

**FDA ADVISORY COMMITTEE BRIEFING
DOCUMENT**

Tecovirimat for the Treatment of Smallpox Disease

**Antimicrobial Division Advisory Committee Meeting
May 1, 2018**

**FINAL ADVISORY COMMITTEE
BRIEFING MATERIALS:
AVAILABLE FOR PUBLIC RELEASE**

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LIST OF ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AUC	Area under the curve
AUC ₀₋₂₄	Area under the plasma concentration time curve from time zero to the 24 hours
BARDA	Biomedical Advanced Research and Development Authority
BID	Twice daily
CC50	50% cytotoxic concentration
CDC	Centers for Disease Control and Prevention
CEV	Cell-associated enveloped virus
CL/F	Total body clearance normalized for fraction of dose absorbed
C _{max}	Maximum plasma concentration
CNS	Central nervous system
CPE	Cytopathic effects
CPXV	Cowpox virus
CYP	Cytochrome P450
EC50	Half maximal effective concentration
ECG	Electrocardiogram
EEV	Extracellular enveloped virus
EFD	Embryo-fetal development
E-IND	Emergency Investigational New Drug Application
EMS	Emergency medical services
ESRD	End-stage renal disease
EV	Enveloped virus
FDA	Food and Drug Administration
HD	Hemodialysis
hERG	Human ether-a-go-go-related gene
ID	Intradermal
IEV	Intracellular enveloped virus
IMV	Intracellular mature virus
IND	Investigational New Drug
ITT	Intent to treat
IV	Intravenous
LLOQ	Lower limit of quantification
LOD	Limit of detection
MPXV	Monkeypox virus
NDA	New Drug Application
NHP	Non-human primate
NIH	National Institutes of Health
NOAEL	No-observed-adverse-effect-level
NOEL	No-observed-effect-level
PD	Pharmacodynamic
pfu	Plaque forming units
PK	Pharmacokinetics
qPCR	Quantitative polymerase chain reaction
QTcF	Federicia-corrected QT
RAC	Accumulation ratio
RPXV	Rabbitpox virus
RPXV-UTR	RPXV strain Utrecht
SAE	Serious adverse event
SD	Standard deviation
SNS	Strategic National Stockpile

TEAE	Treatment-emergent adverse event
TGN	Trans Golgi network
TK	Toxicokinetic
t_{max}	Time to maximum concentration
$t_{1/2}$	Plasma half-life
VACV	Vaccinia virus
VARV	Variola virus
Vz/F	Fraction of dose absorbed
WHO	World Health Organization

1. EXECUTIVE SUMMARY

1.1 Introduction

Tecovirimat (TPOXX[®]) is a novel, oral therapeutic agent intended for the treatment of patients with smallpox, providing a necessary countermeasure in the event of an intentional or accidental outbreak. Tecovirimat inhibits an orthopoxviral protein that is required for the exit of enveloped virions from the infected cell; this block in virus release is sufficient to halt the spread of infection until the body's immune system can clear the virus. Tecovirimat is formulated as immediate release capsules to be taken at a dose of 600 mg twice daily with a meal for 14 days.

While naturally occurring smallpox has been successfully eradicated through global vaccine campaigns, there remains a concern that smallpox could be used as a bioweapon. The Centers for Disease Control and Prevention (CDC) have determined that smallpox is at the highest threat level, and there are currently no therapies other than early vaccination that can alter the outcome of the disease. SIGA has worked together with the National Institutes of Health (NIH) and the Biomedical Advanced Research and Development Authority (BARDA) on development of tecovirimat for use in biodefense.

While the tecovirimat development program was ongoing, the Food and Drug Administration (FDA) determined that there was sufficient evidence to allow tecovirimat to be stockpiled in the US CDC Strategic National Stockpile (SNS), and it has been purchased for the SNS as a bioterrorism countermeasure.

Because tecovirimat received Fast Track designation from FDA, and due to the unusual nature of development of a drug under the Animal Rule, SIGA and FDA had multiple interactions during the course of the tecovirimat program. Tecovirimat also received orphan drug designation. SIGA submitted a New Drug Application (NDA) to the FDA on 08 December 2017 seeking approval of tecovirimat under the FDA Animal Rule.

The FDA granted Priority Review of the NDA on 06 February 2018. Since it is neither ethical nor feasible to conduct human efficacy studies, FDA has invoked the Animal Rule to evaluate efficacy based on adequate and well-controlled studies in animals (FDA Guidance for Industry: Product Development Under the Animal Rule [Oct 2015]). The Animal Rule states that if the following criteria are met, it is reasonable to expect the effectiveness of the drug in animals to be a reliable indicator of its effectiveness in humans:

1. There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product.
2. The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans.
3. The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity.
4. The data or information on the kinetics and pharmacodynamics (PD) of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

Based on the outcome of an Advisory Committee convened by FDA in December 2011 to specifically address the issue of animal models for smallpox as well as further discussions with the FDA, SIGA and FDA agreed that tecovirimat should be studied in two animal models to determine its efficacy. The two models chosen were intravenous (IV) infection of non-human primates (NHPs) with monkeypox virus and intradermal (ID) infection of New Zealand White rabbits with rabbitpox virus. The tecovirimat development program includes six pivotal trials (four in NHPs and two in rabbits) to establish efficacy, and a Phase 3 safety and tolerability study conducted in healthy human volunteers (Table 1). Additionally, toxicology studies were conducted in five species including mice, rats, rabbits, dogs and NHPs.

Table 1: Primary Support for Efficacy and Safety of Tecovirimat

Study	Model/Population	Study Design/Analysis
AP-09-026G	MPXV/NHP	Determination of efficacious dose
FY10-087	MPXV/NHP	Determination of efficacious dose and PK
SR10-037F	MPXV/NHP	Treatment initiation delay
SR10-038F	MPXV/NHP	Treatment duration
SR13-025F	RPXV/Rabbit	Dose exploration and PK
SR14-008F	RPXV/Rabbit	Dose exploration
SIGA-246-008	Human Study	Clinical Phase 3 pivotal safety and pharmacokinetic study

KEY: MPXV = monkeypox virus; NHP = non-human primate; RPXV = rabbitpox virus; PK = pharmacokinetics

This briefing document provides an overview of the tecovirimat development program and substantial evidence in support of the marketing authorization of tecovirimat for the treatment of smallpox.

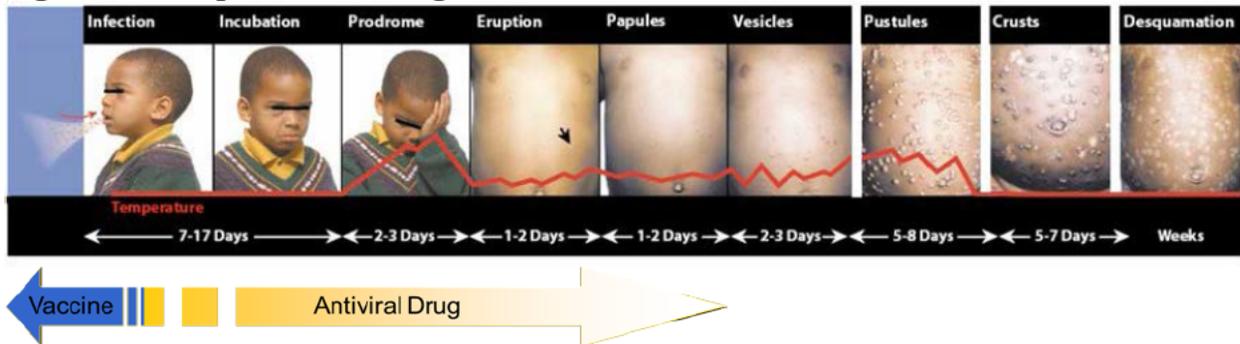
1.2 Background and Unmet Medical Need

Smallpox is a serious, contagious disease caused by the variola virus (VARV). Smallpox is highly communicable and carries exceptionally high morbidity. Secondary attack rates among unvaccinated members of households have been described from 37-88% [1]. Mortality rates are as high as 30% for variola major [1], and all infected will experience significant morbidity with persisting and sometimes permanent disease sequelae. With the advent of biowarfare as an instrument of terrorism and the potential to generate the virus *de novo* using genetic engineering technologies, smallpox is considered a growing public health risk.

Following aerosol exposure to the virus, there is an incubation period of 7-17 days during which no disease is evident, and the infected individual is not contagious (Figure 1). During the incubation period, the virus spreads from the primary infected foci to the regional lymph nodes. The virus then replicates in the lymph nodes and is released into the blood stream (primary viremia). These virus particles seed the spleen, liver, and reticuloendothelial systems, where the virus replicates to high titer and is released into the blood stream, resulting in a secondary viremia and initiating the prodrome phase of the disease. From this point, until disease resolution, individuals are contagious due to oropharyngeal secretion of virus and lesion shedding. The prodrome is characterized by high fever, headaches, backaches, joint pain, and abdominal pain in addition to high levels of viremia. Within 1 to 4 days following onset of the prodrome phase, the virus spreads through the blood and lymph nodes, seeding capillary endothelial cells and initiating replication in the skin and oropharyngeal mucous membranes. After the prodrome, a characteristic rash begins to form on the extremities and face. Pock development follows, progressing from macules, papules, vesicles, crusts, and scabs. In

survivors, pocks are fully resolved within approximately 21 days after their initial appearance, with residual desquamation and scarring of affected tissues.

Figure 1: Smallpox Disease Progression



NOTE: Adapted from Breman and Henderson [1]

Currently, there is no FDA approved drug for the treatment of smallpox. While several vaccines exist, due to vaccine complications, including progressive vaccinia in immunocompromised persons, eczema vaccinatum in individuals with atopic dermatitis, and a newly recognized post vaccinal myocarditis, present policy calls for vaccination of the general public to be initiated only upon confirmation of a smallpox outbreak. The current live virus vaccine would be provided to all persons at risk of infection, including those for whom it would normally be contraindicated. In addition to the safety risks, there are concerns about whether smallpox vaccines could be distributed, health care workers would be available to administer them, and the population would be able to reach them within 3 days after a large-scale biological attack. In 1999, an Institute of Medicine panel recommended the development of new antiviral drugs against smallpox, especially medications that could be taken orally [2]. In contrast to vaccination, which acts indirectly by eliciting the development of an adaptive immune response and must occur soon after exposure to be effective, antiviral therapy could halt the systemic spread of virus within infected individuals immediately and could potentially be effective when begun at any time after exposure to variola virus (Figure 1). Drug treatment would therefore be particularly important for individuals who are too late in the incubation period to benefit from vaccination.

Given the potential for an intentional smallpox outbreak and the absence of any therapeutic drugs, there is an important unmet need for a medication that reduces morbidity and mortality in patients with smallpox.

1.3 Nonclinical Development Program

1.3.1 *In Vitro* and *In Vivo* Pharmacology

The pharmacology of tecovirimat has been evaluated in a program of nonclinical *in vitro* and *in vivo* studies designed to assess the activity and mechanism of action of tecovirimat. The pivotal *in vivo* efficacy studies were conducted in NHPs and rabbits; numerous additional pilot or exploratory studies were also conducted in mouse, prairie dog, squirrel, rabbit, and NHP models.

1.3.1.1 *In Vitro* Efficacy/Pharmacodynamics

Collectively, the results of the pivotal *in vitro* pharmacology studies have demonstrated the following:

- Tecovirimat shows antiviral specificity against multiple species within the Orthopoxvirus genus, inhibiting virus-induced cytopathic effect (CPE) at very low concentrations (10-70 nM range), while exhibiting no cytotoxicity at concentrations up to 40 μ M (limit of solubility in the assay). The therapeutic index is ≥ 4000 .
- The antiviral activity is limited to the parent compound and not to tecovirimat metabolites.
- Tecovirimat inhibits virus dissemination in culture by preventing the formation of egress-competent enveloped virions (as demonstrated by the inhibition of plaque formation), indicating that tecovirimat can prevent cell-to-cell spread and long-range dissemination of orthopoxviruses.
- Tecovirimat inhibits its molecular target, a protein called p37, from interacting with intracellular transport components necessary for the production of enveloped egress-competent virus, and therefore the spread of virus.

Results from supplementary *in vitro* studies have demonstrated the following:

- Human serum does not affect the half maximal effective concentration (EC₅₀) values of tecovirimat.
- The p37 protein target of tecovirimat is highly conserved in all species of orthopoxviruses and is similarly targeted by tecovirimat with equivalent efficiency. There are no mammalian homologs to p37, and no orthologous genes exist outside the *Poxviridae* family. Therefore, no off-target activity has been observed.

1.3.1.2 *In Vivo* Efficacy/Pharmacodynamics (Animal Efficacy)

A total of 6 pivotal *in vivo* primary efficacy studies were conducted in NHPs infected with a lethal dose of monkeypox virus (MPXV) and rabbits infected with a lethal dose of rabbitpox virus (RPXV). Survival rate was the primary efficacy endpoint in all 6 studies. Supportive PD endpoints included lesion formation (NHP studies only) and viral load. The nonclinical studies evaluated tecovirimat administered at doses ranging from 0.3-20 mg/kg daily for between 3 and 14 days in NHPs and from 20-120 mg/kg for 14 days in rabbits

Table 2 briefly describes the pivotal animal efficacy studies.

Table 2: Description of Tecovirimat Efficacy Studies

Study ID	Design	Objective(s)	Dose and Regimen
Pivotal Studies in Nonhuman Primates (Cynomolgus Macaques)			
AP-09-026G (Study 26G)	Double-blind, randomized, placebo-controlled, repeat-dose efficacy study	Determine the minimum effective dose of oral tecovirimat for the treatment of MPXV in the lesional cynomolgus macaque model of smallpox beginning individually on the day of onset of pox lesions in each animal	Placebo (Days 4–17) Tecovirimat: 0.3 mg/kg (Days 4–17) 1 mg/kg (Days 4–17) 3 mg/kg (Days 4–17) 10 mg/kg (Days 4–17)
FY10-087 (Study 87)	Randomized, placebo-controlled, repeat-dose study	Evaluate the PK of tecovirimat in cynomolgus macaques infected via IV injection with MPXV	Placebo (Days 4–17) Tecovirimat: 3 mg/kg (Days 4–17) 10 mg/kg (Days 4–17) 20 mg/kg (Days 4–17)
SR10-037F (Study 37F)	Double-blind, randomized, placebo-controlled, repeat-dose study	Evaluate the protective efficacy of orally administered tecovirimat against an IV lethal challenge of MPXV and determine the time point at which tecovirimat fails to protect from mortality	Placebo (Days 4–19) Tecovirimat: 10 mg/kg (Days 4–17) 10 mg/kg (Days 5–18) 10 mg/kg (Days 6–19)
SR10-038F (Study 38F)	Double-blind, randomized, placebo-controlled, repeat-dose study	Evaluate the protective efficacy of orally administered tecovirimat against an IV lethal challenge of MPXV and determine the duration of dosing necessary to protect from mortality	Placebo (Days 4–13) Tecovirimat: 10 mg/kg (Days 4–6) 10 mg/kg (Days 4–8) 10 mg/kg (Days 4–10) 10 mg/kg (Days 4–13)
Pivotal Studies in Rabbits (New Zealand White)			
SR13-025F (Study 25F)	Double-blind, randomized, repeat-dose study	Evaluate the effect of ID RPXV infection on the oral PK of tecovirimat	Tecovirimat 40 mg/kg (Days 4–17) 80 mg/kg (Days 4–17) 120 mg/kg (Days 4–17)
SR14-008F (Study 08F)	Double-blind, randomized, placebo-controlled, repeat-dose study	Identify a minimum efficacious dose of tecovirimat (and a corresponding blood exposure) that provides maximal survival benefit	Placebo (Days 4–17) Tecovirimat: 20 mg/kg (Days 4–17) 40 mg/kg (Days 4–17) 80 mg/kg (Days 4–17) 120 mg/kg (Days 4–17)

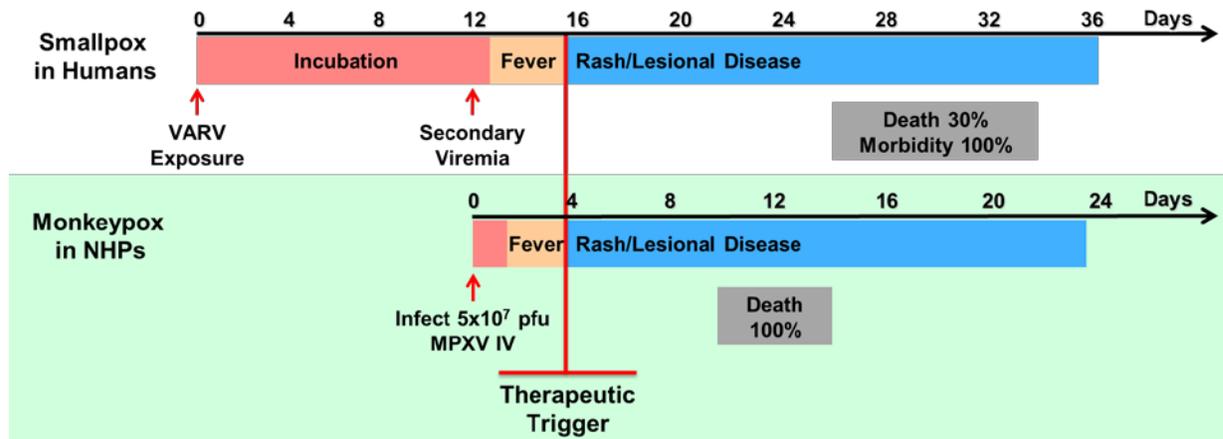
KEY: ID = intradermal; IV = intravenous; MPXV = monkeypox virus; PK = pharmacokinetic(s); RPXV = rabbitpox virus;

1.3.1.3 Animal Models

Both the NHP and rabbit models used to evaluate the efficacy of tecovirimat meet the criteria identified by the 2011 Advisory Committee meeting discussed in Section 1.1.

Based on scientific literature, MPXV infection of cynomolgus macaques is a reliable model that captures many of the aspects of human smallpox. Importantly, the time course and associated pathology of MPXV in the NHP (Figure 2) versus human smallpox is nearly identical from the point of secondary viremia onward. In the IV challenge NHP model, lesions containing virus appear 3-4 days post-challenge and continue to increase in number and progress through stages typical of human smallpox until death. Therefore, the trigger for treatment would be the first appearance of lesions on day 4. A viral challenge of 5×10^7 infectious particles ensuring 100% mortality was chosen.

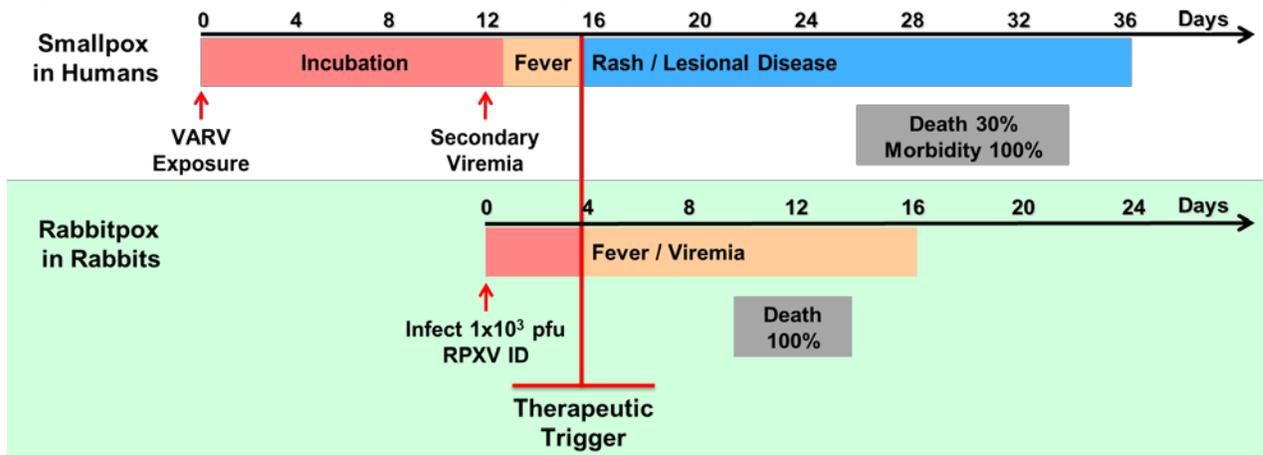
Figure 2: Nonhuman Primate Model of Human Smallpox



KEY: MPXV = monkeypox virus; VARV = variola virus

Recent literature suggests that rabbitpox disease in New Zealand White Rabbits (Figure 3) also closely mimics the steps of smallpox disease in humans. After the initial infection, there is a symptom-free incubation period, followed by fever and the dissemination of virus in the blood and the establishment of a secondary systemic infection, followed by death. In this ID challenge model, a lethal viral challenge of 1,000 plaque-forming units of RPXV was chosen. The trigger in this model was different from the NHP model since most animals die quickly, sometimes even *before* developing lesions. The therapeutic trigger used in this model is fever, which is always observed by day 4. Therefore, treatment started at day 4 in the rabbit models.

Figure 3: Rabbit Model of Human Smallpox



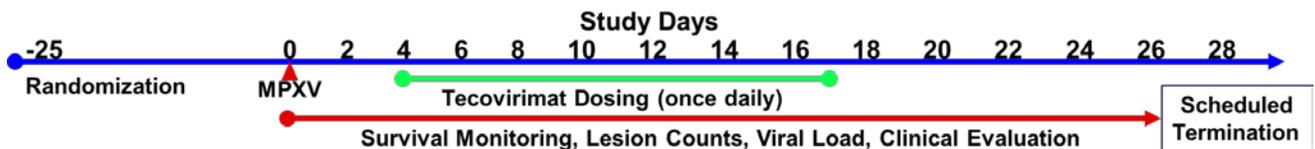
KEY: RPXV = rabbitpox virus; VARV = variola virus

1.3.1.4 Nonhuman Primate Study Overviews

Studies 26G and 87

In Studies 26G and 87, animals were infected via IV injection with MPXV on Day 0 and were randomized by body weight into treatment groups to receive placebo or tecovirimat once daily starting on Day 4 post-infection at doses ranging from 0.3 to 20 mg/kg on Days 4-17 post-infection (see Figure 4 for study timeline). In Study 26G, animals received 0.3, 1, 3, and 10 mg/kg (5 animals each), and in Study 87, animals received 3, 10, and 20 mg/kg (6 animals each). Animals were monitored at least 28 days post-infection for survival, lesions, viral DNA load in the blood, and clinical signs of disease.

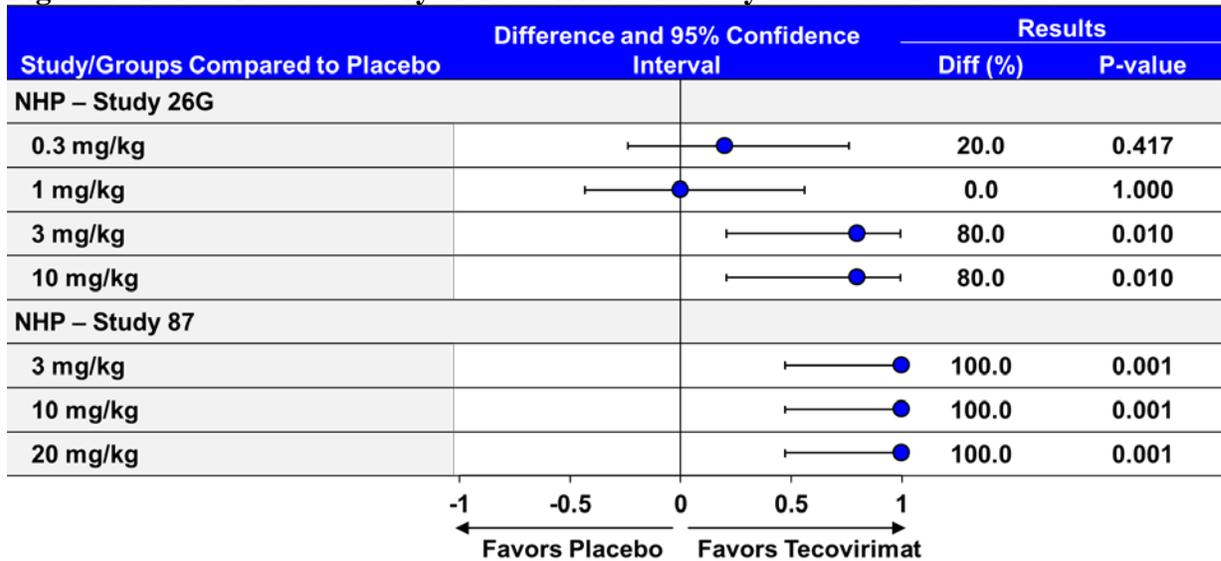
Figure 4: Timeline for Studies 26G and 87



KEY: MPXV = monkeypox virus

Assessment of survival rate demonstrated a significant effect of tecovirimat treatment on mortality in both studies (see Forest Plot, Figure 5). All placebo treated controls succumbed to disease. Tecovirimat at dose levels of ≥ 3 mg/kg/day for 14 days (initiated no later than Day 4 post-infection) resulted in decreased mortality (80 - 100% survival compared to $< 5\%$ survival in NHPs treated with less than 3 mg/kg/day). It should be noted though that the 2 deaths that occurred at the 3 and 10 mg/kg dose in the 26G study were not attributed to monkeypox. Treatment of NHPs with tecovirimat 10 mg/kg/day for 14 days (initiated after onset of lesional disease; approximately 3-4 days post-infection) did not result in further increases in survival but did result in lower circulating MPXV DNA levels, fewer pock lesions, and fewer clinical signs of infection.

Figure 5: Forest Plot Summary of Tecovirimat Efficacy in Studies 26G and 87



LEGEND: Shown is a forest plot summary comparing differences in survival when compared to placebo treatment for each study. The exact 95% confidence interval is based on the score statistic of difference in survival rates. Under Results, Diff (%) is the difference in survival rates compared to the placebo control. The *P*-value is from 1-sided Fisher’s Exact Test compared to the placebo control.

Lesion monitoring data demonstrated a significant effect of tecovirimat treatment on lesion counts (representative results from Study 26G shown in Figure 6). Lesions on animals receiving tecovirimat 3 or 10 mg/kg were fully resolved by Day 23 post-infection, with the 10 mg/kg dose conferring the greatest protection against lesions as assessed by median lesion counts. Lesion count data from Study 87 were not appropriate for statistical analysis and therefore are not presented.

Assessment of viral DNA load from Studies 26G and 87 revealed an effect of tecovirimat on MPXV DNA levels in the blood (representative results from Study 26G shown in Figure 7). All animals lacked detectable circulating MPXV DNA prior to MPXV injection. By Day 6 post-MPXV administration, placebo-treated animals demonstrated a consistent increase in circulating viral DNA load that was maintained until death. Similar to lesion counts, a significant, dose-dependent effect of tecovirimat on MPXV DNA levels in the blood was evident. Animals receiving tecovirimat at 3 or 10 mg/kg had significantly lower viral DNA load than animals in the placebo group, with the 10 mg/kg dose conferring the greatest protection against viremia, while animals receiving <3 mg/kg had viral DNA loads similar to placebo.

Figure 6: Median Lesion Count in Study 26G

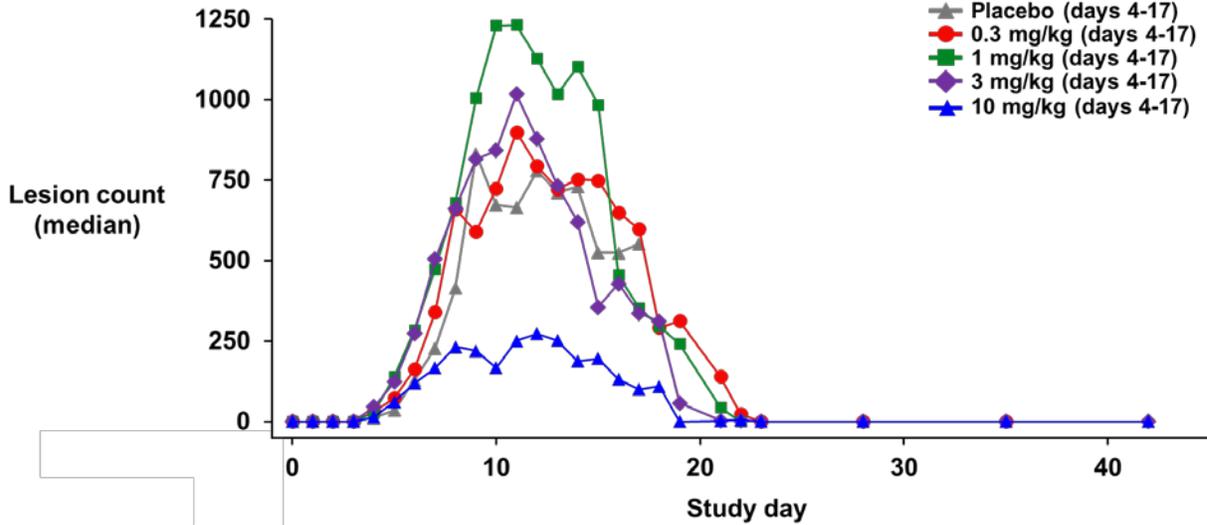
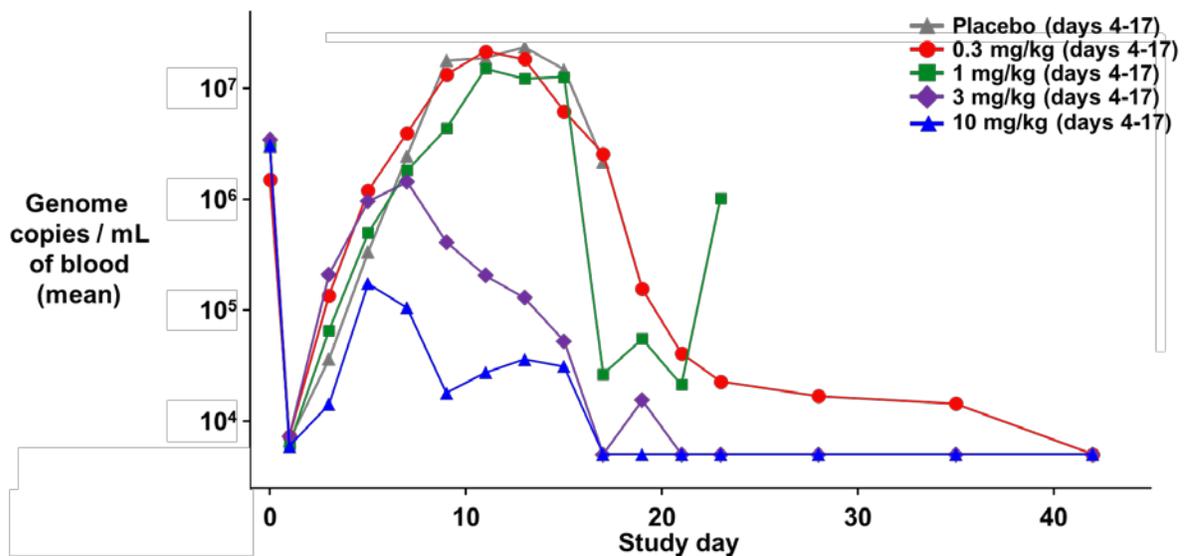


Figure 7: Geometric Mean Viral Load in Study 26G



Overall, in Studies 26G and 87, tecovirimat treatment at doses of at least 3 mg/kg successfully inhibited progression of MPXV infection, as indicated by reductions in mortality, lesion counts, and viremia. Further reductions in lesion counts and viremia were achieved by increasing the dose to 10 mg/kg. For this reason, the 10 mg/kg dose was considered the minimum fully effective dose.

Studies 37F and 38F

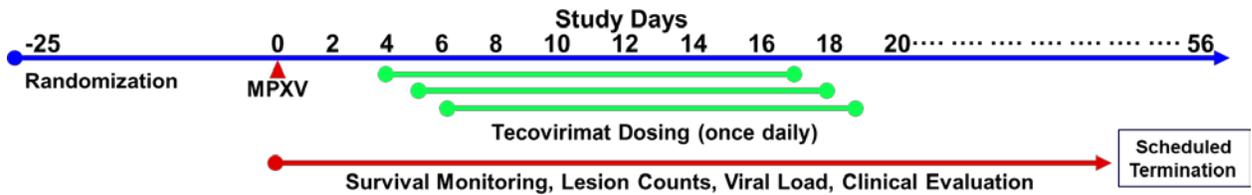
Study 37F was conducted to determine how late in infection tecovirimat (10 mg/kg) remained effective, and the objective of Study 38F was to determine the duration of dosing (10 mg/kg) necessary to protect from mortality.

In Study 37F, animals were infected via IV injection with MPXV on Day 0 and were randomized by body weight and sex into 4 groups. A total of 21 animals were randomized to receive placebo

on Days 4-19 (3 animals) or tecovirimat 10 mg/kg once daily on Days 4-17, 5-18, or 6-19 (6 animals each). The timeline for Study 37F is shown in Figure 8.

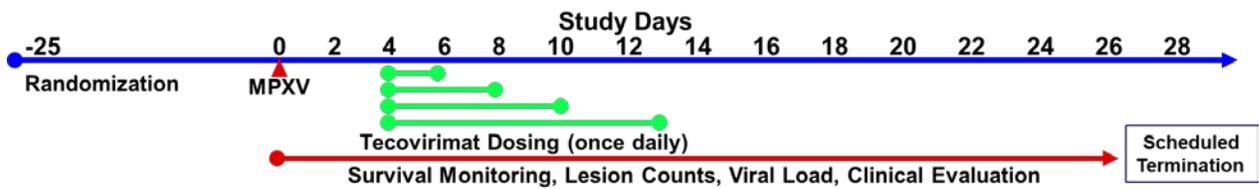
In Study 38F, animals were infected via IV injection with MPXV on Day 0 and were randomized by body weight and sex into 5 groups to receive placebo (4 animals) or tecovirimat 10 mg/kg for 3 days (4 animals), 5 days (6 animals), 7 days (6 animals), or 10 days (5 animals). The study timeline for Study 38F is shown in Figure 9.

Figure 8: Timeline for Study 37F



KEY: MPXV = monkeypox virus

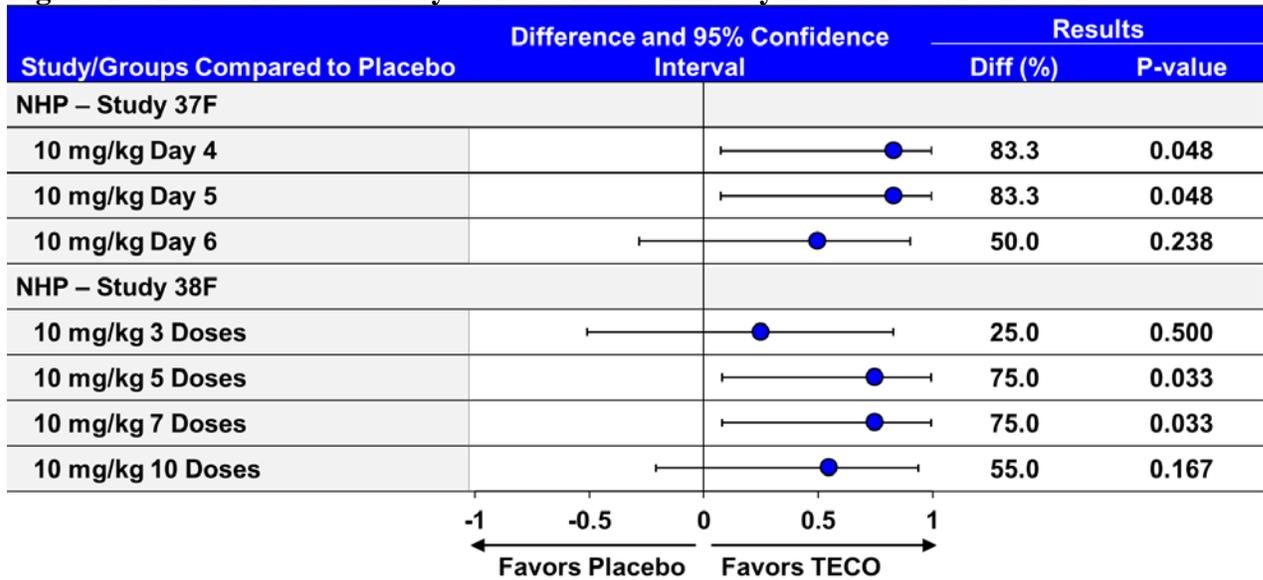
Figure 9: Timeline for Study 38F



KEY: MPXV = monkeypox virus

Assessment of survival rate demonstrated a significant effect of tecovirimat treatment on mortality, with treatment at 10 mg/kg initiated before Day 6 and treatment for at least 5 days conferring the greatest protection against established lethal MPXV disease (see Forest Plot Summary in Figure 10). No placebo treated animals survived to scheduled termination in Study 37F, while 1 of 4 placebo treated animals survived in Study 38F. In the tecovirimat groups initiating treatment on Days 4, 5, and 6, 83%, 83%, and 50% of animals survived, respectively, whereas 50%, 100%, 100%, and 80% of animals survived in the tecovirimat groups receiving treatment for 3, 5, 7, and 10 days, respectively, when treatment was initiated in Day 4 post-infection.

Figure 10: Forest Plot Summary of Tecovirimat Efficacy in Studies 37F and 38F



LEGEND: Shown is a forest plot summary comparing differences in survival when compared to placebo treatment for each study. The exact 95% confidence interval is based on the score statistic of difference in survival rates. Under Results, Diff (%) is the difference in survival rates compared to the placebo control. The *P*-value is from 1-sided Fisher’s Exact Test compared to the placebo control.

Lesion monitoring data demonstrated an effect of tecovirimat treatment on lesion counts, with treatment initiated before Day 6 and treatment for at least 5 days, when initiated on Day 4, conferring the greatest protection against established lethal MPXV disease. By Day 6, all animals across the 4 treatment groups had developed lesions; most lesions were vesicular or pustular. For all treatment groups, total body lesion counts typically peaked between Day 6 and Day 9. Animals receiving tecovirimat initiated on Day 4 or 5 with at least 5 days of treatment had lower median lesion counts than animals receiving placebo or tecovirimat initiated on Day 6 (Figure 26 and 16).

Assessment of viral DNA load revealed a significant effect of tecovirimat on MPXV concentrations in the blood, with treatment initiated on Day 4 conferring the greatest protection against established lethal MPXV disease (Figure 27). Longer durations of tecovirimat treatment of 5, 7, or 10 days were associated with viral DNA levels reaching the lower limit of quantification (LLOQ) by study termination.

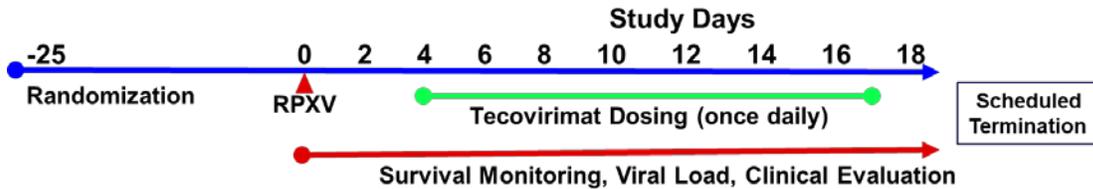
Overall, Studies 37F and 38F demonstrated that protection was greatest when tecovirimat treatment at 10 mg/kg was initiated on Day 4 or 5 and that at least 5 days of treatment was sufficient to demonstrate a survival advantage.

1.3.1.5 Rabbit Study Overviews

Consistent with results observed in the NHP studies, treatment with tecovirimat at doses of 20-120 mg/kg was highly efficacious in animals with established RPXV infection, as indicated by improvements in mortality and viral DNA load. No dose-dependent trends were observed, suggesting that the doses used were above the dose-response range for efficacy.

In **Study 25F**, animals were infected via ID injection with RPXV (1,000 plaque forming units [pfu]) on Day 0. A total of 24 animals were randomized by body weight and sex into 3 groups to receive tecovirimat 40, 80, or 120 mg/kg once daily on Days 4-17 (8 animals each) in this study. The study timeline is shown in Figure 11.

Figure 11: Timeline for Study 25F



KEY: RPXV = rabbitpox virus

Assessment of survival rate was consistent with a protective effect of any tecovirimat treatment evaluated in this study against RPXV-induced mortality. Because the study design did not include a placebo comparator, survival was not assessed statistically (Table 3). However, most animals in the study survived to study termination. Following ID challenge with a lethal dose of RPXV, 1 animal each in the tecovirimat 40 and 80 mg/kg groups was found dead immediately after tecovirimat dosing; this mortality was considered to be a result of the gavage procedure and not caused by RPXV infection. All other animals in the study survived to study termination.

Table 3: Survival Rate in Study 25F

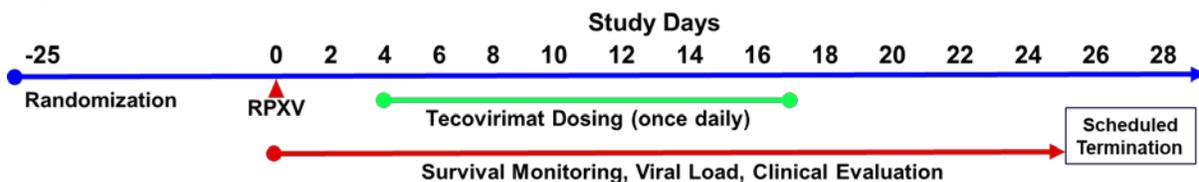
Dose (Regimen)	No. of Animals/ Sex	Survival Rate
		Survival (n [%])
Tecovirimat 40 mg/kg (Days 4–17)	4M/4F	7 (87.5)
Tecovirimat 80 mg/kg (Days 4–17)	4M/4F	7 (87.5)
Tecovirimat 120 mg/kg (Days 4–17)	4M/4F	8 (100)

Key: F= female; M = male; No. = number.

Assessment of viral DNA load revealed consistent patterns of blood RPXV DNA levels across treatment groups (Figure 32). Geometric mean blood viral DNA load generally peaked on Day 4 post-infection for animals in each treatment group and began to decline by Day 7. Across treatment groups, animals demonstrated infection control, as evidenced by levels approaching or falling below the LLOQ by the end of the study.

In **Study 08F**, animals were infected via ID injection with RPXV (1,000 pfu) on Day 0. A total of 50 animals were randomized by body weight and sex into 5 groups to receive placebo or tecovirimat 20, 40, 80, or 120 mg/kg once daily on Days 4-17 post-infection (10 animals each) in this study. The study timeline is shown in Figure 12.

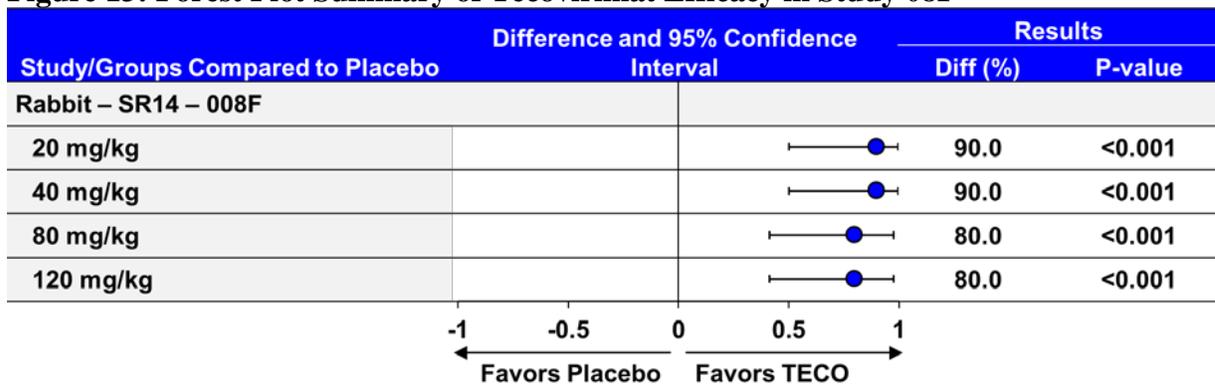
Figure 12: Timeline for Study 08F



KEY: RPXV = rabbitpox virus

Assessment of survival rate demonstrated a significant effect of tecovirimat treatment on mortality (see Forest Plot Summary in Figure 13). No animals survived to scheduled termination in the placebo group, whereas 90%, 90%, 80%, and 80% of animals survived in the tecovirimat 20, 40, 80, and 120 mg/kg groups, respectively. All tecovirimat doses evaluated conferred similar protection from mortality, with no dose-related trends in efficacy observed across the dose range studied.

Figure 13: Forest Plot Summary of Tecovirimat Efficacy in Study 08F



LEGEND: Shown is a forest plot summary comparing differences in survival when compared to placebo treatment for each study. The exact 95% confidence interval is based on the score statistic of difference in survival rates. Under Results, Diff (%) is the difference in survival rates compared to the placebo control. The *P*-value is from 1-sided Fisher’s Exact Test compared to the placebo control.

Assessment of viral DNA load revealed a significant effect of tecovirimat on blood RPXV DNA levels (Figure 33). Following challenge with RPXV on Day 0, placebo-treated animals exhibited high genomic DNA copy number that increased with time and generally peaked at the time of death/euthanasia, usually between Days 5-10. In contrast, tecovirimat-treated animals exhibited significantly lower mean viral DNA loads that peaked at approximately Day 6 and then decreased to complete clearance by study termination for all animals, suggesting that tecovirimat began to reduce virus dissemination through the blood within 2 days after treatment initiation. There were no evident dose-related trends in tecovirimat efficacy, as assessed by viral DNA load, across the dose range studied.

Studies in rabbits demonstrated that oral administration of tecovirimat at dose levels of ≥ 20 mg/kg/day for 14 days (administered no later than Day 4 post-infection) resulted in decreases in the incidences of mortality, blood RPXV DNA levels, and clinical signs of infection. Survival for all dose levels (ranging from 20-120 mg/kg/day) was similar and was approximately 90%, while all untreated rabbits succumbed to disease.

1.3.1.6 Nonclinical Pharmacokinetics

The pharmacokinetics (PK) of orally administered tecovirimat have been investigated in mice, rats, rabbits, and dogs, and NHPs. Key PK findings include the following:

- Following oral administration, tecovirimat rapidly appeared in plasma and reached maximum plasma concentration (t_{max}) values within approximately 5.0 hours.
- In oral repeat-dose studies conducted in mice, rats, rabbits, and NHPs, exposure generally increased with dose, but dose-proportionality was not always observed.

- The oral bioavailability of tecovirimat is approximately 40-45% in mice and 8-29% in rabbits.
- In NHPs, the bioavailability increased approximately 2-fold when administered with food compared to fasted conditions (F_{abs} values of 50% and 28% in fed versus fasted animals, respectively), supporting administration with food.
- The plasma protein binding of [^{14}C]-tecovirimat was moderate to high (77.3-96.3%) in all species studied (mouse, rat, rabbit, dog, NHP, and human), with human binding being on the low end (~80%) and concentration-independent over a wide range of concentrations (0.03-50 μM).
- Following oral administration in mice, [^{14}C]-tecovirimat was systemically distributed to all tissues analyzed with the highest concentrations noted in liver and gall bladder, respiratory tract tissues (i.e., nasal turbinates), and bone marrow.
- Studies in dogs and NHPs indicate that tecovirimat crosses the blood brain barrier.
- *In vitro* studies have demonstrated that [^{14}C]-tecovirimat is stable for at least 1 hour in dog, NHP, and human liver microsomes, but less stable in rat and mouse liver microsomes.
- *In vitro* studies indicate that tecovirimat is not a substrate of major cytochrome P450 (CYP) enzymes, but it is a substrate of human recombinant UGTs (specifically of UGT1A1, 1A3, and 1A4).
- Tecovirimat was found to be metabolized into 3 most abundant metabolites, M4, M5 and TFMBA, which do not have pharmacological activity.

1.3.1.7 Toxicology

The toxicology of tecovirimat has been investigated in mice, rats, rabbits, dogs, and NHPs. Key toxicity findings include the following:

- Oral administration of tecovirimat is generally well-tolerated at dose levels up to 2,000 mg/kg/day (mice).
- Oral administration to NHPs and mice for up to 3 months was well tolerated.
- Dogs were considered more sensitive to tecovirimat than the other species tested, and drug exposure data from dog studies was used to set the maximum safety exposure for humans.
- *In vitro* and *in vivo* genetic toxicity tests were negative.
- In embryo-fetal development studies, maternal toxicity was noted in rabbits receiving a dose of tecovirimat, including mortality and decreases in body weight (due to decreases in food consumption). This was not observed in a similar study in mice.
- Clinical dose exposure (AUC) of tecovirimat in humans is 2.5- and 23-fold lower than the no-observed-effect-level (NOEL) or no-observed-adverse-effect-level (NOAEL) exposure, determined in the studies in NHPs and mice, respectively.

1.4 Clinical Pharmacokinetics and Pharmacology

Of the 12 clinical studies completed, the PK and safety of tecovirimat in humans were evaluated in 11 studies, and safety was evaluated in 1 palatability study where no drug was ingested (Table 4). Across 1 pivotal, 3 supportive multiple-dose, and 7 supportive single-dose studies of tecovirimat, subjects have been exposed to tecovirimat at total daily doses ranging from 100-2,000 mg for between 1 and 21 days.

Table 4: Clinical Studies in Tecovirimat Development Program

Study	Phase	Study Design/Dosing
SIGA-246-008	3	Pivotal safety and pharmacokinetics/600 mg, twice daily for 14 days
SIGA-246-002	1	Ascending dose safety and pharmacokinetics/250, 400, 800 mg once daily for 21 days
SIGA-246-004	2	Safety and pharmacokinetics/400, 600 mg once daily for 14 days
SIGA-246-015	1	Drug-drug interaction/600 mg, twice daily for 15 days
SIGA-246-001	1	Ascending dose safety and pharmacokinetics/500,1000, 2000 mg single dose
SIGA-246-005	1	Safety and pharmacokinetics crossover/400 mg single dose
SIGA-246-006	1	Palatability/600 mg, single dose drug not ingested
SIGA-246-009	1	Absorption, metabolism, and elimination/600 mg single dose
SIGA-246-010	1	Thorough QT/1000 mg single (supratherapeutic) dose
SIGA-246-012	1	Special Population: Safety and pharmacokinetics in subjects with renal impairment/600 mg single dose
SIGA-246-013	1	Special Population: Safety and pharmacokinetics in subjects with hepatic impairment/600 mg single dose
SIGA-246-018	1	Safety and pharmacokinetics/100, 200, 600 mg single dose delivered in food product

1.4.1 Pharmacokinetics

The results of clinical PK and PD studies of tecovirimat demonstrated:

- Rapid absorption with a t_{max} of 6 hours.
- Elimination half-life of approximately 20 hours.
- Moderate inter-individual pharmacokinetic variability.
- Drug exposure enhancement of 39% (AUC_{0-24}) in the presence of food.
- Linear exposure increase across a dose range from 100-600 mg.
- Steady state achieved within 6 days (~40% higher exposure than Day 1).
- Moderately high protein binding (~80%).
- Large volume of distribution (~1,356 L).
- Metabolic clearance as the major route of elimination, producing 3 predominant and pharmacologically inactive metabolites, M4, M5, and TFMBA, in plasma.
- Renal clearance as the major route of drug excretion.
- Less than 0.02% of unchanged drug excreted by the kidney, with a majority of drug excreted in a glucuronidated form.
- Approximately 23% of unchanged drug found in feces.

- While there are insufficient data to conclude whether tecovirimat PK are significantly altered in geriatric or specific racial groups, plasma exposures in all these groups are in the therapeutic range. No studies conducted in pediatric populations.
- Renal impairment has a minor impact on the overall extent of tecovirimat exposure, and the exposure remains well within the expected range for safety and efficacy. Tecovirimat is not substantially cleared by hemodialysis. A 50% reduction in tecovirimat AUC in end-stage renal disease (ESRD) subjects was observed.
- Hepatic impairment has a minor impact on the overall extent of tecovirimat exposure, and the exposure remains well within the expected range for safety and efficacy. Hepatic impairment has a modest effect on the exposure of 3 predominant metabolites.
- Tecovirimat exposure is not likely impacted by other drugs that induce or inhibit major CYP enzymes.
- The exposures of drugs that are substrates for BCRP, CYP2C8, and CYP2C19 may increase while the exposures of drugs that are substrates for CYP3A4 may decrease, when co-administered with tecovirimat.
- No clinically significant effects of tecovirimat or its 3 predominant metabolites on cardiac repolarization or ECG morphological changes were observed in a thorough QT study and the pivotal Phase 3 study.

1.5 Clinical Safety

1.5.1 Pivotal Safety Study SIGA-246-008

In the pivotal study, SIGA-246-008 (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), 359 subjects received 600 mg tecovirimat twice daily, and 90 subjects received placebo. Of the total subjects, the majority were female; i.e., 59% in the tecovirimat arm and 60% in the placebo arm. A diagram of the study design is provided in Section 10.1.

Overall, tecovirimat 600 mg twice daily for 14 days was generally well tolerated in pivotal study SIGA-246-008. Subjects receiving tecovirimat at the proposed human dose of 600 mg twice daily and subjects receiving placebo had similar incidences of treatment-emergent adverse events (TEAEs) (37.3% tecovirimat, 33.3% placebo) and TEAEs leading to treatment discontinuation (1.7% tecovirimat, 2.2% placebo) during the study (Table 5). The most frequent TEAEs for both treatment groups were headache (17.0% tecovirimat, 14.4% placebo) and nausea (5.6% each); the incidence of TEAEs was generally similar between groups, with the difference in incidence of all specific preferred terms being less than 3%. Few subjects experienced severe TEAEs, and one subject experienced a fatal serious adverse event (SAE) of pulmonary embolism that was not considered related to tecovirimat.

Table 5: Overview of Adverse Events in Study SIGA-246-008

	Tecovirimat N=359		Placebo N=90	
	n	%	n	%
TEAEs	134	37.3	30	33.3
Severe TEAEs	4	<1%	1	1%
TEAE leading to treatment discontinuation	6	1.7	2	2.2
SAEs	1	0.3	-	-
Deaths	1	0.3	-	-

KEY: N=number; AE=adverse event

1.5.2 Other Safety Findings

In Study SIGA-246-013 (hepatic impairment study), one subject receiving tecovirimat 800 mg had multiple SAEs of: cholecystitis, sepsis, acute myocardial infarction, and cardiac arrest that resulted in death. The SAEs were not considered related to tecovirimat.

Hypoglycemia was identified as an adverse event (AE) of interest in a supportive multiple-dose drug-drug interaction study (SIGA-246-015). Ten healthy, normal subjects (33.3%) reported AEs of hypoglycemia following the combination of repaglinide 2 mg + tecovirimat. Based on findings from this study and repaglinide's known antidiabetic actions to induce insulin release, it was determined that tecovirimat is a weak inhibitor of CYP2C8 that may result in episodes of mild or moderate hypoglycemia when co-administered with repaglinide. No TEAEs of hypoglycemia were reported in any of the other clinical studies.

Overall, the safety findings provide evidence that tecovirimat is generally safe and well-tolerated at the proposed dose of 600 mg twice daily with a meal for 14 days. The incidence of TEAEs reported in subjects was similar between tecovirimat and placebo. Most TEAEs were mild to moderate, the incidence of TEAEs leading to discontinuation was low, and there were no SAEs related to tecovirimat.

1.5.3 Human Dose Justification Based on Animal Efficacy, Exposure-Response Relationship and Safety Data

Of the 2 animal models studied for efficacy, the NHP is the more conservative of the two animal models as higher tecovirimat plasma exposures are required for maximal efficacy, leading to a higher estimate of required dosing in humans to achieve efficacy. Human dose modeling conducted by both SIGA and FDA, based on NHP efficacy, supports a dose of 600 mg twice daily for 14 days for achievement and maintenance of efficacious exposure levels in humans that are multiple-fold above NHP efficacious exposure levels.

Overall, the nonclinical toxicology of tecovirimat has been well characterized in multiple animal species. Sufficiently large safety margins were established between the NOAEL/NOEL generated in animal studies and the recommended human clinical dose. The exposure at the proposed human clinical dose is below the exposure responsible for the observed safety signals in the dog toxicology studies.

When administered orally, tecovirimat appears to be readily absorbed, and the absorption is enhanced in the presence of food in both animals and humans. Distribution and metabolism characteristics of tecovirimat as well as its potential to interact with other drugs have been evaluated in vitro and in vivo. Protein binding studies conducted using mouse, rat, rabbit, NHP,

and human plasma indicated a higher unbound fraction available for pharmacological activity in humans compared to that in animals.

Based on the exposures required for efficacy in NHPs, and using exposure modeling data, a human clinical trial was conducted to evaluate safety and plasma drug exposures at a dosage predicted to provide several-fold exposure over the effective exposures established in NHP studies but below the NOAEL/NOEL established in toxicological studies. The primary and secondary endpoints of the clinical trial were to evaluate the safety, tolerability, and PK of oral tecovirimat 600 mg twice daily for 14 days in adult subjects.

In summary, triangulation of 1) toxicological data, 2) safety, PK, and efficacy data from two animal efficacy models, and 3) human safety and PK data leads to several findings:

- Human dosing and target exposures are based on PK/PD data from the NHP model, since in this model higher blood exposures are required for maximal efficacy in comparison to the rabbit model.
- The requirements of the Animal Rule are satisfied by dosing at 600 mg twice daily for 14 days in humans. Exposures following 600 mg twice daily dosing exceed efficacious exposures in NHPs. In particular, for C_{min} exposures in humans, which have been established as the critical PK parameter most closely correlated with efficacy in animals, exposure ratios are 7.8-fold greater than maximally efficacious exposures in NHPs.
- The exposure at the proposed human clinical dose is below the exposure responsible for the observed safety signals in the dog toxicology studies.
- Based on the clinical data, tecovirimat appears to be safe in humans. Headache was the only AE occurring with higher frequency in subjects receiving tecovirimat relative to those receiving placebo. Most reported TEAEs were mild and all resolved without sequelae, and withdrawals or discontinuations were rare.

Collectively, the data in animals and humans support the Animal Rule requirement that tecovirimat at a dose of 600 mg twice daily is reasonably likely to produce clinical benefit in humans in the event of a smallpox emergency.

1.6 Benefit/Risk Summary

Tecovirimat is being developed under the FDA Animal Rule for efficacy, and thus animal studies were used to establish drug exposures that are safe and efficacious in animals. The proposed dose of 600 mg twice daily was confirmed as the optimal adult dose by PK and safety data in pivotal clinical study SIGA-246-008.

Risks

The risks of tecovirimat administration are minimal. In clinical safety studies, most TEAEs were mild or moderate and self-limited in nature, with the most common being headache and nausea. Co-administration of tecovirimat with repaglinide, or other blood sugar lowering drugs that are metabolized by CYP2C8, may cause mild to moderate hypoglycemia.

Benefits

Tecovirimat's primary benefit includes providing the only oral treatment for smallpox. Tecovirimat has demonstrated high efficacy as measured by the survival endpoint. Based on

demonstration of therapeutic efficacy in animals, tecovirimat is predicted to be efficacious in symptomatic individuals and can be administered post-exposure. The smallpox vaccine is ineffective in symptomatic individuals and is associated with risk of serious adverse reactions in both the immunosuppressed and certain healthy recipients. For this reason, the smallpox vaccine is reserved for individuals at risk of exposure to variola virus such as members of the armed forces. In contrast, tecovirimat is generally safe and well-tolerated, and it is given orally as a capsule, twice daily for 14 days.

Benefit/Risk Summary

Smallpox is a very serious disease. “Variola virus (VARV), the virus that causes smallpox, is thought to have killed more people throughout history than all other infectious diseases combined.” [3] The mortality of smallpox is as high as 30%, and there is significant morbidity among smallpox survivors, including scarring, myocarditis, blindness and encephalitis. Therefore, considering the safety profile of tecovirimat demonstrated in non-clinical and clinical trials and the efficacy demonstrated in animal models, the risk/benefit profile of tecovirimat is robust and supports tecovirimat’s use for treatment of smallpox disease.

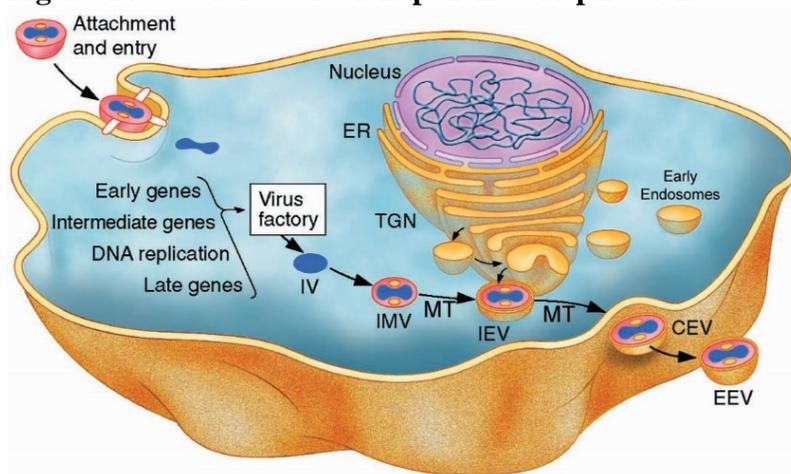
2. BACKGROUND/OVERVIEW

2.1 Overview of Orthopoxvirus Infections

2.1.1 Orthopoxvirus Biology

An overview of the orthopoxvirus replication cycle [4] is shown in Figure 14. Intracellular mature virus (IMV) particles are formed within cytoplasmic factories from non-infectious precursors called crescents and immature virus. IMV represent the majority of infectious progeny and mostly remain within the cell until lysis. However, some IMV leave the factory transported on microtubules and become wrapped by a double layer of intracellular membrane derived from endosomes and/or trans Golgi network (TGN) to form intracellular enveloped virus (IEV). IEV then move to the cell surface (again requiring microtubule transport) where the outer membrane fuses with the plasma membrane exposing an enveloped virion on the cell surface. Particles retained on the cell surface are termed cell-associated enveloped virus (CEV) and those released from the cell are called extracellular enveloped virus (EEV). CEV and EEV are physically and antigenically indistinguishable and are collectively referred to as enveloped virus (EV), and they contain one fewer membrane than IEV and one more membrane than IMV. CEV induce the formation of actin tails that drive the virions away from the cell and are important for cell to cell spread. Both EEV and CEV have a role in dissemination of virus within the host [5]. The general features of the orthopoxvirus replication cycle, including the formation and release of enveloped virion forms, have been shown to be conserved amongst all characterized orthopoxviruses. These viruses include the human pathogens vaccinia virus (VACV) [4], cowpox virus (CPXV) [6], MPXV [7], and VARV [7], as well as ectromelia [8] and rabbitpox [9] viruses which are used as model organisms for orthopoxvirus research.

Figure 14: Overview of Orthopoxvirus Replication



KEY: IV = immature virus; IMV = intracellular mature virus; IEV = intracellular enveloped virus; CEV = cell associated enveloped virus; EEV = extracellular enveloped virus; ER = endoplasmic reticulum; TGN = trans Golgi network; MT = microtubule transport.

NOTE: Figure adapted from Hruby and Byrd [10].

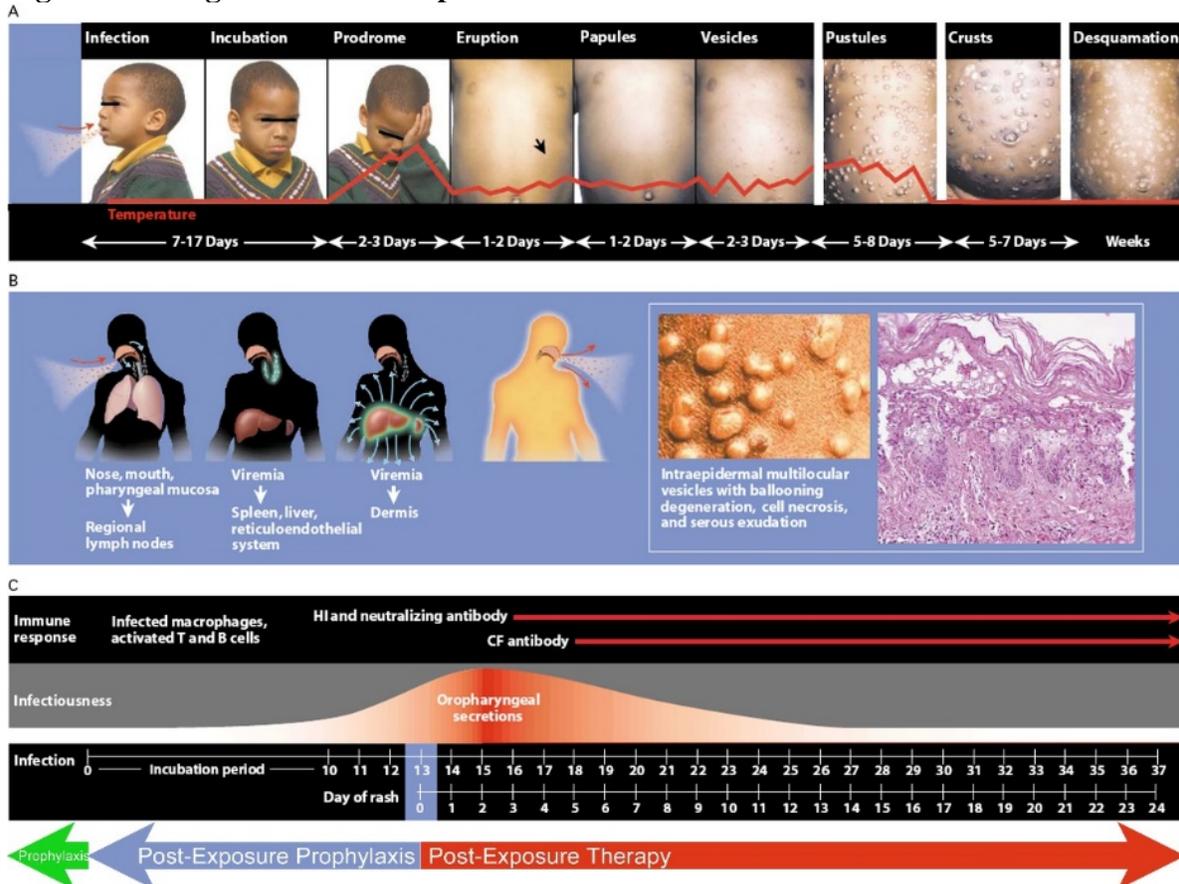
2.1.2 Variola Infection and Smallpox Disease in Humans

Smallpox is a strictly human disease that is most commonly contracted by inhalation of a very small amount of VARV [11]. The virus is spread most often by respiratory droplets during face-

to-face contact but may also be spread by fine particle aerosols capable of traveling significant distances, and by contaminated fomites such as clothing and bedding.

The disease course is outlined in Figure 15. Following aerosol exposure, there is an incubation period of 7–17 days, during which no disease is evident, and the infected individual is not contagious. During the incubation period, the virus spreads from the initial sites of infection to the regional lymph nodes, where it replicates and is released into the blood (primary viremia). These virus particles seed the spleen, liver, and reticuloendothelial systems, where the virus replicates to high titer and is again released into the blood, resulting in a secondary viremia and initiation of the prodromal phase of the disease. From this point, until disease resolution, individuals are contagious due to oropharyngeal secretion of virus and lesion shedding. The prodrome is characterized by high fever and excruciating headaches, backaches, joint pain, and abdominal pain, in addition to high levels of viremia. The virus spreads through the blood and lymph, seeding capillary endothelial cells and initiating replication in the skin and oropharyngeal mucous membranes within 1 to 4 days following onset of the prodrome. This phase is followed by formation of a characteristic rash as the result of virus replication on the extremities and face. Pock development follows in characteristic phases progressing from macules, papules, vesicles, crusts, and scabs. In survivors, pocks are fully resolved within approximately 21 days after their initial appearance with residual desquamation (shedding of the outer layers of the skin) and scarring of affected tissues.

Figure 15: Progression of Smallpox Disease in Humans



NOTE: Adapted from Breman J.G. and Henderson D.A. [1]

Approximately 30% of unvaccinated and 1% of vaccinated individuals will die if they contract smallpox from variola major. Occasionally, the disease manifests as “flat” or “hemorrhagic” smallpox, which are universally fatal. Since smallpox was eradicated prior to the advent of modern molecular techniques, it is difficult to fully ascertain its mechanisms of virulence and relate them to the progression of pathogenic events in animal models. Historically, in humans, death from smallpox was most often attributed to “toxemia,” a non-specific term referring to a “poisoning” of the system due to secondary bacterial infection, immune complex deposition, or toxic levels of inflammatory cytokines in addition to respiratory distress. A re-examination of the pathological record [12] rules out secondary bacterial infection and immune deposition as significant causes of death in smallpox but allows that robust inflammatory cytokine responses, now referred to as a “cytokine storm,” and direct cytopathic effects in multiple organs were the most common causes of death in typical smallpox. For those who survive, smallpox causes life-long scarring and may even lead to blindness or persistent neurological damage.

2.1.3 Medical Countermeasures Against Smallpox Disease

There are no FDA approved medical countermeasures specifically indicated for therapeutic intervention in cases of smallpox. Only one of the products listed below (ACAM2000[®]) currently stockpiled by the US Government for emergency use is licensed.

ACAM2000[®] (Licensed)

ACAM2000 is a live vaccinia virus vaccine approved by the FDA for active immunization against smallpox disease for persons determined to be at high risk for smallpox. ACAM2000 provides limited protection from smallpox when used for post-exposure prophylaxis within 3 days of exposure to VARV, after which the protective efficacy rapidly diminishes [13]. ACAM2000 also provides protection from other orthopoxvirus infections such as monkeypox and cowpox.

Aventis Pasteur Smallpox Vaccine (APSV; Not Licensed)

Aventis Pasteur Smallpox Vaccine is an investigational live vaccinia virus vaccine that is expected to have a similar safety profile and contraindications as ACAM2000.

Imvamune (MVA-BN) (Not Licensed)

Imvamune is an investigational non-replicating smallpox vaccine in the US derived from Vaccinia Ankara by repeated passages in cell culture that is unable to replicate in mammalian cells. Unlike ACAM2000 and APSV, which are administered as a single dose by scarification, Imvamune is administered subcutaneously in 2 doses administered 4 weeks apart. Imvamune is considered safe to administer to those with pre-existing skin disorders or compromised immune function.

Vaccinia Immune Globulin Intravenous (Human) (VIGIV; Not Licensed)

VIGIV is a high titer preparation of human immunoglobulin approved by the FDA for treatment of life-threatening complications of smallpox vaccination and has been used in combination with investigational drugs for this purpose [14-16].

3. PRODUCT BACKGROUND

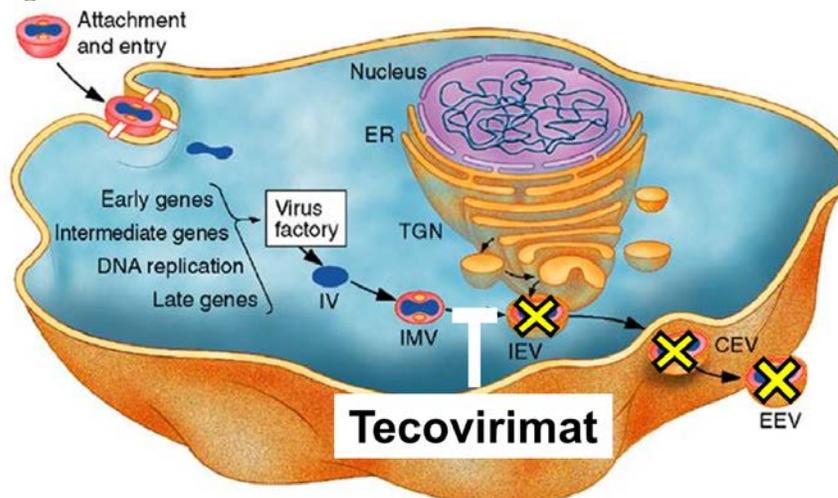
3.1 Product Description

Tecovirimat is a tetracyclic acyl hydrazide compound that was discovered through a deliberate effort to develop oral antiviral drugs for use in biodefense, and it is chemically unrelated to any substance currently approved for human or veterinary therapy. Tecovirimat is supplied as 200 mg capsules in bottles of 42 capsules. Tecovirimat capsules are stable at room temperature for 7 years.

3.2 Mechanism of Action

Tecovirimat inhibits production of extracellular viral forms, which are responsible for systemic spread of infection, thereby inhibiting virus induced cytopathic effects [17]. As shown in Figure 16, tecovirimat does not inhibit the formation of intracellular forms of the virus (IMV); however, by inhibiting envelopment, and therefore precluding the exit of viral particles from an infected cell, infection is slowed to a point where the body's immune system can clear the virus.

Figure 16: Tecovirimat Block of Virion Maturation



KEY: ER = endoplasmic reticulum; TGN = trans-Golgi network; IV = immature virus;

IMV = intracellular mature virus; IEV = intracellular enveloped virus; CEV = cell-associate enveloped virus; EEV = extracellular enveloped virus.

NOTE: Adapted from Hruby and Byrd. 2006. *Microbe*. 1(2):70-75. [10]

Tecovirimat demonstrates a high level of selectivity and specificity for orthopoxviruses. Tecovirimat targets the viral p37 protein, a highly conserved protein that has no homologs outside the Orthopoxvirus genus, inhibiting its function that is required for the envelopment of IMV. Tecovirimat disrupts the cellular localization of p37 and prevents its association with cellular protein involved in membrane trafficking.

3.3 Proposed Indication and Dosing

The proposed indication of tecovirimat is for the treatment of human smallpox disease caused by variola virus in adults and pediatric patients. The proposed treatment regimen in adults is 600 mg by mouth twice daily with a meal for 14 days. Dosing of pediatric patients and those who cannot swallow capsules is currently under labeling discussions with FDA.

3.4 Regulatory History

Introduction

SIGA is seeking regulatory approval for tecovirimat via the FDA Animal Rule (21 CFR §314.600 through §314.650). During Pre-Investigational New Drug (IND) discussions with the FDA Antiviral Division in 2004 and 2005, it became evident that the development path for tecovirimat would be based on animal studies for efficacy and human studies for safety, as it is not possible to study naturally occurring smallpox, and experimental variola infection of humans would be unethical and is thus prohibited. While other orthopoxvirus infections may occur in humans (e.g., monkeypox, cowpox and vaccinia complications), agreement was reached with FDA that studying these infections would either not be feasible (e.g., conducting studies of monkeypox in the Democratic Republic of the Congo), or would not provide sufficient data (e.g., studies in the rare cases of cowpox in Europe or complications caused by the vaccinia virus) to support NDA approval.

Efficacy Program in Animals

Based on the outcome of an Advisory Committee convened by FDA in December 2011 to specifically address the issue of animal models for smallpox, FDA concluded that 3 models were appropriate for evaluation/demonstration of drug efficacy versus smallpox: IV infection of NHPs with monkeypox virus, ID infection of New Zealand White rabbits with rabbitpox virus, and intranasal infection of BALB/c mice with ectromelia virus. The FDA recommended that at least two of these models be utilized to “triangulate” efficacy with humans, and that the most conservative model would serve to establish the appropriate drug exposure that would need to be exceeded in order to establish the human dose.

As agreed to with FDA at a development meeting held in March 2012, the 2 models that SIGA studied for efficacy were the NHP and rabbit models.

Clinical Program in Humans

SIGA submitted the original IND for tecovirimat in November 2005. The first Phase 1 single ascending dose clinical study initiated in 2006, and 10 additional clinical studies and 1 taste masking study have since been completed. All clinical protocols were reviewed by NIH or BARDA and FDA prior to study initiation, and study endpoints for PK and safety were agreed upon. All studies requested by FDA to support this NDA approval have been successfully completed.

Other

In addition to studies conducted under the SIGA-held IND, tecovirimat was provided for Emergency Use under 5 US Emergency IND (E-IND) applications and used on a Compassionate Use basis in Finland (refer to Section 8.13).

While the development program was ongoing, it was determined that there was sufficient evidence to allow tecovirimat to be stockpiled in the US CDC Strategic National Stockpile (SNS). SIGA initiated this activity in March 2013.

Because tecovirimat received Fast Track designation from FDA, and due to the unusual nature of development of a drug under the Animal Rule, SIGA and FDA had multiple interactions during the course of the tecovirimat program. The complete NDA was submitted in December 2017.

No regulatory applications have been filed outside the US to date, and tecovirimat is not marketed in any other country.

4. NONCLINICAL SAFETY

4.1 Summary of Nonclinical Study Results

The toxicology program for tecovirimat includes a comprehensive set of nonclinical toxicology studies designed to support the oral administration of tecovirimat in humans. The effects of tecovirimat have been evaluated in a nonclinical development program including repeat-dose toxicity studies (up to 3 months in duration) in mice and NHPs, a standard battery of *in vitro* and *in vivo* genetic toxicity tests, and a battery of reproductive and developmental toxicity tests including a fertility and early embryonic development study in mice, embryo-fetal development (EFD) studies in mice and rabbits, and a pre-natal and post-natal development study in mice. The *in vivo* studies included toxicokinetic (TK) evaluations.

The safety of tecovirimat on cardiovascular parameters was evaluated in an *in vitro* study on the human ether-a-go-go-related gene (hERG) channel and in *in vivo* studies conducted in cynomolgus macaques. Central nervous system (CNS) function and respiratory assessments were conducted in safety pharmacology studies in mice.

The majority of *in vivo* studies were conducted using the oral (gavage) route of administration, which is the intended clinical route.

4.2 Safety Pharmacology

Central Nervous System Evaluation

Administration of single oral doses of tecovirimat up to 2,000 mg/kg to male and female mice resulted in the development of neurobehavioral effects, including decreased general arousal, defecation counts, and body temperature. At the 2,000 mg/kg dose level, core body temperature declined to a magnitude that was considered adverse. The next lower dose of 1,000 mg/kg, which produced 23-folds above human clinical exposures, was considered to be the NOAEL.

Cardiovascular Function Studies

Tecovirimat at the highest concentration of 30 μ M (27-fold higher than the non-protein bound human maximum plasma concentration [C_{max}]) did not have an inhibitory effect on *in vitro* hERG channel tail current. Oral administration of tecovirimat to NHPs once-daily for 28 days at doses up to 300 mg/kg (1.4-fold of human clinical exposure) was not associated with any effects on cardiovascular function.

Respiratory System Evaluation

Oral administration of tecovirimat to male and female mice at doses up to 2,000 mg/kg (28-fold of human clinical exposure) did not have any effects on respiratory parameters.

4.3 Nonclinical Pharmacokinetics

The absorption, distribution, metabolism, and excretion (ADME) of orally administered tecovirimat have been investigated mainly in the key primary species used to support the animal efficacy rule for tecovirimat (i.e., rabbits and NHPs) and in mice, with limited studies being conducted in rats and dogs.

In vivo oral bioavailability studies conducted with mice, rats, rabbits, and NHPs indicate that tecovirimat has good oral bioavailability. Following oral administration, tecovirimat rapidly appeared in plasma, as indicated by the t_{max} values within approximately 5.0 hours. The plasma

protein binding of [¹⁴C]-tecovirimat was moderate to high (77.3-96.3%) in all species studied (mouse, rat, rabbit, dog, and NHP) and appears to be concentration-independent over a wide range of concentrations (0.03-50 μM). In oral repeat-dose studies, exposure parameters generally increased with dose, but dose-proportionality was not always observed.

Following oral administration in mice, 100 mg of [¹⁴C]-tecovirimat/kg was systemically distributed with the highest concentrations noted in the liver and gall bladder, respiratory tract tissues (i.e., nasal turbinates), and bone marrow. The highest tissue concentrations were observed at 24 hours post-dose and declined to near or below the LLOQ in most tissues beginning at 96 hours post-dose. Studies in dogs and NHPs indicate that tecovirimat crosses the blood brain barrier. In a placental and milk transfer study in mice, [¹⁴C]-associated tecovirimat was noted to be transferred to the offspring through the placenta and the milk.

In vitro studies indicate that tecovirimat is not a substrate of major CYP enzymes, but it is a substrate of human recombinant UGTs (specifically of UGT1A1, 1A3, and 1A4). The percent of tecovirimat remaining after 2 hours of incubation with UGT1A1, 1A3, and 1A4 was 66%, 79%, and 59%, respectively. Tecovirimat was found to be metabolized to M4, M5, and TFMBA in mice, NHPs, and humans. Of these 3 metabolites of tecovirimat, TFMBA has the highest plasma protein binding (50, 97.1, and 98.6% bound in mouse, NHP, and human plasma, respectively) whereas the plasma protein binding of M4 and M5 is low (in a range of 4.6-20.7% for M4 and 16.6-33.0% for M5, in mouse, NHP, and human plasma).

The excretion profile of [¹⁴C]-tecovirimat in mice indicates that feces is the major route of elimination followed by the urine (approximately 71-77% of the dose in feces and 18-24% in urine, within 96 hours post-dose). Overall, in mice, approximately 95% of the administered dose was excreted by 96 hours post-dose. In feces, tecovirimat was excreted unchanged whereas in urine, several metabolites, including TFMBA, were detected and only a trace amount of the parent compound was present.

4.4 Toxicology

A standard toxicology program was completed for tecovirimat, including single-dose and repeat-dose toxicity studies, genotoxicity studies, reproductive and development toxicity studies, and phototoxicity evaluation. These studies were conducted in mice, rats, rabbits, dogs, or NHPs, with mice and NHPs being designated as main toxicological species. The *in vivo* studies included TK evaluations.

4.4.1 Single and Repeat Dose Studies

Pivotal single-dose toxicity studies conducted in mice and NHPs demonstrated that tecovirimat was well tolerated, and no LD₅₀ has been reached even when the drug was given at very high doses (2,000 mg/kg) in both species.

In mice, oral administration of tecovirimat for 28 days and 3 months resulted in significant increases in relative liver and spleen weights at dose levels of 600 mg/kg/day and above; however, these findings were not considered to be of toxicological significance given that there were no microscopic or clinical chemistry findings and the weight changes were absent in the recovery animals. Due to the lack of tecovirimat-related effects at the highest dose levels in the 28-day and 3-month studies, the NOAEL in the 28-day and 3-month mouse studies were 2,000 and 1,000 mg/kg/day, respectively. The exposures achieved in mice at the 1,000 mg/kg/day dose

level in the 3-month study were approximately 23-fold and 29-fold over the human clinical exposure for AUC and C_{max} values, respectively.

In NHPs, oral administration of tecovirimat for 28 days or 3 months did not result in any test article-related effects at the highest tested dose level of 300 mg/kg/day. Thus, this level was determined to be the NOAEL in NHPs following 28 days and 3 months of oral dosing. The dose of 300 mg/kg/day for 3 months in the NHP produced AUC and C_{max} values of 2.5-fold and 2.4-fold over the human exposures, respectively.

The dog is considered more sensitive to tecovirimat than the other species tested. In a maximum tolerated dose study, single oral administration of tecovirimat resulted in multiple clinical signs including convulsions and mortality at 300 mg/kg/day in one male dog (C_{max} value of 16,500 ng/mL); however, in the female dog there were no convulsions or death (C_{max} value of 4875 ng/mL). No apparent seizures or changes in electroencephalogram were noted at 30 or 100 mg/kg/day administered over 7 days. Tecovirimat exposures were higher in male compared to female dogs, which may explain why more CNS signs were observed in the male dog. The dose level of 100 mg/kg in the male dog produced C_{max} value of 5,575 ng/mL, and in the female dog produced C_{max} value of 3,825 ng/mL. Based on these data, the C_{max} value of 5,575 ng/mL (seen in male dog administered 100 mg/kg/day) is considered the maximum allowable exposure level for humans. The dog appears to be hypersensitive to tecovirimat, as the observed CNS side effects were not seen in any of the other animal species tested with tecovirimat, and there have been no reported AEs of seizure in the human clinical trials.

4.4.2 Genotoxicity

Tecovirimat showed no mutagenic effects in *in vitro* bacterial reverse mutation and mouse lymphoma assays and no genotoxic effects in an *in vivo* bone marrow micronucleus assay in mice.

4.4.3 Reproductive and Developmental Toxicity

The EFD NOAEL in mice was determined to be the highest dose level of 1,000 mg/kg/day. Oral gavage administration of tecovirimat to male and female mice was not associated with any adverse effects on male or female fertility, implantation, or early embryonic development at dose levels up to 1,000 mg/kg/day, which produced AUC values approximately 23-fold over the human clinical exposure for AUC. A significant decrease was noted in the rate of viable fetuses at the high-dose level of 1,000 mg/kg/day; however, this finding was observed in the absence of a significant decrease in the fertility/fecundity rates. There were no other tecovirimat-related effects reported on any fertility parameters for females or males.

The EFD NOAELs in rabbits was determined to be the highest dose level of 100 mg/kg/day. Oral administration of tecovirimat resulted in adverse effects on maternal rabbits when given during the period of organogenesis but no effects on EFD or teratogenicity. Maternal toxicity noted in rabbits receiving the highest dose tested (100 mg, 0.35-fold of human AUC) included mortality (in 9 out of 22 rabbits) and significant decreases in body weight. This decrease in body weight at the high-dose level was associated with a significant decrease in food consumption. The weight loss impacted the number of live fetuses per doe and increased the post-implantation losses and early resorption levels; it did not impact the embryo/fetal development at any dose group studied. There were no other tecovirimat-related effects on maternal clinical pathology. The maternal toxicity was not observed in mice. The maternal NOAELs were considered to be

the highest dose level of 1,000 mg/kg/day in mice and the mid-dose level of 30 mg/kg/day in rabbits.

Oral administration of tecovirimat up to 1,000 mg/kg/day did not result in any adverse effects on pre- or post-natal development in mice. Oral administration of tecovirimat to dams can cross the placenta and be transferred to mouse offspring through the milk.

4.4.4 Other Toxicity Studies

In hairless mice (SKH1), administration of tecovirimat at single oral gavage dose levels of up to 2,000 mg/kg followed by ultraviolet radiation did not result in the development of skin reactions indicative of phototoxicity.

4.4.5 Summary of Observed Toxicities in Nonclinical Studies

Because tecovirimat targets a mechanism unique to orthopoxvirus maturation, it is not expected to interfere with host processes. Consistent with this prediction, toxicology testing has not revealed evidence of an injurious effect of high concentrations of the compound. In cell cultures, no effect on cell viability was observed at drug concentrations as high as 40 μ M, which was 4,000 times the concentration that caused 50% inhibition of vaccinia virus replication.

Tecovirimat toxicity has been evaluated in NHPs at 300 mg/kg/day for 3 months resulting in AUC and C_{max} values that are 2.5-fold and 2.4-fold, respectively, higher than human exposures. No toxicity was observed.

In mice, tecovirimat toxicity was assessed at 1,000 mg/kg/day for 3 months resulting in AUC and C_{max} values that were 23-fold and 29-fold, respectively, higher than human exposures. Mice demonstrated a transient increase in liver and spleen weight, but there were no chemistry or histological changes observed.

Because dogs are the only species that showed signs of clear toxicity and death at high doses, it is the species to set toxicity levels for clinical use. The C_{max} value of 5,575 ng/mL is considered the maximum safety limit for the purpose of human exposure, based on the non-lethal dose of 100 mg/kg in dogs.

The maternal toxicity in rabbits at 100 mg/kg/day (0.35-fold of human AUC) was the only noted event observed in a battery of the reproductive and development toxicology studies in mice and rabbits.

The nonclinical data for tecovirimat support its clinical use as an oral treatment of smallpox. Based on the totality of the data, especially the NOEL dose of 300 mg/kg/day after 3 months in the NHP, tecovirimat demonstrates a suitable clinical safety margin.

5. VIROLOGY

Tecovirimat was identified via high-throughput screen of a chemically diverse library of >300,000 unique compounds for their ability to inhibit vaccinia virus-induced CPE. The antiviral potency and selectivity of tecovirimat was measured in CPE assays against a panel of DNA and RNA containing viruses. Tecovirimat was found to be highly potent and specific for orthopoxviruses (including vaccinia, cowpox, ectromelia, rabbitpox, and most notably, monkeypox and variola, which cause serious human disease), without evidence of any activity against other DNA and RNA virus against which it was tested. In these assays, the EC₅₀ for inhibition of orthopoxviruses ranged from approximately 10-70 nM, while the EC₅₀ values for inhibition of unrelated viruses were >40 μM. Tecovirimat has also been evaluated for poxvirus inhibition in primary cell lines including human embryonic lung fibroblasts, primary human keratinocytes, and organotypic endothelial raft cultures [18] as well as standard tissue culture cells such as Vero, BSC-40, and SIRC [17] and was found to display similar activity regardless of cell type.

5.1 Antiviral Potency, Selectivity, and Spectrum of Antiviral Activity

The *in vitro* antiviral potency, selectivity, and spectrum of activity of tecovirimat was evaluated in African green monkey kidney cell lines (Vero, BSC-40) against numerous orthopoxviruses including vaccinia (NYCBH), cowpox (Brighton Red), a cidofovir resistant cowpox, ectromelia, camelpox, monkeypox (Zaire '79), and numerous strains of variola viruses. Tecovirimat potency was determined by measuring the EC₅₀ of the CPE induced in the absence of drug (vehicle treated infected cells). Table 6 shows the results of these assays. The EC₅₀ ranged from approximately 10-70 nM for all orthopoxviruses tested.

Table 6: Spectrum of Antiviral Activity

Virus (Strain)	EC ₅₀ (μM)
Vaccinia (NYCBH)	0.009
Cowpox (Brighton Red)	0.050
Cowpox cidofovir resistant (Brighton Red)	0.030
Ectromelia	0.068
Camelpox	0.012
Monkeypox (Zaire '79)	0.014
Variola (BUT)	0.016
Variola (BSH)	0.046
Variola (BRZ66-39)	0.067
Variola (SLN68-258)	0.037
Variola (SUD47-juba)	0.019
Variola (BSH74-sol)	0.028
Variola (NEP73-175)	0.021
Variola (SOM77-ali)	0.028

The selectivity of tecovirimat was determined in Vero and BSC-40 cell lines by measuring the concentration of compound that inhibited cell growth or was cytotoxic to 50% (CC₅₀) of the cells. Cytotoxicity was evaluated in L929, SIRC, BSC-40, Vero, TREx, and MRC5 cells. The tecovirimat CC₅₀ was >40 μM in all cell lines tested, which is the limit of solubility for tecovirimat in culture medium. In addition, selectivity of tecovirimat was evaluated by measuring antiviral activity against a panel of unrelated DNA and RNA containing viruses. The

results of these assays are shown in Table 7. Tecovirimat had no measurable inhibitory effect on any virus outside of the Orthopoxvirus genus.

Table 7: Tecovirimat Selectivity

Virus	Family	Classification	EC ₅₀ ^{a,b}
Vaccinia	Orthopoxviridae	Double stranded DNA	0.009
Herpes Simplex Virus Type-1	Herpesviridae	Double stranded DNA	>40
Cytomegalovirus	Herpesviridae	Double stranded DNA	>40
Respiratory Syncytial Virus	Paramyxoviridae	Negative single strand RNA	>40 ^{a,b}
Rotavirus	Reoviridae	Double stranded RNA	>40 ^{a,b}
Rift Valley Fever Virus	Bunyaviridae	Negative single strand RNA	>40 ^{a,b}
Tacaribe Virus	Arenaviridae	Ambisense RNA	>40 ^{a,b}
Lymphocytic Choriomeningitis Virus	Arenaviridae	Ambisense RNA	>40

^aEach value represents 2 independent determinations.

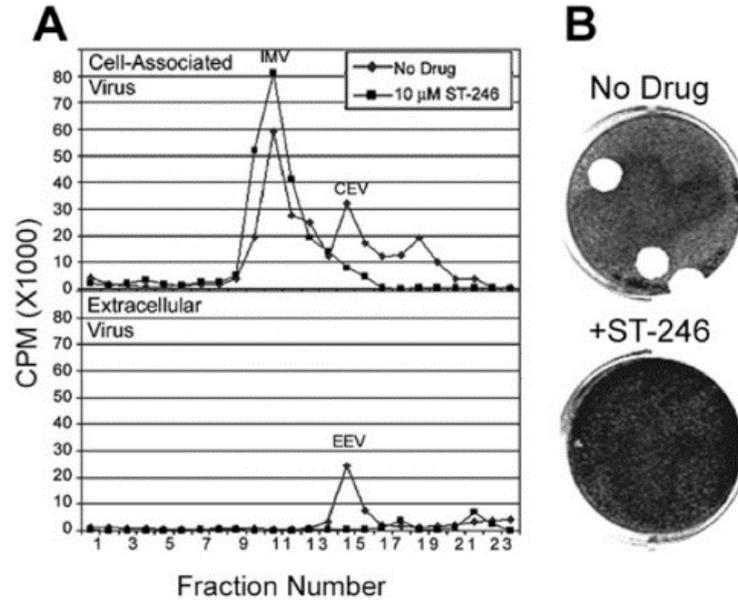
^bAssessment limited by solubility

5.2 Effect of Tecovirimat on the Formation of Enveloped Virus and Dissemination in Cell Culture

Orthopoxviruses produce 2 major forms of virus – intracellular mature virus (IMV), which is fully infectious but disseminates very poorly as it is retained within the cell until released by cell lysis very late in infection, and EV (including CEV and EEV), which is responsible for both cell-to-cell and long-range transmission of virus. Orthopoxviruses cause cytopathic effects in permissive cells which results in the formation of viral plaques on cell monolayers. Efficient plaque formation requires production of extracellular virus. Virus variants that contain deletions in genes required for production of extracellular virus particles form small (micro) plaques in cell culture. Plaque formation is used as a measure of virus replication efficiency and production of extracellular virus. In the assays shown in Figure 17, vaccinia virus infected cells were evaluated for production of EV by gradient separation of cell-associated and cell-free virus as well as the ability to form plaques in the presence and absence of inhibitory concentrations of tecovirimat.

Tecovirimat clearly inhibits the production of EV as shown by the absence of peaks of radioactivity correlating with CEV and EEV in cultures treated with vehicle. Inhibition of EV production also results in poor dissemination in the cell culture as no plaques formed in the presence of tecovirimat even after 7 days of culture. These results are further supported by measuring infectious intracellular and extracellular virus produced in the presence and absence of tecovirimat as shown in Figure 18. To determine the effects of tecovirimat on virus replication, virus yield assays were conducted to measure the amount of intracellular and extracellular virus produced in the presence and absence of compound. The results showed that tecovirimat reduced extracellular virus titers by approximately 10-fold at 24 hour post-infection while having little effect on the level of intracellular virus titers relative to untreated controls. These results suggest that tecovirimat inhibits the formation of egress-competent forms of orthopoxviruses.

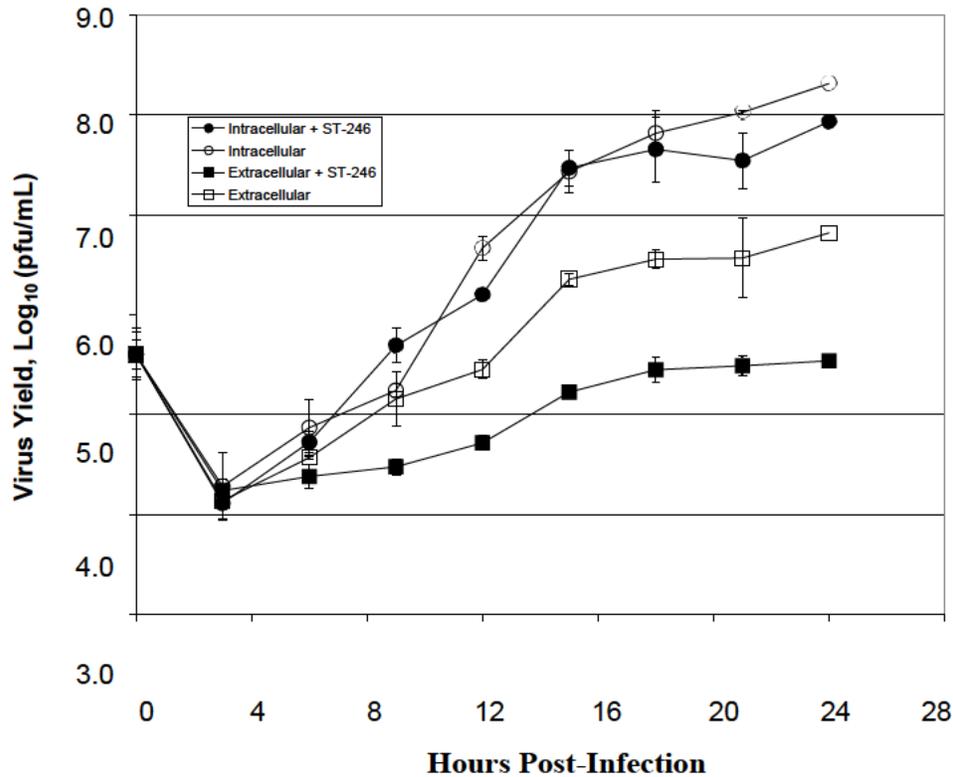
Figure 17: Tecovirimat Inhibits Enveloped Virus Formation and Prevents Dissemination *In Vitro*



(A) Monolayer cultures of cells were infected with vaccinia virus and treated with vehicle or tecovirimat (ST-246). Cultures were labeled with ^{35}S -methionine. Virus was purified from cells (Cell-Associated Virus) and culture supernatants (Extracellular Virus) and separated by centrifugation through CsCl gradients. Typical peaks of radioactivity are detected in untreated cultures (noted as IMV for intracellular mature virus, CEV, and EEV for cell-associated enveloped virus and extracellular enveloped virus, respectively). Note the absence of CEV and EEV in tecovirimat-treated cultures.

(B) Cell monolayers were infected with vaccinia virus at a low multiplicity and treated with vehicle or tecovirimat (ST-246) for seven days post-infection then stained with crystal violet to detect plaques.

Figure 18: Effects of Tecovirimat on Production of Intracellular and Extracellular Virus



Monolayer cultures of cells were infected with vaccinia virus and treated with vehicle or tecovirimat (ST-246). Virus was purified from cells (Intracellular) and culture supernatants (Extracellular) at timepoints indicated on the “x” axis and titered to determine yield.

5.3 Summary

Tecovirimat exhibits dose-dependent broad-spectrum activity against multiple members of the Orthopoxvirus genus, including multiple strains of variola virus. The EC₅₀ for tecovirimat ranges from approximately 10-70 nM for all orthopoxviruses tested including the significant human pathogens, monkeypox virus and variola virus, which causes smallpox. Considering that the cytotoxic concentration exceeded 40 μM, the therapeutic index for tecovirimat is >4,000. Moreover, tecovirimat is active against cidofovir resistant cowpox variant. These results suggest that tecovirimat is a potent and specific inhibitor of a conserved viral target essential for orthopoxvirus replication in cell culture, and that the target is different from that of cidofovir. The target of tecovirimat is the p37 protein, which is essential for the formation of enveloped virions that are necessary for viral spread from the site of inoculation. By targeting p37, tecovirimat inhibits the formation of EV and virion egress from cells, preventing plaque formation and dissemination in culture.

6. BIOPHARMACEUTICS AND CLINICAL (HUMAN) PHARMACOKINETICS

6.1 Pharmacokinetics/Pharmacodynamics

Ten clinical studies were conducted evaluating: dose ranging and tolerability, single-dose and multiple-dose PK, food effect, drug absorption/metabolism/excretion, dose linearity, intrinsic drug interaction factors (renal and hepatic impairment), extrinsic drug interaction factors, and PD (thorough QT).

6.1.1 Absorption and Exposure

Following oral administration, tecovirimat is absorbed rapidly and achieves C_{max} within 6 hours. Administration of tecovirimat at 600 mg twice daily in the fed state results in mean C_{max} of 2,209 ng/mL, C_{min} of 690 ng/mL, and AUC_{0-24} of 30,632 ng•h/mL. Drug absorption is enhanced in presence of food. No changes in the absorption and exposure were observed when tecovirimat capsule contents were administered mixed with applesauce or milk. Accumulation is observed after repeated administration, and the steady state is achieved within 6 days.

6.1.2 Distribution and Protein Binding

Levels of tecovirimat and drug-related materials are approximately 10-40% lower in whole blood compared with plasma, demonstrating a limited degree of partitioning of drug-related material into blood cells. Plasma protein binding for tecovirimat is moderately high (~80%), and tecovirimat is extensively distributed throughout the body with a volume of distribution (V_z/F) of approximately 1,356 L.

6.1.3 Metabolism

In vitro data demonstrated that tecovirimat is not metabolized by major CYP enzymes, but it is a substrate for conjugation by UGT isoforms.

Clinical data indicated that tecovirimat is metabolized by hydrolysis of the amide bond and glucuronide conjugation. Among the 10 identified metabolites, M4, M5, and TFMBA are the most abundant metabolites in the plasma. M4, M5, and TFMBA constitute approximately 10.4%, 5.8%, and 70.4% of total exposure, respectively. *In vitro* data indicated that these 3 metabolites are pharmacologically inactive. No safety concerns for tecovirimat, M4, M5, or TFMBA exposure have been identified in clinical or nonclinical studies.

6.1.4 Elimination

Metabolic clearance is the major route of elimination in humans based on the prevalence of cleavage products (M4, M5, and TFMBA) in plasma and the glucuronide conjugates of tecovirimat and M4 in plasma and urine. After oral administration of 600 mg twice daily for 14 days, the total body clearance normalized for fraction of dose absorbed (CL/F) ranges from 20-30 L/h.

6.1.5 Excretion

Approximately 95% of radiolabeled material was recovered in urine and feces over the 192-hour post-dose period, with approximately 73% of the radioactivity administered being recovered in urine and 23% being recovered in feces, indicating that the urinary pathway is the major route of excretion. The urinary excretion of parent compound was minimal, accounting for less than 0.02%. The majority of excreted drug in urine is in a glucuronidated form.

6.1.6 Dose Proportionality

The relationship between tecovirimat doses and exposures after oral administration was explored in a clinical study in healthy subjects. Data demonstrated a linear exposure increase across a dose range from 100-600 mg.

6.1.7 Accumulation and Time-dependency

After multiple dosing, plasma exposure (i.e., AUC) accumulates with an accumulation factor of 1.6 and reaches steady state by Day 6.

6.1.8 Food Effect

Absorption is enhanced when tecovirimat is administered with food, with plasma exposure (C_{max} and AUC_{0-24}) increasing by 39%. Food increases t_{max} by approximately 2 hours. However, the accumulation ratio (RAC) values are similar when tecovirimat is administered with or without food. The elimination of tecovirimat appears to be similar under fed or fasted conditions, as evidenced by a similar mean $t_{1/2}$ (19.3 versus 23.1 hours, respectively).

6.1.9 Special Populations

6.1.9.1 Age, Sex, and Race

While there are insufficient data to conclude whether tecovirimat PK are significantly altered in geriatric or specific racial groups, plasma exposures in all these groups are in the therapeutic range. No studies were conducted in the pediatric populations.

6.1.9.2 Hepatic and Renal Impairment

Tecovirimat was evaluated in subjects with mild, moderate, or severe hepatic impairment (Child Pugh Class A, B, or C). Clinical data supported that hepatic impairment has a minor impact on exposure to tecovirimat. Peak concentrations are similar across subjects with varying degrees of hepatic function. Although AUCs were shown to be highest among subjects with severe hepatic impairment, the differences from those subjects with normal hepatic function are not substantial. The t_{max} is consistent across subjects with varying degrees of hepatic impairment. The $t_{1/2}$ appears to be shorter; while CL/F is relatively unchanged, the Vz/F decreases with decreasing hepatic function. There is also a modest effect of hepatic impairment on C_{max} and AUC of the 3 predominant metabolites, with M4 increasing by up to 2-fold in subjects with severe hepatic impairment.

Clinical data from mild, moderate, or severe renal impairment or subjects with ESRD requiring hemodialysis (HD) supported that renal impairment has a minor impact on the overall extent of tecovirimat exposure. The C_{max} in subjects with mild or moderate renal impairment appears to be similar to C_{max} for those with normal renal function, while AUCs tend to increase. In subjects with ESRD, AUCs are approximately 50% of those observed in subjects with normal renal function. However, t_{max} was unaffected by renal function. The CL/F and Vz/F appear to increase in subjects with ESRD (pre- and post-HD), and the $t_{1/2}$ is prolonged in some subjects with severe renal impairment and ESRD (pre-HD). Overall, the C_{max} and AUC values and PK profiles for all renal impairment groups are within the expected range for safety and efficacy. Tecovirimat is not substantially cleared by HD, as indicated by similar PK parameters pre- and post-HD. In addition, modest increases in exposure were observed for the metabolites (M4, M5, and TFMBA) in subjects with renal impairment, and M4 appears to be substantially removed by HD.

6.1.10 Drug-Drug Interaction

Tecovirimat is not metabolized by major CYP enzymes; therefore, it is unlikely to be impacted by co-administration of other drugs. *In vitro* data showed that tecovirimat and its metabolites M4 and M5, at the expected clinical dose levels, had a potential to be inhibitors of BCRP and inducers of CYP isoforms 3A4, 2B6, 2C8, 2C9, and 2C19. Further drug-drug interaction evaluation was conducted in a clinical study to evaluate the impact of tecovirimat and its metabolites on CYP isoforms 3A4, 2B6, 2C8, 2C9, and 2C19. Co-administration of tecovirimat and specific probe substrates for these CYP enzymes resulted in the inhibition of CYP2C8 and CYP2C19 and induction of CYP3A4; however, these impacts were considered mild.

Based on these data, the exposures of drugs that are substrates for BCRP, CYP2C8, and CYP2C19 may increase while the exposures of drugs that are substrates for CYP3A4 may decrease, when co-administered with tecovirimat.

6.1.11 Pharmacodynamic Studies: Thorough QTc

In a thorough QT study, no clinically significant effects of tecovirimat or its metabolites (M4, M5, TFMBA) on cardiac repolarization and no ECG morphologic changes were observed after a single supratherapeutic dose of tecovirimat 1,000 mg.

Reports of abnormal ECGs were also uncommon in the clinical studies. In the Phase 3 pivotal study, 9 subjects who received tecovirimat had ECG abnormalities that were considered clinically significant; however, no TEAEs were associated with these abnormalities. Safety ECG data from the Phase 3 pivotal study and the clinical study SIGA-246-015 (DDI) were analyzed to further evaluate the cardiac effects of metabolites at their highest plasma levels since the ECG monitoring was performed in these studies at the maximum steady state metabolite exposure levels. Analysis of the safety ECGs from these studies showed that tecovirimat and its metabolites did not prolong the Federicia-corrected QT (QTcF) interval and there were no significant changes in other cardiac intervals or morphological changes of clinical significance during tecovirimat administration. Tecovirimat and its metabolites did not have any clinically relevant effect on cardiac repolarization (e.g., heart rate and QTc, PR, and QRS intervals).

7. EFFICACY

7.1 Summary of Efficacy Results in Nonhuman Primates

7.1.1 NHP Model Development

In consultation with FDA, SIGA determined that the VARV model in NHPs was not suitable for evaluation of antiviral efficacy for several reasons: 1) the disease course does not resemble smallpox in humans making the interpretation of efficacy data difficult, 2) the lack of reproducibility of the model implies that large numbers of animals and experiments would be required to accumulate the necessary data, and 3) the requirement for the execution of these experiments in a World Health Organization WHO approved institution (the CDC biosafety level-4 facility) and with prior WHO approval for use of live VARV would significantly hinder the ability to provide the FDA with the data (of sufficient quality) needed to evaluate tecovirimat.

FDA Guidance [19] allows that:

“There may be situations in which the application of the Animal Rule requires a more complex development plan. For example, variola virus (the etiologic agent of smallpox) presents a unique challenge because humans are the only known natural host, no animal species has been found to have comparable susceptibility to variola virus, and naturally occurring smallpox has been eradicated. Therefore, efficacy of investigational drugs developed to treat smallpox needs to be studied using other orthopoxviruses in relevant animal species (e.g., monkeypox in nonhuman primates, rabbitpox in rabbits, ectromelia in mice). Depending on the strength of the animal studies and other supporting evidence, the efficacy findings from such studies may support approval of the drug against variola.”

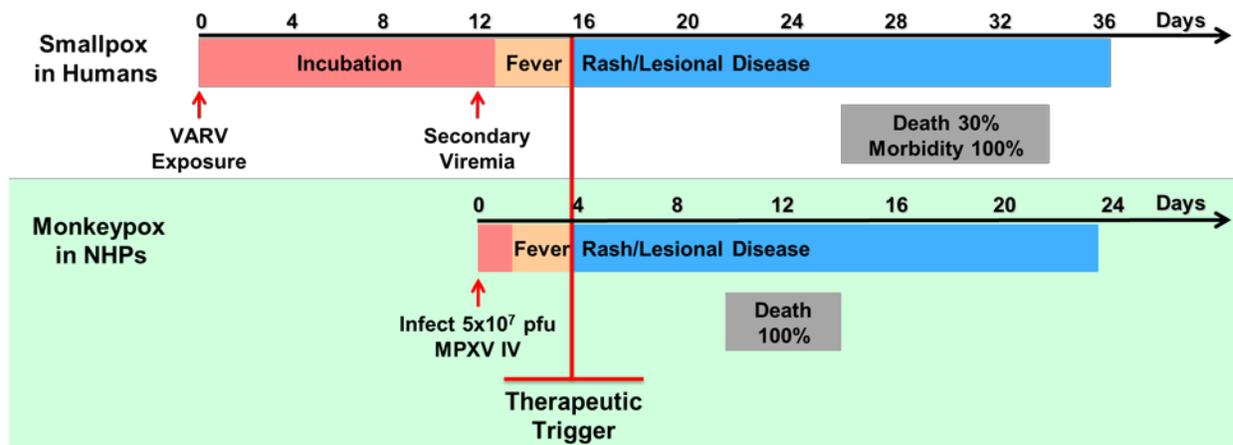
This Guidance is based on the outcome of an Advisory Committee meeting convened by FDA in 2011 to specifically address the issue of animal models for smallpox. The Guidance additionally states, “The effect (should be) demonstrated in more than one animal species expected to react with a response predictive for humans...”. SIGA, working closely with FDA and in partnership with BARDA, has developed and utilized the IV challenge MPXV/NHP and ID challenge RPXV/Rabbit models to demonstrate tecovirimat efficacy.

7.1.1.1 Natural History of MPXV Infection in Cynomolgus Macaques

MPXV infection of cynomolgus macaques is a reliable model described in the scientific literature [20] that captures many of the aspects of human smallpox. Previous experiments have shown that aerosol exposure results in rapid disease onset and mortality, sometimes prior to the formation of skin lesions [21] whereas IV challenge results in a systemic disease that is extremely similar to human smallpox after the secondary viremia stage of the disease (Figure 19). Within 2 days of IV inoculation with 5×10^7 pfu of MPXV (Zaire ‘79 strain), animals become febrile, followed by the development of a skin rash and lesions on the face and extremities reminiscent of the centrifugally distributed rash in human smallpox. Numerous pocks form (500-1,500 total body count by the time of death) and progress through the same developmental stages as human smallpox. Animals develop increasingly high titers of virus in the blood. In particular, measures of viral DNA load and lesion count are considered to be good predictors of mortality and increases in body temperature (i.e., fever), and the development of skin rashes show that NHPs are symptomatic by 72 hours post-infection. Successful intervention

by a pharmaceutical agent (i.e., tecovirimat) at this point in this model would correspond to post-symptomatic therapy in human disease. Mortality in this model is ~95%, and the mean time to death is ~14 days post-infection. Thus, NHPs infected with MPXV is an appropriate model for the investigation of tecovirimat efficacy.

Figure 19: Clinical Course of Smallpox in Humans and Comparison to Monkeypox Infection in Non-Human Primates



7.1.1.2 Trigger for Intervention

Since SIGA is developing tecovirimat for a therapeutic indication, the biomarkers and triggers used for medical intervention in the animal model to the appropriate corresponding symptoms in human smallpox that are definitive of disease must be linked. The most distinctive and unambiguous identification of smallpox was the appearance of a synchronous, centrifugal rash that progressed from an enanthema/exanthema to pustules beginning a few days after severe fever. The nature and progression of this rash was used to clinically differentiate smallpox from other rash-like diseases such as chicken pox. In the IV challenge NHP model, lesions containing virus appear 3-4 days post-challenge and continue to increase in number and progress through stages typical of human smallpox until death. This symptom provides the most direct and obvious link between MPX disease in NHPs and smallpox disease in humans. It is entirely fitting that in this model, the trigger for treatment would be the first appearance of lesions.

In the event of a suspected outbreak of smallpox, it is likely that index cases would not be diagnosed or treated until after pock formation. With the development of modern technologies, a definitive diagnosis of smallpox could be made (particularly in those suspected of exposure) prior to pock formation and probably as early as the prodromal fever (when secondary viremia would be easily detected by quantitative polymerase chain reaction [qPCR]). This highlights that an acceptable animal model must be characterized by post-exposure fever and viremia and preferably followed by the development of a significant number of skin lesions.

7.1.1.3 Selection of a Well-Characterized Challenge Agent (MPXV) for Pivotal Studies

The challenge virus used for each study was monkeypox Zaire '79. The challenge stock used in all NHP studies was derived from virus isolated by Breman, Kalisa [22] from the scab of a severely-ill 1-year-old boy living in Zaire (now the Democratic Republic of Congo) during a 1978-1979 monkeypox outbreak [22, 23]. The “severe disease” experienced by this monkeypox

patient was characterized as >100 lesions, severe incapacity, and requiring medical care. Although it does not appear that this patient died, there were 10 severe illnesses (91%), of which 3 died (~ 27%) out of the 11 reported cases for this outbreak of monkeypox [22]. The one remaining case experienced moderate disease severity with more than 25 lesions, moderate incapacity, and may have required medical care but not hospitalization. The virus from the scab material at CDC was amplified to make the master seed stock. The virus was completely sequenced, and the data were published in 2005 [23]. The material was then further amplified by additional passages to produce the Master Bank and a Working Bank for animal testing. The virus stock was shown to be free of contamination by other orthopoxviruses. Additional testing for each virus stock included 1) confirmation of infectivity by infection of MA-104 cells and observation of cytopathic effect (cell rounding), 2) sequencing of the viral hemagglutinin gene and observation that the sequence was consistent with the published sequence of monkeypox virus Zaire '79, 3) plaque assay to determine titer (reported in the Certificate of Analysis), 4) sterility testing (no microbial growth), 5) mycoplasma testing (none detected), 6) endotoxin testing (results reported, <0.03 EU/mL), and 7) pH (reported, ~8.0).

7.1.2 Study Design Elements Common to All NHP Studies

7.1.2.1 Inclusion/Exclusion Criteria

All animals completed quarantine and were considered to be in good health at the start of the study. The animals were pre-screened for antibodies against vaccinia virus (cross-reactivity with monkeypox and other poxviruses) to eliminate the possibility of prior exposure to poxvirus antigens; only those with negative result were used in the studies.

7.1.2.2 Statistical Analyses

All efficacy analyses were conducted using the Intent to Treat (ITT) population, which included all NHPs in their respective studies that were randomized and received virus injection on Day 0.

All animals received at least one dose of treatment. The ITT population received the virus on Day 0 and received at least one dose of treatment.

Statistical analyses were conducted to compare the tecovirimat dose groups to the placebo group. No statistical analyses were conducted for pairwise comparisons between the tecovirimat dose groups.

The primary endpoint for all studies was survival rate. Supportive PD endpoints included lesion counts and viral DNA load.

7.1.2.2.1 Analysis of the Primary Endpoint

Survival rates were defined as the percentage of animals alive at the day of scheduled study termination. No distinction was made between animals that were euthanized in moribund condition and those that died as a result of infection. The Fisher Exact test was utilized to compare the survival rate for the placebo treated group to the tecovirimat treated groups. The resultant p-values are presented as one-sided with statistical significance declared at the 0.05 level.

7.1.2.2.2 Analysis of the Supportive Pharmacodynamic Endpoints

Viral DNA levels post-injection are summarized by treatment group at each time point, and the geometric mean is reported. Lesion counts were an efficacy endpoint in three of the NHP studies (26G, 37F, and 38F). In each of these studies, lesion counts were obtained and summarized at designated days post-challenge. Total lesion counts were performed for designated body areas, and the sum of the counts from all regions in each animal was computed to determine the total body lesion count. Median lesion counts per study group are reported at each counting interval.

For Study 26G, actual counts were performed on areas that could be enumerated. On areas that had confluent lesions or were too numerous to count, counts were estimated.

For Study 87, lesion formation was monitored, and lesion count was estimated. The manner in which lesion count was reported was not amenable to statistical analysis.

For Studies 37F and 38F, actual counts were performed on areas that could be enumerated. On areas that had confluent lesions or were too numerous to count, a count of 200 was assigned for that anatomical region.

7.1.3 Pivotal NHP Studies

7.1.3.1 Study 26G

7.1.3.1.1 Overview of the Study Design

Study 26G was a double-blind, randomized, placebo-controlled, repeat-dose efficacy study of tecovirimat in cynomolgus macaques (Figure 20). The study was conducted at a single study site. The objective of this study was to determine the minimum effective dose of oral tecovirimat for the treatment of monkeypox in the lesional cynomolgus macaque model of smallpox beginning individually on the day of onset of pox lesions in each animal.

Cynomolgus macaques not previously exposed to any orthopoxvirus were intravenously infected with 5.5×10^7 pfu of Zaire '79 strain of monkeypox on Day 0. NHPs received tecovirimat at 0 (placebo), 0.3, 1, 3, and 10 mg/kg once daily by oral gavage beginning on Day 4 post-infection and continued every 24 ± 2 hours for 14 consecutive days.

Exposure levels of tecovirimat in the blood that corresponded to the lowest protective dose were evaluated. Survival was evaluated statistically for up to 28 days after infection (although survivors were monitored for up to 48 days). Viral DNA levels, total lesions, clinical observations, hematology and clinical chemistry, and gross and microscopic anatomic pathology were evaluated.

Figure 20: Timeline for Study 26G



KEY: MPXV = monkeypox virus

7.1.3.1.2 Results

Survival Rate and Time

Mortality was noted in placebo-treated control NHPs as well as in NHPs treated with tecovirimat. The survival rate analysis and time to death are presented in Table 8.

Table 8: Survival Rate Analysis and Time to Death in Study 26G

Dose (Regimen)	No. of Animals/Sex	Survival Rate		Time to Death
		Survival (n [%])	P-value ^a	Mortality Day (No., Sex)
Placebo (Days 4–17)	7M	0 (0)	--	Day 9 (1M) Day 14 (2M) Day 15 (2M) Day 17 (2M)
Tecovirimat 0.3 mg/kg (Days 4–17)	5M	1 (20)	0.4167	Day 12 (1M) Day 15 (1M) Day 16 (1M) Day 18 (1M)
Tecovirimat 1 mg/kg (Days 4–17)	5M	0 (0)	1.0000	Day 11 (1 M) Day 14 (1 M) Day 15 (1M) Day 16 (1M) Day 27 (1M)
Tecovirimat 3 mg/kg (Days 4–17)	5M	4 (80)	0.0101	Day 5 (1M)
Tecovirimat 10 mg/kg (Days 4–17)	5M	4 (80)	0.0101	Day 11 (1M)

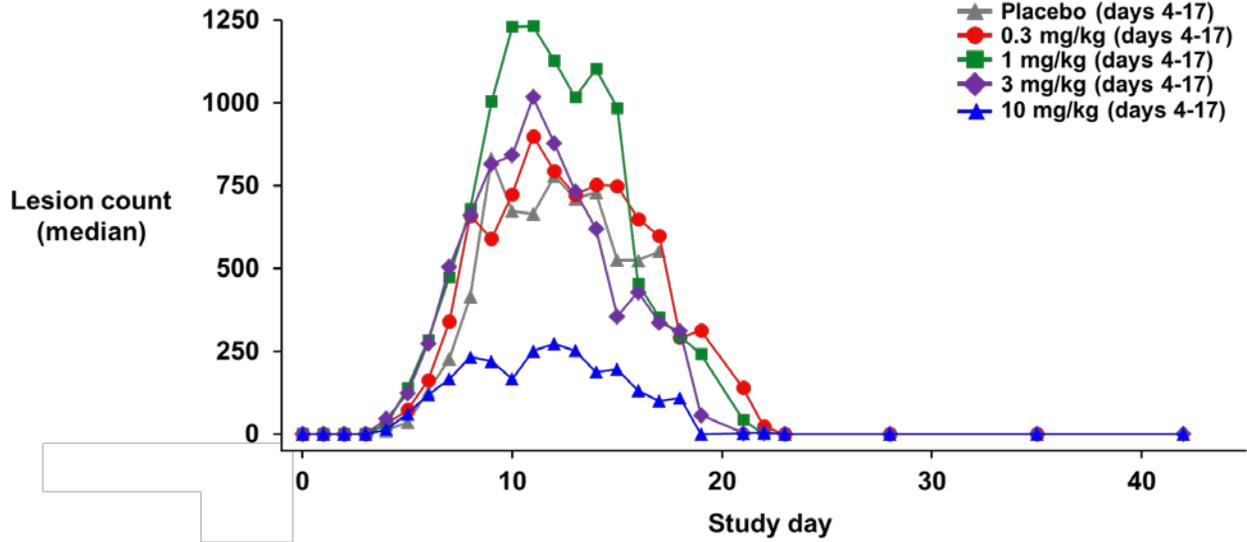
^ap-value is from 1-sided Fisher's Exact Test compared to control

Key: M = male; No. = number.

Lesion Count

All animals were noted to have lesions by Day 3 or 4 post-infection, first appearing in the oral cavity as ulcerating lesions. Within a day of the first appearance in the oral cavity, lesions, characterized as macules, papules, or vesicles, then appeared on the head and extremities and spread further to the rest of the body within another day. By Day 7 to 9, most lesions then became pustular and umbilicated. Scabbed lesions, which are an early indication of resolution, were first noted by Day 11 post-infection. Total body lesion counts typically peaked between Day 9 and Day 12. Placebo-treated control animals and animals treated with 0.3 or 1 mg/kg body weight/day typically died as lesions were progressing from the pustular/umbilicated stage to the scabbing stage between Day 9 and 17 post-infection. For animals treated with 3 or 10 mg/kg body weight/day, scabs began separating by approximately Day 13-15 leaving a desquamated lesion, which fully resolved between 19-23 days post-infection. The median lesion counts are depicted in Figure 21.

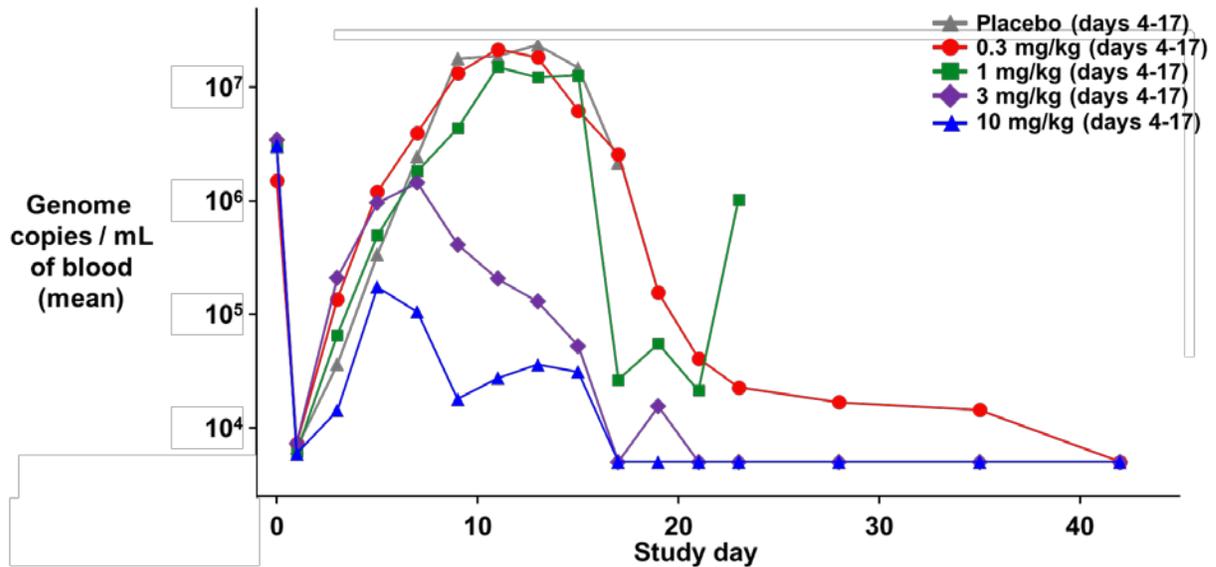
Figure 21: Median Lesion Count in Study 26G



Viral DNA Load

The geometric mean viral DNA load data are depicted in Figure 22. Overall, the results demonstrated that animals receiving tecovirimat had gradual declines in circulating viral DNA by the end of the treatment period. These values were reported to be significantly decreased in the 3 and 10 mg/kg groups compared to the controls. There is a clear dose response in the reduction in circulating viral DNA: viral DNA loads for animals administered tecovirimat doses <3 mg/kg body weight/day were not significantly different than placebo-treated animals, while animals administered tecovirimat doses of 3 or 10 mg/kg body weight/day were significantly reduced, but to different levels. This finding indicates that while both the 3 or 10 mg/kg body weight/day treatment provided equivalent protection from mortality, the 10 mg/kg dose was additionally associated with a significant reduction in lesion count and a more rapid resolution of viral DNA load. Concentrations of MPXV DNA were reduced to the limits of quantitation by the end of the treatment period in animals of the 3 and 10 mg/kg dose groups.

Figure 22: Geometric Mean Viral DNA Load in Study 26G



7.1.3.2 Study 87

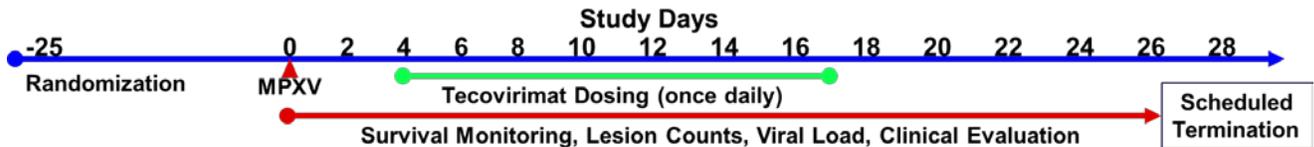
7.1.3.2.1 Overview Study Design

Study 87 was a randomized, placebo-controlled, repeat-dose study of tecovirimat in cynomolgus macaques (Figure 23). The objective of this study was to evaluate the PK of tecovirimat in male and female cynomolgus macaques infected via IV injection with MPXV to establish the exposure-response relationship. The doses evaluated in this study were previously determined to be effective in treating monkeypox disease in NHPs.

Animals were screened prior to placement into the study utilizing a plaque reduction neutralization titer analysis to confirm that all animals randomized into the study were free of detectable MPXV-neutralizing antibody levels. Twenty-eight animals – 14 males and 14 females (3-4 years of age on arrival; 3.03-5.01 kg body weight) – were randomized by body weight into dose groups. Randomization was conducted prior to Day -10 and resulted in similar average group body weights among the groups of females and among the groups of males.

At 10 days prior to MPXV challenge, animals received tecovirimat via the oral (gavage) route at dose levels of 0 (placebo control), 3, 10, or 20 mg/kg body weight and blood was collected for pharmacokinetic (PK) analyses. Following challenge with MPXV via IV injection at a challenge dose of 5×10^7 pfu, treatment (vehicle or tecovirimat) was initiated at 4 days post-infection (a time point at which all animals were noted to have lesions) and continued for a total of 14 days (up to and including Day 17). In addition to PK analysis in non-infected NHPs at 10 days prior to infection, blood was collected for PK analysis after the first and fourteenth (last) day of dosing for population PK modeling, PK/PD analysis, and determination of the exposure-response relationship.

Figure 23: Timeline for Study 87



KEY: MPXV = monkeypox virus

7.1.3.2.2 Results

Survival Rate and Time

Mortality was noted only in placebo-treated control animals, with death occurring in all 6 subjects by Day 16. The survival rate analysis and time to death are presented in Table 9. It should be noted that this study only explored doses shown to be efficacious in the NHP model. Full dose response data are presented in Study 26G (see Section 7.1.3.1).

Table 9: Survival Rate Analysis and Time to Death for Study 87

Dose (Regimen)	No. of Animals/ Sex	Survival Rate		Time to Death
		Survival (n [%])	P-value ^a	Mortality Day (No., Sex)
Placebo (Days 4–17)	3M/3F	0 (0)	--	Day 12 (2M, 1F) Day 13 (1M) Day 14 (1F) Day 16 (1F)
Tecovirimat 3 mg/kg (Days 4–17)	3M/3F	6 (100)	0.0011	--
Tecovirimat 10 mg/kg (Days 4–17)	3M/3F	6 (100)	0.0011	--
Tecovirimat 20 mg/kg (Days 4–17)	3M/3F	6 (100)	0.0011	--

^ap-value is from 1-sided Fisher’s Exact Test compared to control

Key: F= female; M = male; No. = number.

Lesion Formation

By Day 3 post-challenge, lesions (specifically, macules, papules, pustules, or crust) were noted in animals from all study groups. By Day 18 post-challenge, lesions could primarily be described as umbilicated, crusted, or desquamated, with further progression by Day 21 to crusted or desquamated. A decrease was noted in the lesion counts in treated animals; however, a dose-response could not be observed. Study 87 includes data for lesion counts by type of lesion that includes overlapping categories for the number of lesions. The data are not interpretable or appropriate for statistical analysis and therefore are not presented.

Viral DNA Load

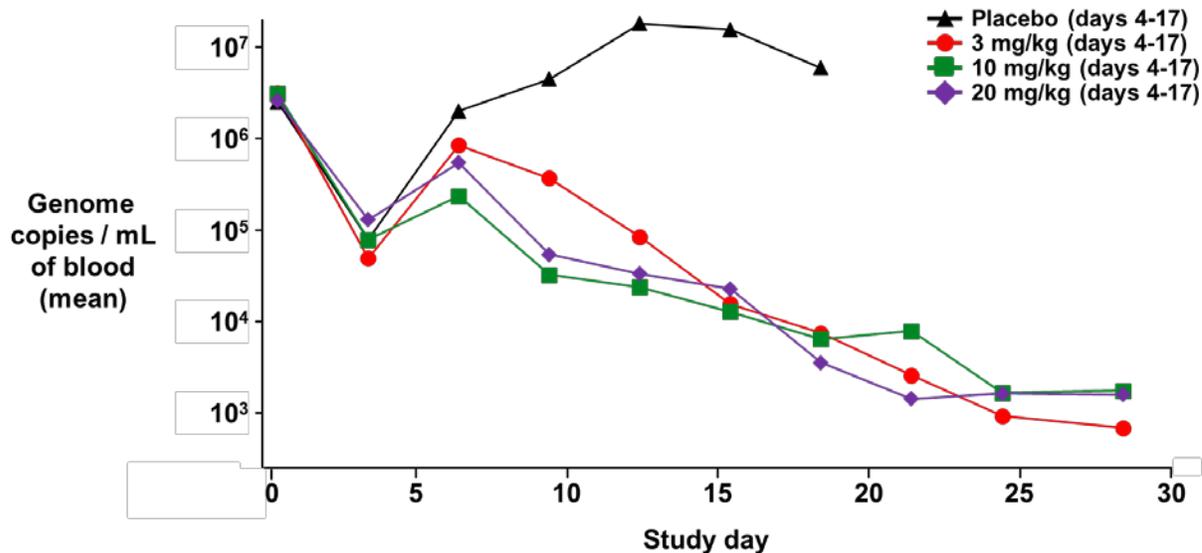
Within 2 minutes of IV administration of MPXV, all groups demonstrated high MPXV DNA levels (~3.11 x 10⁶ copies/mL) of the virus in the blood, thereby indicating successful challenge. Average MPXV DNA levels decreased to 1.11 x 10⁵ genomic copies/mL at 3 days post-challenge and, by 6 days post-challenge, placebo-treated control animals demonstrated a consistent increase in circulating viral DNA load until animals succumbed to infection. The

lower limit of quantification for this assay was defined as 1,000 copies/mL. The terminal or near-terminal samples of MPXV DNA measured in NHPs of the control and treatment groups were as follows:

- Placebo control animals: 5.57×10^6 to 8.32×10^7 copies/mL;
- 3 mg/kg: <1,000 copies /mL to 3.27×10^3 copies/mL;
- 10 mg/kg: <1,000 copies/mL to 8.53×10^3 copies/mL; and
- 20 mg/kg: <1,000 copies/mL to 5.82×10^3 copies/mL.

The geometric mean viral DNA load is depicted in Figure 24. Overall, the results demonstrated that all animals receiving tecovirimat had gradual declines in circulating viral DNA; however, these declines were not demonstrated to be dose-dependent since the doses used in this study are above the dose response range for efficacy (i.e., all doses are ≥ 3 mg/kg body weight/day). Concentrations of MPXV DNA declined to the lower limit of quantitation of the assay on approximately Day 15 (10 mg/kg), 18 (20 mg/kg), or 21 (3 mg/kg) post-challenge.

Figure 24: Geometric Mean Viral DNA Load in Study 87



While Study 26G included a full dose response analysis, Study 87 only explored doses which were demonstrated to be efficacious in the NHP model. The results from Studies 26G and 87 are consistent in demonstrating survival benefit for doses of 3 mg/kg and above.

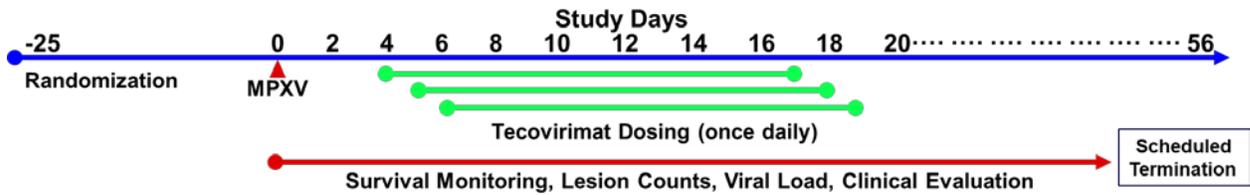
7.1.3.3 Study 37F

7.1.3.3.1 Overview Study Design

Study 37F was a randomized, double-blind, placebo-controlled study of tecovirimat administered orally to cynomolgus macaques infected intravenously with MPXV (Figure 25). Twenty-one (21) randomly selected healthy male and female cynomolgus macaques were assigned to 4 groups according to weight and sex. Cynomolgus macaques negative for poxvirus antibodies were intravenously infected with 5.0×10^7 pfu of Zaire '79 strain of MPXV on Day 0. Animals received tecovirimat at 10 mg/kg by oral gavage beginning on Day 4 (Group 2), 5 (Group 3), and 6 (Group 4) after MPXV inoculation and continued to receive once-daily doses for 14

consecutive days. To accommodate blinding, Groups 2, 3, and 4 were administered placebo on non-tecovirimat dose days during the treatment period. Group 1 received placebo only.

Figure 25: Timeline for Study 37F



KEY: MPXV = monkeypox virus

7.1.3.3.2 Results

Mortality was noted in placebo-treated control animals as well as in NHPs treated with tecovirimat. The survival rate analysis and time to death are presented in Table 10. This time to treatment study successfully demonstrated that treatment should occur prior to Day 6 to ensure maximal survival benefit.

Table 10: Survival Rate Analysis and Time to Death for Study 37F

Dose (Regimen)	No. of Animals/ Sex	Survival Rate		Time to Death
		Survival (n [%])	P-value ^a	Mortality Day (No., Sex)
Placebo (Days 4–19)	1M/2F	0 (0)	--	Day 7 (2F) Day 10 (1M)
Tecovirimat 10 mg/kg (Days 4–17)	3M/3F	5 (83)	0.0476	Day 12 (1M)
Tecovirimat 10 mg/kg (Days 5–18)	3M/3F	5 (83)	0.0476	Day 8 (1M)
Tecovirimat 10 mg/kg (Days 6–19)	3M/3F	3 (50)	0.2381	Day 8 (1M) Day 11 (1M) Day 12 (1F)

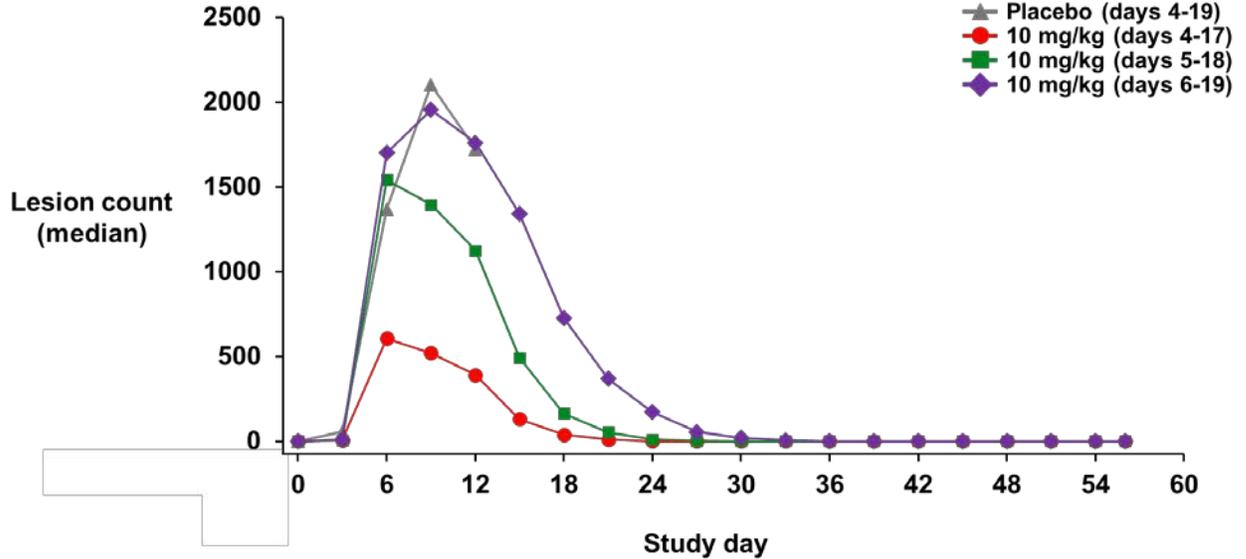
^ap-value is from 1-sided Fisher's Exact Test compared to control

Key: F = female; M = male; No. = number.

Lesion Counts

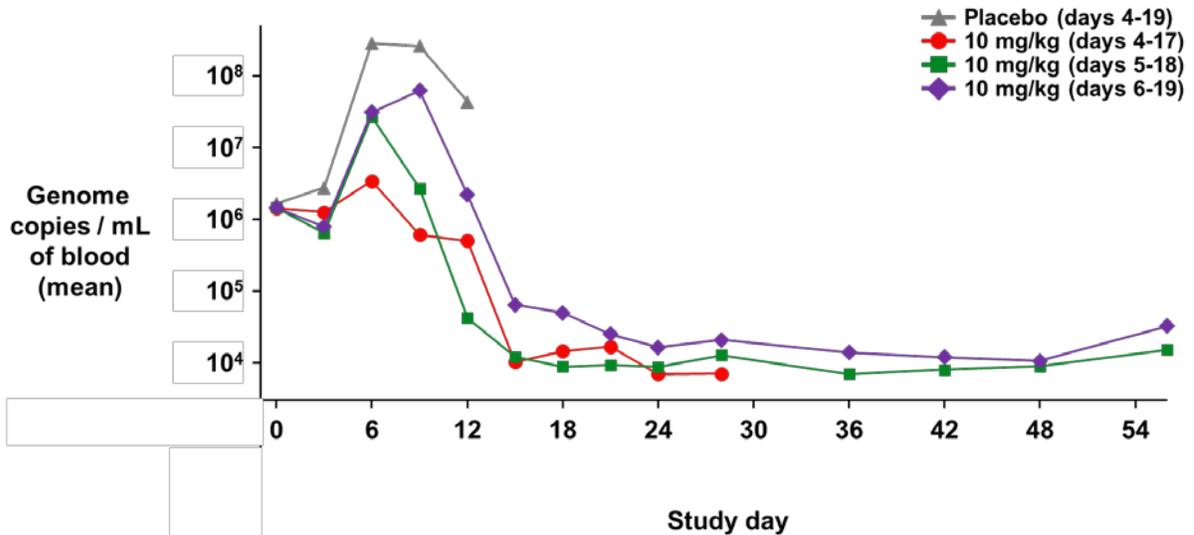
Most animals (16/21) were noted to have lesions by Day 3 post-infection (head and extremities), and all were noted to be lesional prior to administration of the first dose of tecovirimat. Total body lesions counts typically peaked between Day 6 and Day 9. Placebo-treated control animals and animals treated with 10 mg/kg body weight/day that succumbed to disease typically died as lesions were progressing through the vesicular/pustular/umbilicated stage between Day 6 and 12 post-infection. For surviving animals treated with 10 mg/kg body weight/day, scabs began separating by approximately Day 9-15 post-infection, leaving a desquamated lesion, which fully resolved between 19-36 days post-infection. The median lesion counts are depicted in Figure 26.

Figure 26: Median Lesion Count in Study 37F



The geometric mean viral DNA load data are summarized in Figure 27. There was a significant reduction in time-weighted average viral DNA load in all tecovirimat-treated animals (Days 4, 5, and 6 animals combined) compared to the placebo group for treatment Days 1-16 and for post-infection Days 3-24.

Figure 27: Geometric Mean Viral Load in Study 37F



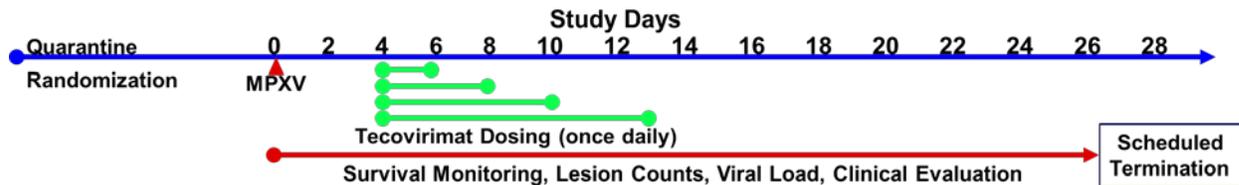
7.1.3.4 Study 38F

7.1.3.4.1 Overview Study Design

Study 38F was a randomized, double-blind, placebo-controlled study of tecovirimat administered orally to cynomolgus macaques infected intravenously with MPXV (Figure 28). Twenty-five (25) randomly selected healthy male and female cynomolgus macaques were assigned to 5 groups according to weight and sex. Cynomolgus macaques negative for poxvirus antibodies

were intravenously infected with 5.0×10^7 pfu of Zaire ‘79 strain of MPXV on Day 0. Animals received tecovirimat 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-tecovirimat dose days during the treatment period. Group 1 received placebo only.

Figure 28: Timeline for Study 38F



KEY: MPXV = monkeypox virus

7.1.3.4.2 Results

Survival Rate and Time

Mortality was noted in placebo-treated control animals as well as in NHPs treated with tecovirimat. Assessment of survival rate demonstrated a significant effect of tecovirimat treatment on mortality, with treatment for at least 5 days sufficient to confer a survival advantage. In the tecovirimat groups receiving treatment for 5, 7, and 10 days, 100%, 100%, and 80% of animals survived, respectively. The survival rate analysis and time to death for this study is presented in Table 11.

Table 11: Survival Rate Analysis and Time to Death in Study 38F

Dose (Regimen)	No. of Animals/ Sex	Survival Rate		Time to Death
		Survival (n [%])	P-value ^a	Mortality Day (No., Sex)
Placebo (Days 4–13)	2M/2F	1 (25)	--	Day 10 (1F) Day 11 (1M) Day 13 (1M)
Tecovirimat 10 mg/kg (Days 4–6)	2M/2F	2 (50)	0.5000	Day 14 (1M) Day 16 (1F)
Tecovirimat 10 mg/kg (Days 4–8)	3M/3F	6 (100)	0.0333	--
Tecovirimat 10 mg/kg (Days 4–10)	3M/3F	6 (100)	0.0333	--
Tecovirimat 10 mg/kg (Days 4–13)	2M/3F	4 (80)	0.1667	Day 11 (1M)

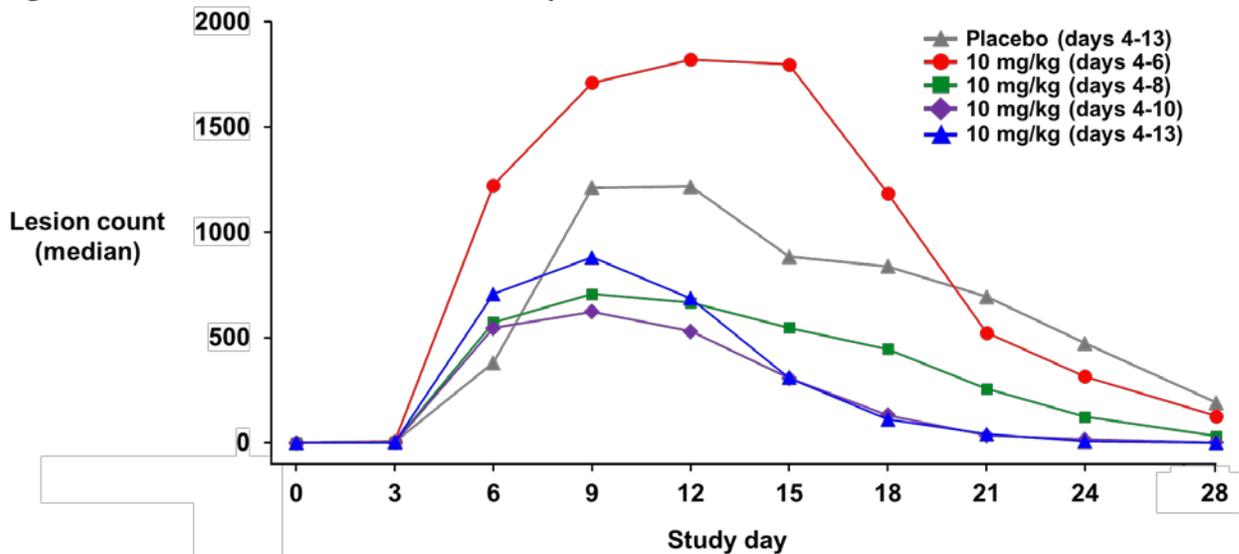
^ap-value is from 1-sided Fisher’s Exact Test compared to control. Key: F = female; M = male; No. = number.

Lesion Counts

Most animals (19/25) were noted to have lesions by Day 3 post-infection (head and extremities), and all were noted to be lesional prior to administration of the first dose of tecovirimat. By Day 6, lesions had developed over the entire body of animals, and most lesions were characterized as vesicular or pustular. Total body lesion counts peaked on approximately Day 9 for tecovirimat treated animals and on Day 12 for placebo-treated animals. Placebo-treated control animals and animals treated with 10 mg/kg body weight/day that succumbed to disease typically died as

lesions were progressing through the vesicular/pustular/umbilicated stage between Day 6 and 12 post-infection. For surviving animals treated with 10 mg/kg body weight/day, scabs began separating by approximately Day 9-15 post-infection leaving a desquamated lesion, which fully resolved by Day 24 post-infection for some animals, but most animals had not fully resolved the desquamated skin by Day 28 when the study was terminated. The median lesion counts are depicted in Figure 29.

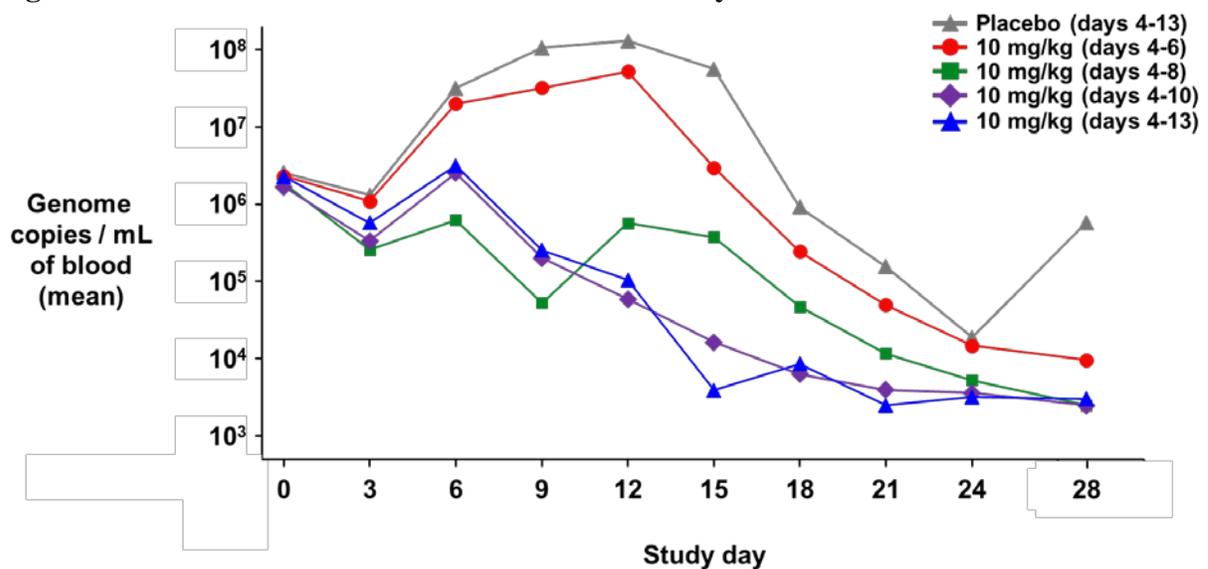
Figure 29: Median Lesion Count in Study 38F



Viral DNA Load

The geometric mean viral DNA load data are summarized in Figure 30. Longer durations of tecovirimat treatment of 5, 7, or 10 days were associated with viral DNA load approaching the lower limit of quantitation by study termination.

Figure 30: Geometric Mean Viral DNA Load in Study 38F



7.2 Summary of Efficacy Results in Rabbits

7.2.1 Rabbit Model Development

Rabbitpox virus (RPXV) is a large (~198 kbp) double-stranded DNA virus within the family Poxviridae and the genus Orthopoxvirus that is most closely related to VACV [24, 25]. RPXV was isolated in 1932 and again in 1941 at the Rockefeller Institute in New York and at the University of Utrecht, the Netherlands, respectively. The University of Utrecht isolate was designated RPXV strain Utrecht (RPXV-UTR) [26]. The disease was named “pockless” rabbitpox since infected rabbits usually died before a rash became evident [27]. Since the Utrecht strain was much more pathogenic and produced a more rapid and consistently fatal disease course than the Rockefeller strain, essentially all published rabbitpox studies in the last 40+ years have been done using RPXV-UTR [28, 29]. A stock of RPXV-UTR was produced following Good Laboratory Practices regulations for use in pivotal rabbit studies.

The scientific literature describes two lethal rabbitpox models, with the route of challenge occurring through aerosol delivery or ID inoculation. The major advantage of an aerosol challenge model is that it exposes the animal via the same respiratory route that smallpox is transmitted in humans. However, since the model is needed to evaluate therapeutic countermeasures, and in the aerosol model lethality appears to be lung-related and not associated with a systemic infection as observed in human smallpox, the tecovirimat program concentrated on the development of an ID challenge model. The ID challenge model is appropriate because infections result in high mortality; the ID route always establishes a “smallpox-like” disease of uniform mortality at low doses. The model is very reproducible, as an ID challenge ensures that every animal receives an identical dose, resulting in a synchronous disease. These features provide a far more evaluable approach for the testing of medical countermeasures. The ability to utilize large group sizes in this model is essential for ensuring that studies have sufficient statistical power.

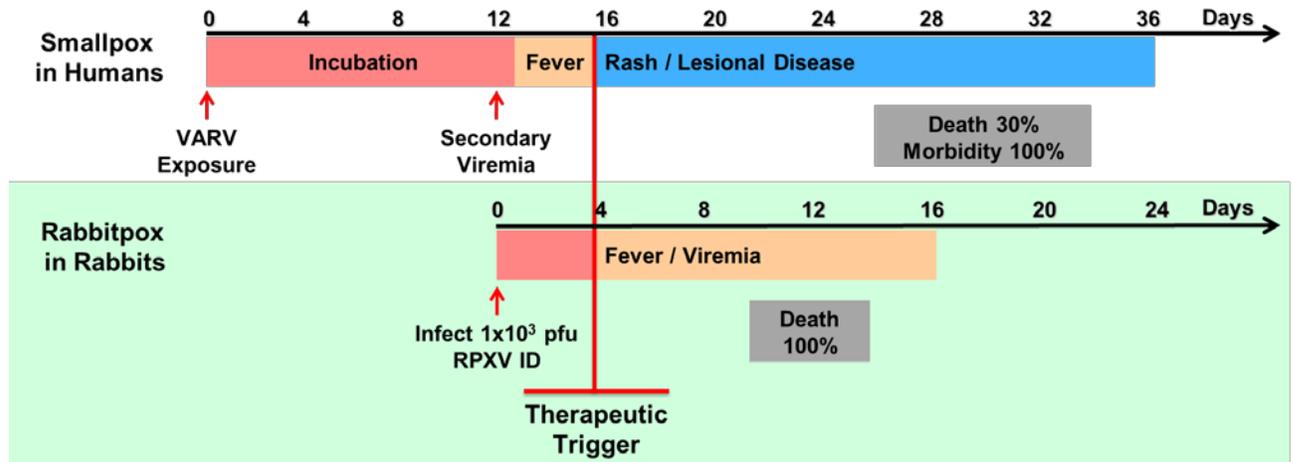
7.2.1.1 Natural History of RPXV Infection in New Zealand White Rabbits

The results from Adams, 2007 [30] suggested that rabbitpox disease in rabbits closely mimics the steps of smallpox disease in humans. After the initial infection, there is a symptom free incubation period, followed by fever and the dissemination of virus in the blood and the establishment of a systemic infection, followed by death. The infections established after ID or aerosol exposure results in a disease that is transmissible [28, 30, 31], and the FDA recommended exploration of the ID rabbitpox model after the Advisory Committee meeting in December 2011. Therefore, the ID challenge model has been used for evaluation of tecovirimat efficacy.

Inoculation of rabbits with 1000 pfu of RPXV-UTR via the ID route induces uniformly lethal disease by Day 6-10 post-infection [30]. The cause of death or justification for humane euthanasia in RPXV-infected rabbits is generally attributed to severe respiratory distress. Within 2 days of inoculation, a raised red swelling becomes evident at the inoculation site, develops to a pustular, black, and necrotic center by Day 5 and covers the entire thigh of the rabbit (up to 10 cm in diameter and 2 cm in thickness) by Days 7 or 8 post-injection. Secondary lesions due to virus spread from the inoculation site may also appear on the ears, eyelids, and other mucocutaneous tissues, such as the nose, lips, tongue, mouth, genitals, and anus by Days 3-5, although not all animals will develop lesions prior to death. Clinical signs of disease include

fever, weight loss, nasal and ocular discharge, and severe respiratory distress requiring euthanasia. Circulating viral DNA is evident within 24 hours of the first observation of fever and increases until death between Days 6 and 10. Rapid decline in temperature from a feverish state to hypothermia (or near hypothermia) signals impending death and warrants humane euthanasia. Upon necropsy, the lungs of euthanized rabbits appear dark and marbled with large regions of hemorrhage. Progression of RPXV disease for comparison to human smallpox is shown in Figure 31.

Figure 31: Clinical Course of Smallpox in Humans and Comparison to Rabbitpox Infection in Rabbits



7.2.1.2 Trigger for Intervention

One of the goals of the natural history studies was to identify biomarkers that are reproducible and unambiguous symptoms of rabbitpox infection in rabbits to provide potential triggers for therapeutic intervention. The 3 most reproducible biomarkers associated with infection were fever (usually first observed by Day 3-4 post-challenge), RPXV DNA in the blood (usually detected by qPCR by Day 2-3 post-challenge), and lesions (first observed Day 5 post-challenge or after). The drawbacks to using lesions as a trigger were discussed in the previous section. The studies supported by SIGA to evaluate tecovirimat used the combination of significant increase in body temperature, as defined in the study protocols and viremia (positive qPCR detection in blood for RPXV DNA) as a reliable and conservative indicator of established disease following a challenge with a lethal dose of RPXV-UTR. Given that fever and qPCR positivity is always observed in all RPXV-infected rabbits by Day 4 post-challenge, tecovirimat treatment initiation was synchronized for all animals on Day 4 regardless of earlier observations of fever.

7.2.2 Study Design Elements Common to All Rabbit Studies

7.2.2.1 Inclusion/Exclusion Criteria

All animals completed quarantine and were considered to be in good health at the start of the study. The animals were pre-screened for antibodies against vaccinia virus (cross-reactivity with monkeypox and other poxviruses) to eliminate the possibility of prior exposure to poxvirus antigens, and only those with negative result were used in the studies.

7.2.2.2 Statistical Analysis of Study Endpoints

All efficacy analyses were conducted using the ITT population, which included all rabbits in their respective studies that were randomized and received virus injection on Day 0. All animals received at least one dose of treatment. The ITT population as defined above had the same number of subjects as a population defined as all animals randomized, received the virus on Day 0, and received at least one dose of treatment. Statistical analyses were conducted to compare the tecovirimat dose groups to the placebo group. No statistical analyses were conducted for pairwise comparisons between the tecovirimat dose groups.

The primary endpoint for all studies was survival rate. Viral DNA load was analyzed as a supportive secondary endpoint.

7.2.2.2.1 Analysis of the Primary Endpoint

Survival rates were defined as the percentage of animals alive at the day of scheduled study termination. No distinction is made between animals that were euthanized in moribund condition and those that died as a result of infection. The same statistical procedures from the NHP studies (see Section 7.1.2.2.1) were utilized to compare the survival rate for the placebo group to the tecovirimat dose groups. The resultant p-values are presented as one-sided with statistical significance declared at the 0.05 level. The 95% confidence intervals for difference in proportions between the results for the placebo group and the tecovirimat groups is graphically displayed by forest plot.

7.2.2.2.2 Analysis of the Supportive Pharmacodynamic Endpoint

Viral DNA levels post-injection are summarized by treatment group at each time point. Viral DNA data for each treatment group was summarized at each time point by the geometric mean.

7.2.3 Pivotal Rabbit Studies

7.2.3.1 Study 25F

7.2.3.1.1 Overview of the Study Design

Study 25F was a double-blind, randomized, repeat-dose efficacy study of tecovirimat in New Zealand White rabbits. The objectives of this study were to evaluate the efficacy of tecovirimat in RPXV-infected rabbits, develop a population PK model, evaluate the effect of RPXV infection on the oral PK of tecovirimat in rabbits, and determine the exposure-response relationship. The treatment regimen consisted of once daily dose treatment by oral gavage for 14 consecutive days. Male and female animals with pre-assigned numbers were randomized into 3 groups of 8 rabbits each based on body weight and gender.

Seven days prior to RPXV challenge, all animals received a single oral (gavage) dose of tecovirimat at levels of 40, 80, or 120 mg/kg, and plasma samples were collected to evaluate tecovirimat PK in non-infected rabbits. Following ID challenge with RPXV at 1,000 pfu, tecovirimat was administered via the oral (gavage) route at dose levels of 40, 80, or 120 mg/kg/day for 14 consecutive days beginning on Day 4 post-infection. In addition to PK analysis in non-infected rabbits at 7 days prior to infection, blood was collected for PK analysis after the first, seventh, and fourteenth (last) day of dosing for population PK modeling, PK/PD analysis, and determination of the exposure-response relationship.

Animals were monitored at least twice daily initially and then once every 4 hours as clinical signs of disease became evident, and at each clinical observation time-point for progression to endpoint euthanasia criteria. Necropsy of all surviving animals occurred on Day 18. DNA eluates from whole blood were assayed for the presence of RPXV genomic material via qPCR. Baseline viral DNA levels were obtained prior to infection. Following infection on Day 0, viral DNA levels were obtained on Days 4, 7, 10, 13, 15, and 18. For animals that succumbed prior to study termination, viral DNA levels were obtained at the same interval as survivor animals until the time of death/euthanasia.

7.2.3.1.2 Results

Both Studies Study 25F and Study 08F (Section 7.2.3.2) were intended to be dose-response studies. Based on survival results, it should be noted that for both studies, the doses administered are above the dose-response range, as survival was similar for all rabbits that received any dose of tecovirimat.

Following ID challenge with a lethal dose of RPXV, 1 of 8 rabbits treated with 40 mg/kg/day and 1 of 8 rabbits treated with 80 mg/kg/day were found dead on Days 16 and 17, respectively. See Table 12 for details. These 2 animals were found dead immediately after the daily dosing procedure, and it was determined that this mortality was a result of the gavage procedure and not caused by RPXV infection. All rabbits (8/8) treated with 120 mg/kg body weight/day were protected against lethal RPXV challenge and survived to the scheduled termination on Day 18 post-challenge. Statistical analysis for time to death and survival rate for this study were not performed as there are no placebo comparators in this study.

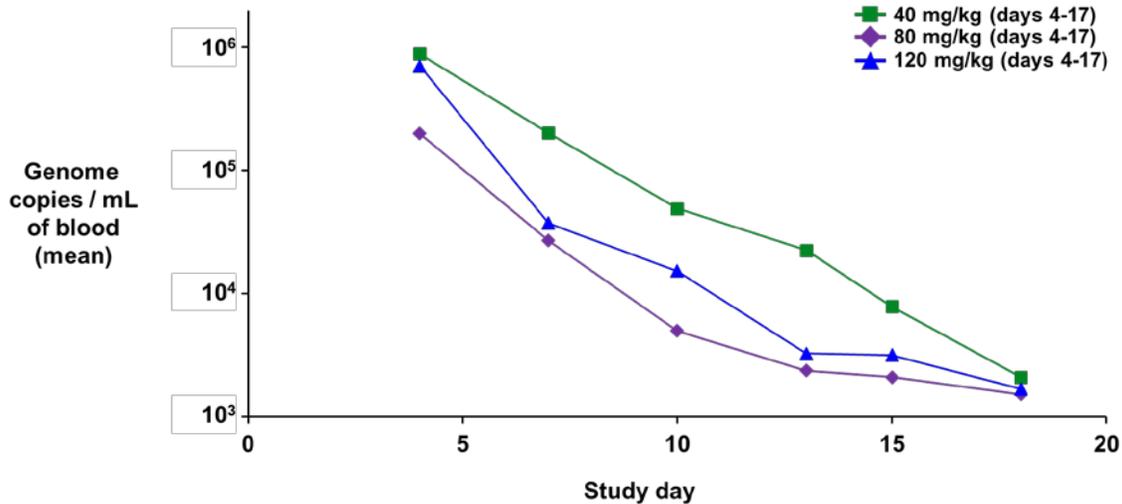
Table 12: Survival Rate and Time to Death in Study 25F

Dose (Regimen)	No. of Animals/ Sex	Survival Rate	Time to Death
		Survival (n [%])	Mortality Day (No., Sex)
Tecovirimat 40 mg/kg (Days 4–17)	4M/4F	7 (87.5)	Day 16 (1F)
Tecovirimat 80 mg/kg (Days 4–17)	4M/4F	7 (87.5)	Day 17 (1M)
Tecovirimat 120 mg/kg (Days 4–17)	4M/4F	8 (100)	--

Key: F= female; M = male; No. = number.

Prior to RPXV challenge (Day -7), all animals demonstrated a viral DNA load below the LLOQ of 4,000 genome copies/mL. On Day 0, all animals were challenged with an ID challenge dose of RPXV and on Day 4, tecovirimat treatment was initiated in all rabbits. The mean viral DNA load data are summarized in Figure 32. All rabbits produced a measurable viral DNA load by Day 4 post-infection, which represented the peak for most animals. Some animals in each treatment group reached peak viral DNA load after Day 4 post-infection, with one animal reaching peak viral DNA load on Day 13. Generally, by Day 7, a decline in viral DNA load was detected for most animals. Reduced viral DNA load was sustainable, as noted by levels approaching the LLOQ by study termination for animals treated with 40 mg/kg body weight/day and below the LLOQ in animals treated with 80 or 120 mg/kg body weight/day.

Figure 32: Geometric Mean Viral DNA Load in Study 25F



7.2.3.2 Study 08F

7.2.3.2.1 Overview Study Design

Study 08F was a double-blind, randomized, placebo-controlled, repeat-dose efficacy study of tecovirimat in New Zealand White rabbits. The objective of this study was to evaluate various doses of tecovirimat for efficacy against lethal ID RPXV challenge in rabbits in order to identify a minimum efficacious dose that provides maximal survival benefit.

Male and female animals were randomized based on body weight and gender into 5 groups of 10 animals per group. Animals were monitored at least twice daily initially, but more frequently if warranted, and at each clinical observation time-point for progression to endpoint euthanasia criteria. Necropsy of all surviving animals occurred over 2 days, on Days 30 and 31.

DNA eluates from whole blood were assayed for the presence of RPXV genomic material via qPCR. Baseline viral DNA levels were obtained prior to infection. Following infection on Day 0, viral DNA levels were obtained on Days 2, 3, or 4 depending on when the animals became feverish, and were scheduled to be obtained on Days 4, 6, 8, 10, 12, 14, 16, 18, 22, 26, and 30. For animals that succumbed prior to study termination, viral DNA levels were obtained at the same interval as survivor animals until the time of death/euthanasia.

7.2.3.2.2 Results

Mortality was noted in placebo-treated control animals as well as in rabbits treated with tecovirimat. Following ID challenge with a lethal dose of RPXV, mortality was noted in all placebo-treated control animals between Days 5 and 10 post-challenge. In contrast, the majority of animals administered tecovirimat treatment on Day 4 post-challenge were protected from mortality. Ninety percent of rabbits that received 20 or 40 mg/kg body weight/day were protected from mortality. Eighty percent of rabbits that received 80 or 120 mg/kg body weight/day were protected from mortality.

The survival rate analysis and time to death are presented in Table 13.

Table 13: Survival Rate Analysis and Time to Death for Study 08F

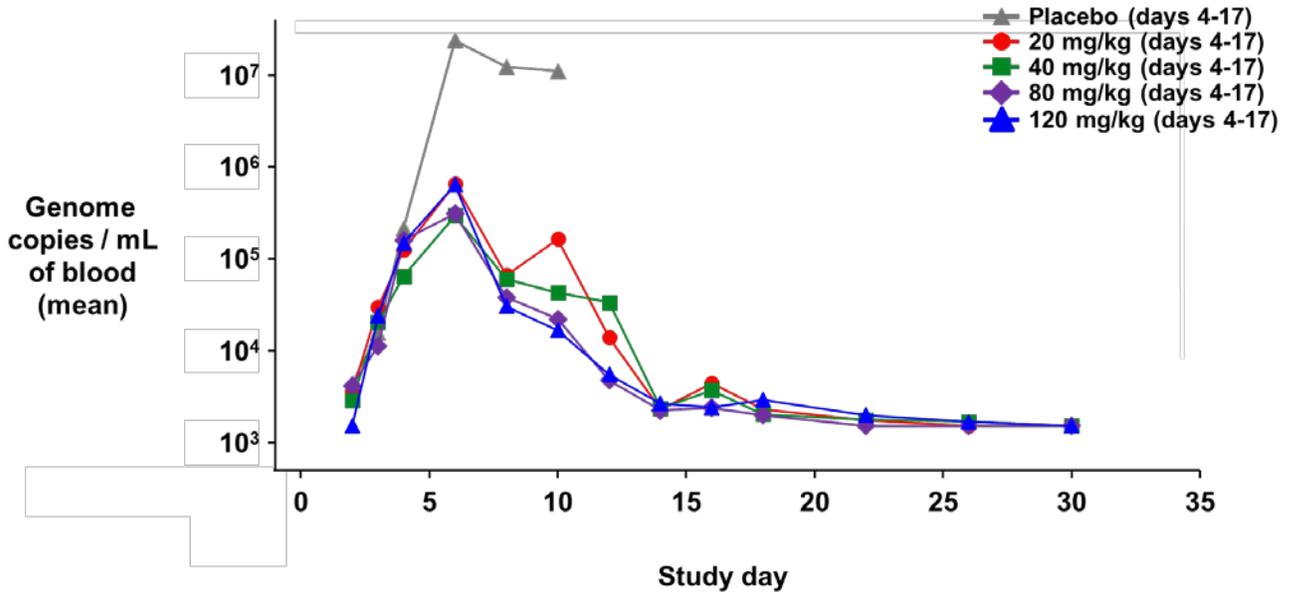
Dose (Regimen)	No. of Animals/ Sex	Survival Rate		Time to Death
		Survival (n [%])	P-value ^a	Mortality Day (No., Sex)
Placebo (Days 4–13)	5M/5F	0 (0)	--	Day 5 (1F) Day 6 (2M) Day 7 (1M/2F) Day 8 (1M/1F) Day 9 (1F) Day 10 (1M)
Tecovirimat 20 mg/kg (Days 4–17)	5M/5F	9 (90)	0.0001	Day 14 (1M)
Tecovirimat 40 mg/kg (Days 4–17)	5M/5F	9 (90)	0.0001	Day 12 (1M)
Tecovirimat 80 mg/kg (Days 4–17)	5M/5F	8 (80)	0.0004	Day 9 (1F) Day 13 (1F)
Tecovirimat 120 mg/kg (Days 4–17)	5M/5F	8 (80)	0.0004	Day 9 (1F) Day 12 (1M)

^ap-value is from 1-sided Fisher's Exact Test compared to control

Key: F = female; M = male; No. = number.

Prior to RPXV challenge, all animals demonstrated a viral DNA load below the limit of detection (LOD) of 3,040 genome copies/mL and LLOQ of 4,000 genome copies/mL of blood. All the animals demonstrated genomic DNA levels in the blood above both the LOD and LLOQ by the time treatment was initiated on Day 4 post-challenge. The geometric mean viral DNA load data are summarized in Figure 33. Following challenge with RPXV on Day 0, the RPXV-infected control animals exhibited high genomic DNA copy number. The viral DNA load increased as the infection progressed and generally peaked at the time of necropsy. In contrast, the tecovirimat-treated animals that were infected with RPXV exhibited a much lower genomic copy number post-initiation of treatment and demonstrated better control of viral DNA in the blood compared to the placebo treated animals.

Figure 33: Geometric Mean Viral DNA Load in Study 08F



7.2.4 Overall Summary of NHP and Rabbit Efficacy

As detailed above, 4 pivotal studies were conducted in the MPXV/NHP model for human smallpox, and 2 pivotal studies were conducted in the RPXV/rabbit model. Generally, these studies were randomized, blinded, and placebo-controlled investigations conducted to evaluate the efficacy of tecovirimat following lethal MPXV or RPXV infection. One NHP study was not conducted blind (Study 87), and one rabbit study did not include a placebo comparator group (Study 25F).

Overall, oral administration of tecovirimat to NHPs beginning at a dose level of 3 mg/kg from Days 4-17 post-infection with MPXV resulted in almost complete survival of the animals in the treatment groups. The data also demonstrated that oral administration of 10 mg/kg of tecovirimat to NHPs beginning on Days 4 or 5 post-infection resulted in a statistically significant increase in survival in the animals compared to administration beginning on Day 6 post-infection and that administration for at least 5 days is required for an increase in survival. A summary of these results is presented in the Forest plot summary for differences in survival (compared to placebo) for the studies in Figure 34.

In NHPs, oral administration of tecovirimat beginning at the 10 mg/kg dose level following administration on Day 4 post-infection resulted in an evident decrease in the median lesion count in these animals. Additionally, administration of tecovirimat to NHPs beginning on Days 4 or 5 post-infection and lasting for at least 5 days resulted in an earlier decline in the median lesion counts. Oral administration of tecovirimat beginning at the 3 mg/kg dose level on Day 4 post-infection resulted in an evident decrease in the mean viral DNA load in these animals. Administration of a 10 mg/kg dose further decreased viral DNA in the blood relative to the 3 mg/kg dose, indicating that, while both the 3 and 10 mg/kg doses provide equivalent survival benefit, additional reduction in viral DNA load is provided by the 10 mg/kg dose. Additionally, administration of tecovirimat to NHPs beginning on Days 4 or 5 post-infection and lasting for at least 5 days resulted in an earlier decline in the mean viral DNA levels. Seven days of treatment seem to be slightly more effective than 5 days of treatment as there was no rebound in viral DNA

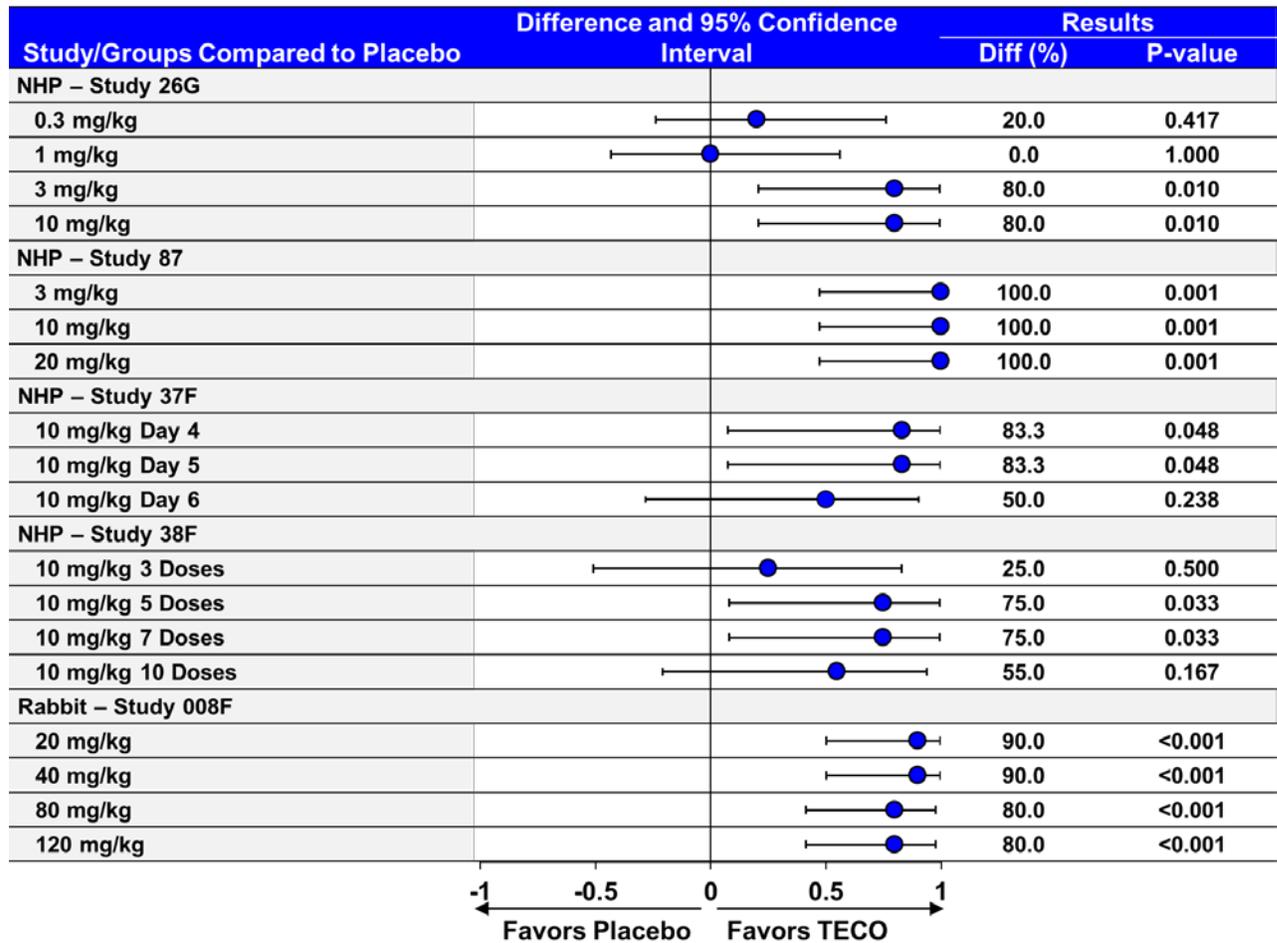
when stopping treatment after 7 daily doses, but there was a slight rebound when stopping after 5 daily treatments. A dose of 10 mg/kg initiated on day 4 or 5 post-infection for at least 7 consecutive days of dosing provides maximal survival benefit and significant reductions in viral DNA in the blood and lesion count.

In rabbits, oral administration of tecovirimat at dose levels of ≥ 20 mg/kg from Days 4-17 post-infection resulted in a statistically significant increase in survival. Survival was approximately 90% for all treatment doses ranging from 20-120 mg/kg, indicating that the 20 mg/kg dose likely represents the minimum dose providing maximal survival benefit in rabbits. A summary of these results is presented in the Forest plot summary for differences in survival (compared to placebo) for the studies in Figure 34.

Tecovirimat doses ≥ 20 mg/kg from Days 4-17 post-infection resulted in statistically significant decreases in viral DNA in the blood. The decreases in viral DNA were very similar for all dosing groups ranging from 20-120 mg/kg, indicating that 20 mg/kg was the minimum dose providing maximal benefit in terms of reducing viral load.

Overall, the data from studies conducted in NHPs and rabbits indicate that tecovirimat is efficacious at increasing survival beginning at dose levels of 3 mg/kg in NHPs and beginning at dose levels of 20 mg/kg in rabbits when dosing is initiated on Day 4 post-infection. In NHPs, additional benefit (i.e., reduction in total body lesion counts and viral DNA in the blood) was provided by increasing the dose to 10 mg/kg, but no further benefit was evident when the dose was increased to 20 mg/kg. This conclusion is supported by the increase in survival rates and the decrease in mean viral DNA loads (primary and secondary indicators of treatment efficacy) noted in both species and reduction in median total body lesion counts noted in NHPs.

Figure 34: Forest Plot of Differences in Survival Compared to Placebo in Tecovirimat NHP and Rabbit Studies



LEGEND: Studies, groups, and study details are as defined in the text. Shown is a forest plot summary comparing differences in survival when compared to placebo treatment for each study. The exact 95% confidence interval is based on the score statistic of difference in survival rates. Under Results, Diff (%) is the difference in survival rates compared to the placebo control. The *P*-value is from 1-sided Fisher’s Exact Test compared to the placebo control. Data from the Rabbit – Study 25F study are not shown on the forest plot as this study did not include a placebo control.

8. CLINICAL OVERVIEW

8.1 Summary of Safety Results

The overall safety of tecovirimat administered orally has been evaluated in Phase 1, 2, and 3 clinical studies (Table 4). Of the 12 clinical studies conducted, 11 clinical studies were undertaken to evaluate the safety and tolerability of oral tecovirimat in healthy subjects and subjects with renal and hepatic impairment: one pivotal study, 3 supportive multiple-dose studies, and 7 supportive single-dose studies. In addition, a palatability/taste assessment study has also been included as a supportive single-dose study since AE data were gathered and reported. Safety data are also available from cases of tecovirimat Emergency and Compassionate Use. Overall, the size of the safety database from the pivotal, supportive multiple-dose, and supportive single-dose clinical studies enables adequate meaningful assessment of the safety and tolerability profile of tecovirimat. The proposed human dosing regimen for tecovirimat, 600 mg twice daily for 14 days with a meal, was selected based on human PK and safety data as well as animal safety, PK and efficacy data. In the supportive studies, tecovirimat was administered alone and in combination with other agents at doses ranging from 100-2,000 mg daily for between 1 and 21 days.

8.2 Overall Safety Population

Across all pivotal, supportive multiple-dose, and supportive single-dose studies of tecovirimat, a total of 788 adult subjects have been exposed to tecovirimat at total daily doses ranging from 100-2,000 mg for between 1 and 21 days (Table 14). In the Phase 3 pivotal safety study, Study SIGA-246-008 (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--see study diagram, Appendix 10.1), 336 of 359 subjects (93.6%) receiving tecovirimat administered at the proposed clinical dose of 600 mg twice daily for 14 days completed greater than 80% of the dosing regimen. In the supporting drug-drug interaction study, an additional 78 subjects received tecovirimat 600 mg twice daily for 15 days, bringing the total exposure of the proposed clinical dose to 414 adult subjects.

Table 14: Summary of Tecovirimat Clinical Studies

	Studies n	All Subjects n	Tecovirimat Group n
Total	12	907	788
Phase 3	1	449	359
Phase 2	1	107	91
Phase 1	10	372	359

8.3 Demographics and Duration of Study Drug Administration

Clinical studies of tecovirimat have enrolled adult male and female subjects of various races and ethnicities. Across all studies, subject age ranged from a minimum of 18 to a maximum of 80 years. Demographic data for the pivotal, supportive multiple-dose, and supportive single-dose studies are summarized below.

Overall, the mean (standard deviation [SD]) subject age across both treatment groups in the Phase 3 pivotal study was 40.7 (15.70) years (overall range: 18-80 years). More females (59.0%

in the tecovirimat arm and 60% in the placebo arm) than males were enrolled in the study. Most subjects in the study were White and not Hispanic or Latino.

There were no notable differences in height (overall median: 168.70 cm), weight (overall median: 85.10 kg), or body mass index (overall median: 29.30 kg/m²) between treatment groups. Demographic characteristics for the supportive multiple- and single-dose studies were similar to those in the pivotal study. Table 15 shows the demographic characteristics of subjects.

Table 15: Safety Demographic Characteristics in Study SIGA-246-008

	Tecovirimat	Placebo
	N=359	N=90
Female	59%	60%
Race		
White	69%	69%
Black	28%	29%
Asian	<1%	1%
American Indian or Alaska Native	<1%	-
Native Hawaiian or Other Pacific Islander	<1%	1%
Other	<1%	-
Age, yrs, mean (SD) (range)	40 (15.7) (18-80)	42 (15.9) (18-79)
Height (cm) (range)	169 (152.4-190.5)	169 (144.7-194.3)
Weight (kg) (range)	89 (51.4-190.5)	90 (49.1-188.0)
Body Mass Index (kg/m ²) (range)	31 (19.5-78.1)	31 (17.4-61.1)

KEY: N=number; SD=standard deviation

8.4 Treatment-Emergent Adverse Events (TEAEs)

In the Phase 3 pivotal safety study, Study 008, 134 subjects receiving tecovirimat and 30 subjects receiving placebo reported at least one TEAE (37.3% and 33.3%, respectively). All TEAEs occurring in at least 2% of subjects in either treatment group are presented by preferred term in Table 16. For both treatment groups, the most frequent TEAEs were headache (17.0% tecovirimat, 14.4% placebo) and nausea (5.6% each). The reported TEAEs and incidence of TEAEs were generally similar between groups, with the difference in incidence (tecovirimat versus placebo) of all specific preferred terms being less than 3%.

The majority of TEAEs were of mild intensity. For subjects receiving tecovirimat, TEAEs of severe or greater intensity were infrequent and occurred for 1.1% of subjects in the pivotal study. The only TEAE preferred term reported with an intensity of severe or greater in more than 1 subject across all tecovirimat clinical studies was headache, which was reported for two subjects receiving tecovirimat 600 mg twice daily. There were no consistent dose- or duration-related trends in the incidence of TEAEs of severe or greater intensity.

Table 16: Treatment-Emergent Adverse Events Experienced by at Least 2% of Subjects in Either Treatment Group by Preferred Term and Descending Frequency Overall (Safety Population) Phase 3 Pivotal Study

Preferred Term	Placebo N = 90	Tecovirimat 600 mg BID N = 359
	n (%)	n (%)
No. of Subjects with ≥ 1 TEAE	30 (33.3)	134 (37.3)
Headache	13 (14.4)	61 (17.0)
Nausea	5 (5.6)	20 (5.6)
Diarrhea	3 (3.3)	11 (3.1)
Dizziness	3 (3.3)	9 (2.5)
Fatigue	4 (4.4)	5 (1.4)
Vomiting	0	9 (2.5)
Constipation	2 (2.2)	5 (1.4)
Somnolence	2 (2.2)	2 (0.6)
Back pain	2 (2.2)	1 (0.3)
Oropharyngeal pain	2 (2.2)	1 (0.3)

KEY: BID = twice daily; n = number of subjects; TEAE = treatment-emergent adverse event

NOTE: Adverse events were coded by using MedDRA version 18.0.

8.5 Deaths

Throughout the clinical development of tecovirimat, 2 deaths were reported. One subject receiving tecovirimat 600 mg twice daily in the Phase 3 pivotal Study, SIGA-246-008, died as a result of a SAE of pulmonary embolism. One subject receiving a single 600 mg dose of tecovirimat in the hepatic impairment study (SIGA-246-013) experienced the following SAEs: cholecystitis, sepsis, acute myocardial infarction, and cardiac arrest which resulted in death. Neither death was attributed to tecovirimat (See Appendix 10.3 for additional information).

8.6 Serious TEAEs

Across all clinical studies, 5 serious TEAEs were reported in 2 subjects. As mentioned above, one subject in Study SIGA-246-008 had an SAE of pulmonary embolism, and one subject in the hepatic impairment study (SIGA-246-013) had SAEs of: cholecystitis, sepsis, acute myocardial infarction, and cardiac arrest. For both subjects, the serious TEAEs were fatal (refer to previous section).

8.7 Discontinuation of Dosing Due to TEAEs

Across all clinical studies, the incidence of TEAEs leading to treatment discontinuation was low. In the Phase 3 pivotal Study SIGA-246-008, the incidence of TEAEs leading to treatment discontinuation was low in both the tecovirimat (6/359, 1.7%) and placebo (2/90, 2.2%) treatment groups. Of TEAEs leading to treatment discontinuation, the most common among discontinued subjects were nausea, fatigue, headache, and pyrexia. All other TEAE preferred terms led to discontinuation of a single subject each.

8.8 Events of Interest

8.8.1 Hypoglycemia

Hypoglycemia was identified as an AE of interest in the supportive multiple-dose drug-drug interaction study (SIGA-246-015). During the combination treatment period, 10 subjects (33.3%) reported AEs of hypoglycemia after taking the combination of repaglinide + tecovirimat.

Approximately 3 hours after dosing, 3 subjects had events of lightheadedness and tremor/feeling shaky/jittery, which prompted glucose monitoring for 9 out of the 10 subjects with similar or related symptoms. All 10 subjects presenting with related symptoms initially had AEs of mild hypoglycemia. Four of the subjects' (13.3%) glucose readings fell below 50 mg/dL, and the event intensity was increased to moderate. These subjects were administered glucose. After receiving lunch and oral glucose (where applicable), most subjects reported that their symptoms had subsided, and the events resolved. Within a few hours of event onset, glucometer readings returned to normal range. Based on findings from this study and repaglinide's known antidiabetic actions to induce insulin release, it was determined that co-administered of tecovirimat with repaglinide may result in episodes of mild or moderate hypoglycemia. No additional events of hypoglycemia were reported as TEAEs in any of the other pivotal, supportive multiple-dose, or supportive single-dose clinical studies of tecovirimat.

8.9 Overdose

Overdose with tecovirimat has not occurred. Single doses of tecovirimat up to 2000 mg and repeated doses of up to 800 mg daily and 600 mg twice daily have been well tolerated.

8.10 Safety in Other Populations

Safety findings in the supportive multiple-dose and single-dose studies were consistent with those in the pivotal study.

In the supportive multiple-dose studies, the percentage of subjects with at least 1 TEAE ranged from 25.0-75.0%, with no clear dose- or duration-related trends across studies (Appendix 10.2). Similarly, treatment-related TEAEs occurred in 0-62.5% of tecovirimat-treated subjects across studies and did not show clear dose- or duration-related trends across studies. Consistent with the pivotal study, TEAEs leading to treatment discontinuation were infrequent. No deaths or SAEs occurred during these studies.

In the supportive single-dose studies (excludes SIGA-246-006 where drug was not ingested), the percentage of subjects with at least 1 TEAE was generally lower than in the pivotal or multiple-dose studies (range: 0-34.2%) and showed no clear dose-related trends across studies. Similarly, treatment-related TEAEs were also less frequent than in the pivotal or multiple-dose studies (range: 0-25.0%) and did not show clear dose-related trends across studies. Consistent with the low incidence observed in the pivotal study, no subjects had a TEAE leading to treatment discontinuation. As mentioned in Section 8.5, one subject receiving tecovirimat in Study SIGA-246-013 had fatal SAEs of cholecystitis, sepsis, acute myocardial infarction, and cardiac arrest.

8.11 Human Dose Selection

The selection of a dose for product approval under the FDA Animal Rule requires the use of animal efficacy data in order to establish the human dose in the absence of efficacy data in humans. In order to provide confidence that the human dose will be effective during a smallpox emergency, it is important to understand the PK factors that influence efficacy and, ideally, to provide a margin of drug exposure in humans above that which is efficacious in animals. The proposed human dose that meets the requirements for efficacy must also be safe at the effective dose.

The *in vivo* ability of tecovirimat to protect a host against a lethal poxvirus disease was demonstrated in many animal models and against many orthopoxviruses. Triangulation of 1)

toxicology data, 2) safety, PK, and efficacy data from 2 pivotal animal models and 3) human PK and safety data leads to several conclusions:

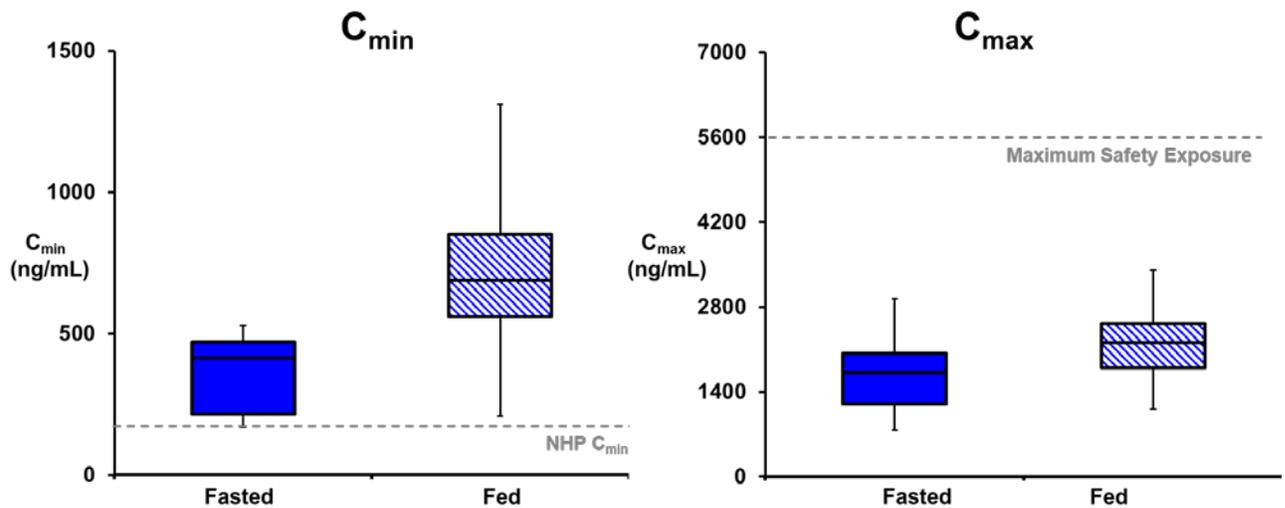
- Human dosing and target exposures are based on PK/PD data from the NHP model since in the NHP model, higher blood exposures are required for maximal efficacy in comparison to the rabbit model, making it the more rigorous standard. This is not surprising as the high dose IV challenge in the NHP model bypasses the early stages of natural infection and immediately establishes a systemic disease and widely disseminated viral infection typical of late stage smallpox in humans. The endpoint for product evaluation is the prevention of mortality and, using this endpoint, a statistically significant reduction of mortality was observed at 3 mg/kg in the IV MPXV/NHP model. However, the 10 mg/kg dose not only reduced mortality, but also led to a reduction in morbidity as represented by clinical scores, lesion count, and viral DNA load. In order to provide a greater margin of error, and more closely represent a preferred operational strategy where reduction in morbidity will additionally reduce transmission and patient suffering, the human dose is based on the higher dose of 10 mg/kg in the NHP.
- The requirements of the Animal Rule are satisfied by dosing humans at 600 mg twice daily for 14 days. The Animal Rule states “The dose and regimen for humans should be selected to provide exposures that exceed those associated with the fully effective dose in animals, ideally by several-fold...”. Exposures following 600 mg twice daily dosing in humans clearly exceed efficacious exposures in non-human primates, most notably for C_{min} (Table 17 and Figure 35). The proposed dose of tecovirimat, 600 mg twice daily, will provide C_{min} exposures in excess (7.8-fold higher) of those demonstrated to be efficacious in the NHP model.

Table 17: Geometric Mean of Non-Compartmental Exposures in NHPs and Humans

Comparisons	Treatment Day	C_{max} (ng/mL)	C_{min} (ng/mL)	C_{avg} (ng/mL)	AUC ₀₋₂₄ (ng.h/mL)
Human 600 mg BID	1 (first dose)	1516	477	875	20879
NHP 10 mg/kg		749	158	318	7629
Human to NHP Ratio (Unbound Ratio)		2.0 (3.3)	3.0 (4.9)	2.8 (4.5)	2.7 (4.4)
Human 600 mg BID	14 (steady state)	2106	587	1207	29131
NHP 10 mg/kg		1403	143	569	13650
Human to NHP Ratio (Unbound Ratio)		1.5 (2.4)	4.1 (6.7)	2.1 (3.4)	2.1 (3.5)

BID=twice daily, NHP=non-human primate

Figure 35: Tecovirimat Human Exposure Modeling



Box: Interquartile Range (IQR) with Mean
Whisker: $Q1 - 1.5 \cdot IQR$, $Q3 + 1.5 \cdot IQR$

- The exposure at the proposed human clinical dose is below the exposure responsible for the observed safety signals in the dog toxicology studies.
- Based on the data available, tecovirimat dosing at 600 mg twice daily with a meal for 14 days demonstrates an adequate safety profile in humans. Headache was the only AE occurring with higher frequency in subjects administered tecovirimat relative to those who received placebo. Most reported AEs were mild, and all resolved without sequelae, and withdrawals/discontinuations were minimal.

The non-clinical safety and efficacy data, and the clinical safety data demonstrate that the tecovirimat dose of 600 mg twice daily for 14 days is safe and provides exposures in excess of those that were effective in the animal models, we believe that the proposed dose of tecovirimat 600 mg twice daily for 14 days has met the essential standard of the animal rule in that it is “reasonably likely to produce clinical benefit in humans” in the event of a smallpox emergency.

8.12 Safety Conclusions

The recommended dose of tecovirimat of 600 mg twice daily for 14 days was safe and well-tolerated when administered orally in adult subjects. Headache and nausea were the most common TEAEs in both the tecovirimat and placebo groups. Most TEAEs were mild or moderate with TEAEs of severe or greater intensity reported in 1.1% of subjects. There was one reported SAE of pulmonary embolism that resulted in death in a subject in the tecovirimat 600 mg group. The SAE was not considered to be related to study drug. A total of 8 subjects discontinued study drug because of a TEAE: 6 subjects in the tecovirimat 600 mg group (1.7%), and 2 subjects in the placebo group (2.2%). This conclusion is supported across all single- and multiple dose studies where tecovirimat was administered to adult subjects alone and in combination with other agents at doses ranging from 100-2000 mg daily for between 1 and 21 days.

Additionally, across all supportive single- and multiple dose studies, the majority of TEAEs were of mild intensity with TEAEs of severe or greater intensity reported in 0-3.1% and 0-8.3% of subjects, respectively. Headache was the only preferred term reported with an intensity of severe or greater in more than 1 subject across all tecovirimat clinical studies. One subject receiving tecovirimat 600 mg in a single-dose supportive study experienced four SAEs including cholecystitis, sepsis, acute myocardial infarction, and cardiac arrest resulting in death. These SAEs were not considered to be related to study drug. There were no other SAEs or deaths reported for any of the other single- or multiple-dose supportive studies.

8.13 Patients Treated with Tecovirimat (E-IND/Compassionate Use Cases)

Tecovirimat has been provided for emergency use in 5 cases under US E-IND applications and in 1 case of compassionate use in Finland. These cases include 1 pediatric male, 2 adult males, and 3 adult female patients. The efficacy of tecovirimat could not be determined in any of these cases because of other concomitant antiviral and/or immunologic treatments, as well as the unknown contributions for a patient's own immune response in clearing the infections.

8.13.1 E-IND No. 74,773

In (b) (6), SIGA provided tecovirimat for treatment of a 28-month-old, 10 kg child with eczema vaccinatum who had been exposed to virus through direct contact with a smallpox vaccine. The child's skin samples were positive for nonvariola orthopoxvirus. Following issuance of the E-IND, tecovirimat was orally administered daily for 14 days at a dose of 50 mg (2 days), 75 mg (2 days), and 100 mg (10 days) once daily via a nasogastric tube. The child also received one dose of cidofovir along with repeated doses of Vaccinia Immune Globulin Intravenous (Human). Clinical signs of improvement were observed within 1 week of antiviral intervention, and the child was subsequently discharged. The child had no AEs that could be attributed to tecovirimat. As of (b) (6), the child was thriving and continued to do well.

8.13.2 E-IND NO. 104,793

In (b) (6), SIGA provided tecovirimat for treatment of a 20-year-old male patient with progressive vaccinia and acute myelogenous leukemia who had been exposed to the virus through the military smallpox vaccine and whose lesion was positive for orthopoxvirus. Following issuance of the E-IND, oral and topical tecovirimat treatment was administered. The patient received treatment for 73 days with daily oral tecovirimat (400-1,200 mg; total of nearly 75 g) and for 68 days with topical tecovirimat (39.7-1,110 ng/mL). The patient also received repeated doses of Vaccinia Immune Globulin Intravenous (Human), topical imiquimod, and CMX001. Although the patient developed a methicillin-resistant *Staphylococcus aureus* infection, *Pseudomonas aeruginosa* sepsis, and multiorgan failure requiring excessive vasopressor support and bilateral transtibial amputation, none of these events were clearly attributable to any investigational therapy. Despite his protracted clinical course, the patient was discharged and continued to do well as of (b) (6).

8.13.3 E-IND NO. 106,338

In (b) (6), SIGA provided tecovirimat for treatment of a 37-year-old female patient taking immunosuppressant therapy for Crohn's disease who had vesiculopustular skin lesions on the arm and hand due to exposure to recombinant-vaccinia-based rabies vaccine. The lesions were positive for nonvariola orthopoxvirus. Following issuance of the E-IND, tecovirimat 400 mg was

administered orally once daily for 14 days. The patient also received 2 doses of Vaccinia Immune Globulin Intravenous (Human). The lesions healed, and the patient was discharged. Information on AEs with an onset after tecovirimat treatment initiation was not provided.

8.13.4 E-IND NO. 112,324

In ^{(b) (6)}, SIGA provided tecovirimat for treatment of a 25-year-old female patient with a possible contact vaccinia infection who had been exposed to the virus through direct contact with a smallpox vaccine. After issuance of the E-IND, tecovirimat 400 mg was administered once daily for 14 days. The patient also received Vaccinia Immune Globulin Intravenous (Human). The patient responded well to treatment, with no apparent side effects. As of ^{(b) (6)}, the patient was doing well, and the lesions had completely healed with minimal scarring.

8.13.5 E-IND NO. 116,039

In ^{(b) (6)}, SIGA provided tecovirimat for treatment of a 19-year-old male patient with acute myeloid leukemia who had been exposed to the virus through the military smallpox vaccine. Tecovirimat 600 mg twice daily was administered for approximately 2 months. The patient also received 2 doses of Vaccinia Immune Globulin Intravenous (Human). The patient was reported to have tolerated the extended course of tecovirimat well. Information on AEs with an onset after tecovirimat treatment initiation was not provided.

8.13.6 Compassionate Use in Europe

In ^{(b) (6)}, SIGA provided tecovirimat for treatment of a 32-year-old female patient with severe keratoconjunctivitis. Eye samples were positive for cowpox virus. Following approval of the compassionate use protocol, tecovirimat 400 mg was orally administered once daily for 14 days. The patient also received a variety of other treatments for the condition (initiation: ^{(b) (6)}). No drug-related AEs were reported during the course of tecovirimat treatment, and clinical laboratory evaluations on Day 6 of tecovirimat treatment revealed no notable findings related to tecovirimat treatment. After a series of medical procedures, the cornea was cleared, and vision was improved.

9. LIST OF REFERENCES

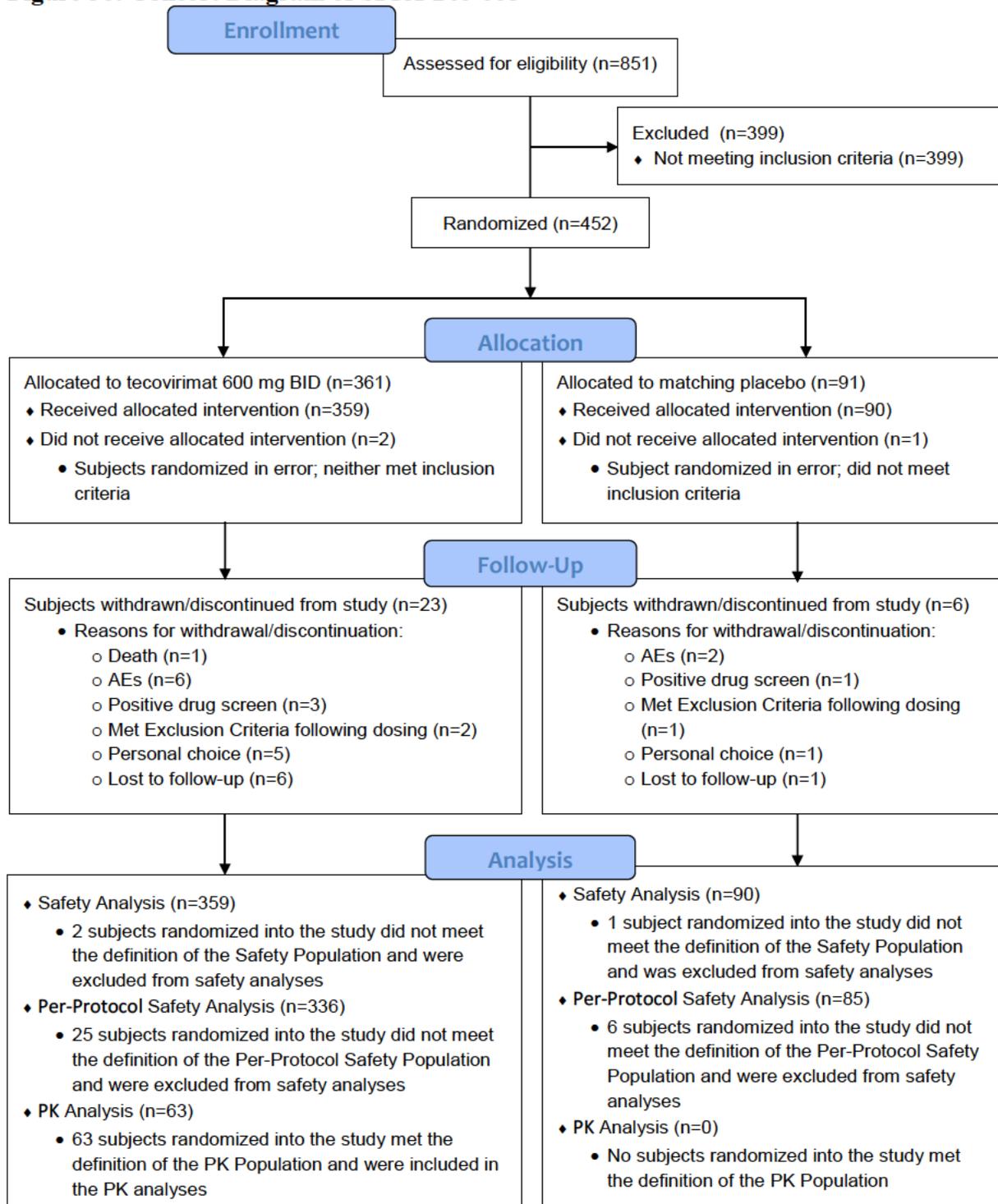
1. Breman, J.G. and D.A. Henderson, *Diagnosis and management of smallpox*. N Engl J Med, 2002. **346**(17): p. 1300-8.
2. LeDuc, J.W., et al., *Smallpox research activities: U.S. interagency collaboration, 2001*. Emerg Infect Dis, 2002. **8**(7): p. 743-5.
3. Kennedy, R. and A. Gregory, *Poland*, in *Vaccines for Biodefense and Emerging and Neglected Diseases*, in *Smallpox*. 2009.
4. Smith, G.L., A. Vanderplasschen, and M. Law, *The formation and function of extracellular enveloped vaccinia virus*. J Gen Virol, 2002. **83**(Pt 12): p. 2915-31.
5. Doceul, V., et al., *Repulsion of superinfecting virions: a mechanism for rapid virus spread*. Science, 2010. **327**(5967): p. 873-876.
6. Payne, L.G., *The existence of an envelope on extracellular cowpox virus and its antigenic relationship to the vaccinia envelope*. Arch Virol, 1986. **90**(1-2): p. 125-33.
7. Reeves, P.M., et al., *Variola and monkeypox viruses utilize conserved mechanisms of virion motility and release that depend on abl and SRC family tyrosine kinases*. J Virol, 2011. **85**(1): p. 21-31.
8. Roscoe, F., R.H. Xu, and L.J. Sigal, *Characterization of ectromelia virus deficient in EVM036, the homolog of vaccinia virus F13L, and its application for rapid generation of recombinant viruses*. J Virol, 2012. **86**(24): p. 13501-7.
9. Martinez-Pomares, L., R.J. Stern, and R.W. Moyer, *The ps/hr gene (B5R open reading frame homolog) of rabbitpox virus controls pock color, is a component of extracellular enveloped virus, and is secreted into the medium*. J Virol, 1993. **67**(9): p. 5450-62.
10. Hruby, D.E. and C.M. Byrd, *Less is More: Poxvirus Proteolysis*. Microbe, 2006. **1**: p. 70-75.
11. Fenner, F., et al., *Smallpox and its Eradication*. 1988: Geneva: WHO.
12. Martin, D.B., *The cause of death in smallpox: an examination of the pathology record*. Mil Med, 2002. **167**(7): p. 546-51.
13. Keckler, M.S., et al., *The effects of post-exposure smallpox vaccination on clinical disease presentation: addressing the data gaps between historical epidemiology and modern surrogate model data*. Vaccine, 2013. **31**(45): p. 5192-201.
14. Lederman, E.R., et al., *Progressive vaccinia: case description and laboratory-guided therapy with vaccinia immune globulin, ST-246, and CMX001*. J Infect Dis, 2012. **206**(9): p. 1372-85.
15. Shearer, J.D., et al., *Biological activity of an intravenous preparation of human vaccinia immune globulin in mouse models of vaccinia virus infection*. Antimicrob Agents Chemother, 2005. **49**(7): p. 2634-41.
16. Vora, S., et al., *Severe eczema vaccinatum in a household contact of a smallpox vaccinee*. Clin Infect Dis, 2008. **46**(10): p. 1555-61.
17. Yang, G., et al., *An orally bioavailable antipoxvirus compound (ST-246) inhibits extracellular virus formation and protects mice from lethal orthopoxvirus Challenge*. J Virol, 2005. **79**(20): p. 13139-49.
18. Duraffour, S., et al., *Activity of the anti-orthopoxvirus compound ST-246 against vaccinia, cowpox and camelpox viruses in cell monolayers and organotypic raft cultures*. Antivir Ther, 2007. **12**(8): p. 1205-16.

19. United States Department of Health and Human Services, F.a.D.A., Center for Evaluation and Research/Center for Biologics Evaluation and Research., *Product Development Under the Animal Rule, Guidance for Industry*. 2015.
20. Earl, P.L., et al., *Immunogenicity of a highly attenuated MVA smallpox vaccine and protection against monkeypox*. Nature, 2004. **428**(6979): p. 182-5.
21. Zaucha, G.M., et al., *The pathology of experimental aerosolized monkeypox virus infection in cynomolgus monkeys (Macaca fascicularis)*. Lab Invest, 2001. **81**(12): p. 1581-600.
22. Breman, J.G., et al., *Human monkeypox, 1970-79*. Bull World Health Organ, 1980. **58**(2): p. 165-82.
23. Likos, A.M., et al., *A tale of two clades: monkeypox viruses*. J Gen Virol, 2005. **86**(Pt 10): p. 2661-72.
24. Li, G., et al., *Complete coding sequences of the rabbitpox virus genome*. J Gen Virol, 2005. **86**(Pt 11): p. 2969-77.
25. Wittek, R., et al., *HindIII and Sst I restriction sites mapped on rabbit poxvirus and vaccinia virus DNA*. J Virol, 1977. **23**(3): p. 669-78.
26. Jansen, J., *Todliche Infektionen von Kanichen durch ein filtrierbares Virus (Fatal Infections in Rabbits by a Filtrable virus)*. Zentralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten (Central Journal for Bacteriology, Parasitology, and Infectious Diseases), 1941. **148**: p. 65-68.
27. Christensen, L.R., E. Bond, and B. Matanic, *"Pock-less" rabbit pox*. Lab Anim Care, 1967. **17**(3): p. 281-96.
28. Bedson, H.S. and M.J. Duckworth, *Rabbit pox: an experimental study of the pathways of infection in rabbits*. J Pathol Bacteriol, 1963. **85**: p. 1-20.
29. Chapman, J.L., et al., *Animal models of orthopoxvirus infection*. Vet Pathol, 2010. **47**(5): p. 852-70.
30. Adams, M.M., A.D. Rice, and R.W. Moyer, *Rabbitpox virus and vaccinia virus infection of rabbits as a model for human smallpox*. J Virol, 2007. **81**(20): p. 11084-95.
31. Westwood, J.C., et al., *Experimental respiratory infection with poxviruses. I. Clinical virological and epidemiological studies*. Br J Exp Pathol, 1966. **47**(5): p. 453-65.

10. APPENDICES

10.1 Consort Diagram of SIGA-246-008

Figure 36: Consort Diagram of SIGA-246-008



10.2 Adverse Events in Supportive Multiple-Dose Studies

Table 18: Treatment-Emergent Adverse Events Occurring in at Least 2% of Subjects – Supportive Multiple-Dose Studies in Treatment Groups by Preferred Term and Descending Frequency Overall

Preferred Term	Study No.					
	Daily Dose (mg)					
	SIGA-246-015	SIGA-246-002			SIGA-246-004	
	600 BID N=78	250 N=8	400 N=8	800 N=8	400 N=45	600 N=46
	n (%)	n (%)	n (%)	n (%)	n (%)	
No. of Subjects with ≥1 TEAE	34 (43.6)	6 (75.0)	2 (25.0)	5 (62.5)	23 (51.1)	19 (41.3)
Hypoglycemia	10 (12.8)	--	--	--	--	--
Headache	7 (9.0)	5 (62.5)	2 (25.0)	4 (50.0)	5 (11.1)	8 (17.4)
Nausea	6 (7.7)	1 (12.5)	1 (12.5)	1 (12.5)	3 (6.7)	2 (4.3)
Abdominal pain	5 (6.4)	--	--	--	0	1 (2.2)
Infrequent bowel movements	5 (6.4)	--	--	--	--	--
Dizziness	5 (6.4)	--	--	--	2 (4.4)	1 (2.2)
Decreased appetite	4 (5.1)	--	--	--	--	--
Diarrhea	3 (3.8)	--	--	--	0	--
Insomnia	3 (3.8)	--	--	--	--	--
Acne	3 (3.8)	--	--	--	--	--
Vomiting	2 (2.6)	1 (12.5)	1 (12.5)	0	--	--
Nasopharyngitis	2 (2.6)	--	--	--	1 (2.2)	1 (2.2)
Pharyngitis	2 (2.6)	--	--	--	1 (2.2)	0
Papule	2 (2.6)	--	--	--	--	--
Axillary pain	1 (1.3)	--	--	--	1 (2.2)	0
Musculoskeletal pain	1 (1.3)	--	--	--	1 (2.2)	0
Paresthesia	1 (1.3)	--	--	--	1 (2.2)	0
Somnolence	1 (1.3)	0	0	1 (12.5)	--	--
Flushing	1 (1.3)	--	--	--	1 (2.2)	1 (2.2)
Abdominal discomfort	1 (1.3)	--	--	--	1 (2.2)	0
Abdominal distention	1 (1.3)	--	--	--	1 (2.2)	0
Dry mouth	0	1 (12.5)	0	1 (12.5)	0	1 (2.2)
Fatigue	--	1 (12.5)	0	0	1 (2.2)	2 (4.3)
Back pain	--	1 (12.5)	0	0	3 (6.7)	0
Hand fracture	--	1 (12.5)	0	0	--	--
Ecchymosis	--	0	1 (12.5)	0	--	--
Procedural complication	--	0	1 (12.5)	0	--	--
Abnormal sensation in eye	--	0	0	1 (12.5)	--	--
Upper respiratory tract infection	--	--	--	--	2 (4.4)	1 (2.2)
Urine analysis abnormal	--	--	--	--	2 (4.4)	0
Dyspepsia	--	--	--	--	1 (2.2)	1 (2.2)
Urticaria	--	0	0	0	1 (2.2)	0
Abdominal pain lower	--	--	--	--	1 (2.2)	0
Influenza	--	--	--	--	1 (2.2)	0
Pharyngitis streptococcal	--	--	--	--	1 (2.2)	0
Urinary tract infection	--	--	--	--	1 (2.2)	0
Postprocedural hematoma	--	--	--	--	1 (2.2)	0
White blood cell count decreased	--	--	--	--	1 (2.2)	0
Arthralgia	--	--	--	--	1 (2.2)	0
Joint stiffness	--	--	--	--	1 (2.2)	0
Neck pain	--	--	--	--	1 (2.2)	0

Preferred Term	Study No. Daily Dose (mg)					
	SIGA-246-015	SIGA-246-002			SIGA-246-004	
	600 BID N=78	250 N=8	400 N=8	800 N=8	400 N=45	600 N=46
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Pain in extremity	--	--	--	--	1 (2.2)	0
Neuralgia	--	--	--	--	1 (2.2)	0
Cough	--	--	--	--	1 (2.2)	0
Dry throat	--	--	--	--	1 (2.2)	0
Oropharyngeal pain	--	--	--	--	1 (2.2)	2 (4.3)
Pharyngeal erythema	--	--	--	--	1 (2.2)	0
Postnasal drip	--	--	--	--	1 (2.2)	0
Rhinorrhoea	--	--	--	--	1 (2.2)	0
Throat irritation	--	--	--	--	1 (2.2)	0
Acne cystic	--	--	--	--	1 (2.2)	0
Pruritus	--	--	--	--	1 (2.2)	0
Haematoma	--	--	--	--	1 (2.2)	1 (2.2)
Myalgia	--	--	--	--	0	2 (4.3)
Constipation	--	--	--	--	0	1 (2.2)
Irritability	--	--	--	--	0	1 (2.2)
Excoriation	--	--	--	--	0	1 (2.2)
Foot fracture	--	--	--	--	0	1 (2.2)
Muscle strain	--	--	--	--	0	1 (2.2)
Blood pressure systolic increased	--	--	--	--	0	1 (2.2)
Joint swelling	--	--	--	--	0	1 (2.2)
Tension headache	--	--	--	--	0	1 (2.2)
Nasal congestion	--	--	--	--	0	1 (2.2)
Hyperhidrosis	--	--	--	--	0	1 (2.2)
Rash	--	--	--	--	0	1 (2.2)

KEY: BID = twice daily; n = number of subjects; TEAE = treatment-emergent adverse event; -- = not applicable/data not available.

NOTE: Table presents subjects by maximum tecovirimat dose. Adverse events were coded using MedDRA (versions are as specified in the individual study reports). Events are presented by preferred term.

10.3 Serious Adverse Events Resulting in Death

Phase 3 Pivotal Safety Study SIGA-246-008

This was a 46-year-old female subject who volunteered for this study and participated in the PK subset of the expanded study. Ongoing medical conditions included irregular menstruation and seasonal allergies. In addition, she had a history of deep vein thrombosis in her right leg from (b) (6) to (b) (6), but no current anticoagulant use was reported. No history of smoking was reported. Ongoing concomitant medications at the time of the event included Depo-Provera 150 mg every 3 months. The subject was randomized to the active treatment arm of the study.

The subject received her first dose of study drug (tecovirimat 600 mg twice daily) on the morning of (b) (6) and her last dose on the evening of (b) (6). She completed the Day 15 visit on (b) (6). On (b) (6), the subject experienced a pulmonary embolus. The subject developed acute severe shortness of air and chest pain in the early morning while at home. Emergency medical services (EMS) were called. The subject was talkative when EMS arrived; however, pulseless electrical activity developed in route to the hospital. The subject arrived at the emergency room in pulseless electrical activity at 06:38. Resuscitation efforts were performed to no avail. The subject was pronounced dead at (b) (6). On the evening of (b) (6) the investigator spoke with the forensic pathologist and confirmed the cause of death was pulmonary embolus. An autopsy was performed after tissue donation procurement and revealed extensive pulmonary embolism. Anterior fractures in multiple bilateral ribs were consistent with resuscitative procedures and were not contributory to the subject's death. No other significant gross or microscopic abnormalities were observed. Toxicology results revealed no ethanol or drugs of abuse in the heart blood. The manner of death was determined to be natural. The investigator considered the event of pulmonary embolism to be Grade 5 (death) in intensity and not related to study drug.

Phase 1 Single Dose Supportive Study: Hepatic Impairment SIGA-246-013

This was a 64-year-old male with history of hepatitis C, alcoholism with cirrhosis, Type 2 diabetes, COPD, hypertension, ascites, acid reflux, depression, and insomnia. Ongoing concomitant medications at the time of the event included omeprazole, gabapentin, atenolol, furosemide, citalopram, trazodone, and levimir. This subject was assigned to Cohort 3 (moderate hepatic impairment) of the study and was administered a single oral dose of 600 mg tecovirimat in the morning on Day 1. This subject was discharged from the Clinical Research Unit (CRU) and completed the study 13 days after signing the ICF.

Twelve days after discharge from the CRU, the subject experienced a total of 4 SAEs. The first pair of SAEs of cholecystitis and sepsis occurred on (b) (6) 18 days after administration of the study drug. These SAEs were considered by the Investigator to be not related to the study drug. The subject was hospitalized and was given an endoscopic retrograde cholangiopancreatogram with subsequent surgery for placement of one stent into the gallbladder and one stent into the common bile duct. The 2nd pair of SAEs of acute myocardial infarction and acute cardiac arrest occurred on (b) (6), 20 days after administration of the study drug. A complete list of the medications used to treat these SAEs are presented in Table 19. These SAEs were also considered by the Investigator to be not related to the study drug. Cardiopulmonary resuscitation was unsuccessful, and the subject died on (b) (6).

Table 19: Concomitant Medications for the Treatment of Treatment Emergent Adverse Events

Medication	Start Date/ Stop Date	Dose (Units)	Route	Frequency	Indication
normal saline	(b) (6)	1000 (mL)	IV	once	cholecystitis (hematemesis)
Protonix®	(b) (6)	40 (µg)	IV	once	cholecystitis (hematemesis)
Zofran®	(b) (6)	4 (mg)	IV	once	cholecystitis (hematemesis)
Dilaudid®	(b) (6)	0.5 (mg)	IV	once	abdominal pain due to cholecystitis
Angiomax®	(b) (6)	0.75 (mg/kg)	IV	once	acute myocardial infarction with cardiac arrest
Angiomax®	(b) (6)	1.75 (µg/kg/h)	IV	once	acute myocardial infarction with cardiac arrest
aspirin	(b) (6)	325 (mg)	IV	once	acute myocardial infarction with cardiac arrest
Cetacaine Spray® (benzocaine 14.0 %, butamben 2.0 %, tetracaine hydrochloride 2.0 %)	(b) (6)	unknown (spray)	topical	once	endoscopic retrograde cholangiopancreatog ram test
chloraprep before (chlorhexidine gluconate 2%, isopropyl alcohol 70%)	(b) (6)	unknown	topical	once	acute myocardial infarction with cardiac arrest
diphenhydramine	(b) (6)	25 (mg)	IV	once	sedation for esophagogastroduod enoscopy
epinephrine	(b) (6)	0.4 (µg/kg/min)	IV	once	acute myocardial infarction with cardiac arrest
epinephrine	(b) (6)	1 (mg)	IV	3 times	acute myocardial infarction with cardiac arrest
Fentanyl®	(b) (6)	200 (µg)	IV	once	sedation for esophagogastroduod enoscopy
Kengreal® (mannitol, sorbitol, and sodium hydroxide)	(b) (6)	4 (µg/kg/min)	IV	once	acute myocardial infarction with cardiac arrest
lidocaine 1%	(b) (6)	unknown	SQ	once	acute myocardial infarction with cardiac arrest

midazolam HCL	(b) (6)	5 (mg)	IV	once	sedation for esophagogastrod enoscopy
Neo-Syneprine® (phenylephrine)		200 (µg)	IV	2 times	acute myocardial infarction with cardiac arrest
Neo-Syneprine® (phenylephrine)		100 (µg)	IV	once	acute myocardial infarction with cardiac arrest
normal saline 0.9%		1000 (mL)	IV	unknown	acute myocardial infarction
Omnipaque® (iohexol)		350 (mg)	IV	once	angiography dye
Ticagrelor®		180 (mg)	oral	once	acute myocardial infarction

Table abbreviation: IV: intravenous, PRN QD: once a day as needed, SQ: subcutaneous, TEAE: treatment emergent adverse event