FDA Briefing Document
Meeting of the Antimicrobial Drugs Advisory Committee
May 1, 2018

Agenda: The committee will discuss new drug application (NDA) 208627 for tecovirimat, sponsored by SIGA Technologies Inc., for the proposed indication of the treatment of smallpox disease caused by variola virus in adults and pediatric patients. This product was developed under the Animal Rule (21 CFR part 314, subpart I).

Food and Drug Administration
Center for Drug Evaluation and Research
Meeting of the Antimicrobial Drug Advisory Committee Meeting
May 1, 2018

Table of Contents

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. In the context of the Applicant's development plan described below, this package provides follow-up to the 2011 Advisory Committee's discussion and input on the scientific issues and challenges in the development of antiviral products for the treatment of human smallpox disease under the Animal Rule. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

1.0 Introduction and Charge to the Committee

Tecovirimat (ST-246) is a drug (small molecule) developed for the treatment of human smallpox. The purpose of this backgrounder is to provide the Division of Antiviral Products' perspective on the adequacy of the available data in support of the approval of tecovirimat under the FDA's Animal Rule for this indication.

The Advisory Committee will be charged with rendering an opinion as to whether the risk-benefit profile of tecovirimat for the treatment of human smallpox is acceptable based on the available data.

2.0 Background

2.1 Brief Description of the Disease and Intended Population

Smallpox is a human disease caused by infection with variola virus, which is in the orthopoxvirus genus of viruses. As a result of an intense global vaccination campaign, no cases of human smallpox have occurred since 1978, and the disease was declared eradicated from the world in 1980. Despite the eradication of naturally acquired smallpox, variola virus is categorized by the National Institute of Allergy and Infectious Diseases (NIAID) as a Category A priority pathogen. Category A pathogens are those organisms/biological agents that pose the highest risk to national security and public health. Routine vaccination in the U.S. ended in the 1970s, so most of the population is immunologically susceptible to smallpox. Medical countermeasures, including antiviral therapies, are needed in the event of a variola (smallpox) virus outbreak.

The conventional historical picture of smallpox is that of a human-to-human communicable disease characterized by an asymptomatic incubation period (averaging close to two weeks but with substantial variability), an initial period of nonspecific symptoms lasting a few days (fever, headache, back pain, prostration), then evolution of skin manifestations followed by death or by gradual recovery with varying degrees of scarring. The classic dermatologic manifestation was a centrifugally-distributed rash. The rash evolved from macule-to-papule-to-vesicle-to-pustule-to-scab-to-scar, with initial stages of a day or two each, scab evolution and separation over a period of a few weeks, and scarring over a few months' time.

Most of the clinical descriptions are based on variola major, the more serious form that was also more prevalent (at least more widely recognized) throughout most of the history of the disease, and that is also the focus of concerns regarding potential biothreat uses of variola virus. Historic mortality in variola major was commonly cited as about 30% but was reported to vary widely among outbreaks from as little as 5% to 40% or more (Breman 2002).

2.2 Brief Description of the Drug and its Viral Target

Tecovirimat is an orally bioavailable antiviral drug (small molecule) developed for the treatment of human smallpox. Tecovirimat inhibits efficient viral spread to uninfected cells by targeting an orthopoxvirus protein (P37) involved in the production of extracellular enveloped virus. The viral P37 protein is highly conserved across different orthopoxviruses, and cell culture studies demonstrated that tecovirimat has broad antiviral activity and similar potency against orthopoxviruses, including variola (smallpox) virus, monkeypox virus, rabbitpox virus and vaccinia virus. The identification of amino acid substitutions in the viral P37 protein associated with tecovirimat resistance in cell culture and animal challenge studies confirmed the P37 drug target, and also indicated tecovirimat has a relatively low resistance barrier. Antiviral activity of tecovirimat is limited only to orthopoxviruses.

2.3 Regulatory Considerations and Development Strategy Under the FDA Animal Rule

Because smallpox is a potentially serious threat but does not occur naturally, clinical efficacy trials are not feasible, and human challenge studies in healthy subjects are unethical. Therefore, animal models may provide important information for the evaluation of treatment effect and may contribute directly to drug approval under 21 CFR part 314, subpart I, if a suitable approach is agreed upon.[i]

Because of the unique complexities of drug development in this area, extensive discussion with multiple stakeholders has taken place, including an FDA public workshop in 2009[ii] and an FDA public Advisory Committee meeting in 2011[iii]. During the 2011 Antiviral Drugs Advisory Committee meeting, the advisory committee agreed with the FDA's assessment that current lethal non-human primate (NHP) models using variola virus are not consistently reproducible, do not mimic what is known about human smallpox disease, and present numerous feasibility challenges due to the worldwide restriction of variola virus research to two maximum containment laboratories. Because scientific limitations of the available variola virus/NHP model preclude definitive efficacy assessments, and uncertainty exists whether an adequate variola virus model can be developed, the FDA and the advisory committee agreed that data from a combination of other lethal animal models using surrogate orthopoxviruses (e.g. non-human primate studies with monkeypox virus, rabbit studies with rabbitpox virus, mouse studies with ectromelia virus) could be used as evidence along with, or potentially instead of, animal studies using variola virus. This assumes a mechanistically plausible target for the candidate drug, and the drug target being conserved across different orthopoxviruses.

---

[i] For general discussion of the animal rule, see the guidance for industry *Product Development Under the Animal Rule*. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm399217.pdf.

[ii] https://www.federalregister.gov/documents/2009/08/18/E9-19781/development-of-antiviral-products-for-treatment-of-smallpox-and-related-poxvirus-infections-public

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

Based on multiple discussions with stakeholders (including the aforementioned 2011 Antiviral Drugs Advisory Committee), the DAVP recommended the following: 1) Data from at least two lethal animal models of non-variola orthopoxvirus infection should be obtained to evaluate drug efficacy; 2) Non-variola orthopoxvirus animal models proposed for use in regulatory decision-making (i.e., efficacy studies) must be well-characterized and generate reproducible results that are reasonably expected to predict efficacy in variola virus infected or exposed humans, and; 3) Mortality, based on prospectively defined criteria for euthanasia, should be the primary endpoint for efficacy studies. The recommendation for use of multiple non-variola orthopoxvirus animal models acknowledges the unique challenges and uncertainties associated with this area of drug development, and the fact that no orthopoxvirus animal model is known to be predictive of human response to the treatment of smallpox.

As part of drug development under the Animal Rule, Applicants are required to establish an adequate human safety database. The size and composition of the human safety database necessary to support drug approval depend on issues such as the proposed indication, the drug's toxicity, and/or the extent of the Agency's experience with a particular drug class. For a drug intended for the treatment of a specified life-threatening disease or condition, greater known risks or greater uncertainty about undefined risks may be acceptable when the drug offers a clear benefit for those patients. A database of at least 300 individuals allows for reasonably reliable detection of adverse reactions occurring at a rate of 1% or greater.

3.0 Summary of Tecovirimat Development for Treatment of Smallpox

3.1 Overview of Nonclinical and Clinical Studies

Using the NHP/monkeypox virus (MPXV) and rabbit/rabbitpox virus (RPXV) animal models, the Applicant demonstrated tecovirimat was effective for the treatment of these surrogate orthopoxvirus diseases using treatment initiation triggers and disease endpoints (i.e., mortality) that are relevant to human smallpox. Non-clinical toxicology and safety pharmacology studies were conducted to assess the safety of tecovirimat. Clinical (human) studies were conducted in healthy volunteers to evaluate tecovirimat safety and pharmacokinetics. Data generated in the animal and human studies were used to identify a human dose. Finally, during product development tecovirimat was provided under single-patient Emergency Investigational New Drug applications (EINDs) to a small number of patients with vaccinia virus infections, and limited data on safety, pharmacokinetics and antiviral activity were collected from these anecdotal cases. The following sections summarize the results from these key studies and the development milestones for tecovirimat.

3.2 Preliminary and Exploratory Animal Efficacy Studies

The Applicant utilized a variety of animal models of orthopoxvirus infection to characterize tecovirimat antiviral activity and efficacy. Early studies primarily using small animal models characterized the preliminary antiviral activity of the drug against

various orthopoxviruses and evaluated the effects of a wide range of study variables, including drug doses, dosing regimens, treatment times relative to viral exposure and evolution of disease, differences in viral species, strain and inoculum, route of viral exposure, and host immune function. Exploratory studies were also conducted using a variola virus/NHP model, which indicated an antiviral effect of tecovirimat, but also demonstrated some of the limitations of this model, including inconsistent disease and lethality, and the need for an unnaturally high viral challenge inoculum.

3.3 Primary Animal Efficacy Studies

Primary efficacy studies were conducted using a NHP/MPXV animal model and a rabbit/RPXV animal model. The Applicant and the Division reached consensus on key study design and study conduct parameters prior to the initiation of the studies. These parameters included, but were not limited to, the following:

- Mortality as the primary endpoint (assumed to be the principal outcome of interest for human smallpox)
- Detailed documentation of the euthanasia decision for each animal
- Viral strain including origin and passage history
- Route of viral inoculation
- Viral inoculum size
- Doses evaluated
- Timing of treatment initiation
- Duration of treatment and post-treatment follow-up
- Obtaining pharmacokinetic (PK) and pharmacodynamic (PD) information in animals to allow selection of an effective dose regimen in humans
- Detailed clinical observations and laboratory studies in the animals
- Quantification of viral burden in blood and tissues
- Drug resistance assessments
- Statistical issues, e.g. sample size, randomization, blinding
- Animal welfare, husbandry, supportive/palliative care, other veterinary interventions (e.g., anesthesia)

<u>NHP/MPXV Efficacy Studies</u>

In the NHP/MPXV efficacy studies (Appendix I), cynomolgus macaques were challenged intravenously with a high viral challenge dose of 5×10^7 plaque-forming units (PFU) of the MPXV Zaire ’79 strain. This strain was originally collected from a severely ill child survivor during a 1978-1979 MPXV outbreak in Zaire (now Democratic Republic of Congo) in which there was high mortality. Disease in this model is rapid, resulting in a systemic viremia and disease signs such as fever, rash and skin lesions that resemble features of human smallpox. Mortality is nearly universal, with a mean time to death or moribund disease requiring humane euthanasia at approximately 14 days post-challenge. The appearance of skin lesions, which first occurs 3-4 days post-challenge, was selected as a trigger for initiation of tecovirimat treatment that would be relevant to the treatment of human smallpox.

Using the NHP/MPXV model, the Applicant completed four studies in which tecovirimat was started at the time of lesion onset. All four studies were randomized and placebo-controlled; three of four were double-blinded. Development of skin lesions was determined to be a consistent and reproducible trigger for treatment initiation in this animal model. Day 4 after virus inoculation corresponds to the time-point when all animals had developed skin lesions.

A statistically significant treatment benefit over placebo for the primary endpoint of mortality was shown for all treatment arms in one study in which tecovirimat was dosed at 3, 10, or 20 mg/kg/day for 14 days starting at day 4 after virus inoculation. Maximum efficacy was observed at 3 mg/kg thus the fully effective dose of tecovirimat defined by the Animal Rule guidance is 3 mg/kg in NHPs. However, PK and efficacy were further characterized at 10 mg/kg in subsequent studies in order to evaluate a dose that provides exposures that exceed those associated with the fully effective dose. Therefore, for the purpose of human dose selection, the NHP dose was determined to be 10 mg/kg/day for 14 days.

These studies also underwent evaluation by the Office of Study Integrity and Surveillance (OSIS); OSIS's inspection confirmed the data integrity of these studies. The Agency has concluded that the NHP/MPXV model appears to be sufficiently characterized for scientific regulatory purposes and that the studies summarized in Appendix I constitute completion of the Applicant's NHP/MPXV program.

Rabbit/RPXV Efficacy Studies

In the rabbit/RPXV efficacy studies (Appendix II), 16-week-old New Zealand white rabbits were challenged intradermally with 1,000 PFU of the RPXV Utrecht strain. Disease in this model is rapid and universally fatal, and consistent with what is known about variola virus infection of humans, only a very low viral challenge dose is required to cause severe disease (LD_{50} < 4.66 PFU). Disease signs include fever, changes in respiratory rate and erythema, edema, scabbing and necrosis at the injection site. Systemic viremia is observed by Day 3-4 post-challenge and increases to high levels until the time of death (approximately 6-9 days after lethal challenge). Fever, which consistently occurs by Day 4 post-challenge, was selected as a trigger for initiation of tecovirimat treatment that would be relevant to treatment of human smallpox.

Using the rabbit/RPXV model, the Applicant completed two randomized studies in which tecovirimat was started at the time of fever onset. The pivotal efficacy study was placebo-controlled, but the PK study was not. Development of fever was determined to be a consistent and reproducible trigger for treatment initiation in this animal model. Day 4 after virus inoculation corresponds to the time-point when all animals had developed fever.

A statistically significant treatment benefit over placebo for the primary endpoint of mortality was shown for all treatment arms in one study in which tecovirimat was dosed

at 20, 40, 80, or 120 mg/kg/day for 14 days starting at day 4 after virus inoculation. Maximum efficacy was observed at 20 mg/kg thus the fully effective dose of tecovirimat defined by the Animal Rule guidance is 20 mg/kg in the rabbit/RPXV model. However, PK and efficacy were further characterized at 40 mg/kg in subsequent studies in order to evaluate a dose that provides exposures that exceed those associated with the fully effective dose. Therefore, for the purpose of human dose selection, the rabbit dose was determined to be 40 mg/kg/day for 14 days.

These studies also underwent evaluation by the Office of Study Integrity and Surveillance (OSIS); OSIS's inspection confirmed the data integrity of these studies. The Agency has concluded that the rabbit/RPXV model appears to be sufficiently characterized for scientific regulatory purposes and that the studies summarized in Appendix II constitute completion of the Applicant's rabbit/RPXV program.

Please refer to section 4.4 for information on the PK of tecovirimat in NHP/MPXV and rabbit/RPXV models and selection of the proposed human efficacious dose.

3.4 Non-Clinical Toxicology and Safety Pharmacology

Repeat-dose general toxicology studies with tecovirimat have been conducted in mice, rats, dogs and monkeys. No adverse drug-related findings were observed in the pivotal 3-month studies in mice or monkeys up to the highest doses tested, and the findings in a single 12-day rat study were limited to decreased body weight and food consumption, and mild liver toxicity. Likewise, no adverse findings were noted in the dedicated safety pharmacology studies, and all genotoxicology studies were negative.

In a 7-day toxicology study in Beagle dogs, adverse findings at the high dose of 300 mg/kg included convulsions (tonic and clonic), tremors, ataxia, stereotypic walk, excessive blinking, face-twitching, jerky head movements, panting, emesis, salivation and vocalization starting about 30 minutes post-dose on Day 1, and the male animal was euthanized *in extremis* on Day 1. The findings at the 300 mg/kg dose correspond to a C_{max} of 16,500 ng/mL in humans. Electroencephalogram (EEG) testing indicated that a high dose of 300 mg/kg can result in lowered seizure thresholds and/or frank seizures on the first day of dosing. Findings at the mid-dose of 100 mg/kg consisted of tremors, face-twitching, vocalization, licking and excessive salivation. No drug-related EEG findings were observed at the mid-dose, however. The findings at the 100 mg/kg dose correspond to a C_{max} of 5,575 ng/mL in humans. No neurologic findings were observed at the low-dose of 30 mg/kg, though clinical signs including soft feces, red discolored ears and vulvar discharge were noted in these animals. Drug was detectable in the brain and cerebrospinal fluid at all dose levels, indicating that tecovirimat crosses the blood-brain barrier in this species. At the 30 and 100 mg/kg dose levels, the brain/plasma ratio was approximately 0.35, and the CSF/plasma ratio was approximately 0.06. Brain and CSF concentrations were not determined in the high-dose group. A NOAEL could not be defined in this study due to the limited number of animals, the lack of concurrent controls, and the absence of histopathology data. However, the 100 mg/kg dose was considered the NOAEL for convulsions in this study.

Based on these data, the Applicant selected a C_{max} of 5,575 ng/mL, the C_{max} at the 100 mg/kg dose from the repeat-dose toxicology study in dogs, as the maximum allowable exposure level for humans, and the Phase 3 clinical trial (Study 008) included EEG testing for subjects in the lead-in cohort and in the PK subset of the expanded study.

3.5 Human Safety in Clinical Trials of Healthy Volunteers

The total human safety database for tecovirimat includes 788 subjects. This includes 359 healthy adult volunteers who received the proposed human efficacious regimen consisting of tecovirimat 600 mg twice daily (BID) for 14 days. These subjects were evaluated in Study 008, a double-blind, randomized, placebo-controlled, multi-center trial that assessed the safety, tolerability, and pharmacokinetics of tecovirimat administered orally for 14 days. The successful completion of Study 008 yielded a safety database of approximately 300 subjects for the proposed treatment regimen, consistent with FDA's Animal Rule guidance.

In Study 008, adverse drug reactions (i.e., adverse events [AEs] judged related to study drug), all grades, reported in ≥ 2% of subjects in the tecovirimat group included headache (12%), nausea (5%), abdominal pain (2%), vomiting (2%), and diarrhea (2%). Adverse drug reactions (ADRs), all grades, reported in ≥ 2% of subjects in the placebo group included headache (8%), nausea (4%), and diarrhea (2%). Table 1 provides a high-level safety overview of Study 008. The death, serious adverse event (SAE) and discontinuations due to AEs occurring in the tecovirimat arm are described below.

Table 1. Study 008: High-Level Safety Overview

Subjects Experiencing Event n (%)	Tecovirimat N=359	Placebo N=90
Any AE	134 (37%)	30 (33%)
Grade 2, 3, or 4 AE	30 (8%)	8 (9%)
Grade 3 or 4 AE	4 (1%)	1 (1%)
Related AE	71 (20%)	15 (17%)
Related Grade 3 or 4 AE	1 (<1%)	0
SAE	1 (<1%)	0
Related SAE	0	0
Discontinuation of study drug due to AE	6 (2%)	2 (2%)
Death	1 (<1%)	0

There was one death/SAE in Study 008: Subject (b) (6) was a 46-year-old female with a history of irregular menstruation and right leg deep venous thrombosis (DVT). Concomitant medications included Depo-Provera 150 mg every 3 months. She completed 14 days of tecovirimat on (b) (6). No adverse events were reported during treatment. On (b) (6) (i.e. 7 days post-completion of dosing), she developed acute severe shortness of breath and chest pain at home. The subject was talkative when emergency medical services arrived; pulseless electrical activity developed in route to the hospital and the subject died. Autopsy revealed extensive pulmonary embolism. No other significant gross or microscopic abnormalities were observed. Toxicology results were

negative. The AE of pulmonary embolism was considered Grade 5, fatal, and not related to study drug. Based on the subject's history of DVT and concomitant Depo-Provera use, the Agency agrees with the investigator's assessment.

Adverse Events (AEs) leading to study drug discontinuation in the tecovirimat arm are summarized below (Table 2). Unless noted otherwise[§], these AEs were considered related to study drug by investigator.

As previously noted, non-clinical toxicology studies in dogs demonstrated neurological effects (e.g., tremors, seizures) at higher than anticipated clinical exposures of tecovirimat. As a precaution, electroencephalograms (EEGs) were assessed in a cohort of subjects (65 in the tecovirimat arm, 16 in the placebo arm) in Study 008. No seizure events were reported, but one asymptomatic subject (described in Table 2) discontinued tecovirimat due to an abnormal EEG, the clinical significance of which is unknown.

Table 2. AEs Leading to Discontinuation of Tecovirimat

ID#	Preferred Term	Day, Start of AE	Day, End of AE	SAE	Grade	Outcome	Duration of tecovirimat (days)
(b) (6)	Abnormal EEG	2	14	No	1	Resolved	5
	Abdominal discomfort	3	5	No	1	Resolved	3
	Dry mouth	3	5	No	1	Resolved	
	Dysphoria	3	5	No	1	Resolved	
	Disturbance in attention	3	6	No	1	Resolved	
	Fever	2	4	No	1	Resolved	3
	Diarrhea	2	4	No	2	Resolved	
	Nausea	2	4	No	1	Resolved	
	Headache	2	6	No	3	Resolved	
	Palpable purpura	2	16	No	1	Resolved	2
	Nausea	8	13	No	1	Resolved	8
	Chills[§]	12	13	No	1	Resolved	
	Fever[§]	12	13	No	1	Resolved	
	Erythema	2	5	No	1	Resolved	1
	Pruritus	2	5	No	1	Resolved	
	Facial swelling	2	5	No	1	Resolved	

[§] = Not related to tecovirimat per investigator

Based on the results of Study 008, the Agency assessed tecovirimat (600 mg BID for 14 days) as safe and well tolerated when administered to healthy adult subjects. Notably, the healthy population which composes the safety database may differ considerably from the general population which could receive tecovirimat in the setting of a smallpox emergency. Additionally, tecovirimat has not been studied in pediatric subjects, pregnant or lactating women, or subjects with seizure disorder.

Please refer to section 4.4 for detailed information on the PK of tecovirimat in healthy volunteers and the selection of the proposed human efficacious dose.

3.6 Clinical Experience from the Emergency Use of Tecovirimat

In the United States (US), tecovirimat has been provided via EINDs to 4 patients with complications of smallpox vaccination (live vaccinia virus). There was also one ex-US case of keratoconjunctivitis possibly due to cowpox virus. Information from these 5 cases does not allow conclusions regarding the relative contribution to outcomes of tecovirimat, other investigational or approved specific therapeutics, supportive care, or patient immune response. In one tecovirimat-treated patient with disseminated vaccinia virus infection, resistance-associated amino acid substitutions were detected in the viral population, and virus isolates became phenotypically less susceptible to tecovirimat. Please see Appendix III for a summary description of EIND cases.

4.0 Addressing the Requirements of the Animal Rule

The following sub-sections summarize several of the key requirements of FDA's Animal Rule as outlined in the Code of Federal Regulations (21CFR 314.610) and provide the Agency's perspective on whether these requirements have been successfully met by the Applicant for tecovirimat.

4.1 Issues Related to Pathophysiology

The first tenet of the Animal Rule calls for a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product.

In the situation under discussion, the toxic substance is variola virus and the toxicity of concern is the illness likely to develop if humans were exposed to variola virus (either lacking timely vaccination or with illness developing despite vaccination). Although human smallpox has been eradicated, variola virus remains a NIAID Category A priority pathogen due to its risk to national security and public health. Therefore, development of medical countermeasures is necessary; and animal studies appear to be the best option for drug development for this indication. As smallpox was eradicated nearly 40 years ago, the pathophysiology of variola virus infection (smallpox) is not well understood, making it difficult to know which elements of variola virus infection and pathogenesis in humans are most important to recapitulate in an animal model of variola virus infection.

Current NHP models using variola virus are not consistently reproducible and do not mimic what is known about human smallpox disease. The limitations of the variola model were discussed at the 2011 Advisory Committee meeting and it was determined that data from at least two lethal animal models of non-variola orthopoxvirus infection should be obtained to evaluate drug efficacy. This assumes a mechanistically plausible target for the candidate drug, and the drug target being conserved across different orthopoxviruses. The Agency appreciates that extrapolating from animal models of non-variola orthopoxvirus infection to human smallpox generates additional uncertainty. However, the Agency concludes that these uncertainties have been addressed to the extent feasible via studies demonstrating (1) the broad antiviral activity and similar potency of tecovirimat against orthopoxviruses, including variola virus, and (2) a clear

mortality benefit in two well-characterized, lethal non-variola orthopoxvirus animal models.

4.2 Issues Related to Model Selection

The second tenet of the Animal Rule calls for the effect to be 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 response in humans.

Variola virus infection in established NHP models thus far does not closely resemble human smallpox except for development of a (usually mild) rash illness. Typically, a large viral inoculum via the intravenous route has been required to establish serious disease, potentially bypassing the initial steps in smallpox pathogenesis. Because scientific limitations of the available NHP/variola model preclude definitive efficacy assessments, and uncertainty exists whether an adequate variola model can be developed, the FDA and the advisory committee agreed that data from at least two lethal animal models of non-variola orthopoxvirus infection should be obtained to evaluate drug efficacy. The Agency concludes that the Applicant has successfully demonstrated the effect of tecovirimat in two well-characterized animal models: the NHP/MPXV model and the rabbit/RPXV model.

4.3 Issues Related to Study Endpoints

The third tenet of the Animal Rule states that the animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity.

In the Applicant's NHP/MPXV and rabbit/RPXV studies, mortality (based on prospectively defined euthanasia criteria) has been evaluated as the primary endpoint since mortality has been assumed to be the principal outcome of interest for human smallpox. Statistically significant treatment benefit over placebo for the primary endpoint of mortality was observed in the Applicant's NHP/MPXV and rabbit/RPXV studies. The Agency concludes that the Applicant's NHP/MPXV and rabbit/RPXV studies evaluated and confirmed treatment benefit using a primary efficacy endpoint that is clearly related to the desired benefit in humans.

4.4 Issues Related to Pharmacokinetics and Dose Selection

The fourth tenet of the Animal Rule calls for data or information on the pharmacokinetics (PK) and pharmacodynamics (PD) of the product or other relevant data or information in animals and humans that would allow selection of an effective dose in humans.

Human PK data of the investigational agent, combined with PK and PD data obtained in the same animal models that are used to demonstrate animal efficacy, are essential for identification of an efficacious dose in humans under the Animal Rule. 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, if the drug's safety profile allows such dosing. Applicants should obtain PK data for the investigational agent in healthy subjects as well as in healthy and infected animals such that exposure in animals can be appropriately bridged to select a dose for humans.

The Applicant collected PK/PD data in the NHP/MPXV and rabbit/RPXV studies, as well as PK data in uninfected NHPs and rabbits. PK data at the proposed dosing regimen, 600 mg BID under fed conditions, were also collected in healthy volunteers from the Phase 3 human safety study (Study 008). As stated previously (section 3.3), 10 mg/kg/day for 14 days in NHP/MPXV and 40 mg/kg/day for 14 days in rabbit/RPXV were selected as the fully effective doses in animal models for human dose selection, thus the PK of tecovirimat were compared between humans and animal models. The exposures in healthy humans are significantly higher than those associated with the fully effective doses in either NHP/MPXV or rabbit/RPXV (Table 3).

Table 3. Tecovirimat pharmacokinetic parameters in healthy volunteers, NHP/MPXV, and rabbit/RPXV

		Cmax (ng/mL)	AUC24 (ng/mL·hr)	Cmin (ng/mL)
Day1	Human (N=48)	1516 (761-3290, 32%)	20879 (10627-45733, 35%)	477 (143-2020, 65%)
	NHP (N=6)	749 (378-1320, 42%)	7629 (4577-13294, 39%)	134 (37.3-339, 68%)
	Rabbit (n=8)	518 (204-1180, 51%)	6881 (2349-14331, 53%)	144 (28-235, 64%)
Steady state	Human (N=48)	2106 (1120-4460, 33%)	28791 (15504-73568, 35%)	689 (2.5-1360, 38%)
	NHP (n=6)	1403 (936-2010, 37%)	13650 (6975-18614, 31%)	143 (88.7-344, 97%)
	Rabbit (N=8)	596 (319-1340, 49%)	8025 (4480-19330, 54%)	117 (25-314, 71%)

- Data are expressed as geometric mean values (range, %CV)
- PK in human: tecovirimat 600 mg BID under fed conditions for 14 days in healthy volunteers (Study 008).
- PK in NHP: tecovirimat 10 mg/kg/day for 14 days (FY 10-087)
- PK in rabbits: tecovirimat 40 mg/kg/day for 14 days (SR14-008)
- Steady state PK data: 14^{th} day dosing for human and NHP and 7^{th} day dosing for rabbits. As the PK of tecovirimat in rabbits were lower on Day 14 as compared to Day 7, comparisons were made using Day 7 data as a conservative assessment for human dose selection.

Inter-species differences in ADME (absorption, distribution, metabolism, and elimination) of tecovirimat, effects of orthopoxvirus infection on the PK of tecovirimat in NHPs and rabbits, and intrinsic and extrinsic factors that may influence the PK of tecovirimat were also characterized to determine the effective human dose of tecovirimat; there was no significant difference in protein binding and the free fraction of tecovirimat in plasma among NHPs, rabbits, and humans. Tecovirimat exposures are decreased by certain intrinsic and extrinsic factors such as fasting conditions, higher body weight, and

end-stage renal disease. However, the exposures are still higher than those associated with effectiveness in NHP/MPXV and rabbit/RPXV. Pediatric doses are also proposed based on modeling and simulation.

The Agency concludes that the Applicant adequately addressed the pharmacokinetic and dosing issues and we agree with the proposed dosing regimen, 600 mg BID under fed conditions.

4.5 Issues Related to Clinical Safety

The Animal Rule requires clinical safety to be established for the new drug product. As summarized in section 3.5, tecovirimat administered to healthy adult subjects at the proposed dosing regimen of 600 mg BID for 14 days was demonstrated to be safe and well tolerated.

5.0 Preliminary Topic for the Advisory Committee

The Division is convening this meeting to solicit the committee's comments on the following topic. Please note, however, that this is a preliminary topic and still subject to change.

1. Based on the available data, does the risk-benefit profile of tecovirimat support its use for the treatment of human smallpox?

Appendix I: Summary of selected non-human primate (NHP)/monkeypox virus (MPXV) studies with tecovirimat

Study	Description	Viral Inoculum	tecovirimat regimen	Timing of tecovirimat relative to viral inoculation	Survival n/N (%)	Boschloo's 1-sided P-value
AP-09-026G	Double-blind, randomized, placebo-controlled study to evaluate the minimum effective therapeutic dose of oral tecovirimat Polyform I in cynomolgus monkeys infected with MPXV	MPXV strain ZAI 1979-005 $5x10^7$ PFU IV	Placebo	N/A	0/7 (0%) at Day 42 PI	
			0.3 mg/kg/day x 14 days	Day 4 PI in 5/5 NHPs	1/5 (20%) at Day 42 PI	0.2541
			1 mg/kg/day x 14 days	Day 4 PI in 5/5 NHPs	0/5 (0%) at Day 42 PI	NA
			3 mg/kg/day x 14 days	Day 4 PI in 5/5 NHPs	4/5 (80%) at Day 42 PI	0.0038
			10 mg/kg/day x 14 days	Day 4 PI in 5/5 NHPs	4/5 (80%) at Day 42 PI	0.0038
SR10-037F	Double-blind, randomized, placebo-controlled study to evaluate the impact of delayed tecovirimat treatment on efficacy following intravenous (IV) challenge with lethal MPXV challenge	MPXV strain ZAI 1979-005 $5x10^7$ PFU IV	Placebo	N/A	0/3 (0%) at Day 56 PI	
			10 mg/kg/day x 14 days	Day 4 PI in 6/6 NHPs	5/6 (83%) at Day 56 PI	0.0151
			10 mg/kg/day x 14 days	Day 5 PI in 6/6 NHPs	5/6 (83%) at Day 56 PI	0.0151
			10 mg/kg/day x 14 days	Day 6 PI in 6/6 NHPs	3/6 (50%) at Day 56 PI	0.1231
SR10-038F	Double-blind, randomized, placebo-controlled study to evaluate the impact of duration of tecovirimat treatment on efficacy following intravenous (IV) challenge with lethal MPXV challenge in cynomolgus monkeys	MPXV strain ZAI 1979-005 $5x10^7$ PFU IV	Placebo	N/A	1/4 (25%) at Day 28 PI	
			10 mg/kg/day x 3 days	Day 4 PI in 4/4 NHPs	2/4 (50%) at Day 28 PI	0.3633
			10 mg/kg/day x 5 days	Day 4 PI in 6/6 NHPs	6/6 (100%) at Day 28 PI	0.0133
			10 mg/kg/day x 7 days	Day 4 PI in 6/6 NHPs	6/6 (100%) at Day 28 PI	0.0133
			10 mg/kg/day x 10 days	Day 4 PI in 5/5 NHPs	4/5 (80%) at Day 28 PI	0.0962
FY10-087	Randomized, placebo-controlled study to evaluate tecovirimat pharmacokinetics in cynomolgus monkeys infected intravenously with MPXV **Not blinded.**	MPXV strain ZAI 1979-005 $5x10^7$ PFU IV	Placebo	N/A	0/6 (0%) at Day 28 PI	
			3 mg/kg/day x 14 days	Day 4 PI in 6/6 NHPs	6/6 (100%) at Day 28 PI	0.0002
			10 mg/kg/day x 14 days	Day 4 PI in 6/6 NHPs	6/6 (100%) at Day 28 PI	0.0002
			20 mg/kg/day x 14 days	Day 4 PI in 6/6 NHPs	6/6 (100%) at Day 28 PI	0.0002

Euthanasia criteria were prospectively defined. Mortality is assessed as unscheduled euthanasia prior to the pre-specified end-of-study.
Development of skin lesions was determined to be a consistent and reproducible trigger for treatment initiation in this animal model.
PFU, plaque forming units; PI, post-inoculation; MPXV, monkeypox virus; N/A, not applicable.
MPXV was administered via intravenous inoculation. Day 4 PI corresponds to onset of skin lesions.
Pre-specified end-of-study date was Day 42 PI in AP-09-026G, Day 56 PI in SR10-037F, Day 28 PI in SR10-038F, and Day 28 PI in FY10-087.
Boschloo's 1-sided P-value is for the test between the tecovirimat group vs. placebo group without any multiplicity adjustment.

Appendix II: Summary of selected rabbit/rabbitpox virus (RPXV) studies with tecovirimat

Study	Description	Viral Inoculum	tecovirimat regimen	Timing of tecovirimat relative to viral inoculation	Survival n/N (%)	Boschloo's 1-sided P-value
SR14-008F	Double-blind, randomized, placebo-controlled study to evaluate dose-response relationship between tecovirimat plasma exposure and efficacy in 16-week old rabbits following lethal intradermal (ID) RPXV Utrecht strain inoculation	1000 PFU ID	Placebo	N/A	0/10 (0%) at Day 30 PI	
			20 mg/kg/day x 14 days	Day 4 PI	9/10 (90%) at Day 30 PI	0.0
			40 mg/kg/day x 14 days	Day 4 PI	9/10 (90%) at Day 30 PI	0.0
			80 mg/kg/day x 14 days	Day 4 PI	8/10 (80%) at Day 30 PI	0.0001
			120 mg/kg/day x 14 days	Day 4 PI	8/10 (80%) at Day 30 PI	0.0001
SR13-025F	Double-blind, randomized study to evaluate the impact of RPXV Utrecht strain (ID inoculation) on oral PK of tecovirimat in 16-week old rabbits	1000 PFU ID	40 mg/kg/day x 14 days	Day 4 PI	7/8* (87.5%) at Day 18 PI	
			80 mg/kg/day x 14 days	Day 4 PI	7/8* (87.5%) at Day 18 PI	
			120 mg/kg/day x 14 days	Day 4 PI	8/8 (100%) at Day 18 PI	

Euthanasia criteria were prospectively defined. Mortality is assessed as unscheduled euthanasia prior to the pre-specified end-of-study.
Development of fever was determined to be a consistent and reproducible trigger for treatment initiation in this animal model.
PFU, plaque forming units; PI, post-inoculation; RPXV, rabbitpox virus; ID, intradermal; N/A, not applicable.
RPXV was administered via intradermal inoculation. Day 4 PI corresponds to onset of fever.
Pre-specified end-of-study date was Day 30 PI in SR14-008F and Day 18 PI in SR13-025F.
*In Study SR13-025F: One animal in Group 1 was found dead on Day 16 PI; one animal in Group 2 was found dead on Day 17 PI; all other animals survived until Day 18 PI (pre-specified end-of-study).
Boschloo's 1-sided P-value is for the test between the tecovirimat group vs. placebo group without any multiplicity adjustment.

Appendix III: Summary of Compassionate Use with tecovirimat (n=5; US [#1-4]; ex-US [#5])

Description	Tecovirimat regimen	Other interventions	Comments
20 month old boy diagnosed with eczema vaccinatum (EV) on (b) (6) due to exposure from direct contact with a smallpox vaccine "take site" in another individual	(b) (6) 50 mg/day (i.e. 5 mg/kg/day) x 2 days (b) (6) 75 mg/day (i.e. 7.5 mg/kg/day) x 2 days (b) (6) 100 mg/day (i.e. 10 mg/kg/day) x 10 days	VIG (13 doses, given over (b) (6) IV cidofovir (5 mg/kg, one dose, given on (b) (6)	Tecovirimat doses were adjusted due to suboptimal plasma exposure. No new skin lesions were noted from (b) (6) onward.
21 year-old immunosuppressed male diagnosed with progressive vaccinia (PV) on (b) (6) following smallpox vaccination *(Vaccination occurred ~ 2 weeks before being diagnosed with acute myelogenous leukemia; had undergone induction chemotherapy when PV developed)*	(b) (6) 400 mg/day x 15 days (b) (6) 800 mg/day x 5 days (b) (6) 1200 mg/day x 55 days	VIG (14 doses, given over (b) (6) Topical tecovirimat[a] (b) (6) Oral CMX001[b]: 2 mg/kg ((b) (6)), then 1 mg/kg (5 doses, given over (b) (6)) Topical imiquimod (b) (6))	Tecovirimat doses were adjusted due to suboptimal plasma exposure and development of new vaccinia satellite skin lesions ((b) (6)) while receiving tecovirimat. Genotypic and phenotypic evidence that the viral population became less susceptible to tecovirimat during treatment.
35 year-old female developed localized vaccinia skin lesions on her hand on (b) (6) due to a cut after handling a packet of rabbit bait that had a vaccinia vector[c] (Medical history notable for Crohn's disease, receiving azathioprine and infliximab)	400 mg/day x 14 days (b) (6)	VIG ((b) (6))	(b) (6) Initial lesions noted to be crusted. Specifics on when secondary lesions (on hand and wrist) resolved were not provided.
25 year-old immunocompetent female, history of acne, with vaccinia infection on her chin on (b) (6) due to exposure from direct contact with a smallpox vaccine "take site" in another individual	400 mg/day x 14 days (b) (6)	VIG (b) (6))	Tecovirimat initiated after clinical improvement had occurred.
(Ex-US): 32 year-old immunocompetent female with severe keratoconjunctivitis[d] (samples taken in (b) (6) subsequently tested positive by viral	400 mg/day x 14 days (b) (6)	Topical corticosteroids (b) (6) Systemic corticosteroids (initiated on	Applicant assessed that it is possible that CPXV infection had resolved prior to the start of tecovirimat in (b) (6)

culture, PCR and electron microscopy, for cowpox virus [CPXV])		(b) (6)) Topical ophthalmic idoxuridine (initiated on (b) (6))	as CPXV virus was still detectable by PCR but not by viral culture of ocular samples.

Vaccinia immune globulin (VIG); Intravenous (IV); PCR, polymerase chain reaction; EIND, Emergency Investigational New Drug application.

[a]Topical tecovirimat is an investigational drug; no human data are available other than in the EIND described above.

[b]CMX001 (oral, lipid conjugate of cidofovir) is an investigational drug with activity in cell culture against orthopoxviruses.

[c]Baits laden with oral rabies vaccines are used in the management of wildlife rabies in the United States. One type of oral rabies vaccine consists of a live recombinant vaccinia vector, expressing rabies virus glycoprotein (V-RG) (Raboral V-RG). This program is conducted by U.S. Department of Agriculture in collaboration with state and local health agencies, as well as the Centers for Disease Control (MMWR 2013; 62(14): 267-269).

[d]Prior to CPXV diagnosis, patient received topical and systemic corticosteroids, intravenous immunoglobulins, broad-spectrum systemic antibiotics, and topical trifluridine.

References

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

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

Lederman E, Davidson W, Groff H, et al. Progressive Vaccinia: Case description and laboratory-guided therapy with vaccinia immune globulin, ST-246, and CMX001. J Infect Dis. 2012;206(9):1372-85.

Vora S, Damon I, Fulginiti V, et al. Severe Eczema Vaccinatum in a Household Contact of a Smallpox Vaccinee. Clinical Infectious Diseases 2008; 46(10): 1555-61.