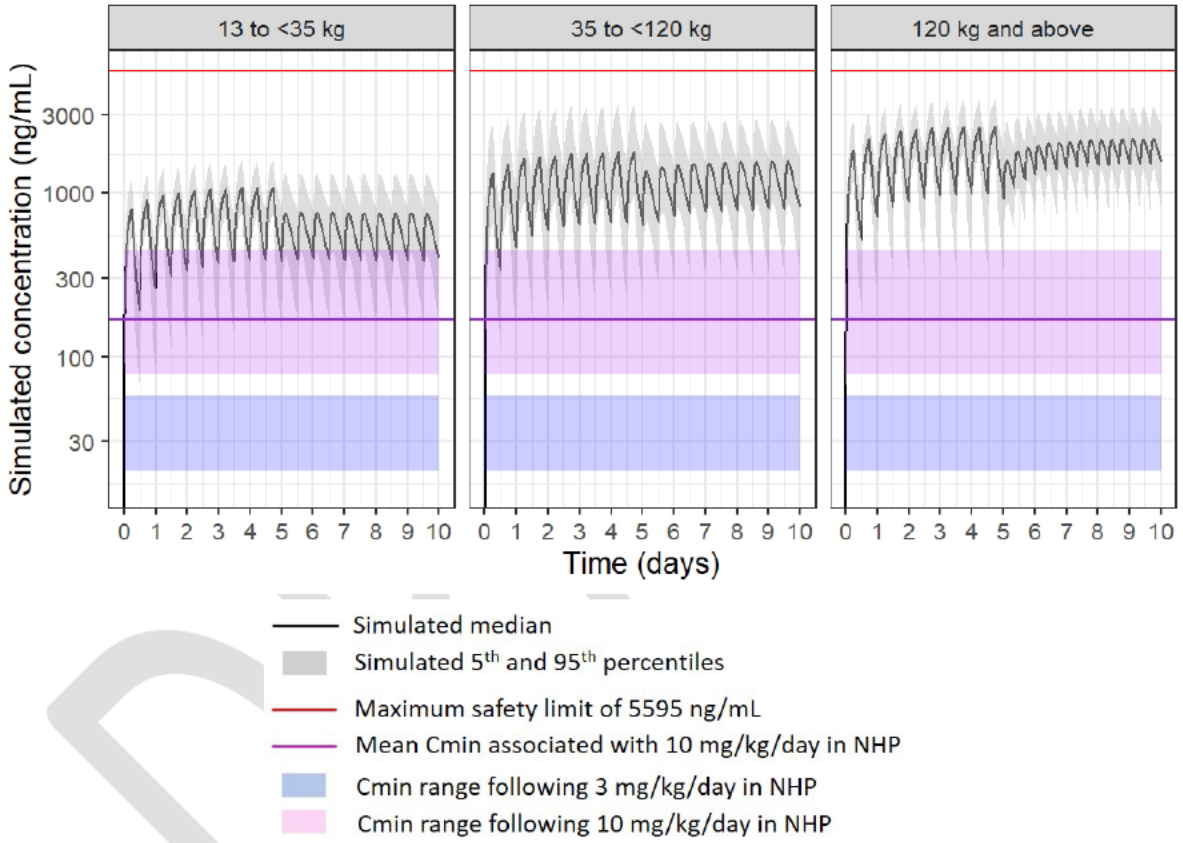
The simulation results are shown in Figure 23 to Figure 26. Overall, the simulated exposure using the modified combined popPK model seemed slightly lower than that simulated using the popPK model based on IV formulation only. Nevertheless, the simulated concentration-time profiles in different scenarios were overall all within the target exposure range between the maximum safety limit of 5595 ng/mL and mean Cmin of 169 ng/mL associated with 10 mg/kg/day in NHP in all simulated scenarios regardless the timing of switching. Thus, the switching could happen anytime if necessary. This result is not unexpected, considering that the target exposure range for dose selection was the same for both oral and IV formation. The direct switching between the formulations would provide exposures in the same range. Thus, FDA review team recommend that the switch between oral and IV administration could happen anytime during the treatment.

Figure 23 Simulated tecovirimat concentration-time profile following the dosing regimen in scenario 1



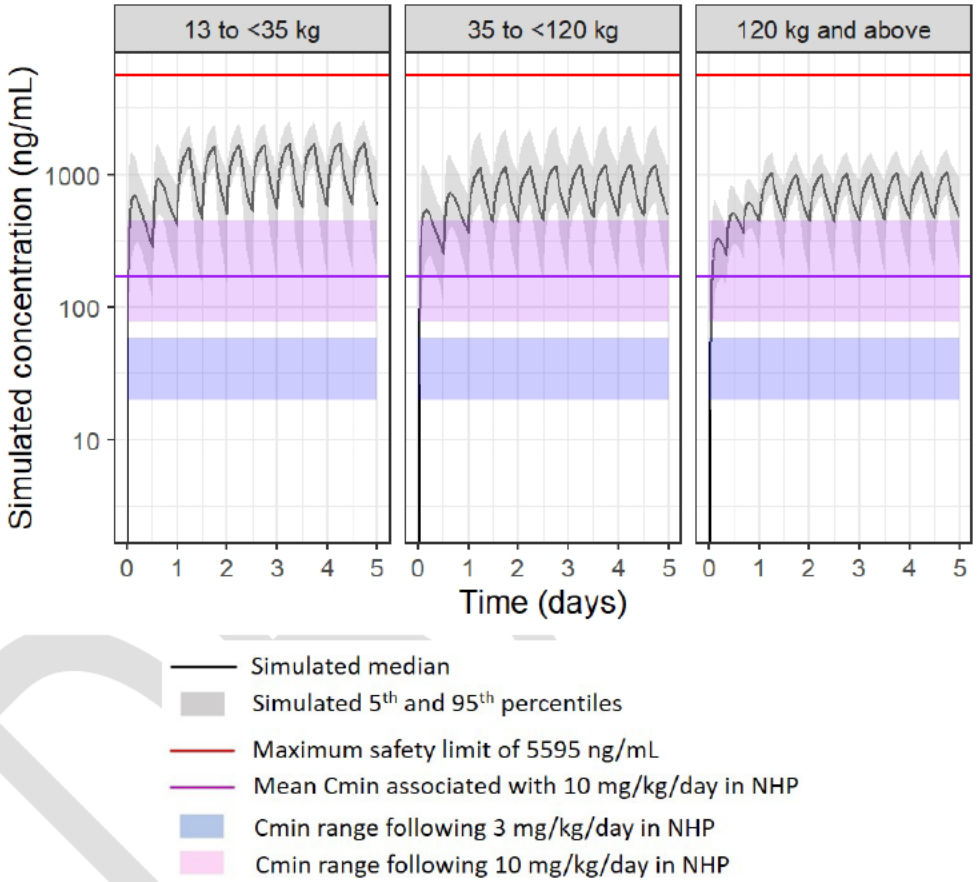
Source: Reviewer's analysis

Figure 24 Simulated tecovirimat concentration-time profile following the dosing regimen in scenario 2



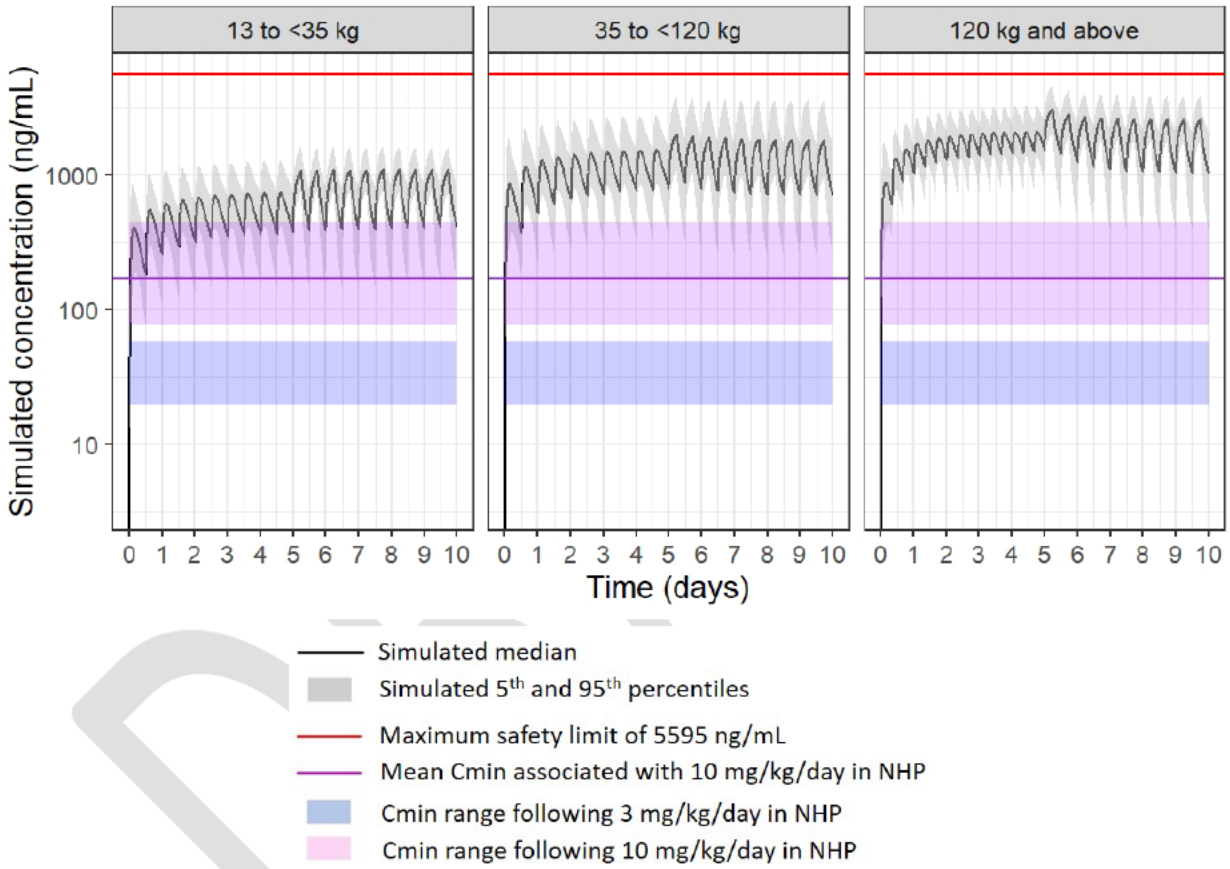
Source: Reviewer's analysis

Figure 25 Simulated tecovirimat concentration-time profile following the dosing regimen in scenario 3



Source: Reviewer's analysis

Figure 26 Simulated tecovirimat concentration-time profile following the dosing regimen in scenario 4



Source: Reviewer's analysis

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application Numbers:	214518
Supporting Document Number/s:	1
CDER Receipt Date:	April 30th, 2021
Applicant:	SIGA Technologies, Inc.
Product:	TPOXX® (Tecovirimat)
Pharmacologic Class:	Inhibitor of the orthopoxvirus VP37 envelope wrapping protein
Indication:	Treatment of human smallpox disease in adult and pediatric patients
Therapeutic area:	Anti-viral
Clinical Review Division:	Division of Antivirals (DAV)
Pharm/Tox Division	Division of Pharm/Tox for Infectious Diseases (DPT-ID)
Reviewers:	David McMillan, Ph.D., DABT
Supervisor/Team Leader:	L. Peyton Myers, Ph.D., DABT
Project Manager:	Andrew Gentles, Pharm.D.
Reviewer Completion Date:	April 13, 2022

Disclaimer

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TABLE OF CONTENTS

GLOSSARY

AUC	Area under the plasma vs. time concentration curve
C_{max}	Maximum observed plasma concentration
EOI	End of infusion
GLP	Good laboratory practice
HPβCD	Hydroxypropyl β-cyclodextrin
IV	Intravenous
NOAEL	No observed adverse effect level
PK	Pharmacokinetics
QSAR	Quantitative structure-activity relationship
SOI	Start of infusion

1 Executive Summary

1.1 Introduction

SIGA Technologies, Inc., has submitted an NDA for an intravenous formulation of tecovirimat, an inhibitor of the orthopoxvirus VP37 envelope wrapping protein, for the treatment of human smallpox disease in adults and pediatric patients weighing ≥3 kg. The NDA for oral tecovirimat (NDA 208627) was approved on July 13th, 2018, for the same indication in adults and pediatric patients weighing ≥13 kg. The present formulation is intended for subjects who are unable to take oral tecovirimat and would be the only formulation of this drug available for pediatric subjects weighing <13 kg. This application was submitted under the Animal Rule (21 CFR 314.610), and clinical trials were limited to Phase 1 data in healthy adult volunteers.

1.2 Brief Discussion of Nonclinical Findings

All pivotal toxicology studies required to assess the systemic toxicity of tecovirimat, as well as all pivotal efficacy studies in monkey/monkeypox and rabbit/rabbitpox models of smallpox infection and disease, were conducted under NDA 208627. To support the intravenous formulation of tecovirimat, the Applicant has submitted a GLP 2-week repeat-dose toxicology study in cynomolgus monkeys, multiple PK studies in mice, rabbits and monkeys, quantitative structure-activity relationship (QSAR) analyses on two degradants of concern, (b) (4) and a risk assessment of the levels (b) (4) hydroxypropyl β-cyclodextrin (HPβCD), in the present formulation. No drug-related or formulation-related toxicities were observed in the GLP 2-week monkey study, and no meaningful concerns were identified with the two degradants. Each 20-mL vial of IV tecovirimat contains 8000 mg (400 mg/mL or 40% w/v) of HPβCD, which corresponds to 267 mg/kg/day in a 60-kg adult and up to 800 mg/kg/day in pediatric subjects <13 kg. These levels of HPβCD are equivalent to those used in an approved, though now discontinued, IV formulation of itraconazole for adults, but they exceed those used in other approved IV drugs for pediatric subjects. A theoretical risk of osmotic nephrosis and extra-renal adverse events has also been noted with HPβCD use in pediatric subjects <2 years of age due to their inherently lower renal function. Given that the IV form of tecovirimat will be administered to a likely small number of patients for a maximum of 2 weeks for a life-threatening indication, that the risk of osmotic nephrosis and extra-renal adverse events is entirely theoretical, and that no pediatric/juvenile-specific toxicities with HPβCD have been noted in the literature, the proposed formulation and dosing regimens are considered acceptable for both adult and pediatric subjects.

1.3 Recommendations

1.3.1 Approvability

The nonclinical data submitted are sufficient to support approval.

1.3.2 Additional Nonclinical Recommendations

No additional nonclinical studies are recommended at this time.

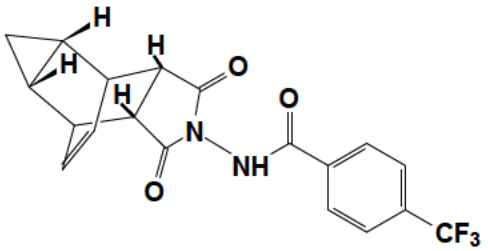
1.3.3 Labeling

Final labeling will be reflected in the approval package.

2 Drug Information

2.1 Drug

CAS Registry Number: 1162664-19-8
Generic Name: Tecovirimat
Code Name: ST-246, SIGA-246
Chemical Name: 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide
Molecular Formula/Weight: $C_{19}H_{15}F_3N_2O_3 \cdot H_2O$ (376.33 g/mol)
Structure:



Pharmacologic Class: Orthopoxvirus VP37 envelope wrapping protein inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 208627 (oral tecovirimat), IND 69019 (oral tecovirimat) and IND 111360 (IV tecovirimat).

2.3 Drug Formulation

Note: All tables are excerpted from the Applicant's reports.

Table 1: Tecovirimat IV drug product formulation

Ingredient	Function	Quality Standard	200 mg/20 mL Vial[a]	
			Quantity per Vial	% Weight by Volume
Tecovirimat[b]	Active	In-house	200 mg	1% (w/v)
Hydroxypropyl-β-cyclodextrin	(b) (4)	NF, Ph. Eur.	8000 mg	40% (w/v)
Water for Injection		USP/Ph. Eur.	q.s. to 20 mL	q.s. to 20 mL

[a]Each vial has a target overfill of (b) (4) Total Fill Volume)
[b]Tecovirimat is the active moiety. (b) (4)
(b) (4)

2.4 Comments on Novel Excipients

As seen in **Table 1**, each 20-mL vial of tecovirimat IV drug product contains 8000 mg (400 mg/mL or 40% w/v) of (b) (4) HPβCD. The daily dose of HPβCD administered to a 60-kg adult, based on a twice-daily, 6-hour infusion of 200 mg tecovirimat, is therefore 16 g/day (16000 mg/day), or 267 mg/kg/day. These levels of HPβCD were also approved in a now-discontinued IV formulation of itraconazole for adults under NDA 020966. The levels of tecovirimat and HPβCD, which will be administered by weight band, are presented in **Table 2**. Subjects weighing either 35 to <120 kg or ≥120 kg would receive either 400 or 600 mg/day tecovirimat, respectively, but those weighing 3 to <35 kg (e.g., pediatric subjects) would receive a twice-daily dose based on a fixed 6-hour infusion of 6 mg/kg. As a result, the HPβCD concentration is fixed at 480 mg/kg/day and the total amount ranges from 1440 to <16800 mg/day in the 3 to <35 kg body weight group. Of note, oral tecovirimat is currently approved for pediatric subjects as low as 13 kg, and brincidofovir (NDAs 214460 and 214461), the only other drug approved for this indication, may be administered only to subjects ≥10 kg, so the present formulation would be the sole option available to this subpopulation. These levels of HPβCD exceed those seen in other approved IV drugs for pediatric subjects. No nonclinical juvenile toxicity studies were conducted to support these levels of HPβCD in pediatric subjects, and the proposed pediatric dosing regimen is based entirely on modeling (no clinical pediatric safety data are available), but the Applicant did conduct a risk assessment of HPβCD use in their IV formulation. There are no FDA-specific guidelines on the use of HPβCD as an excipient. The 2017 EMA guideline, "Cyclodextrins used as excipients"[1], recommends that cyclodextrin use in subjects <2 years old (roughly <13 kg) by any route should be limited to a maximum of 20 mg/kg/day (24-fold below what is present in the tecovirimat IV formulation) due to a theoretical concern of osmotic nephrosis and extra-renal adverse events due to inherently lower kidney function in this population. However, this guideline also states that the currently available clinical and nonclinical data, however limited, suggest that no pediatric/juvenile-specific toxicities have been observed with HPβCD[2-4], and that "a case-by-case judgement should be made regarding the risk/benefit for the patient". Given that the IV formulation of tecovirimat will be administered to a likely small number of patients for a maximum of 2 weeks for a life-threatening indication, that the risk of osmotic nephrosis and extra-renal adverse events is entirely theoretical, and that no pediatric/juvenile-specific toxicities with HPβCD have been noted in the literature, the proposed formulation and dosing regimens are considered acceptable for both adult and pediatric subjects. No additional nonclinical studies are recommended at this time.

Table 2: Levels of HPβCD based on the proposed pediatric dosing regimen

Weight (kg)	Tecovirimat		HPβCD	
	Dose (mg/day)	Volume (mL/day)	Dose (mg/day)	Dose (mg/kg/day)
3 to <35	36 to <420	3.6 to <42	1440 to <16800	480
35 to <120	400	40	16000	133 to 457
≥120	600	60	24000	≤200

2.5 Comments on Impurities/Degradants of Concern

Five degradants (b) (4) have been identified in the tecovirimat IV drug product. Of these, (b) (4) were identified as degradants of concern in the tecovirimat IV drug product in a forced degradation study. To determine whether the presence of these degradants is a concern, QSAR analyses of (b) (4) were requested on September 4th, 2019. The Applicant submitted QSAR analyses conducted using both DEREK NEXUS and SARAH NEXUS on December 13th, 2019, under IND 111390 as well as the present NDA. According to these analyses, (b) (4) were considered inconclusive and positive for genotoxicity, respectively, and both were deemed Class 3 according to ICH M7(R1). The Agency also conducted QSAR analyses using DEREK NEXUS, Leadscope, and CASE Ultra and determined that (b) (4) were negative and positive, respectively. At the pre-NDA stage, the Applicant stated that meaningful levels of (b) (4) are formed only when the tecovirimat IV drug product is left at or above room temperature for extended periods of time, and not when the product is stored under refrigerated conditions as recommended. Under normal conditions, exposure to these degradants remains well below the cumulative lifetime exposure limit of (b) (4) mg, as established by ICH M7(R1). Given that the levels of these degradants are well below the specifications for the tecovirimat IV drug product under normal conditions, and that this drug is indicated for the treatment of a severe disease (smallpox infection), the risk associated with these impurities is considered negligible. In addition, 5 compounds were identified in an extractables study on the IV tubing. No concerns were identified based on these data.

2.6 Proposed Clinical Population and Dosing Regimen

Oral tecovirimat was approved under NDA 208627 for the treatment of human smallpox disease in adults and pediatric patients weighing at least 13 kg daily for 14 days. Adults and pediatric subjects weighing ≥40 kg receive 600 mg BID (1200 mg/day), while pediatric subjects weighing 25 to <40 kg receive 400 mg BID, and those weighing 13 to <25 kg receive 200 mg BID. The Applicant is currently seeking approval of the IV formulation for the treatment of human smallpox disease in adults and pediatric patients weighing ≥3 kg. Adults would receive 200 mg BID (400 mg/day) IV tecovirimat for 14 days, and pediatric subjects would follow the regimen proposed in **Table 3**.

Table 3: Proposed pediatric dose levels of IV tecovirimat

(b) (4)

[a]The doses presented here are derived from a Population PK Model developed by SIGA from data obtained from clinical studies and have not been thoroughly reviewed by the FDA.

(b) (4)

2.7 Regulatory Background

Tecovirimat was developed as a medical countermeasure for the treatment of human smallpox disease under the Animal Rule (21 CFR 314.610) with efficacy studies performed in animal models of disease. The product was discussed as part of the development program for smallpox treatments at an FDA Antiviral Drugs Advisory Committee (AC) Meeting on December 14th and 15th, 2011. The Applicant, SIGA Technologies, Inc., submitted an NDA for oral tecovirimat on December 8th, 2017 (NDA 208627), and the product was discussed in another AC meeting on May 1st, 2018. The Agency subsequently approved oral tecovirimat for the treatment of human smallpox disease in adults and pediatric patients weighing ≥13 kg on July 13th, 2018.

3 Studies Submitted

3.1 Studies Reviewed

1) ST-246: Evaluation of Pharmacokinetics and Tolerability of Bolus Intravenous Administration of ST-246 Intravenous Formulation in BALB/c Mice (#ASM246)
2) ST-246: Evaluation of Pharmacokinetics and Tolerability of ST-246 Intravenous Formulation in Catheterized BALB/c Mice (#ASM250)
3) ST-246: Pilot Evaluation of Pharmacokinetics and Tolerability of ST-246 Intravenous Formulation in Catheterized CD-1 Mice (#ASM257)
4) Evaluation of Pharmacokinetics and Tolerability of ST-246 Intravenous Formulation in Catheterized CD-1 Mice (#ASM260)
5) ST-246: Evaluation of Pharmacokinetics and Tolerability of ST-246 Intravenous Formulation in New Zealand White Rabbits (#ASM253)
6) Pilot Evaluation of Pharmacokinetics and Tolerability of an Infusion of an Intravenous Formulation of ST-246 in New Zealand White Rabbits (#ASM258)
7) Pharmacokinetic Assessment of IV Administered ST-246 in NZW Rabbits (#SR11-005F)
8) An Intravenous Infusion Pharmacokinetics Study of ST-246 in Cynomolgus Monkeys (#1151-067)
9) ST-246: A Pharmacokinetic Study Following a Single Intravenous Infusion to Cynomolgus Monkeys (#MDA00051/246-TX-018)
10) A Single-Dose Pharmacokinetic Study of ST-246 by Intravenous Infusion in Cynomolgus Monkeys (#20002163/246-TX-019)
11) A Pharmacokinetic Study of ST-246 by Intravenous Infusion Administration in Cynomolgus Monkeys (#20002757/246-TX-020)
12) A 14-Day Toxicity, Toxicokinetics, Local Tolerability and Safety Pharmacology of ST-246 by Intravenous Infusion in Cynomolgus Monkeys with a 2-Week Recovery Period (#20012981/246-TX-021)
13) In Silico ICH M7 Assessment of (b) (4) using DEREK and SARAH (#20223864A)
14) In Silico ICH M7 Assessment of (b) (4) DEREK and SARAH (#20223864B)
15) Hydroxypropyl Betacyclodextrin Use With Tecovirimat Injection, 10 mg/mL (risk assessment)

3.3 Previous Reviews Referenced

All nonclinical safety and efficacy studies supporting the approval of oral tecovirimat (ADME, safety pharmacology, genotoxicity, general toxicology, and reproductive toxicology studies as well as pivotal efficacy studies in rabbit/rabbitpox and monkey/monkeypox models) were reviewed under NDA 208627. Carcinogenicity studies with tecovirimat were not required given the short treatment duration of 14 days. No new efficacy, genotoxicity or reproductive toxicology studies were submitted to the present NDA. Please refer to the respective pharmacology/toxicology review under NDA 208627 for more information.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

All PK studies evaluating the distribution, metabolism and excretion of tecovirimat were conducted and reviewed under NDA 208627. To support the IV formulation of tecovirimat, multiple single-dose and repeat-dose absorption studies were conducted in mice (either BALB/c or CD-1), New Zealand White Rabbits and cynomolgus monkeys with varying formulations of IV tecovirimat. Concentrations of HPβCD were either 32% or 40% (w/v) in mice, 32% in rabbits, and 13.3% to 32% in monkeys. Higher concentrations of HPβCD were not well-tolerated in some animals. Administration of tecovirimat in 40% HPβCD by IV bolus injection resulted in mortality of 67% (8 of 12) BALB/c mice across all tecovirimat and control groups in one study (#ASM246), and the HPβCD concentration was lowered to 32% for the remainder of this study. Importantly, 32% HPβCD was generally well-tolerated in this study, and no mortality was observed in catheterized BALB/c and CD-1 mice receiving tecovirimat in 40% HPβCD by IV slow bolus infusion at a rate of 40 or 20 µL/min for 5 or 10 minutes, respectively, at tecovirimat concentrations up to 100 mg/kg (#ASM250, ASM257 and ASM260). PK parameters from the 100 mg/kg group in study #ASM250 could not be obtained due to procedural issues unrelated to either tecovirimat or HPβCD, so parameters from study #ASM260 in which 75 mg/kg was evaluated are presented in **Table 4**.

Table 4: PK parameters from the single-dose mouse PK study (#ASM260)

Parameters	3 mg/kg	10 mg/kg	30 mg/kg	75 mg/kg
Terminal half-life ($T_{1/2}$) (hr)	4.5	2.8	2.5	2.8
T_{max} (hr)	0.17	0.17	0.17	0.17
C_{max} (ng/mL)	16900	63500	147333	238333
AUC_{last} (hr*ng/mL)	67907	407609	709202	1252858
AUC_{inf} (hr*ng/mL)	69444	408058	710167	1256128
Vz_obs (mL/kg)	282	100	154	243
Cl_obs (mL/hr/kg)	43	25	42	60
Vss_obs (mL/kg)	222	144	171	291

Administration of IV tecovirimat by slow bolus infusion over 5 or 15 minutes was also evaluated in rabbits at tecovirimat concentrations up to 60 mg/kg (#ASM253 and ASM258). Rabbits receiving 60 mg/kg IV tecovirimat experienced transient narcosis

and labored breathing which resolved 30-60 minutes post end-of-infusion (EOI), but no mortality or other meaningful findings were observed at any dose level. PK parameters from study #ASM253 in which rabbits received up to 60 mg/kg IV tecovirimat are presented in **Table 5**. A non-GLP absorption study in rabbits was also conducted to evaluate the PK of IV tecovirimat following once-daily, 6-hour IV infusions via a surgically-implanted vascular access port with 40 mg/kg/day tecovirimat in 40% HPβCD for 14 days (#SR11-005F). No drug-, formulation- or procedure-related issues were observed in this study, and the PK parameters are presented in **Table 6**.

Table 5: PK parameters from the single-dose rabbit PK study (#ASM253)

Parameters	Female			Male		
	3 mg/kg	30 mg/kg	60 mg/kg	3 mg/kg	30 mg/kg	60 mg/kg
Elimination Half-Life ($T_{1/2}$) (hr)	3.2	8.1	5.7	3.2	16.3	4.6
C_{max} (ng/mL)	3335	37050	88250	2720	39950	99850
AUC_{last} (hr*ng/mL)	3214	14867	60057	1868	16220	72327
AUC_{inf} (hr*ng/mL)	3263	14935	60167	1904	16424	72424
Vz_obs (mL/kg)	4179	23602	8225	7277	42904	5534
Cl_obs (mL/hr/kg)	919	2009	997	1575	1827	828

Table 6: PK parameters from the non-GLP 14-day rabbit PK study (#SR11-005F)

PK Parameters	Day 1 (N = 4)	Day 14 (N = 4)
C_{max} (ng/mL)	3608	3311
T_{max} (h)	5	3
$t_{½}$ (h)	1.4	0.9
$AUC_{0-\infty}$ (h•ng/mL)	19695	15939
AUC_{last}	19583	15912
AUC_{tau} (h•ng/mL)	19692	15937

Monkeys received IV tecovirimat by slow bolus IV infusion over 2, 4 or 6 hours at tecovirimat concentrations up to 30 mg/kg in 13.3 to 32% HPβCD (#1151-067, 246-TX-018, 246-TX-019 and 246-TX-020). One monkey receiving 3 mg/kg IV tecovirimat died prematurely on Day 6 in study #1151-067. A cause of death was not determined, but this was considered unrelated to either drug or formulation due to the absence of similar findings at higher dose levels. Tremors were observed in 3 of 4 monkeys dosed with 30 mg/kg IV tecovirimat at 13.3% HPβCD via 4-hour infusion in study #246-TX-019. These findings were seen at EOI on Day 1 but resolved at approximately 2 hours post-EOI and were not detected through the remainder of the study. Further, tremors were not detected at any other dose level or at the same dose administered via a 6-hour infusion, nor were they seen in any other study conducted in any species with any formulation of IV tecovirimat. The C_{max} in the 30 mg/kg groups was approximately 30% lower with a 6-hour, compared to a 4-hour, infusion, suggesting that this may be a C_{max}-related effect similar to the seizures and tremors noted in dogs receiving oral tecovirimat. However, as this was observed only once in a single study, was reversible, and was not

accompanied by seizures or other adverse findings as seen in dogs, the risk associated with this finding was considered negligible. PK parameters from study #246-TX-019 are also presented in **Table 7**. Based on these findings, doses of 3, 10 and 30 mg/kg IV tecovirimat administered by 6-hour slow bolus IV infusion were evaluated in the pivotal GLP 2-week repeat-dose toxicology study in cynomolgus monkeys (#246-TX-021). The PK data collected under the present NDA were considered sufficient to support approval of the IV formulation of tecovirimat.

Table 7: PK parameters from the single-dose monkey PK study (#246-TX-019)

IV Infusion Duration (hr)	Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{last} (ng.hr/mL)	$AUC_{0\text{-}inf}$ (ng.hr/mL)	$t_{1/2}$ (hr)	CL or CL/F (mL/hr/kg)	V_z or V_z/F (mL/kg)
4	20	11845	4	59272	59640	8.7	353	4457
	30	20065	4	99850	100117	7.8	307	3462
6	20	7482	6	47642	47864	6.6	433	4082
	30	13883	6	87006	87202	6.9	362	3618

6 General Toxicology

6.2 Repeat-Dose Toxicity

6.2.1 Study Title: A 14-Day Toxicity, Toxicokinetics, Local Tolerability and Safety Pharmacology of ST-246 by Intravenous Infusion in Cynomolgus Monkeys with a 2-Week Recovery Period

Study no.: 246-TX-021
Study report location: 4.2.3.2
Study initiation date: November 9, 2011
Conducting laboratory and location: (b) (4)
Duration: 14
Duration Units: days
GLP compliance: Y
Drug, lot #, and % purity: ST-246 (lot #SG-10A11-Q; purity = 95.4%)

Key Findings

NOAEL = 30 mg/kg/dose IV ($AUC_{0\text{-}tau}$ = 76555.5 ng.hr/mL, C_{max} = 12263.5 ng/mL at Day 14). Nine animals died prematurely due to infection caused by procedure-related breaks in sterility at the surgical sites. There were no drug-related findings in this study.

Methods

Doses: 0, 3, 10 & 30 mg/kg
Frequency of dosing: Once daily
Number/Sex/Group: 1-3/sex/group (see **Table 8**)
Dose volume: 10 mL/kg
Formulation/Vehicle: (b) (4) HPβCD in (b) (4) Sodium Chloride for Injection, USP

Route of administration:	INTRAVENOUS
Species:	MONKEY
Strain:	CYNOMOLGUS
Age:	2.8-5.2 years old
Comment on Study Design and Conduct:	All animals were dosed once daily via a 6-hour IV infusion through a surgically-implanted venous access port for 14 consecutive days (Days 1-14) using a battery-powered infusion pump. All animals were scheduled to be euthanized on either Day 15 or 29. Nine animals were euthanized prematurely between Days 6 and 16 due to signs of infection at or around the port and/or telemetry site. Three of these animals were replaced with alternates. See **Table 8** and the "Mortality" section for more information.
Dosing Solution Analysis:	All samples met acceptance criteria

Table 8: Design of the 14-Day IV Study in Cynomolgus Monkeys

Group No.	No. of Animals[a]				Test Material	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)	Dose Volume (mL/kg/day)	Infusion Duration (hr)	Infusion Rate (mL/kg/hr)
	Main Study		Recovery							
	Male	Female	Male	Female						
1	3	1[b]	2	2	Control Article	0	0	10	6	1.67
2	3	3	1[b]	1[b]	ST-246	3	0.3	10	6	1.67
3	2[b]	3	1[b]	2	ST-246	10	1.0	10	6	1.67
4	3	3	2	2	ST-246	30	3.0	10	6	1.67

[a] Main study animals were euthanized on Day 15. Recovery animals were euthanized on Day 29.
[b] A total of 9 animals were euthanized early due to non-ST-246-related surgical procedure complications. Only 3 of these 9 animals were able to be replaced by alternates, leading to the reduced number of animals at the Main Study and Recovery necropsies.

Observations and Results

Mortality

Assessed twice daily. Nine animals (3 control, 1 low-dose, 1 mid-dose and 1 high-dose on Day 6, 1 mid-dose on Day 7, 1 low-dose on Day 15, and 1 low-dose on Day 16) were euthanized prematurely due to infection associated with the port and/or telemetry surgical sites. Changes in clinical pathology parameters in these animals, particularly the decreased A/G ratio, were consistent with an acute-phase inflammatory response. Purulent fluid accumulation and subacute inflammation were also observed at the surgical sites. The study director considered all infections and subsequent deaths to be attributed to procedure-related breaks in sterility and unrelated to either drug or vehicle. The present reviewer agrees with this assessment.

Clinical Signs

Exams performed at least once daily. No drug-related findings.

Body Weights

Measured at least once weekly. No drug-related changes.

Food Consumption
Measured qualitatively once daily. No drug-related findings.

Ophthalmoscopy
Evaluated pre-treatment and toward the end of Week 2. No drug-related findings.

Neurologic Examinations
Exams performed in main study animals only pre-treatment and once daily at the end of infusion. No drug-related findings.

Cardiovascular, Respiratory and Temperature Parameters
Heart rate, blood pressures, ECG parameters, respiratory rate, tidal volume, minute volume, and body temperatures were measured on Days 1, 7, 14 and 28. No drug-related changes.

Hematology and Coagulation
Blood samples were collected pre-treatment, on Days 14 and 28, and prior to euthanasia when possible. No drug-related changes.

Clinical Chemistry
Blood samples were collected pre-treatment, on Days 14 and 28, and prior to euthanasia when possible. No drug-related changes.

Urinalysis
Urine samples were collected pre-treatment, on Days 14 and 28, and prior to euthanasia when possible. No drug-related changes.

Gross Pathology
Evaluated at necropsy on Days 15 and 29 and following all unscheduled deaths. No drug-related findings.

Organ Weights
Measured at necropsy on Days 15 and 29 and following all unscheduled deaths. Kidney weight was increased 18.3% in the high-dose males on Day 15. This was considered incidental due to the lack of a histopathological correlate and the absence of a similar finding in females.

Histopathology
Adequate Battery: Yes
Peer Review: No
Evaluated at necropsy on Days 15 and 29 and following all unscheduled deaths. The following were observed on Day 15:

- Minimal to moderate granuloma at the catheter entrance in 3 males/2 females at the low dose, 2 males/3 females at the mid-dose, 2 males/1 female at the high dose, and 2 male/1 female controls. No apparent correlation between severity and dose level.

- Mild congestion in the muscularis (smooth muscle layer) of the colon in 1 high-dose male.
- Minimal to mild hypocellularity in the thymus in 1 mid-dose, 3 high-dose, and 1 control females. Mild only in 1 high-dose female.

The following were observed on Day 29:

- Minimal to moderate granuloma at catheter entrance in 1 male/12 female at the low dose, 1 male/1 female at the mid-dose, 1 male/1 female at the high dose, and 2 male/2 female controls. Moderate only in the high-dose male.
- Minimal hypocellularity in the thymus in 1 mid-dose female, 1 male/1 female at the high dose, and 1 female control.

The following was observed in the animals that were euthanized prematurely:

- Purulent fluid accumulation, moderate subacute inflammation, and/or thickening in the skin surrounding the venous access port and/or telemetry site.

The colon and thymus findings were considered incidental due to the low severity and/or low number of animals affected. The findings in the skin and catheter entrance and tip were attributed to breaks in sterility involving the surgical implantation sites, which was the cause of all unscheduled euthanasias in this study. There were no drug-related findings.

Toxicokinetics

Blood samples were collected in main study animals on Days 1 and 14 prior to the start of infusion (SOI), 0.5 and 2 hours post-SOI, at EOI, and 0.25, 0.5, 2, 4, 6, 8, 12 and 16 hours post-EOI. In the recovery animals, blood samples were collected on Days 1 and 14 prior to SOI and 0.5, 4 and 16 hours post-EOI, and on Days 24 and 29. Toxicokinetic parameters from Day 14 are presented in **Table 9**.

Table 9: Day 14 Toxicokinetic Parameters from the 14-Day IV Study

TK Parameter	Male			Female		
	Group 2	Group 3	Group 4	Group 2	Group 3	Group 4
	3 mg/kg/day (n=3)	10 mg/kg/day (n=2)	30 mg/kg/day (n=2)[d]	3 mg/kg/day (n=3)	10 mg/kg/day (n=3)	30 mg/kg/day (n=3)
AUC_{0-t} (ng•h/ml)	3899 (12.1)	26846 (58.6)	75895 (11.9)	6067 (26.2)	27069 (14.2)	76638 (28.8)
AUC_{0-inf} (ng•h/ml)	4450 (NC)[c]	27526 (60.1)	77032 (10.8)	6997 (22.0)[b]	30755 (22.3)	77592 (28.9)
AUC_{0-tau} (ng•h/ml)	4402 (NC)[c]	26989 (58.9)	76203 (11.7)	6839 (20.5)[b]	27387 (14.3)	76908 (28.8)
C_{max} (ng/ml)	659.33 (15.9)	4390.0 (58.0)	11700 (13.3)	904.00 (25.1)	4256.7 (20.2)	12827 (20.6)
t_{max}[a] (h)	6.00 (6.00 - 6.00)	6.01 (6.00 - 6.02)	6.00 (6.00 - 6.00)	6.00 (2.03 - 6.00)	6.00 (6.00 - 6.00)	6.00 (6.00 - 6.02)
CL (ml/h/kg)	766 (NC)[c]	495 (58.1)	434 (12.0)	506 (21.1)[b]	415 (14.8)	472 (34.2)
$t_{1/2}$ (h)	3.92 (NC)[c]	4.95 (12.3)	3.96 (28.7)	4.78 (29.4)[b]	11.7 (83.0)	3.58 (16.8)
V_d (ml/kg)	4335 (NC)[c]	3410 (47.5)	2520 (40.0)	3387 (8.5)[b]	6755 (76.7)	2368 (22.0)
V_{ss} (ml/kg)	2122 (NC)[c]	1200 (15.5)	1441 (18.3)	1807 (5.0)[b]	2503 (53.6)	1620 (42.2)

[a] Median (Min - Max), [b] n=2, [c] n=1, [d]Animal 4104 excluded due to incomplete ST-246 dosing, NC = Not calculated

11 Integrated Summary and Safety Evaluation

SIGA Technologies, Inc., has submitted an NDA for an intravenous formulation of tecovirimat, an inhibitor of the orthopoxvirus VP37 envelope wrapping protein, for the treatment of human smallpox disease in adults and pediatric patients weighing ≥3 kg. The Applicant previously submitted an NDA for oral tecovirimat (NDA 208627), which was approved on July 13th, 2018, for the same indication in adults and pediatric patients weighing ≥13 kg. The present formulation is intended for subjects who are unable to take oral tecovirimat and would be the only formulation of this drug available for pediatric subjects weighing <13 kg. This application was submitted under the Animal Rule (21 CFR 314.610), so clinical trials were limited to Phase 1 safety and pharmacokinetic (PK) trials in healthy adult volunteers. No clinical pediatric safety data were collected as part of this program, and the pediatric dosing regimen is based entirely on modeling.

All pivotal toxicology studies required to assess the systemic toxicity of tecovirimat, as well as all pivotal efficacy studies in monkey/monkeypox and rabbit/rabbitpox models of smallpox infection and disease, were conducted under NDA 208627. To support the IV formulation of tecovirimat, the Applicant has submitted a GLP 2-week repeat-dose toxicology study in cynomolgus monkeys, multiple PK studies in mice, rabbits and monkeys, QSAR analyses on two degradants of concern, (b) (4) and a risk assessment on the use of HPβCD in the present formulation. No drug-related or formulation-related toxicities were observed in the GLP 2-week monkey study, and no meaningful concerns were identified with the two degradants. In one of the monkey PK studies, tremors were observed in 3 of 4 animals dosed with 30 mg/kg IV tecovirimat at 13.3% HPβCD via 4-hour infusion. These findings were seen at EOI on Day 1 but resolved at approximately 2 hours post-EOI and were not detected through the remainder of the study. Further, tremors were not detected at any other dose level or at the same dose administered via a longer, 6-hour infusion, nor were they seen in any other study conducted in any species with any formulation of IV tecovirimat. Further, these were not accompanied by seizures or other adverse findings, as was observed in dogs with oral tecovirimat. As such, the risk associated with this finding was considered negligible.

Each 20-mL vial of IV tecovirimat contains 8000 mg (400 mg/mL or 40% w/v) of HPβCD, which corresponds to 267 mg/kg/day in a 60-kg adult and up to 800 mg/kg/day in pediatric subjects <13 kg. These levels of HPβCD are equivalent to those used in an approved, though now discontinued, IV formulation of itraconazole for adults, but they exceed those used in other approved IV drugs for pediatric subjects. A theoretical risk of osmotic nephrosis and extra-renal adverse events has also been noted with HPβCD use in pediatric subjects <2 years of age due to their inherently lower renal function. Given that the IV form of tecovirimat will be administered to a likely small number of patients for a maximum of 2 weeks for a life-threatening indication, that the risk of extra-renal adverse events is entirely theoretical, and that no pediatric/juvenile-specific toxicities with HPβCD have been noted in the literature, the proposed formulation and pediatric dosing regimen are considered acceptable.

Overall, the data submitted under the present NDA were considered adequate to support approval of the IV formulation of tecovirimat. No additional nonclinical studies are recommended at this time.

12 References

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