

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208627Orig1s000**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/BLA Serial Number:** 208,627 / S-0000

**Drug Name:** ST-246 (tecovirimat)

**Indication(s):** The treatment of human smallpox disease in adults and pediatric patients

**Applicant:** SIGA Technologies, Inc.

**Date(s):** Submitted: December 8, 2017  
Received: December 8, 2017  
PDUFA Date: August 8, 2018  
Draft Review Completed: May 1, 2018  
Final Review Completed: May 8, 2018

**Review Priority** Priority

**Biometrics Division:** Division of Biometrics IV (HFD-725)

**Statistical Reviewer:** Wen Zeng, Ph.D.

**Concurring Reviewers:** Thamban Valappil, Ph.D. Statistical Team Leader

**Medical Division:** Division of Antiviral Drug Products (HFD-530)

**Clinical Team:** Medical Reviewer: Kirk Chan-Tack, MD  
Medical team leader: Adam Sherwat, MD  
Medical division director: Debra Birnkrant, MD

**Project Manager:** Andrew Gentiles, PharmD, BCPS AQ-ID

**Keywords:** Smallpox, Tecovirimat, Animal model, Monkeypox, and Rabbitpox.

# Table of Contents

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES .....	1
FOOD AND DRUG ADMINISTRATION .....	1
STATISTICAL REVIEW AND EVALUATION .....	1
LIST OF TABLES .....	3
<b>1. EXECUTIVE SUMMARY .....</b>	<b>4</b>
<b>2. INTRODUCTION .....</b>	<b>5</b>
2.1 OVERVIEW .....	5
2.1.1 <i>Trials Reviewed</i> .....	6
2.2 DATA SOURCES .....	7
<b>3. STATISTICAL EVALUATION .....</b>	<b>8</b>
3.1 DATA AND ANALYSIS QUALITY.....	8
3.2 EVALUATION OF EFFICACY.....	8
3.2.1 <i>Trial Design and Endpoints</i> .....	8
3.2.2 <i>Demographics</i> .....	15
3.2.3 <i>Statistical Methodologies</i> .....	15
3.2.4 <i>Results and Conclusions</i> .....	15
3.3 EVALUATION OF SAFETY .....	19
<b>4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS .....</b>	<b>19</b>
<b>5. SUMMARY AND CONCLUSIONS .....</b>	<b>20</b>
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE .....	20
5.2 CONCLUSIONS AND RECOMMENDATIONS .....	20
5.3 LABELING RECOMMENDATIONS .....	20

## LIST OF TABLES

Table 1	List of Animal Trials Included in This Review .....	6
Table 2	Assignment of Treatment Group for Trial AP-09-026G .....	9
Table 3	Trial Group Assignment for Trial SR10-037F .....	10
Table 4	Trial Group Assignment for Trial RS10-038F .....	11
Table 5	Trial Group Layout for Trial FY10-087 .....	13
Table 6	Trial Group Layout for Trial SR14-008F .....	14
Table 7	Trial Group Layout for Trial SR13-025F .....	14
Table 8:	Survival Rate for Monkeypox Trial AP-09-026G (ITT).....	16
Table 9:	Sensitivity Analysis of the Survival Rate for Monkeypox Trial AP-09-026G .....	16
Table 10:	Survival Rate for Monkeypox Trial SR10-037F (ITT) .....	16
Table 11:	Survival Rate for Monkeypox Trial SR10-038F (ITT) .....	17
Table 12:	Survival Rate for Monkeypox Trial FY10-087 (ITT) .....	17
Table 13:	Survival Rate for Rabbitpox Trial SR14-008F (ITT).....	18
Table 14:	Sensitivity Analysis of the Survival Rate for Rabbitpox Trial SR14-008F .....	18
Table 15:	Survival Rate for Rabbitpox Trial SR13-025F (ITT).....	19
Table 16:	Sensitivity Analysis of the Survival Rate for Rabbitpox Trial SR13-025F .....	19
Table 17:	Monkey's Body Weight at the randomization and Study Day -1 For Trial AP-09-026G .....	22
Table 18:	Monkey's Gender and Body Weight at Study Day -11and Study Day -1 For Trial SR10-037F .....	22
Table 19:	Monkey's Gender and Body Weight at Study Day -11and Study Day -1 For Trial SR10-038F .....	22
Table 20:	Monkey's Gender and Body Weight at Study Day -35 and Study Day -10 For Trial FY10-087 .....	22
Table 21:	Rabbit's Body Weight at Study Day 0 and Study Day 1 For Trial SR14-008F .....	23
Table 22:	Rabbit's Body Weight at Study Day 0 and Study Day 1 For Trial SR13-025F .....	23
Table 23:	Multiplicity Adjusted Boschloo's P-value of Primary Efficacy Endpoint Analysis for Trial AP-09-026G.....	23
Table 24:	Multiplicity Adjusted Boschloo's P-value of Primary Efficacy Endpoint Analysis for Trial SR10-037F.....	23
Table 25:	Multiplicity Adjusted Boschloo's P-value of Primary Efficacy Endpoint Analysis for Trial SR10-038F.....	24
Table 26:	Multiplicity Adjusted Boschloo's P-value of Primary Efficacy Endpoint Analysis for Trial FY10-087 .....	24

## 1. EXECUTIVE SUMMARY

This is a statistical review of New Drug Application (NDA) 208627 submitted by SIGA Technologies (the Applicant) for tecovirimat (ST-246) 600 mg twice daily. The proposed indication is for the treatment of human smallpox disease in adults and pediatric patients weighing at least 13 kg. It is not ethical to conduct efficacy trials in humans for smallpox infection as the disease was declared eradicated from the world in 1980, and traditional drug development based on the clinical demonstration of efficacy in humans is not feasible. Thus, tecovirimat has been developed under the Animal Rule. The main objective of this review is to evaluate whether the efficacy presented in the six animal trials submitted, 4 trials of non-human primate (NHP) monkeys (monkeypox) and 2 trials of rabbits (rabbitpox), supports the indication sought by the applicant under the Animal Rule.

Four monkey trials were submitted. The first monkey trial was a dose-ranging trial, AP-09-026G, which was a randomized, double-blind, placebo-controlled, repeated-dose trial to evaluate a series of doses (0.3, 1, 3, and 10 mg/kg/day for 14 days) compared to a placebo control to determine the lowest effective dose. The primary efficacy endpoint was the survival rate at Day 28 post-infection. It demonstrated that the lowest effective dose is 3 mg/kg/day for 14 days starting at Day 4 after virus inoculation.

The second monkey trial was a delayed treatment trial, SR10-037F. It was a randomized, double-blind, placebo-controlled trial to evaluate a series of starting days (4, 5, or 6 days' post-infection with a dose of 10 mg/kg/day for 14 days) against a placebo control to determine treatment starting day. The primary efficacy endpoint was the survival rate up to Day 56 post-infection. It demonstrated that the starting day must be no later than 4 or 5 days' post-infection to avoid failing to protect animals from mortality.

The third monkey trial was a treatment duration trial, SR10-038F, which was a randomized, double-blind, placebo-controlled trial to evaluate the duration of treatment (3, 5, 7, and 10 consecutive days of treatment of 10 mg/kg/day dose). The primary efficacy endpoint was the survival rate up to Day 28 post-infection. The trial demonstrated that a minimum of 5 days of 10 mg/kg/day tecovirimat was needed to avoid failing to protect animals from mortality.

The fourth monkey trial was a pharmacokinetics (PK) trial, FY10-087. It was a randomized, placebo-controlled trial to evaluate the PK and survival of different dose levels (3, 10, and 20 mg/kg/day dose for 14 day starting at 4 days' post-infection). The primary efficacy endpoint was the survival rate up to Day 28 post-infection. It demonstrated that the 3 mg/kg/day for 14 days starting at Day 4 after virus inoculation is the lowest effective dose.

In summary, a statistically significant treatment benefit over placebo was demonstrated in monkeypox trials for the primary endpoint of survival rate when tecovirimat was dosed at 3, 10, or 20 mg/kg/day for at least 5 days starting at day 4 or day 5 after virus inoculation.

There were two rabbit trials in the submission. The first rabbit trial was a dose-ranging trial, SR14-008F, which was a randomized, double-blind, placebo-controlled trial to evaluate a series of doses (20, 40, 80, and 120 mg/kg/day for 14 days starting at 4 days' post-infection) compared

to a placebo control to determine the lowest effective dose. The primary efficacy endpoint was the survival rate until Day 30 or 31 post-infection. Based on the evidence, the lowest effective dose was 20 mg/kg/day for 14 days starting at Day 4 after virus inoculation.

The second rabbit trial was a PK trial, SR13-025F, which was a randomized trial to evaluate the PK and survival of different dose levels (40, 80, and 120 mg/kg/day dose for 14 day starting at 4 days' post-infection). The primary efficacy endpoint was the survival rate up to Day 18 post-infection. The survival rates observed in the trial were similar to those observed in trial SR14-008F.

In summary, a statistically significant treatment benefit in survival over placebo was demonstrated in rabbitpox trials when tecovirimat was dosed at 20, 40, 80, or 120 mg/kg/day for 14 days starting at day 4 after virus inoculation.

For human dose selection, a tecovirimat dose of 10 mg/kg/day for 14 days starting at day 4 after virus inoculation was selected in monkeypox trials to provide exposures that exceed those associated with fully effective dose. A tecovirimat dose of 40 mg/kg/day for 14 days starting at day 4 after virus inoculation was selected in rabbitpox trials to provide exposures that exceed those associated with fully effective dose for human dose selection. The dose regimen for human subjects was 600 mg twice daily (please refer to the clinical review for details).

In conclusion, the results from the two animal models reviewed demonstrated that tecovirimat (600 mg twice daily) is efficacious as the treatment of human smallpox disease under the Animal Rule.

**Key statistical issue:** There was no major statistical issue identified in this submission.

## 2. INTRODUCTION

### 2.1 Overview

Smallpox is a human disease caused by infection with variola (smallpox) virus, which is in the orthopoxvirus genus of viruses. No case of human smallpox has occurred since 1978 due to the global vaccination campaign and the disease was declared eradicated from the world in 1980. Routine vaccination in the U.S. ended in the 1970s, so most of the population is immunologically susceptible to smallpox. Despite the eradication of naturally acquired smallpox, the disease remains as a threat because variola virus could be developed as a bioterrorism agent. Mortality in variola virus is commonly cited around 30%, but has been reported to vary widely among outbreaks from as little as 5% to 40% or more (Breman 2002). Medical countermeasures, including antiviral therapies, are needed in the event of a smallpox virus outbreak.

Tecovirimat (ST-246) is a small molecule developed for the treatment of human smallpox. Traditional drug development based on the clinical demonstration of efficacy in humans is not ethical or feasible; therefore, tecovirimat has been developed under the Animal Rule. Based on the discussion of 2011 Antiviral Drugs Advisory Committee meeting, the FDA and the advisory

committee agreed that data from a combination of other lethal animal models using surrogate orthopoxviruses (e.g. non-human primate studies with monkeypox virus, rabbit studies with rabbitpox virus, mouse studies with ectromelia virus) could be used as evidence for a NDA application. Please refer the clinical review by Dr. Chan-Tack for more details regarding the Animal Rule for this NDA application.

In the NDA submission, the efficacy data from two independent animal models, which included 4 trials of non-human primate (NHP) monkeys (monkeypox) and 2 trials of rabbits (rabbitpox), were submitted. One trial SIGA-246-008 was also submitted for human safety evaluation and was not included as part of this statistical efficacy review.

### 2.1.1 Trials Reviewed

The detailed description of the six trials is listed in Table 1. Four trials, AP-09-026G, SR10-037F, SR10-038F, and FY10-087, were conducted using monkeypox virus in monkeys and two trials, SR14-008F and SR13-025F, were conducted using rabbitpox virus in rabbits.

**Table 1** List of Animal Trials Included in This Review

<b>Trial ID</b>	<b>Design</b>	<b>Treatment</b>	<b>Endpoint /Analysis</b>	<b>Preliminary Findings (Survival Rate)</b>
AP-09-026G (GLP)	Double-blind, randomized, placebo-controlled trial to evaluate the minimum effective therapeutic dose of oral ST-246 Polyform I in cynomolgus monkeys infected with MPXV. <b>ST-246 was given Day 4 PI.</b>	Placebo	The primary efficacy endpoint is the proportion of animals that survived until Day 28 PI.	0/7 (0%)
		0.3 mg/kg/day x 14 days		1/5 (20%)
		1 mg/kg/day x 14 days		0/5 (0%)
		3 mg/kg/day x 14 days		4/5 (80%)
		10 mg/kg/day x 14 days		4/5 (80%)
SR10-037F (Non-GLP)	Double-blind, randomized, placebo-controlled trial to evaluate the impact of delayed ST-246 treatment on efficacy following intravenous (IV) challenge with lethal MPXV challenge.	Placebo	The primary efficacy endpoint was survival to Day 56 PI	0/3 (0%)
		10 mg/kg/day x 14 days (Day 4 PI in 6/6 NHPs)		5/6 (83%)
		10 mg/kg/day x 14 days (Day 5 PI in 6/6 NHPs)		5/6 (83%)
SR10-038F (Non-GLP)	Double-blind, randomized, placebo-controlled trial to evaluate the impact of duration of ST-246 treatment on efficacy following intravenous (IV) challenge with lethal MPXV challenge in cynomolgus monkeys. <b>ST-246 was given Day 4 PI.</b>	Placebo	The primary efficacy endpoint was survival to Day 28 PI	1/4 (25%)
		10 mg/kg/day x 3 days		2/4 (50%)
		10 mg/kg/day x 5 days		6/6 (100%)
		10 mg/kg/day x 7 days		6/6 (100%)
		10 mg/kg/day x 10 days		4/5 (80%)
FY10-087	Randomized, placebo-controlled trial to evaluate ST-246 pharmacokinetics in cynomolgus	Placebo	The primary efficacy endpoint is the proportion	0/6 (0%)
		3 mg/kg/day x 14 days		6/6 (100%)

(GLP)	monkeys infected intravenously with MPXV. <b>ST-246 was given Day 4 PI. Not blinded.</b>	10 mg/kg/day x 14 days	of animals that survived until Day 28 PI	6/6 (100%)
		20 mg/kg/day x 14 days		6/6 (100%)
SR14-008F  (GLP)	Double-blind, randomized, placebo-controlled trial to evaluate dose-response relationship between ST-246 plasma exposure and efficacy in 16-week old rabbits following lethal intradermal (ID) RPXV Utrecht strain inoculation. <b>ST-246 was given Day 4 PI.</b>	Placebo	The primary efficacy endpoint is the proportion of animals that survived until Day 30 or 31 PI	0/10 (0%)
		20 mg/kg/day x 14 days		9/10 (90%)
		40 mg/kg/day x 14 days		9/10 (90%)
		80 mg/kg/day x 14 days		8/10 (80%)
		120 mg/kg/day x 14 days		8/10 (80%)
SR13-025F (GLP)	Double-blind, randomized trial to evaluate the impact of RPXV Utrecht strain (ID inoculation) on oral PK of ST-246 in 16-week old rabbits. <b>ST-246 was given Day 4 PI.</b>	40 mg/kg/day x 14 days	The primary efficacy endpoint is the proportion of animals that survived until Day 18 PI	7/8 (87.5%)
		80 mg/kg/day x 14 days		7/8 (87.5%)
		120 mg/kg/day x 14 days		8/8 (100%)

PFU, plaque forming units; PI, post-inoculation; MPXV, monkeypox virus; GLP, Good Laboratory Practices; N/A, not applicable. MPXV was administered via intravenous inoculation. Day 4 PI corresponds to onset of skin lesions. Source: the reviewer assembled.

The detailed design characteristics of the six trials are described in section 3.2.1.

## 2.2 Data Sources

All trials submitted were animal trials and SEND format datasets were submitted for all six trials under Module 4 instead of Module 5 for human clinical trials. Some trials also included a legacy subfolder, which contained some analysis-like datasets. This reviewer conducted efficacy analyses to verify the applicant's results.

1. Reviewed protocols, statistical analysis plans, efficacy results and conclusions in the following submitted documents entitled "Statistics Section":
  - Module 1- labeling materials
  - Module 2- 2.5 Clinical Overview and 2.7.3 Summary of Clinical Efficacy
  - Module 4- Clinical Study Reports (CSRs) of all six animal studies.
2. The SEND datasets are under CDER Electronic Document Room (EDR) directory.

Monkey trials:

<\\cdsesub1\EVSPROD\NDA208627\0001\m4\datasets\ap-09-026g\tabulations\send>  
<\\cdsesub1\EVSPROD\NDA208627\0001\m4\datasets\SR10-037F\tabulations\send>  
<\\cdsesub1\EVSPROD\NDA208627\0001\m4\datasets\SR10-038F\tabulations\send>  
<\\cdsesub1\EVSPROD\NDA208627\0001\m4\datasets\fy10-087\tabulations\send>

Rabbit trials:

<\\cdsesub1\EVSPROD\NDA208627\0001\m4\datasets\sr14-008f\tabulations\send>  
<\\cdsesub1\EVSPROD\NDA208627\0001\m4\datasets\sr13-025f\tabulations\send>

### 3. STATISTICAL EVALUATION

Six trials; four monkey trials and two rabbit trials, were reviewed separately under each of following sections. All tables and figures were generated by the statistical reviewer unless otherwise cited.

#### 3.1 Data and Analysis Quality

Overall, the quality of the data was acceptable and the reviewer was able to reproduce primary efficacy results presented in the CSRs.

#### 3.2 Evaluation of Efficacy

##### 3.2.1 Trial Design and Endpoints

In all trials, no specific sample size calculation was presented in the protocols.

*Reviewer comment: Assuming of near zero percent survival rate in the placebo arm and approximately 90% survival rate in the treatment arm, 5 animals per arm will have about 90% power to detect the difference using a Fisher's exact test at 2-sided 0.05 significant level without adjustment for multiplicity.*

*For the analyses and the associated multiplicity, a closed-testing procedure was mentioned in some protocols in this section below using a fixed sequence starting from the highest daily dose compared to placebo. However, multiplicity adjusted p-values were not provided. The reviewer used Holm procedure for multiplicity adjustment based on Boschloo's test p-values.*

##### 3.2.1.1 Monkeypox Model – Four Trials

For all four monkeypox trials, cynomolgus macaques were challenged intravenously with a high viral challenge dose of  $5 \times 10^7$  plaque-forming units (PFU) of MPXV Zaire '79 strain.

###### ❖ Trial AP-09-026G – A dose-ranging trial

Trial AP-09-026G was a randomized, double-blind, placebo-controlled, repeated-dose efficacy trial assessing the minimum effective therapeutic dose of oral ST-246 Polyform I in cynomolgus monkeys infected with monkeypox virus (MPXV).

This trial evaluated a series of doses (0.3, 1, 3, and 10 mg/kg) with concurrent placebo control to determine the lowest effective (protective) dose of ST-246 in this animal model.

Animals were infected via IV injection with MPXV ( $5.5 \times 10^7$  pfu) on Day 0. Animals were randomized into 5 groups to receive placebo once daily or tecovirimat 0.3, 1, 3, or 10 mg/kg

once daily beginning on the day, the lesions first appeared on an animal (ie, Day 4 post-inoculation (PI)) and continuing for 14 consecutive days (Days 4-17).

Per the protocol, the trial was divided into two iterations of the same experiment due to the total number of animals being infected and the laboratory space available for use that was available for use. An additional two infected animals (one for each iteration) were included to replace any animal that did not meet the criteria for successful infection. All animals enrolled into the trial were male.

**Table 2** Assignment of Treatment Group for Trial AP-09-026G

Iteration 1					
Group	Number per Group <sup>a</sup> (male)	ST-246 Dose (mg/kg)	Volume (mL/kg)	Target Concentration [mg/mL (w/v)]	Actual Average Concentration <sup>b</sup> [mg/mL (w/v)]
1	3	10	2	5.0 ± 0.25	4.5401**
2	3	3	2	1.5 ± 0.08	1.3480**
3	3	1	2	0.5 ± 0.03	0.4566**
4	3	0.3	2	0.15 ± 0.008	0.1334**
5	4	0	2	0.0 ± 0.0	N/A*
Iteration 2					
Group	Number per Group <sup>a</sup> (male)	ST-246 Dose (mg/kg)	Volume (mL/kg)	Target Concentration [mg/mL (w/v)]	Actual Average Concentration <sup>b</sup> [mg/mL (w/v)]
1	2	10	2	5.0 ± 0.25	4.8325
2	2	3	2	1.5 ± 0.08	1.4963
3	2	1	2	0.5 ± 0.03	0.4858
4	2	0.3	2	0.15 ± 0.008	0.1319**
5	3	0	2	0.0 ± 0.0	0.00

Source: Table 2 in CSR

Animals were monitored daily for moribundity and mortality through Day 42 (animals found moribund were euthanized, and animals surviving to trial termination were euthanized on Day 42 or 43). Lesion counts were done daily on Days -6, 0-23, 28, 35, and 42. Viral load was assessed on Days -6, 0, 1, 3, 5, 7, 9, 11, 13, 15, 17, 21, 23, 28, 35, and 42.

The trial began on November 24, 2009 (-10 Day) and was completed on June 22, 2011. Trial AP-09-026G was conducted at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). Trial AP-09-026G was conducted in accordance with Good Laboratory Practices (GLP).

The **primary efficacy endpoint** was survival rate at Day 28 post-infection.

The intent to treat (ITT) population included all monkeys that were randomized and received at least one dose of test article.

Per protocol, the primary efficacy analysis method is the Fisher's exact test at the significance level of 0.05 (2-sided) to analyze the survival rate difference between each individual active dose group and placebo group as well as between all active doses combined and placebo in the ITT population. To handle the issue of multiplicity, the closed-test procedure had a fixed sequence starting from the highest daily dose compared to placebo, continuing to the second highest daily dose, until there was no significant difference between a daily dose and placebo.

There was no sample size calculation presented in the protocol.

*Reviewer comment: The CSR did not report the multiplicity adjusted results or the reviewer could access it as part of the submission.*

❖ **Trial SR10-037F – A delayed treatment trial**

Trial SR10-037F was a randomized, double-blind, placebo-controlled trial assessing the effect of delayed ST-246 treatment on efficacy following intravenous (IV) MPXV challenge. ST-246 treatment was delayed until 4, 5, or 6 days post-challenge to determine the time point at which ST-246 failed to protect animals from mortality.

Twenty-one (21) randomly selected healthy male and female cynomolgus monkeys were randomized per their weight and sex to four groups: placebo (group 1, 3 animals), ST-246 at 10 mg/kg by oral gavage beginning on Day 4 (Group 2, 6 animals), 5 (Group 3, 6 animals), and 6 (Group 4, 6 animals) after inoculation and continued to received once-daily doses for 14 consecutive days (Table 3 below).

**Table 3** Trial Group Assignment for Trial SR10-037F

Group <sup>a</sup>	No. of Animals		MPXV Challenge Dose (Day 0)	ST-246 Dose Level	Dosage Schedule <sup>b</sup>	
	M	F			ST-246	Placebo
1 – Placebo <sup>c</sup>	1	2	5 x 10 <sup>7</sup> PFU IV	0 mg/kg	N/A	Days 4-19
2 – ST-246 Day 4	3	3	5 x 10 <sup>7</sup> PFU IV	10 mg/kg	Days 4-17	Days 18 and 19
3 – ST-246 Day 5	3	3	5 x 10 <sup>7</sup> PFU IV	10 mg/kg	Days 5-18	Days 4 and 19
4 – ST-246 Day 6	3	3	5 x 10 <sup>7</sup> PFU IV	10 mg/kg	Days 6-19	Days 4 and 5

<sup>a</sup>Group numbers were assigned to aid in clarity in the protocol. The animals were arranged by animal number, not by group.

<sup>b</sup>In addition to being dosed with ST-246, the animals in Groups 2-4 received placebo on the days indicated to accommodate blinding.

<sup>c</sup>Animals in Group 1 were administered the drug vehicle by oral gavage and served as placebo controls.

**KEY:** PFU = plaque-forming units; N/A = not applicable; IV = intravenous

Source: Table 3.3-1 in CSR

The trial began on July 23, 2010 and was completed on January 4, 2011. Trial SR10-037F was conducted at (b) (4)

**The primary efficacy endpoint** was the proportion of animals that survived after MPXV inoculation for up to 56 days. For survival analyses, no distinction was made between animals that were euthanized in moribund condition per standard criteria and those that died as a result of MPXV infection.

The intent to treat (ITT) population included all monkeys that were randomized and received at least one dose of test article. ITT population was used for the primary efficacy endpoint analysis.

The differences of survival rates between each individual active treatment group and placebo were analyzed using Fisher’s exact test at the significance level of 0.05 (2-sided). The differences of survival rates between all treatment groups combined and placebo were also analyzed using Fisher’s exact test at the significance level of 0.05 (2-sided).

Due to multiple comparisons, the determination of statistical significance of the proportion analysis between each individual active dose and placebo was based on a closed-test procedure to handle the issue of multiplicity. The closed-test procedure had a fixed sequence starting from the earliest treatment initiation (Group 2 on Day 4) compared to placebo, continuing to the second earliest treatment initiation (Group 3 on Day 5), until there was no significant difference between time of treatment initiation and placebo.

There was no sample size calculation presented in the protocol.

*Reviewer comment: The CSR did not report the multiplicity adjusted results or the reviewer could not access it.*

**❖ Trial SR10-038F – A treatment duration trial**

Trial SR10-038F was a randomized, double-blind, placebo-controlled trial assessing the effect of duration of ST-246 treatment on efficacy following intravenous (IV) MPXV challenge.

Twenty-five (25) randomly selected healthy male and female cynomolgus monkeys were assigned to five groups per weight and sex.

**Table 4** Trial Group Assignment for Trial RS10-038F

Group <sup>a</sup>	No. of Animals		MPXV Challenge Dose (Day 0)	ST-246 Dose Level	Dosage Schedule <sup>b</sup>	
	M	F			ST-246	Placebo
1 – Placebo <sup>c</sup>	2	2	5 x 10 <sup>7</sup> PFU IV	0 mg/kg	N/A	Days 4-13
2 – ST-246 3 doses	2	2	5 x 10 <sup>7</sup> PFU IV	10 mg/kg	Days 4-6	Days 7-13
3 – ST-246 5 doses	3	3	5 x 10 <sup>7</sup> PFU IV	10 mg/kg	Days 4-8	Days 9-13
4 – ST-246 7 doses	3	3	5 x 10 <sup>7</sup> PFU IV	10 mg/kg	Days 4-10	Days 11-13
5 – ST-246 10 doses	2	3	5 x 10 <sup>7</sup> PFU IV	10 mg/kg	Days 4-13	N/A

PFU = plaque-forming units; N/A = not applicable; IV = intravenous

Source: Table 3.3-1 in CSR

Animals received ST-246 at 10 mg/kg by oral gavage for 3, 5, 7, or 10 consecutive days beginning on Day 4 after inoculation. To accommodate blinding, Groups 2, 3, and 4 were administered placebo on non-ST-246 dose days during the treatment period. Group 1 received placebo only.

The trial began on October 8, 2010 and was completed on January 4, 2011. Trial SR10-038F was conducted at (b) (4)

**The primary efficacy endpoint** was the proportion of animals that survived after MPXV inoculation for up to 28 days. For survival analyses, no distinction was made between animals that were euthanized in moribund condition and those that died because of monkeypox virus infection.

The intent-to-treat (ITT) population consisted of all animals that were properly inoculated and received at least the first dose of the study drug.

The primary efficacy endpoint of proportion of animals surviving or died (including euthanized due to moribund condition) through Day 28 was analyzed for differences between all treatment groups combined and placebo, as well as between each individual active treatment group and placebo, using Fisher's exact test at the significance level of 0.05 (2-sided), for the ITT population.

Since multiple comparisons were involved in assessing individual treatment groups against placebo for the primary efficacy endpoint, the determination of statistical significance of the proportion analysis between each individual active dose and placebo was based on a closed-test procedure to handle the issue of multiplicity. The closed-test procedure had a fixed sequence starting from the longest treatment duration (Group 5; 10 days) compared to placebo, continuing to the second longest treatment duration (Group 4; 7 days), until there was no significant difference between active treatment duration time and placebo. There was no sample size calculation presented in the protocol.

*Reviewer comment: The CSR did not report the multiplicity adjusted results*

#### ❖ Trial FY10-087 – A PK trial

Trial FY10-087 was a randomized, placebo-controlled, repeat-dose trial to evaluate the PK of tecovirimat in male and female cynomolgus monkeys infected via intravenous (IV) injection with MPXV. *This trial was not double-blind.*

A total of 24 animals were randomized by body weight to receive placebo (6 animals) or tecovirimat 3, 10, or 20 mg/kg (6 animals each) in this trial. All 24 animals were included in the ITT population.

**Table 5** Trial Group Layout for Trial FY10-087

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)

Source: Table 1 in CSR

Animals were infected via IV injection with MPXV (5 x 10<sup>7</sup> pfu) on Day 0. Animals received placebo once daily or tecovirimat 3, 10, or 20 mg/kg once daily on Day -10 (for PK baseline in uninfected animals) and Days 4-17 post-infection. Animals were monitored twice daily for moribundity and mortality through Day 28 (animals found moribund were euthanized, and animals surviving to trial termination were euthanized on Day 28).

**The primary efficacy endpoint** was the proportion of animals that survived until Day 28 PI. No inferential statistical analysis will be planned. Only summary statistics (means, standard deviation, charts, graphs, etc.) will be generated to analyze the data on this pharmacokinetic trial. There was no sample size calculation presented in the protocol.

*Reviewer comment: the applicant reported 1-sided Boschloo test p-value in the summary of clinical efficacy.*

### 3.2.1.2 Rabbitpox Model – Two Trials:

In two rabbit trials, 16-week-old New Zealand white rabbits were challenged intradermally with 1,000 PFU of the RPXV Utrecht strain

#### ❖ Trial SR14-008F – A dose-ranging trial

Trial SR14-008F was a randomized, double-blinded, placebo-controlled trial to evaluate the dose-response relationship between tecovirimat plasma exposure and therapeutic efficacy in NZW rabbits intradermally-infected with a lethal dose of rabbitpox virus.

Fifty (50, 25 male/25 female) 16-week old NZW rabbits were randomized into 5 groups of 10 animals based on gender and body weight (Table 6 below). On Day 0, all animals were challenged intradermally with RPXV at a target dose of 1,000 PFU. On Day 4 post-challenge (a day by which all RPXV-infected animals are historically expected to exhibit fever and viral DNA in the blood as a therapeutic trigger), all animals started once daily dosing by oral gavage of tecovirimat corresponding to each group's dose level and continued for 14 consecutive days.

**Table 6** Trial Group Layout for Trial SR14-008F

Group	Treatment <sup>1</sup> Group	Number of Animals/group (Male/Female)	RPXV ID Challenge Dose <sup>2</sup>
1	Placebo	10 (5/5)	1,000 PFU
2	Tecovirimat 20 mg/kg/day	10 (5/5)	1,000 PFU
3	Tecovirimat 40 mg/kg/day	10 (5/5)	1,000 PFU
4	Tecovirimat 80 mg/kg/day	10 (5/5)	1,000 PFU
5	Tecovirimat 120 mg/kg/day	10 (5/5)	1,000 PFU

<sup>1</sup>All animals were treated with the specified dose once daily for 14-consecutive days from Day 4 to Day 17 post-challenge.

<sup>2</sup>The target challenge dose for each animal was 1,000 PFU/200 uL given by bilateral intradermal injections, one injection of 100 uL in each shaved thigh using 2 syringes of 100 uL (500 PFU) each.

Source: Table 2 in CSR.

The **primary efficacy endpoint** was the proportion of animals that survived until Day 30 or 31 PI. Fisher Exact tests were conducted to compare survival rate between Groups 1-5. There was no sample size calculation presented in the protocol.

*Reviewer comment: the applicant reported 1-sided Boschloo test p-value in the summary of clinical efficacy.*

#### ❖ Trial SR13-025F – A PK trial

Trial SR13-025F was a randomized, double-blinded trial to evaluation of the impact of rabbitpox virus infection on oral PK of tecovirimat in male and female New Zealand White rabbits.

Twenty-four (24) NZW rabbits were randomized into 3 groups of 8 animals each based on gender and body weight. On Day -7 (7 days prior to challenge day), all animals received one single dose of tecovirimat corresponding to each dose group (Table 7). On Day 0, all animals were challenged intradermally with RPXV. On Day 4 post-challenge, all animals started once daily dosing by oral gavage of tecovirimat corresponding to each dose group and continued for 14 consecutive days.

**Table 7** Trial Group Layout for Trial SR13-025F

Group	Treatment <sup>1</sup> Group	RPXV Intradermal Challenge Dose <sup>2</sup>	Animal ID Number
1	Tecovirimat 40 mg/kg/day	1000 PFU	992, 994, 1001, 1005, 1011, 1012, 1017, 1022
2	Tecovirimat 80 mg/kg/day	1000 PFU	993, 1000, 1002, 1006, 1014, 1019, 1020, 1023
3	Tecovirimat 120 mg/kg/day	1000 PFU	995, 996, 999, 1003, 1015, 1016, 1018, 1021

<sup>1</sup>All animals were treated with the specified dose on Day -7, and once daily for 14-consecutive days from Day 4 to Day 17 post-challenge.

<sup>2</sup>The target challenge dose for each animal was 1,000 PFU/200 uL given by bilateral intradermal injections, one injection of 100 uL in each shaved thigh using 2 syringes of 100 uL (500 PFU) each.

Source: Table 2 in CSR.

**The primary efficacy endpoint** was the proportion of animals that survived until Day 18 PI. Fisher Exact tests were conducted to compare survival rate between Groups 1-3. There was no sample size calculation presented in the protocol.

*Reviewer comment: the applicant reported 1-sided Boschloo test p-value in the summary of clinical efficacy.*

### **3.2.2 Demographics**

#### **3.2.2.1 Demographics**

The reviewer has checked the randomization for all six trials. Body weights were balanced among groups within trials where body weight was used as a stratification factor even though the reviewer's results were slightly different from the CSR results. The reviewer was able to reproduce the gender distribution, presented in CSRs, among treatment groups in trials where gender was used as a stratification factor. Please see Tables in Appendix Part A for details.

### **3.2.3 Statistical Methodologies**

The exact 95% CI of survival rate difference was based on the inverted two one-sided test in PROC Binomial in StatXact. **The Boschloo's test p-value was calculated with option of  $\gamma=0.000001$  as default value.** The multiplicity adjustment of Boschloo's p-values was conducted using Holm procedure.

*Reviewer comment: the applicant presented the 1-sided Boschloo test p-value with  $\gamma=0.001$  in the summary of clinical efficacy instead of the 2-sided Fisher's exact test p-value, which was presented in the CSRs. Boschloo's test, which is an unconditional test, is uniformly more powerful test than the Fisher's exact test and therefore the reviewer will use Boschloo test in the review.*

### **3.2.4 Results and Conclusions**

#### **3.2.4.1 Primary Efficacy Results in Monkeypox Trials**

##### **❖ Trial AP-09-026G – A dose-ranging trial**

The survival rates of 5 groups were listed in Table 8. The survival rates in 3 and 10 mg/kg/day for 14 days starting at Day 4 after virus inoculation groups were significant higher than that in the placebo group.

**Table 8:** Survival Rate for Monkeypox Trial AP-09-026G (ITT)

Group	Survival Rate % (n/N)	Exact 95% CI <sup>a</sup>	Rate Diff & Exact 95% CI of (trt – Placebo) <sup>b</sup>	Boschloo's 1-sided P-value <sup>c</sup>
1 Placebo	0% (0/7)	(0%, 41.0%)		
2 0.3 mg/kg/day x 14 days	20% (1/5)	(0.5%, 71.6%)	20% (-23.8%, 71.6%)	0.2541
3 1 mg/kg/day x 14 days	0% (0/5)	(0%, 52.2%)	0% (-41.0, 52.2%)	NA
4 3 mg/kg/day x 14 days	80% (4/5)	(28.4%, 99.5%)	80% (20.8%, 99.5%)	0.0038
5 10 mg/kg/day x 14 days	80% (4/5)	(28.4%, 99.5%)	80% (20.8%, 99.5%)	0.0038

<sup>a</sup>: The exact Clopper-Pearson 95% CI.

<sup>b</sup>: The exact confidence interval of rate difference was based on inverting two one-sided tests in StatXact.

<sup>c</sup>: P-value is based on a Boschloo's test with gamma=0.000001 compared with placebo group.

### Sensitivity analysis:

Per the clinical review and listing 2 of disposition details in CSR, three animals (#19, #27, and #21), one from each of 1, 3, and 10 mg/kg/day group respectively, were found dead although the typical MPXV disease was not apparent. A sensitivity analysis was conducted by excluding these three animals from the analysis (Table 9). The results still suggested that the survival rates in 3 and 10 mg/kg/day groups were significant higher than that in the placebo group.

**Table 9:** Sensitivity Analysis of the Survival Rate for Monkeypox Trial AP-09-026G

Group	Survival Rate % (n/N)	Rate Diff & exact 95% CI of (trt – Placebo) <sup>a</sup>	Boschloo's 1-sided P-value <sup>b</sup>
1: Placebo	0% (0/7)		
2: 0.3 mg/kg/day x 14 days	20% (1/5)	20% (-23.8%, 71.6%)	0.2541
3: 1 mg/kg/day x 14 days	0% (0/4)	0% (-43.7%, 60.2%)	NA
4: 3 mg/kg/day x 14 days	100% (4/4)	100% (37.7%, 100%)	0.0007
5: 10 mg/kg/day x 14 days	100% (4/4)	100% (37.7%, 100%)	0.0007

<sup>a</sup>: The exact confidence interval of rate difference was based on inverting two one-sided tests in StatXact.

<sup>b</sup>: P-value is based on a Boschloo's test with gamma=0.000001 compared with placebo group.

### ❖ Trial SR10-037F – A delayed treatment trial

The survival rates of 4 groups were listed in Table 10. The survival rates in 10 mg/kg/day for 14 days starting at Day 4 and Day 5 after virus inoculation groups were significant higher than that in the placebo group.

**Table 10:** Survival Rate for Monkeypox Trial SR10-037F (ITT)

Group	Survival Rate % (n/N)	Exact 95% CI <sup>a</sup>	Rate Diff & Exact 95% CI of (trt – Placebo) <sup>b</sup>	Boschloo's 1-sided P-value <sup>c</sup>
1: Placebo	0% (0/3)	(0%, 70.8%)		
2: 10 mg/kg on Day 4	83.3% (5/6)	(35.9%, 99.6%)	83.3% (7.5%, 99.6%)	0.0151
3: 10 mg/kg on Day 5	83.3% (5/6)	(35.9%, 99.6%)	83.3% (7.5%, 99.6%)	0.0151
4: 10 mg/kg on Day 6	50% (3/6)	(11.8%, 88.2%)	50% (-28.3%, 90.2%)	0.1231

<sup>a</sup>: The exact Clopper-Pearson 95% CI.

<sup>b</sup>: The exact confidence interval of rate difference was based on inverting two one-sided tests in StatXact.

c: P-value is based on a Boschloo's test with gamma=0.000001 compared with placebo group.

### ❖ Trial SR10-038F – A treatment duration trial

The survival rates of 5 groups were listed in Table 11. The survival rates in 10 mg/kg/day for 5 and 7 days starting at Day 4 after virus inoculation groups were significantly higher than those in the placebo group, but the same was not evident for 3 days after inoculation in Group 2. The survival rate in the group with 10 days of treatment was slightly lower than that in the groups receiving for 5 or 7 days, however, the survival rate in the group with 10 days of treatment was not statistically different from the placebo group.

**Table 11:** Survival Rate for Monkeypox Trial SR10-038F (ITT)

Group	Survival Rate % (n/N)	Exact 95% CI <sup>a</sup>	Rate Diff & Exact 95% CI of (trt – Placebo) <sup>b</sup>	Boschloo's 1-sided P-value <sup>c</sup>
1 Placebo	25% (1/4)	(0.6%, 80.6%)		
2 10 mg/kg for 3 days	50% (2/4)	(6.8%, 93.2%)	25% (-51.0%, 83.0%)	0.3633
3 10 mg/kg for 5 days	100% (6/6)	(54.1%, 100%)	75% (8.1%, 99.4%)	0.0133
4 10 mg/kg for 7 days	100% (6/6)	(54.1%, 100%)	75% (8.1%, 99.4%)	0.0133
5 10 mg/kg for 10 days	80% (4/5)	(28.4%, 99.5%)	55% (-20.9%, 93.7%)	0.0962

a: The exact Clopper-Pearson 95% CI.

b: The exact confidence interval of rate difference was based on inverting two one-sided tests in StatXact.

c: P-value is based on a Boschloo's test with gamma=0.000001 compared with placebo group.

### ❖ Trial FY10-087 – A PK trial

The survival rates of 3 groups were listed in Table 12. The survival rates in 3, 10, and 20 mg/kg/day for 14 days starting at Day 4 after virus inoculation groups were significant higher than those in the placebo group.

**Table 12:** Survival Rate for Monkeypox Trial FY10-087 (ITT)

Group	Survival Rate % (n/N)	Exact 95% CI <sup>a</sup>	Rate Diff & Exact 95% CI of (trt – Placebo) <sup>b</sup>	Boschloo's 1-sided P-value <sup>c</sup>
1 Placebo	0%(0/6)	(0%, 45.9%)		
2 3 mg/kg for 14 days	100% (6/6)	(54.1%, 100%)	100% (47.1%, 100%)	0.0002
3 10 mg/kg for 14 days	100% (6/6)	(54.1%, 100%)	100% (47.1%, 100%)	0.0002
4 20 mg/kg for 14 days	100% (6/6)	(54.1%, 100%)	100% (47.1%, 100%)	0.0002

a: The exact Clopper-Pearson 95% CI.

b: The exact confidence interval of rate difference was based on inverting two one-sided tests in StatXact.

c: P-value is based on a Boschloo's test with gamma=0.000001 compared with placebo group.

In summary, a statistically significant treatment benefit over placebo was demonstrated in monkeypox trials for the primary endpoint of survival rate when tecovirimat was dosed at 3, 10, or 20 mg/kg/day for at least 5 days starting at Day 4 or Day 5 after virus inoculation.

### 3.2.4.2 Primary Efficacy Results in Rabbitpox Trials

#### ❖ Trial SR14-008F – A dose-ranging trial

The survival rates of 5 groups were listed in Table 13. The survival rates in 20, 40, 80, and 120 mg/kg/day for 14 days starting at day 4 after virus inoculation groups were significant higher than that in the placebo group.

**Table 13:** Survival Rate for Rabbitpox Trial SR14-008F (ITT)

Group	Survival Rate % (n/N)	Exact 95% CI <sup>a</sup>	Rate Diff & Exact 95% CI of (trt – Placebo) <sup>b</sup>	Boschloo's 1-sided P-value <sup>c</sup>
<b>1 Placebo</b>	<b>0% (0/10)</b>	(0%, 30.9%)		
2 20 mg/kg/day for 14 days	90% (9/10)	(55.5%, 99.8%)	90% (50.3%, 99.8%)	0.0
3 40 mg/kg/day for 14 days	90% (9/10)	(55.5%, 99.8%)	90% (50.3%, 99.8%)	0.0
4 80 mg/kg/day for 14 days	80% (8/10)	(44.4%, 97.5%)	80% (41.4%, 97.5%)	0.0001
5 120 mg/kg/day for 14 days	80% (8/10)	(44.4%, 97.5%)	80% (41.4%, 97.5%)	0.0001

<sup>a</sup>: The exact Clopper-Pearson 95% CI.

<sup>b</sup>: The exact confidence interval of rate difference was based on inverting two one-sided tests in StatXact.

<sup>c</sup>: P-value is based on a Boschloo's test with gamma=0.000001 compared with placebo group.

#### Sensitivity analysis:

Two animals, rabbit 990 in placebo group (group 1) and rabbit 989 in 80 mg/kg/day group (group 4), were found dead. The CSR stated that the cause of death was inconclusive, but the trial investigators assessed the death as unlikely to be severe RPXV disease. These two rabbits were excluded from the analysis (Table 14). The results still suggested that the survival rates in 20, 40, 80, and 120 mg/kg/day groups were significantly higher than those in the placebo group.

**Table 14:** Sensitivity Analysis of the Survival Rate for Rabbitpox Trial SR14-008F

Group	Survival Rate % (n/N)	Rate Diff & exact 95% CI of (trt – Placebo) <sup>a</sup>	Boschloo's 1-sided P-value <sup>b</sup>
<b>1: Placebo</b>	<b>0% (0/9)</b>		
2: 20 mg/kg/day for 14 days	90% (9/10)	90% (47.7%, 99.8%)	0.0
3: 40 mg/kg/day for 14 days	90% (9/10)	90% (47.7%, 99.8%)	0.0
4: 80 mg/kg/day for 14 days	88.9% (8/9)	88.9% (45.4%, 99.7%)	0.0001
5: 120 mg/kg/day for 14 days	80% (8/10)	80% (40.2%, 97.5%)	0.0001

<sup>a</sup>: The exact confidence interval of rate difference was based on inverting two one-sided tests in StatXact.

<sup>b</sup>: P-value is based on a Boschloo's test with gamma=0.000001 compared with placebo group.

### ❖ Trial SR13-025F – A PK trial

The survival rates of 3 groups were listed in Table 15. The survival rates in 40, 80, and 120 mg/kg/day for 14 days starting at day 4 after virus inoculation groups were similar to those observed in trial SR14-008F.

**Table 15:** Survival Rate for Rabbitpox Trial SR13-025F (ITT)

Group	Survival Rate % (n/N)	Exact 95% CI <sup>a</sup>
1: 40 mg/kg/day for 14 days	87.5% (7/8)	87.5% (47.4%, 99.7%)
2: 80 mg/kg/day for 14 days	87.5% (7/8)	87.5% (47.4%, 99.7%)
3: 120 mg/kg/day for 14 days	100% (8/8)	100% (63.1%, 100%)

<sup>a</sup>: The exact Clopper-Pearson 95% CI.

#### Sensitivity analysis:

Two animals, rabbit 1011 in 40 mg/kg/day group (group 1) and rabbit 993 in 80 mg/kg/day group (group 2), were found dead during the trial. The CSR stated that these two rabbits were found dead immediately after tecovirimat dosing. This mortality was a result of the gavage procedure and not caused by RPXV disease therefore, these two rabbits were excluded from the analysis (Table 16). The results did not change the conclusion.

**Table 16:** Sensitivity Analysis of the Survival Rate for Rabbitpox Trial SR13-025F

Group	Survival Rate % (n/N)	Exact 95% CI <sup>a</sup>
1: 40 mg/kg/day for 14 days	100% (7/7)	100% (59.0%, 100%)
2: 80 mg/kg/day for 14 days	100% (7/7)	100% (59.0%, 100%)
3: 120 mg/kg/day for 14 days	100% (8/8)	100% (63.1%, 100%)

<sup>a</sup>: The exact confidence interval of rate difference was based on inverting two one-sided tests in StatXact.

In summary, a statistically significant treatment benefit over placebo was demonstrated in rabbitpox trials for the primary endpoint of survival rate when tecovirimat was dosed at 20, 40, 80, and 120 mg/kg/day for 14 days starting at Day 4 after virus inoculation.

### 3.3 Evaluation of Safety

Please see the clinical review for the evaluation of safety.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Due to the limited sample sizes in these animal trials, no subgroup analysis was conducted.

## **5. SUMMARY AND CONCLUSIONS**

### **5.1 Statistical Issues and Collective Evidence**

There was one minor statistical issue. The multiplicity adjusted p-values were not presented in the CSR nor in the summary of clinical efficacy even though a few trial protocols stated that a closed-test procedure will be conducted (see section 3.2.1 for details). The reviewer did use Holm procedure for multiplicity adjustment based on Boschloo's test p-values. Even though most of p-values were changed slightly due to multiplicity adjustment, the conclusions were not changed (Please see results in the Appendix).

Overall in the monkeypox trials, a statistically significant survival benefit over placebo was shown for treatment groups in which tecovirimat was dosed at 3, 10, or 20 mg/kg/day for 14 days starting at Day 4 after virus inoculation. The survival rates ranged from 80% to 100% in the group treated with 3 mg/kg/day and from 75% to 100% in the group treated with 10 mg/kg/day for at least 5 consecutive days. A 100% survival rate was observed in the group treated with 20 mg/kg/day for 14 days.

A statistically significant treatment benefit over placebo for the primary endpoint of survival rate in rabbitpox trials was shown for all treatment groups in which tecovirimat was dosed at 20, 40, 80, or 120 mg/kg/day for 14 days starting at Day 4 after virus inoculation. The survival rates in all treatment groups with at least 20 mg/kg/day were at least 80%.

### **5.2 Conclusions and Recommendations**

The applicant has demonstrated that tecovirimat is efficacious in the two animal models, Monkeypox infection in monkeys and rabbitpox infection in rabbits. By the Animal Rule, these results support the recommendation of approving tecovirimat as a treatment of adult and pediatric patients who have been infected with smallpox.

### **5.3 Labeling Recommendations**

The dose regimen for human subjects is 600 mg twice daily (please refer to the clinical review for details regarding the dose determination).

For human dose selection, a tecovirimat dose of 10 mg/kg/day for 14 days starting at day 4 after virus inoculation was selected in Monkeypox trials to provide exposures that exceed those associated with fully effective dose. A tecovirimat dose of 40 mg/kg/day for 14 days starting at day 4 after virus inoculation was selected in Rabbitpox trials to provide exposures that exceed those associated with fully effective dose for human dose selection. For these reasons, only

groups treated with tecovirimat dose of 10 mg/kg/day for 14 days were selected in Monkeypox trials and tecovirimat dose of 40 mg/kg/day for 14 days were selected in Rabbitpox trials to present in section 14 of the label. [The following table is the current table in the label, which has not been finalized by now and is subject to change.](#)

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

	Treatment Initiation <sup>a</sup>	Survival Percentage (# survived/n)		p-value <sup>b</sup>	Survival Rate Difference <sup>c</sup> (b) (4) 95% CI <sup>d</sup>
		Placebo	Tecovirimat		
<b>NZW Rabbits</b>					
Study 1	Day 4	0% (0/10)	90% (9/10)	<0.0001	90% (50.3%, 99.8%)
Study 2	Day 4	NA <sup>e</sup>	88% (7/8)	NA	NA
<b>Cynomolgus Macaques</b>					
Study 1	Day 4	0% (0/7)	80% (4/5)	0.0038	80% (20.8%, 99.5%)
Study 2	Day 4	0% (0/6)	100% (6/6)	0.0002	100% (47.1%, 100%)
Study 3	Day 4	0% (0/3)	83% (5/6)	0.0151	83% (7.5%, 99.6%)
	Day 5		83% (5/6)	0.0151	83% (7.5%, 99.6%)
	Day 6		50% (3/6)	0.1231	50% (-28.3%, 90.2%)

<sup>a</sup>: Day post-challenge tecovirimat treatment was initiated

<sup>b</sup>: p-value is from 1-sided Boschloo Test (with Berger-Boos modification of gamma = 0.000001) compared to placebo.

<sup>c</sup>: Survival percentage in tecovirimat treated animals minus survival percentage in placebo treated animals.

<sup>d</sup>: Exact 95% confidence interval based on the score statistic of difference in survival rates.

<sup>e</sup>: NA = Not Applicable. A placebo control group was not included in this study.

[Note: For NZW Rabbits trials in the table above, Study 1 was SR14-008F and Study 2 was SR13-025F. For Cynomolgus Macaques trials in the table above, Study 1 was Ap-09-026G, Study 2 was FY10-087, and Study 3 was SR10-037F.](#)

**Reference**

Breman JG, Henderson DA. Diagnosis and management of smallpox. N Engl J Med. 2002;346(17):1300-8. StatXact manual.

## APPENDICES

### Part A: Body Weight and Gender Distribution

**Table 17:** Monkey's Body Weight at the randomization and Study Day -1 For Trial AP-09-026G

Group / Treatment	Day -10 BW (11/24/2009) in iteration 1 or Day -8 BW (02/25/2010) in iteration 2				Day -1 BW (kg)			
	N	Mean	Median	Range	N	Mean	Median	Range
1: Placebo	7	5.37	5.4	4.2, 6.2	7	5.36	5.4	4.2, 6.2
2: 0.3 mg/kg/day x 14 days	5	5.86	5.6	4.4, 8.6	5	5.86	5.6	4.4, 8.6
3: 1 mg/kg/day x 14 days	5	5.38	5.4	4.3, 6.4	5	5.38	5.4	4.3, 6.4
4: 3 mg/kg/day x 14 days	5	5.52	5.3	4.8, 6.8	5	5.52	5.3	4.8, 6.8
5: 10 mg/kg/day x 14 days	5	5.44	5.5	5.0, 5.8	5	5.44	5.5	5.0, 5.8

**Table 18:** Monkey's Gender and Body Weight at Study Day -11 and Study Day -1 For Trial SR10-037F

Group / Treatment	Sex	Day -11 BW (7/23/2010)				Day -1 BW (8/2/2010)			
	M/F	N	Mean	Median	Range	N	Mean	Median	Range
1: Placebo	1/2	3	2.87	2.77	2.64, 3.20	3	2.7	2.59	2.49, 3.02
2: 10 mg/kg on Day 4	3/3	6	3.01	3.09	2.60, 3.34	6	2.87	2.91	2.49, 3.15
3: 10 mg/kg on Day 5	3/3	6	3.08	3.03	2.74, 3.66	6	2.94	2.95	2.67, 3.19
4: 10 mg/kg on Day 6	3/3	6	3.03	3.03	2.77, 3.28	6	2.93	2.91	2.71, 3.27

**Table 19:** Monkey's Gender and Body Weight at Study Day -11 and Study Day -1 For Trial SR10-038F

Group / Treatment	Sex	Day -11 BW (10/11/2010)				Day -1 BW (10/21/2010)			
	M/F	N	Mean	Median	Range	N	Mean	Median	Range
1: Placebo	2/2	4	3.56	3.45	2.98, 4.34	4	3.52	3.37	2.89, 4.44
2: 10 mg/kg for 3 days	2/2	4	3.45	3.44	2.93, 4.01	4	3.40	3.37	2.81, 4.04
3: 10 mg/kg for 5 days	3/3	6	3.53	3.41	2.77, 4.52	6	3.52	3.42	2.71, 4.56
4: 10 mg/kg for 7 days	3/3	6	3.51	3.29	2.56, 4.36	6	3.52	3.18	2.58, 4.39
5: 10 mg/kg for 10 days	2/3	5	3.27	3.33	2.75, 3.73	5	3.19	3.20	2.71, 3.68

**Table 20:** Monkey's Gender and Body Weight at Study Day -35 and Study Day -10 For Trial FY10-087

Group / Treatment	Sex	Day -35 (8/13/2010) or -37 BW (8/11/2010)				Day -10 BW (9/7/2010)			
	M/F	N	Mean	Median	Range	N	Mean	Median	Range
1: Placebo	3/3	6	3.7	3.61	3.01, 4.94	6	3.87	3.83	2.96, 5.02
2: 3 mg/kg for 14 days	3/3	6	3.59	3.53	3.09, 4.15	6	3.70	3.68	3.00, 4.40
3: 10 mg/kg for 14 days	3/3	6	3.58	3.48	2.80, 4.44	6	3.82	3.81	2.86, 4.58
4: 20 mg/kg for 14 days	3/3	6	3.66	3.74	2.91, 4.40	6	3.91	3.92	3.12, 4.94

**Table 21:** Rabbit's Body Weight at Study Day 0 and Study Day 1 For Trial SR14-008F

Group / Treatment	Day 0 BW (2/20/2014)		Day 1 BW (2/21/2014)	
	Mean	Range	Mean	Range
1: Placebo	2.33	2.1- 2.7	2.31	2.0 – 2.7
2: 20 mg/kg/day x 14 days	2.36	2.1- 2.6	2.32	2.1 – 2.5
3: 40 mg/kg/day x 14 days	2.31	2.0 – 2.5	2.30	2.0 – 2.6
4: 80 mg/kg/day x 14 days	2.31	2.1 – 2.8	2.29	2.0 – 2.8
5: 120 mg/kg/day x 14 days	2.35	2.1 – 2.6	2.35	2.1 – 2.6

**Table 22:** Rabbit's Body Weight at Study Day 0 and Study Day 1 For Trial SR13-025F

Group / Treatment	Day 0 BW (4/24/2015)		Day 1 BW (4/25/2015)	
	Mean	Range	Mean	Range
1: 40 mg/kg/day x 14 days	2.51	2.4 – 2.7	2.53	2.4 – 2.6
2: 80 mg/kg/day x 14 days	2.58	2.4 – 2.8	2.56	2.4 – 2.7
3: 120 mg/kg/day x 14 days	2.59	2.3 – 2.8	2.54	2.3 – 2.8

**Part B: Multiplicity Adjustment on the Primary Efficacy Endpoint Analysis****Table 23:** Multiplicity Adjusted Boschloo's P-value of Primary Efficacy Endpoint Analysis for Trial AP-09-026G

Group Comparison	Fisher's Exact Test 2-sided P-value	Boschloo's 1-sided P-value <sup>a</sup>	Multiplicity Adjusted P-value	
			Holm <sup>b</sup>	Hochberg <sup>b</sup>
1 vs. 2	0.4167	0.2541	0.7623	0.5156
1 vs. 3	NA	NA		
1 vs. 4	0.0101	0.0038	0.0342	0.0304
1 vs. 5	0.0101	0.0038	0.0342	0.0304
2 vs. 3	1.0	0.2578	0.7623	0.5156
2 vs. 4	0.2063	0.0547	0.2735	0.2188
2 vs. 5	0.2063	0.0547	0.2735	0.2188
3 vs. 4	0.0476	0.0107	0.0749	0.0642
3 vs. 5	0.0476	0.0107	0.0749	0.0642
4 vs. 5	1.0	0.6211	0.7623	0.6211

<sup>a</sup>: P-value is based on a Boschloo's test with gamma=0.000001 compared with placebo group.

<sup>b</sup>: Only 9 test p-values from Boschloo's test were used for the multiple adjustment. Using 10 test p-values by imputed 1 vs. 3 to 1.00, the Holm and Hochberg results changed a bit and did not change the story.

**Table 24:** Multiplicity Adjusted Boschloo's P-value of Primary Efficacy Endpoint Analysis for Trial SR10-037F

Group Comparison	Fisher's Exact Test 2-sided P-value	Boschloo's 1-sided P-value <sup>a</sup>	Multiplicity Adjusted P-value	
			Holm	Hochberg
1 vs. 2	0.0476	0.0151	0.0906	0.0755
1 vs. 3	0.0476	0.0151	0.0906	0.0755
1 vs. 4	0.4643	0.1231	0.4924	0.3028

2 vs. 3	1.0	0.6133	0.6133	0.6133
2 vs. 4	0.5455	0.1514	0.4924	0.3028
3 vs. 4	0.5455	0.1514	0.4924	0.3028

a: P-value is based on a Boschloo's test with gamma=0.000001 compared with placebo group.

**Table 25:** Multiplicity Adjusted Boschloo's P-value of Primary Efficacy Endpoint Analysis for Trial SR10-038F

Group Comparison	Fisher's Exact Test 2-sided P-value	Boschloo's 1-sided P-value <sup>a</sup>	Multiplicity Adjustment	
			Holm <sup>b</sup>	Hochberg <sup>b</sup>
1 vs. 2	1.0	0.3633	0.9948	0.3633
1 vs. 3	0.0333	0.0133	0.1197	0.1064
1 vs. 4	0.0333	0.0133	0.1197	0.1064
1 vs. 5	0.2063	0.0962	0.4844	0.3633
2 vs. 3	0.1333	0.0692	0.4844	0.3633
2 vs. 4	0.1333	0.0692	0.4844	0.3633
2 vs. 5	0.5238	0.2487	0.9948	0.3633
3 vs. 4	NA	NA		
3 vs. 5	0.4545	0.2997	0.9948	0.3633
4 vs. 5	0.4545	0.2997	0.9948	0.3633

a: P-value is based on a Boschloo's test with gamma=0.000001 compared with placebo group.

b: Only 9 test p-values from Boschloo's test were used for the multiple adjustment. Using 10 test p-values by imputed 3 vs. 4 to 1.00, the Holm and Hochberg results changed a bit and did not change the story.

**Table 26:** Multiplicity Adjusted Boschloo's P-value of Primary Efficacy Endpoint Analysis for Trial FY10-087

Group Comparison	Fisher's Exact Test 2-sided P-value	Boschloo's 1-sided P-value <sup>a</sup>	Multiplicity Adjustment	
			Holm <sup>b</sup>	Hochberg <sup>b</sup>
1 vs. 2	0.0022	0.0002	0.0006	0.0002
1 vs. 3	0.0022	0.0002	0.0006	0.0002
1 vs. 4	0.0022	0.0002	0.0006	0.0002
2 vs. 3	NA	NA		
2 vs. 4	NA	NA		
3 vs. 4	NA	NA		

a: P-value is based on a Boschloo's test with gamma=0.000001 compared with placebo group.

b: Only 3 test p-values from Boschloo's test were used for the multiple adjustment. Using 6 test p-values by imputed NA to 1.00, the Holm and Hochberg results changed a bit and did not change the story.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

WEN ZENG  
05/08/2018

THAMBAN I VALAPPIL  
05/08/2018