

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208627Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## Office of Clinical Pharmacology Review Addendum

NDA Number	208,627
Link to EDR	<a href="\\CDSESUB1\evsprod\NDA208627\0003">\\CDSESUB1\evsprod\NDA208627\0003</a> <a href="\\CDSESUB1\evsprod\NDA208627\0001">\\CDSESUB1\evsprod\NDA208627\0001</a>
Submission Date	December 8, 2017
PDUFA Goal Date	August 8, 2018
Submission Type	505(b)1, NME NDA, priority review
Brand Name	TPOXX
Generic Name	Tecovirimat
Dosage Form and Strength	200 mg capsule
Route of Administration	Oral administration
Proposed Indication	Treatment of smallpox infection
Applicant	SIGA Technologies, Inc
Associated IND	69,019
OCP Review Team	Su-Young Choi, Pharm.D., Ph.D Ruojing Li, Ph.D Qin Sun, Ph.D Chao Liu, Ph.D Shirley Seo, Ph.D
OCP Final Signatory	John Lazor, Pharm.D Director, Division of Clinical Pharmacology IV

This addendum addresses key issues discussed after finalizing the primary reviews in DARRTS.

### 1. Clinical recommendations for drug interactions

Tecovirimat is a weak inducer of CYP3A and a weak inhibitor of CYP2C8 and CYP2C19. However, as shown in Table 1, the magnitude of interaction is relatively small (less than a 2-fold change) when tecovirimat was co-administered with sensitive index substrates of CYP2C8, CYP2C19, and CYP3A. The Office of Clinical Pharmacology made the following conclusions during labeling negotiations.

- Based on the small magnitude of interaction, the possible severity of disease and practical clinical management issues, and a relatively short duration of tecovirimat therapy (14

days),

(b) (4)

- Further discussions took place for specific index substrate drugs evaluated in the drug interaction trial (SIGA-246-015). For repaglinide, monitoring glucose levels and monitoring for hypoglycemic events are recommended based on adverse events observed during the drug interaction trial (Section 7). For midazolam, a clinical comment regarding possible reduced effectiveness was added as midazolam is expected to be commonly used in the setting of bioterrorism or in critically ill subjects (Section 7). While the magnitude of interaction is relatively small (~30% reduction in AUC), a small proportion of patients may experience a suboptimal response to midazolam. For omeprazole, no clinical comments were made as the magnitude of interaction (less than 2-fold) and the duration of therapy (2 weeks) do not warrant a dose adjustment (per email communication with Dr. Insook Kim, clinical pharmacology team lead, DCP3).

**Table 1. Summary of the Effects of Tecovirimat on the PK of CYP2C8, CYP2C19, and CYP3A**

Drug (index substrate)	Metabolic pathway	% change in C <sub>max</sub> by tecovirimat	% Change in AUC <sub>inf</sub> by tecovirimat
Repaglinide 2 mg	CYP2C8	↑27 % (↑ 23-45 %)	↑ 29 % (↑ 19-40 %)
Omeprazole 20 mg	CYP2C19	↑ 86 % (↑ 51-131 %)	↑ 72 % (36-119 %)
Midazolam 2 mg	CYP3A	↓ 39 % (↓ 32-46 %)	↓ 32 % (27-37 %)

Study: SIGA-246-015

Data are expressed geometric mean ratio 90% Confidence Interval (CI)

## 2. Clinical Pharmacology Post-Marketing Commitment (PMC)

Based on the clinical pharmacology review, the following PMCs will be issued.

### 1. PMC 3417-4

Conduct a study to determine the pharmacokinetics of tecovirimat in subjects with body weight greater than 120 kilograms (>120 kg) and to further determine if a change in dosing regimen is needed in these subjects.

Draft Protocol Submission: 04/2019

Final Protocol Submission: 07/2019

Study/Trial Completion: 08/2020

Final Report Submission: 02/2021

### 2. PMC 3417-5

Conduct an in vitro study to determine the potential for a drug interaction between tecovirimat and phosphate binders. If the results of the study are inconclusive or indicate binding of phosphate binders to tecovirimat is significant, conduct an in vivo study to determine the magnitude of interaction to inform the dosing regimen in patients who concomitantly take phosphate binders.

Draft Protocol Submission, : 4/2019

Final Protocol Submission: 7/2019

Study/Trial Completion: 8/2020

Final Report Submission: 2/2021

The two review issues (lower tecovirimat exposures in subjects with higher body weight and subjects with End-Stage-Renal Disease taking phosphate binders) have been addressed in the Office of Clinical Pharmacology Review and the review team has concluded a further investigation is needed to determine the optimal dosing regimen of tecovirimat for these subpopulations.

PMC 3417-5 (drug interaction with phosphate binders) was discussed with Drs. Xiaolei Pan and Sudharshan Hariharan (cardio-renal team, DCP1). Drs. Pan and Hariharan agreed that it is reasonable to conduct an in vitro study to determine the necessity for further in vivo studies regarding drug interactions with phosphate binders.

The sponsor agreed with the two PMC studies and timelines.

3. A typographical error was noted in the primary review. The geometric mean value of steady-state  $C_{\min}$  is 587 ng/mL, not 689 ng/mL. 689 ng/mL is the arithmetic mean value of steady-state  $C_{\min}$ .

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/s/  
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SU-YOUNG CHOI  
07/10/2018

SHIRLEY K SEO  
07/10/2018

### Office of Clinical Pharmacology Review

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## 1. Executive Summary

The Applicant is seeking approval of TPOXX® (tecovirimat) for the treatment of smallpox infection. Naturally occurring smallpox was eradicated in 1980. However, there is the potential for natural re-emergence, as well as accidental or deliberate release of the live virus, which can be a potentially serious threat to public health and national security. Since smallpox does not naturally occur and it is a life-threatening disease, conducting an efficacy trial in humans is neither feasible nor ethical. Therefore, this product was developed under the Animal Rule (21 CFR part 314, subpart I).

The pivotal data supporting the efficacy of tecovirimat for the treatment of smallpox infection is provided by two lethal animal models; cynomolgus monkeys representing a non-human primate [NHP] model infected with monkeypox virus (MPXV) via IV route and New Zealand White rabbits infected with rabbitpox virus (RPXV) via intradermal route. In both animal models, tecovirimat demonstrated dose-dependent survival benefit over placebo. The fully effective doses in animal models are 10 mg/kg/day in MPXV/NHP and 40 mg/kg/day in RPXV/rabbits. The Applicant's proposed dose in humans is 600 mg twice daily (BID) for 14 days. At the proposed human dosing regimen, the mean values of  $C_{max}$ ,  $AUC_{24hr}$ , and  $C_{min}$  are approximately 2-fold, 2-fold, and 4-fold higher, respectively, in healthy volunteers as compared to those associated with the fully effective dose in NHPs. There are no significant safety concerns at the proposed dosing regimen in healthy volunteers as demonstrated in the pivotal safety trial, SIGA-246-008 (N=359 administered tecovirimat).

### 1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the application and determined that this NDA is approvable from a clinical pharmacology perspective. The key review issues, specific recommendations, and comments are summarized below.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	<p>The pivotal data for the effectiveness of tecovirimat for the treatment of smallpox infection is provided by two lethal animal models; cynomolgus monkeys infected monkeypox virus via IV route (MPXV/NHP) and New Zealand White rabbit infected with rabbitpox virus via intradermal route (RPXV/rabbits). In both animal models, tecovirimat demonstrated dose-dependent survival benefit over placebo.</p> <p>Clinical pharmacology information provides pivotal evidence of effectiveness because the translation of the effective animal to</p>

	human dose relied on developing a dose/exposure-survival relationship in animals and subsequently translating to a human dose.
General dosing instructions	The proposed dosing regimen, 600 mg BID for 14 days, is acceptable.
Dosing in patient subgroups	No dose adjustments are recommended based on intrinsic and extrinsic factors.  The review team disagrees with the Applicant's proposed pediatric dosing regimens which may result in (b) (4) exposures in pediatric patients as compared to adult patients. The Office of Clinical Pharmacology review team is proposing alternative dosing regimens. Refer to Sections 2.3 and 3.3.3
Labeling	The labeling is generally acceptable. For specific contents and formatting recommendations, refer to Section 2.4
Bridging between the to-be-marketed and clinical trial formulation	No bridging is needed as the to-be-marketed formulation is identical to the formulation used in the PK/safety trial that provided pivotal PK data for the translation of the effective animal dose.

## 1.2 Post-Marketing Requirements and Commitments

Post-marketing requirements and commitments are still under active discussion at the time this review was finalized. The review team is considering post-marketing commitment studies to

(b) (4)  
to characterize the pharmacokinetics of tecovirimat in subjects with higher body weight.

## 2. Summary of Clinical Pharmacology Assessment

### 2.1 Summary of Clinical Pharmacology and Clinical Pharmacokinetics

The proposed mechanism of action of tecovirimat for the treatment of smallpox infection is to prevent viral exit from the cell by inhibiting protein P37 (or its ortholog). This results in blocking viral dissemination in the host. The pharmacokinetics of tecovirimat are summarized in Table 2.1

**Table 2.1 Summary of Tecovirimat Pharmacokinetics in Humans Following Oral Administration of Tecovirimat**

<b>Absorption</b>	Tmax: 4-6 hours Food increases the absorption (approximately 40% increase in AUC under moderate fat conditions)
<b>Distribution</b>	Vc/F: 220 L (CV: 24%), Vp/F: 341 L (CV: 77%) Plasma protein binding: 80%
<b>Metabolism</b>	Major: amide hydrolysis Minor: primary and secondary glucuronidation Major metabolites in plasma: M4, M5, TFMBA (4-trifluoromethyl benzoic acid)
<b>Elimination</b>	CL/F: 35.5 L/hr (CV: 36%) Apparent elimination half-life: 21 hours Unchanged drug: mostly eliminated in feces (23% of the dose administered was recovered in feces as unchanged drug. Unchanged tecovirimat was not detected in urine.) Metabolites: mostly eliminated in urine
<b>Potential for drug interactions</b>	Tecovirimat is a weak inducer of CYP3A and weak inhibitor of CYP2C19 and CYP2C8. Tecovirimat exposures can be increased or decreased by the concomitant use of UGT1A1/4 inhibitors or inducers, respectively.

## 2.2 Dosing and Therapeutic Individualization

### 2.2.1 General Dosing

The proposed dosing regimen, 600 mg BID PO under fed conditions, is acceptable.

The proposed dosing regimen provides higher exposures in humans as compared to those associated with the identified fully effective dose in NHPs (10 mg/kg/day for 14 days). At the proposed dosing regimen, the mean values of  $C_{max}$ ,  $AUC_{24hr}$ , and  $C_{min}$  are approximately 2-fold, 2-fold, and 4-fold higher, respectively in healthy adult volunteers as compared to the fully effective dose in NHPs. Exposure comparison was made between humans and NHPs as a conservative assessment of efficacy because higher exposures were required to achieve maximum efficacy in NHPs as compared with rabbits. The proposed dosing regimen is acceptable under the animal rule where human dosing regimens that provide exposures exceeding those associated with the fully effective dose in animals is recommended.

## 2.2.2 Therapeutic Individualization

Therapeutic individualization is not necessary based on the following intrinsic factors; sex, age (in adult patients), (b) (4) race, hepatic impairment, or renal impairment.

## 2.3 Outstanding Issues

### Pediatric dosing regimen

The OCP review team has concluded that the proposed pediatric dosing regimens from the Applicant are not acceptable and recommends the following dosing regimens (Table 2.3). (b) (4)

(b) (4)  
(b) (4)  
(b) (4)  
review of the human factor study requested by DMEPA.

**Table 2.2. Applicant-Proposed Pediatric Dosing Regimens**

(b) (4)

**Table 2.3 FDA Recommended Pediatric Dosing Regimens**

Weight (kg)	< 6	6 to < 13	13 to < 25	25 to < 40	40 and above
Dose	(b) (4)		200 mg BID	400 mg BID	600 mg BID

### Lower exposures in subjects with renal impairment

Tecovirimat exposures were unexpectedly lower in subjects with End-Stage Renal Disease (ESRD, defined as subjects with chronic kidney disease receiving hemodialysis) as compared to subjects with normal renal function (33% lower  $C_{max}$  and 48% lower  $AUC_{inf}$ , respectively) as observed in the dedicated renal impairment study, SIGA-246-012. The lower exposures in ESRD subjects were not due to dialysis as tecovirimat was not removed by hemodialysis in the same study. The underlying mechanism is currently unknown; however, it is unlikely due to impaired renal function itself. It is potentially due to underlying comorbidity (e.g., gastroparesis in diabetes patients) or concomitant medications that those subjects were receiving (e.g., phosphate binders).

Although the review team recommends no dose adjustment in this population based on the exposures associated with efficacy in NHPs, the review team is currently discussing whether additional post-marketing studies are needed to identify the potential cause of lower exposures in subjects with ESRD. If it is caused by one or more intrinsic or extrinsic factors typically associated with ESRD patients (such as concomitant medications or co-morbidity), the study results may not have reflected the worst case scenario for these factors. In addition, the identification of an underlying mechanism will help to inform the most appropriate dosing recommendations for this patient population.

## 2.4 Summary of Labeling Recommendations

OCP is providing the following general labeling recommendations. In addition, the inclusion of animal PK and exposure-response (survival) data in Section 12 is under discussion.

**Table 2.4 Summary of Labeling Issue Identification and Recommendations**

Section/heading	Comment
2.2 and 2.3 Pediatric dosing regimens	Update the dosing regimen based on FDA recommendations
7. Drug Interactions	<p>Retain clinically relevant drug interactions with clinical recommendations only (e.g., clinical recommendations for the weak induction of tecovirimat by CYP3A4) [REDACTED] (b) (4)</p> <p>Given the magnitude of effects of tecovirimat on CYP3A, CYP2C8, and CYP2C9 activities, sensitive substrates of these enzymes can be co-administered with tecovirimat with close monitoring of safety and efficacy.</p>
12.3 Pharmacokinetics	<p>Overall, this section (as well as section 7.3) needs to be streamlined to follow the current labeling practice.</p> <p>Add results of hepatic and renal impairment studies.</p> <p>Add the description for the method determining pediatric doses and present simulated data.</p>

### **3. Comprehensive Clinical Pharmacology Review**

#### **3.1 Overview of the Product and Regulatory Background**

Tecovirimat is a small molecule antiviral drug directed against orthopoxviruses. It inhibits an orthopoxvirus protein (P37) involved in the production of extracellular enveloped virus. Tecovirimat is active against a range of orthopoxvirus species such as Vaccinia, Cowpox, Monkeypox, and Variola virus.

Tecovirimat was developed for the treatment of smallpox infection. Smallpox infection is caused by Variola virus and it is highly contagious and lethal (mortality rates as high as 30%). Naturally occurring smallpox was eradicated more than three decades ago. However, there is the potential for the accidental or deliberate release of the live virus which can be a potentially serious threat. Despite the potential threat to public health, there is no treatment option other than early vaccination which is no longer routinely conducted. Since smallpox infection does not naturally occur and it is a life-threatening disease, conducting an efficacy trial in humans is neither feasible nor ethical. Therefore, the product was developed under the Animal Rule (21 CFR part 314, subpart I).

The Investigational New Drug application (IND) for tecovirimat was submitted in Nov 2005. Fast track designation for tecovirimat for treatment of human smallpox disease was granted in Dec 2005. Orphan Designation was granted in Dec 2006.

There have been extensive discussions among multiple stakeholders for the best approach to determine the efficacy of tecovirimat for smallpox infection. In a public advisory committee meeting held in 2011, it was concluded that with the appropriate validation, at least two lethal animal models using surrogate orthopoxvirus should be used to determine the efficacy of a drug for the treatment of smallpox infection. The Applicant accordingly chose MPXV/NHP and RPXV/rabbit models to determine tecovirimat efficacy.

#### **3.2 General Pharmacological and Pharmacokinetic Characteristics**

##### **Mechanism of action**

Tecovirimat prevents viral egression from the cell by inhibiting protein P37 or its ortholog in orthopoxviruses. This results in blocking viral dissemination in hosts.

##### **Absorption**

Tecovirimat  $C_{max}$  is achieved 4-6 hours after administration under fed conditions (moderate fat meal). Steady-state is achieved within 7 days of dosing. Tecovirimat  $C_{max}$ ,  $AUC_{24hr}$ ,  $C_{min}$  values are approximately 40% higher at steady-state as compared to Day 1. The mean  $C_{max}$  and  $AUC_{24}$

values were higher by 31% and 41% higher, respectively under fed conditions as compared to fasted conditions following the administration of tecovirimat twice daily.

*In vitro*, tecovirimat is not a substrate of P-gp and BCRP.

### **Dose proportionality**

Tecovirimat exposures are increased in a slightly less than proportional manner between 200 mg and 600 mg. In SIGA-246-018, a dose increase from a single dose of 200 mg to a single dose 600 mg (i.e., 3-fold increase) resulted in an approximately 2-fold increase in  $AUC_{inf}$  and  $C_{max}$ . In study 004, a dose increase from 400 mg to 600 mg (i.e., 50% higher dose) upon multiple dose administration resulted in an approximately 30% increase in  $AUC_{tau}$ .

The trend of exposure increasing in a less than dose proportional manner is more apparent above the clinical dose, 600 mg. In SIGA-246-002, a dose increase from 400 mg to 800 mg resulted in an  $AUC_{24}$  increase of approximately 50% at steady state. In SIGA-246-001, a dose increase from 500 mg to 2000 mg resulted in an  $AUC_{inf}$  increase of approximately 2-fold.

### **Absolute bioavailability**

Absolute bioavailability data has not been submitted to the NDA.

### **Distribution**

Tecovirimat is approximately 80%, 88%, and 89% bound to plasma proteins in humans, NHPs, and rabbits, respectively. The estimated central ( $V_c/F$ ) and peripheral ( $V_p/F$ ) volume of distribution values are 220 L (CV: 24%) and 341 L (CV: 77%), respectively, based on the population pharmacokinetic modeling.

### **Elimination**

The apparent half-life of tecovirimat following the administration of 600 mg in healthy volunteers is approximately 21 hours. The estimated  $CL/F$  based on the population pharmacokinetic modeling is 35.5 L/hr (CV: 36%).

### Metabolism

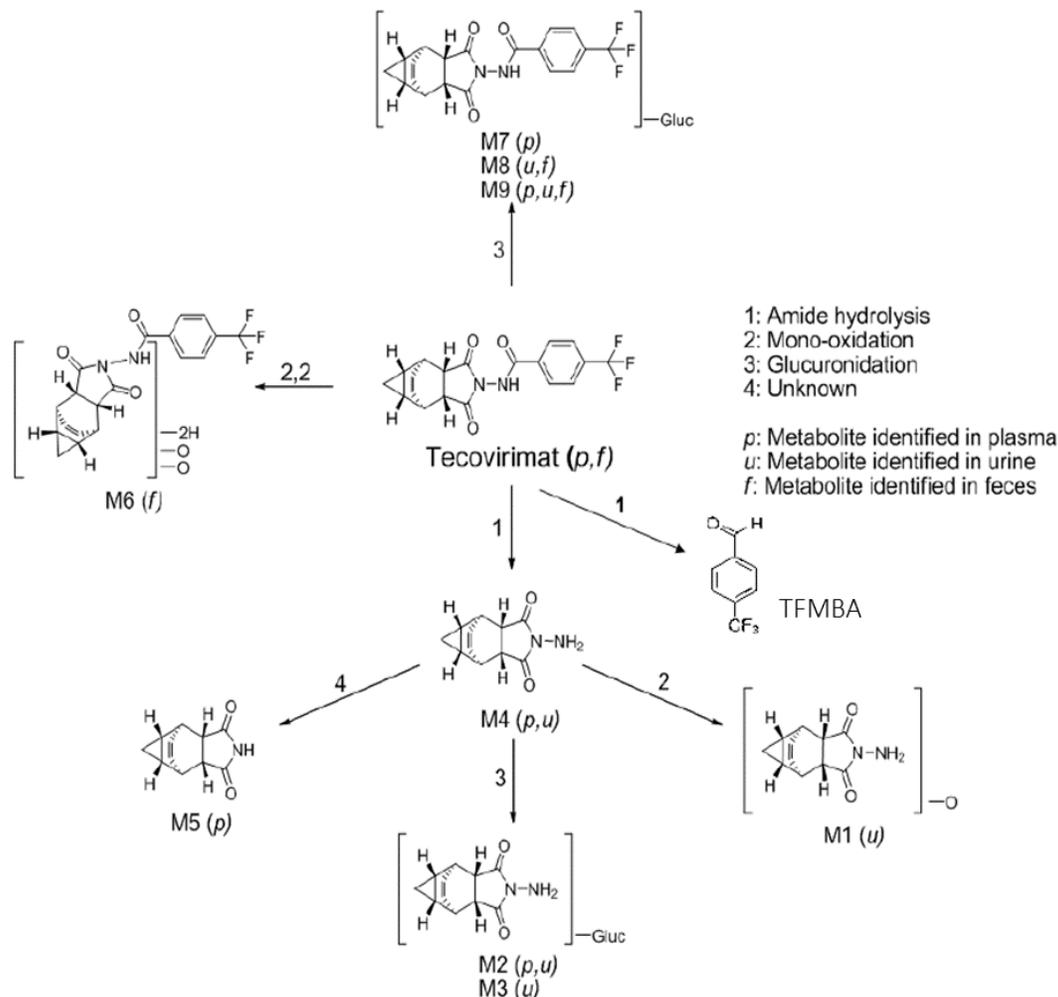
In a mass balance trial, nine metabolites of tecovirimat were detected. Metabolites are formed by amide hydrolysis, deamination, and primary/secondary glucuronidation (See Fig. 3.1). Of the metabolites, M4, M5, and TFMBA are considered the major circulating metabolites. Following the administration of tecovirimat 600 mg BID, the  $AUC_{24}$  values of M4, M5, and TFMBA are approximately 76%, 42%, and 520%, respectively, of the  $AUC_{24}$  value of tecovirimat at steady-state. M4 and TFMBA are formed by amide hydrolysis and M4 is further metabolized into M5 by deamination. The major metabolites (M4, M5, and TFMBA) do not have antiviral activity against orthopoxviruses.

The specific enzymes responsible for hydrolysis and demethylation have not been identified. However, tecovirimat was stable (< 15% metabolism within 2 hours) in human plasma, whole blood, human brush border membrane, human hepatocytes, and microsomes, indicating that intestine, liver, or blood are not major sites of tecovirimat biotransformation. Tecovirimat is not significantly metabolized by major hepatic CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4). *In vitro*, tecovirimat is not a substrate of OATP1B1/3.

#### Excretion

In the mass balance trial, 23% of the radioactivity administered was recovered in feces (mostly unchanged parent) and 72% of the radioactivity administered was recovered in urine, mostly as metabolites (glucuronidation products of tecovirimat or its metabolites). TFMBA is expected to be present mainly in urine, but was not determined in the mass balance trial because none of the radiolabeled carbons were a part of the molecule's structure.

**Fig 3.1. Proposed Biotransformation Pathway of Tecovirimat in Humans**



### Other pharmacokinetic characteristics

The pharmacokinetic difference between healthy volunteers and patients could not be determined as there have been no controlled studies in patients with smallpox. Although a limited number of sparse samples were collected in several EIND patients who had orthopoxvirus infection (such as vaccinia complications), the effects of orthopoxvirus infection on tecovirimat pharmacokinetics could not be determined based on the EIND cases due to a limited number of cases and characteristics of the patients such as underlying conditions (e.g., leukemia) and concomitant medications, which confounded analysis.

### 3.3 Clinical Pharmacology Review Questions

#### 3.3.1. To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The pivotal data for the effectiveness of tecovirimat for the treatment of smallpox infection is provided by two lethal animal models of non-variola orthopoxvirus infection. The applicant completed 4 pivotal studies in NHPs and 2 pivotal studies in rabbits including pivotal PK studies (Table 3.1). The primary endpoint of efficacy was survival and this review focuses on the dose-survival relationship to determine an effective dose for humans. Secondary endpoints such as viral DNA levels and total pox lesions were reviewed by clinical virology and pharm/tox review teams. Among these studies, FY10-087F and SR13-025F are considered the pivotal PK studies as these studies provide PK data to determine tecovirimat exposures associated with the fully effective dose in animal models.

**Table 3.1 Pivotal Studies Conducted in MPXV/NHPs and RPXV/Rabbits**

	Description	Key findings (Survival rate)
NHPs		
AP-09-026G	Dose-response study (0, 0.3, 1, 3, 10 mg/kg once daily for 14 days)	Survival benefit was observed from 3 mg/kg/day and 10 mg/kg/day was determined as the fully effective dose. Refer to Section 3.3.2.
SR10-087F	Dose-response and PK study (0, 3, 10, or 20 mg/kg once daily for 14 days)	
SR10-037F	Delayed treatment initiation study 10 mg/kg/once daily for 14 days Treatment initiated on Day 4, 5, or 6	Day 4: 83% (5/6) Day 5: 83% (5/6) Day 6: 50% (3/6)
SR10-038F	Treatment duration study 10 mg/kg once daily for 3, 5, 7, or 10 consecutive days	3 Days: 50% (2/4) 5 Days: 100% (6/6) 7 Days: 100% (6/6) 10 Days: 80% (4/5)
Rabbits		
SR14-008F	Dose-response study (0, 20, 40, 80, or 120 mg/kg/once daily for 14 days)	Survival benefit was observed from 20 mg/kg/day and 40 mg/kg/day was determined as the fully effective dose. Refer to Section 3.3.2
SR13-025F	Dose-response and PK study (40, 80, or 120 mg/kg/once daily for 14 days)	

Except SR10-037F, tecovirimat was administered once daily upon the onset of lesion (Day 4 post infection) in NHPs and upon the onset of fever (Day 4 post infection) in rabbits, respectively.

Tecovirimat demonstrated statistically significant survival (primary endpoint) as compared to placebo in MPVX/NHPs and RPVX/rabbits when tecovirimat was administered at the time of lesion onset for NHPs and at the time of fever development for rabbits. Refer to Section 3.3.2 for dose-response relationship and fully effective dose for tecovirimat efficacy.

Clinical pharmacology information provides pivotal evidence of effectiveness because the translation of effective animal to human dose relied heavily on developing a PK/PD relationship in animals and subsequently translating to a human dose after taking into consideration several factors such as PK differences in uninfected and infected animals, differences in ADME between animals and humans, PK variability, and effects of intrinsic and extrinsic factors. See section 3.3.2 for additional details.

### **3.3.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?**

Yes, we agree that the proposed dosing regimen, 600 mg BID for 14 days, is appropriate for the general patient population.

Under the Animal Rule, there are several approaches to determine an effective dose in humans depending on the availability of previously established PK/PD for other relevant indications, qualified biomarkers, and acceptable target PK values. For tecovirimat for the treatment of smallpox infection, the review team decided to use a “conservative” approach to human dose selection with the assumption of a similar exposure-response relationship between animal models and humans. Conservative approach is defined as selection of human dosing regimens to provide exposures that exceed those associated with the fully effective dose in animals, ideally by several-fold, if the drug’s safety profile allows such dosing.

To select an effective dose in humans, fully effective doses were determined in MPXV/NHP and RPXV/rabbits (Table 3.2). In MPXV/NHPs, efficacy was observed starting at 3 mg/kg/day and 10 mg/kg/day was chosen as the fully effective dose. In RPXV/rabbits, efficacy was observed starting at 20 mg/kg/day and 40 mg/kg/day was chosen as the fully effective dose. Because higher exposures were required to achieve maximum efficacy in NHPs as compared to rabbits, the 10 mg/kg/day dose was used to translate to an effective human dose.

At the selected human dose of 600 mg BID, tecovirimat plasma concentrations are higher than those at the effective doses in NHPs and rabbits on day 1 and at steady-state (Fig 3.2). At the proposed dosing regimen, the mean values of  $C_{max}$ ,  $AUC_{24hr}$ , and  $C_{min}$  are approximately 2-fold, 2-fold, and 4-fold higher, respectively, in humans as compared to MPXV/NHPs (Table 3.3).

**Table 3.2 Tecovirimat Dose-Response Relationship for Survival in Animal Models**

a. MPXV/NHPs

Tecovirimat dose (X 14 days)	Survival
Placebo	0 % (0/13)
0.3 mg/kg/day	20 % (1/5)
1.0 mg/kg/day	0 % (0/5)
3 mg/kg/day	91 % (10/11)
10 mg/kg/day	88 % (15/17)
20 mg/kg/day	100 % (6/6)

Combined efficacy results from AP-09-026G, SR-10-037F, and FY10-087

Tecovirimat was administered once daily upon the onset of lesion (Day 4 post infection) in cynomolgus monkeys infected with monkeypox virus via IV route.

b. RPXV/rabbits

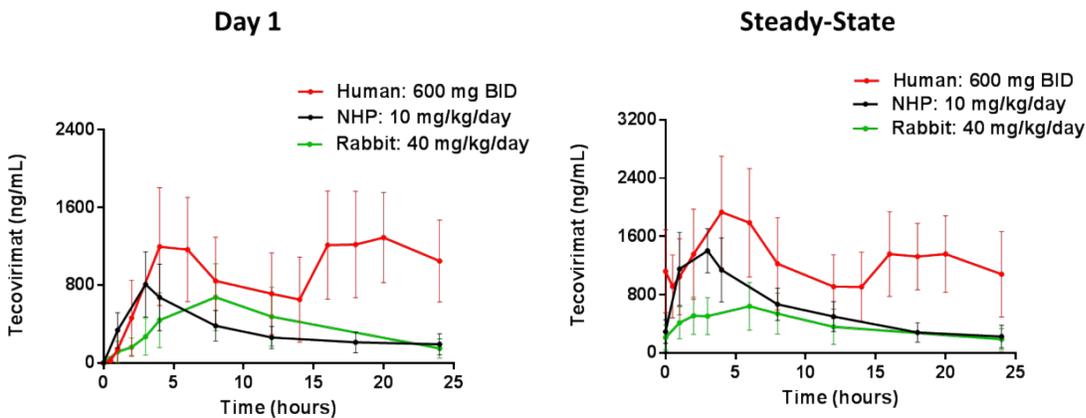
Tecovirimat dose (X 14 days)	Survival
Placebo	0% (0/10)
20 mg/kg/day	90 % (9/10)
40 mg/kg/day	88 % (16/18)
80 mg/kg/day	83 % (15#/18)
120 mg/kg/day	89% (16#/18)

Combined efficacy results from SR13-025F and SR14-008F.

Tecovirimat was administered once daily upon the onset of fever (Day 4 post infection) in New Zealand White rabbit infected with rabbitpox virus via intradermal route.

# One animal in this group died likely due to gavage procedure, not from rabbitpox virus infection

**Fig 3.2 Comparison of Tecovirimat Plasma Concentration-Time Profiles in MPXV/NHPs, RPXV/rabbits, and Healthy Volunteers**



**Table 3.3 Tecovirimat Exposure Parameters in MPXV/NHPs and Humans.**

		<b>C<sub>max</sub> (ng/mL)</b>	<b>AUC<sub>24</sub> (ng/mL·hr)</b>	<b>C<sub>min</sub> (ng/mL)</b>
<b>Day 1</b>	Human (N=48)	1516 (761-3290, 32%)	20879 (10627-45733, 35%)	477 (143-2020, 65%)
	NHP (N=6)	749 (378-1320, 42%)	7629 (4577-13294, 39%)	156 (37.3-339, 56%)
	Human/NHP ratio	2.0	2.7	3.6
<b>Day 14</b>	Human (N=48)	2106 (1120-4460, 33%)	28791 (15504-73568, 35%)	689 (2.5-1360, 38%)
	NHP (n=6)	1403 (936-2010, 27%)	13650 (6975-18614, 31%)	156 (88.7-344, 55%)
	Human/NHP ratio	1.5	2.1	4.4

NHP - 10 mg/kg once daily for 14 days (FY-10-087);

Human- 600 mg BID under fed conditions (SIGA-246-008)

C<sub>min</sub> is defined as the lowest concentration after the first C<sub>max</sub>

Data are expressed as geometric mean (min-max, % CV)

One subject had unexpectedly lower C<sub>min</sub> on Day 14. After excluding this subject's value, the lowest C<sub>min</sub> value in this group was 205 ng/mL.

Multiple doses higher than 600 mg BID were not evaluated; for single doses above 600 mg, exposures increased in a less than dose proportional manner. Additionally, decreasing the dosing interval (i.e., 600 mg TID) was predicted to reach C<sub>max</sub> concentrations (5575 ng/mL) associated with an adverse event (seizure) in dogs. While there was no clinical evidence that tecovirimat is associated with a risk of seizure, it was the major adverse event found in preclinical species and it had a clear temporal relationship with C<sub>max</sub>.

As for the duration of the therapy, a 14-day treatment was evaluated in animal models and proposed for the treatment of smallpox infection in humans. While Study SR10-038 results indicated that a minimum 5-day dosing period is required to achieve the maximum efficacy (survival) in MPXV/NHPs, a 14 day dosing regimen was evaluated and recommended to cover the duration of smallpox symptoms, which are known to last approximately 2 weeks.

600 mg BID is an acceptable dosing regimen after considering the differences in protein binding across species and the effects of orthopoxvirus infection on the pharmacokinetics in animal models. Tecovirimat plasma protein binding is 80%, 88%, and 89% in humans, NHPs, and rabbits, respectively, in vitro. Therefore, it is predicted that unbound (pharmacologically active) tecovirimat AUC<sub>24hr</sub> and C<sub>min</sub> are 3.5- and 6-fold higher in humans as compared to NHPs.

No significant PK differences were observed between uninfected and infected NHPs. In rabbits, tecovirimat exposures were approximately 50% lower on day 14 as compared to Day 1 or Day 7 in RPVX/rabbits due to an unknown mechanism. This unexpected decrease in tecovirimat exposures was only observed in RPVX/rabbits (not in uninfected rabbits or other preclinical species) and the underlying mechanism and clinical relevance are unknown at this time.

### **3.3.3. Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?**

No dose adjustment is required for subpopulations based on the following intrinsic factors: age (in adults), sex, <sup>(b) (4)</sup>, hepatic impairment and renal impairment.

#### **Renal impairment**

The effects of renal impairment on the PK of tecovirimat were determined following the administration of a single 600 mg dose of tecovirimat in SIGA-246-012. Tecovirimat pharmacokinetics were similar in subjects with mild or moderate renal impairment compared to subjects with normal renal function. In subjects with severe renal impairment (eGFR < 30 mL/min/1.73 m<sup>2</sup>), an approximately 33% lower C<sub>max</sub>, but comparable AUC<sub>t(120hr)</sub> values, were observed as compared to subjects with normal renal function. However, C<sub>max</sub> and AUC<sub>inf</sub> values were 33% and 48% lower, respectively, in subjects with ESRD (subjects with chronic kidney disease receiving hemodialysis) as compared to subjects with normal renal function. The lower exposures in subjects with ESRD were not due to dialysis as tecovirimat was not removed by hemodialysis in SIGA-246-012. It is postulated that the altered drug absorption in subjects is due to an underlying disease (e.g., gastroparesis in diabetes patients) or unexpected drug interactions with one or more concomitant medications in these subjects such as phosphate binders.

While lower exposures were observed in subjects with ESRD, no dose increase is recommended at this time. There is insufficient information as to whether lower exposures are due to impaired renal function by an unknown mechanism or concomitant medications/underlying disease conditions. Also, a dose increase would result in significant accumulation of major metabolites, specifically TFMBA. Meanwhile, a 50% lower tecovirimat exposure in humans is still comparable to those observed in NHPs at 10 mg/kg/day where maximal efficacy (survival) was observed.

#### **Hepatic impairment**

The effects of hepatic impairment on the PK of tecovirimat were determined in SIGA-246-013. The PK of tecovirimat were not significantly altered in subjects with mild (Child-Pugh A), moderate (Child-Pugh -B), and severe (Child-Pugh -C) hepatic impairment as compared to subjects with normal hepatic function following the administration of a single dose of tecovirimat 600 mg.

**Other intrinsic factors**

No dose adjustment is needed based on age (in adults), sex (male vs. female), race (White vs. Non-White), (b) (4)

**Pediatric population**

Tecovirimat has not been studied in children. Due to ethical concerns, a PK study cannot be conducted in healthy children, thus pediatric dosing regimens have been determined solely based on modeling and simulation.

The Applicant submitted the following pediatric dosing regimens by applying fixed mg/kg (b) (4) mg/kg BID) doses across the weight bands (Table 3.4). The review team conducted independent analysis to evaluate pediatric dosing using an updated population PK (PPK) model by the reviewer. According to the simulations conducted by the review team, the applicant’s proposed dosing regimen for pediatrics (Table 3.3) (b) (4)

(b) (4) After weighing the balance between the risk and benefit for the proposed indication, alternative pediatric dosing regimens are proposed based on the simulation results (Table 3.5). (b) (4)

(For detailed review for modeling and simulation refer to Appendix Section 4.4 Pediatric Dosing).

**Table 3.4. Applicant-Proposed Pediatric Dosing Regimens**

(b) (4)

**Table 3.5 FDA Recommended Pediatric Dosing Regimens**

Weight (kg)	< 6	6 to <13	13 to <25	25 to <40	40 and above
Dose	(b) (4)		200 mg BID	400 mg BID	600 mg BID

\*

(b) (4)

**Fig 3.3 Simulated tecovirimat exposures in pediatric patients using FDA recommended dosing regimens presented in Table 3.5 (at steady-state under fed conditions).**



(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block] (b) (4) the human factor study requested by DMEPA.

(b) (4)

**3.3.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?**

**Food-drug interactions**

Tecovirimat exposures are higher under fed conditions as compared to fasted conditions; food effects at the proposed dosing regimen were evaluated in two lead-in parallel cohorts of SIGA-246-008. Tecovirimat 600 mg BID was administered under fed (moderate fat meal) and fasted

conditions for 14 days. Tecovirimat mean  $AUC_{24hr}$  values were 33% and 25% lower under fasted conditions as compared to fed conditions on Day 1 and Day 14, respectively.

To achieve exposures that are significantly higher than those associated with the fully effective dose in NHPs, it is recommended to take tecovirimat under fed conditions. However, it is possible that some critically-ill patients may not be able to take tecovirimat under fed conditions. For these patients under fasting conditions, tecovirimat exposures are still predicted to be slightly higher (20% higher  $C_{min}$  and 60% higher in  $AUC_{24hr}$  on Day 1) to those associated with maximum efficacy in NHPs (10 mg/kg/day).

## **Drug interactions**

### Effects of other drugs on tecovirimat

*In vitro*, tecovirimat is not a substrate of the following metabolic enzymes or transporters; major CYP isoforms (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4), P-gp, BCRP, OATP1B1 and OATP1B3. Glucuronidation is a minor metabolic pathway of tecovirimat based on the results from the mass balance trial. *In vitro*, tecovirimat was metabolized by UGT1A1 (*in vitro* half-life: approximately 200 min) and UGT1A4 (*in vitro* half-life: approximately 150 min). Therefore, tecovirimat exposures can be increased or decreased by the concomitant use of strong UGT1A1/4 inhibitors or inducers, respectively.

### Effects of tecovirimat on other drugs

*In vitro*, tecovirimat and its metabolites (M4, M5, and TFMBA) are not inhibitors of the following enzymes at clinically relevant concentrations; major CYP isoforms (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4), P-gp, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2. Tecovirimat and its metabolites (M4 and M5) induced mRNA expression of CYP3A4 and CYP2B6 at concentrations that were higher than 10  $\mu$ M. Tecovirimat inhibited BCRP with an  $IC_{50}$  value of 6.03  $\mu$ M, which may be clinically relevant ( $I_{gut}/IC_{50} \geq 10$ ). Metabolites of tecovirimat did not inhibit BCRP.

Because tecovirimat and its metabolites induced CYP3A4 and CYP2B6 expression in hepatocytes, it is possible that tecovirimat and its metabolites can induce CYP2C isoforms as these enzymes share an underlying molecular mechanism for induction. Therefore, to determine the clinical effects of tecovirimat on CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4, a drug interaction trial using a cocktail of index substrates was conducted (SIGA-246-015).

In SIGA-246-015, the effects of tecovirimat 600 mg BID on the PK of index substrates (bupropion for CYP2B6, repaglinide for CYP2C8, flurbiprofen for CYP2C9, omeprazole for CYP2C19, midazolam for CYP3A) were determined. Based on the trial results, tecovirimat is a weak inducer of CYP3A and a weak inhibitor of CYP2C8 and CYP2C19. Tecovirimat did not alter CYP2B6 or CYP2C9 activity. Based on the magnitude of interaction, it is recommended to

monitor safety or efficacy of drugs that are sensitive substrates of CYP2C8, CYP2C19, and CYP3A4.

**Table 3.6 Summary of the Effects of Tecovirimat on the PK of CYP Index Substrates**

Drug (index substrate)	Metabolic pathway	% change in C <sub>max</sub> by tecovirimat	% Change in AUC <sub>inf</sub> by tecovirimat
Bupropion 150 mg	CYP2B6	↓14 % (↓ 7-21 %)	↓ 16 % (↓ 11-22 %)
Repaglinide 2 mg	CYP2C8	↑27 % (↑ 23-45 %)	↑ 29 % (↑ 19-40 %)
Flurbiprofen 50 mg	CYP2C9	↑7% (↓2- ↑17 %) #	↑4% (↓1- ↑9%) #
Omeprazole 20 mg	CYP2C19	↑ 86 % (↑ 51-131 %)	↑ 72 % (36-119 %)
Midazolam 2 mg	CYP3A	↓ 39 % (↓ 32-46 %)	↓ 32 % (27-37 %)

Data are expressed geometric mean ratio (90% Confidence Interval (CI))

# No change: geometric mean ratio and 90% CI are within 80-125%.

#### Hypoglycemia in subjects receiving concomitant tecovirimat and repaglinide

Several hypoglycemia cases were reported in SIGA-246-015 in Cohort 2 where the drug interaction between tecovirimat and repaglinide was evaluated. There were 10 subjects (33%) who had mild to moderate symptoms of hypoglycemia approximately 3 hours post-dose (e.g., tremor, lightheadedness) when they received tecovirimat and repaglinide together. Meanwhile, no cases of hypoglycemia were reported when repaglinide was administered alone. Of note, blood glucose levels were determined only in subjects who had symptoms due to hypoglycemia.

It is unlikely that a drug interaction (increased repaglinide concentrations) is solely responsible for the significant increases in hypoglycemia cases given that the magnitude of interaction is minimal (<30%). In the reviewer's opinion, hypoglycemia likely occurred when subjects received repaglinide alone, but it was not properly captured. Repaglinide is an insulin secretagogue; therefore, it can cause hypoglycemia in non-diabetic healthy subjects. In diabetic patients, the starting dose is 0.5 mg and the drug should be given right before a meal. Therefore, it is reasonable to predict that a 2 mg dose of repaglinide taken after a meal likely could cause hypoglycemia in non-diabetic patients. When repaglinide was given alone, it is possible that some subjects had subclinical hypoglycemia but it was not captured as blood glucose levels were not measured. Interestingly, when repaglinide was administered alone, 3 AE cases were reported that can potentially be symptoms of hypoglycemia (increased appetite, headache, presyncope) but the Applicant concluded that those AEs are not related to the study drug.

(b) (4)  
 based on the information available (clinical recommendations for the use of repaglinide with CYP2C8 inhibitors in PRANDIN® (repaglinide) USPI, the review team concluded that repaglinide can be co-administered with tecovirimat with clinical recommendations of close/frequent monitoring of blood glucose levels.

## 4. Appendices

### 4.1 Summary of Bioanalytical Method Validation

The following validated bioanalytical assays were used for quantification of tecovirimat and its metabolites in study samples. All samples were analyzed using validated HPLC-MS/MS methods. (b) (4) have been inspected by OSIS and the data from these two bioanalytical labs are acceptable to be used to support the approval of the proposed dosing regimens in humans.

The bioanalytical methods and validation results are summarized in Table 4.1. All methods were adequately validated. The standard curve and QC data indicated that assays were precise and accurate. All samples were stored and processed in the time frame supported by the stability data.

**Table 4.1 Summary of Bioanalytical Method Validation for Tecovirimat**

Validation	(b) (4) 023748	AV13-ST246-01	(b) (4) 1151-034 1151-061	AV11-ST246-02
Lab	(b) (4)			
Anticoagulant Matrix	Li-Heparin NHP plasma	Li-Heparin NHP plasma	K <sub>3</sub> EDTA	K <sub>3</sub> EDTA
Methods	Methanol extraction	SLE (supported liquid extraction)	Methanol extraction	SLE (supported liquid extraction)
Internal standard	<sup>13</sup> C <sub>4</sub> -tecovirimat			
Calibration range	5-2000 ng/mL	5-2000 ng/mL	50 to 4000 ng/mL	50 to 4000 ng/mL
QC levels	15, 105, 1500 ng/mL	15, 100, 1600 ng/mL	150, 600, 3000 ng/mL	150, 600, 3200 ng/mL
Inter-day precision range (%CV) of QC samples	3.6 to 11%	4.2 to 7.8%	3.8 to 4.4%	0.6 to 6.0 %
Inter-day accuracy range (RE%) of QC samples	1.4 to 7.6%	-5.0 to 0.7%	-2.7 to 1%	4.2 to 6.4%
Study supported by this	FY-10-087	SR-13-025F	SIGA-246-002 SIGA-246-004	SIGA-246-015 SIGA-246-018

**Table 4.2 Summary of Bioanalytical Method Validation for Tecovirimat and Its Metabolites**

Drug	Tecovirimat	M4	M5	TFMBA
Lab	(b) (4)			
Anticoagulant Matrix	K <sub>3</sub> EDTA and cross validated with K <sub>2</sub> EDTA			
Methods	Acetonitrile precipitation			
Internal standard	<sup>13</sup> C <sub>4</sub> -tecovirimat			
Calibration range	5-2000 ng/mL	5-2000 ng/mL	10 to 4000 ng/mL	5-2000 ng/mL
QC levels	15, 150, 1600 ng/mL	15, 150, 1600 ng/mL	30, 300, and 3200 ng/mL	15, 150, 1600 ng/mL
Inter-day precision range (%CV) of QC samples	3.7% to 10.2%	4.2% to 11.9%	4.2% to 11.9%	4.2% to 11.9%
Inter-day accuracy range (RE%) of QC samples	-3.0% to 3.3%	-3.0% to 3.3%	-7.0% to 5.7%	-3.5% to 3.3%
Study supported by this	SIGA-246-008, SIGA-246-010, SIGA-246-012, SIGA-246-013			

## 4.2 Population PK Analysis

In 4.2 to 4.5 review sections, the pharmacometrics reviewer reviewed applicant's analyses, and performed independent analyses to optimize the population PK model in human adults, as well as evaluated the PK of the proposed dose in adults and pediatric subjects. The overall objective was to determine whether the proposed dosing for adults and pediatric subject are adequate.

The applicant submitted population PK and PK/PD analysis reports titled "POPULATION PK/PD MODELING OF TECOVIRIMAT (ST-246) IN RABBITS TO SUPPORT HUMAN DOSE SELECTION", "POPULATION PHARMACOKINETIC MODELING OF ST-246 TO SUPPORT HUMAN DOSE SELECTION" and "ST-246® SURVIVAL PHARMACODYNAMIC ANALYSIS IN MONKEYS INFECTED BY MONKEYPOX VIRUS". These reports included population PK analyses for healthy and infected rabbits, healthy and infected monkeys, and healthy humans with simulations for infected humans. A survival analysis based on combined animal data to inform the fully effective dose was also included in the reports.

**Objectives:** the objectives of the analysis were the following:

1. Characterize tecovirimat population pharmacokinetics (PK) in healthy and infected New Zealand White (NZW) rabbits, in healthy and infected cynomolgus monkeys, and in healthy humans.
2. Develop survival models to describe tecovirimat dose-response in rabbits and cynomolgus monkeys.
3. Identify an tecovirimat dose that is likely to be maximally efficacious for preclinical efficacy trials for treatment of smallpox using modeling.
4. Extend the human PK model to include a term for the effect of smallpox infection on exposure based on information from infected cynomolgus monkey PK model.
5. Perform population PK simulations using the 'infected' human model to derive tecovirimat human exposures for the proposed dose.

The results of applicant's analysis and reviewer's analysis are summarized in this section as follows.

### 4.2.1 Applicant's Analysis

#### 4.2.1.1 Data:

Seven studies were included in the population PK modeling and survival analysis, with one in healthy rabbits (029251), two in Rabbitpox Virus infected rabbits (SR14-008F, SR13-025F), one in healthy cynomolgus monkeys (Study 1151-065), two in infected cynomolgus monkeys (Study SIGA FY10-087, Study SIGA AP-06-21G), and one in healthy humans (Study SIGA-246-004). In the combined healthy and infected rabbit dataset, there were 82 NZW rabbits with 1430 quantifiable PK samples. For the cynomolgus monkey population PK dataset, there were 60 monkeys with 1558 plasma concentrations included. For the human population PK dataset, there were 88 subjects with 1511 plasma concentration from one study in healthy humans.

#### 4.2.1.2 Methods

### Population PK Modeling:

The applicant developed one population PK model with Phoenix™ WinNonlin® 6.4. for New Zealand White (NZW) rabbits; two population PK models with Phoenix NLME software (version 6.2.0.416), one for cynomolgus monkeys, and one for healthy human volunteers, respectively.

#### 4.2.1.3 Results:

##### Population PK Modeling for New Zealand White Rabbits

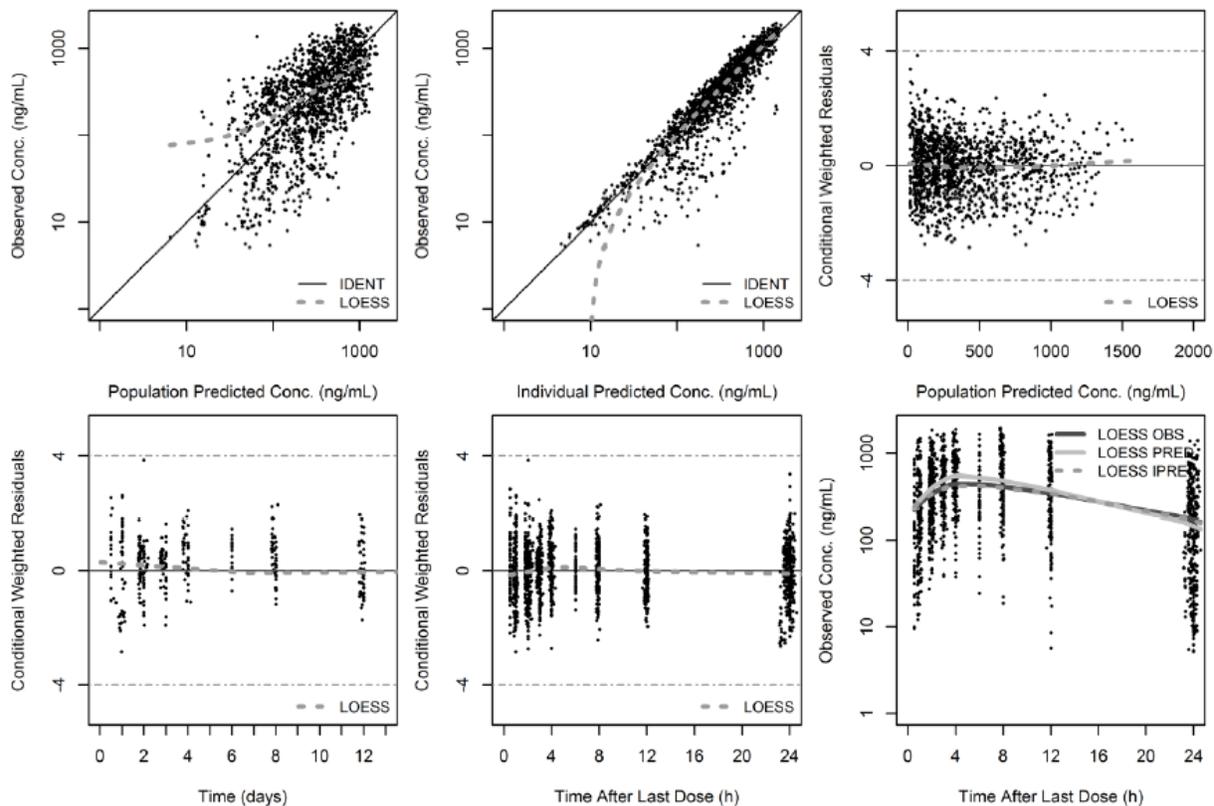
The tecovirimat PK in rabbits was described by a one-compartment model with zero-order absorption and first-order elimination. The applicant's PK modeling parameter estimates and goodness-of-fit plots for NZW rabbits are shown in Table 4.3 and Figure 4.1, respectively.

**Table 4.3 Population PK Parameters of Tecovirimat in Rabbits**

PK Parameter <sup>*</sup>	Typical Values (%RSE)	BSV % (%RSE) <sup>a</sup>	IOV (%RSE)
K0 (h)	3.65 (7.2)	57.1 (0.6)	NE
CL/F (L/h)	17.0 (2.8)	38.1 (0.6)	52.9 (1.0)
Vc/F (L)	Uninfected: 170 (3.8) Infected: 239 (9.0)	55.0 (0.9)	21.7 (0.6)
Error (%)	43.0 (1.1)		

Source: Applicant's Rabbit PK/PD Report Page 25, Table 4.2.3.

##### Figure 4.1 PK Model Goodness-of-fit plots



Source: Applicant's Rabbit PK/PD Report Page 37, Appendix 1.

Reviewer's comments: The population PK analysis of tecovirimat in NZW rabbits is acceptable. The goodness-of-fit plots indicate that the observed tecovirimat concentration data in NZW rabbit were reasonably described by the final model.

### Population PK Modeling for Cynomolgus Monkeys

Population PK model was developed in NHP to describe tecovirimat PK and to estimate the post-hoc parameters for the exposure comparisons between in monkeys and humans.

The tecovirimat PK in monkeys were described by a two-compartment model with zero-order absorption and first-order elimination. The PK modeling parameter estimates and goodness-of-fit plots for cynomolgus monkeys are shown in Table 4.4 and Figure 4.2, respectively.

**Table 4.4 Final Population PK Parameters of Tecovirimat in Monkeys - Studies 1151-065, AP-06-021G and FY10-087**

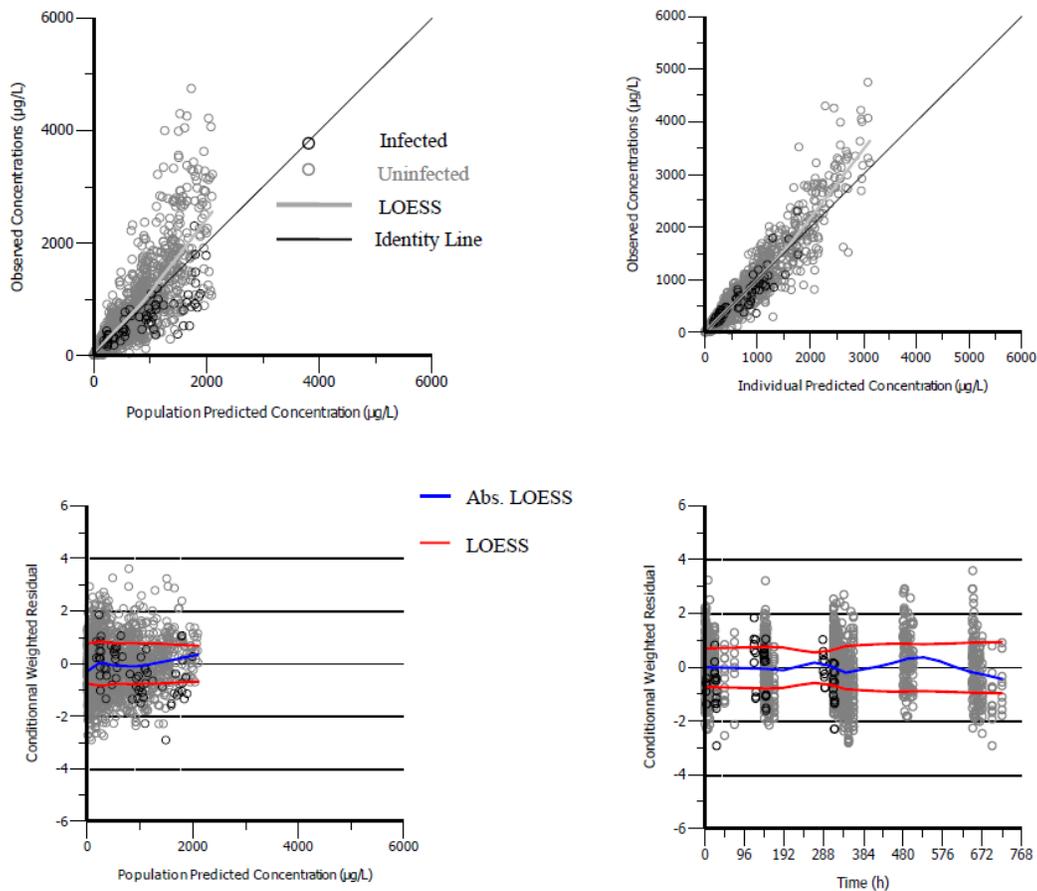
Population PK Parameters		Population Estimates	Inter-Individual Variability (%)	Inter-Occasion Variability (%)
Ka (h <sup>-1</sup> )	Infected	0.868 * (DOSE/10) <sup>0.160</sup>	11.13%	31.78%
	Uninfected	0.586 * (DOSE/10) <sup>0.160</sup>		
TLAG (h)		0.302	NA	---
CL/F (L/h)	Infected	2.809 * (WT/3.105) <sup>0.75</sup> * (DOSE/10) <sup>0.093</sup>	31.01%	14.37%
	Uninfected	2.827 * (WT/3.105) <sup>0.75</sup> * (DOSE/10) <sup>0.093</sup>		
Vc /F(L)		20.054 * (WT/3.105) * (DOSE/10) <sup>0.623</sup>	46.61%	---
Q/F(L/h)		3.244 * (WT/3.105) <sup>0.75</sup>	74.51%	---
Vp/F (L)		13.338 * (WT/3.105)	54.57%	---
<b>Error Model</b>				
Additive Error		0.133	NA	
Proportional Error (%)		30.06%	NA	

Correlation between CL/F and Vc/F = 0.945

CL/F: Apparent clearance; Ka: Absorption rate constant; Q/F: Apparent peripheral clearance; TLAG: Lag time of absorption; Vc/F: Apparent central volume of distribution; Vp/F: Apparent peripheral volume of distribution; NA: Not available

Source: Applicant's Population PK Modeling of tecovirimat in Monkeys and Humans, page 32.

Figure 4.2 Goodness of Fit: Final Population PK Model of Tecovirimat in Monkeys



Source: Applicant's Population PK Modeling of tecovirimat in Monkeys and Humans, page 31.

In addition to population PK modeling, the applicant simulated systemic exposure of tecovirimat in uninfected and infected monkeys. Similar AUC/Dose,  $C_{max}$ /Dose and  $C_{min}$ /Dose ratios were observed between infected and uninfected monkeys as shown in Table 4.5.

**Table 4.5 Systemic Exposure of Tecovirimat in Uninfected and Infected Monkeys on Day 1 and at Steady-State (SS)**

	Statistics	AUC/Dose ( $\mu\text{g}\cdot\text{h/L}$ )/(mg/kg)		$C_{max}$ /Dose ( $\mu\text{g/L}$ )/(mg/kg)		$C_{min}$ /Dose ( $\mu\text{g/L}$ )/(mg/kg)	
		Day 1	SS	Day 1	SS	Day 1	SS
<b>Uninfected Monkeys</b>	n	48	48	48	48	48	48
	Mean	1034.1	1256.9	104.6	119.8	14.2	18.3
	SD	316.9	360.4	49.6	50.9	5.2	6.9
	Min	361.8	524.5	23.9	33.7	4.9	7.0
	Median	1062.9	1268.4	95.5	110.2	14.3	17.6
	Max	1652.9	2016.4	262.4	275.2	32.0	39.1
	CV%	30.7	28.7	47.4	42.5	36.5	37.9
	Geom. Mean	980.7	1201.0	94.0	109.8	13.3	17.0
	CV% Geom. Mean	35.5	32.6	50.6	44.9	38.3	40.0
<b>Infected Monkeys</b>	N	30	30	30	30	30	30
	Mean	945.8	1217.8	88.3	106.3	15.5	20.9
	SD	332.1	380.0	38.6	39.4	5.7	8.3
	Min	431.1	527.9	29.6	42.8	4.9	7.0
	Median	924.5	1276.8	83.5	103.6	15.8	20.5
	Max	1644.2	2014.4	198.5	216.9	30.0	36.8
	CV%	35.1	31.2	43.7	37.1	36.6	39.6
	Geom. Mean	890.0	1156.9	80.3	99.2	14.4	19.1
	CV% Geom. Mean	37.2	34.6	47.4	40.0	43.2	48.3

Source: Applicant's Population PK Modeling of tecovirimat in Monkeys and Humans, page 33.

Reviewer's comments: Tecovirimat concentrations at higher range tend to be under-predicted by the model (Figure 4.2). It may due to the inadequate description of the saturable absorption of tecovirimat in monkeys. However, the individual predictions based on the post-hoc PK parameters were less deviated from the observed data. Other than that, the model may reasonably describe the concentration-time profile of tecovirimat in monkeys.

### Population PK Modeling for Healthy Human Adults

The tecovirimat PK in humans were described by a two-compartment model with zero-order absorption and first-order elimination. The PK modeling parameter estimates and goodness-of-fit plots for healthy human adults are shown in Table 4.6 and Figure 4.3, respectively.

**Table 4.6 Final Population PK Parameters of Tecovirimat in Uninfected Humans**

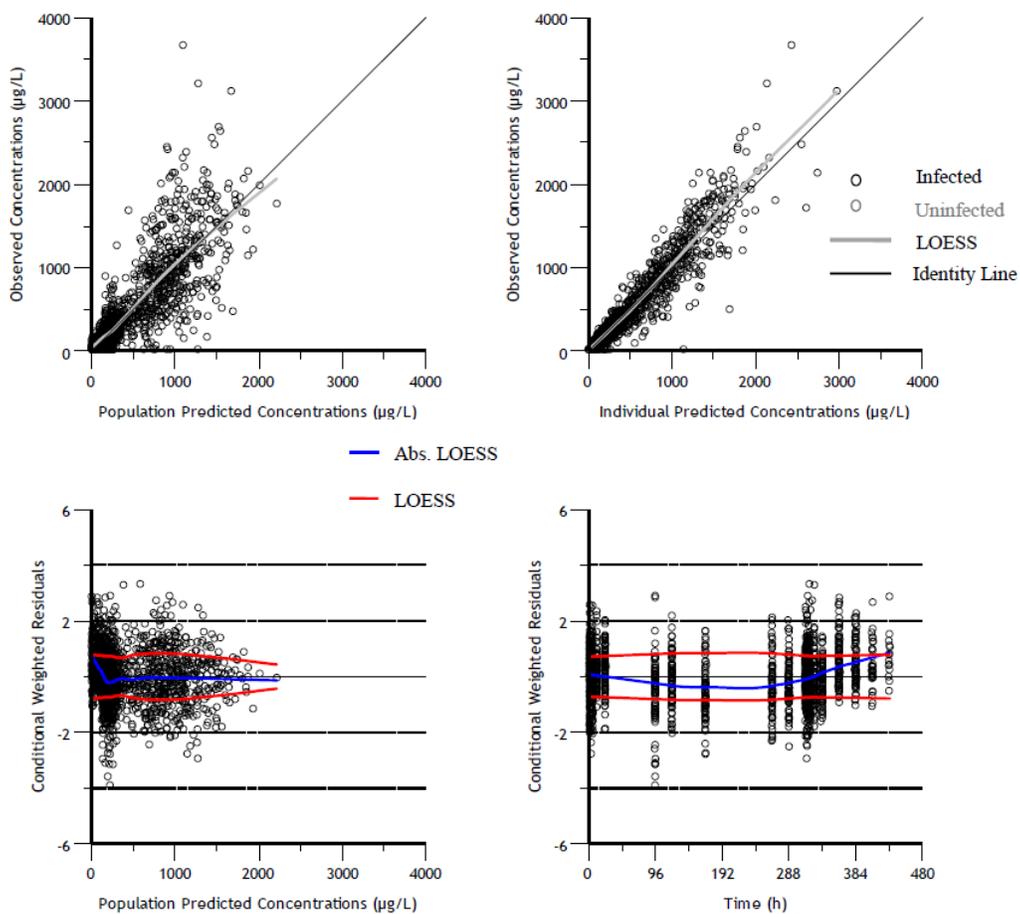
Population PK Parameters		Population Estimates	IIV (%)
Ka (h <sup>-1</sup> )		1.06	41.03%
TLAG (h)		1.46	16.74%
CL/F (L/h)		41.15x (WT/78.35) <sup>0.75</sup>	30.87%
Vc /F(L)	Female	281.51x (WT/78.35)	28.12%
	Male	217.44x (WT/78.35)	
Q /F(L/h)		36.79x (WT/78.35) <sup>0.75</sup>	54.39%
Vp/F (L)		413.53x (WT/78.35)	53.58%
<b>Error Model</b>			
Additive error (µg/L)		10.92	NA
Proportional Error (%)		26.76%	NA

Correlation between CL/F and Vc/F=0.887

CL/F: Apparent clearance; Ka: Absorption rate constant; Q/F: Apparent peripheral clearance; TLAG: Lag time of absorption; Vc/F: Apparent central volume of distribution; Vp/F: Apparent peripheral volume of distribution; NA: Not available

Source: Applicant's Population PK Modeling of tecovirimat in Monkeys and Humans, page 39.

**Figure 4.3 Goodness-of-fit plots of Final Population PK Model of Tecovirimat in Uninfected Humans**



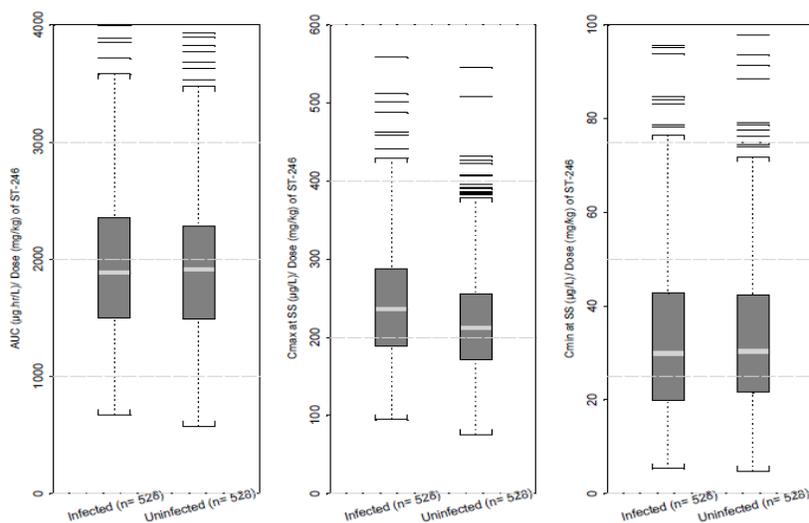
Source: Applicant's Population PK Modeling of tecovirimat in Monkeys and Humans, page 38.

## Comparison of Simulated Tecovirimat Exposure in Healthy and Infected Humans

As no PK data were available for infected humans, the applicant simulated the exposure of tecovirimat in healthy and infected humans.

The typical  $K_a$  was adjusted using the ratio of typical  $K_a$  obtained from infected and uninfected monkeys by 1.48-fold. Simulations were performed to determine the systemic exposure of tecovirimat following daily oral administrations of 400 or 600 mg. For each dose level, two subgroups of 264 subjects were included according to the infection status (infected/uninfected). Each subgroup of 264 subjects had the same demographic characteristics as the SIGA-246-004 study population. Box plots of dose-normalized exposure (AUC,  $C_{max}$  and  $C_{min}$ ) of tecovirimat at steady state versus uninfected and infected humans are presented in Figure 4.4. Similar dose-normalized AUC and  $C_{min}$  values of tecovirimat were obtained in infected and uninfected humans, whereas dose-normalized  $C_{max}$  values were 1.12-fold higher in infected humans as compared to uninfected ones.

**Figure 4.4 Dose-Normalized Simulated Exposure of Tecovirimat Under Steady State Conditions in Uninfected and Infected Humans**



Source: Applicant's Population PK Modeling of tecovirimat in Monkeys and Humans, page 41.

Reviewer's comments: The applicant's final population PK model was able to describe the tecovirimat PK data collected from study SIGA-246-004. However, FDA reviewer found the following aspects that limited the model's application on dose evaluations for adults and pediatrics: 1) the applicant's final population PK model in human adults did not include the dosing regimen that proposed by the applicant (600mg BID). Thus, the information regarding to 600 mg BID of tecovirimat in human adults for proposing pediatric dosing regimen was not incorporated; 2) the applicant's final population PK model in human adults did not include any dosing regimen less than 400 mg. Thus, any PK information regarding to doses less than 400 mg was not incorporated; 3) the applicant's final population PK model in human adults did not include food effect, given all the subjects included in the population PK modeling were fed. Thus, the exposure of pediatric dosing regimen under fasted condition could not be evaluated. FDA reviewer conducted independent analysis to optimize the population PK model in healthy humans. The results are summarized in Section 4.2.2 Reviewer's Analysis

*The applicant's conclusion that there would be no significant difference in exposure in infected and uninfected human was acceptable. This assumed that infection has the same effects on PK between NHPs and humans. FDA reviewer conducted independent simulation using the updated population PK model. The results are summarized in Reviewer's Analysis*

## 4.2.2 Reviewer's Analysis

### 4.2.2.1 Objectives

1. Optimize applicant's population PK model for healthy humans.
2. Conduct simulations comparing tecovirimat exposure parameters in healthy and infected humans under fed and fasted condition and compare those to the exposures in infected monkeys at various doses.
3. Determine whether the proposed dose for general adult population and pediatric subjects is acceptable, and if not, determine alternative dosing recommendations.
4. Evaluate the dosing regimen in high body weight patients.

### 4.2.2.2 Data

The datasets for population PK analysis in humans were generated using the applicant's datasets from three clinical studies summarized in Table 4.7. In addition to Study 004, the new dataset generated by the reviewer included other two studies' datasets (Studies 018 and 008) for the following reasons:

- (1) Study 018 included the PK data of tecovirimat from the dose as low as 100 mg.
- (2) Study 008 included the PK data of tecovirimat from 600 mg BID, the dosing regimen that the applicant is seeking FDA approval.
- (3) Study 008 included the PK data of tecovirimat from both fed and fasted subjects.

**Table 4.7 Analysis Datasets**

Study Number	File name	Description	Link to EDR
SIGA-246-018	ADPC.xpt	PK Concentration data	\\cdsesub1\evsprod\nda208627\0003\m5\datasets\siga-246-018\analysis\adam\datasets\adpc.xpt
	ADSL.xpt	Subject-level analysis dataset	\\cdsesub1\evsprod\nda208627\0003\m5\datasets\siga-246-018\analysis\adam\datasets\adsl.xpt
SIGA-246-004	pkhuman.xpt	Applicant's datasets for population PK analysis in human	\\cdsesub1\evsprod\nda208627\0008\m5\datasets\siga-ras-003\analysis\legacy\datasets\pkhuman.xpt
SIGA-246-008	ADEX.xpt	Exposure analysis dataset	\\cdsesub1\evsprod\nda208627\0003\m5\datasets\siga-246-008\analysis\adam\datasets\adex.xpt
	ADPC.xpt	PK concentration data	\\cdsesub1\evsprod\nda208627\0003\m5\datasets\siga-246-008\analysis\adam\datasets\adpc.xpt
	ADSL.xpt	Subject-level analysis dataset	\\cdsesub1\evsprod\nda208627\0003\m5\datasets\siga-246-008\analysis\adam\datasets\adsl.xpt

### 4.2.2.3 Methods

NONMEM (Version 7.3) was used for all population PK analyses. The R software was used for data table generation and post-NONMEM graphing and reporting.

The applicant's final population PK model was used as the starting point for optimization. Testing the fitting adequacy and evaluating the parameter estimates were conducted on the updated population PK model.

### 4.2.2.4 Results

#### Population PK model development:

The updated population PK model was based on applicant's two-compartment model. In addition to retaining the effects of body weight on apparent clearance (CL/F) and central volume distribution (V2/F), the new model also includes food effect on Ka and relative bioavailability (F1). In Study 004 and 008, CL/F for the 75<sup>th</sup> – 100<sup>th</sup> percentile of body weight is approximately 68 % higher than that in 0<sup>th</sup> – 25<sup>th</sup> percentiles. The Ka for fasted condition is approximately 50 % lower than that in fed condition, and the F1 for fasted condition is approximately 30 % lower than that in fed condition. In addition, a study effect of Study 018 was added on F1 due to the difference between Study 018 and Study 004/008. The model estimated F1 was 24 % higher in Study 008 compared to that in other two studies (Studies 004 and 008). Compared to the applicant's final population PK model, the effect of gender on V2/F was removed because of lacking clinical relevance. The effect of body weight on CL/F and V2/F was fixed at 0.75 and 1, respectively. In the sensitivity analysis by the FDA reviewer, a data-driven estimate of allometric coefficient is 0.898 with a 95% confidence interval including 0.75.

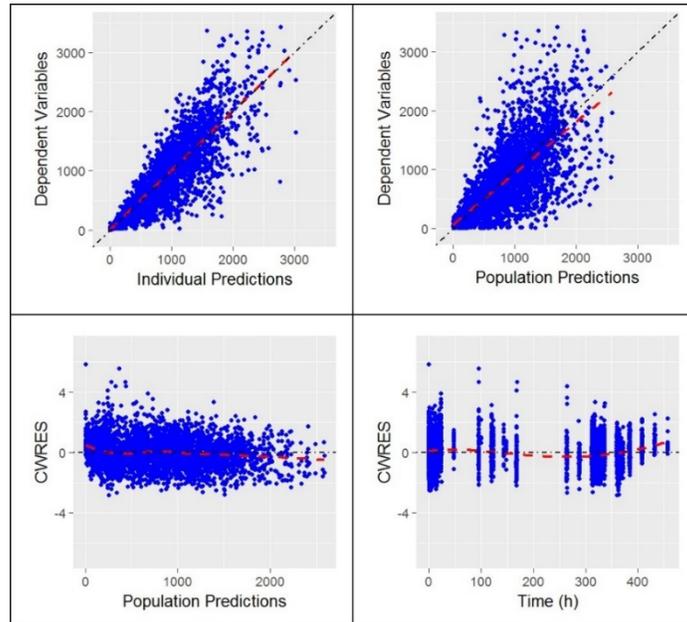
The parameters estimated by the updated final population PK model are shown in Table 4.8.

**Table 4.8 FDA reviewer's Final Population PK parameters of Tecovirimat in Healthy Humans**

Population PK Parameters	Population Estimates		IIV (%)
Ka (h <sup>-1</sup> )	Fed	0.406	45.5 %
	Fasted	0.193	
TLAG (h)	0.368		97.5 %
CL/F (L/h)	$35.5 \times (WT/79.8)^{0.75}$		35.5 %
V2/F (L)	$220 \times (WT/79.8)$		23.8 %
Q/F (L/h)	$31.5 \times (WT/79.8)^{0.75}$		48.6 %
V3/F (L)	$341 \times (WT/79.8)$		77.7 %
F1	Fed & study 004 & 008	1	N/A
	Fasted	0.707	N/A
	Study 018	1.24	N/A
<b>Error Model</b>			
Additive error (µg/L)	450		N/A
Proportional error (%)	11.8 %		N/A

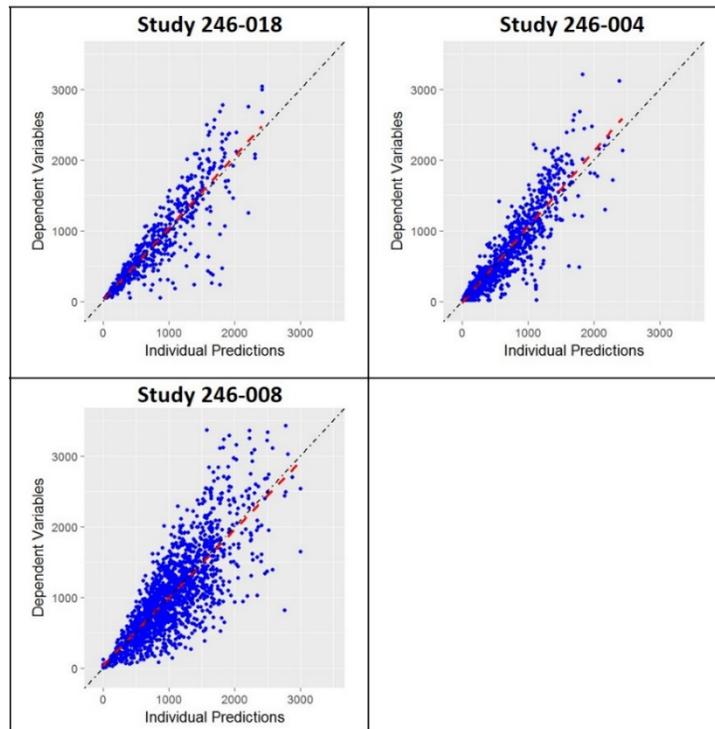
The goodness-of-fit plots using the updated final population PK model for all healthy humans and stratified by study are shown in Figure 4.5 and Figure 4.6, respectively. Based on these diagnostic plots, there was a good agreement between observed tecovirimat concentrations and model-predicted concentrations

**Figure 4.5 Goodness-of-fit Plots for Updated Final Population PK Model in All Healthy Humans**



Note: the red lines are smooth lines showing the trend

**Figure 4.6 Predicted versus Observed Plasma Tecovirimat Concentrations in Healthy Humans by Study**



Note: the red lines are smooth lines showing the trend

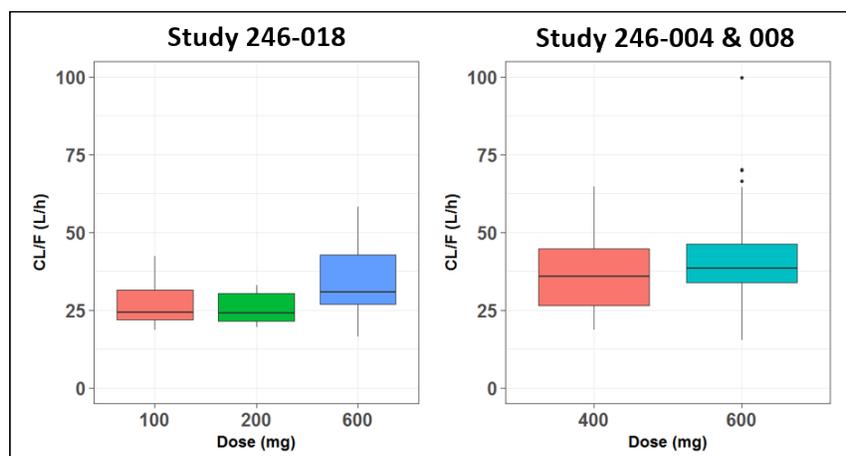
In addition to fixing body weight effect on CL/F at 0.75, the reviewer also conducted a sensitivity analysis to estimate the body weight effect on apparent clearance. The model structure and covariates included are identical to the updated final population PK model. The estimated parameters are shown in Table 4.9.

**Table 4.9 Population PK parameters of Tecovirimat in Healthy Humans for Model Estimated Body Weight Effect**

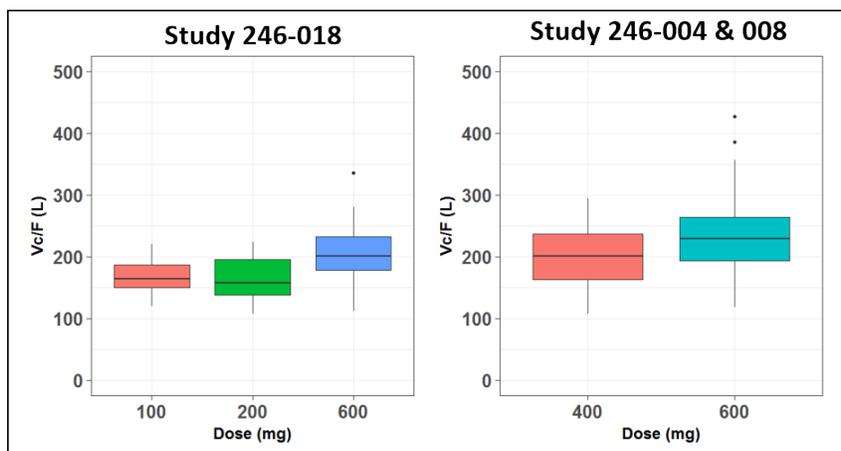
Population PK Parameters	Population Estimates		IIV (%)
Ka (h <sup>-1</sup> )	Fed	0.407	44.9 %
	Fasted	0.238	
TLAG (h)	0.317		101.5 %
CL/F (L/h)	$35.8 \times (WT/79.8)^{0.898}$		31 %
V2/F (L)	$218 \times (WT/79.8)$		27.7 %
Q/F (L/h)	$33.2 \times (WT/79.8)^{0.75}$		49.1 %
V3/F (L)	$362 \times (WT/79.8)$		75.8 %
F1	Fed & study 004 & 008	1	N/A
	Fasted	0.678	N/A
	Study 018	1.26	N/A
<b>Error Model</b>			
Additive error (µg/L)	458		N/A
Proportional error (%)	12 %		N/A

The post-hoc analyses for CL/F and V2/F stratified by study are shown in Figure 4.7 and Figure 4.8, respectively. The boxplots indicate the nonlinearity within 100 – 600 mg dose. Due to the same trend in the CL/F and V2/F obtained from post-hoc analyses, it's likely that the extent of tecovirimat absorption may decrease from 200 mg to 600 mg. Within Study 018, the geometric mean of both CL/F and V2/F for 600 mg dose is approximately 1.3-fold of those for 100 or 200 mg dose. (b) (4)

**Figure 4.7 Post-hoc Analysis for Apparent Clearance (CL/F) Versus Dose by Study**



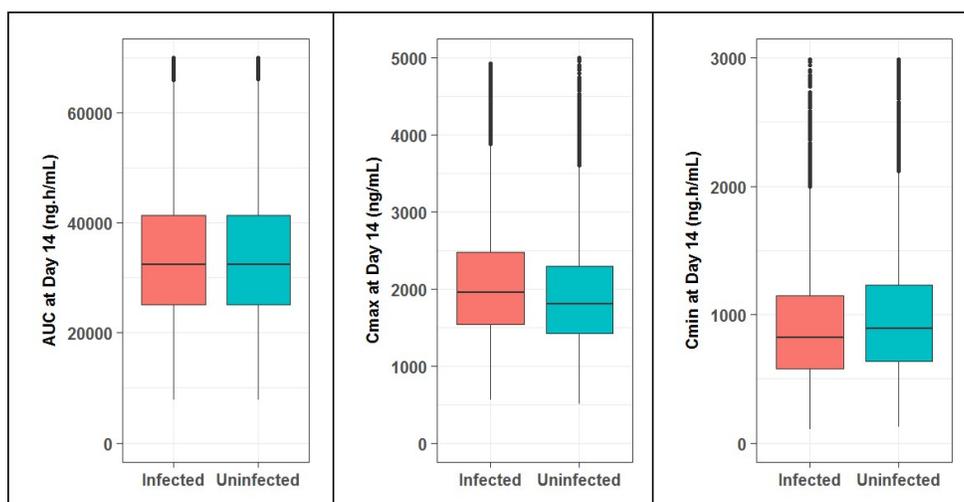
**Figure 4.8 Post-hoc Analysis for Apparent Central Volume Distribution (Vc/F) Versus Dose by Study**



**Comparison of Predicted Tecovirimat Exposure in Healthy and Infected Humans**

A difference in  $K_a$  in population PK analysis of tecovirimat was observed in infected monkeys compared to healthy monkeys. Infected monkeys had about 48% higher  $K_a$  relative to healthy monkeys, whereas a minor effect of infection on  $CL/F$  was obtained. The reviewer conducted simulations based on the updated final population PK model with  $K_a$  adjusted by 1.48-fold, to determine the systemic exposure of tecovirimat following oral administration of 600 mg BID under fed condition. Two subgroups of 9600 subjects were simulated according to the infection status (infected/uninfected). Each subgroup of the 9600 subjects had the same demographic characteristics as the Study 008 population. Boxplots of exposure ( $AUC$ ,  $C_{max}$  and  $C_{min}$ ) of tecovirimat at steady state versus uninfected and infected humans are shown in Figure 4.9

**Figure 4.9 Simulated Exposure of Tecovirimat At Steady State Under Fed Condition in Uninfected and Infected Humans at Steady State**



Similar  $AUC$  values of tecovirimat were obtained in infected and uninfected humans. Geometric mean of  $C_{max}$  values was 1.08-fold higher in infected humans as compared to that in uninfected ones, whereas

geometric mean of  $C_{min}$  values was 1.08-fold higher in uninfected ones compared to that in infected ones. Similar trends were obtained with the simulation of tecovirimat exposure at Day 1. The magnitude of 8% change in  $C_{max}$  or  $C_{min}$  is unlikely to be clinically significant.

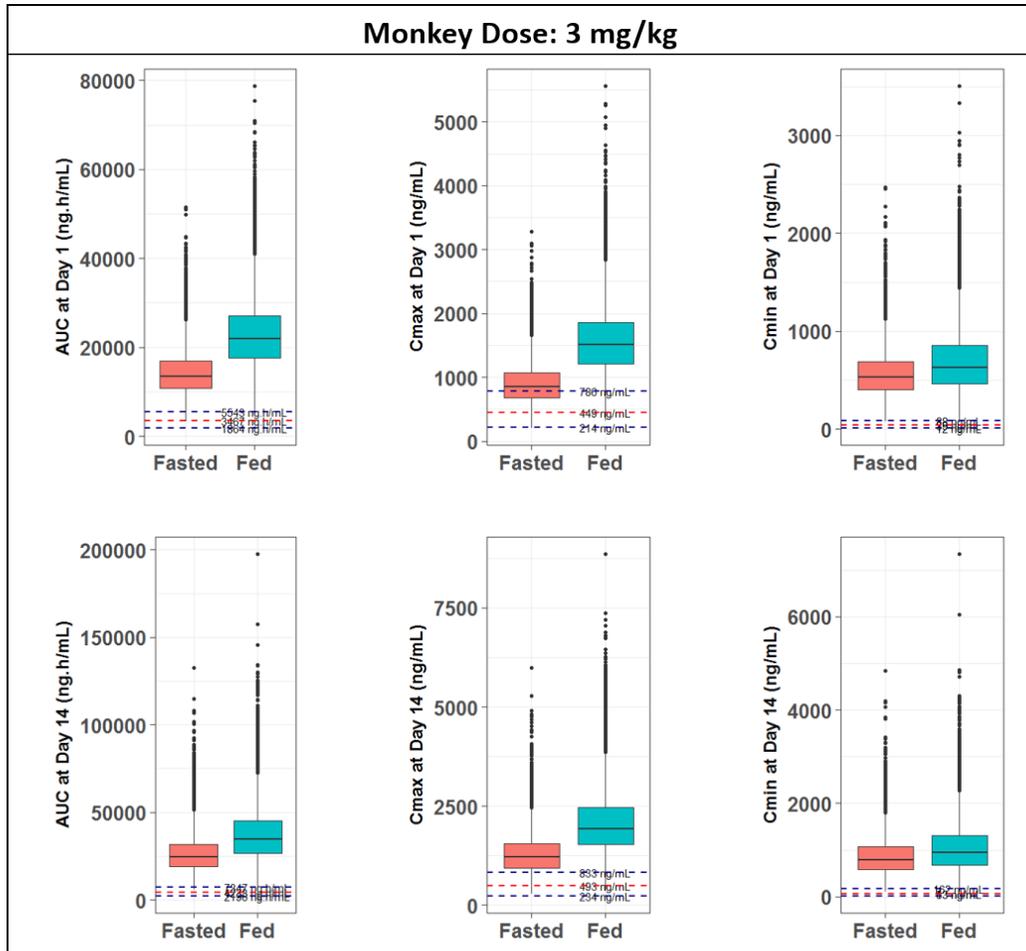
### Comparison of Tecovirimat Exposure in Fasted/Fed Human and Infected Monkeys

Exposure of tecovirimat in fed subjects is approximately 30% higher compared to that in fasted subjects. To determine the systemic exposure following oral administration of 600 mg BID under fasted condition, the reviewer conducted independent simulation based on the updated final population PK model. A subgroup of 19900 subjects were simulated according to the dietary status (fed/fasted). These 19900 subjects had the same demographic characteristics as the population from Studies 018, 004 and 008. The systemic exposure and the comparison with the exposure in infected monkeys from applicant's post-hoc analysis table (\\cdsesub1\evsprod\nda208627\0003\m5\datasets\sigar-003\analysis\legacy\datasets\simdatmk.xpt) are shown in Table 4.10 and Figure 4.10, respectively. According to the simulation results, the fasted condition decreases the AUC by 30% ~ 40% on Day 1 or at steady state compared to fed condition.  $C_{max}$  and  $C_{min}$  were decreased approximately 40% and 20%, respectively, under fasted condition compared to those in fed condition. In addition, the treatment of 3 mg/kg QD in monkeys showed similar survival benefit to the dose of 10 mg/kg (refer to section 3.3.2 Table 3.2 and section 4.3 Dose/Exposure Response Analysis). The exposures of tecovirimat under fasted condition in humans is generally several-fold higher than exposures in infected monkeys administered 3 mg/kg dose.

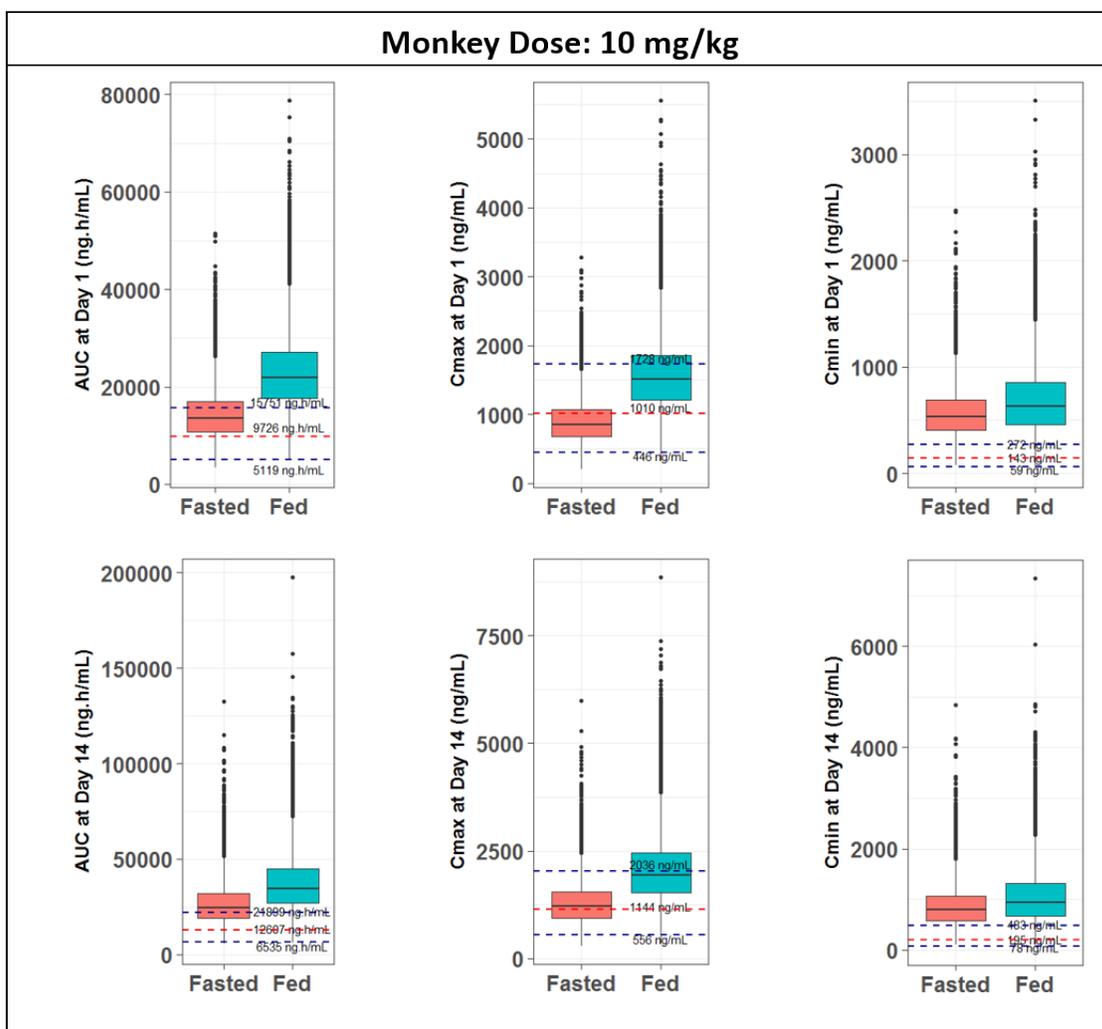
**Table 4.10 Systemic Exposure of Tecovirimat in Fed and Fasted Humans on Day 1 and Day 14 (Steady State)**

	Statistics	AUC ( $\mu\text{g}\cdot\text{h/L}$ )		$C_{max}$ ( $\mu\text{g/L}$ )		$C_{min}$ ( $\mu\text{g/L}$ )	
		Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
<b>Fed Humans</b>	n	19900	19900	19900	19900	19900	19900
	<b>Median</b>	<b>21861</b>	<b>34650</b>	<b>1505</b>	<b>1931</b>	<b>631</b>	<b>942</b>
	Maximum	78759	197700	5561	8858	3506	7344
	95 <sup>th</sup> percent	37008	65981	2551	3504	1295	2071
	5 <sup>th</sup> percent	12907	18460	880	1076	278	398
	Minimum	4912	6172	324	355	65	111
<b>Fasted Humans</b>	n	19900	19900	19900	19900	19900	19900
	<b>Median</b>	<b>13536</b>	<b>24520</b>	<b>852</b>	<b>1209</b>	<b>532</b>	<b>790</b>
	Maximum	51482	132700	3283	5988	2474	4846
	95 <sup>th</sup> percent	23543	46281	1488	2207	1003	1620
	5 <sup>th</sup> percent	7718	12970	481	659	266	363
	Minimum	3356	5762	205	295	79	108

**Figure 4.10 Comparison of Systemic Exposure of Tecovirimat in Fed and Fasted Humans on Day1 and Steady State with Monkeys**



Note: blue dash lines show the values of 95<sup>th</sup> and 5<sup>th</sup> percentiles in monkeys; red dash lines show the median values in monkeys; boxplots show the simulated exposures in humans.



Note: blue dash lines show the values of 95<sup>th</sup> and 5<sup>th</sup> percentiles in monkeys; red dash lines show the median values in monkeys; boxplots show the simulated exposures in humans.

### 4.3 Dose/Exposure Response Analysis

The overall survival was employed as the endpoint for the dose/exposure-response analysis. The dose-survival relationship was assessed using the Kaplan-Meier approach. The survival analyses were performed using S-PLUS Version 8.1 (Tibco, Seattle, WA, USA) and the ROC analysis was performed using the ROC 5 (Stanford University) program.

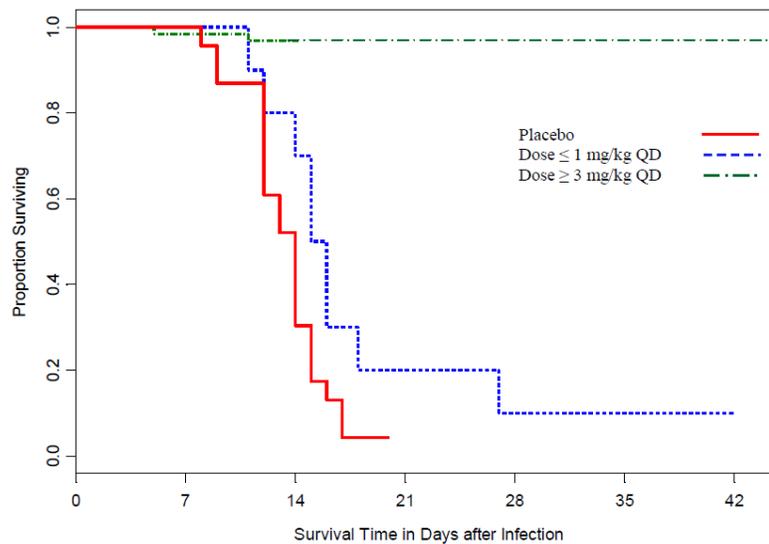
#### 4.3.1 Applicant's Analysis

##### Survival Analysis in Monkeys

In a group of monkeys treated with placebo, 69.6 % of mortality was observed after 14 days post-infection and 95% died after 17 days post-infection. All 23 monkeys in the placebo group died after 20 days postinfection. In groups of monkeys treated with 0.3 or 1 mg/kg, the percentage of survival after 15 and 14 days postinfection, respectively, was 60% and then dropped to 20% after 18 and 16 days, respectively. Overall, administering ST-246 at doses of 0.3 to 1 mg/kg exhibited weak rescue effects

(20%) in infected monkey. At the dose levels of 3 mg/kg (n=14) and 10 mg/kg (n=25), the survival probabilities of treated monkeys at early stage of infection were 92.9% on Day 5 and 96.0% on Day 11, respectively. This was due to one dead monkey in each group that was reported in the histology/pathology report to be unrelated to infection. At higher dose levels (> 10 mg/kg), all monkeys survived until the end of the study (i.e., up to 42 days). The Kaplan-Meier survival probability plots stratified by dose groups are presented in Figure 4.11. Taken together, these results indicated that ST-246 exhibited dose dependent rescue effects on MPXV-infected monkeys and the 100% survival probability was observed at a QD dose of 3 mg/kg.

**Figure 4.11 Survival Kaplan-Meier Plot by Treatment Categories - AI Monkeys Included**



*Source: Applicant’s Survival PD Analysis of ST-246 in Monkeys study report page 19.*

The ROC analysis was used to statistically determine these cut-off values, with an equal emphasis on false positive and false negative. The treatment of 3 mg/kg QD was statistically determined to be the cut-off value for survival of 96 monkeys with a sensitivity and specificity of 94.1% and 98.4%, respectively.

*Reviewer’s comments: The applicant’s survival analysis is acceptable. The determination of 3 mg/kg QD as the minimal fully effective monkey dose that showed similar survival benefit to the dose of 10 mg/kg is appropriate.*

## 4.4 Pediatric Dosing

### 4.4.1 Applicant’s Analysis

The applicant submitted a proposal for pediatric dose selection titled “Tecovirimat Pediatric Dose Determination”.



(b) (4)

*Reviewer's comment: The applicant's approach for pediatric dose selection is not acceptable. The applicant's approach to derive pediatric dosing regimen (b) (4)*

*In addition, the threshold to initiate the pediatric dose adjustment at (b) (4) is not scientifically justified. FDA reviewer conducted independent analyses to evaluate applicant proposed pediatric dosing regimens, as well as made new recommendations. The results were summarized in section 4.4.2 Reviewer's Analysis*

#### **4.4.2 Reviewer's Analysis**

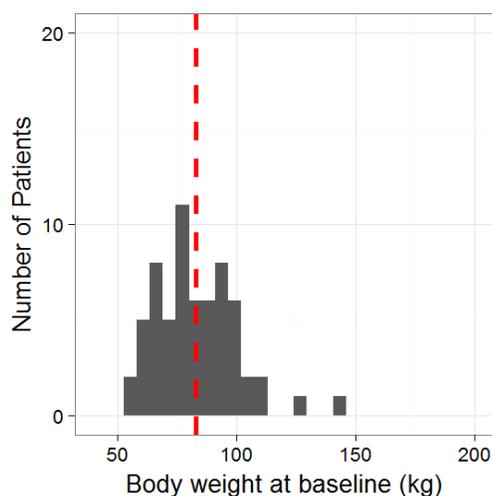
The approach that the applicant used to propose pediatric dose selection is not acceptable (see reviewer's comment in section 4.4.1). Thus, the reviewer conducted independent simulation based on the updated final population PK model (refer to section 4.2.2.4 Table 4.8) to evaluate the applicant proposed dosing regimen, as well as propose new dose recommendation for pediatric subjects.

The allometric coefficient for tecovirimat clearance used for estimating pediatric exposure was fixed at 14 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

#### 4.5 Exposure of Tecovirimat in High Body Weight Subjects (> 150 kg)

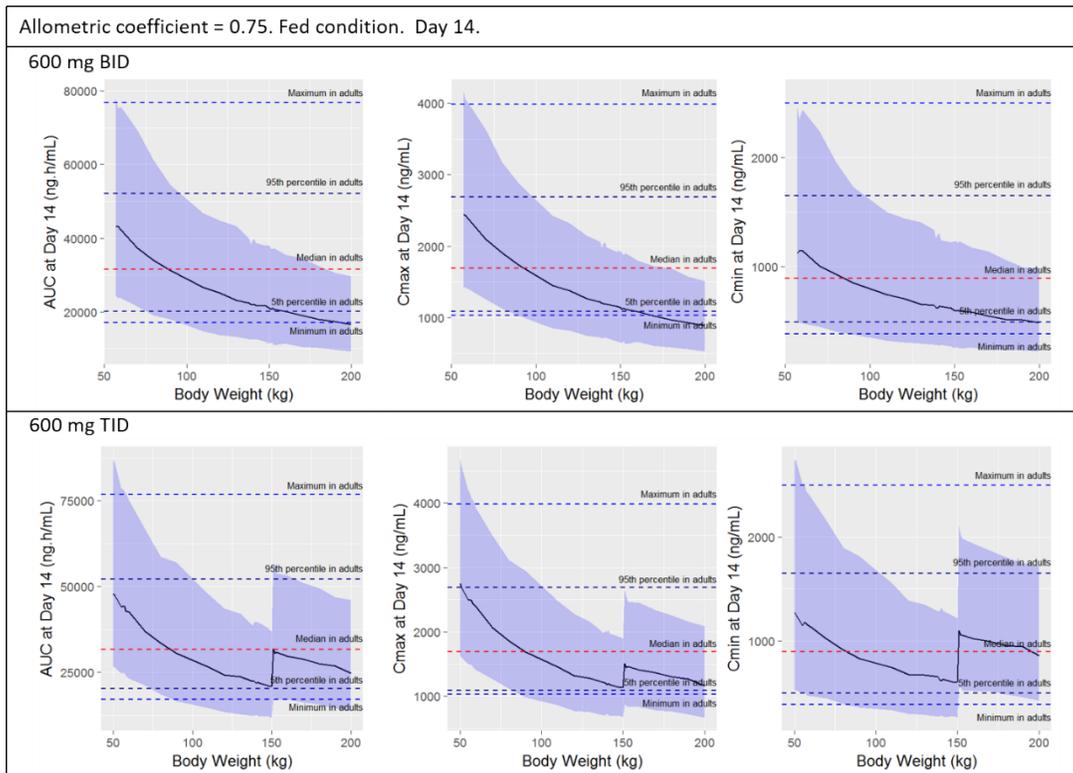
The maximum body weight in Study 008 is 145.4 kg (body weight distribution for Study 008 PK population is shown in Figure 4.18). No PK data of tecovirimat are available in subjects with body weight greater than 150 kg. Based on the available data and post-hoc analysis, lower exposures were associated with higher body weight in an allometric manner. In the pivotal study, AUC,  $C_{\min}$  and  $C_{\max}$  in the subjects with the lowest 25 % body weight are approximately 1.8-fold, 2-fold and 1.14-fold higher than those in the subjects with the highest 25 % body weight. Thus, the reviewer conducted simulations for high body weight patients to evaluate the PK with 600 mg BID and 600 mg TID respectively. As shown in Figure 4.19, under 600 mg BID, when the body weight is greater than 150 kg, the exposure would be significantly lower than that observed in general adult population from the pivotal study. On the other hand, 600 mg TID may yield higher exposures that might be able to match the exposures obtained from the pivotal study. This simulation considered the allometric scaling alone in terms of the effect of body weight on PK parameters. Various pathophysiological changes that are associated with higher body weights, such as the changes in absorption and distribution due to body composition differences<sup>1</sup>, changes in metabolism due to fatty liver<sup>2</sup>, increased hepatic blood flow and cardiac output<sup>3</sup>, and increased GFR<sup>4</sup>, etc, was not taken into account in this analysis.

**Figure 4.18 Distribution of Body Weight in Study 008 PK Population**



Note: red dash line shows the mean value.

**Figure 4.19 Simulation for High Body Weigh Patients**



Note: 1. Solid lines shows the median values of the simulated exposure. 2. Shadows show the distribution of 5<sup>th</sup> to 95<sup>th</sup> percentile of the simulated exposure.

## References

1. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. *Clin Pharmacokinet.* 2010;49(2):71-87.
2. Dietrich CG, Rau M, Jahn D, Geier A. Changes in drug transport and metabolism and their clinical implications in non-alcoholic fatty liver disease. *Expert Opin Drug Metab Toxicol.* 2017 Jun;13(6):625-640.
3. Cheymol G. Clinical pharmacokinetics of drugs in obesity. An update. *Clin Pharmacokinet.* 1993 Aug;25(2):103-14.
4. Lemoine S, Guebre-Egziabher F, Sens F, Nguyen-Tu MS, Juillard L, Dubourg L, Hadj-Aissa A. Accuracy of GFR estimation in obese patients. *Clin J Am Soc Nephrol.* 2014 Apr;9(4):720-7.

## 4.6 Individual Clinical Pharmacology Report Reviews

### 4.6.1 In vivo studies in animal models

#### 4.6.1.1 FY10-087

**Title:** Evaluation of the Pharmacokinetics of ST-246 in Cynomolgus Macaques Infected Intravenously with Monkeypox Virus (FY10-087)

**Objective:** to evaluate the pharmacokinetics of tecovirimat in cynomolgus macaques infected via intravenous injection with monkeypox virus (MPXV).

#### Study Design

Tecovirimat (3, 10, or 20 mg/kg) or vehicle was administered in cynomolgus macaques beginning 4 days following MPXV infection for a total of 14 days. Animals also received a single dose of tecovirimat or vehicle on Day -10 to determine the effects of monkeypox infection on tecovirimat PK. PK samples were collected on Day -10 (pre-infection, 10 samples up to 72 hours post-dose), Day 4 post-infection (PI, 1<sup>st</sup> dose, 7 samples up to 24 hours post-dose), Day 10 PI (7<sup>th</sup> dose, 7 samples up to 24 hours post-dose), and Day 17 PI (14<sup>th</sup> dose, 10 samples up to 72 hours post-dose). Secondary endpoints such as lesion counts and viral DNA levels were determined throughout the study, but not presented in this review.

**Table 1. Study Design**

Group	#NHP	MPXV
1 – Vehicle	6 (3 male/3 female)	5x10 <sup>7</sup> pfu IV
2 – ST-246 <sup>a</sup> 3 mg/kg	6 (3 male/3 female)	5x10 <sup>7</sup> pfu IV
3 – ST-246 <sup>a</sup> 10 mg/kg	6 (3 male/3 female)	5x10 <sup>7</sup> pfu IV
4 – ST-246 <sup>a</sup> 20 mg/kg	6 (3 male/3 female)	5x10 <sup>7</sup> pfu IV

<sup>a</sup>ST-246 treatment was initiated at 96 hours (Day 4) post-infection via oral delivery (gavage) and was continued as once-a-day dosing for 14 total doses (up to and including Day 17)

#### Pharmacokinetic Assessments

Plasma concentrations were determined by validated LC/MS/MS methods. PK parameters (noncompartment analysis) were obtained using WinNonlin®.

## Results

### 1. Efficacy Results

**Table 2. Summary of Efficacy - Survival until Day 28 PI**

Group	Dose	Survival (rate %)
1	Placebo	0/6 (0%)
2	3 mg/kg/once daily X 14 days	6/6 (100%)
3	10 mg/kg/once daily X 14 days	6/6 (100%)
4	20 mg/kg/once daily X 14 days	6/6 (100%)

### 2. Pharmacokinetic Results

**Table 3. Pharmacokinetic Parameters of Tecovirimat in NHPs**

Dose		C <sub>max</sub> (ng/mL)	AUC <sub>24</sub> (ng·hr/mL)	C <sub>min</sub> (ng/mL)
3 mg/kg/day (n=6)	Day -10 (Pre-infection)	344 (44%, 193-678)	2914 (35%, 1757-4381)	29 (62%, 16-68)
	Day 4 PI	403 (55%, 178-860)	3093 (29%, 1677-4272)	25 (84%, 8-84)
	Day 10 PI	455 (16%, 377-548)	3656 (23%, 2773-4945)	37 (42%, 20-58)
	Day 17 PI	419 (41%, 226-768)	2858 (53%, 1543-6144)	25 (62%, 10-59)
10 mg/kg/day (n=6)	Day -10 (Pre-infection)	999 (40%, 435-1650)	9775 (49%, 3269-17537)	180 (56%, 63-344)
	Day 4 PI	749 (42%, 378-1320)	7629 (39%, 4577-13294)	156 (56%, 37.3-339)
	Day 10 PI	1355 (34%, 540-1960)	12812 (36%, 4581-18848)	227 (50%, 78-446)
	Day 17 PI	1403 (26%, 936-2010)	13650 (31%, 6975-18615)	156 (55%, 89-344)
20 mg/kg/day (n=6)	Day -10 (Pre-infection)	1776 (56%, 840-4000)	22641 (56%, 10130-48761)	514 (54%, 244-1070)
	Day 4 PI	1149 (43%, 616-1980)	15881 (51%, 7298-28532)	407 (57%, 185-926)
	Day 10 PI	2752 (45%, 1520-4750)	29346 (46%, 14339-49458)	439 (50%, 217-887)
	Day 17 PI	2233 (41%, 973-3440)	24045 (47%, 10084-46814)	342 (63%, 159-870)

- Mean weight: 3.2 kg for female NHPs and 4.2 kg in Male NHPs
- Data are expressed as geometric mean (%CV, min-max)
- C<sub>min</sub> is defined as the lowest concentration after the first C<sub>max</sub>
- Median T<sub>max</sub>: 3 hours post-dose, mean Half-life: 10 hours

The sponsor did not collect predose concentrations for Day 4 and Day 10. For Day 4, predose concentrations were imputed as zero. For Day 10, predose concentrations were imputed as C<sub>24</sub> of Day 10.

*Reviewer comments*

*1. The effects of infection on tecovirimat PK*

*Overall, no consistent trend was observed for the effects of infection on tecovirimat PK. While exposures were lower on Day 4 PI (first dose post-infection) compared to Day -10 (single dose pre-infection) at 10 mg/kg/day and 20 mg/kg/day, no difference was seen at 3 mg/kg/day and the differences at 10 and 20 mg/kg were not consistent when the individual animal's PK data were analyzed.*

*2. Both the study site [REDACTED] (b) (4) and the bioanalytical site [REDACTED] (b) (4) were inspected by OSIS. VAI was issued for the study site and NAI was issued for the bioanalytical site. Overall, OSIS concluded that the data are acceptable. Refer to the individual inspection review for detailed information.*

*3. The study provided pivotal PK data associated with the effective dose in NHPs (10 mg/kg/day) used for the selection of an effective dose in humans.*

**Conclusion**

Tecovirimat PK were characterized in uninfected and MPXV-infected NHPs at 3, 10, and 20 mg/kg once daily for 14 days. Tecovirimat PK were not significantly altered by MPXV infection in NHPs.

The PK data collected in this study were utilized to determine an effective dose in human.

#### 4.6.1.2 SR13-025F

##### **Title: Evaluation of the impact of rabbitpox virus infection on oral pharmacokinetics of tecovirimat in male and female New Zealand White rabbits (SR13-025F)**

**Objective:** to evaluate the effect of rabbitpox virus infection on the oral pharmacokinetics (PK) of tecovirimat in New Zealand White (NZW) rabbits using a treatment regimen consisting of once daily dose treatment by oral gavage for 14 consecutive days.

##### **Study Design**

Twenty four 16-week old NZW rabbits were randomized into three groups of 8 animals based on weight (2.3 to 2.7 kg) and sex.

- Group 1: tecovirimat 40 mg/kg/once daily for 14 days
- Group 2: tecovirimat 80 mg/kg/once daily for 14 days
- Group 3: tecovirimat 120 mg/kg/once daily for 14 days

On Day -7 (7 days prior to challenge day), all animals received one treatment dose of tecovirimat corresponding to each dose group. All animals were challenged intradermally with RPXV 1,000 PFU on Day 0. Animals received tecovirimat at 40, 80, and 120 mg/kg once daily by gavage beginning on Day 4 PI (post-infection) and for 14 days. PK samples were collected on Day -7 (pre-infection), Day 4 post-infection (PI, 1<sup>st</sup> dose), Day 10 PI (7<sup>th</sup> dose), and Day 17 PI (14<sup>th</sup> dose). Eight PK samples over a 24 hour period were collected on each PK sampling day. Secondary endpoints such as lesion counts and viral DNA levels were also determined throughout the study period, but not presented in this review

##### **Pharmacokinetic Assessments**

Plasma concentrations were determined by validated LC/MS/MS methods. PK parameters (noncompartment analysis) were obtained using WinNonlin®.

##### **Results**

###### **1. Efficacy Results**

**Table 1. Summary of Efficacy – Survival until Day 18 PI.**

Group	Dose	Survival (rate %)
1	40 mg/kg/day x 14 days	7 <sup>#</sup> /8 (87.5%)
2	80 mg/kg/day x 14 days	7 <sup>#</sup> /8 (87.5%)
3	120 mg/kg/day x 14 days	8/8 (100%)

#One animal in this group died likely due to gavage procedure, not from rabbitpox virus infection

## 2. Pharmacokinetic results

**Table 2. Plasma pharmacokinetic parameters of tecovirimat in rabbits**

Dose		C <sub>max</sub> (ng/mL)	AUC <sub>24</sub> (ng·hr/mL)	C <sub>min</sub> (ng/mL)
40 mg/kg/day	Day -7 (n=8)	614 (51%, 256-1210)	7285 (53%, 2555-14791)	119 (64%, 33-305)
	Day 4 PI (n=8)	518 (57%, 204-1180)	6771 (53%, 2348-14331)	144 (55 %, 28-325)
	Day 10 PI (n=8)	596 (49%, 319-1340)	8025 (55%, 4480-19330)	128 (77%, 25-386)
	Day 17 PI (n=7)	374 (51%, 184-737)	3167 (63%, 1158-7532)	20 (97%, 0-106)
80 mg/kg/day	Day -7 (n=8)	964 (43%, 438-1700)	11393 (47%, 5124-21480)	210 (66%, 74-579)
	Day 4 PI (n=8)	806 (47%, 396-1570)	11717 (47%, 4509-21180)	389 (53%, 105-773)
	Day 10 PI (n=8)	820 (54%, 349-1940)	11501 (62%, 3407-29503)	278 (70%, 90-793)
	Day 17 PI (n=7)	484 (52%, 170-922)	4715 (53%, 1959-8870)	51 (70%, 27-127)
120 mg/kg/day	Day -7 (n=8)	1149 (30%, 496-620)	15680 (37%, 6139-24644)	396 (57%, 181-974)
	Day 4 PI (n=8)	1080 (38%, 290-1850)	16058 (40%, 3693-26442)	494 (49%, 110-952)
	Day 10 PI (n=8)	1325 (28%, 689-1730)	22974 (35%, 11001-35231)	679 (48%, 250-1380)
	Day 17 PI (n=8)	742 (35%, 233-1110)	8965 (54%, 2824-21986)	159 (101%, 44-745)

C<sub>min</sub> is defined as the lowest concentration after the first C<sub>max</sub>.

Data are expressed as geometric mean (%CV, min-max).

### Reviewer comments

*Tecovirimat exposures were unexpectedly lower on Day 17 PI (14<sup>th</sup> dosing) as compared to previous study days (preinfection, 1<sup>st</sup> and 7<sup>th</sup> dosing). Median T<sub>max</sub> values were also shifted from 8 hours (Day -7 and Day 4) to 4 hours post dose. It is unlikely due to errors in dosing or variability. Similar trends were observed at multiple doses in the same study and other efficacy studies where sparse samples were collected (SR13-007F, SR14-008F). Interestingly, this was only observed in infected rabbits, not in healthy rabbits (Study 246-PK-001). In NHPs, no significant difference in tecovirimat PK was observed between uninfected and infected animals. The underlying mechanism and the relevance to humans are unknown at this point.*

< Sparse PK data collected in RPXV-infected rabbits >

Study	Dose	Day 4 PI C <sub>min</sub> (ng/mL)	Day 10 PI C <sub>min</sub> (ng/mL)	Day 17 PI C <sub>min</sub> (ng/mL)
SR13-007F	80 mg/kg N=6	147 (101-313) *	55 (29-166)	52 (48-280)
SR13-007F	80 mg/kg N=6	NA	180 (56-1040)	75 (44-133)
SR13-007F	80 mg/kg N=4	NA <sup>#</sup>	158 (42-392)	13 (6.6 to 35)
SR14-008F	20 mg/kg N=10	36 (0-115)	30 (12-137)	13 (0-34)
SR14-008F	40 mg/kg N=10	135 (18-345)	102 (10-444)	51 (14-232)
SR14-008F	80 mg/kg N=10	354 (119-667)	298 (105-717)	77 (13-552)
SR14-008F	120 mg/kg N=10	523 (262-939)	371 (108-887)	148 (42-385)

The first doses were administered on day 4 post infection except \* (Day 3) and # (Day 5)

Data are expressed as geometric mean (min-max)

## Conclusion

In this study, tecovirimat PK was characterized in rabbitpox virus infected and uninfected rabbits at 40, 80, and 120 mg/kg/day for 14 days. Lower tecovirimat exposures were observed on Day 17 (14<sup>th</sup> dosing) as compared to the previous study days (pre-infection, 1<sup>st</sup>, and 7<sup>th</sup> dosing) due to unknown mechanisms. The fully effective dose of tecovirimat in RPXV/rabbits was 40 mg/kg/day for 14 days.

## 4.6.2 In Vivo Studies in Healthy Volunteers

### 4.6.2.1 SIGA-246-008

**Title:** An Expanded Double-Blind, Randomized, Placebo-Controlled, Multicenter Trial to Assess the Safety, Tolerability, and Pharmacokinetics of the Anti-Orthopoxvirus Compound Tecovirimat When Administered Orally for 14 Days in Subjects (SIGA-246-008)

#### Study Design

This was a multicenter, double-blind, randomized, placebo-controlled study to assess the safety, tolerability, and pharmacokinetics of tecovirimat 600 mg BID for 14 days in healthy adult subjects. For subjects taking study drug in the fed state, all doses of study drug were taken within 30 minutes after moderate fat meals (600 calories and 25 g of fat).

- Lead in PK cohorts (n=40 planned, tecovirimat: placebo = 4:1)
  - Fed cohort (n=20): tecovirimat 600 mg BID for 14 days
  - Fasted cohort (n=20): tecovirimat 600 mg BID for 14 days
- Expanded cohort (n=382 planned, tecovirimat: placebo = 4:1)
  - All subjects received tecovirimat 600 mg BID for 14 days under fed conditions including 32 subjects in PK subset.

#### Pharmacokinetic Assessments

Plasma samples for PK assessments were collected on Day 1 (13 samples at pre-dose and up to 24 hours post-dose), Day 6 (pre-dose, 4 hours post-dose), and Day 14 (13 samples at pre-dose, and up to 24 hours post-dose). In lead-in cohorts, additional samples were collected up to 144 hours after Day 14 AM dose. Validated bioanalytical methods (LC/MS/MS) were used to analyze plasma samples for tecovirimat and its metabolites. Noncompartmental PK parameters for tecovirimat and its metabolites were calculated by using Phoenix® Version 6.4.

## Results

### 1. Study Subjects

Three hundred fifty-nine (359) subjects received at least one dose of tecovirimat. Ninety (90) subjects received at least one dose of placebo. Pharmacokinetic parameters of tecovirimat and its metabolites were determined using plasma samples collected from 63 subjects (48 subjects under fed conditions and 15 subjects under fasted conditions).

### 2. Pharmacokinetic Results

Tecovirimat PK parameters following the administration of tecovirimat 600 mg BID under fed or fasted conditions are summarized in Table 1. The PK parameters of major metabolites of tecovirimat following the administration of tecovirimat 600 mg BID under fed conditions are summarized in Table 2.

**Table 1. Tecovirimat plasma pharmacokinetic parameters under fed and fasted conditions**

	Conditions	<sup>s</sup> C <sub>max</sub> (ng/mL)	AUC <sub>24hr</sub> (ng·hr/mL)	C <sub>min</sub> (ng/mL)
Day1	Fed (n=48)	1516 (761-3290, 32%)	20879 (10627-45733, 35%)	477 (143-2020, 65%)
	Fasted (n=15)	1178 (581-2480, 38%)	13997 (6735-24086, 40%)	162 (62-553, 72%)
Day 14	Fed (n=48)	2106 (1120-4460, 33%)	28791 (15504-73568, 35%)	689 (2.5 <sup>#</sup> -1360, 38%)
	Fasted (n=15)	1581 (766-3770, 65%)	21708 (9853-58318, 48%)	355 (170-1140, 65%)

Data are expressed as geometric mean (min-max, %CV)

C<sub>min</sub> is defined as the lowest concentration after the first C<sub>max</sub>.

<sup>s</sup>: T<sub>max</sub> was observed 4-6 hours post-dose.

<sup>#</sup> One subject had unexpectedly lower C<sub>min</sub> on Day 14. After excluding this subject's value, the lowest C<sub>min</sub> value in this group was 205 ng/mL.

**Table 2. Plasma pharmacokinetic parameters for tecovirimat, M4, M5, and TFMBA in fed subjects**

	C <sub>max</sub> (ng/mL)		AUC <sub>24hr</sub> (ng·hr/mL)		T <sub>max</sub> <sup>#</sup>	T <sub>1/2</sub> <sup>#</sup>
	Day 1	Day 14	Day 1	Day 14	Day 14	Day 14
Tecovirimat	1516 (761-3290, 32%)	2106 (1120-4460, 33%)	20879 (10627-45733, 35%)	28791 (15504-73568, 35%)	5	20
M4	862 (358-1970, 35%)	1230 (534-2780, 34%)	10682 (5296-23836, 31%)	22969 (10174-50169, 33%)	10	17
M5	99 (28-272, 42%)	578 (180-2430, 61%)	904 (191-2498, 46%)	11260 (3206-54371, 62%)	15	38
TFMBA	4797 (2410-15000, 43%)	7391 (3620-15600, 39%)	62839 (35759-173822, 36%)	142506 (70773-315221, 41%)	11	21

Data are expressed as geometric mean (min-max, %CV) except T<sub>max</sub> and T<sub>1/2</sub> (mean values only).

<sup>#</sup>T<sub>max</sub> of major metabolites on Day 1 were near 24 hours.

### Reviewer comments

1. This was the pivotal PK and safety trial conducted in healthy adult volunteers to support the approval of tecovirimat for the treatment of smallpox infection under the Animal rule

2. The bioanalytical site (b) (4) was inspected by OSIS and VAI was issued at the end of inspection due to sample reinjection without a detailed rationale. OSIS concluded that the bioanalytical data are still acceptable. Two clinical sites were also inspected and it was found that the sponsor submitted an incorrect randomization schedule in the NDA. The sponsor acknowledged it and submitted the corrected randomization schedule. OSIS concluded that data are acceptable.

## Conclusion

In this study, the pharmacokinetics of tecovirimat at the proposed dosing regimen were determined. The study confirmed that the proposed dosing regimen is acceptable under the Animal rule.

### 4.6.2.2 SIGA-246-009

#### Title

“An Open Label Study to Determine the Absorption, Metabolism, and Excretion of [<sup>14</sup>C]-Tecovirimat (ST-246<sup>®</sup>) in Healthy Male Subjects Following a Single Oral Dose Administration”

#### Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted by [REDACTED]<sup>(b) (4)</sup> from June 13, 2014 to July 24, 2014.

#### Objectives

##### Primary objectives:

To determine the mass balance and routes of elimination of [<sup>14</sup>C]-tecovirimat following oral administration of a single dose of [<sup>14</sup>C]-tecovirimat;

To assess the pharmacokinetics (PK) of a single dose of tecovirimat and any metabolites in plasma, urine, and feces;

To assess the PK of total tecovirimat-associated radioactivity in whole blood, plasma, urine, and feces.

#### Trial Design and Dose

This study was an open-label, non-randomized, absorption, metabolism, and excretion study of [<sup>14</sup>C]-tecovirimat. A single dose of tecovirimat, consisting of 600 mg tecovirimat administered as three 200-mg tecovirimat oral capsules and 0.69 mg (100 µCi) of [<sup>14</sup>C]-tecovirimat administered as three 0.23 mg (~33.3 µCi) capsules filled with dissolved [<sup>14</sup>C]-tecovirimat powder, was administered to 6 healthy male subjects within 30 minutes of a meal consisting of 667 calories and 24 grams of fat.

Blood, urine, and fecal samples were collected to measure concentrations of tecovirimat and any metabolites, total radioactivity concentrations, and metabolic profiling and identification up to Day 10 (clinic discharge) or early termination.

#### Reviewer's comments:

*The recommended dosage for tecovirimat is 600 mg orally twice daily for 14 days, taken within 30 minutes after a full meal of moderate or high fat. A single oral dose at 600 mg after a moderate calorie and fat meal was used in this mass balance study, and it is reasonable for evaluation of ADME in healthy subjects.*

#### Excluded Medications and Restrictions

A standard exclusion list of use of all prescription and non-prescription medications was included in the protocol.

#### Sample Collection and Bioanalysis

##### *Sample Collection*

Plasma, urine, and fecal samples were collected up to Day 10 (clinic discharge) or early termination.

#### *Bioanalytical method*

The precision and accuracy were acceptable for standard curve and QC runs. All samples were analyzed within the long-term storage stability duration (stored at -10 to -30°C) of 44, 49, and 62 days for plasma, urine and feces samples, respectively.

#### **Results**

All 6 subjects were included in the mass balance analysis and only those metabolites containing radiolabel were analyzed (metabolite TFMBA [4-(trifluoromethyl)-benzoic acid] was not characterized due to lack of radiolabel after amide hydrolysis). Approximately 95% of the radiolabeled material was recovered in urine and feces over the 192-hour postdose period, with ~72% recovered in urine and 23% recovered in feces. In plasma, the major circulating components were M4 (amide hydrolysis metabolite), tecovirimat, and M5 (amide hydrolysis followed by deamination metabolite) at 44%, 20.5%, and 19% of total radioactivity exposure (AUC). In urine, the most abundant radioactive components were M9 (primary tecovirimat glucuronide conjugate) and M2 (M4 glucuronide conjugate) accounting for 24.4% and 30.3% of dose, respectively. In total, glucuronide conjugates accounted for approximately 95% of urine radioactivity or approximately 64% of dose. Unchanged tecovirimat was not detected in urine. In feces, tecovirimat was the predominant radioactive component and accounted for 15.9% of the dose.

There were no protocol deviations that were considered to have any implications on the conduct of the study or the integrity of the study results.

#### **Conclusions**

The [<sup>14</sup>C]-tecovirimat-derived radioactivity was readily absorbed after an oral dose and underwent extensive metabolism primarily by direct glucuronide conjugation and by hydrolysis of the amide bond. The abundant excretion of [<sup>14</sup>C]-tecovirimat as glucuronide conjugates in urine, the prevalence of cleavage products (M4 and M5) in plasma and the glucuronide conjugates of M4 in urine, and the low excretion of unchanged [<sup>14</sup>C]-tecovirimat in feces indicate that metabolism was the major route of elimination of [<sup>14</sup>C]-tecovirimat in humans.

#### **Reviewer's comments:**

*Per sponsor's in vitro assays, tecovirimat was found to be a substrate of UGT1A1, UGT1A3, and UGT1A4. However, it appears to be stable in whole blood, plasma, human hepatocytes, human liver microsomes, recombinant human CYP enzymes, and in the human intestinal brush border membrane, thus the source of M4 (amide hydrolysis metabolite) and M5 (amide hydrolysis followed by deamination metabolite) hasn't been identified per sponsor's submitted assays. The potential involvement of gut bacteria metabolism hasn't been evaluated by the sponsor.*

### 4.6.2.3 SIGA-246-012

**Study title:** A Phase 1, Open-Label, Non-Randomized Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Oral Tecovirimat in Subjects with Varying Degrees of Renal Impairment and Healthy Matched Control Subjects with Normal Renal Function

#### Study Design

This was a Phase 1, open-label, non-randomized, parallel-group study to evaluate the PK, safety, and tolerability of a single oral dose of 600 mg tecovirimat under fed conditions (600 Kcal, 25 g fat) in subjects with varying degrees of renal function.

**Table 1. Study Design**

Cohort	Renal Function Classification	Estimated CL <sub>CR</sub> or eGFR	Cohort Size
1	Normal	CL <sub>CR</sub> ≥ 90 mL/min	7
2	Mild Impairment	eGFR ≥ 60 to < 90 mL/min/1.73 m <sup>2</sup>	8
3	Moderate Impairment	eGFR ≥ 30 to < 60 mL/min/1.73 m <sup>2</sup>	8
4	Severe Impairment	eGFR < 30 mL/min/1.73 m <sup>2</sup>	7
5	ESRD	HD required (average of 3 sessions/week)	8

Abbreviation: CL<sub>CR</sub> = creatinine clearance; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HD = hemodialysis.

\*Cohort 5 received a single dose of study drug twice: post-HD (on Day 1 for Period I) and pre-HD (on Day 8 for Period II). \*Demographically matched subjects (gender, body mass index [BMI] ±20%, and age [±10 years]) to Cohort 4 were enrolled in Cohort 1. eGFR was calculated using Modification of Diet in Renal Disease (MDRD) equation.

#### Pharmacokinetic assessment and bioanalysis

Blood samples were collected for PK analysis of tecovirimat and its metabolites (14 samples up to 120 hours post-dose). PK parameters (noncompartment analysis) were obtained using Phoenix® software. Plasma concentrations were determined by validated LC/MS/MS methods.

## Results

**Table 2. Summary of the effect of varying degrees of renal impairment on the pharmacokinetics of tecovirimat and its major metabolites** [data are expressed as geometric mean ratio (90% CI) compared to PK parameters in subjects with normal renal function]

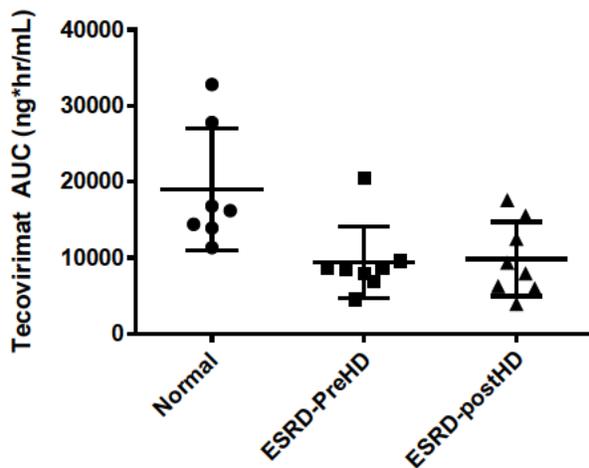
		Tecovirimat	M4	M5	TFMBA
Mild	C <sub>max</sub>	1.17 (0.87-1.56)	1.11 (0.83-1.49)	1.15 (0.85-1.56)	1.16 (0.87-1.54)
	AUC*	1.07 (0.75-1.53)	1.26 (0.89-1.77)	1.37 (0.97-1.93)	1.33 (0.92-1.93)
Moderate	C <sub>max</sub>	1.16 (0.87-1.55)	1.44 (1.07-1.94)	1.67 (1.23-2.27)	1.30 (0.98-1.72)
	AUC	1.21 (0.82-1.78)	1.73 (1.23-2.44)	1.79 (1.23-2.62)	1.49 (1.03-2.15)
Severe	C <sub>max</sub>	0.66 (0.49-0.89)	1.02 (0.75-1.39)	0.79 (0.71-1.34)	0.90 (0.67-1.21)
	AUC	1.07 (0.77-1.48)	1.63 (1.14-2.33)	1.35 (0.95-1.92)	1.56 (1.06-2.28)
ESRD#	C <sub>max</sub>	0.66 (0.48-0.89)	1.27 (0.93-1.73)	1.21 (0.87-1.68)	1.13 (0.84-1.53)
	AUC	0.52 (0.36-0.75)	2.30 (1.63-3.24)	1.45 (0.99-2.10)	2.60 (1.75-3.85)

\*AUC<sub>inf</sub> values were primarily used for tecovirimat analysis except in the case of severe renal impairment. For metabolites (for all stages of renal impairment) and tecovirimat in subjects with severe renal impairment, AUC<sub>t</sub> (120 hours) were used for the analyses. In those subjects, AUC<sub>inf</sub> could not be calculated in many subjects due to long apparent half lives.

# Based on pre-HD PK results

The results are from the sponsor's report based on ANCOVA analysis. Reviewer's independent analyses obtained similar results.

**Fig 1. Tecovirimat AUC in subjects with ESRD or normal renal function**



**Table 3. Effects of dialysis – expressed as geometric mean ratio (90% CI) of PK parameters of post-dialysis (test) as compared to pre-dialysis (reference)**

	Tecovirimat	M4	M5	TFMBA
Cmax	1.13 (0.75-1.70)	0.75 (0.64-0.89)	1.21 (0.95-1.52)	1.26 (1.06-1.51)
AUC*	1.02 (0.78-1.33)	0.68 (0.27-1.70)	0.93 (0.77-1.11)	1.14 (0.97-1.34)

\*AUCinf for tecovirimat, AUC120hour for metabolites

*Reviewer’s assessments*

*Overall, the study design and methods for PK assessment, including bioanalysis, are reasonable.*

*Unexpectedly lower exposures of tecovirimat were observed in subjects with ESRD. The effect was not due to dialysis. It is postulated that the altered drug absorption in subjects is due to an underlying disease (e.g., gastroparesis in diabetes patients) or unexpected drug interactions with one or more concomitant medications in these subjects.*

*With respect to concomitant medications, most subjects were using various forms of phosphate binders that can potentially reduce the absorption of tecovirimat. Both tecovirimat and phosphate binders are to be given with food. In fact, there was only one subject who didn’t use any phosphate binders in the ESRD cohort and this subject’s AUC value was the highest in the ESRD cohort (and comparable to those observed in subjects with normal renal function).*

*While lower exposures were observed in subjects with ESRD, the review team has concluded that a dose increase is not recommended. There is insufficient information as to whether lower exposures are due to impaired renal function by an unknown mechanism or concomitant medications/underlying disease conditions. A 50 % lower exposure of tecovirimat is still comparable to those observed in NHPs at 10 mg/kg/day where maximum efficacy (survival) was observed.*

*The review team is considering a post marketing commitment to explore the potential mechanism.*

**Conclusion**

Approximately 50% lower tecovirimat exposures in subjects with ESRD compared to subjects with normal renal function. The underlying mechanism is unknown at this time.

**4.6.2.4 SIGA-246-013**

**SIGA-246-013: Hepatic Impairment Study for Tecovirimat**

**Title**

“A Phase 1, Open-Label, Non-Randomized Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Oral Tecovirimat in Subjects with Varying Degrees of Hepatic Impairment and Healthy Matched Control Subjects with Normal Hepatic Function”

**Information Regarding the Clinical Trial Site and Duration of the Trial**

The trial was conducted by [REDACTED] (b) (4) from June 22, 2016 to January 22, 2017.

## Objectives

### Primary objective:

To evaluate the PK profiles of tecovirimat following oral administration in subjects with varying degrees of hepatic impairment (HI) compared to healthy matched control subjects with normal hepatic function

## Trial Design and Dose

This was a Phase 1, open-label, non-randomized, parallel-group study to evaluate the PK, safety, and tolerability of a single oral dose of 600 mg tecovirimat in subjects with varying degrees of hepatic function. Subjects were enrolled into 4 cohorts per hepatic function status (normal, mild/moderate/severe HI [child-pugh classification], n=8 per cohort). Subjects in the control cohort with normal hepatic function were matched with a subject in the moderate HI cohort based on gender, body mass index ([BMI]  $\pm 20\%$ ) and age ( $\pm 10$  years).

Tecovirimat 600 mg (three 200 mg capsules) was administered orally as a single dose within 30 minutes after a meal containing ~ 600 kcal and 25 g of fat. Blood samples were collected for PK analysis of tecovirimat and tecovirimat metabolites (M4, M5, and 4-(trifluoromethyl)-benzoic acid [TFMBA]) in subjects with varying degrees of HI and healthy matched control subjects.

### Reviewer's comments:

*The recommended dosage for tecovirimat is 600 mg orally twice daily for 14 days, taken within 30 minutes after a full meal of moderate or high fat. A single oral dose at 600 mg after a moderate calorie and fat meal is reasonable for this hepatic impairment study.*

## Sample Collection and Bioanalysis

### *Sample Collection*

Blood samples for PK analysis were collected at 14 planned time points up to 120 h post-dose.

### *Bioanalytical method*

The precision and accuracy were acceptable for standard curve and QC runs. All samples were analyzed within the long-term storage stability duration of 416 days for tecovirimat, M4, M5, and TFMBA.

## Results

All 32 subjects were included in the PK analysis. There was no significant change of tecovirimat exposure in hepatic impairment groups (Table 1). There was a modest impact of moderate to severe hepatic impairment on the exposure of M4, M5 and TFMBA, with the greatest increase observed in the severe group (Table 2, Table 3, and Table 4). In severe hepatic impairment group, the increase of M4, M5, and TFMBA exposures, by AUC, are up to 2, 1.6, and 1.6-fold, respectively. The increase in exposures of the three metabolites should not have a clinical effect since none of them are pharmacologically active. In addition, even with the 2-fold increase, the M4 metabolite exposure is still within the safety margin, per the sponsor.

There were no protocol deviations that were considered to have any implications on the conduct of the study or the integrity of the study results.

**Table 1: Summary of the PK Parameters of Tecovirimat and Statistical Analysis Following Single Oral Doses of 600 mg in Subjects with Varying Degrees of Hepatic function**

Cohort	PK Parameter								
	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (hr)	AUC <sub>0-24</sub> (hr*ng/mL)	AUC <sub>0-last</sub> (hr*ng/mL)	AUC <sub>0-∞</sub> (hr*ng/mL)	t <sub>1/2</sub> (hr)	λ <sub>z</sub> (1/h)	Cl/F (L/hr)	V <sub>z</sub> /F (L)
Cohort 1	1070 (20.5) (n = 8)	4.00 (4.00, 6.03) (n = 8)	9280 (16.1) (n = 8)	16200 (22.1) (n = 8)	16300 (19.6) (n = 7)	24.4 (54.1) (n = 7)	0.0284 (54.1) (n = 7)	36.8 (19.6) (n = 7)	1290 (37.1) (n = 7)
Cohort 2	862 (50.7) (n = 8)	4.00 (1.00, 6.00) (n = 8)	7590 (52.0) (n = 8)	10900 (63.2) (n = 8)	11300 (62.3) (n = 8)	14.8 (27.2) (n = 8)	0.0469 (27.2) (n = 8)	53.3 (62.3) (n = 8)	1140 (57.4) (n = 8)
Cohort 3	1220 (23.6) (n = 8)	4.00 (4.00, 18.00) (n = 8)	11400 (30.0) (n = 8)	17700 (46.4) (n = 8)	18200 (47.8) (n = 8)	14.5 (45.7) (n = 8)	0.0479 (45.7) (n = 8)	33 (47.8) (n = 8)	689 (54.6) (n = 8)
Cohort 4	1150 (17.7) (n = 8)	4.00 (2.00, 8.00) (n = 8)	13300 (25.8) (n = 8)	18300 (39.9) (n = 8)	18600 (39.2) (n = 8)	10.1 (16.8) (n = 8)	0.0688 (16.8) (n = 8)	32.3 (39.2) (n = 8)	469 (37.4) (n = 8)

Parameter	Cohort	Geometric	Ratio of	
		Mean	Geometric Mean	90% CI for Ratio
AUC <sub>0-24</sub> (hr*ng/mL)	Cohort 2 (Test) Cohort 1 (Reference)	7590 9280	81.7	62.13 - 107.53
AUC <sub>0-last</sub> (hr*ng/mL)	Cohort 2 (Test) Cohort 1 (Reference)	12400 21000	59.0	41.67 - 83.58
AUC <sub>0-∞</sub> (hr*ng/mL)	Cohort 2 (Test) Cohort 1 (Reference)	12800 21100	60.8	42.34 - 87.26
C <sub>max</sub> (ng/mL)	Cohort 2 (Test) Cohort 1 (Reference)	862 1070	80.8	62.73 - 104.08
AUC <sub>0-24</sub> (hr*ng/mL)	Cohort 3 (Test) Cohort 1 (Reference)	11400 9280	123	93.30 - 161.47
AUC <sub>0-last</sub> (hr*ng/mL)	Cohort 3 (Test) Cohort 1 (Reference)	22800 21000	109	77.73 - 152.15
AUC <sub>0-∞</sub> (hr*ng/mL)	Cohort 3 (Test) Cohort 1 (Reference)	23500 21100	112	78.67 - 158.32
C <sub>max</sub> (ng/mL)	Cohort 3 (Test) Cohort 1 (Reference)	1220 1070	114	88.50 - 146.84
AUC <sub>0-24</sub> (hr*ng/mL)	Cohort 4 (Test) Cohort 1 (Reference)	13300 9280	143	108.97 - 188.60
AUC <sub>0-last</sub> (hr*ng/mL)	Cohort 4 (Test) Cohort 1 (Reference)	19500 21000	93.1	64.79 - 133.83
AUC <sub>0-∞</sub> (hr*ng/mL)	Cohort 4 (Test) Cohort 1 (Reference)	19800 21100	94.2	64.65 - 137.11
C <sub>max</sub> (ng/mL)	Cohort 4 (Test) Cohort 1 (Reference)	1150 1070	108	83.83 - 139.11

Cohort 1/2/3/4: normal/mild/moderate/severe hepatic impairment

Geometric Mean (%CV) are shown except for t<sub>max</sub> where median and range (minimum, maximum) are shown.

**Table 4: Summary of the PK Parameters of TFMBA Following Single Oral Doses of 600 mg in Subjects with Varying Degrees of Hepatic function**

Cohort	PK Parameter						
	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (hr)	AUC <sub>0-24</sub> (hr*ng/mL)	AUC <sub>0-last</sub> (hr*ng/mL)	AUC <sub>0-∞</sub> (hr*ng/mL)	t <sub>1/2</sub> (hr)	λ <sub>z</sub> (1/hr)
Cohort 1	2230 (18.6) (n = 8)	7.00 (4.00, 8.00) (n = 8)	33700 (19.1) (n = 8)	64600 (17.3) (n = 8)	69400 (17.2) (n = 8)	26.2 (54.0) (n = 8)	0.0265 (54.0) (n = 8)
Cohort 2	2590 (42.8) (n = 8)	7.00 (4.00, 12.03) (n = 8)	40600 (47.1) (n = 8)	71000 (64.0) (n = 8)	72100 (65.5) (n = 8)	13.2 (35.9) (n = 8)	0.0524 (35.9) (n = 8)
Cohort 3	3070 (31.6) (n = 8)	7.00 (4.00, 24.00) (n = 8)	45700 (21.1) (n = 8)	90200 (35.3) (n = 8)	93000 (36.0) (n = 8)	16.6 (62.3) (n = 8)	0.0417 (62.3) (n = 8)
Cohort 4	3230 (34.4) (n = 8)	10.00 (6.00, 24.00) (n = 8)	54100 (31.6) (n = 8)	96400 (47.3) (n = 8)	96800 (47.0) (n = 8)	10.7 (16.0) (n = 8)	0.0645 (16.0) (n = 8)

Cohort 1/2/3/4: normal/mild/moderate/severe hepatic impairment

Geometric Mean (%CV) are shown except for t<sub>max</sub> where median and range (minimum, maximum) are shown.

## Conclusions

The results indicate that hepatic impairment has a small impact on the exposure of tecovirimat, while has a modest effect on the exposure of metabolite M4, M5, and TFMBA with up to 2-fold AUC increase. However, the increase in exposures of the three metabolites should not have a clinically significant effect on safety.

### 4.6.2.5 SIGA-246-015: DDI Study for the Effect of Tecovirimat on CYP2C8, CYP2C9, CYP2C19, CYP2B6 and CYP3A4

#### Title

“A Phase 1, Open-Label, Drug-Drug Interaction Study to Evaluate the Effect of Repeated Doses of Tecovirimat on the Single-Dose Pharmacokinetics (PK) of Flurbiprofen, Omeprazole, Midazolam, Bupropion, and Repaglinide in Healthy Subjects”

#### Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted by (b) (4) from October 19, 2016 to December 19, 2016.

#### Objectives

##### Primary objective:

To evaluate the effect of repeated doses of tecovirimat on the single-dose PK of probe substrates flurbiprofen (CYP2C9 substrate), omeprazole (CYP2C19 substrate), midazolam (CYP3A4 substrate), repaglinide (CYP2C8 substrate), and bupropion (CYP2B6 substrate)

#### Trial Design and Dose

This was a Phase 1, open-label, parallel, 3-arm, single-center, fixed-sequence, drug-drug interaction study in healthy subjects to evaluate the effect of repeated doses of tecovirimat on

the single-dose PK of probe substrates flurbiprofen, omeprazole, midazolam, repaglinide, and bupropion.

A total of 78 healthy subjects were randomly assigned to 1 of 3 parallel arms as follows:

Arm 1: flurbiprofen 50 mg tablet, omeprazole 20 mg capsule, and midazolam 2 mg oral syrup given alone and in combination with tecovirimat 600 mg BID.

Arm 2: repaglinide 2 mg tablet given alone and in combination with tecovirimat 600 mg BID

Arm 3: bupropion 150 mg tablet given alone and in combination with tecovirimat 600 mg BID

All probe substrate drugs were administered on Day 1, followed by a washout period (Days 2 to 7), then co-administered with tecovirimat on Day 22. Tecovirimat was administered for 14 days (Day 8 to 22) to provide steady-state level of CYP induction. All drugs were administered with a meal consisting of ~ 600 calories and 25 g fat.

**Reviewer's comments:**

*Tecovirimat: 600 mg BID with a moderate calorie and fat meal is the recommended dosage in the labeling.*

*Probe substrate (flurbiprofen, omeprazole, midazolam, repaglinide, and bupropion): the doses selected for this study are close or up to 80% lower than the USPI recommended dose and are reasonable for the DDI study. The washout of 7 days is over 5 half-lives for all probe substrates.*

**Sample Collection and Bioanalysis**

*Sample Collection*

Blood samples were collected up to 48 h for Arm 1 and 2 (15 planned time points), and up to 96 h for Arm 3 (17 planned time points) post-dose on Day 1 and Day 22 for PK analysis of probe substrates. In each arm, blood samples for PK analysis of tecovirimat were collected prior to morning tecovirimat dosing on Days 20, 21, and 22.

*Bioanalytical method*

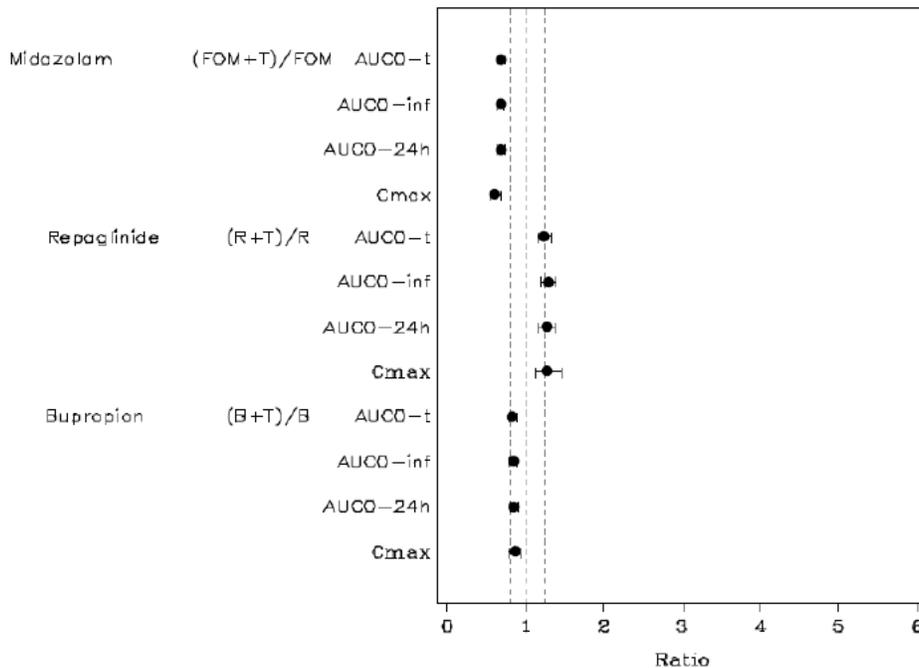
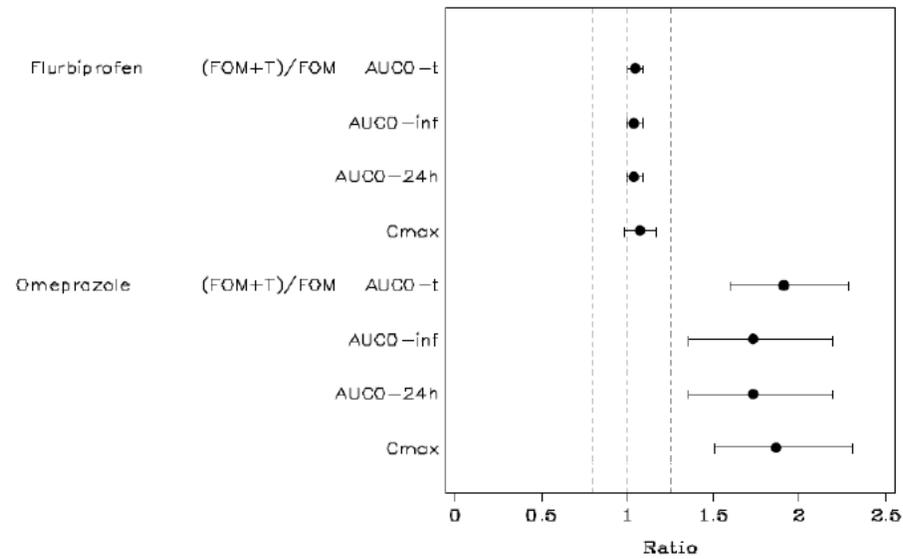
The precision and accuracy are acceptable for standard curve and QC runs. All samples were analyzed within the long-term storage stability duration of 221 days.

**Results**

All 78 subjects were included in the PK analysis. Visual inspection of the mean trough plots of tecovirimat indicated that steady state appeared to have been reached by Day 22, following BID dosing of 600 mg tecovirimat for 14 days (Day 8 to 22). The DDI results are summarized in Figure 1. With co-administration of tecovirimat, there were no meaningful effects on the exposure of flurbiprofen (CYP2C9 substrate) and bupropion (CYP2B6 substrate). The exposure of repaglinide (CYP2C8 substrate) was 23% to 29% higher, the exposure of omeprazole (CYP2C19 substrate) was 73% to 91% higher, and the exposure of midazolam (CYP3A4) was 31% to 39% lower, when co-administered with tecovirimat compared to probe substrate alone.

There were no protocol deviations that were considered to have any implications on the conduct of the study or the integrity of the study results.

Figure 1: Forest Plot for All Analytes/Parameters Comparisons



## Conclusions

Tecovirimat did not affect CYP2C9 and CYP2B6. Tecovirimat was a weak inhibitor of CYP2C19 and CYP2C8, and a weak inducer of CYP3A4.

### Reviewer's comments:

*Tecovirimat increased the exposure of repaglinide minimally (<30%), and the reason is unknown for the higher rate of hypoglycemia (33%) from the combination of repaglinide and tecovirimat, compared to none from repaglinide alone, in the healthy subjects.*

*Repaglinide in the DDI study was administered at a dose of 2 mg, instead of 0.5 mg recommended for subjects with HbA1c < 8%. The half-life of repaglinide is short at 1h, and the dose may have been chosen to ensure the PK profile is captured accurately.*

#### **4.6.2.6 SIGA-246-018**

**Study Title:** A Phase 1, Randomized, Open-Label, Single Oral Dose, Partial Crossover Pharmacokinetic Study of Escalating Doses of Tecovirimat Mixed in Food or Liquid

##### **Objective**

To determine the pharmacokinetics of tecovirimat after administration of various doses as capsule contents that had been mixed with a food or liquid in healthy subjects in the fed state

To compare the pharmacokinetics of tecovirimat 600 mg, after administration as capsule contents mixed with a food or liquid with the pharmacokinetics of tecovirimat 600 mg, after administration as intact capsules in healthy subjects in the fed state.

##### **Study Design**

This was a Phase 1, randomized, open-label, partial crossover study to evaluate the pharmacokinetics and safety of tecovirimat after administration of single doses (100, 200, and 600 mg) as capsule or mixed with vehicles. A total of 48 healthy adult volunteers were randomly assigned to 1 of 4 cohorts (n=12 per cohort). Tecovirimat was administered under fed conditions (600 calories and 25 g of fat).

Cohort 1: A half portion of 200 mg tecovirimat capsule contents mixed in 2% milk

Cohort 2: 200 mg tecovirimat capsule content mixed in applesauce

Cohort 3:

- Period 1: 600 mg tecovirimat capsule content mixed in 2% milk
- Period 2: 600 mg tecovirimat intact capsules

Cohort 4:

- Period 1: 600 mg tecovirimat capsule contents mixed in applesauce
- Period 2: 600 mg tecovirimat intact capsule

##### **Pharmacokinetic assessments**

Plasma samples for PK analysis were collected pre-dose and up to 48 hours (11 samples).

Tecovirimat concentrations were determined using a validated LC/MS/MS methods.

Noncompartmental PK parameters were calculated using Phoenix ® Version 6.4.

##### **Pharmacokinetic Results**

Tecovirimat pharmacokinetic parameters following the administration of tecovirimat 100 mg, 200 mg, and 600 mg in various vehicles are summarized in Table 1.

**Table 1. Summary of Plasma Pharmacokinetic Parameters of Tecovirimat by Cohort and Treatment**

	Cohort 1	Cohort 2	Cohort 3 (cross-over)		Cohort 4 (cross-over)	
Treatment	100 mg 2% milk (n=12)	200 mg Applesauce (n=12)	600 mg 2% milk (n=12)	600 mg Capsules (n=11)	600 mg Applesauce (n=12)	600 mg Capsules (n=12)
$C_{max}$ (ng/mL)	472 (317- 796, 27%)	965 (671- 1330, 21%)	2018 (1180- 3930, 36%)	1757 (1230- 3000, 27%)	1654 (997- 2780, 34%)	1622 (994- 2570, 32%)
$AUC_{inf}$ (ng·hr/mL)	3644 (1596- 7832, 55%)	10014 (5479- 14442, 36%)	23586 (12798- 47547, 46%)	23062 (8921 – 52233, 48%)	21419 (10638 - 43696, 42%)	18605 (9889- 27695, 33%)

Data are expressed as geometric mean (min-max, %CV)

No significant differences in  $T_{max}$  (median 4 hours) or half-life (~ 21 hours) were observed across treatment groups. In many subjects receiving lower doses,  $AUC_{inf}$  could not be calculated as concentrations were below the quantitation limit before the last sampling time point (48 hours post dose). In these subjects,  $AUC_{48hrs}$  was used in lieu of  $AUC_{inf}$ . In some subjects receiving higher doses,  $AUC_{inf}$  could not be calculated due to an insufficient log-linear elimination phase to determine the elimination constant. In these subjects,  $AUC_{48hrs}$  used in lieu of  $AUC_{inf}$ . Sensitivity analysis was also conducted to confirm that such substitutions did not change the overall conclusion of the study.

#### *Reviewer comments*

*Tecovirimat exposures are increased in a slightly less than proportional manner between 200 mg and 600 mg; a dose increase from a single dose of 200 mg to a single dose 600 mg (i.e., 3-fold increase) resulted in an approximately 2-fold increase in  $AUC_{inf}$  and  $C_{max}$ .*

#### **Conclusion**

- Tecovirimat exposures are increased in a slightly less than proportional manner between 200 mg and 600 mg.
- Following the administration of 600 mg tecovirimat contents mixed with applesauce or 2% milk under fed conditions, tecovirimat exposures were comparable to those following the administration of 600 mg capsules under fed conditions.

### 4.6.3 In Vitro Studies

Unless otherwise noted, concentrations evaluated in in vitro studies are clinically relevant and all positive controls confirmed the validity of assays.

#### 4.6.3.1 Characterization of tecovirimat metabolism, stability, and plasma protein binding

##### 1. CYP0781\_R5

<b>Title</b>	Study to Investigate Cytochrome P450 Reaction Phenotyping of the Test Compound, Tecovirimat Monohydrate (CYP0781_R5)
<b>Test system</b>	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 Bactosomes™ (cDNA expressed human CYP450 enzyme with co-expressed human NADPH P450 reductase)
<b>Description</b>	The metabolic stability of tecovirimat in recombinant CYP isoforms was determined using recombinant CYP isoforms. Tecovirimat was incubated up to 45 min in each CYP isoform containing reaction mixture.
<b>Substrates</b>	Tecovirimat 1 μM and 10 μM
<b>Positive control</b>	Ethoxycoumarine as a CYP1A2 substrate Efavirenz as a CYP2B6 substrate Amodiaquine as a CYP2C8 substrate Diclofenac as a CYP2C9 substrate Diazepam as a CYP2C19 substrate Dextromethorphan as a CYP2D6 substrate Testosterone as a CYP3A4 substrate
<b>Results</b>	Tecovirimat was stable (> 90% remained as tecovirimat in the reaction mixture) up to 45 min for all CYP isoforms tested.
<b>Conclusion</b>	Tecovirimat is not metabolized by CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.

##### 2. CYP0781\_R6

<b>Title</b>	Study to Investigate the Hepatocyte Stability of the Test Compound, Tecovirimat Monohydrate, and to Monitor the Formation of Known Metabolites (CYP0781_R6)
<b>Test system</b>	Hepatocyte suspension (pooled hepatocytes from 10 donors)
<b>Description</b>	The stability of tecovirimat and the formation of the major metabolites were determined in human hepatocyte suspensions up to 120 min.
<b>Substrates</b>	Tecovirimat 1 μM and 10 μM
<b>Positive control</b>	Verapamil 3 μM and umbelliferone 3 μM: drugs known to be extensively metabolized by hepatocytes
<b>Results</b>	The remaining tecovirimat in hepatocyte suspensions was 80% at 1 μM and 100% at 10 μM, respectively, following 120 min incubation. The intrinsic clearance of tecovirimat at 1 μM was low (3.5 μL/min/million cells). M4 and TFMBA were detected in the reaction mixture, but the amount was not quantified.
<b>Conclusion</b>	Tecovirimat is not extensively metabolized by hepatocytes.

### 3. 15SIGAP5

<b>Title</b>	Determination of the Metabolic Stability of Test Article in Brush Border Membrane (BBM) of Human Intestine (15SIGAP5)
<b>Test system</b>	Human brush border membrane (hBBM) preparation isolated from one donor
<b>Description</b>	The stability of tecovirimat 5 $\mu\text{M}$ in hBBM was determined (up to 60 min). The formation of M4 and M5 was also monitored.
<b>Substrates</b>	tecovirimat 5 $\mu\text{M}$
<b>Positive control</b>	None
<b>Results</b>	Following incubation in hBBM for 60 min, 80% of tecovirimat remained in the reaction mixture. The estimated half-life was 258 min. M4 and M5 were not detected in the reaction mixture. However, due to the lack of positive controls to confirm the enzymatic activity in the prepared hBBM, a definitive conclusion cannot be made in this study.
<b>Conclusion</b>	Tecovirimat was stable in hBBM but a definitive conclusion cannot be made due to the lack of positive controls.

### 4. 15SIGAP12R1

<b>Title</b>	Tecovirimat Stability in Human Whole Blood (15SIGAP12R1)
<b>Test system</b>	Human whole blood from pooled donors
<b>Description</b>	Tecovirimat stability (0.3 $\mu\text{M}$ ) was determined in human whole blood. The potential metabolism of tecovirimat by acetylcholinesterase in blood was also determined by adding an acetylcholinesterase inhibitor, BW284c51.
<b>Positive control</b>	Acetylcholinesterase activity assay kit
<b>Results and conclusion</b>	Tecovirimat was stable in human whole blood up to 120 min. Tecovirimat was not metabolized by acetylcholinesterase in blood.

### 5. 10010334

<b>Title</b>	ADME-Tox study of ST-246 (UGT mediated metabolism) 10010334
<b>Test system</b>	Recombinant UGT enzymes
<b>Description</b>	The metabolic stability of tecovirimat in recombinant UGT isoforms was determined using recombinant UGT enzymes (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15). Tecovirimat was incubated up to 2 hours in each UGT isoform containing reaction mixture.
<b>Substrates</b>	Tecovirimat 1 $\mu\text{M}$
<b>Positive control</b>	HFC 0.1 $\mu\text{M}$ as a substrate of UGT1A1, UGT1A3, UGT1A6, UGT1A9, UGT2B7, and UGT1B15 TFP 0.1 $\mu\text{M}$ as a substrate of UGT1A4
<b>Results</b>	Following 120 min incubation, 65% and 59% of tecovirimat remained intact in UGT1A1 and UGT1A4 reaction mixtures, respectively. Tecovirimat was stable (% compound remaining > 80%) in UGT1A3, UGT1A6, UGT1A9, UGT2B7, and UGT2B15 reaction mixtures.
<b>Conclusion</b>	Tecovirimat is a substrate of UGT1A1 and UGT1A4.

## 6. 246-AD-001

<b>Title</b>	Plasma Protein Binding in Mouse (BALB/c), Rat (Sprague-Dawley), Dog (Beagle), Monkey (Cynomolgus), and Human Plasma for [ <sup>14</sup> C]-ST-246 (246-AD-001)																																																											
<b>Test system</b>	Mouse, rat, dog, monkey, and human plasma and equilibrium dialysis (molecular weight cut of 12000-14000 Da)																																																											
<b>Description</b>	Equilibrium dialysis was conducted for 24 hours with tecovirimat up to 50 μM.																																																											
<b>Results</b>	<table border="1"> <thead> <tr> <th rowspan="2">[<sup>14</sup>C]-ST-246 Concentration (μM)</th> <th colspan="5">% Plasma Protein Binding</th> </tr> <tr> <th>Mouse</th> <th>Rat</th> <th>Dog</th> <th>Monkey</th> <th>Human</th> </tr> </thead> <tbody> <tr> <td>0.03</td> <td>BLQ</td> <td>BLQ</td> <td>BLQ</td> <td>BLQ</td> <td>82.2</td> </tr> <tr> <td>0.1</td> <td>88.3</td> <td>BLQ</td> <td>92.2</td> <td>87.8</td> <td>79.7</td> </tr> <tr> <td>0.3</td> <td>87.3</td> <td>96.0</td> <td>91.4</td> <td>87.6</td> <td>80.1</td> </tr> <tr> <td>1</td> <td>88.0</td> <td>96.1</td> <td>90.8</td> <td>87.9</td> <td>80.5</td> </tr> <tr> <td>3</td> <td>87.3</td> <td>96.3</td> <td>90.9</td> <td>87.6</td> <td>80.3</td> </tr> <tr> <td>10</td> <td>87.1</td> <td>95.8</td> <td>90.4*</td> <td>87.1</td> <td>79.1</td> </tr> <tr> <td>30</td> <td>88.1</td> <td>95.5</td> <td>89.8*</td> <td>87.1</td> <td>77.3</td> </tr> <tr> <td>50</td> <td>87.9</td> <td>95.1</td> <td>88.9</td> <td>87.5</td> <td>78.5</td> </tr> </tbody> </table> <p>BLQ = PBS concentrations below the Limit of Quantification  Limit of Quantification = 43.2 DPM  All results are the mean of duplicate determinations except for:  * single determination due to human error (pipetting error)</p>	[ <sup>14</sup> C]-ST-246 Concentration (μM)	% Plasma Protein Binding					Mouse	Rat	Dog	Monkey	Human	0.03	BLQ	BLQ	BLQ	BLQ	82.2	0.1	88.3	BLQ	92.2	87.8	79.7	0.3	87.3	96.0	91.4	87.6	80.1	1	88.0	96.1	90.8	87.9	80.5	3	87.3	96.3	90.9	87.6	80.3	10	87.1	95.8	90.4*	87.1	79.1	30	88.1	95.5	89.8*	87.1	77.3	50	87.9	95.1	88.9	87.5	78.5
[ <sup>14</sup> C]-ST-246 Concentration (μM)	% Plasma Protein Binding																																																											
	Mouse	Rat	Dog	Monkey	Human																																																							
0.03	BLQ	BLQ	BLQ	BLQ	82.2																																																							
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0.3	87.3	96.0	91.4	87.6	80.1																																																							
1	88.0	96.1	90.8	87.9	80.5																																																							
3	87.3	96.3	90.9	87.6	80.3																																																							
10	87.1	95.8	90.4*	87.1	79.1																																																							
30	88.1	95.5	89.8*	87.1	77.3																																																							
50	87.9	95.1	88.9	87.5	78.5																																																							
<b>Conclusion</b>	Tecovirimat plasma protein binding is 87%, 96%, 90%, 88%, and 80%, in mice, rats, dogs, monkeys, and humans, respectively.																																																											

## 7. 17SIGAP1

<b>Title</b>	Binding to Rabbit Plasma Proteins (17SIGAP1)
<b>Test system</b>	Rabbit plasma and equilibrium dialysis (molecular weight cut of 8000 Da)
<b>Positive control</b>	Warfarin as a high plasma protein binding drug
<b>Description</b>	Equilibrium dialysis was conducted for 4 hours with tecovirimat at 5 μM.
<b>Results and Conclusion</b>	Tecovirimat protein binding is 88.7% in rabbit plasma.

## 8. 15SIGAP2

<b>Title</b>	Binding of Metabolites to Human, Mouse, and Monkey Plasma Proteins (15SIGAP2)
<b>Test system</b>	Human plasma, CD-1 mouse plasma, and Cynomolgus monkey plasma and equilibrium dialysis (molecular weight cut of 8000 Da)
<b>Positive control</b>	Warfarin as a high plasma protein binding drug
<b>Description</b>	Equilibrium dialysis was conducted for 4 hours with M4, M5, and TFMBA at 5 μM.

<b>Results and Conclusion</b>	<b>Test Article</b>	<b>Species</b>	<b>% Bound</b>
	SG-1 hydrazide (M4)	Human	20.7
		Mouse	4.6
		Monkey	15.8
	SG-1 isoindole (M5)	Human	33.0
		Mouse	16.6
		Monkey	17.6
	TFMBA	Human	98.6
		Mouse	50.0
		Monkey	97.1

#### 4.6.3.2 Potential for CYP mediated induction and inhibition

##### 1. 15SIGAP4

<b>Title</b>	Time-Dependent Inhibition of Cytochrome P450 Enzymes in Human Liver Microsomes (15SIGAP4)
<b>Test system</b>	Human Liver Microsome
<b>Description</b>	Time-dependent CYP inhibition by tecovirimat was evaluated by a 30 min preincubation of tecovirimat followed by enzyme activity assays using <i>in vitro</i> index substrates. The potential for time-dependent inhibition was determined based on IC <sub>50</sub> shift.
<b>Substrates</b>	Phenacetin (63 µM) for CYP1A2 Coumarin (1 µM) for CYP2A6 Bupropion (75 µM) for CYP2B6 Amodiaquine (2 µM) for CYP2C8 Diclofenac (10 µM) for CYP2C9 S-mephenytoin (40 µM) for CYP2C19 Bufuralol (7 µM) for CYP2D6 Chlorzoxazone (27 µM) for CYP2E1 Testosterone (55 µM) for CYP3A Midazolam (2.5 µM) for CYP3A
<b>Inhibitor</b>	Tecovirimat up to 100 µM
<b>Positive control</b>	Troleandomycin (known CYP3A4 time-dependent inhibitor) up to 100 µM
<b>Result</b>	IC <sub>50</sub> values were all above 100 µM
<b>Conclusion</b>	Tecovirimat is not a time-dependent inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A.

##### 2. 15SIGAP7

<b>Title</b>	Evaluation of the Potential of Three Metabolites (M4, M5, and TFMBA) of Tecovirimat for Time-dependent Inhibition of Cytochrome P450 Enzymes in Human Liver Microsomes (15SIGAP7)
<b>Test system</b>	Human Liver Microsome
<b>Description</b>	Time-dependent CYP inhibition by M4, M5, and TFMBA was evaluated by a 30 min preincubation of tecovirimat followed by enzyme activity assays using <i>in vitro</i>

	index substrates. The potential for time-dependent inhibition was determined based on IC <sub>50</sub> shift.
<b>Substrates</b>	Phenacetin (63 µM) for CYP1A2 Bupropion (75 µM) for CYP2B6 Amodiaquine (2 µM) for CYP2C8 Diclofenac (10 µM) for CYP2C9 S-mephenytoin (40 µM) for CYP2C19 Bufuralol (7 µM) for CYP2D6 Testosterone (55 µM) for CYP3A Midazolam (2.5 µM) for CYP3A
<b>Inhibitors</b>	Tecovirimat up to 100 µM
<b>Positive control</b>	Known time-dependent inhibitors of CYP isoforms Furafylline (up to 30 µM) for CYP1A2 Thio-TEPA (up to 30 µM) for CYP2B6 Gemfibrozil glucuronide (up to 40 µM) for CYP2C8 Tienilic acid (up to 30 µM) for CYP2C9 Ticlopidine (up to 30 µM) for CYP2C19 Paroxetine (up to 30 µM) for CYP2D6 Troleandomycin (up to 100 µM) for CYP3A
<b>Result</b>	Slight time dependent inhibition was observed at 100 µM as follows. IC <sub>50</sub> values were > 100 µM for other CYPs  M4: CYP2C19, CYP3A M5: CYP3A TFMBA: CYP3A  IC <sub>50</sub> shifts could not be calculated as IC <sub>50</sub> values were predicted to be above the highest concentration evaluated in the study.
<b>Conclusion</b>	M4, M5, and TFMBA are not time-dependent inhibitors for CYP1A2, CYP2B6, CYP2C9, CYP2D6, or CYP3A. Weak time-dependent inhibition was observed for CYP3A4 (M4, M5, and TFMBA), CYP2C19 (M4) at the concentrations evaluated in this study (up to 100 µM).

### 3. 246-AD-003

<b>Title</b>	Evaluation of inhibition of the catalytic activities of cytochromes P450 in human liver microsomes by the test substance, ST246 (246-AD-003).
<b>Test system</b>	Human liver microsomes
<b>Description</b>	The potential for CYP inhibition by tecovirimat was determined by enzyme activity assays using <i>in vitro</i> index substrates.
<b>Substrate</b>	Phenacetin (50 µM) for CYP1A2 Bupropion (80 µM) for CYP2B6 Paclitaxel (10 µM) for CYP2C8 Diclofenac (6 µM) for CYP2C9 S-mephenytoin (50 µM) for CYP2C19 Bufuralol (10 µM) for CYP2D6 Para-nitrophenol (100 µM) for CYP2E1 Testosterone (120 µM) for CYP3A Midazolam (4 µM) for CYP3A

<b>Inhibitor</b>	Tecovirimat up to 300 $\mu\text{M}$
<b>Positive control</b>	Alpha-Naphthoflavone (1 $\mu\text{M}$ ) for CYP1A2 Thio-TEPA (20 $\mu\text{M}$ ) for CYP2B6 Montelukast (2 $\mu\text{M}$ ) for CYP2C8 Sulfaphenazole (5 $\mu\text{M}$ ) for CYP2C9 (+)-N-3-benzylrivanol (5 $\mu\text{M}$ ) for CYP2C19 Quinidine (1 $\mu\text{M}$ ) for CYP2D6 4-Methylpyrazole (50 $\mu\text{M}$ ) for CYP2E1 ketoconazole (1 $\mu\text{M}$ ) for CYP3A
<b>Results</b>	IC <sub>50</sub> values are all above 300 $\mu\text{M}$ .
<b>Conclusion</b>	Tecovirimat is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A.

#### 4. 15SIGAAP6

<b>Title</b>	Evaluation of the Potential for Inhibition of Cytochrome P450 Enzymes in Human Liver Microsomes by Three Metabolites (M4, M5, and TFMBA) of Tecovirimat (ST 246) (15SIGAAP6).
<b>Test system</b>	Human liver microsome
<b>Description</b>	The potential for CYP inhibition by M4, M5, and TFMBA was determined by enzyme activity assays using <i>in vitro</i> index substrates
<b>Substrates</b>	Phenacetin (63 $\mu\text{M}$ ) for CYP1A2 Bupropion (75 $\mu\text{M}$ ) for CYP2B6 Amodiaquine (2 $\mu\text{M}$ ) for CYP2C8 Diclofenac (10 $\mu\text{M}$ ) for CYP2C9 S-mephenytoin (40 $\mu\text{M}$ ) for CYP2C19 Bufuralol (7 $\mu\text{M}$ ) for CYP2D6 Testosterone (55 $\mu\text{M}$ ) for CYP3A Midazolam (2.5 $\mu\text{M}$ ) for CYP3A
<b>Inhibitor</b>	M4, M5, and TFMBA at 10 $\mu\text{M}$
<b>Positive control</b>	7,8-Benzoflavone (0.3 $\mu\text{M}$ ) for CYP1A2 Tranlycypromine (100 $\mu\text{M}$ ) for CYP2B6 Quercetin (30 $\mu\text{M}$ ) for CYP2C8 Sulfaphenazole (3 $\mu\text{M}$ ) for CYP2C9 Tranlycypromine (100 $\mu\text{M}$ ) for CYP2C19 Quinidine (1 $\mu\text{M}$ ) for CYP2D6 ketoconazole (1 $\mu\text{M}$ ) for CYP3A
<b>Results</b>	M4, M5, and TFMBA at 10 $\mu\text{M}$ did not inhibit CYP isoforms tested in the study
<b>Conclusion</b>	M4, M5, and TFMBA are not inhibitors of the following CYP isoforms. (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A). The TFMBA concentration used in this study is lower than the C <sub>max</sub> of TFMBA at steady-state (328 $\mu\text{M}$ ) but comparable to the unbound C <sub>max</sub> of TFMBA at steady-state (predicted to be ~5 $\mu\text{M}$ based on <i>in vitro</i> protein binding assay results).

#### 5. CYP0781\_R1

<b>Title</b>	Evaluation of Induction Potential of Cytochrome P450 Isoforms by ST246 in Cultured Human Hepatocytes (CYP0781_R1).
<b>Test system</b>	Primary cultured human hepatocytes from 4 different donors

Description	Freshly isolated hepatocytes were exposed to tecovirimat for 3 days. The induction potential of tecovirimat was determined by changes in the catalytic activities for CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and 3A4 using <i>in vitro</i> index substrates.
Substrate	Phenacetin (100 $\mu$ M) for CYP1A2 S-mephenytoin (100 $\mu$ M) for CYP2B6 (N-demethylation) Diclofenac (100 $\mu$ M) for CYP2C9 S-mephenytoin (100 $\mu$ M) for CYP2C19 (4-hydroxylation) Testosterone (120 $\mu$ M) for CYP3A4
Inducer	Tecovirimat up to 100 $\mu$ M
Positive control	Beta-naphthoflavone (20 $\mu$ M) for CYP1A2 Phenobarbital (2 mM) for CYP2B6 Rifampin (20 $\mu$ M) for CYP2Cs and CYP3A4
Results	CYP1A2: no induction CYP2B6: 2 to 5-fold increased activity by tecovirimat 100 $\mu$ M CYP2C9: 4 to 10-fold increased activity by tecovirimat 100 $\mu$ M CYP2C19: mixed results (induction and inhibition) CYP3A: 3 to 12-fold increased activity by tecovirimat 100 $\mu$ M
Conclusion	Tecovirimat is an inducer of CYP2B6, CYP2C9, and CYP3A4 activities at 100 $\mu$ M.

## 6. 15SIGAP8R

Title	Evaluation of the Potential for Induction of Cytochrome P450 Enzymes in Human Hepatocytes by Three Metabolites (M4, M5, and TFMBA) of Tecovirimat (ST 246) (15SIGAP8R1)
Test system	Primary cultured human hepatocytes from 3 different donors
Description	Plated fresh human hepatocytes were treated with each test article (M4, M5, and TFMBA) at three concentrations for 72 hours. CYP induction was evaluated with changes in mRNA expression, measured by qPCR.
Substrate	None (mRNA quantitation)
Inducer	M4: 10.4, 104 and 412 $\mu$ M M5: 7.9, 79, and 266 $\mu$ M TFMBA: 0.9, 9, and 132 $\mu$ M
Positive control	Known inducers Omeprazole (50 $\mu$ M) for CYP1A2 Phenobarbital (1 mM) for CYP2B6 Rifampin (50 $\mu$ M) for and CYP3A4
Results	CYP1A2: no induction by M4, M5 or TFMBA CYP2B6: induced by M4 and M5 <ul style="list-style-type: none"> <li>• M4: 27% and 60% of phenobarbital induction at 104 <math>\mu</math>M and 412 <math>\mu</math>M, respectively</li> <li>• M5: 37% and 46% of phenobarbital induction at 79 <math>\mu</math>M and 266 <math>\mu</math>M, respectively</li> <li>• No induction by TFMBA</li> </ul> CYP3A4: induced by M4 and M5 <ul style="list-style-type: none"> <li>• M4: 27% and 50% of rifampin induction at 104 <math>\mu</math>M and 412 <math>\mu</math>M, respectively.</li> <li>• M5: 6% and 17% of rifampin induction at 79 <math>\mu</math>M and 266 <math>\mu</math>M, respectively.</li> </ul>

	<ul style="list-style-type: none"> <li>No induction by TFMBA</li> </ul>
Conclusion	<p>M4 and M5 are inducers of CYP2B6 and CYP3A4 in a concentration-dependent manner. TFMBA is not an inducer of CYP2B6 or CYP3A4.</p> <p>M4, M5, and TFMBA are not inducers of CYP1A2.</p>

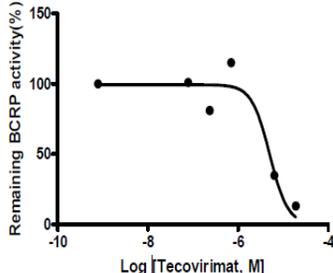
#### 4.6.3.3 Potential for transporter and UGT inhibition by tecovirimat and its metabolites

##### 1. 11SIGAP2

<b>Title</b>	P-glycoprotein Substrate and Inhibitor Potential for Test Compound (ST-246) (11SIGAP2)											
<b>Test system</b>	Caco-2 cell monolayers											
<b>Description</b>	<p>1. Tecovirimat as a P-gp substrate The bi-directional permeability of tecovirimat at 3 different doses was evaluated in Caco-2 cell monolayers.</p> <p>2. Tecovirimat as a P-gp inhibitor The bi-directional permeability of digoxin was determined in the absence and presence of tecovirimat.</p>											
<b>Substrates</b>	Tecovirimat: 0.48, 1.9 and 19 $\mu$ M Digoxin 10 $\mu$ M as a P-gp substrate											
<b>Positive control</b>	Cyclosporine 5 $\mu$ M for P-gp inhibition Ketoconazole 20 $\mu$ M P-gp inhibition											
<b>Results</b>	<p>1. Tecovirimat as a P-gp substrate The efflux ratio of tecovirimat was less than 1.22 at the concentrations evaluated in this study.</p> <p>2. Tecovirimat as a P-gp inhibitor</p> <table border="1"> <thead> <tr> <th>Treatment</th> <th>Efflux ratio of digoxin</th> </tr> </thead> <tbody> <tr> <td>Digoxin</td> <td>13.7</td> </tr> <tr> <td>Digoxin + tecovirimat 19 <math>\mu</math>M</td> <td>9.45</td> </tr> <tr> <td>Digoxin + cyclosporine 5 <math>\mu</math>M</td> <td>0.99</td> </tr> <tr> <td>Digoxin + ketoconazole 20 <math>\mu</math>M</td> <td>1.13</td> </tr> </tbody> </table>		Treatment	Efflux ratio of digoxin	Digoxin	13.7	Digoxin + tecovirimat 19 $\mu$ M	9.45	Digoxin + cyclosporine 5 $\mu$ M	0.99	Digoxin + ketoconazole 20 $\mu$ M	1.13
Treatment	Efflux ratio of digoxin											
Digoxin	13.7											
Digoxin + tecovirimat 19 $\mu$ M	9.45											
Digoxin + cyclosporine 5 $\mu$ M	0.99											
Digoxin + ketoconazole 20 $\mu$ M	1.13											
<b>Conclusion</b>	<p>1. Tecovirimat is not a P-gp substrate.</p> <p>2. Tecovirimat weakly inhibited P-gp at 19 <math>\mu</math>M. Clinical relevance is unknown at this time, but it is unlikely a potent P-gp inhibitor based on the results with positive controls (ketoconazole or cyclosporine).</p>											

##### 2. 12SIGAP1

<b>Title</b>	In Vitro Breast Cancer Resistance Protein, Organic Anion Transporting polypeptide 1B1 and 1B3 Substrate and Inhibition Potential for ST-246 (12SIGAP1)
<b>Test system</b>	CPT-P1 cells for BCRP-mediated transport HEK293 cells transfected with OATP1B1 or OATP1B3
<b>Description</b>	1. Tecovirimat as a BCRP substrate:

	<p>The bi-directional transport of tecovirimat was measured in CPT-P1 cells.</p> <p>2. Tecovirimat as a BCRP inhibitor: The bi-directional transport of cladribine was determined in the absence of and presence of tecovirimat in CPT-P1 cells</p> <p>3. Tecovirimat as an OATP1B1 or 1B3 substrate: OATP1B1 or OATP1B3 -mediated uptake of tecovirimat was measured in transfected HEK293 cells.</p> <p>4. Tecovirimat as an OATP1B1 or 1B3 inhibitor The uptake transport of atorvastatin was determined in the absence of and presence of tecovirimat in CPT-P1 cells.</p>																				
<b>Substrates</b>	<p>Tecovirimat 0.5, 2, and 19 <math>\mu\text{M}</math> Cladribine 10 <math>\mu\text{M}</math> as a BCRP substrate Atorvastatin 0.15 <math>\mu\text{M}</math> as a OATP1B substrate</p>																				
<b>Positive control</b>	<p>Ko143 10 <math>\mu\text{M}</math> as a BCRP inhibitor FTC 10 <math>\mu\text{M}</math> as a BCRP inhibitor Rifamycin 10 <math>\mu\text{M}</math> as an OATP1B inhibitor</p>																				
<b>Results</b>	<p>1. Tecovirimat as a BCRP substrate The efflux ratio of tecovirimat in CPT-P1 was less than 1.1 at the concentrations evaluated in this study.</p> <p>2. Tecovirimat as a BCRP inhibitor The efflux ratio of cladribine was decreased in the presence of tecovirimat in a tecovirimat-concentration dependent manner. The <math>\text{IC}_{50}</math> value of tecovirimat for BCRP inhibition was 6 <math>\mu\text{M}</math>. Since <math>I_{\text{gut}} (6 \text{ mM})/\text{IC}_{50}</math> value is <math>&gt; 10</math>, tecovirimat is potentially a clinically relevant BCRP inhibitor.</p>  <table border="1"> <caption>Data points for BCRP activity vs. Tecovirimat concentration</caption> <thead> <tr> <th>Log [Tecovirimat, M]</th> <th>Remaining BCRP activity (%)</th> </tr> </thead> <tbody> <tr><td>-9.5</td><td>100</td></tr> <tr><td>-7.5</td><td>100</td></tr> <tr><td>-7.0</td><td>100</td></tr> <tr><td>-6.5</td><td>100</td></tr> <tr><td>-6.0</td><td>100</td></tr> <tr><td>-5.5</td><td>100</td></tr> <tr><td>-5.0</td><td>85</td></tr> <tr><td>-4.5</td><td>35</td></tr> <tr><td>-4.0</td><td>10</td></tr> </tbody> </table> <p>3. Tecovirimat as an OATP1B1 or OATP1B3 substrate Tecovirimat was not actively transported by OATP1B1 or OATP1B3 at 0.5 <math>\mu\text{M}</math>, 2 <math>\mu\text{M}</math>, and 19 <math>\mu\text{M}</math> in OATP1B1 or OATP1B3-transfected HEK293 cells.</p> <p>4. Tecovirimat as an OATP1B1/3 inhibitor Tecovirimat (at 19 <math>\mu\text{M}</math>) did not inhibit OATP1B1 or OATP1B3 mediated atorvastatin transport in OATP1B1 or OATP1B3-transfected HEK293 cells</p>	Log [Tecovirimat, M]	Remaining BCRP activity (%)	-9.5	100	-7.5	100	-7.0	100	-6.5	100	-6.0	100	-5.5	100	-5.0	85	-4.5	35	-4.0	10
Log [Tecovirimat, M]	Remaining BCRP activity (%)																				
-9.5	100																				
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-6.0	100																				
-5.5	100																				
-5.0	85																				
-4.5	35																				
-4.0	10																				
<b>Conclusion</b>	<p>1. Tecovirimat is not a substrate of BCRP. 2. Tecovirimat inhibited BCRP in vitro. Based on the <math>\text{IC}_{50}</math> value, tecovirimat may be a clinically relevant BCRP inhibitor. 3. Tecovirimat is not a substrate of OATP1B1 or OATP1B3. 4. Tecovirimat is not an inhibitor of OATP1B1 or OATP1B3.</p>																				

### 3. 15SIGAP10

<b>Title</b>	In Vitro Evaluation of the Transporter Inhibitor Potential of Sponsor's Test Articles, M4, M5, and TFMBA (15SIGAP10)																						
<b>Test system</b>	C2BBel cells for P-gp and BCRP																						
<b>Description</b>	<p>1. Metabolites as P-gp inhibitors: The bi-directional transport of digoxin was determined in the absence of and presence of M4, M5, or TFMBA in C2BBel cells.</p> <p>2. Metabolites as BCRP inhibitors The bi-directional transport of cladribine was determined in the absence of and presence of M4, M5, or TFMBA in C2BBel cells.</p> <p>3. Metabolites as OATP1B inhibitors The uptake of atorvastatin by OATP1B1 or OATP1B3 was compared in the absence of, and presence of, tecovirimat in transfected HEK cells.</p> <p>M4, M5, and TFMBA concentrations used in this study were 104 <math>\mu\text{M}</math>, 97.3 <math>\mu\text{M}</math>, and 131 <math>\mu\text{M}</math>, respectively.</p>																						
<b>Substrates</b>	Digoxin 10 $\mu\text{M}$ as a P-gp substrate Cladribine 10 $\mu\text{M}$ as a BCRP substrate Atorvastatin 0.15 $\mu\text{M}$ as a OATP1B substrate																						
<b>Positive control</b>	Valspodar 1 $\mu\text{M}$ as a P-gp inhibitor Ko143 10 $\mu\text{M}$ as a BCRP inhibitor Rifamycin 10 $\mu\text{M}$ as an OATP1B inhibitor																						
<b>Results</b>	<table border="1"> <thead> <tr> <th></th> <th>M4</th> <th>M5</th> <th>TFMBA</th> </tr> </thead> <tbody> <tr> <td>P-gp</td> <td>46% inhibition*</td> <td>None</td> <td>None</td> </tr> <tr> <td>BCRP</td> <td>None</td> <td>None</td> <td>None</td> </tr> <tr> <td>OATP1B1</td> <td>None</td> <td>None</td> <td>None</td> </tr> <tr> <td>OATP1B3</td> <td>None</td> <td>None</td> <td>None</td> </tr> </tbody> </table> <p>While M4 inhibited P-gp mediated digoxin transport, <math>C_{\text{max}}</math>/estimated <math>\text{IC}_{50}</math> is less than 0.1. Therefore, M4 is unlikely a clinically relevant P-gp inhibitor and no in vivo study is warranted.</p>				M4	M5	TFMBA	P-gp	46% inhibition*	None	None	BCRP	None	None	None	OATP1B1	None	None	None	OATP1B3	None	None	None
	M4	M5	TFMBA																				
P-gp	46% inhibition*	None	None																				
BCRP	None	None	None																				
OATP1B1	None	None	None																				
OATP1B3	None	None	None																				
<b>Conclusion</b>	M4, M5, and TFMBA are not inhibitors of P-gp, BCRP, OATP1B1, and OATP1B3																						

### 4. 15SIGAP1R1

<b>Title</b>	Determining if the Sponsor's Test Article Inhibits the Renal Transporters Organic Anion Transporter 1, Organic Anion Transporter 3, and Organic Cation Transporter 2 (15SIGAP1R1)
<b>Test system</b>	HEK cells transfected with OAT1, OAT3 or OCT2
<b>Description</b>	The inhibition potential of tecovirimat (10 $\mu\text{M}$ or 20 $\mu\text{M}$ ) for OAT1, OAT3, and OCT2 was determined by comparing the uptake of a transporter-specific index substrate in the absence of, and presence of, tecovirimat in transfected HEK cells.

<b>Substrates</b>	PAH (20 $\mu$ M) as an OAT1 substrate Furosemide (10 $\mu$ M) as an OAT3 substrate MPP+ (10 $\mu$ M) as an OCT2 substrate
<b>Positive control</b>	Probenecid (100 $\mu$ M) as an inhibitor of OAT1 or OAT3 Imipramine (300 $\mu$ M) as an inhibitor of OCT2
<b>Results</b>	OAT1, OAT3, and OCT2-mediated transport in HEK cells was not inhibited by tecovirimat up to 20 $\mu$ M.
<b>Conclusion</b>	Tecovirimat is not an inhibitor of OAT1, OAT3, or OCT2

### 5. 15SIGAP11 and 16SIGAP1R1

<b>Title</b>	In Vitro Evaluation of the Transporter Inhibitor Potential of Sponsor's Test Articles, M4, M5, and TFMBA (15SIGAP11)  In Vitro Evaluation of the Transporter Inhibitor Potential of Sponsor's Test Article, TFMBA, a Major Metabolite of Tecovirimat (16SIGAP1R1)
<b>Test system</b>	HEK cells transfected with OAT1, OAT3 or OCT2
<b>Description</b>	The inhibition potential of tecovirimat's major metabolites (M4, M5, and TFMBA) for OAT1, OAT3, and OCT2 was determined by comparing the uptake of a transporter-specific index substrate in the absence of, and presence of, metabolites in transfected HEK cells. M4, M5, and TFMBA concentrations used in this study were 82.4 $\mu$ M, 53.1 $\mu$ M, and 1.84 $\mu$ M, respectively.  16SIGP1R1: the inhibition potential of TFMBA at a higher concentration (11.5 $\mu$ M) for OAT1, OAT3, and OCT2 was determined.
<b>Substrates</b>	PAH (10 $\mu$ M) as an OAT1 substrate Furosemide (5 $\mu$ M) as an OAT3 substrate MPP+ (5 $\mu$ M) as an OCT2 substrate
<b>Positive control</b>	Probenecid (100 $\mu$ M) as an inhibitor of OAT1 or OAT3 Imipramine (300 $\mu$ M) as an inhibitor of OCT2
<b>Results</b>	OAT1, OAT3, and OCT2-mediated transport in HEK cells was not inhibited by tecovirimat metabolites (M4, M5, and TFMBA).
<b>Conclusion</b>	Tecovirimat metabolites are not inhibitors of OAT1, OAT3, and OCT2.

### 6. 15SIGAP9

<b>Title</b>	Evaluation of the Potential for Inhibition of UGT Enzymes by Three Metabolites of Tecovirimat (15SIGAP9)
<b>Test system</b>	Human recombinant UGT isoforms
<b>Description</b>	The potential for inhibition of UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15 by M4, M5, and TFMBA was evaluated using human recombinant UGT enzymes (hrUGTs). Inhibition of UGT isoforms was determined by comparing enzymes activities using UGT index substrates in the absence of, and presence of, metabolites.
<b>Substrates</b>	7-hydroxy-4-triflyoromethylcoumarin (HFC) for UGT1A1, UGT1A3, UGT1A6, UGT1A9, UGT2B7, and UGT2B15 Trifluoperazine for UGT1A4
<b>Positive control</b>	Bilirubin for UGT1A1 Buprenorphine for UGT1A3

	Hecogenin for UGT1A4 1-Naphthol for UGT1A6 Niflumic Acid for UGT1A9 Diclofenac for UGT2B7 and UGT2B15
<b>Results</b>	None to minimal (< 11%) UGT inhibition by M4, M5, and TFMBA was observed
<b>Conclusion</b>	M4, M5, and TFMBA are not inhibitors of the following UGT isoforms: UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15

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