CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

208627Orig1s007

Trade Name:	TPOXX
Generic or Proper Name:	Tecovirimat
Sponsor:	SIGA Technologies, Inc.
Approval Date:	May 18, 2022
Indication:	TPOXX (tecovirimat) is indicated for the treatment of human smallpox disease in adults and pediatric patients weighing at least 3 kg.

CENTER FOR DRUG EVALUATION AND RESEARCH

208627Orig1s007

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	
Multidiscipline Review(s) • **Summary Review** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Product Quality Review(s)	X
Clinical Microbiology / Virology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208627Orig1s007

APPROVAL LETTER

NDA 208627/S-007

sNDA APPROVAL – ANIMAL EFFICACY

SIGA Technologies, Inc
Attention: Paul Long, RPh, MBA
Senior Director, Regulatory Affairs
4575 SW Research Way
Suite 110
Corvallis, OR 97333

Dear Mr. Long:

Please refer to your supplemental new drug application (sNDA) dated and received April 18, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TPOXX (tecovirimat) capsules, 200 mg.

This "Prior Approval" supplemental new drug application provides for the following changes to the labeling:

- Addition of data to support a new a dosage form,TPOXX (tecovirimat) 200 mg injection, for use in adults and pediatric patients weighing at least 3 kg who are unable to tolerate oral dosing
- Updates the INDICATIONS and USAGE, DOSAGE and ADMINISTRATION, WARNINGS and PRECAUTIONS, ADVERSE REACTIONS, Clinical Trials Experience, USE in SPECIFIC POPULATIONS and CLINICAL PHARMACOLOGY sections of the USPI with pharmacokinetic and safety data from studies SIGA-246-IV-202 and Study SIGA-246-IV-201
- Updates the approved Patient Package Insert to support the addition of the new TPOXX (tecovirimat) 200 mg injection, dosage form

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, and Instructions for Use), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

SUBPART I APPROVAL REQUIREMENTS

Approvals under 21 CFR Part 314, Subpart I (Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible) are subject to three requirements:

1. *Approval with restrictions to ensure safe use.* This subsection permits the Agency to require postmarketing restrictions as are needed to ensure safe use of the drug product, commensurate with the specific safety concerns presented by the drug product. We have concluded that TPOXX® (tecovirimat) can be safely used without restrictions on distribution or use.

2. *Information to be provided to patient recipients.* This subsection requires applicants to prepare labeling to be provided to patient recipients for drug products approved under this subpart. We conclude that the FDA-Approved Patient Labeling and Instructions For Use for TPOXX (tecovirimat) meets the requirements of this subsection. We remind you that the patient labeling and

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

instructions for use must be available with the product to be provided, when possible, prior to administration or dispensing of the drug product for the use approved under this subpart.

3. *Postmarketing Studies.* This subsection requires you to conduct postmarketing studies, such as field studies, to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. Reference is also made to the postmarketing study requirement, PMR 3417-1 listed in the original NDA 208627, which was approved on July 13, 2018. Further reference is also made to the Agency's release and reissue of this field study PMR issue on September 13, 2021.

4. We remind you of your postmarketing requirement specified in the Agency's communication dated September 13, 2021. This requirement, along with any agreed upon completion dates, is listed below.

3417-7	Collaborate with US public health agencies to conduct a field study to evaluate the clinical response, drug concentrations, and safety profile of tecovirimat when used for the treatment of human smallpox disease due to variola virus infection. This trial should evaluate tecovirimat vs. brincidofovir vs. tecovirimat and brincidofovir combination therapy. Final Report Submission: 07/2022

Submit clinical protocols to your IND 069019 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) include a status summary of each commitment in your annual report to this NDA. The status summary should include expected study/trial completion and final report submission dates, any changes in plans since the last annual report, and, for studies/trials, the number of patients entered into each study/trial. All submissions, including supplements, relating to this postmarketing commitment should be prominently labeled **"Postmarketing Protocol," "Postmarketing Final Report," or "Postmarketing Correspondence."**

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart I Postmarketing Requirements**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[3]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

If you have any questions, call Andrew Gentles, PharmD, BCPS AQ-ID, Senior Regulatory Project Manager, at (240) 402-5708 or the mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antivirals
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEBRA B BIRNKRANT
05/18/2022 03:39:12 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208627Orig1s007

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TPOXX® safely and effectively. See full prescribing information for TPOXX.

TPOXX (tecovirimat) capsules, for oral use
TPOXX (tecovirimat) injection, for intravenous use
Initial U.S. Approval: 2018

RECENT MAJOR CHANGES

Indications and Usage (1.1)	5/2022
Dosage and Administration (2.1, 2.2, 2.3, 2.4, 2.5)	5/2022
Contraindications (4)	5/2022
Warnings and Precautions (5.2)	5/2022

INDICATIONS AND USAGE

TPOXX is an inhibitor of the orthopoxvirus VP37 envelope wrapping protein and is indicated for the treatment of human smallpox disease in adults and pediatric patients weighing at least 3 kg. (1.1)

Limitations of Use:

- The effectiveness of TPOXX for treatment of smallpox disease has not been determined in humans because adequate and well controlled field trials have not been feasible, and inducing smallpox disease in humans to study the drug's efficacy is not ethical. (1.2)
- TPOXX efficacy may be reduced in immunocompromised patients based on studies demonstrating reduced efficacy in immunocompromised animal models. (1.2)

DOSAGE AND ADMINISTRATION

- Pediatric and Adult Patients weighing 40 kg or more (2.3) (Oral Dosing):
  - 40 kg to less than 120 kg: 600 mg of TPOXX every 12 hours for 14 days
  - 120 kg or more: 600 mg of TPOXX every 8 hours for 14 days
- Pediatrics and adult patients weighing 13 kg or more and those who cannot swallow capsules (2.3) (Oral Dosing): TPOXX Capsules can be administered by carefully opening the number of capsule noted below and mixing and administering the entire contents in 30 mL of liquid (e.g., milk, chocolate milk) or soft food (e.g., apple sauce, yogurt):
  - 13 kg to less than 25 kg: 200 mg (1 Capsule) of TPOXX every 12 hours for 14 days
  - 25 kg to less than 40 kg: 400 mg (2 Capsules) of TPOXX every 12 hours for 14 days
  - 40 kg to less than 120 kg: 600 mg (3 Capsules) of TPOXX every 12 hours for 14 days.
  - 120 kg or more: 600 mg (3 capsules) every 8 hours for 14 days
- Patients weighing 3 kg and above (2.5) (Intravenous Dosing):
  - 3 kg to less than 35 kg: 6 mg/kg every 12 hours by intravenous infusion over 6 hours for up to 14 days
  - 35 kg to less than 120 kg: 200 mg every 12 hours by intravenous infusion over 6 hours for up to 14 days
  - 120 kg and above: 300 mg every 12 hours by intravenous infusion over 6 hours for up to 14 days.
- Pediatric patients weighing 13 kg or more should be switched to TPOXX Capsules to complete the 14-day treatment course as soon as oral therapy can be tolerated.
- Administration Instruction for TPOXX Capsules: Take within 30 minutes after a full meal containing moderate or high fat. (2.1, 2.3)
- Administration Instructions for TPOXX Injection: Infuse over 6 hours via infusion pump. (2.5)
- See Full Prescribing Information for additional information on the administration and preparation of TPOXX Capsules and Injection. (2)

DOSAGE FORMS AND STRENGTHS

Capsules
- 200 mg of tecovirimat (2.4)

Injection
- A single-dose vial containing 200 mg of tecovirimat in 20 mL for further dilution prior to intravenous infusion. (3)

CONTRAINDICATIONS

- TPOXX capsules: None
- TPOXX injection: TPOXX Injection is contraindicated in patients with severe renal impairment (defined as creatinine clearance below 30 mL/min) (4, 5.2)

WARNINGS AND PRECAUTIONS

Hypoglycemia: Co administration with repaglinide may cause hypoglycemia. Monitor blood glucose and monitor for hypoglycemic symptoms during co-administration. (5.1)

ADVERSE REACTIONS

The most common adverse reactions are:
- TPOXX Capsules (incidence ≥ 2%): headache, nausea, abdominal pain, and vomiting. (6.1)
- TPOXX Injection (incidence ≥ 4%): administration site reactions and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact SIGA Technologies Inc. at 1-888-899-3472 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.1, 7, 12.3)

USE IN SPECIFIC POPULATIONS

Lactation: Breastfeeding is not recommended in patients with smallpox. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1. Treatment of Human Smallpox Disease

TPOXX® is indicated for the treatment of human smallpox disease caused by variola virus in adults and pediatric patients weighing at least 3 kg.

1.2. Limitations of Use

The effectiveness of TPOXX for treatment of smallpox disease has not been determined in humans because adequate and well-controlled field trials have not been feasible, and inducing smallpox disease in humans to study the drug's efficacy is not ethical *[see Clinical Studies (14)]*.

TPOXX efficacy may be reduced in immunocompromised patients based on studies demonstrating reduced efficacy in immunocompromised animal models.

2. DOSAGE AND ADMINISTRATION

2.1. Important Dosing Instructions

It is recommended that patients 13 kg and above initiate oral treatment with TPOXX capsules if possible. If patients are unable to take oral TPOXX capsules or Drug-Food Preparation, treatment may be initiated with TPOXX injection as a 6 hour intravenous (IV) infusion. If IV treatment is necessary, conversion from IV to oral TPOXX is recommended as soon as oral treatment can be tolerated *[see Dosage and Administration (2.3)]*. 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.

TPOXX capsules

Take TPOXX capsules within 30 minutes after a full meal containing moderate or high fat.

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.

TPOXX injection

Administer TPOXX injection by IV infusion over 6 hours via an infusion pump. Must dilute TPOXX Injection prior to use *[see Dosage and Administration (2.5)]*.

2.2. Testing Before Initiating and During Treatment with TPOXX Injection

Determine creatinine clearance in all patients before starting TPOXX injection and monitor while receiving TPOXX injection as clinically appropriate [*see Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.2) and Use in Specific Populations (8.4, 8.6)*].

2.3. TPOXX Oral Dosage for Pediatric Patients Weighing at Least 13 kg and Adults

The recommended dosage of TPOXX capsules in pediatric patients weighing at least 13 kg and adults is displayed in Table 1 below.

Table 1: Recommended Dosage and Preparation Instructions for TPOXX Capsules in Pediatric Patients Weighing at Least 13 kg and Adults

Body Weight	**Oral Dosage for 14 Days[a]**	
	Dosage (Number of Capsules)	**Drug Food Preparation for Patients Who Cannot Swallow Capsules**
13 kg to less than 25 kg	200 mg (1 capsule) every 12 hours	Carefully open the required number of capsules and mix contents of capsule(s) of TPOXX with 30 mL of liquid (e.g., milk, chocolate milk) or soft food (e.g., apple sauce, yogurt). The entire mixture should be administered within 30 minutes of its preparation.
25 kg to less than 40 kg	400 mg (2 capsules) every 12 hours	
40 kg to less than 120 kg	600 mg (3 capsules) every 12 hours	
120 kg and above	600 mg (3 capsules) every 8 hours	

[a]TPOXX capsules should be taken within 30 minutes after a full meal containing moderate or high fat *[see Clinical Pharmacology (12.3)]*

2.4. Renal Impairment

TPOXX injection is contraindicated in patients with creatinine clearance below 30 mL per minute *[see Contraindications (4)]*.

2.5. Dosage and Administration of TPOXX Injection for Intravenous Infusion

The recommended dosage of TPOXX injection in pediatric patients weighing at least 3 kg and adults is displayed in Table 2 below.

TPOXX injection is supplied in a single-dose clear glass vial containing 200 mg/20 mL (10 mg/mL). Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. To administer:

- Use aseptic technique when preparing TPOXX injection.
- Withdraw the quantity of TPOXX injection (Table 2), add this volume to the syringe then dilute with two equal parts of either 0.9% (w/v) sodium chloride injection (normal saline) or 5% (w/v) dextrose injection in a syringe of suitable size. Injection with diluents other than 0.9% sodium chloride or 5% dextrose solution has not been studied. **NOT FOR IV BOLUS INJECTION. Do not use prefilled infusion bags for product preparation and administration.**
- The diluted TPOXX injection may be stored refrigerated (2°C - 8°C) for up to 24 hours or at room temperature (15°C - 25°C) for up to 4 hours.
- Gently swirl the syringe of in-use solution prior to inserting into the syringe pump and infuse over 6 hours every 12 hours for 14 days.
- Do not re-use the single-dose vial once it has been punctured.

Table 2: Recommended Pediatric and Adult Dosage and Preparation Instructions TPOXX Injection for IV Infusion[a]

Body Weight	Dosage for up to 14 days	Volume of TPOXX Injection[b]	Volume of Diluent[c]
3 kg to less than 35 kg	6 mg/kg every 12 hours by intravenous infusion over 6 hours[a]	0.6 mL/kg	1.2 mL/kg
35 kg to less than 120 kg	200 mg every 12 hours by intravenous infusion over 6 hours	20 mL	40 mL
120 kg and above[d]	300 mg every 12 hours by intravenous infusion over 6 hours	30 mL	60 mL

[a]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.
[b]10 mg/mL TPOXX solution containing 40% hydroxypropyl betadex (8 g per vial) with water for injection *[see Dosage Forms and Strengths (3)]*.
[c]Diluent is either 0.9% (w/v) sodium chloride injection or 5% (w/v) dextrose injection solution.
[d]Depending on size of syringe available with syringe pump system, two separate syringes may be needed for each 6 hour administration.

3. DOSAGE FORMS AND STRENGTHS

TPOXX Capsules

TPOXX capsules are hard gelatin with an opaque orange body imprinted in white ink with "SIGA" followed by the SIGA logo followed by "®", and an opaque black cap imprinted in white ink with "ST-246®", containing white to off-white powder. Each capsule contains 200 mg of tecovirimat.

TPOXX Injection

TPOXX injection: 200 mg/20 mL (10 mg/mL) of tecovirimat as a clear, colorless to pale yellow solution in a single-dose vial for further dilution.

4. CONTRAINDICATIONS

TPOXX Capsules:

None.

TPOXX Injection:

The excipient hydroxypropyl-β-cyclodextrin is eliminated through glomerular filtration. Therefore, TPOXX Injection is contraindicated in patients with severe renal impairment (defined as creatinine clearance below 30 mL/min). *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*

5. WARNINGS AND PRECAUTIONS

5.1. Hypoglycemia When Co-Administered with Repaglinide

Co-administration of repaglinide and tecovirimat may cause mild to moderate hypoglycemia. Monitor blood glucose and monitor for hypoglycemic symptoms when administering TPOXX with repaglinide *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

In a drug interaction study, 10 of 30 healthy subjects experienced mild (6 subjects) or moderate (4 subjects) hypoglycemia following co-administration of repaglinide (2 mg) and TPOXX capsules. Symptoms resolved in all subjects after intake of food and/or oral glucose.

5.2. Risks of Hydroxypropyl-β-Cyclodextrin Excipient for Patients with Renal Insufficiency and Pediatric Patients < 2 Years of age

Patients with renal insufficiency

TPOXX Injection: In healthy patients and in patients with mild to severe renal insufficiency, the majority of an 8 g dose of hydroxypropyl-β-cyclodextrin (per 200 mg tecovirimat/20 mL solution) is eliminated in the urine. It is known that clearance of hydroxypropyl-β-cyclodextrin is reduced in patients with mild, moderate, and severe renal impairment, resulting in higher exposure to hydroxypropyl-β-cyclodextrin; in these patients, half-life values are increased over normal values by approximately two-, four-, and six-fold, respectively. In these patients, successive infusions may result in accumulation of hydroxypropyl-β-cyclodextrin until steady state is reached.

In patients with mild (defined as creatinine clearance 60-89 mL/min) and moderate (defined as creatinine clearance 30-59 mL/min) renal impairment, TPOXX Injection should be used with caution. Creatinine clearance should be closely monitored and, if renal toxicity is suspected, consideration should be given to administering TPOXX orally if possible or to using an alternative medication. TPOXX Injection is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min) *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

Pediatric patients

TPOXX Injection: In pediatric patients less than 2 years of age, there are limited data regarding the use of hydroxypropyl-β-cyclodextrin. Given that renal tubular function rapidly matures over the first few years of life, clearance of hydroxypropyl-β-cyclodextrin may be reduced in young pediatric patients, resulting in higher exposure to hydroxypropyl-β-cyclodextrin. TPOXX Injection should be used with caution in this population given that animal studies have shown potential for nephrotoxicity at very high exposure levels of hydroxypropyl-β-cyclodextrin. 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 *[see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)]*.

6. ADVERSE REACTIONS

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TPOXX has not been studied in patients with smallpox disease.

TPOXX Clinical Trial (Oral Administration)

The safety of TPOXX was evaluated in 359 healthy adult subjects ages 18-79 years in a Phase 3 clinical trial. Of the subjects who received at least one 600 mg dose of TPOXX, 59% were female, 69% were White, 28% were Black/African American, 1% were Asian, and 12% were Hispanic or Latino. Ten percent of the subjects who participated in the study were age 65 or older. Of these 359 subjects, 336 subjects received at least 23 of 28 doses of 600 mg TPOXX in a twice daily (every 12 hours) regimen for 14 days.

Most Frequently Reported Adverse Reactions

The most frequently reported adverse reactions were headache and nausea. Adverse reactions that occurred in at least 2% of subjects in the TPOXX treatment group are shown in Table 3.

Table 3: Treatment-Related Adverse Reactions Reported in ≥ 2% of Healthy Adult Subjects Receiving at Least One Dose of TPOXX Capsules 600 mg

Adverse Reaction	**TPOXX 600 mg N = 359 (%)**	**Placebo N = 90 (%)**
Headache	12	8
Nausea	5	4
Abdominal pain[a]	2	1
Vomiting	2	0

[a]Includes abdominal pain, abdominal pain upper, abdominal distension, abdominal discomfort, abdominal pain lower, epigastric pain

Adverse Reactions Leading to Discontinuation of TPOXX
Six subjects (2%) had their treatment with TPOXX discontinued due to adverse reactions. Each of these subject's adverse reactions (with severity) is listed below:

- EEG change, abnormal
- Mild upset stomach, dry mouth, decreased concentration and dysphoria
- Mild nausea and fever, moderate diarrhea, severe headache
- Mild palpable purpura
- Mild nausea, fever and chills
- Mild facial redness, facial swelling and pruritus

Less Common Adverse Reactions

Clinically significant adverse reactions that were reported in < 2% of subjects exposed to TPOXX and at rates higher than subjects who received placebo are listed below:

- Gastrointestinal: dry mouth, chapped lips, dyspepsia, eructation, oral paresthesia
- General and administration site: pyrexia, pain, chills, malaise, thirst
- Investigations: abnormal electroencephalogram, hematocrit decreased, hemoglobin decreased, heart rate increased
- Musculoskeletal and connective tissue: arthralgia, osteoarthritis
- Nervous system: migraine, disturbance in attention, dysgeusia, paresthesia
- Psychiatric: depression, dysphoria, irritability, panic attack
- Respiratory, Thoracic and Mediastinal Disorders: oropharyngeal pain
- Skin and subcutaneous tissue: palpable purpura, rash, pruritic rash, facial redness, facial swelling, pruritus

TPOXX Clinical Trial (Intravenous Administration)

The safety of multiple doses of 240 mg of TPOXX injection for IV infusion was evaluated in 26 healthy adult subjects ages 23-62 years, inclusive. An additional 6 subjects received placebo. TPOXX injection was administered over a 6 hour period via infusion pump twice daily (every 12 hours) for 7 days. Of the 26 subjects administered TPOXX, 42% were female, 69% were White, 23% were Black/African American, and 42% were Hispanic or Latino.

Most Frequently Reported Adverse Reactions

The most frequently reported adverse reactions included infusion site pain, infusion site swelling, infusion site erythema, infusion site extravasation, and headache. Adverse reactions that occurred in at least 4% of subjects in the TPOXX treatment group are shown in Table 4.

Table 4: Treatment-Related Adverse Reactions Reported in ≥ 4% of Healthy Adult Subjects Receiving at Least One Dose of TPOXX Injection 240 mg

	TPOXX 240 mg N =26 (%)	**Placebo N = 6 (%)**
Infusion Site Pain	73	67
Infusion Site Swelling	39	67
Infusion Site Erythema	23	67
Infusion Site Extravasation	19	50
Headache	15	0

Adverse Reactions Leading to Discontinuation of TPOXX Injection

Three subjects (12%) had their treatment with TPOXX injection discontinued due to adverse reactions. One subject had two adverse reactions. Each of these subject's adverse reactions (with severity) are listed below:

- Moderate Infusion site extravasation
- Mild Infusion site extravasation
- Mild Infusion site swelling and mild infusion site pain

Less Common Adverse Reactions

Clinically significant adverse reactions that were reported in < 4% of subjects exposed to TPOXX injection and at rates higher than subjects who received placebo are listed below:

- General and administration site: infusion site discomfort, infusion site edema
- Musculoskeletal and connective tissue: myalgia, arthritis, back pain, muscle tightness
- Gastrointestinal: diarrhea
- Eye: photophobia
- Skin and Subcutaneous Tissue: pruritus generalized

7. DRUG INTERACTIONS

7.1. Effect of TPOXX on Other Drugs

Tecovirimat is a weak inducer of cytochrome P450 (CYP)3A and a weak inhibitor of CYP2C8 and CYP2C19. However, the effects are not expected to be clinically relevant for most substrates of those enzymes based on the magnitude of interactions and the duration of treatment of TPOXX. See Table 5 for clinical recommendations for select sensitive substrates.

7.2. Established Drug Interactions

Table 5 provides a listing of established or significant drug interactions *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

Table 5: Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Effect/Recommendation
Blood Glucose-Lowering Agent:		
Repaglinide[b]	↑ repaglinide	Monitor blood glucose and monitor for hypoglycemic symptoms in patients when TPOXX is co-administered with repaglinide *[see Warnings and Precautions (5.1)]*.
CNS Depressant:		
Midazolam[b]	↓ midazolam	Monitor for effectiveness of midazolam.

[a] ↓ = decrease, ↑ = increase
[b] These interactions have been studied in healthy adults.

7.3. Drugs Without Clinically Significant Interactions With TPOXX

Based on a drug interaction study, no clinically significant drug interactions have been observed when TPOXX is co-administered with bupropion, flurbiprofen, or omeprazole *[see Clinical Pharmacology (12.3)]*.

7.4. Vaccine Interactions

No vaccine-drug interaction studies have been performed in human subjects. Some animal studies have indicated that co-administration of TPOXX at the same time as live smallpox vaccine (vaccinia virus) may reduce the immune response to the vaccine. The clinical impact of this interaction on vaccine efficacy is unknown.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

There are no available data on the use of tecovirimat in pregnant individuals to evaluate for a drug-associated risk of major birth defects, miscarriage, and other adverse maternal and fetal outcomes.

In animal reproduction studies, no embryofetal developmental toxicity was observed in mice during the period of organogenesis at tecovirimat exposures (area under the curve [AUC]) up to 23 times higher than human exposure at the recommended human dose (RHD). In rabbits, no embryofetal developmental toxicity was observed during organogenesis at tecovirimat exposures (AUC) less than human exposures at the RHD. In a mouse pre-/post-natal development study, no toxicities were observed at maternal tecovirimat exposures up to 24 times higher than human exposure at the RHD *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown, and the estimated background risk of miscarriage for the indicated population is higher than the general population. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Tecovirimat was administered orally to pregnant mice at doses up to 1,000 mg/kg/day from gestation Days 6-15. No embryofetal toxicities were observed at doses up to 1,000 mg/kg/day (approximately 23 times higher than human exposure at the RHD).

Tecovirimat was administered orally to pregnant rabbits at doses up to 100 mg/kg/day from gestation Days 6-19. No embryofetal toxicities were observed at doses up to 100 mg/kg/day (0.4 times the human exposure at the RHD).

In the pre-/post-natal development study, tecovirimat was administered orally to pregnant mice at doses up to 1,000 mg/kg/day from gestation Day 6 to post-natal Day 20. No toxicities were observed at doses up to 1,000 mg/kg/day (approximately 24 times higher than human exposure at the RHD).

8.2. Lactation

Risk Summary

Because of the potential for variola virus transmission through direct contact with the breastfed infant, breastfeeding is not recommended in patients with smallpox. There are no data on the presence of tecovirimat in human milk, the effects of the drug on the breastfed infant, or on milk production. Tecovirimat was present in animal milk *(see Data)*. When a drug is present in animal milk, it is likely to be present in human milk.

Data

In a lactation study at doses up to 1,000 mg/kg/day, mean tecovirimat milk to plasma ratios up to approximately 0.8 were observed at 6 and 24 hours post-dose when administered orally to mice on lactation Day 10 or 11.

8.3. Females and Males of Reproductive Potential

Infertility

There are no data on the effect of tecovirimat on human fertility. Decreased fertility due to testicular toxicity was observed in male mice *[see Nonclinical Toxicology (13.1)]*.

8.4. Pediatric Use

As in adults, the effectiveness of TPOXX in pediatric patients is based solely on efficacy studies in animal models of orthopoxvirus disease. As exposure of healthy pediatric subjects to TPOXX with no potential for direct clinical benefit is not ethical, pharmacokinetic simulation was used to derive dosing regimens that are predicted to provide pediatric patients with exposures comparable to the observed exposure in adults receiving 600 mg orally twice daily (every 12 hours) or 200 mg intravenously twice daily (every 12 hours). The dosage for pediatric patients is based on weight *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

TPOXX Injection:

There are limited data regarding the use of hydroxypropyl-β-cyclodextrin, an ingredient in TPOXX injection, 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 *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

8.5. Geriatric Use

Clinical studies of TPOXX did not include sufficient numbers of subjects aged 65 and over to determine whether the safety profile of TPOXX is different in this population compared to younger subjects. Of the 359 subjects in the clinical study of oral TPOXX, 10% (36/359) were ≥ 65 years of age, and 1% (4/359) were ≥ 75 years of age. No alteration of dosing is needed for patients ≥ 65 years of age *[see Clinical Pharmacology (12.3)]*.

8.6. Renal Impairment

TPOXX Capsules:

No dosage adjustment is required for patients with mild, moderate or severe renal impairment or patients with end stage renal disease (ESRD) requiring hemodialysis *[see Clinical Pharmacology (12.3)]*.

TPOXX Injection:

Hydroxypropyl-β-cyclodextrin, an ingredient in TPOXX injection, when administered intravenously, is eliminated through glomerular filtration. No dosage adjustment is required for patients with mild (creatinine clearance 60-89 mL/min) or moderate (creatinine clearance 30-59 mL/min) renal impairment. TPOXX Injection is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min) *[see Contraindications (4)]*.

8.7. Hepatic Impairment

No dosage adjustment is required for patients with mild, moderate or severe hepatic impairment (Child Pugh Class A, B, or C) *[see Clinical Pharmacology (12.3)]*.

10. OVERDOSAGE

There is no clinical experience with overdosage of TPOXX. In case of overdosage, monitor patients for any signs or symptoms of adverse effects. Hemodialysis will not significantly remove TPOXX in overdosed patients.

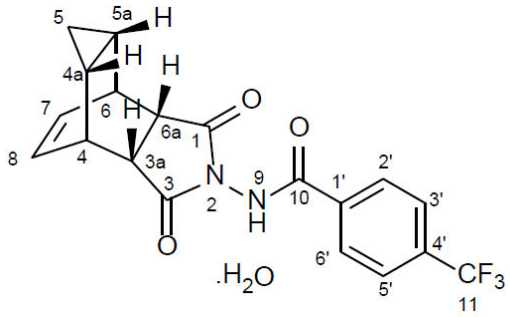
11. DESCRIPTION

TPOXX capsules and TPOXX injection contains tecovirimat, an inhibitor of the orthopoxvirus VP37 envelope wrapping protein.

TPOXX (tecovirimat) capsules, for oral use are immediate release capsules containing tecovirimat monohydrate equivalent to 200 mg of tecovirimat for oral administration. The capsules include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The capsule shell is composed of gelatin, FD&C blue #1, FD&C red #3, FD&C yellow #6, and titanium dioxide.

TPOXX (tecovirimat) injection, for intravenous use is a sterile, colorless to pale yellow solution free of visible particles that is intended for intravenous use following dilution. Tecovirimat injection is available in a single-dose vial containing 200 mg/20 mL (10 mg/mL) of tecovirimat and 8,000 mg (400 mg/mL) of Hydroxypropyl Betadex, NF (hydroxypropyl β-cyclodextrin) and Water for Injection, USP/NF.

Tecovirimat monohydrate is a white to off-white crystalline solid with the chemical name Benzamide, N-[(3a*R*,4*R*,4a*R*,5a*S*,6*S*,6a*S*)-3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6 ethenocycloprop[f]isoindol-2(1H)-yl]-4-(trifluoromethyl), rel-(monohydrate). The chemical formula is $C_{19}H_{15}F_3N_2O_3 \cdot H_2O$ representing a molecular weight of 394.35 g/mol. The molecular structure is as follows:



Tecovirimat monohydrate is practically insoluble in water and across the pH range of 2.0-6.5 (< 0.1 mg/mL).

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

Tecovirimat is an antiviral drug against variola (smallpox) virus *[see Microbiology (12.4)]*.

12.2. Pharmacodynamics

Cardiac Electrophysiology

TPOXX does not prolong the QT interval to any clinically relevant extent at the anticipated therapeutic exposure.

12.3. Pharmacokinetics

At the recommended oral dosage of 600 mg every 12 hours administered in healthy adults weighing less than 120 kg, the mean steady-state values of tecovirimat $AUC_{0\text{-}24hr}$, C_{max}, and $C_{tau/trough}$ are 29816 hr·ng/mL (n, CV: 43, 34%), 2159 ng/mL (n, CV: 46, 32%), and 845 ng/mL (n, CV: 45, 47%), respectively. At the recommended intravenous dosage of 200 mg every 12 hours administered by IV infusion over 6 hours in healthy adults, the mean steady-state values of tecovirimat $AUC_{0\text{-}24hr}$, C_{max}, and C_{min} are 39405 hr.ng/mL (n, CV: 22, 23%), 2630 ng/mL (n, CV: 22, 22%), and 747 ng/mL (n, CV: 22, 29%). Refer to Table 6 for pharmacokinetic parameters of tecovirimat. Tecovirimat steady-state is achieved by Day 4-6.

Table 6: Pharmacokinetic Properties of Tecovirimat

Absorption	**200 mg intravenous**	**600 mg oral**
Median T_{max} (h) (Range)	6 (6-6.5)	6 (2-24)[a]
Effect of food (relative to fasting)	NA	↑39% [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 or Vz/F, L) (CV%)	383 (46%)	1030
Metabolism		
Metabolic pathways[c]	Hydrolysis, UGT1A1[d], UGT1A4	
Elimination		
Major route of elimination	Metabolism	
Clearance (CL or CL/F, L/hr) (CV%)	13 (23%)	31
$t_{½}$ (h)[e] (CV%)	21 (45%)	19(29%)
% of dose excreted in urine[f]	NA	73, predominantly as metabolites
% of dose excreted in feces[f]	NA	23, predominantly as tecovirimat

[a]Value reflects administration of drug with food.
[b]Value refers to mean systemic exposure (AUC_{24hr}). Meal: ~ 600 kcal, ~ 25 g fat.
[c]Tecovirimat is metabolized by hydrolysis of the amide bond and glucuronidation. The following inactive metabolites were detected in plasma: M4 (N-{3,5-dioxo-4-azatetracyclo[5.3.2.0{2,6}.0{8,10}]dodec-11-en-4-yl}amine), M5 (3,5 dioxo-4-aminotetracyclo[5.3.2.0{2,6}.0{8,10}]dodec-11-ene), 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.
[f]Single dose administration of [^{14}C]-tecovirimat in mass balance study.
KEY: NA = Not Applicable or Not Available

Comparison of Animal and Human PK Data to Support Effective Human Dose Selection

Because the effectiveness of TPOXX cannot be tested in humans, a comparison of tecovirimat exposures achieved in healthy human subjects to those observed in animal models of orthopoxvirus infection (nonhuman primates and rabbits infected with monkeypox virus and rabbitpox virus, respectively) in therapeutic efficacy studies was necessary to support the dosage regimen of 600 mg every 12 hours for treatment of smallpox disease in humans. Humans achieve greater systemic exposure (AUC, C_{max}, and C_{min}) of tecovirimat following a dose of 600 mg every 12 hours when compared to the therapeutic exposures in these animal models.

Specific Populations

No clinically significant differences in the pharmacokinetics of tecovirimat were observed based on age, sex, ethnicity, renal impairment (based on estimated GFR), or hepatic impairment (Child Pugh Scores A, B or C). At the 600 mg twice-daily oral dosage, tecovirimat exposure was reduced in adult subjects weighing more than 120 kg compared to the exposures in adult subjects weighing less than 120 kg. Specifically, in 34 adult subjects weighing more than 120 kg who received 600 mg TPOXX orally every 12 hours, the observed mean steady state values of $AUC_{0\text{-}24hr}$, C_{max}, and C_{trough} were 19500 hr•ng/mL (CV: 23%), 1300 ng/mL (CV: 29%), and 585 ng/mL (CV: 31%), respectively.

Pediatric Patients

TPOXX pharmacokinetics has not been evaluated in pediatric patients. The recommended pediatric dosing regimen is expected to produce tecovirimat exposures that are comparable to those in adult subjects based on a population pharmacokinetic modeling and simulation approach *[see Dosage and Administration (2.2) and Use in Specific Populations (8.4)]*.

Hydroxypropyl-β-cyclodextrin, when administered intravenously, is eliminated through glomerular filtration which may be reduced in pediatric patients with renal immaturity *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.4)]*.

Drug Interaction Studies

The effect of tecovirimat on the exposure of co-administered drugs are shown in Table 7.

Table 7: Drug Interactions – Changes in Pharmacokinetic Parameters for Co Administered Drug in the Presence of TPOXX[a]

Co-Administered Drug	Dose of Co-Administered Drug (mg)	N	Mean Ratio (90% CI) of Co-Administered Drug PK With/Without TPOXX No Effect = 1.00	
			C_{max}	AUC_{∞}
Flurbiprofen + omeprazole + midazolam[b]	omeprazole 20 single dose	24	1.87 (1.51, 2.31)	1.73 (1.36, 2.19)
	midazolam 2 single dose		0.61 (0.54, 0.68)	0.68 (0.63, 0.73)
Repaglinide	2 single dose	30	1.27 (1.12, 1.44)	1.29 (1.19, 1.40)
Bupropion	150 single dose	24	0.86 (0.79, 0.93)	0.84 (0.78, 0.89)

[a]All interaction studies conducted in healthy volunteers with tecovirimat 600 mg twice daily (every 12 hours).
[b]Comparison based on exposures when administered as flurbiprofen + omeprazole + midazolam.

No pharmacokinetic changes were observed for the following drug when co-administered with tecovirimat: flurbiprofen.

Cytochrome P450 (CYP) Enzymes: Tecovirimat is a weak inhibitor of CYP2C8 and CYP2C19, and a weak inducer of CYP3A4. Tecovirimat is not an inhibitor or an inducer of CYP2B6 or CYP2C9.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically

CYP Enzymes: Tecovirimat is not an inhibitor of CYP1A2, CYP2D6, CYP2E1 or CYP3A4, and is not an inducer of CYP1A2. Tecovirimat is not a substrate for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4.

UGT Enzymes: Tecovirimat is a substrate of UGT1A1 and UGT1A4.

Transporter Systems: Tecovirimat inhibited Breast Cancer Resistance Protein (BCRP) *in vitro*.

Tecovirimat is not an inhibitor of P-glycoprotein (P-gp), organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1 and OATP1B3), organic anion transporter 1 (OAT1), OAT3, and organic cation transporter 2 (OCT2). Tecovirimat is not a substrate for P-gp, BCRP, OATP1B1, and OATP1B3.

12.4. Microbiology

Mechanism of Action

Tecovirimat targets and inhibits the activity of the orthopoxvirus VP37 protein (encoded by and highly conserved in all members of the orthopoxvirus genus) and blocks its interaction with cellular Rab9 GTPase and TIP47, which prevents the formation of egress competent enveloped virions necessary for cell to cell and long-range dissemination of virus.

Activity in Cell Culture

In cell culture assays, the effective concentrations of tecovirimat resulting in a 50% reduction in virus induced cytopathic effect (EC_{50}), were 0.016-0.067 μM, 0.014-0.039 μM, 0.015 μM, and 0.009 μM, for variola, monkeypox, rabbitpox, and vaccinia viruses, respectively. Ranges given for variola and monkeypox viruses are reflective of results from multiple strains assayed.

Non-antagonistic antiviral activity of tecovirimat and brincidofovir against orthopoxviruses has been demonstrated in cell culture and animal models.

Resistance

There are no known instances of naturally occurring tecovirimat resistant orthopoxviruses, although tecovirimat resistance may develop under drug selection. Tecovirimat has a relatively low resistance barrier, and certain amino acid substitutions in the target VP37 protein can confer large reductions in tecovirimat antiviral activity. The possibility of resistance to tecovirimat should be considered in patients who either fail to respond to therapy or who develop recrudescence of disease after an initial period of responsiveness.

Cross-resistance

Cross-resistance between tecovirimat and brincidofovir is not expected based on their distinct mechanisms of action. Where tested, orthopoxvirus isolates resistant to cidofovir (the active metabolite of brincidofovir) have not been resistant to tecovirimat. Likewise, orthopoxvirus isolates resistant to tecovirimat retain their sensitivity to cidofovir.

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been conducted with tecovirimat.

Tecovirimat was not genotoxic in *in vitro* or *in vivo* assays, including a bacterial reverse mutation assay, a mammalian mutagenicity assay in mouse lymphoma L5178Y/TK$^{\pm}$ cells, and in an *in vivo* mouse micronucleus study.

Impairment of Fertility

In a fertility and early embryonic development study in mice, no effects of tecovirimat on female fertility were observed at tecovirimat exposures (AUC) approximately 24 times higher than human exposure at the RHD. In male mice, decreased male fertility associated with testicular toxicity (increased percent abnormal sperm and decreased sperm motility) was observed at 1,000 mg/kg/day (approximately 24 times the human exposure at the RHD).

13.2. Animal Toxicology and/or Pharmacology

In a repeat-dose toxicology study in dogs, convulsions (tonic and clonic) were observed in one animal within 6 hours of a single dose of 300 mg/kg (approximately 4 times higher than the highest observed human exposure at the RHD based on C_{max}). Electroencephalography (EEG) findings in this animal were consistent with seizure activity during the observed convulsions. Tremors, which were considered non-adverse, were observed at 100 mg/kg/dose (similar to the highest observed human exposure at the RHD based on C_{max}), although no convulsions or EEG findings were observed at this dose.

14. CLINICAL STUDIES

Overview

The effectiveness of TPOXX for treatment of smallpox disease has not been determined in humans because adequate and well-controlled field trials have not been feasible, and inducing smallpox disease in humans to study the drug's efficacy is not ethical. Therefore, the effectiveness of TPOXX for treatment of smallpox disease was established based on results of adequate and well-controlled animal efficacy studies of non-human primates and rabbits infected with non-variola orthopoxviruses. Survival rates observed in the animal studies may not be predictive of survival rates in clinical practice.

Study Design

Efficacy studies were conducted in cynomolgus macaques infected with monkeypox virus, and New Zealand white (NZW) rabbits infected with rabbitpox virus. The primary efficacy endpoint for these studies was survival. In non-human primate studies, cynomolgus macaques were lethally challenged intravenously with 5 x 10^7 plaque-forming units of monkeypox virus; tecovirimat was administered orally once daily at a dose level of 10 mg/kg for 14 days, starting at Day 4, 5 or 6 post-challenge. In rabbit studies, NZW rabbits were lethally challenged intradermally with 1,000 plaque-forming units of rabbitpox virus; tecovirimat was administered orally once daily for 14 days at a dose level of 40 mg/kg, starting at Day 4 post-challenge. The timing of tecovirimat dosing in these studies was intended to assess efficacy when treatment is initiated after animals have developed clinical signs of disease, specifically dermal pox lesions in cynomolgus macaques, and fever in rabbits. Clinical signs of disease were evident in some animals at Day 2-3 post-challenge but were evident in all animals by Day 4 post-challenge. Survival was monitored for 3-6 times the mean time to death for untreated animals in each model.

Study Results

Treatment with tecovirimat for 14 days resulted in statistically significant improvement in survival relative to placebo, except when given to cynomolgus macaques starting at Day 6 post-challenge (Table 8).

Table 8: Survival Rates in Tecovirimat Treatment Studies in Cynomolgus Macaques and NZW Rabbits Exhibiting Clinical Signs of Orthopoxvirus Disease

	Treatment Initiation[a]	**Survival Percentage (No. survived/n)**		**p-value[b]**	**Survival Rate Difference[c] (95% CI)[d]**
		Placebo	**Tecovirimat**		
Cynomolgus Macaques					
Study 1	Day 4	0% (0/7)	80% (4/5)	0.0038	80% (20.8%, 99.5%)
Study 2	Day 4	0% (0/6)	100% (6/6)	0.0002	100% (47.1%, 100%)
Study 3	Day 4	0% (0/3)	83% (5/6)	0.0151	83% (7.5%, 99.6%)
	Day 5		83% (5/6)	0.0151	83% (7.5%, 99.6%)
	Day 6		50% (3/6)	0.1231	50% (-28.3%, 90.2%)
NZW Rabbits					
Study 4	Day 4	0% (0/10)	90% (9/10)	< 0.0001	90% (50.3%, 99.8%)
Study 5	Day 4	NA[e]	88% (7/8)	NA	NA

[a]Day post-challenge tecovirimat treatment was initiated
[b]p-value is from 1-sided Boschloo Test (with Berger-Boos modification of gamma = 0.000001) compared to placebo
[c]Survival percentage in tecovirimat treated animals minus survival percentage in placebo treated animals
[d]Exact 95% confidence interval based on the score statistic of difference in survival rates
[e]A placebo control group was not included in this study.
KEY: NA = Not Applicable

16. HOW SUPPLIED/STORAGE AND HANDLING

TPOXX Capsule

How Supplied

Each TPOXX capsule contains 200 mg of tecovirimat. TPOXX capsules are hard gelatin with an opaque orange body imprinted in white ink with "SIGA" followed by the SIGA logo followed by "®", and an opaque black cap imprinted in white ink with "ST-246®", containing white to off-white powder. Each bottle contains 42 capsules (NDC 50072-200-42) with an induction seal and child-resistant cap.

Storage and Handling

Store capsules in the original bottle at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

TPOXX Injection

How Supplied

TPOXX injection is supplied in a 30 mL single-dose vial as a clear, colorless to pale yellow solution for intravenous administration containing 200 mg/20 mL (10 mg/mL) of tecovirimat (NDC 50072-010-30). This solution is intended for dilution with either 0.9% (w/v) sodium chloride injection or 5% (w/v) dextrose injection solution. The vial stopper is not made with natural rubber latex. The vials are packed in cartons of seven vials. Short-term (up to 24 hours) storage and handling at an ambient temperature is acceptable.

Storage and Handling

Store TPOXX injection in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze.

The diluted solution(s) of TPOXX injection with either 0.9% (w/v) sodium chloride (normal saline) or 5% (w/v) dextrose solution should be used within 4 hours of preparation if stored at room temperature or within 24 hours of preparation if stored at 2°C to 8°C *[see Dosage and Administration (2.5)]*.

17. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Efficacy Based on Animal Models Alone

Inform patients that the efficacy of TPOXX is based solely on efficacy studies demonstrating a survival benefit in animals and that the effectiveness of TPOXX has not been tested in humans with smallpox disease *[see Clinical Studies (14)]*.

Important Dosage and Administration Information

Advise patients to take TPOXX capsules as directed within 30 minutes of eating a full meal containing moderate or high fat with 6-8 oz. of water *[see Clinical Pharmacology (12.3)]*. Inform patients to take TPOXX for the entire duration without missing or skipping a dose *[see Dosage and Administration (2)]*.

Inform patients who cannot swallow capsules to refer to the Instructions for Use *[see Dosage and Administration (2)]*.

Drug Interactions

Inform patients that TPOXX may interact with other drugs. Advise patients to report to their healthcare provider the use of other prescription drugs. Co-administration of TPOXX with repaglinide may cause hypoglycemia *[see Warnings and Precautions (5.1) and Drug Interactions (7.2)]*.

TPOXX injection: Hydroxypropyl-β-cyclodextrin, a required component of TPOXX injection, is eliminated through glomerular filtration. Therefore, in patients with severe renal impairment (defined as creatinine clearance below 30 mL/min), the use of TPOXX injection is contraindicated. *[see Contraindications (4)]*. In patients with mild (defined as creatinine clearance 60-89 mL/min) and moderate (defined as creatinine clearance 30-59 mL/min) renal impairment, TPOXX injection should be used with caution *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*.

Lactation

Instruct individuals with smallpox not to breastfeed their infant because of the risk of passing variola virus to the breastfed infant *[see Use in Specific Populations (8.2)]*.

TPOXX capsules manufactured by:

Catalent Pharma Solutions, LLC

1100 Enterprise Drive

Winchester, KY 40391

TPOXX injection manufactured by:
Patheon Manufacturing Services LLC
5900 Martin Luther King Jr. Highway
Greenville, NC 27834

Distributed by:
SIGA Technologies, Inc.
4575 SW Research Way, Suite 110
Corvallis, OR 97333

PATIENT INFORMATION

TPOXX® (Tē-Pox or Tee-pahx) **(tecovirimat)** **capsules, for oral use**	**TPOXX® (Tē-Pox or Tee-pahx)** **(tecovirimat)** **injection, for intravenous use**

What is TPOXX?

TPOXX is a prescription medicine used to treat smallpox disease caused by a type of virus called variola virus in adults and children who weigh at least 7 pounds (3 kg).

- The effectiveness of TPOXX has been studied only in animals with orthopoxvirus diseases. There have been no human studies in people who have smallpox disease.
- The safety of TPOXX was studied in adults. There have been no studies of TPOXX in children 17 years of age and younger.
- TPOXX may not work well in people who have a weakened immune system (immunocompromised).

Who should not receive TPOXX injection?

Do not receive TPOXX injection if you or your child have severe kidney problems TPOXX injection contains an ingredient called hydroxypropyl β-cyclodextrin which is cleared from your body through the kidneys. Tell your healthcare provider if you or your child have kidney problems because receiving TPOXX injection may not be right for you or your child.

Before taking or receiving TPOXX, tell your healthcare provider about all of your or your child's medical conditions, including if you or your child:

- have diabetes.
- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if TPOXX can harm the unborn baby. Tell your healthcare provider if you or your child become pregnant during treatment with TPOXX.
- are breastfeeding or plan to breastfeed. It is not known if TPOXX passes into your breast milk. **You should not breastfeed during treatment with TPOXX.**
    - You should not breastfeed if you have smallpox because of the risk of passing variola virus to the breastfed infant.
    - Talk to your healthcare provider about the best way to feed the baby during treatment with TPOXX.

Tell your healthcare provider about all of the medicines you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Using TPOXX with certain other medicines may affect each other causing possible serious side effects. You can ask your healthcare provider or pharmacist for a list of medications that interact with TPOXX.

Especially tell your healthcare provider if you take a medicine used to treat type 2 diabetes called repaglinide.

Know the medicines you or your child take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine. Do not start taking a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take TPOXX with other medicines.

How should I take TPOXX?

- **Stay under the care of your healthcare provider during treatment with TPOXX.**

TPOXX capsules:

- Take TPOXX capsules exactly as your healthcare provider tells you. Do not change the dose or stop taking TPOXX without talking to your healthcare provider.
- **For adults and children who weigh at least 40 kg and less than 120 kg**, take 3 capsules of TPOXX 2 times a day (every 12 hours) by mouth for 14 days.
- **For adults and children who weigh at least 120 kg**, take 3 capsules of TPOXX 3 times a day (every 8 hours) by mouth for 14 days.
- TPOXX should be taken within 30 minutes after eating a full meal of moderate or high fat (approximately 600 calories and 25 grams of fat). Swallow capsules whole with 6 to 8 ounces of water. Talk to your healthcare provider about examples of foods that you can eat that contain about 25 grams of fat. **Always take TPOXX with food.**
- See the "Instructions for Use" that comes with your TPOXX capsules for instructions on how to prepare and take a dose of TPOXX if:

- your child weighs less than 88 pounds (40 kg), **or**
- you or your child have trouble swallowing TPOXX capsules.

- It is important to take TPOXX for the full 14 day course of treatment. Do not miss or skip a dose of TPOXX.
- If you miss an oral dose of TPOXX, you should take the dose as soon as possible and anytime up to 8 hours before the next scheduled dose. If less than 8 hours remain before the next scheduled dose, do not take the missed dose, and take your next dose as scheduled.
- If you take too much TPOXX, call your healthcare provider or go to the nearest hospital emergency room right away.

TPOXX Injection for Intravenous Infusion (IV)

TPOXX injection is given to you or your child by intravenous (IV) infusion into a vein slowly over 6 hours using an infusion pump by a health care provider.

What are the possible side effects of TPOXX?

TPOXX may cause serious side effects, including:

- **Low blood sugar (hypoglycemia).** Low blood sugar can happen when TPOXX is taken or received with repaglinide, a medicine used to treat type 2 diabetes. Tell your healthcare provider if you get any of the following symptoms of low blood sugar:
  - headache
  - drowsiness
  - hunger
  - feeling jittery or shaky
  - dizziness
  - confusion
  - sweating
  - weakness
  - fast heartbeat
  - irritability

The most common side effects of TPOXX capsules include:

- headache
- nausea
- stomach pain
- vomiting

The most common side effects of TPOXX injection include:

- reactions at the site of your IV infusion

These are not all the possible side effects of TPOXX.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088

How should I store TPOXX capsules?

- Store TPOXX at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep TPOXX in its original container.

Keep TPOXX and all other medicines out of the reach of children.

General information about the safe and effective use of TPOXX.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TPOXX for a condition for which it was not prescribed. Do not give TPOXX to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TPOXX that is written for health professionals.

What are the ingredients in TPOXX?

TPOXX capsules: 200 mg

Active ingredient: tecovirimat

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The capsule shell is made of gelatin, FD&C blue No.1, FD&C red No.3, FD&C yellow No.6, and titanium dioxide.

TPOXX injection: 200 mg in each 20 mL vial

Active ingredient: tecovirimat

Inactive ingredients: hydroxypropyl β-cyclodextrin and water for injection.

TPOXX capsules manufactured by:

Catalent Pharma Solutions,

1100 Enterprise Drive,

Winchester, KY 40391

TPOXX injection manufactured by:
Patheon Manufacturing Services LLC,
5900 Martin Luther King Jr. Highway,
Greenville, NC 27834

Distributed By:
SIGA Technologies, Inc.
4575 SW Research Way, Suite 110
Corvallis, OR 97333
For more information, go to www.SIGA.com or call 1-888-899-3472.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 05/2022

INSTRUCTIONS FOR USE
TPOXX® (Tē-Pox or Tee-pahx)
(tecovirimat)
capsules, for oral use

This Instructions for Use contains information on how to prepare and give a dose of TPOXX capsules to children who weigh 28 pounds (13 kg) to less than 88 pounds (40 kg) or adults or children who have trouble swallowing TPOXX capsules whole.

Read this Instructions for Use before taking TPOXX capsules. There may be new information. This Instructions for Use does not take the place of talking to your healthcare provider about your medicinal condition or treatment.

Step 1: Gather the supplies you need to prepare a dose of TPOXX:

- 1 bottle of TPOXX (1 capsule = 200 mg of medicine)
- 1 tablespoon
- 1 small bowl or cup
- Your choice of liquid or soft food:
  - Liquid such as milk, chocolate milk or infant formula
  - Soft food such as applesauce or yogurt

Step 2: Find the weight of the person taking the medicine on the TPOXX Dosing Table (see **Figure A**).

Step 3: Find the prescribed dose in the same row as the weight of the person taking the medicine on the TPOXX Dosing Table (See **Figure A**).

Step 4:

- Get a small bowl or cup and place it on a flat surface.
- Add 2 tablespoons (30 mL) of liquid or soft food to the bowl or cup.

Step 5: Find the number of TPOXX capsules needed in the same row as the weight of the person taking the medicine on the TPOXX Dosing Table (see **Figure A**).

- Take out the correct number of TPOXX capsules from the bottle.

Step 6: Hold the TPOXX capsule in a sideways (horizontal) position directly over the bowl or cup to make sure none of the medicine is lost.

- Hold the ends of the TPOXX capsule between the thumb and index (pointer) finger of both hands.
- Gently and slowly twist the ends of the capsule and pull it apart. Empty the contents of the capsule into the bowl or cup. Repeat this for each capsule that is needed for the total prescribed dose.
- Throw away the empty capsule shells.

Step 7: Use the tablespoon to mix together the capsule contents and the liquid or soft food.

- The powder may not completely dissolve.
- The TPOXX medicine mixture is now ready to take.

Step 8: Swallow the TPOXX medicine mixture.

All the TPOXX medicine mixture should be swallowed to make sure the entire dose it taken.

- The TPOXX mixture must be taken within 30 minutes after a meal containing approximately 25 grams of fat **and** within 30 minutes after mixing it.
- **For people weighing 28 pounds (13 kg) to less than 264 pounds (120 kg), TPOXX medicine mixture should be given 2 times a day (every 12 hours), by mouth, for 14 days.**
- **For people weighing 264 pounds (120 kg) and above, TPOXX medicine mixture should be given 3 times a day (every 8 hours), by mouth, for 14 days.**

TPOXX Dosing Table (Figure A)

Body Weight	Prescribed Dose	Amount of Liquid or Soft Food	Number of Capsules	Food and Medicine Mixture Instructions
28 pounds (13 kg) to less than 55 pounds (25 kg)[a]	200 mg (1 capsule) Every 12 hours	2 tablespoons	1 TPOXX capsule	Mix entire contents of 1 TPOXX capsule with 2 tablespoons of liquid or soft food.
55 pounds (25 kg) to less than 88 pounds (40 kg)[a]	400 mg (2 capsules) Every 12 hours	2 tablespoons	2 TPOXX capsules	Mix entire contents of 2 TPOXX capsules with 2 tablespoons of liquid or soft food.
88 pounds (40 kg) to less than 265 pounds (120 kg)[a]	600 mg (3 capsules) Every 12 hours	2 tablespoons	3 TPOXX capsules	Mix entire contents of 3 TPOXX capsules with 2 tablespoons of liquid or soft food.
265 pounds (120 kg) and above[b]	600 mg (3 capsules) Every 8 hours	2 tablespoons	3 TPOXX capsules	Mix entire contents of 3 TPOXX capsules with 2 tablespoons of liquid or soft food.

[a]Given twice daily every 12 hours, by mouth, for 14 days.

[b]Given three times a day every 8 hours, by mouth, for 14 days.

How should I store TPOXX Capsules?

- Store TPOXX at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep TPOXX in its original container

Keep TPOXX and all medicines out of the reach of children.

TPOXX capsules Manufactured by:
Catalent Pharma Solutions
1100 Enterprise Drive
Winchester, KY 40391

TPOXX injection manufactured by:
Patheon Manufacturing Services LLC
5900 Martin Luther King Jr. Highway
Greenville, NC 27834

Distributed by:
SIGA Technologies, Inc.
4575 SW Research Way, Suite 110
Corvallis, OR 97333

This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Revised: 05/2022

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208627Orig1s007

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

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

Date	May 4, 2022
From	Division of Antivirals Debra Birnkrant, MD, Division Director Kimberly Struble, PharmD, CDTL Kirk Chan-Tack, MD, Medical Officer Division of Infectious Disease Pharmacology /Office of Clinical Pharmacology/Office of Translational Sciences Abhay Joshi, PhD, Clinical Pharmacology Reviewer Kunyi Wu, PharmD, Clinical Pharmacology Team Leader Ruojing Li, PhD, Pharmacometrics Reviewer Lian Ma, PhD, Pharmacometrics Team Leader
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>
</table>

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)
	$\mathbf{T_{max}}$ (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 (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

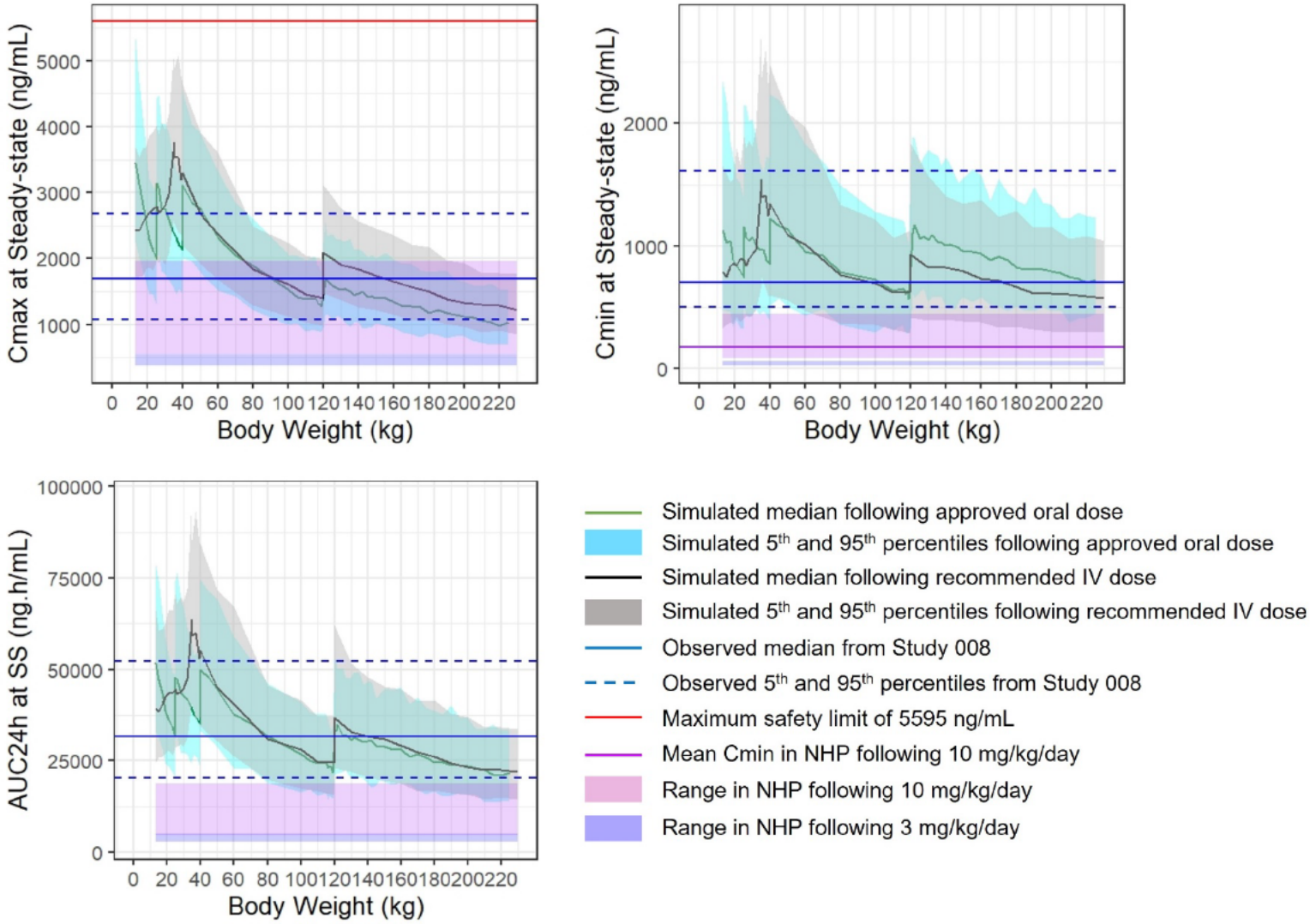
(b) (4)

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.

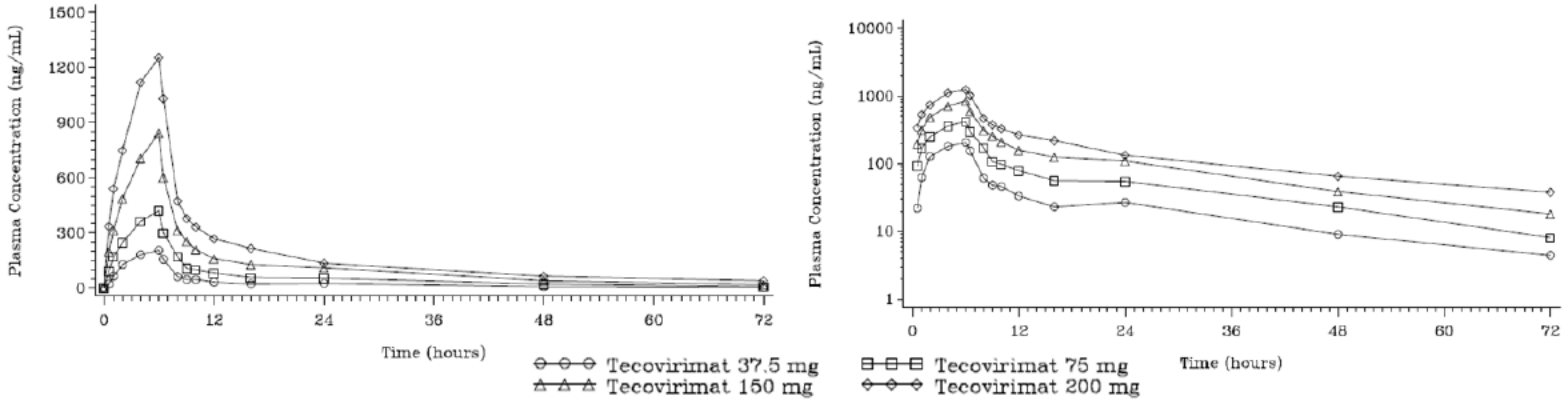
The subjects remained at the study site for PK sample collection until discharge at 72 hours post-dose. For PK assessments, 15 blood samples were collected between pre-dose to 72 hours post-dose. Tecovirimat and its metabolites' (M4, M5, and 4-trifluoromethyl-benzoic acid (TFMBA)) concentrations in plasma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

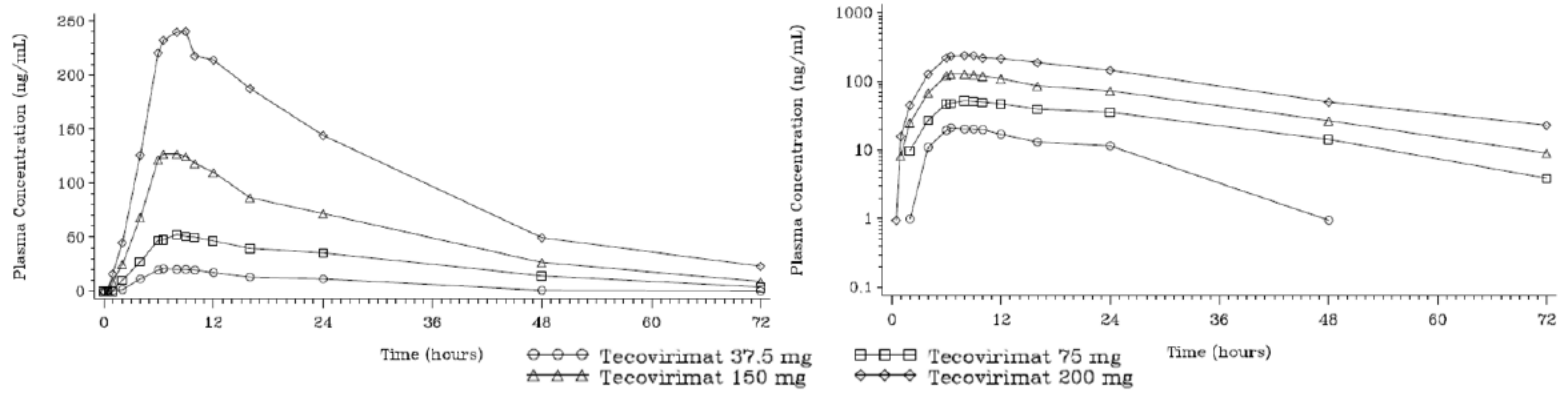
Mean plasma concentration-time profiles for tecovirimat and its metabolites are presented in Figure 2 to Figure 5. The plasma concentrations of tecovirimat and its metabolites were analyzed using noncompartmental analysis to derive PK parameter estimates reported in Table 9. Dose proportionality for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



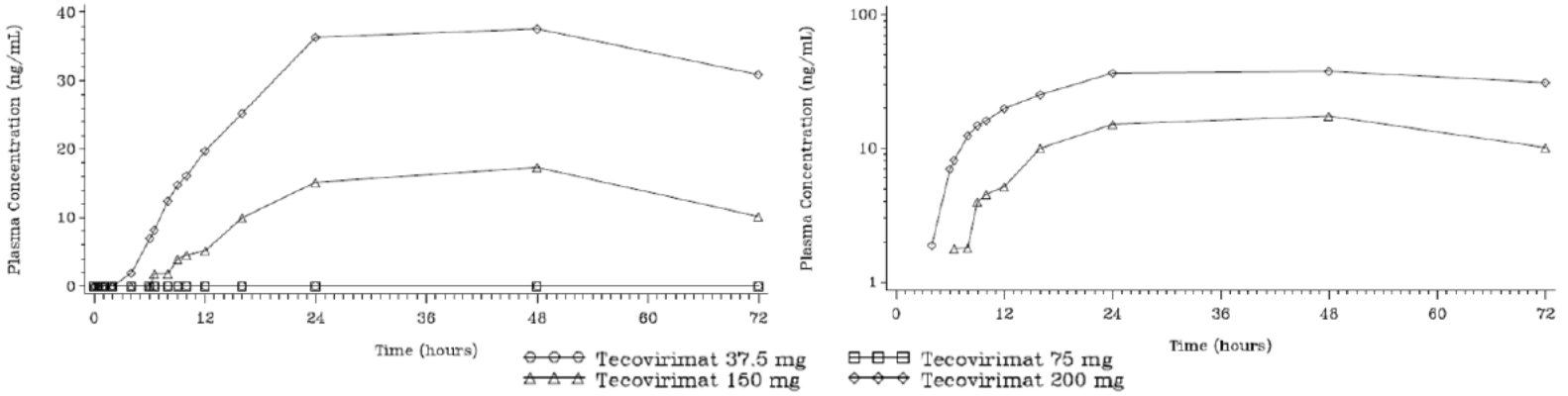
Source: Adapted from Study SIGA-246-IV-201 report

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



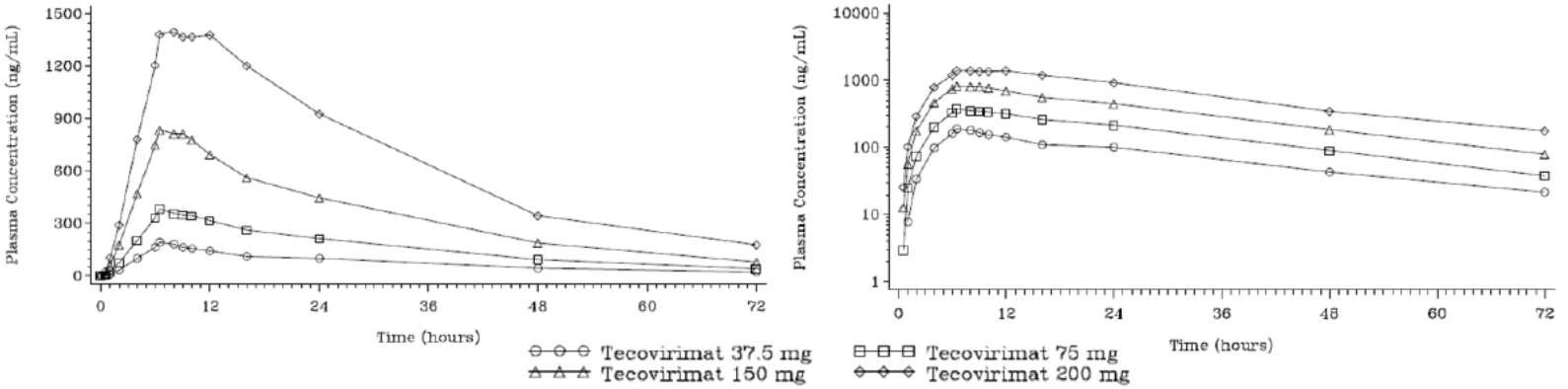
Source: Adapted from Study SIGA-246-IV-201 report

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)



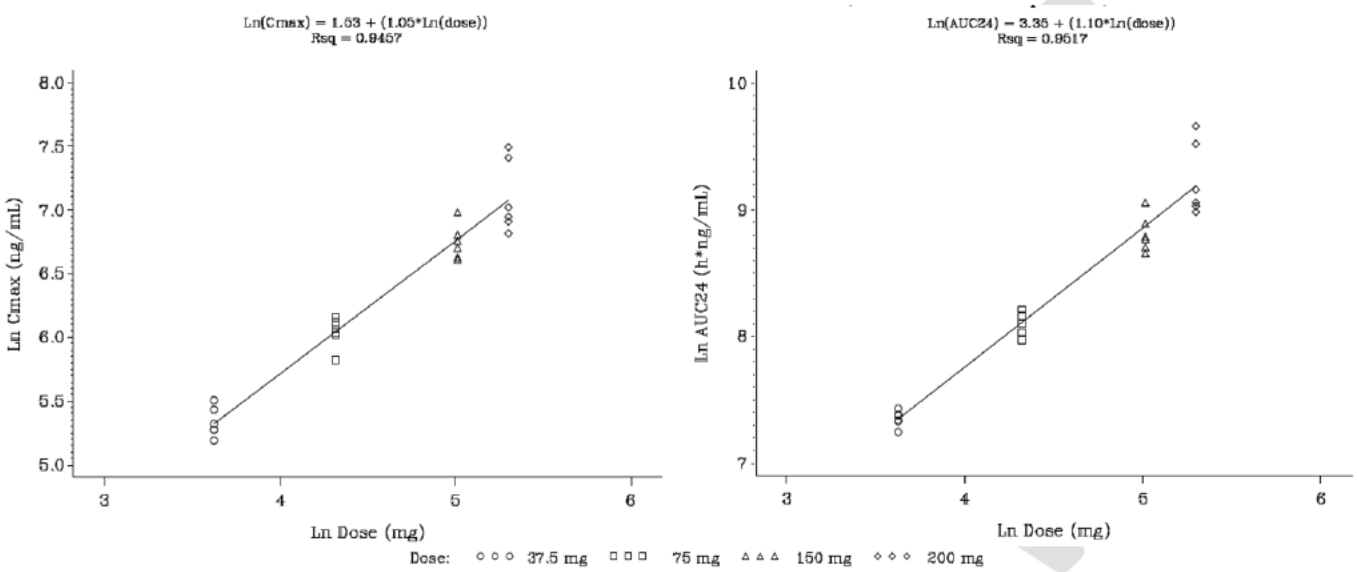
Source: Adapted from Study SIGA-246-IV-201 report

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.

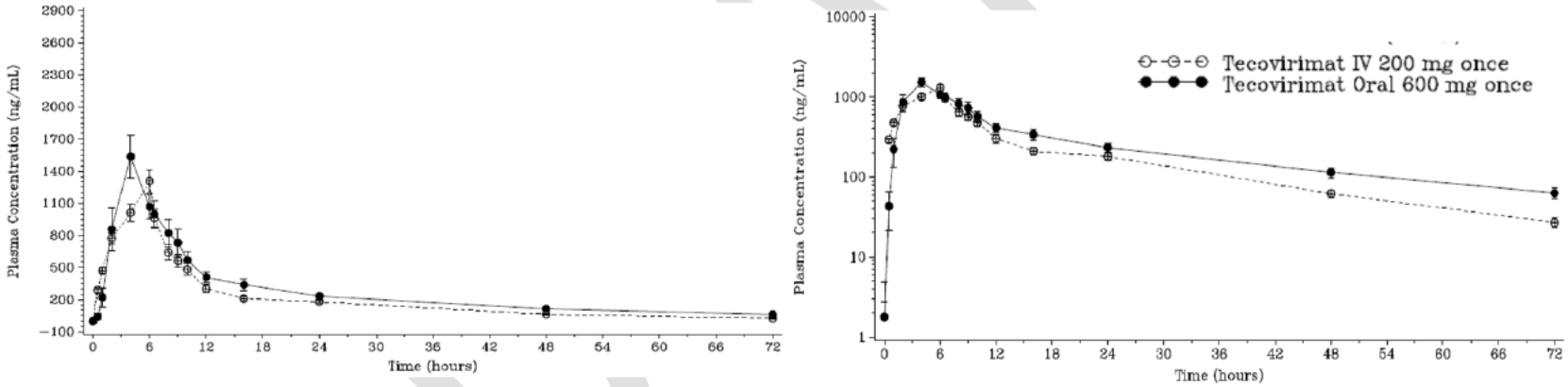
During the conduct of the study, there were major protocol deviations reported for 10 subjects. Other than early termination related deviations, none of the major deviations appear to be related to dosing or PK related assessment. These deviations were deemed (by the Applicant) unlikely to affect the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

Pharmacokinetic Results:

Periods 1 and 2

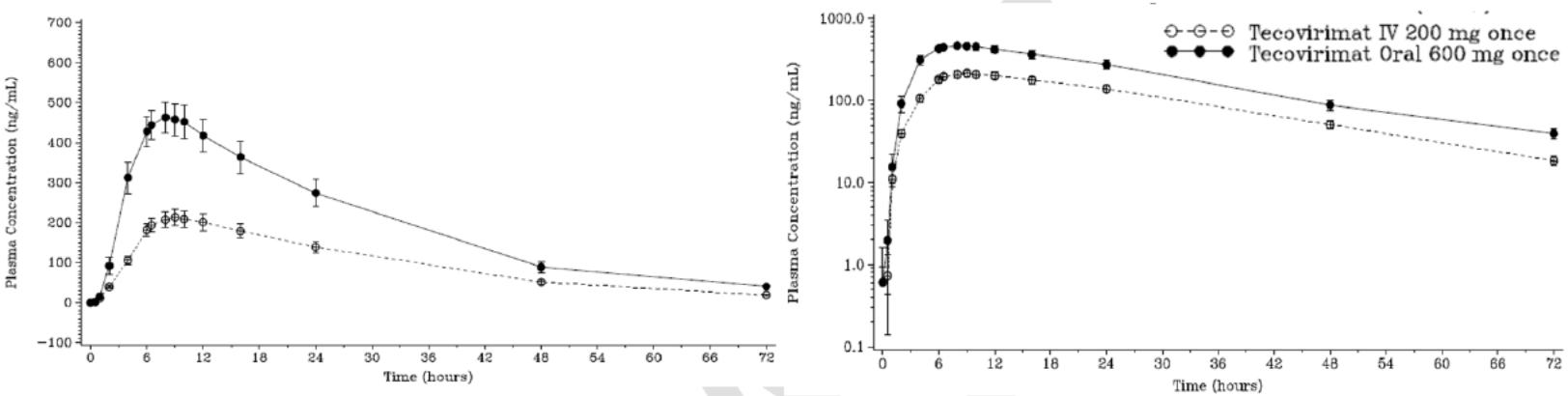
Mean plasma concentration-time profiles for tecovirimat and its metabolites are presented in Figure 7 to Figure 10. The plasma concentrations of tecovirimat and its metabolites were analyzed using noncompartmental analysis to derive PK parameter estimates reported in Table 10. The mean absolute oral 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)



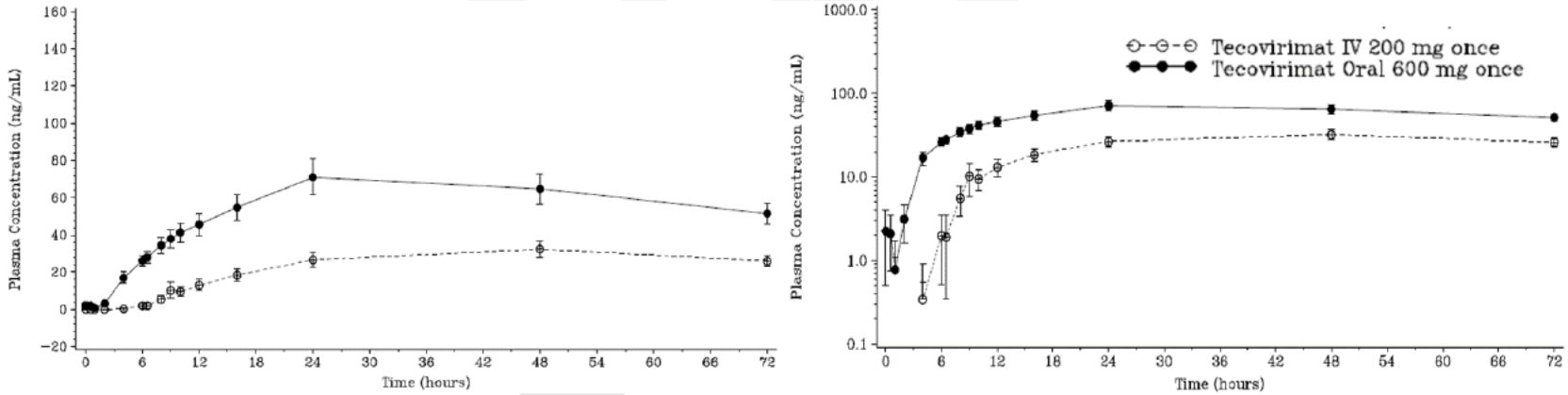
Source: Adapted from Study SIGA-246-IV-202 report

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



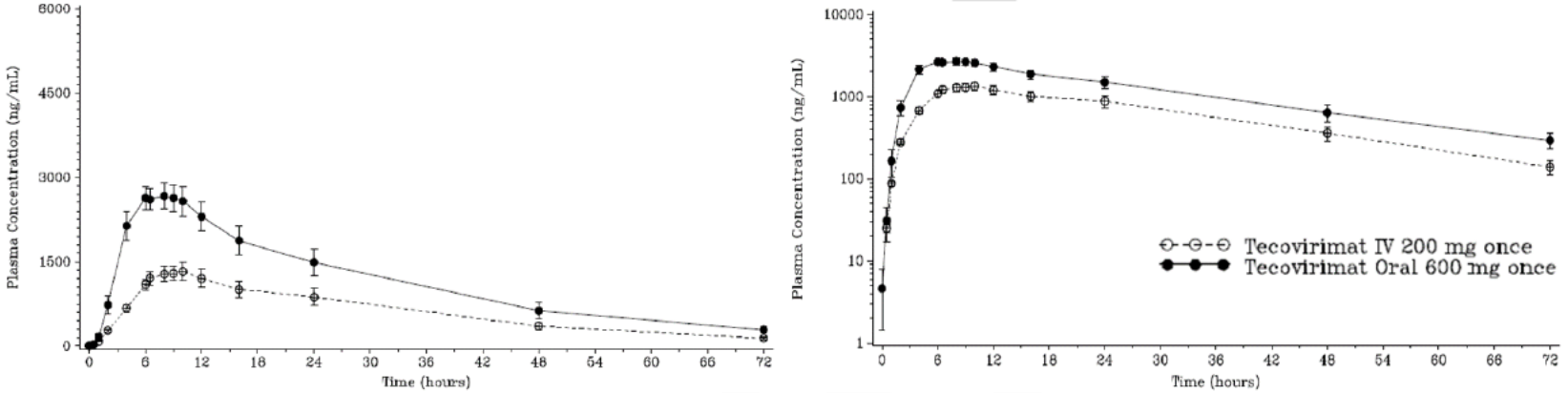
Source: Adapted from Study SIGA-246-IV-202 report

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					

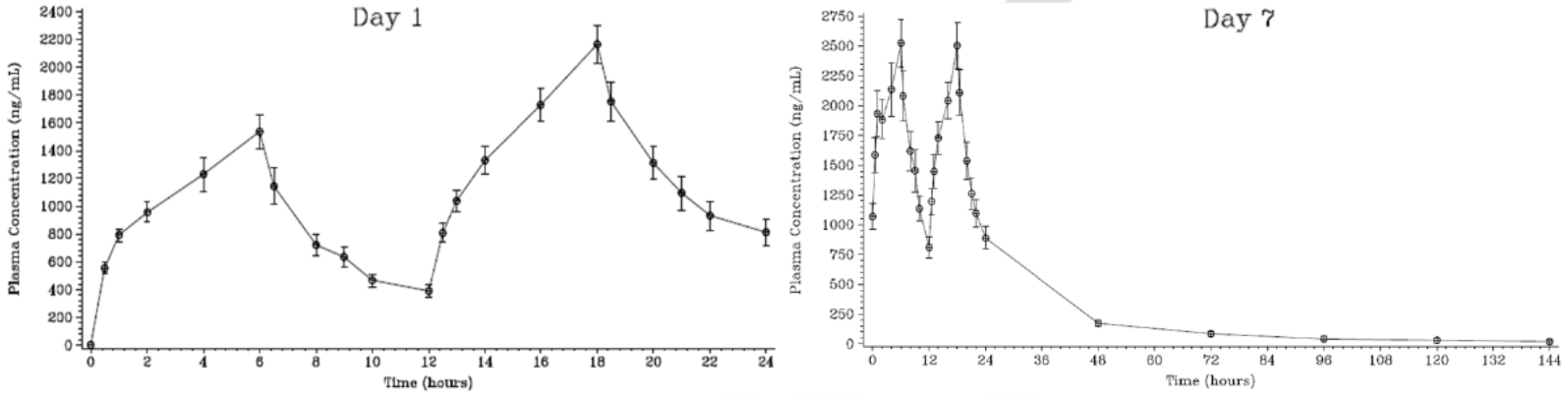
Table 11: Statistical Analysis of Plasma Pharmacokinetic Parameters of Tecovirimat

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

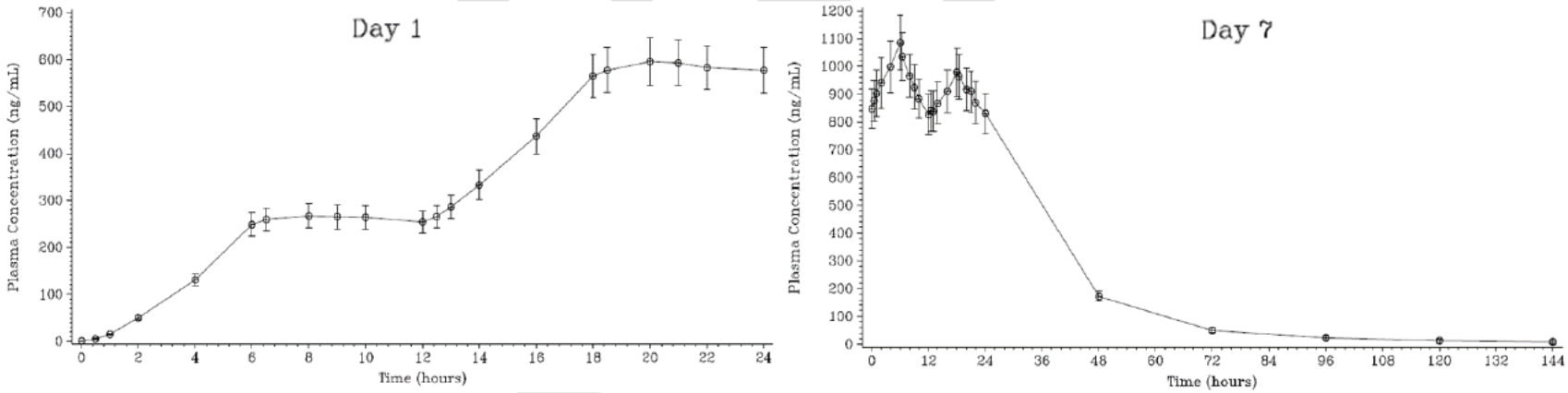
Mean plasma concentration-time profiles for tecovirimat and its metabolites on Day 1 and Day 7 are presented in Figure 11 to Figure 14. The plasma concentrations of tecovirimat and its metabolites were analyzed using noncompartmental analysis to derive PK parameter estimates reported in Table 12.

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



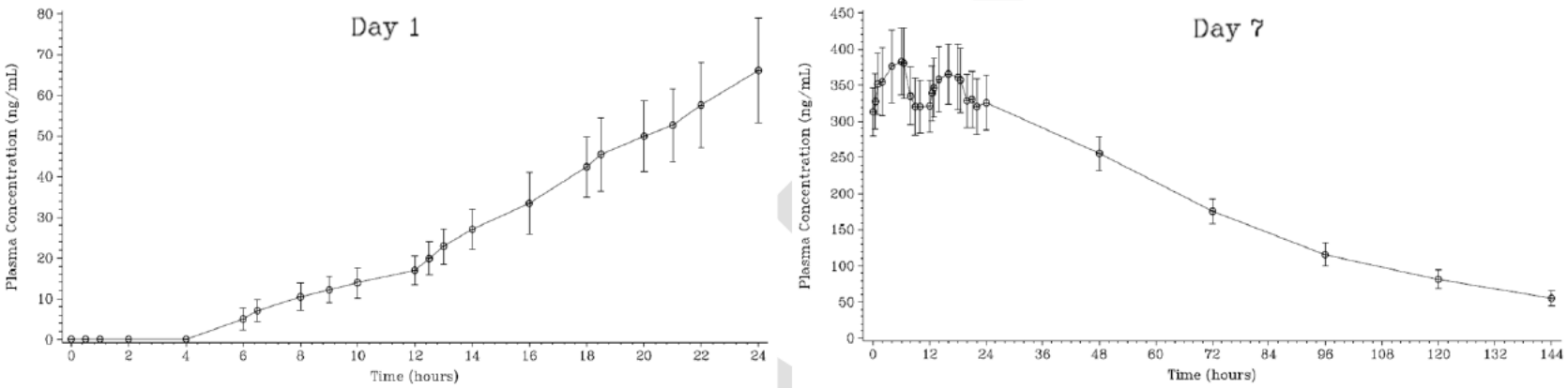
Source: Adapted from Study SIGA-246-IV-202 report

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



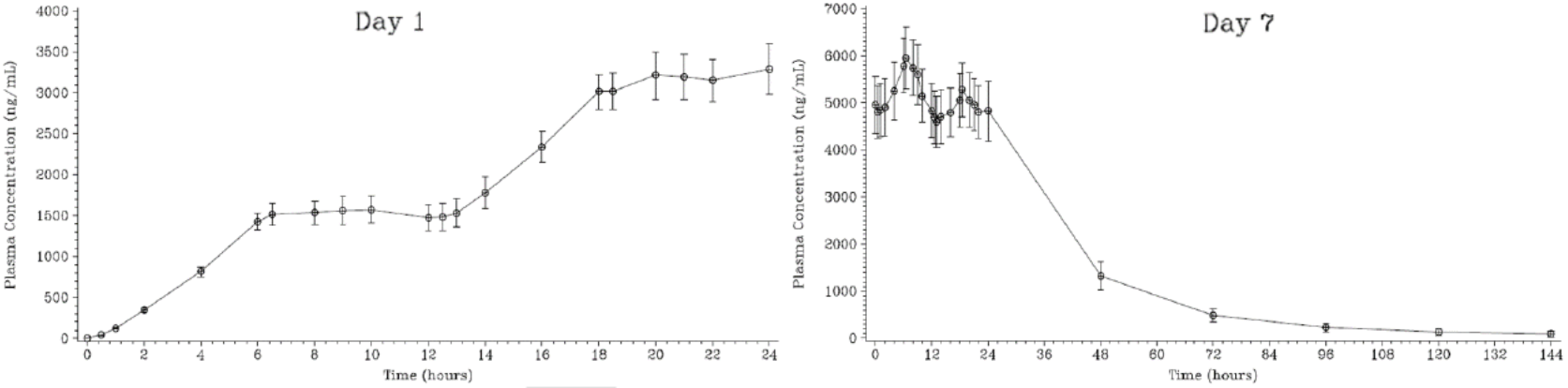
Source: Adapted from Study SIGA-246-IV-202 report

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

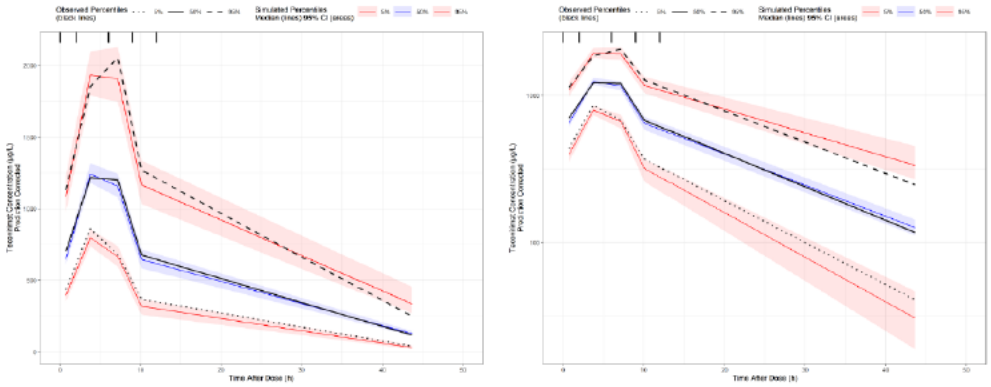
The Applicant claimed a linear PK observed from the subjects received tecovirimat IV infusion. However, dose level was identified as a significant covariate on CL. Population estimates of CL and V2 were respectively 23% and 41% lower in subjects received tecovirimat dose ≥200 mg BID compared to those 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

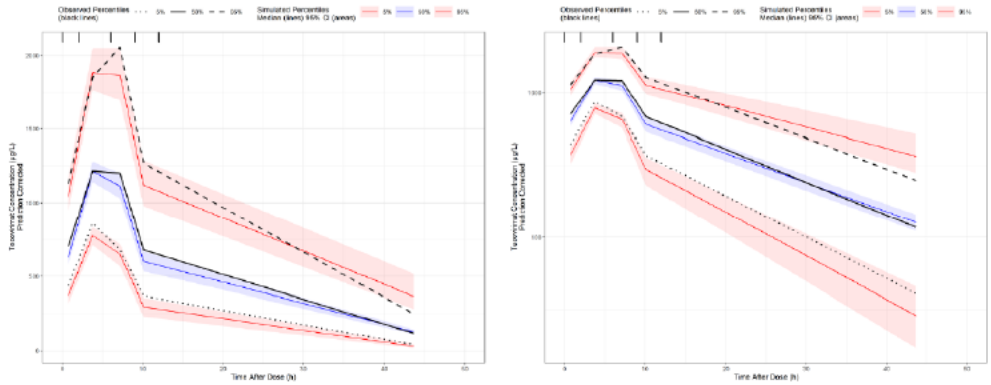
Linear Scale **Semi-Log Scale**



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

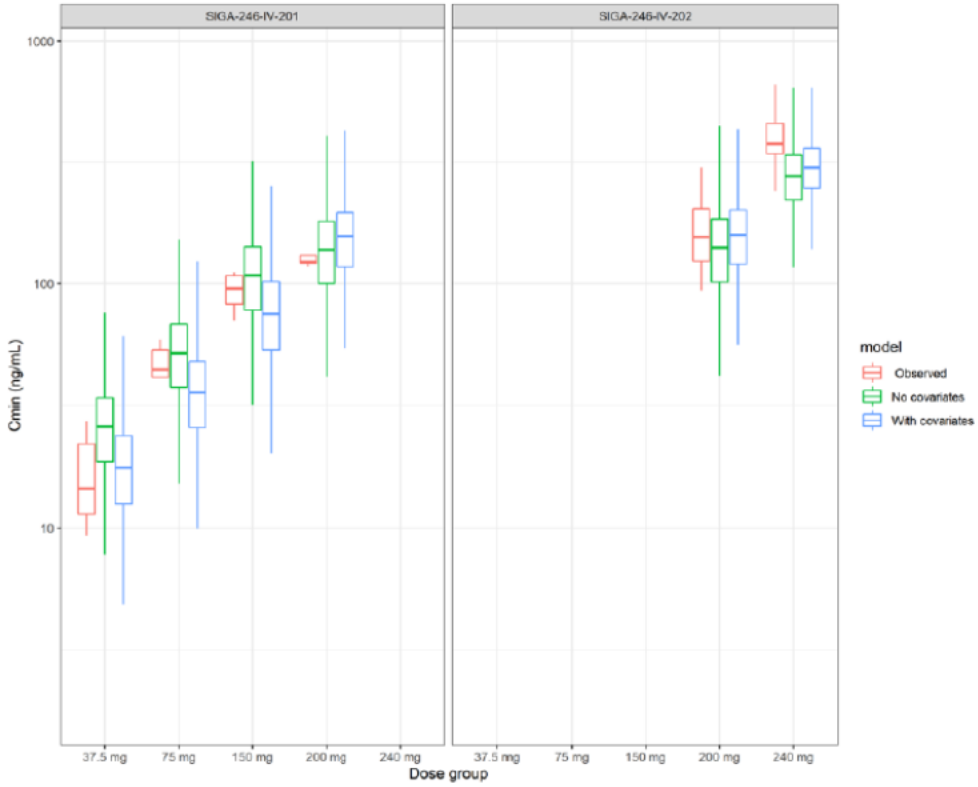
Figure 16 Visual Predictive Check Plots of Population PK Model Without Covariates (base model) -- linear and semi-log scales

Linear Scale **Semi-Log Scale**

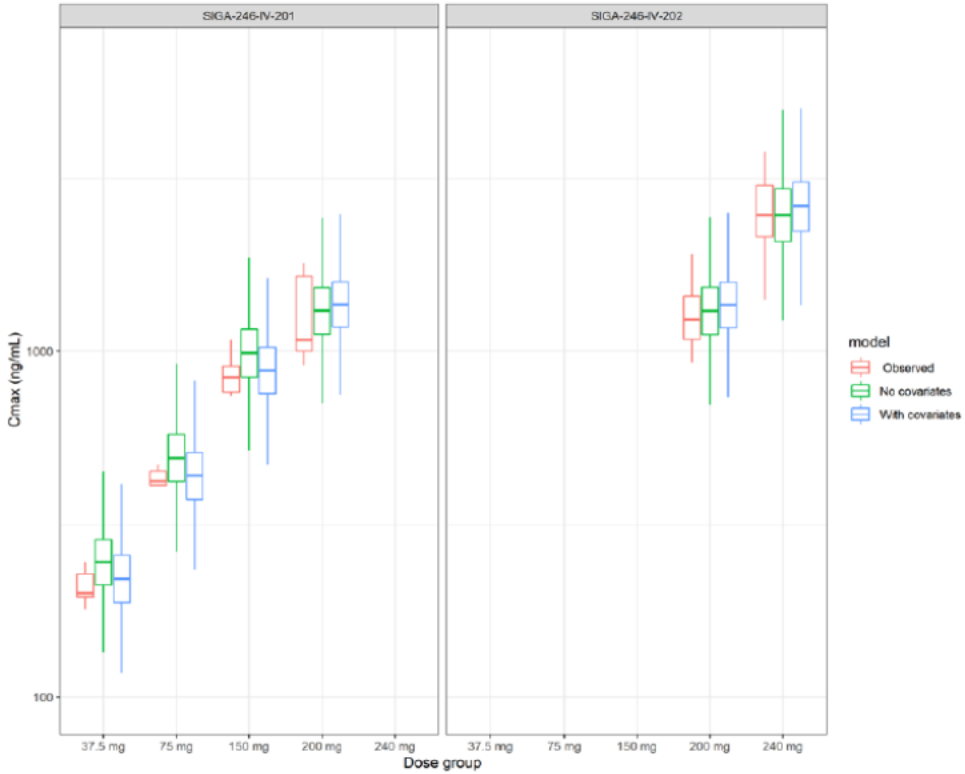


Source: Applicant response to FDA Clin Pharm IR sent on Sep 22, 2021

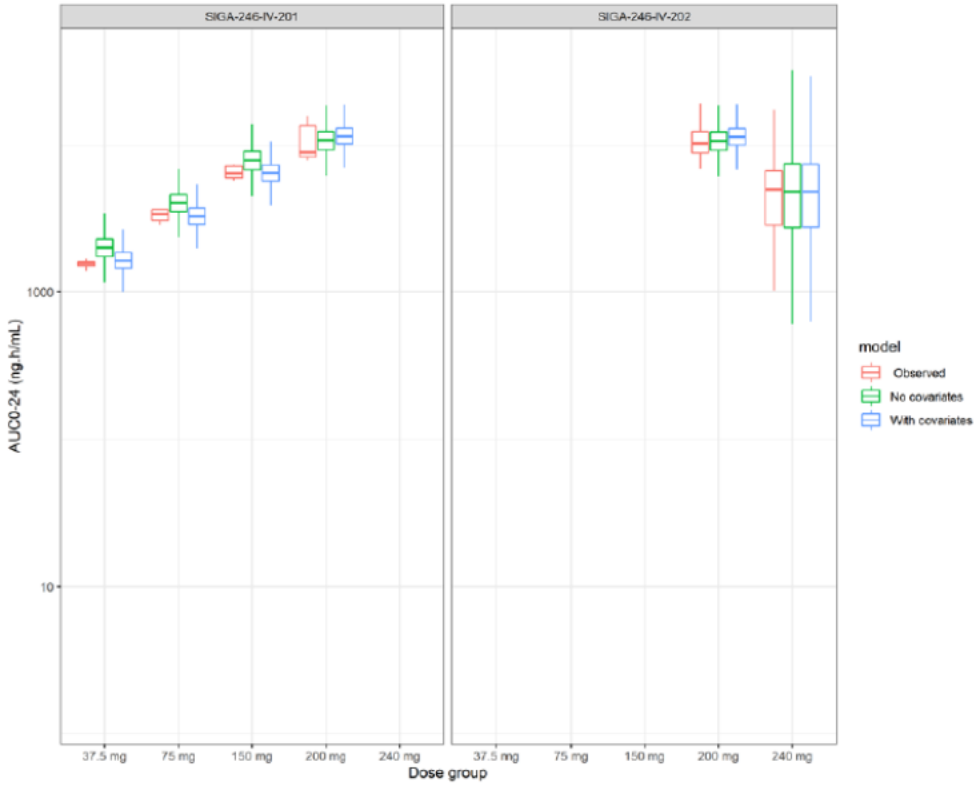
Figure 17 Distribution of Cmin, Cmax and AUC0-24 simulated with models with and without dose effects vs dose group, compared to observed Cmin, Cmax and AUC0-24, respectively.



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

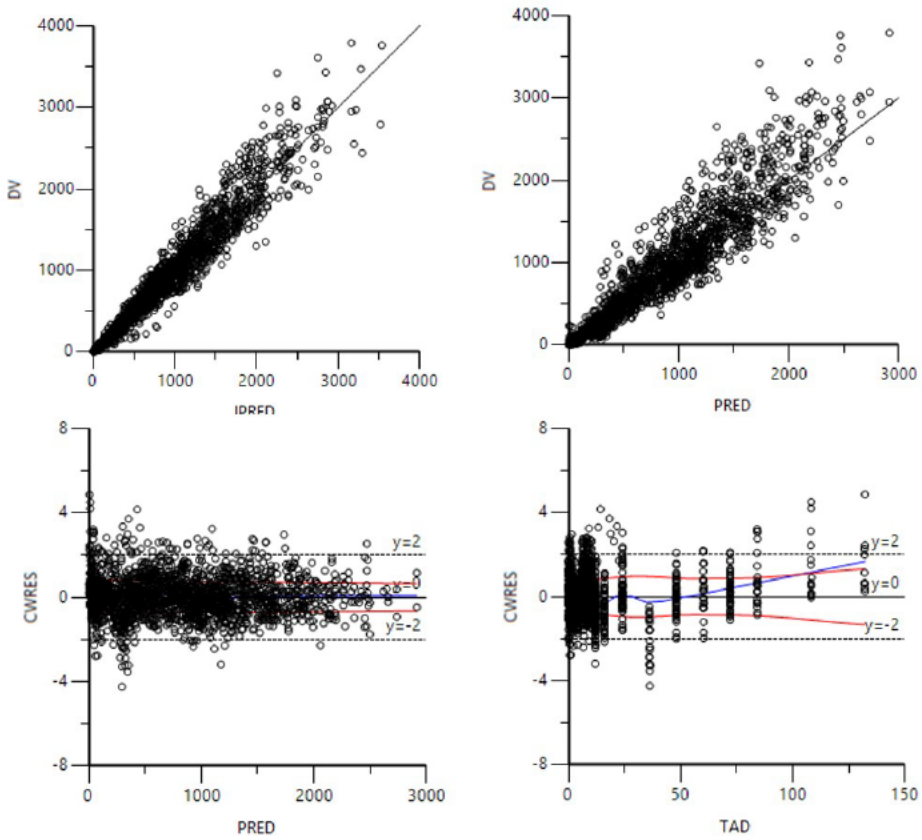
analysis by fitting the popPK model using the fixed allometric scaling coefficients at 0.75 for CL and CL2, and 1 for V and V2. The -2 × Log Likelihood (-2LL) and model estimated parameters are similar to those in the Applicant's final population PK model (Table 15). The goodness-of-fit plots of the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

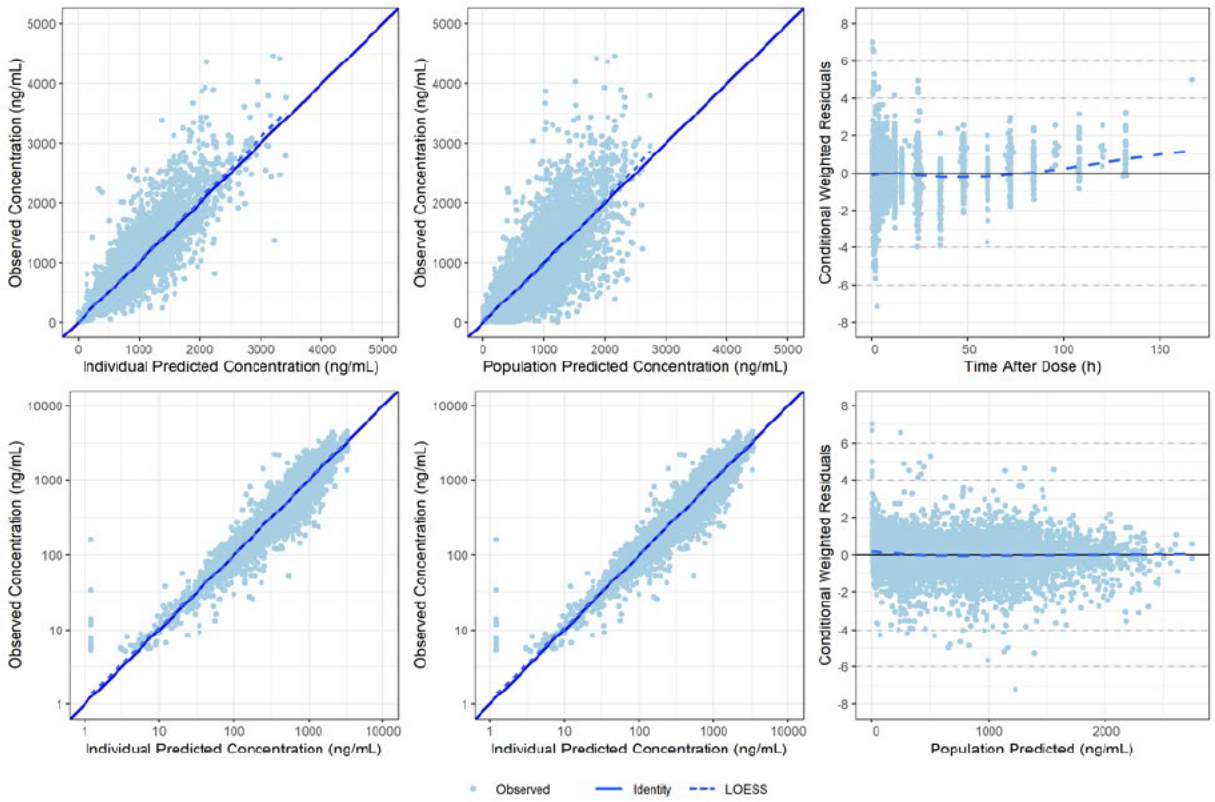
KEY: BSV= between subject variability; CI=confidence interval; CL=clearance; CL2 =inter-compartmental clearance; F=oral bioavailability; Ka=absorption rate constant; RSE= relative standard error; Vc= central volume of distribution; V2=peripheral volume of distribution

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

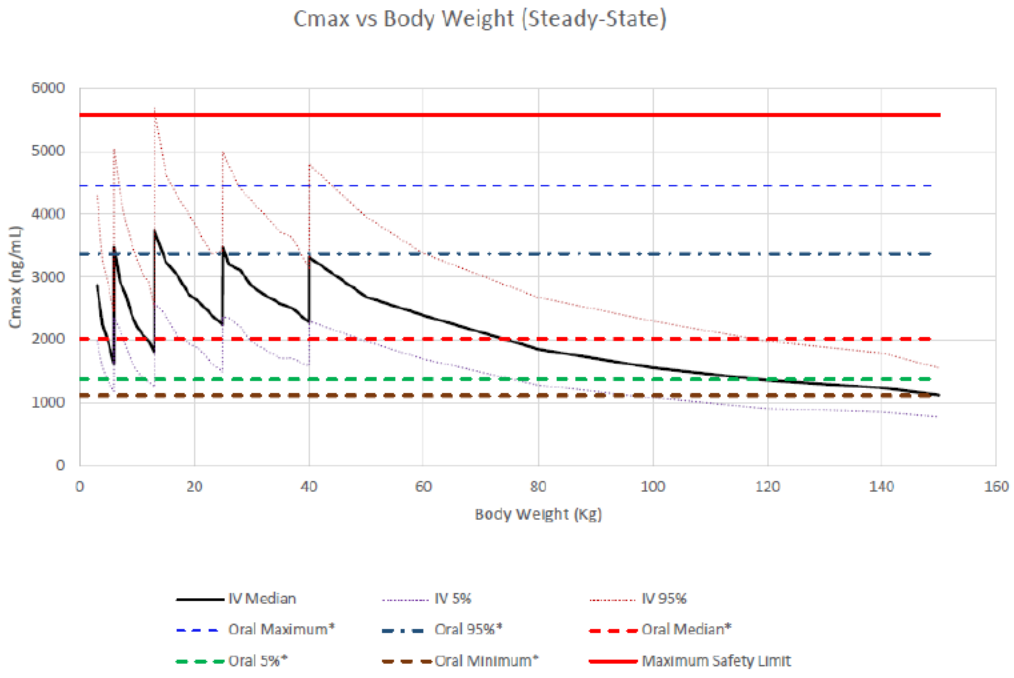
The Applicant simulated rich concentration-time profiles of tecovirimat for their proposed dosing regimen of IV infusion (Table 18) using the original popPK model developed based on IV data. They estimated individual PK parameters of tecovirimat, and derived the

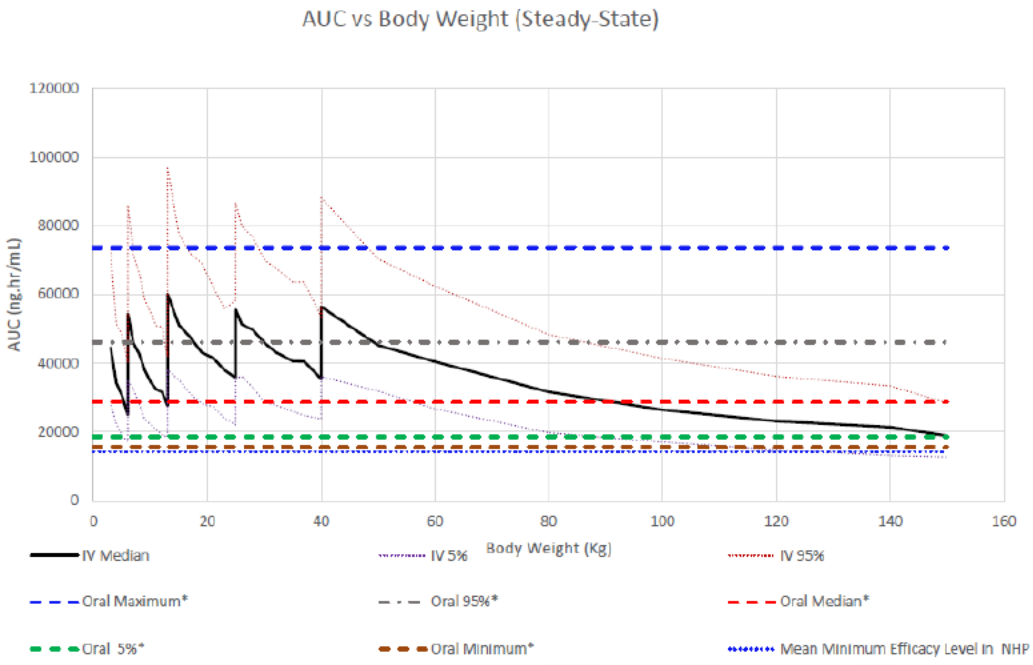
exposure metrics (Cmax, Cmin and AUC24h of Day 1 and steady-state) for each individual. The virtual population was constructed with the body weight range from 3 to 150 kg, which was divided into 5 body weight groups. The simulations were replicated (n=250) to generate a distribution of values for each 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.

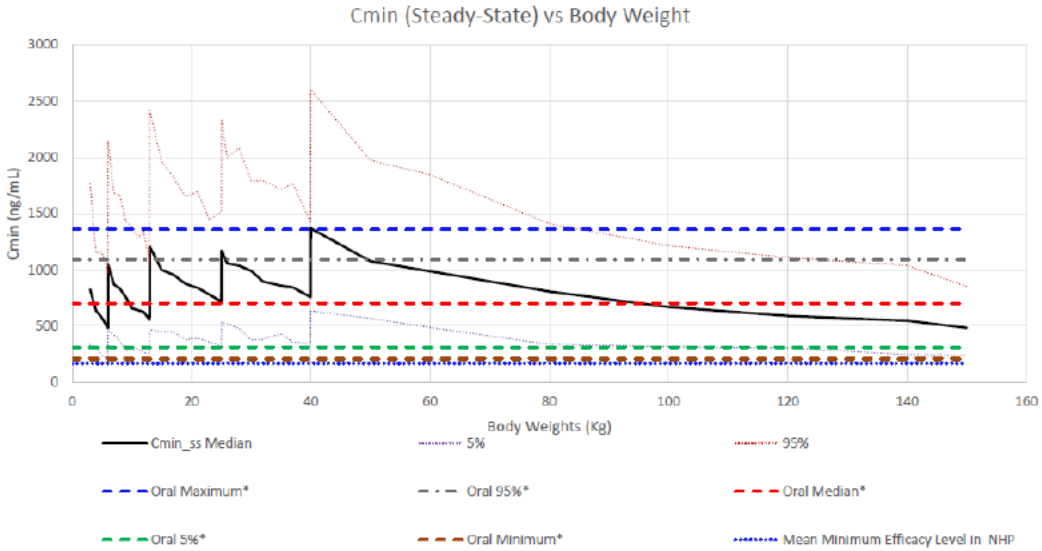
Table 18 Applicant proposed dosing regimens for different body weight groups following IV infusion

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

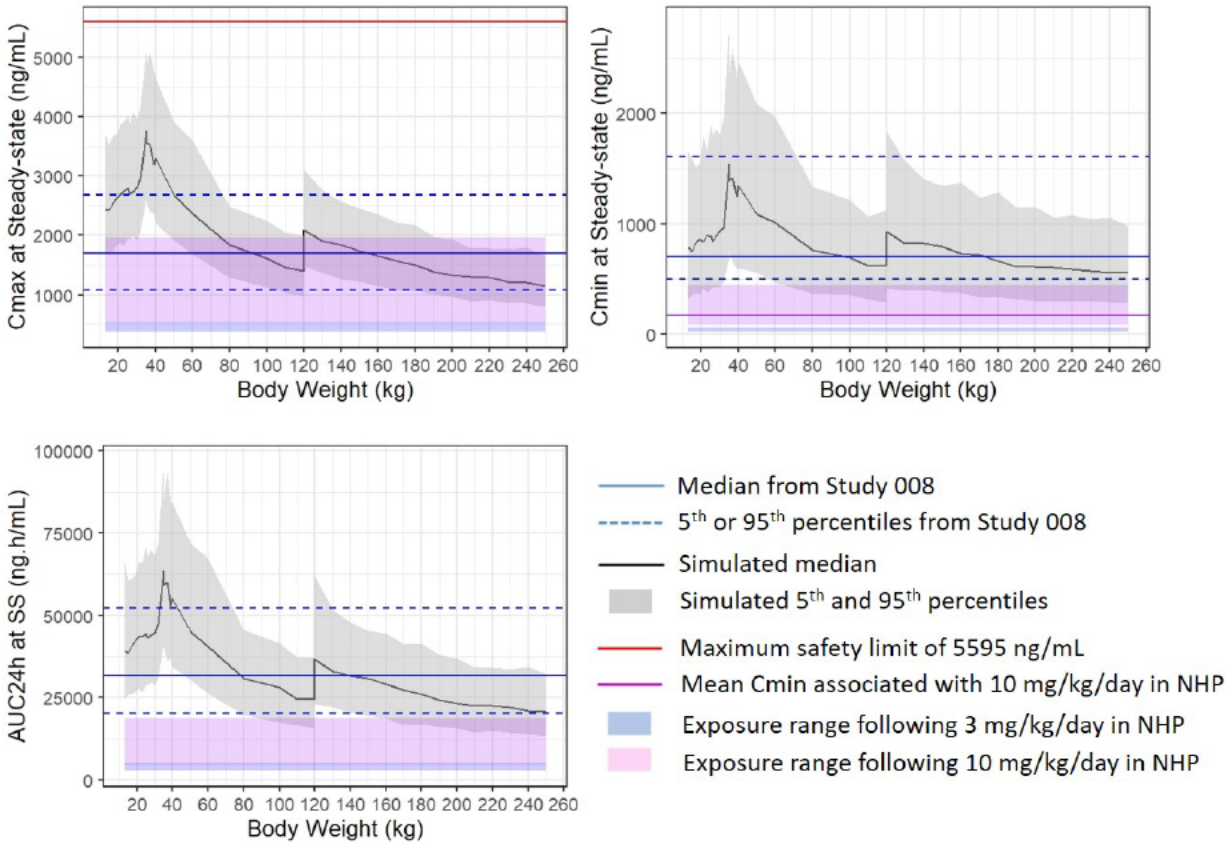
As discussed in section 3.3.2, following the Applicant proposed [redacted] (b) (4) may exceed the safety limit of 5595 ng/mL from dog toxicology study (Figure 20). In addition, the administered amount of β-cyclodextrin in subjects with the lowest body weight was considered high [redacted] (b) (4). Furthermore, 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.

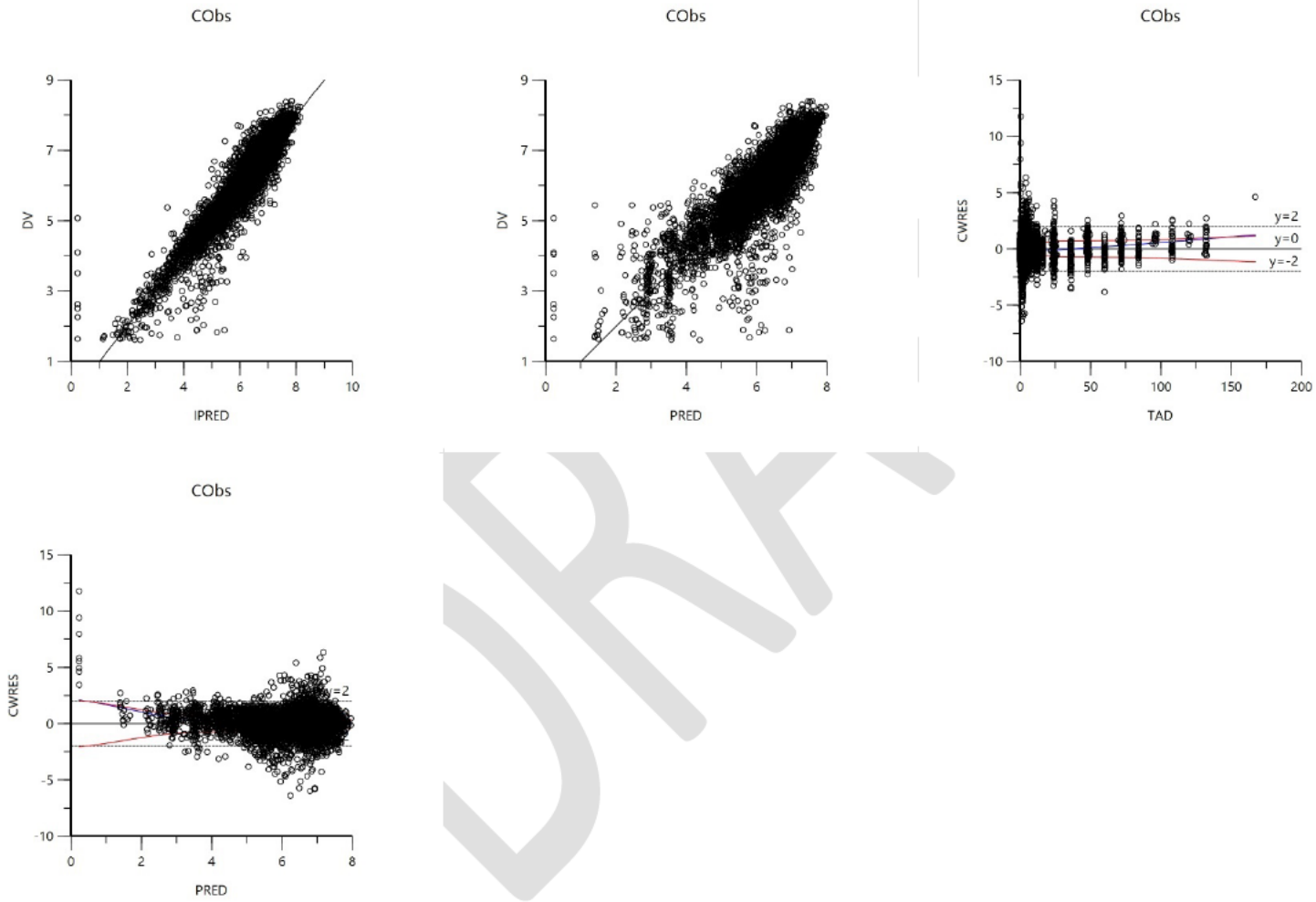
Table 19 PK parameters estimated by FDA review team updated popPK model based on combined data from IV and oral formulations

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.

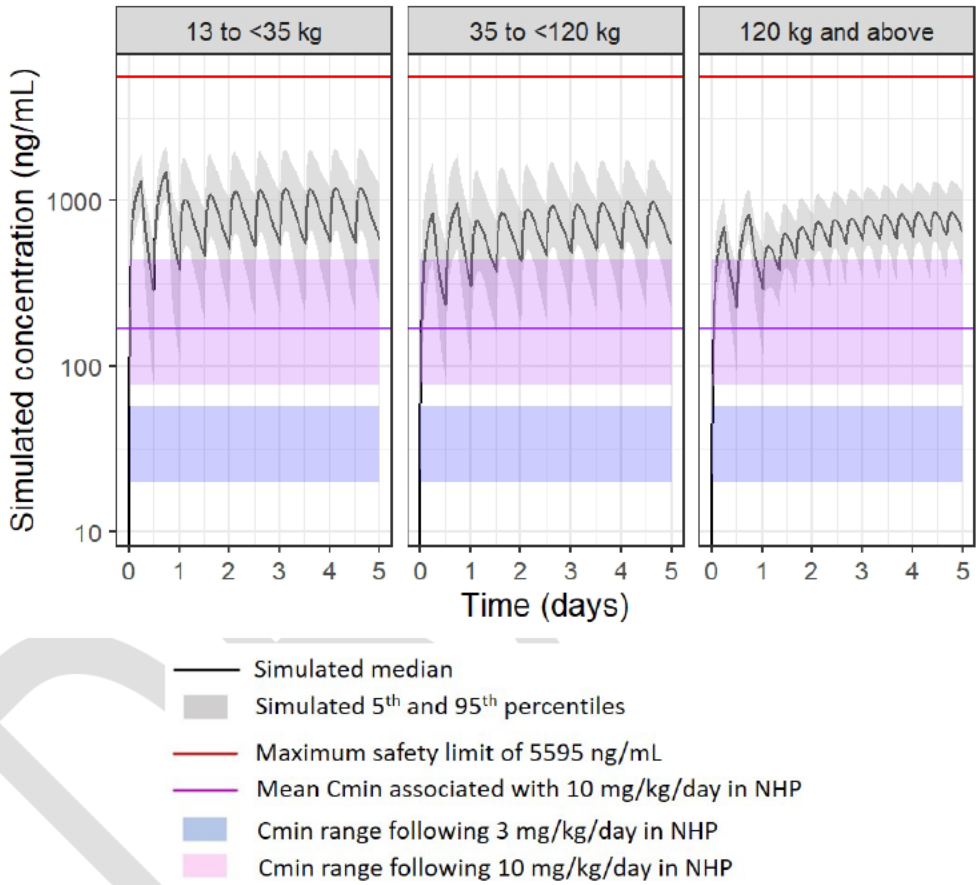
Table 20 Simulated scenarios for formulation switch

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

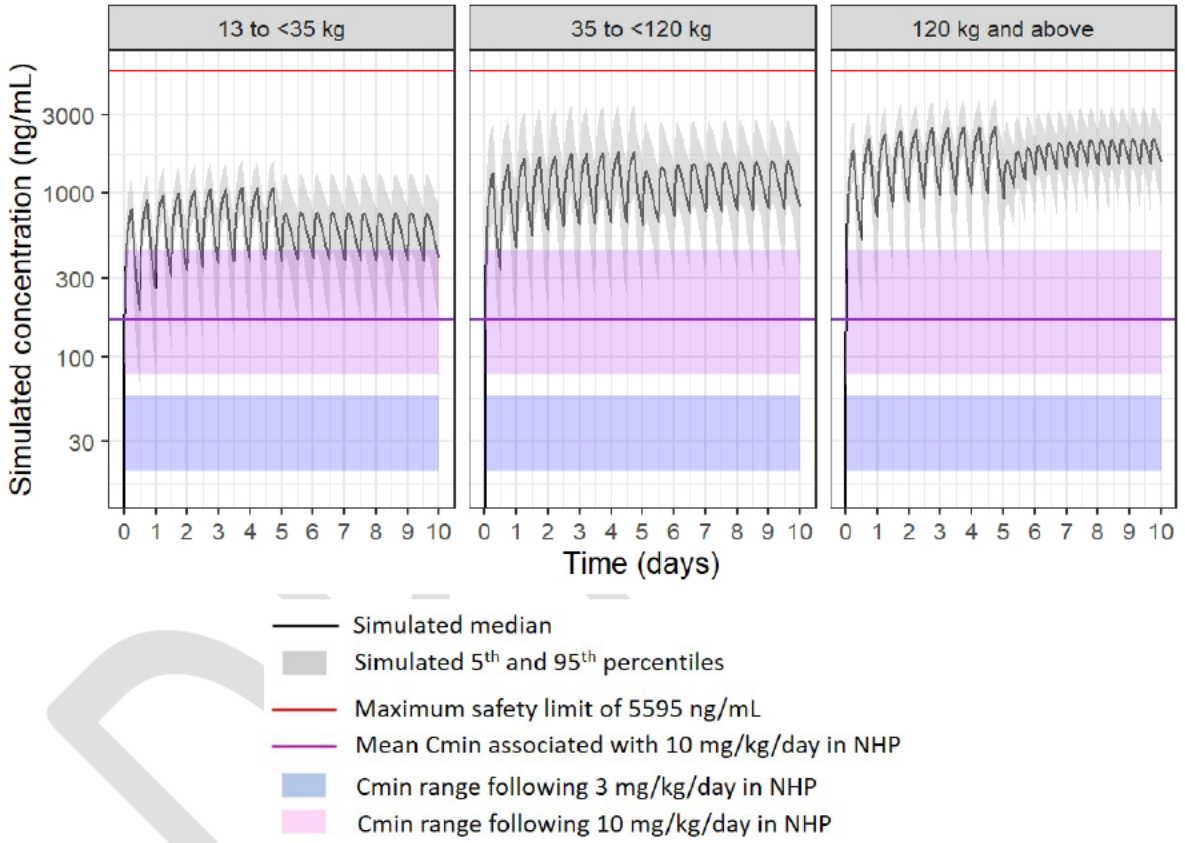
The simulation results are shown in Figure 23 to Figure 26. Overall, the simulated exposure using the modified combined popPK model seemed slightly lower than that simulated using the popPK model based on IV formulation only. Nevertheless, the simulated concentration-time profiles in different scenarios 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



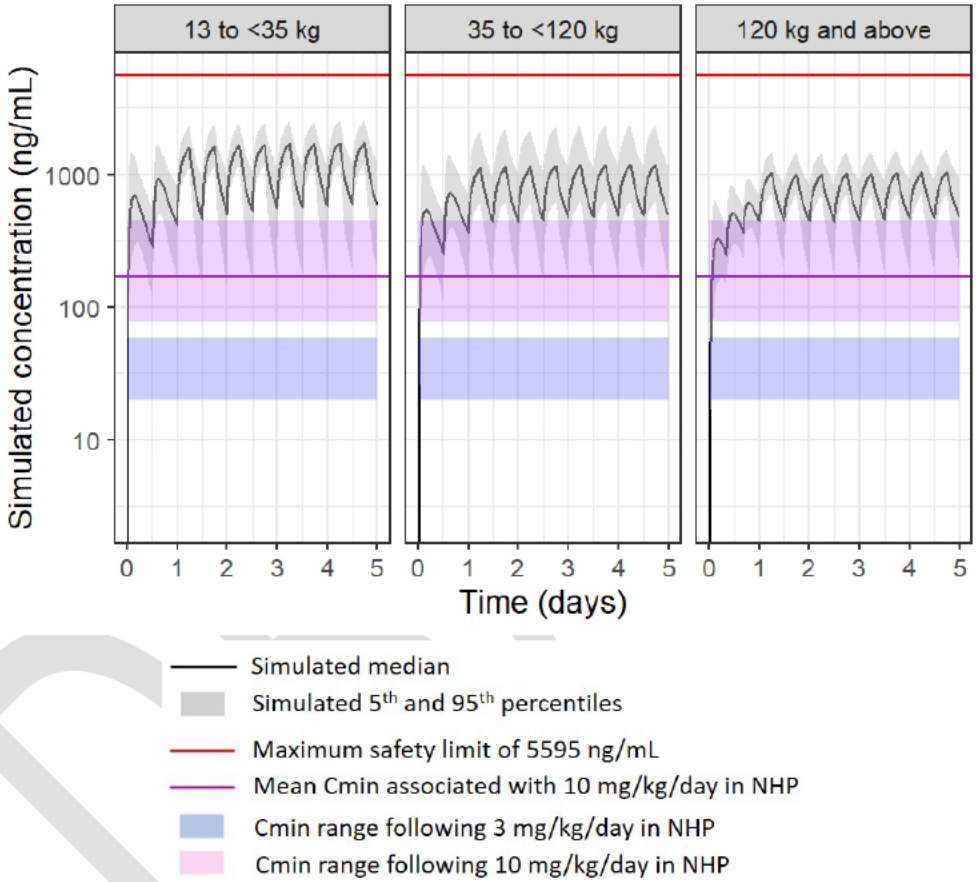
Source: Reviewer's analysis

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



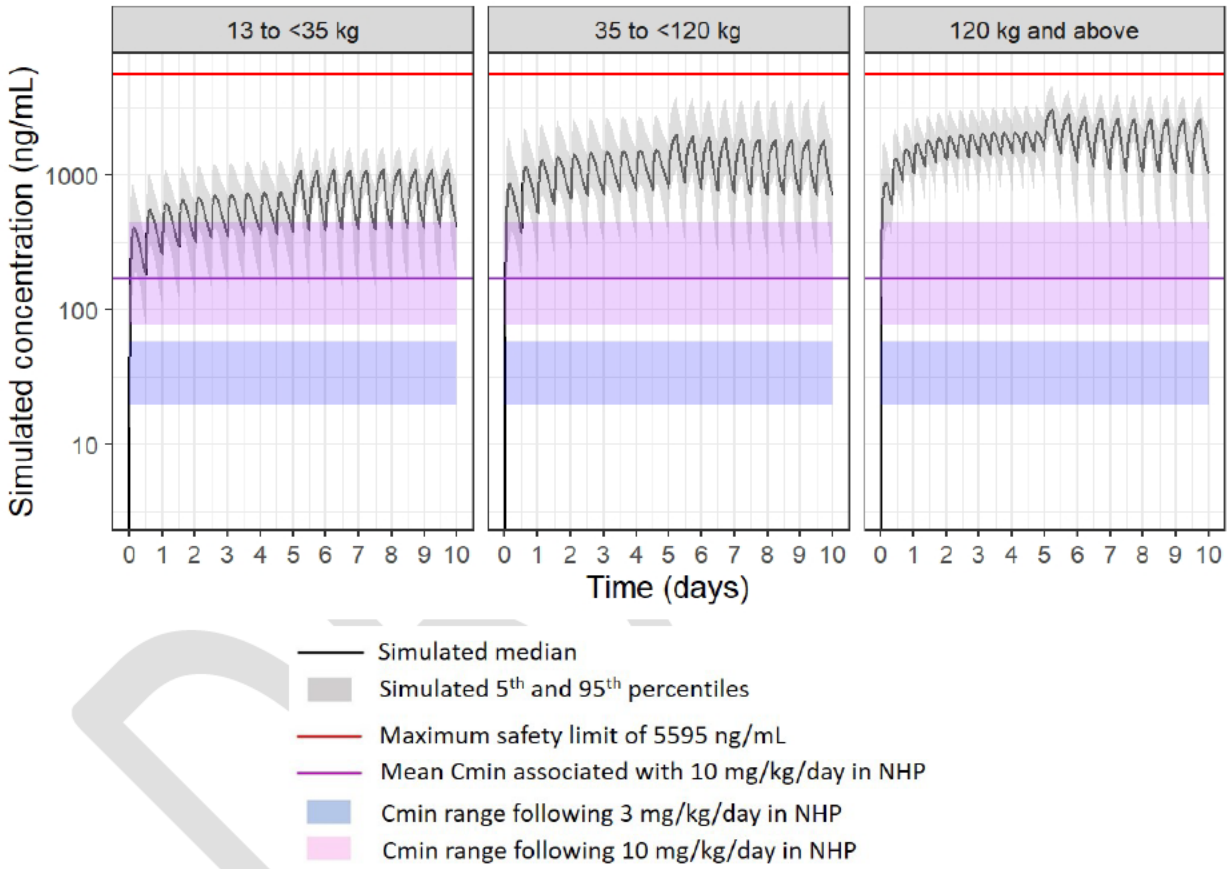
Source: Reviewer's analysis

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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ABHAY JOSHI
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KUNYI WU
05/06/2022 11:26:06 AM

LIAN MA on behalf of RUOJING LI
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208627Orig1s007

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number: NDA-208627-SUPPL-07**
   sNDA Recommendation: Approval
   sNDA Managed by: OND

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PA	04/18/2022	04/18/2022	04/26/2022	10/18/2022	05/12/2022

3. **Provides For:**
   Revisions to the labeling to include both the oral formulation; TPOXX® (tecovirimat) Capsules (NDA 208627) and the intravenous formulation; TPOXX® (tecovirimat) Injection (NDA 214518, which is currently under review).

4. **Review #**: 1

5. **Clinical Review Division**: OID/DAV

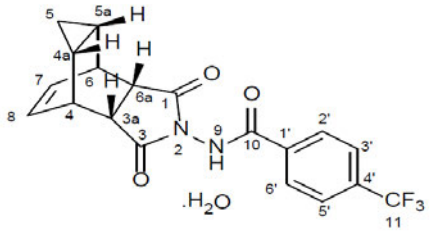
6. **Name and Address of Applicant**:

   SIGA Technologies, Inc.
   4575 SW Research Way, Suite 110
   Corvallis, OR
   USA 97333

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
TPOXX® (tecovirimat) Capsules	Capsule	200 mg	Oral	Rx	No

8. Chemical Name and Structure of Drug Substance:

	**USAN:** Tecovirimat **Chemical name:** Benzamide, N-[(3a*R*,4*R*,4a*R*,5a*S*,6*S*,6a*S*)-3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6 ethenocycloprop[f]isoindol-2(1H)-yl]-4-(trifluoromethyl), rel-(monohydrate) **Molecular formula:** $C_{19}H_{15}F_3N_2O_3 \cdot H_2O$ **MW:** 394.35 g/moL

9. Indication: Treatment of Smallpox Infection

10. Supporting/Related Documents: The Categorical Exclusion from the requirement for Environmental Assessment (EA) was provided in the SDN 119, 05/04/2022.

11. Disciplines/Consults: None

12. Executive Summary:

This Prior Approval Efficacy supplement provides for revisions to the labeling to combine both the oral formulation; TPOXX® (tecovirimat) Capsules (NDA 208627) and the intravenous formulation; TPOXX® (tecovirimat) Injection (NDA 214518, which is currently under review).

There were no changes proposed for the quality information for TPOXX capsules and no revisions to the associated sections of the USPI for the capsules. Information for the injection was included in the combined labeling (assessment was deferred to ONDP, since the NDA for the injection product is not approved yet).

Environmental Analysis

SIGA Technologies, Inc. claims that approval of this New Drug Application qualifies for a categorical exclusion in accordance with 21 CFR 25.31(b) and that, to the best of the applicant's knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment.

There will be a total of (b) (4) therapy courses of TPOXX® capsules and TPOXX® injection in the Strategic National Stockpile at any given time. This can be broken down to (b) (4) capsules and (b) (4) vials. This amount is not anticipated to change over the first 5 years after approval of the intravenous product (NDA 214,518). It is not anticipated that this drug will be used unless an outbreak occurs, in which case it is not known if a portion of this amount or the whole amount would be used. For purposes of this equation, SIGA has used the worst-case scenario in which all (b) (4) therapy courses are needed in one year. This will result in (b) (4) kg of drug being used in an outbreak (capsule at 200 mg each and vials at 200 mg each). Under this NDA, the original amount of drug estimated was (b) (4) kg of drug being used in a year (b) (4) capsules at 200 mg each) as the (b) (4) therapy courses was originally comprised of only oral capsules. For purposes of this equation, and as total count of drug in the Strategic National Stockpile fluctuates as product expires, SIGA will continue to use the (b) (4) kg amount of tecovirimat for purposes of this assessment.

Once tecovirimat is absorbed, the majority is metabolized to three main metabolites (M4, M5, and TFMBA) and glucuronide conjugates (Table 11-2, Study SIGA-246-009, Section 5.3.3.1) and none of these are pharmacologically active. Only 22.7% of administered tecovirimat is detected from feces and urine. An additional amount of 4.8% of the input drug is unidentified and therefore is considered conservatively as pharmacologically active upon leaving the human body. Therefore, a total of 27.5% of administered drug may be introduced to the environment. When this metabolism is considered, the A value is calculated to be (b) (4) and the expected introduction concentration (EIC) is calculated to (b) (4) ppb (see below).

EIC-Aquatic (ppb) = A x B x C x D

A = (b) (4) kg/year of pharmacologically active drug produced (b) (4)

B = $1/1.214 \times 10^{11}$ liters per day entering publicly owned treatment works

C = year/365 days

D = 10^9 µg/kg

The EIC = (b) (4) ppb.

Taking the EIC, the Effect Ratio (ER) value (Huggett et al., 2003, Section 4.3) is determined to be the following:

ER = $H_TPC/F_{SS}PC$

$H_TPC = C_{max}$ of (b) (4) µg/mL

$F_{SS}PC = EC \times (P_{Blood:Water})$

Log $P_{Blood:Water}$ = (b) (4) x Log K_{ow} (Log $D_{pH=7}$ = (b) (4)

EC = EIC = (b) (4)

ER = (b) (4) which is greater than the ratio of 1,000 recommended for aquatic life safety.

Please refer to Section 1.12.14 of NDA 214,518 for further details of SIGA's evaluation of the potential of tecovirimat to disrupt sewage treatment plant (STP) microbial communities under an emergency use scenario. Under this scenario, the Agency requested additional information to evaluate whether a high release/limited timeframe scenario has the potential to disrupt biological systems within STPs.

The applicant submitted a claim of categorical exclusion for Tecovirimat on the basis that there will be no change in level (less than 1 ppb) of the expected concentration of drug substance active moiety at the point of entry into the aquatic environment. The applicant has also provided a statement of no extraordinary circumstances. The claim of categorical exclusion as specified in 21CFR 25.31 (b) for NDA 208627-SUPPL-07 is acceptable.

13. Conclusions & Recommendations:

This supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:
Rishi Thakur, Ph.D., CMC reviewer, Branch II, DPMAI, OLDP, OPQ

16. Secondary Reviewer:
David B. Lewis, Ph.D., Branch Chief, Branch II, DPMAI, OLDP, OPQ

Rishi Thakur

Digitally signed by Rishi Thakur
Date: 5/12/2022 10:31:13AM
GUID: 5407887b000a1c7a2c99827ec2cd922d

David Lewis

Digitally signed by David Lewis
Date: 5/12/2022 11:05:28AM
GUID: 508da72000029f287fa31e664741b577
Comments: concur; recommend approval from the standpoint of CMC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208627Orig1s007

OTHER REVIEW(S)

Division of Antivirals

REGULATORY PROJECT MANAGER LABELING REVIEW

Applications: NDA 208627/S-007
NDA 214518

Name of Drug: TPOXX (tecovirimat) 200 mg capsules, for oral use
TPOXX (tecovririmat) 200 mg injection for intravenous use

Applicant: SIGA Technologies, Inc

Labeling Reviewed

Submission Date: May 17, 2022

Receipt Date: May 17, 2022

Background and Summary Description:

On April 30, 2021, SIGA Technologies, Inc submitted New Drug Application (NDA), NDA 214518 for TPOXX (tecovirimat) 200 mg injection. This new NDA allows for the administration of tecovirimat injection for intravenous use in pediatric patients weighing at least 3 kg and adults who are unable to take oral tecovirimat. Dosing for this new patient population was supported by 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 were submitted to support the proposed tecovirimat IV regimen.

Additionally, on April 18, 2022, SIGA Technologies, Inc submitted a supplemental New Drug Application (sNDA) efficacy supplement to NDA 208627 for TPOXX (tecovirimat) oral capsule. This efficacy supplement was submitted to update the labeling with this pharmacokinetic data that will support the new dosage form, TPOXX (tecovirimat) injection for use in adults and pediatric patients weighing at least 3 kg who are unable to tolerate oral dosing. As both formulations share one label, on May 17, 2022, the Sponsor submitted revised labels to NDA 214518 and NDA 208627/S-007 to ensure alignment across the oral and IV formulation of TPOXX.

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Review

General Changes: Throughout the labeling, formatting changes were made such as spacing, edits in the titles of subheadings, renumbering of tables and grammatical edits. Additionally, for each recent major change (RMC) listed in the HIGHLIGHTS, the modified text in the FULL PRESCRIBING INFORMATION was marked with a vertical line on the left edge.

HIGHLIGHTS OF PRESCRIBING INFORMATION

- TPOXX (tecovirimat) injection for intravenous use was added to the reflect the new dosage form.

RECENT MAJOR CHANGES (RMC)

Under Recent Major Changes the following changes were noted:

- Indications and Usage (1.1)
- Dosage and Administration (2.1, 2.2, 2.3, 2.4, 2.5)
- Contraindications (4)
- Warnings and Precautions (5.2)

Note:

- Previous RMC changes made in November 2021 under S-006 are now summarized concisely under Dosage and Administration.

INDICATIONS AND USAGE

- Indication statement for the TPOXX was revised from 13 kg to now reflect dosing down to adults and pediatric patients weighing at least 3 kg

DOSAGE AND ADMINISTRATION

This section was revised into three categories of dosing recommendations for patient populations based on their weight (kg and those who cannot swallow capsules. In addition, the dosing frequencies for TPOXX oral dosing was revised (please see below)

- Pediatric and Adult Patients weighing 40 kg or more (2.3) (Oral Dosing):
    - Dosing frequency changed from twice daily to now every 12 hours and from three times daily to every 8 hours
- Pediatrics and adult patients weighing 13 kg or more and those who cannot swallow capsules (2.3) (Oral Dosing):
    - Dosing frequency changed from twice daily to now every 12 hours and from three times daily to every 8 hours
    - Additional examples provided to describe moderate or high-fat meal
- Patients weighing 3 kg and above (2.5) (Intravenous Dosing):

DOSAGE FORMS AND STRENGTHS

Intravenous dosage formulation added in this section

- A single-dose vial containing 200 mg of tecovirimat in 20 mL for further dilution prior to intravenous infusion. (3)

CONTRAINDICATIONS

The following statement was added:

- TPOXX injection: TPOXX Injection is contraindicated in patients with severe renal impairment (defined as creatinine clearance below 30 mL/min) (4,5.2)

ADVERSE REACTIONS

This section was revised as follows:

- TPOXX Capsules (incidence ≥ 2%): headache, nausea, abdominal pain, and vomiting. (6.1)
- TPOXX Injection (incidence ≥ 4%): administration site reactions and headache. (6.1)

USE IN SPECIFIC POPULATIONS

This is a new heading in Highlights with the following language added:

- Lactation: Breastfeeding is not recommended in patients with smallpox. (8.2)

Revision Date

Date has been revised and will be updated to reflect when action is taken

FULL PRESCRIBING INFORMATION: Contents*

New subsections added are:

DOSAGE AND ADMINISTRATION

- 2.4 – Renal Impairment
- 2.5 – Dosage and Administration of TPOXX Injection for Intravenous Infusion

WARNINGS AND PRECAUTIONS

- 5.2 - Risks of Hydroxypropyl-β-Cyclodextrin Excipient for Patients with Renal Insufficiency and Pediatric Patients < 2 Years of age

FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

1.1 Treatment of Human Smallpox Disease

Dosing modified from 13kg to reflect dosing down to adults and pediatric patients weighing at least 3 kg

DOSAGE AND ADMINISTRATION

2.1 Important Dosing Instructions

Subheading title was changed and language added to provide dosing and administration instructions based on the indication for oral capsules vs intravenous (IV) infusion and timing of missed oral TPOXX dose

2.2 Testing Before Initiating and During Treatment with TPOXX Injection

	Subheading title was changed and language added on monitoring creatinine clearance prior to starting and during TPOXX injection **2.3 TPOXX Oral Dosage for Pediatric Patients Weighing at Least 13 Kg and Adults** Subheading title was changed and dosing table 2 on recommended oral TPOXX capsules in pediatric patients weighing at least 13 kg and adults renumbered. Additional edits made to dosing frequency and drug food preparation for patients who cannot swall capsules **2.4 Renal Impairment** New subsection added to indicate that TPOXX injection is contraindicated in patients with creatinine clearance below 30 mL per minute **2.5 DOSAGE and Administration of TPOXX Injection for Intravenous Infusion** New subsection and Table added to provide dosing and administration information for the new formulation, TPOXX injection
3	**DOSAGE FORMS AND STRENGTHS** Additional information added for TPOXX injection
4	**CONTRAINDICATIONS** New contraindication information added for TPOXX injection as it relates to the excipient hydroxypropyl-β-cyclodextrin
5	**WARNINGS AND PRECAUTIONS** **5.2 Risks of Hydroxypropyl-β-Cyclodextrin Excipient for Patients with Renal Insufficiency and Pediatric Patients < 2 Years of age** New subsection added to provide information on the risk of the excipient hydroxypropyl-β-cyclodextrin with TPOXX injection in patients with renal insufficiency and pediatric patients less than 2 years of age
6	**ADVERSE REACTIONS** **6.1 Clinical Trials Experience** Edits made include: o New heading titled “TPOXX Clinical Trial (Oral Administration) along with edits to Table 3 in the title. o New heading titled “TPOXX Clinical Trial (Intravenous Administration) with the addition of adverse reaction data of TPOXX injection data from the Phase 1 clinical studies, Study SIGA-246-IV- 202 and Study SIGA-246-IV-201 along with a new Table on Treatment- Related Adverse Reactions
7	**DRUG INTERACTIONS** Table renumbering noted
8	**USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy** Edits and additional language added in the Risk Summary section **8.2 Lactation** Additional language added describing the potential for variola virus

	transmission through direct contact with the breastfed infant and that breastfeeding is not recommended in patients with smallpox.
8.3	**Females and Males of Reproductive Potential** Language revised to remove “female and male reproductive potential” and add “human fertility”
8.4	**Pediatric Use** New section added “TPOXX Injection” describing the limited data on the use of hydroxypropyl-β-cyclodextrin, an ingredient in TPOXX injection, in pediatric patients less than 2 years of age and the potential for drug accumulation in this population
8.6	**Renal Impairment** New section added “TPOXX Injection” describing hydroxypropyl-β-cyclodextrin, an ingredient in TPOXX injection and warnings based on the level or renal impairment due to creatinine clearance.
11	**DESCRIPTION** Additional language added to describe new formulation, TPOXX (tecovirimat) injection
12	**CLINICAL PHARMACOLOGY**
	This section was revised with updated pharmacokinetic information from healthy adults based on results from the two Phase 1 clinical studies, Study SIGA-246-IV-202 and Study SIGA-246-IV-201 SIGA-246-022 and Table 6 which summarizes the pharmacokinetic properties of Tecovrimat. In addition, information on the elimination of Hydroxypropyl-β-cyclodextrin through glomerular filtration was added in this section.
16	**HOW SUPPLIED/STORAGE AND HANDLING** Additional information was added to describe how the new formulation, TPOXX injection is supplied and stored and handled.
17	**PATIENT COUNSELING INFORMATION** This section was revised to provide information on the following: Important Dosage and Administration Information for oral TPOXX Information on Hydroxypropyl-β-cyclodextrin, a required component of TPOXX injection and warnings based on the level or renal impairment due to creatinine clearance.
PATIENT INFORMATION	
	Patient information was also revised as follows: o New patient information for the new dosage form, TPOXX injection for intravenous use. This new information was added to ensure alignment with the USPI o New language was also added to clarify the dosing intervals for TPOXX capsules that should be used by adults and children who weigh at least 7 pounds (3 kg)
INSTRUCTIONS FOR USE	

	Instructions for use was updated to align with changes in the USPI. This includes edits to the oral dosing frequency located in the TPOXX Dosing Table (Figure A)
	Please Note: The Sponsor indicated that they do not intend to dispense the IFU with TPOXX injection. As a result it was not included in the approval letter for NDA 214518.

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The changes as proposed in the new drug application (NDA 214518) and efficacy supplement (NDA 208627/S-007) are acceptable.

Andrew Gentles	5/17/2022
Regulatory Project Manager	Date
Karen Winestock	5/18/2022
Chief, Project Management Staff	Date

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANDREW A GENTLES
05/18/2022 03:52:40 PM

KAREN D WINESTOCK
05/18/2022 04:14:57 PM