

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208627Orig1s000

CLINICAL REVIEW(S)

1.0 Regulatory overview/Background

Approval of a drug under Animal Rule includes a requirement for post-marketing studies (e.g., field studies) to provide evaluation of safety and clinical benefit if circumstances arise in which a study would be feasible and ethical (i.e., in the event an emergency arises and drug is used). Applicant plans to meet post-marketing commitment by conducting a field study. Applicant submitted logistics and a revised draft study synopsis for review.

1.1 FDA March 2, 2018 comments

After review of the Applicant's 12/8/17 proposals, the following recommendations were provided to the Applicant regarding the proposed field study

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/s/

KIRK M CHAN-TACK
05/16/2018

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05/16/2018

Clinical Review
Kirk Chan-Tack, MD
NDA 208627
TPOXX (tecovirimat)

CLINICAL REVIEW

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| Application Type | New Drug Application |
| Application Number(s) | 208627 |
| Priority or Standard | Priority |
| Submit Date(s) | December 8, 2017 |
| Received Date(s) | December 8, 2017 |
| PDUFA Goal Date | 208627 |
| Division/Office | Division of Antiviral Products/Office of Antimicrobial Products |
| Reviewer Name(s) | Kirk Chan-Tack, MD |
| Review Completion Date | May 5, 2018 |
| Established Name | Tecovirimat |
| (Proposed) Trade Name | TPOXX™ |
| Applicant | SIGA Technologies, Inc. |
| Formulation(s) | 600 mg capsule |
| Dosing Regimen | Three capsules orally twice daily |
| Applicant Proposed Indication(s)/Population(s) | Treatment of adult and pediatric patients with human smallpox disease caused by variola virus |
| Recommendation on Regulatory Action | Approval |
| Recommended Indication(s)/Population(s) (if applicable) | Treatment of adult and pediatric patients with human smallpox disease caused by variola virus |

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Glossary

| | |
|--------|--|
| AVDAC | Antiviral Drugs Advisory Committee |
| ADR | adverse drug reaction |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| BRF | Benefit Risk Framework |
| CDER | Center for Drug Evaluation and Research |
| CFR | Code of Federal Regulations |
| CK | creatinine kinase |
| CMC | chemistry, manufacturing, and controls |
| CSF | cerebrospinal fluid |
| CSR | clinical study report |
| CYP | cytochrome P450 |
| DAIDS | Division of AIDS |
| DAVP | Division of Antiviral Products |
| DSMB | Data Safety Monitoring Board |
| DDI | drug-drug interaction |
| DILI | drug-induced liver injury |
| ECG | electrocardiogram |
| ECI | event of clinical interest |
| eCTD | electronic common technical document |
| EEG | electroencephalogram |
| eGFR | estimated glomerular filtration rate |
| EIND | Emergency Investigational New Drug |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| FU | follow up |
| GLP | Good Laboratory Practices |
| ICH | International Conference on Harmonization |
| ID | intradermal |
| IND | Investigational New Drug |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| IV | intravenous |
| LLN | lower limit of normal |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MPXV | monkeypox virus |
| NDA | new drug application |

Clinical Review
Kirk Chan-Tack, MD
NDA 208627
TPOXX (tecovirimat)

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| NIAID | National Institute of Allergy and Infectious Diseases |
| NME | new molecular entity |
| OSI | Office of Scientific Investigation |
| OSIS | Office of Study Integrity and Surveillance |
| PBO | placebo |
| PD | pharmacodynamics |
| PFU | plaque forming units |
| PI | post inoculation |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PPI | patient package insert |
| PREA | Pediatric Research Equity Act |
| PT | Preferred Term (aka Dictionary Derived Term) |
| RPXV | rabbitpox virus |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SOC | system organ class |
| TEAE | treatment emergent adverse event |
| TW | treatment week |
| UDP | uridine diphosphate |
| UGT | uridine-glucuronosyl transferas |
| ULN | upper limit of normal |
| US | United States |
| VARV | variola virus |
| WHO | World Health Organization |

1 Executive Summary

TPOXX® (tecovirimat) is a small molecule developed for the treatment of human smallpox. This review provides the clinical perspective on the adequacy of the available data to support the approval of tecovirimat under the FDA's Animal Rule for this indication.

1.1. Product Introduction

TPOXX® (tecovirimat) is a new molecular entity (NME) antiviral agent that interferes with critical steps in the replication cycle of variola virus. The mechanism of action of tecovirimat involves preventing the production of extracellular enveloped virus necessary for spread of orthopoxvirus infection.

The Applicant's proposed indication is treatment of patients with human smallpox disease caused by variola virus. The recommended dosage for adult and pediatric patients weighing at least 40 kg is three capsules by mouth twice daily for 14 days. The proposed doses, based on simulation, for pediatric patients in other weight bands is summarized below:

- 25 kg to < 40 kg: two capsules by mouth twice daily for 14 days
- 13 kg to < 25 kg: one capsule by mouth twice daily for 14 days

1.2. Conclusions on the Substantial Evidence of Effectiveness

Data from the pivotal animal efficacy studies in two lethal animal models of non-variola orthopoxvirus infection included in this application provide substantial evidence of effectiveness as required by law 21 CFR part 314, subpart I to support approval of tecovirimat x 14 days for treatment of treatment of patients with human smallpox disease caused by variola virus. The Applicant's non-human primate (NHP)/monkeypox virus (MPXV) and rabbit/rabbitpox virus (RPXV) studies evaluated and confirmed statistically significant treatment benefit using a primary efficacy endpoint that is clearly related to the desired benefit in humans.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Tecovirimat is an oral antiviral with a proposed indication for the treatment of human smallpox infection under the Animal Rule. The mechanism of action of tecovirimat involves preventing the production of extracellular enveloped virus necessary for spread of orthopoxvirus infection.

The 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. Most of the clinical descriptions are based on variola major, the more serious form that was also more prevalent throughout most of the history of the disease, and that is also the focus of concerns regarding potential bioterrorism uses of variola virus. Mortality in variola major is commonly cited as about 30% but was reported to vary widely among outbreaks from as little as 5% to 40% or more. In 1980, following an historic global campaign of surveillance and vaccination, the World Health Assembly declared smallpox eradicated – the only infectious disease to achieve this distinction. Despite the eradication of naturally acquired smallpox, the disease remains a threat as variola virus could be developed as a bioterrorism agent. 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. Due to the mortality and severe morbidity associated with smallpox, the World Health Organization (WHO) states that preparedness to deal with any kind of smallpox event – whether natural re-emergence, accidental or deliberate release of the live virus, or created through synthetic biology – requires global and national attention.

Because smallpox is a potentially serious threat but does not occur naturally, clinical 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.

Because of the unique complexities of drug development in this area, extensive discussion with multiple stakeholders has occurred, including an FDA public workshop in 2009 and an FDA public Advisory Committee meeting in 2011. During the 2011 Antiviral Drugs Advisory Committee (AVDAC) 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 and do not mimic what is known about human smallpox disease. 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 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) 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.

Based on multiple discussions with stakeholders (including the aforementioned 2011 Antiviral Drugs Advisory Committee), the FDA 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 single orthopoxvirus animal model is known to be the best predictor of human responses to treatments for smallpox.

The Applicant focused on the non-human primate (NHP)/monkeypox virus (MPXV) animal model and the rabbit/rabbitpox virus (RPXV) animal model. In these animal studies, key study design issues were discussed by the Applicant and the Division and consensus was reached before these studies were conducted. The Agency concludes that the Applicant closely followed the FDA's recommendations and demonstrated a mortality benefit in the NHP/MPXV animal model and in the rabbit/RPXV animal model. In these NHP and rabbit studies, mortality (based on euthanasia criteria) was evaluated as the primary endpoint since mortality has been assumed to be the principal outcome of interest for human smallpox. Evaluation of the specific euthanasia criteria used in each study was done to help assure the clinical significance of a mortality-based primary endpoint.

For the NHP/MPXV model, the Applicant completed studies (randomized, placebo-controlled, double-blinded [in 3 of 4 studies], two of which were performed under Good Laboratory Practices [GLP]) in which tecovirimat was started at the time of lesion onset. 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 the NHP/MPXV model. 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' inspection confirmed the data integrity of these studies. The Agency assessed that the NHP/MPXV model is sufficiently characterized for scientific regulatory purposes. The Agency also assessed that the studies summarized in this review constitute completion of the Applicant's NHP/MPXV program.

For the rabbit/RPXV model, the Applicant completed studies (randomized, placebo-controlled [in 1 of 2 studies], double-blinded, performed under GLP) in which tecovirimat was started at the time of fever onset. 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' inspection confirmed the data integrity of these studies. The Agency assessed that the rabbit/RPXV model is sufficiently characterized for scientific regulatory purposes. The Agency also assessed that the studies summarized in this review constitute completion of the Applicant's rabbit/RPXV program.

Available human data with tecovirimat are limited to healthy adult volunteer studies completed for evaluation of safety and pharmacokinetics and a small number of single-patient Emergency INDs for vaccinia infection. No major safety issues unique to tecovirimat were identified in this review. The most frequent adverse drug reactions were headache, nausea, and abdominal pain. Tecovirimat has been associated with mild-to-moderate hypoglycemia when co-administered with blood glucose-lowering drugs and the label includes a Warning and Precaution regarding this risk.

Approval of tecovirimat under the FDA's Animal Rule for treatment of human smallpox disease caused by variola virus infection is fully supported by the available evidence of efficacy and safety. Based on thorough analysis of efficacy, safety, pharmacokinetic, and virology data overall, tecovirimat for 14 days is recommended for adult and pediatric patients with human smallpox disease caused by variola virus.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|-----------|----------------------------|-------------------------|
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| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|--|--|---|
| <p>Analysis of Condition</p> | <ul style="list-style-type: none"> • 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 throughout most of the history of the disease, and that is also the focus of concerns regarding potential bioterror uses of variola virus. Mortality in variola major is commonly cited as about 30% but was reported to vary widely among outbreaks from as little as 5% to 40% or more. | <p>Smallpox is a potentially serious threat but does not occur naturally. When infected with variola virus, patients can experience symptoms that are severe, debilitating, and can be fatal.</p> |
| <p>Current Treatment Options</p> | <ul style="list-style-type: none"> • There are no approved treatments for human smallpox disease caused by variola virus. • 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. • Due to the mortality and severe morbidity associated with smallpox, the WHO Advisory Committee on Variola Virus Research states that preparedness to deal with any kind of smallpox event – whether natural re-emergence, accidental or deliberate release of the live virus, or created through synthetic biology – requires global and national attention. | <p>Due to concerns regarding potential bioterror uses of variola virus, a specific unmet medical need exists for effective antiviral regimens for subjects who develop smallpox disease caused by variola virus because no approved regimens are available.</p> |
| <p>Benefit</p> | <ul style="list-style-type: none"> • Because smallpox is a potentially serious threat but does not occur naturally, clinical 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 | <p>Uncertainties inherent in drug development under the Animal Rule have been addressed to the extent possible via animal studies</p> |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|-----------|--|---|
| | <p>approval under 21 CFR part 314, subpart I, if a suitable approach is agreed upon.</p> <ul style="list-style-type: none"> Because of the unique complexities of drug development in this area, extensive discussion with multiple stakeholders has occurred, including an FDA public workshop in 2009 and an FDA public Advisory Committee meeting in 2011. During the 2011 Antiviral Drugs Advisory Committee (AVDAC) meeting, the advisory committee agreed with the FDA’s assessment that current lethal NHP models using variola virus are not consistently reproducible and do not mimic what is known about human smallpox disease. 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 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) 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. Based on multiple discussions with stakeholders (including the aforementioned 2011 Antiviral Drugs Advisory Committee), the FDA 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 | <p>demonstrating a clear, statistically significant mortality benefit in two well-characterized, lethal non-variola orthopoxvirus animal models. These studies have also allowed for the selection of a human dose with an acceptable safety profile and which satisfies the other tenets of the Animal Rule.</p> |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|-----------|--|---|
| | <p>animal models acknowledges the unique challenges and uncertainties associated with this area of drug development, and the fact that no single orthopoxvirus animal model is known to be the best predictor of human responses to treatments for smallpox.</p> <ul style="list-style-type: none"> • The efficacy of tecovirimat was established in the NHP/MPXV animal model and the rabbit/RPXV animal model. • For the NHP/MPXV model, efficacy studies evaluated tecovirimat when treatment was started at the time of lesion onset. 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. • 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 the NHP/MPXV model. 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; this dose and duration were evaluated in the following NHP/MPXV studies: <ul style="list-style-type: none"> ○ AP-09-026G: Randomized, double-blind, placebo-controlled study assessing the minimum effective therapeutic dose of oral tecovirimat. ○ SR10-037F: Randomized, double-blind, placebo-controlled study assessing the effect of delayed tecovirimat treatment on efficacy. ○ FY10-087: Randomized, placebo-controlled study assessing tecovirimat PK parameters. • For the rabbit/RPXV model, efficacy studies evaluated tecovirimat when treatment was started at the time of fever onset. Development of fever was determined to be a consistent and reproducible trigger for treatment initiation | <p>The studies in these two lethal animal models of non-variola orthopoxvirus infection provide substantial evidence of effectiveness of tecovirimat x 14 days.</p> <p>The Applicant’s NHP/MPXV and rabbit/RPXV studies evaluated and confirmed statistically significant treatment benefit using a primary efficacy endpoint that is clearly related to the desired benefit in humans.</p> |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons | | | | | | | | | | | | | | | | |
|------------|--|-------------------------|--|-----------------------|-------------------|------------|-------|-----------|----------|-----------|-------|-----------|----------|--------|-----------|--------|-----------|---|
| | <p>in this animal model. Day 4 after virus inoculation corresponds to the time-point when all animals had developed fever.</p> <ul style="list-style-type: none"> 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; this dose and duration were evaluated in the following rabbit/RPXV studies: <ul style="list-style-type: none"> SR14-008F: Randomized, double-blind, placebo-controlled study assessing the dose-response relationship between tecovirimat plasma exposure and efficacy. SR13-025F: Randomized, double-blind study assessing tecovirimat PK parameters. The primary efficacy endpoint was proportion of animals that survived to the pre-specified end-of-study, as survival is clearly related to the desired benefit in humans and satisfies one of the tenets of the Animal Rule. As displayed in the tables below, survival in treated animals overall ranged from 80-100% when treatment was initiated at day 4 after virus inoculation. <p>NHP/MPXV studies with tecovirimat 10 mg/kg x 14 days: Survival by Treatment Arm n (%)</p> <table border="1" data-bbox="359 1170 1478 1390"> <thead> <tr> <th>Study</th> <th>Treatment Initiation (# of days after viral inoculation)</th> <th>Tecovirimat x 14 days</th> <th>Placebo x 14 days</th> </tr> </thead> <tbody> <tr> <td>AP-09-026G</td> <td>Day 4</td> <td>4/5 (80%)</td> <td>0/7 (0%)</td> </tr> <tr> <td rowspan="3">SR10-037F</td> <td>Day 4</td> <td>5/6 (83%)</td> <td rowspan="3">0/3 (0%)</td> </tr> <tr> <td>Day 5*</td> <td>5/6 (83%)</td> </tr> <tr> <td>Day 6*</td> <td>3/6 (50%)</td> </tr> </tbody> </table> | Study | Treatment Initiation (# of days after viral inoculation) | Tecovirimat x 14 days | Placebo x 14 days | AP-09-026G | Day 4 | 4/5 (80%) | 0/7 (0%) | SR10-037F | Day 4 | 5/6 (83%) | 0/3 (0%) | Day 5* | 5/6 (83%) | Day 6* | 3/6 (50%) | <p>Tecovirimat demonstrated a mortality benefit in the NHP/MPXV animal model and in the rabbit/RPXV animal model.</p> <p>Tecovirimat fills an important</p> |
| Study | Treatment Initiation (# of days after viral inoculation) | Tecovirimat x 14 days | Placebo x 14 days | | | | | | | | | | | | | | | |
| AP-09-026G | Day 4 | 4/5 (80%) | 0/7 (0%) | | | | | | | | | | | | | | | |
| SR10-037F | Day 4 | 5/6 (83%) | 0/3 (0%) | | | | | | | | | | | | | | | |
| | Day 5* | 5/6 (83%) | | | | | | | | | | | | | | | | |
| | Day 6* | 3/6 (50%) | | | | | | | | | | | | | | | | |

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|--|--|--|----------------------|------------|----------|-------|---|--------------------------|----------------------|-----------|-------|------------|-----------|-----------|-------|-----------|---|--|
| | <table border="1" data-bbox="359 315 1478 347"> <tr> <td data-bbox="359 315 548 347">FY10-087</td> <td data-bbox="548 315 989 347">Day 4</td> <td data-bbox="989 315 1241 347">6/6 (100%)</td> <td data-bbox="1241 315 1478 347">0/6 (0%)</td> </tr> </table> <p data-bbox="359 354 1478 418"><i>*These cohorts evaluated the effect of delayed treatment initiation on efficacy and were done for exploratory purposes.</i></p> <p data-bbox="359 467 1478 500">Rabbit/RPXV studies with tecovirimat 40 mg/kg x 14 days: Survival by Treatment Arm n (%)</p> <table border="1" data-bbox="359 500 1478 646"> <thead> <tr> <th data-bbox="359 500 548 573">Study</th> <th data-bbox="548 500 989 573">Treatment Initiation (# of days after viral inoculation)</th> <th data-bbox="989 500 1241 573">Tecovirimat x 14 days</th> <th data-bbox="1241 500 1478 573">Placebo x 14 days</th> </tr> </thead> <tbody> <tr> <td data-bbox="359 573 548 605">SR14-008F</td> <td data-bbox="548 573 989 605">Day 4</td> <td data-bbox="989 573 1241 605">9/10 (90%)</td> <td data-bbox="1241 573 1478 605">0/10 (0%)</td> </tr> <tr> <td data-bbox="359 605 548 646">SR13-025F</td> <td data-bbox="548 605 989 646">Day 4</td> <td data-bbox="989 605 1241 646">7/8 (88%)</td> <td data-bbox="1241 605 1478 646">-</td> </tr> </tbody> </table> <ul data-bbox="359 695 1478 922" style="list-style-type: none"> • In the NHP/MPXV model, a 14 day course of tecovirimat (10 mg/kg) is effective when treatment was initiated at day 4 after virus inoculation (i.e. the time-point when all animals had developed skin lesions). • In the rabbit/RPXV model, a 14 day course of tecovirimat (40 mg/kg) is effective when treatment was initiated at day 4 after virus inoculation (i.e. the time-point when all animals had developed fever). | FY10-087 | Day 4 | 6/6 (100%) | 0/6 (0%) | Study | Treatment Initiation (# of days after viral inoculation) | Tecovirimat x 14 days | Placebo x 14 days | SR14-008F | Day 4 | 9/10 (90%) | 0/10 (0%) | SR13-025F | Day 4 | 7/8 (88%) | - | <p data-bbox="1535 321 1980 354">unmet medical need.</p> |
| FY10-087 | Day 4 | 6/6 (100%) | 0/6 (0%) | | | | | | | | | | | | | | | |
| Study | Treatment Initiation (# of days after viral inoculation) | Tecovirimat x 14 days | Placebo x 14 days | | | | | | | | | | | | | | | |
| SR14-008F | Day 4 | 9/10 (90%) | 0/10 (0%) | | | | | | | | | | | | | | | |
| SR13-025F | Day 4 | 7/8 (88%) | - | | | | | | | | | | | | | | | |
| <p data-bbox="184 1089 243 1122">Risk</p> | <ul data-bbox="329 938 1514 1279" style="list-style-type: none"> • The safety database for tecovirimat was primarily based on Trial 008, a Phase 3 clinical trial in healthy adults. This trial included 359 subjects who received tecovirimat and 90 subjects who received placebo. The safety database is considered adequate. • No major safety issues were encountered during this review. • Headache, nausea, and abdominal pain were the three most commonly reported adverse drug reactions (ADRs). • In the Phase 1 drug-drug interaction Study 015, co-administration of repaglinide and tecovirimat caused mild-to-moderate hypoglycemia in 10 out of 30 subjects. | <p data-bbox="1535 938 1980 1003">Tecovirimat demonstrated an overall favorable safety profile.</p> | | | | | | | | | | | | | | | | |
| <p data-bbox="121 1312 306 1385">Risk Management</p> | <ul data-bbox="329 1295 1514 1403" style="list-style-type: none"> • Although no significant safety signals were detected in this review, the tecovirimat prescribing information will include safety information from the Study 008 population. | <p data-bbox="1535 1295 1980 1403">Safety concerns associated with tecovirimat are adequately addressed in product labeling.</p> | | | | | | | | | | | | | | | | |

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| | <ul style="list-style-type: none">• ADRs of interest such as rash, palpable purpura, abnormal electroencephalogram, and depression, will be included under Less Common Adverse Reactions.• A Warning about the risk of hypoglycemia when co-administered with blood glucose-lowering drugs will also be included. | |

1.4. Patient Experience Data

Table 1 contains a summary of Patient Experience Data Relevant to this Application.

Table 1. Patient Experience Data Relevant to this Application

| √ | The patient experience data that was submitted as part of the application include: | Section where discussed, if applicable |
|---|---|--|
| | <input type="checkbox"/> Clinical outcome assessment (COA) data, such as | |
| | <input type="checkbox"/> Patient reported outcome (PRO) | |
| | <input type="checkbox"/> Observer reported outcome (ObsRO) | |
| | <input type="checkbox"/> Clinician reported outcome (ClinRO) | |
| | <input type="checkbox"/> Performance outcome (PerfO) | |
| | <input type="checkbox"/> Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | |
| | <input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports | |
| | <input type="checkbox"/> Observational survey studies designed to capture patient experience data | |
| | <input type="checkbox"/> Natural history studies | |
| | <input type="checkbox"/> Patient preference studies (e.g., submitted studies or scientific publications) | |
| | <input checked="" type="checkbox"/> Other: (Emergency Investigational New Drug applications) | 13.3 |
| | <input type="checkbox"/> Patient experience data that were not submitted in the application, but were considered in this review: | |
| | <input type="checkbox"/> Input informed from participation in meetings with patient stakeholders | |
| | <input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports | |
| | <input type="checkbox"/> Observational survey studies designed to capture patient experience data | |
| | <input type="checkbox"/> Other: (Please specify) | |
| | <input type="checkbox"/> Patient experience data was not submitted as part of this application. | |

2 Therapeutic Context

2.1. Analysis of Condition

The 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. Most of the clinical descriptions are

based on variola major, the more serious form that was also more prevalent throughout most of the history of the disease, and that is also the focus of concerns regarding potential biothreat uses of variola virus. Mortality in variola major is commonly cited as about 30% but was reported to vary widely among outbreaks from as little as 5% to 40% or more.¹ In 1980, following an historic global campaign of surveillance and vaccination, the World Health Assembly declared smallpox eradicated – the only infectious disease to achieve this distinction.² Despite the eradication of naturally acquired smallpox, the disease remains a threat as variola virus could be developed as a bioterrorism agent. 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.³ 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. Due to the mortality and severe morbidity associated with smallpox, the World Health Organization (WHO) states that preparedness to deal with any kind of smallpox event – whether natural re-emergence, accidental or deliberate release of the live virus, or created through synthetic biology – requires global and national attention.⁴

Due to concerns regarding potential biothreat uses of variola virus, a specific unmet medical need exists for effective antiviral regimens for subjects who develop smallpox disease caused by variola virus because no approved regimens are available. Approval of tecovirimat would provide the first antiviral to address this unmet medical need.

In the current NDA, the Applicant seeks approval under the Animal Rule for tecovirimat for the treatment of adult and pediatric patients with human smallpox disease caused by variola virus.^{5,6}

2.2. Analysis of Current Treatment Options

There are no approved treatment options for human smallpox disease caused by variola virus.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This is the first marketing application for any product containing tecovirimat, a new molecular entity.

3.2. Summary of Presubmission/Submission Regulatory Activity

This section will summarize and focus only on the notable events which directly impacted the current tecovirimat NDA.

An Investigational New Drug application (IND) for tecovirimat was submitted on November 9, 2005 by SIGA Technologies, Inc. Fast track designation for tecovirimat for treatment of human smallpox disease caused by variola virus was granted on December 22, 2005. Orphan Designation for treatment of human smallpox disease caused by variola virus was granted on December 27, 2006.

Clinical protocols, animal protocols, and the development plan were reviewed by the Division throughout the tecovirimat development program, with feedback provided regarding issues of animal model selection, efficacy endpoints, trigger for treatment initiation, dose selection, treatment duration, treatment regimen, and clinical trial population for the Phase 3 safety study.

During the 2011 Antiviral Drugs Advisory Committee (AVDAC) meeting, the advisory committee agreed with the FDA's assessment that current lethal NHP models using variola virus are not consistently reproducible and do not mimic what is known about human smallpox disease. 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 a combination of other lethal animal models using surrogate orthopoxviruses (e.g. NHP studies with MPXV, rabbit studies with RPXV, mouse studies with ectromelia) 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. The Applicant focused on the NHP/MPXV animal model and the rabbit/RPXV animal model. In these animal studies, key study design issues were discussed by the Applicant and the Division and consensus was reached before these studies were conducted.

A Type A meeting was held on October 29, 2014 to discuss the Phase 3 clinical trial and the proposed registration plan to support the Applicant's proposed indication, treatment of patients with human smallpox disease caused by variola virus. The final Phase 3 clinical trial protocol design later submitted to the Division was determined to be acceptable.

Preliminary pre-NDA comments were provided on October 11, 2016 regarding the NDA preparation and submission strategy. One agreement resulting from the preliminary pre-NDA comments was that animal efficacy would focus on four NHP/MPXV studies (AP-09-026G, SR10-037F, SR10-038F, Study FY10-087) and two rabbit/RPXV studies (SR14-008F, SR13-025F), and that no further animal efficacy studies are required.

A pre-NDA meeting (teleconference) was held on February 6, 2017 to discuss the NDA preparation and submission strategy. One agreement resulting from the pre-NDA meeting was submitting Module 4 as a rolling NDA review.

Another pre-NDA meeting (teleconference) was held on August 11, 2017 to discuss the

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possibility of REMS, encourage submission of data to support pediatric dosing, provide general comments regarding draft labeling, and further discuss the NDA preparation and submission strategy.

The details of the milestone meetings can be found in the official meeting minutes archived in the Document Archiving, Reporting and Regulatory Tracking System (DARRTS). All previous reviews can also be accessed in DARRTS for additional information.

3.3. Foreign Regulatory Actions and Marketing History

At the time this review was finalized, tecovirimat has not been marketed in any country.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations and Surveillance (OSIS)

Inspection sites were selected from Study 008 as these contributed to the safety database for the proposed indication. A total of 3 sites were selected from the large number of sites per study based on high enrollment and/or protocol deviations and/or screen failure rate. All sites were domestic, as conducting Study 008 in the US only was assessed as appropriate for this development program.

The final reports from the clinical site inspections were pending at the time this review was finalized.

4.2. Product Quality

The commercial tecovirimat drug product is an immediate-release capsule containing 200 mg equivalent of the active ingredient (tecovirimat) in the form of tecovirimat monohydrate. The capsules include the following inactive ingredients: colloidal silicon dioxide, (b) (4) croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. (b) (4)

Over the course of its clinical development, a slightly different formulation was used in the Phase 1 trials (same excipients, slightly different amounts) relative to the 200 mg capsule formulation used in the Phase 3 trial and commercially. Tecovirimat capsule clinical supplies and stability lots were manufactured at the designated commercial manufacturing site, Catalent Pharma Solutions (Winchester, KY).

The container closure system was selected based on the drug product attributes required to

(b) (4). The bottle size was selected (b) (4) coil. The (b) (4) coil type was (b) (4). The long-term and accelerated stability data demonstrate that the packaging is appropriate to maintain the quality of the drug product.

Please refer to the CMC Reviews by Dr. Yushi Feng, Dr. Katherine Windsor, Dr. Iwona Weidlich, and Dr. Yang Zhao for further details on manufacturing processes, process controls, formulation specifications, and the adequacy of data provided to assure drug stability, strength, purity, and quality for tecovirimat. The final report from the inspection of the production facilities was not available at the time this review was finalized.

4.3. Clinical Microbiology

This section includes a brief summary of key tecovirimat nonclinical virology characteristics based on *in vitro* and *in vivo* assessments. Specific discussions of virology assessments conducted during the pivotal animal efficacy studies are provided in Sections 6 and 7 (efficacy).

During orthopox viral assembly, intracellular mature virus (IMV) particles are wrapped by a double-bilayer membrane to form intracellular enveloped virus (IEV) particles. Viral protein 37 (VP37) is one of multiple key proteins required for this step. Tecovirimat is a small molecule antiviral drug that targets the orthopoxvirus VP37 protein within an infected cell, ultimately resulting in inhibition of viral spread to uninfected cells.

In cell culture assays, tecovirimat has activity against a variety of orthopoxviruses, including two different isolates of VARV, with EC50 values of 9-68 nM. *In vivo* antiviral activity was demonstrated in several animal models evaluating different orthopoxvirus infections, including mice (vaccinia, cowpox, ectromelia viruses), rabbits (rabbitpox virus), golden ground squirrels (monkeypox virus), prairies dogs (monkeypox virus), and monkeys (monkeypox and variola viruses). Sections 6 and 7 detail the six pivotal animal efficacy trials: four using the NHP/MPXV model, and two using the rabbit/RPXV model.

(b) (4)

Please refer to Dr. Patrick Harrington's Clinical Virology review for additional details.

4.4. **Nonclinical Pharmacology/Toxicology**

This section summarizes the key findings from the pharmacology/toxicology discipline review. Please see the Pharmacology/Toxicology review by Drs. L. Peyton Myers and David McMillan for full details.

The oral bioavailability of tecovirimat was 45% in mice, 15% in rabbits, and 50% in NHPs. *In vitro* protein binding ranged from 77% to 96% in all species, including human.

Following an oral dose of ¹⁴C-tecovirimat in pigmented C57 mice, radioactivity was widely distributed. Tissues with the highest to lowest C_{max} values were bone marrow, liver, kidney, lung, pigmented skin, thyroid, bone, eye, testis, and brain. The presence of radioactivity in brain and testes indicated that ¹⁴C-tecovirimat derived radioactivity crossed the blood-brain and brain-testis barriers.

Tecovirimat was not associated with clinically relevant adverse effects on cardiovascular or respiratory endpoints evaluated in safety pharmacology studies.

Neurological adverse effects were identified in the maximum tolerated dose (MTD, 246-TX-015) study in dogs:

- Single dose oral administration at 300 mg/kg/day (n=2) resulted in seizures and death in the male dog.
- At 100 mg/kg/day x 7 days (n=2), the following findings were observed: salivation, licking, and twitching (male dog) and increased activity and tremors (female dog).
- At 30 mg/kg/day x 7 days (n=6), no neurologic findings were observed.
- Tecovirimat was detectable in the brain and cerebrospinal fluid (CSF) at all dose levels, indicating that tecovirimat crosses the blood-brain barrier in dogs.
- Based on these data, the Applicant assessed C_{max} 5,575 ng/mL as the maximum allowable exposure level for humans. The Phase 3 clinical trial (Study 008) included electroencephalogram (EEG) testing for subjects in the lead-in cohort and in the PK subset of the expanded study (see Section 8.5.3).

After the Study 246-TX-015 findings, the distribution of tecovirimat into the brain and CSF was evaluated in a 12-day oral toxicity study (246-TX-016) where 12 cynomolgus monkeys received 300 mg/kg/day for 12 days via oral (gavage). Although no clinical findings were observed, tecovirimat was detectable in the brain and CSF, indicating that tecovirimat crosses the blood-brain barrier in monkeys.

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There were no clinically relevant adverse effects observed in pivotal repeat-dose general toxicology studies, a male and female fertility study, embryofetal development studies, or a pre/post-natal development study.

Tecovirimat was not considered genotoxic based on negative results in the *in vitro* bacterial mutation assay, *in vitro* mammalian chromosome aberration assay, and *in vivo* rat micronucleus assay. As tecovirimat was not genotoxic and will be administered to humans for only 14 days, carcinogenicity studies were not required.

4.5. Clinical Pharmacology

This section summarizes the key findings from the clinical pharmacology discipline review, including highlights of pharmacokinetics (PK), pharmacodynamics (PD), and dose-response relationships that support dose selection. Please see the Clinical Pharmacology review by Dr. Su-Young Choi for full details.

4.5.1. Mechanism of Action

The mechanism of action of tecovirimat involves preventing the production of extracellular enveloped virus necessary for spread of orthopoxvirus infection.

4.5.2. Human Dose Selection

The results from the six pivotal animal efficacy trials, four using the NHP/MPXV model (Study AP-09-026G, Study SR10-037F, Study SR10-038F, and Study FY10-087) and two using the rabbit/RPXV model (Study SR14-008F and Study SR13-025F) formed the basis for selecting the 600 mg BID dose as well as the 14 day treatment duration studied in Trial 008, the Phase 3 clinical trial in healthy adults.

- In the NHP/MPXV model, 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. However, PK and efficacy were further characterized at 10 mg/kg in subsequent studies 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.
- In the rabbit/RPXV model, 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. However, PK and efficacy were further characterized at 40 mg/kg in subsequent studies 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.
- Exposures from the 10 mg/kg dose in the NHP/MPXV model were compared with exposures from the 40 mg/kg dose in the rabbit/RPXV model. To achieve the same efficacy of tecovirimat, a higher exposure of tecovirimat is needed in NHPs compared to rabbits (Table 2).

Table 2. Tecovirimat exposures in rabbits, NHPs, and humans

| | | 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, 56%) |
| | Rabbit (N=8) | 518 (204-1180, 57%) | 6771 (2349-14331, 53%) | 144 (28-325, 55%) |
| Steady state | Human (N=48) | 2106 (1120-4460, 33%) | 28791 (15504-73568, 35%) | 689 (2.5-1360, 38%) |
| | NHP (N=6) | 1403 (936-2010, 27%) | 13650 (6975-18614, 31%) | 156 (88.7-344, 56%) |
| | Rabbit (N=8) | 596 (319-1340, 49%) | 8025 (4480-19330, 55%) | 128 (25-386, 77%) |

Data are expressed as geometric mean values (range, %CV)

NHP – 10 mg/kg/day in infected animals (FY-10-087), 14th day of dosing; rabbit – 40 mg/kg/day 7th day of dosing (SR14-008); human- 600 mg under fed conditions, 14th day of dosing (Study 008).

Cmin is defined as the lowest concentration after the first Cmax

- Therefore, PK data from NHPs was primarily used to determine the human dose (Table 3).

Table 3. Tecovirimat exposures in NHPs and humans

| | | 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%) |
| | H/N ratio | 2.0 | 2.7 | 3.6 |
| Steady state | Human (N=48) | 2106 (1120-4460, 33%) | 28791 (15504-73568, 35%) | 689 (2.5-1360, 38%) |
| | NHP (n=6) | 1403 (936-2010, 27%) | 13650 (6975-18614, 31%) | 156 (88.7-344, 56%) |
| | H/N Ratio | 1.5 | 2.1 | 4.4 |

Data are expressed as geometric mean values (range, %CV); H/N, human-to-NHP

NHP – 10 mg/kg/day in infected animals (FY-10-087), 14th day of dosing; rabbit – 40 mg/kg/day 7th day of dosing (SR14-008); human- 600 mg under fed conditions, 14th day of dosing (Study 008).

Cmin is defined as the lowest concentration after the first Cmax

- The exposure-response data from these two animal models allowed for selection of a dosing regimen for humans that would provide exposures that exceed, by several-fold, those associated with the fully effective dose in animals.
- With the proposed dosing regimen, Cmax, AUC, and Cmin are approximately 2-fold, 2-fold, and 4-fold higher, respectively, in humans as compared to NHPs.
- The Agency's rationale for recommending evaluation of 600 mg BID in the Phase 3

clinical trial included the following considerations:

- The uncertainties involved in the animal models. These uncertainties are clearly reflected in the Animal Rule Guidance recommending that 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, and that variability of exposures in humans should be accounted for such that any low outlying values of exposure in humans will be greater than those associated with efficacy in animals.
- The currently available clinical PK data including the observed food effect. Tecovirimat exposure is reduced by approximately 40% in patients in fasted versus fed states. It would not be realistic to expect symptomatic smallpox patients to comply with food related dosing recommendations. The proposed dosing regimen still provides comparable exposures to 10mg/kg/day in NHPs (fully effective dose) under fasted conditions.
- The failure of initial dosing in the most critically ill EIND patients to achieve the targeted exposures that were projected from previously available dosing and exposure data.
- Tecovirimat's safety and tolerability profile based on the available clinical data.

Pediatric dosing regimens

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



(b) (4)

Based on the Office of Clinical Pharmacology (OCP) review team's updated population pharmacokinetic modeling and simulation (including data from SIGA-246-008 and SIGA-246-018), the Applicant's proposed dosing regimen would likely result in exposures ^{(b) (4)} than those observed in adult healthy volunteers receiving tecovirimat 600 mg BID.

Therefore, the OCP review team recommended the following dosing regimen based on their independent population pharmacokinetic analysis and simulation (Table 5).

Table 5. FDA Recommended Pediatric Dosing Regimen

| Weight (kg) | < 6 | 6 to < 13 | 13 to < 25 | 25 to < 40 | 40 and above |
|----------------|-----|--------------------|------------|------------|--------------|
| Dose (14 days) | | ^{(b) (4)} | 200 mg BID | 400 mg BID | 600 mg BID |

Applicant has agreed to conduct a human factors study to evaluate proposed doses that would require caregivers to subdivide a capsule (b) (4)

4.5.3. Pharmacokinetics

Absorption, Distribution, Metabolism, and Elimination

The pharmacokinetic properties of tecovirimat have been evaluated in healthy subjects. Following oral administration of tecovirimat under fed conditions at 600 mg (i.e., administered within 30 minutes after a full meal of moderate fat), tecovirimat reached peak plasma concentrations at about 4-6 hours post-dose. Tecovirimat capsules are recommended to be administered under fed conditions, and food increases tecovirimat exposure by approximately 33% at steady-state. Tecovirimat exposures are increased in a slightly less than proportional manner between 200 mg and 600 mg. The trend of exposure increasing in a less than dose proportional manner is more apparent above the clinical dose, 600 mg. Tecovirimat is approximately 80% bound to human plasma proteins.

The major metabolic pathway for tecovirimat is non-CYP mediated metabolism (by amide hydrolysis and deamination) with minor glucuronidation. The major metabolites (> 10% of parent drug's amount in plasma) are M4, TFMBA, and M5. Tecovirimat is a weak inducer of CYP3A and a weak inhibitor of CYP2C19 and CYP2C8.

Renal clearance is the major (73%) elimination pathway for the metabolites in humans. Biliary excretion is the major route of elimination for unchanged tecovirimat (23% as parent in feces). The median terminal half-life is approximately 21 hours.

Intrinsic Factors

- Renal Impairment

The PK of tecovirimat was studied in adults with mild, moderate, and severe renal impairment following a single dose of 600 mg, and in subjects with end stage renal disease (ESRD) requiring hemodialysis following a single dose of 600 mg prior to dialysis and following a single dose of 600 mg after dialysis. Tecovirimat pharmacokinetics were similar in subjects with mild or moderate renal impairment compared to subjects with normal renal function. In subjects with severe renal impairment, an approximately 33% lower C_{max} , but comparable AUC_t values, were observed as compared to subjects with normal renal function. However, C_{max} and AUC_{inf} values were 33% and 48% lower, respectively, in subjects with ESRD as compared to subjects with normal renal function. The lower exposures in subjects with ESRD were not due to dialysis as tecovirimat was not removed by hemodialysis. It is postulated that the altered drug absorption in subjects is due to an underlying disease (e.g., gastroparesis in diabetic patients) or

unexpected drug interactions with one or more concomitant medications in these subjects such as phosphate binders.

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

No adjustment in tecovirimat dose is recommended for subjects with mild, moderate or severe renal impairment or subjects with ESRD requiring hemodialysis.

- **Hepatic Impairment**

The PK of tecovirimat was studied with a single dose of 600 mg in adults with mild, moderate, and severe hepatic impairment (Child Pugh Class A, B, and C). The PK of tecovirimat were not significantly different in subjects with mild (CP-A), moderate (CP-B), and severe (CP-C) hepatic impairment as compared to subjects with normal hepatic function following the administration of a single dose of tecovirimat 600 mg.

No adjustment in tecovirimat dose is recommended for subjects with mild, moderate or severe hepatic impairment (Child Pugh Class A, B, or C).

- **Other intrinsic factors**

No dose adjustment is needed based on sex (male vs. female), race (White vs. Non-White), or weight. It is noted that weight is a significant covariate for the clearance of tecovirimat within the range observed in SIGA-246-008 (54 kg to 145 kg) and thus lower exposures are predicted in patients with higher body weight. However, the effect does not warrant a dose adjustment at this time until further information is collected on how the physiologic changes associated with obesity may impact tecovirimat PK.

Extrinsic Factors: Drug Interactions

Tecovirimat is a substrate for UGT1A1 and UGT1A4. Therefore, tecovirimat exposures can be increased or decreased by the concomitant use of strong UGT1A1/4 inhibitors or inducers. Tecovirimat is a weak inducer of CYP3A and weak inhibitor of CYP2C19 and CYP2C8. Therefore, it is recommended to monitor safety or efficacy of drugs that are sensitive substrates of CYP2C8, CYP2C19, and CYP3A4.

4.6. Devices and Companion Diagnostic Issues

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Not applicable

4.7. Consumer Study Reviews

Not applicable

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 6 contains a summary of the Phase 3 trial and pertinent Phase 1 trial with the proposed to-be-marketed dose that were submitted with this application.

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Table 6. Summary of Relevant Clinical Trials

| Trial Identity | Phase | Trial Design | Regimen | Study Population | No. of patients enrolled | Study Endpoint | No. of Centers and Countries |
|--|-------|--|---|------------------|--|----------------|------------------------------|
| Studies to Support Safety | | | | | | | |
| Study 008 | 3 | Randomized, double-blind, placebo-controlled trial with 4:1 randomization | Tecovirimat (600 mg BID) 14 days or placebo (PBO) 14 days | Healthy adults | 449 in total: 359 tecovirimat 90 PBO | Safety | 12 sites (in US) |
| Other Studies Pertinent to the Review of Safety | | | | | | | |
| Study 015 | 1 | Randomized, open-label, parallel, 3-arm, fixed-sequence, drug-drug interaction (DDI) study | <ul style="list-style-type: none"> • Arm 1 (CYP2C9 + CYP2C19 + CYP3A4): Probe substrates (flurbiprofen 50 mg, omeprazole 20 mg, and midazolam 2 mg) given alone and in combination with tecovirimat 600 mg BID • Arm 2 (CYP2C8): Probe substrate (repaglinide 2 mg) given alone and in combination with tecovirimat 600 mg BID • Arm 3 (CYP2B6): Probe substrate (bupropion 150 mg) given alone and in combination with tecovirimat 600 mg BID | Healthy adults | 78 in total: 24 - Arm 1 30 - Arm 2 24 - Arm 3 | Safety | 1 site (in US) |

The Applicant provided datasets, summaries of key safety events, narratives, and case report forms for these studies.

5.2. Review Strategy

The clinical efficacy review is based on the six pivotal animal efficacy trials: four using the non-human primate (NHP)/monkeypox virus (MPXV) model (Study AP-09-026G, Study SR10-037F, Study SR10-038F, and Study FY10-087), and two using the rabbit/rabbitpox virus (RPXV) model (Study SR14-008F and Study SR13-025F). The clinical reviewer along with the nonclinical, virology, and statistical reviewers collaborated extensively during the review process, and a number of analyses included in this review were performed by the nonclinical reviewer, Dr. L. Peyton Myers, the virology reviewer, Dr. Patrick Harrington, and the statistical reviewer, Dr. Wen Zeng. In addition, there were significant interactions with the clinical pharmacology, pharmacometrics, and chemistry manufacturing and controls reviewers. Their assessments are summarized in this document in the relevant sections, but complete descriptions of their findings are available in their respective discipline reviews.

For treatment studies, therapeutic intervention was defined as the initiation of the drug at the onset of clinically evident illness. In the NHP/MPXV model, the development of skin lesions was determined to be a consistent and reproducible trigger for treatment initiation. In the rabbit/RPXV model, the development of fever was determined to be a consistent and reproducible trigger for treatment initiation.

In both animal models, initiation of the drug at other later time-points (e.g. 24 hours after the onset of clinically evident illness) was also evaluated in the Applicant's treatment studies.

Only the primary efficacy endpoint, proportion of animals that survived to the pre-specified end-of-study, will be discussed in detail in this review, as survival is clearly related to the desired benefit in humans and satisfies one of the tenets of the Animal Rule. The primary efficacy endpoint analyses are accompanied by a discussion regarding virologic and nonclinical findings in animals that died prior to the pre-specified end-of-study. Detailed analyses of secondary endpoints will not be discussed as the clinical significance of extrapolating these exploratory secondary endpoints from animal studies to human disease is unclear.

The clinical safety review was primarily based on Study 008, a Phase 3 clinical trial in healthy adults. In addition, data from subjects in the Phase 1 drug-drug interaction (DDI) study 015 who received the dose and duration of the proposed to-be-marketed tecovirimat regimen were reviewed. Pooling of this Phase 1 DDI study with the Phase 3 safety study was not done because the trial design and conduct of these studies were different. Any notable findings that were not observed in, or differed from Study 008, are presented where applicable (see Section 8.5.8). JMP software was used to conduct the safety analyses presented in this review; any analyses performed by the Applicant or other members of the FDA review team will be labeled as such.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study AP-09-026G

6.1.1. Study Design

Overview and Objective

Study AP-09-026G was a randomized, double-blind, placebo-controlled study assessing the minimum effective therapeutic dose of oral tecovirimat Polyform I in cynomolgus monkeys infected with monkeypox virus (MPXV). The trial began on November 24, 2009 and was completed on June 22, 2011. Study AP-09-026G was conducted at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). Study AP-09-026G was conducted in accordance with Good Laboratory Practices (GLP).

Trial Design

The statistician randomly selected 27 healthy male cynomolgus monkeys of Mauritius descent from the USAMRIID colony that had successfully completed quarantine. Animals were randomized so that at least five animals/group were inoculated.

Cynomolgus monkeys not previously exposed to any orthopoxvirus were intravenously inoculated with 5.5×10^7 PFU of Zaire 79 strain of monkeypox on Day 0. Monkeys received tecovirimat at 0 (placebo), 0.3, 1, 3, and 10 mg/kg once daily by orogastric gavage beginning on the day lesions first appeared on an animal (Day 4 post-inoculation [PI]) and continued every 24 ± 2 hours for 14 consecutive days.

Reviewer Comment: Tecovirimat was initiated individually for each NHP when skin lesions were observed. In all NHPs, skin lesions were first identified at Day 4 PI.

Blood levels of tecovirimat were collected to establish the fully effective dose, i.e. the dose that achieved maximum efficacy (survival) and above which, no further increases in survival were observed. Survival was evaluated statistically for up to Day 23 post-inoculation (PI), although surviving NHPs were monitored for up to Day 42 PI. Viral DNA levels, skin lesions, clinical observations (vital signs, body weights, food consumption, and signs of illness), hematology and clinical chemistry, and gross and microscopic anatomic pathology were evaluated.

Please refer to Dr. L. Peyton Myers' nonclinical review and Dr. Patrick Harrington's virology review for complete details.

Study Endpoints

The primary efficacy endpoint is the proportion of animals that survived until Day 28 PI.

Mortality was assessed as unscheduled euthanasia prior to the pre-specified end-of-study. Mortality was based on prospectively defined criteria for euthanasia. To be declared moribund and meet the criteria for euthanasia, an animal must meet either of two criteria:

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- 1) Persistent prostration (for a period of 4 hours or longer) and unresponsive to gentle prodding through the bottom of the cage, OR
- 2) Persistent prostration (for a period of 4 hours or longer) but responsive to gentle prodding through the bottom of the cage, and has a rectal temperature of less than 34°C.

Reviewer Comment: The Applicant's analyses assessed the primary endpoint as survival at Day 23 PI, but the rationale was not specified. This reviewer's efficacy analyses and the statistical reviewer's efficacy analyses used the pre-specified primary endpoint, i.e. proportion of animals that survived until Day 28 PI (Tables 7 and 8), and is also consistent with the Statistical Analysis Plan.

Statistical Analysis Plan

Statistical Analysis Plan for this study described analysis through Day 28 PI. This review focuses on the analysis of the primary efficacy endpoint (i.e. proportion of animals that survived until Day 28 PI).

Please refer to Dr. Wen Zeng's statistics review for complete details.

Protocol Amendments

Seven protocol amendments were made. In amendment 1, the study was extended to Day 42 PI to enable additional data collection in surviving NHPs. In amendment 5, the post-mortem pathology procedures were revised to enable gram stains to be performed on tissues with evidence of secondary bacterial infection. None of the other amendments significantly impact the conduct of the trial.

6.1.2. Study Results

Efficacy Results – Primary Endpoint

Table 7 summarizes the proportion of animals that survived until Day 28 PI.

Table 7. Study AP-09-026G Primary Efficacy Results (intent to treat [ITT] population)

| Group | Tecovirimat regimen* | ID# | Date of death (Days PI) | Death rationale | Survival at Day 28 PI |
|-------|-------------------------|-----|-------------------------|--|-----------------------|
| 1 | Placebo | 2 | 15 | Euthanized in moribund condition; typical MPXV disease apparent | 0/7 (0%) |
| | | 3 | 15 | Found dead; typical MPXV disease apparent | |
| | | 11 | 14 | Died under anesthesia; typical MPXV disease apparent | |
| | | 13 | 9 | Euthanized in moribund condition; typical MPXV apparent | |
| | | 18 | 17 | Euthanized in moribund condition; typical MPXV disease apparent | |
| | | 23 | 17 | Euthanized in moribund condition; typical MPXV disease apparent | |
| | | 26 | 14 | Euthanized in moribund condition; typical MPXV disease apparent | |
| 2 | 0.3 mg/kg/day x 14 days | 7 | 15 | Euthanized in moribund condition; typical MPXV disease apparent | 1/5 (20%) |
| | | 8 | 18 | Euthanized in moribund condition; typical MPXV disease apparent | |
| | | 9 | 16 | Euthanized in moribund condition; typical MPXV disease apparent | |
| | | 20 | Survived | N/A | |
| | | 22 | 12 | Euthanized in moribund condition; typical monkeypox disease apparent | |
| 3 | 1 mg/kg/day x 14 days | 4 | 11 | Euthanized in moribund condition; typical MPXV disease apparent | 0/5 (0%) |
| | | 6 | 16 | Found dead; typical MPXV disease apparent | |
| | | 12 | 14 | Died under anesthesia; typical MPXV disease apparent | |
| | | 17 | 15 | Euthanized in moribund condition; typical MPXV disease apparent | |
| | | 19 | 27 | Found dead; typical MPXV disease was not apparent | |
| 4 | 3 mg/kg/day x 14 days | 14 | Survived | N/A | 4/5 (80%) |
| | | 15 | Survived | N/A | |
| | | 16 | Survived | N/A | |
| | | 25 | Survived | N/A | |
| | | 27 | 5 | Died under anesthesia; typical MPXV disease was not apparent | |
| 5 | 10 mg/kg/day x 14 days | 1 | Survived | N/A | 4/5 (80%) |
| | | 5 | Survived | N/A | |
| | | 10 | Survived | N/A | |
| | | 21 | 11 | Died under anesthesia; typical MPXV disease was not apparent | |
| | | 24 | Survived | N/A | |

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Mortality is assessed as unscheduled euthanasia prior to the end-of-study.

PFU, plaque forming units; PI, post-inoculation; NHP, non-human primate; MPXV, monkeypox virus (MPXV strain ZAI 1979-005; inoculum per animal = 5.5×10^7 PFU; administered via IV inoculation); N/A not applicable.

*Treatment was initiated individually for each NHP when skin lesions were observed. In all NHPs, skin lesions were first identified at Day 4 PI.

Reviewer Comment: A statistically significant treatment benefit over placebo for the primary endpoint of survival was shown for tecovirimat dosed at 3 or 10 mg/kg/day for 14 days starting at Day 4 after virus inoculation (i.e. after development of skin lesions). The fully effective dose of tecovirimat was 3 mg/kg (Table 8).

Table 8. Study AP-09-026G Primary Efficacy Results by Dose (ITT)

| Group (Dose) | Survival rate % (n/N) | Rate diff and exact 95% CI of (tecovirimat – placebo) | Boschloo’s 1-sided P-value | Barnard’s 1-sided P-value |
|---------------|-----------------------|---|----------------------------|---------------------------|
| 1 - Placebo | 0% (0/7) | | | |
| 2 - 0.3 mg/kg | 20% (1/5) | 20% (-23.8%, 71.6%) | 0.2541 | 0.1997 |
| 3 - 1 mg/kg | 0% (0/5) | 0% (-41.0, 52.2%) | NA | 1.0 |
| 4 - 3 mg/kg | 80% (4/5) | 80% (20.8%, 99.9%) | 0.0038 | 0.0038 |
| 5 - 10 mg/kg | 80% (4/5) | 80% (20.8%, 99.9%) | 0.0038 | 0.0038 |

Source: Analysis performed by Dr. Wen Zang, Statistics Reviewer

Additional analyses for animals that died or underwent euthanasia

Overall, 18 NHPs died or were euthanized at an unscheduled interval prior to the pre-specified end-of-study. MPXV-related findings that were observed prior to death or euthanasia included persistent prostration, unresponsiveness, decreased food consumption, no feces, not fully formed feces, dehydration, nasal discharge, lymphadenopathy, bleeding at sites other than the venipuncture site, and/or severe edema.

Of these 18 NHPs, 6 NHPs were euthanized that did not meet the protocol-defined euthanasia criteria; typical MPXV disease symptoms were present for each of these 6 NHPs; these 6 NHPs were euthanized for humane reasons (summarized below) as determined by the Study Director:

- Animal 18 (placebo) was euthanized on the afternoon of Study Day 17 (18 March 2010). The animal had profuse bleeding, a rectal body temperature of 33.4°C, and was severely unresponsive.
- Animal 23 (placebo) was euthanized on the afternoon of Study Day 17 (18 March 2010). The animal had severe edema, was unresponsive, and its rectal body temperature was 33.8°C.

- Animal 26 (placebo) was euthanized on Study Day 14 (15 March 2010). The animal had profuse bleeding of the nares and oral cavity, severe swelling, and a rectal body temperature of 33°C.
- Animal 22 (0.3 mg/kg) was euthanized on Study Day 12 (13 March 2010). The animal was severely swollen, its eyes were swollen shut, and its oral cavity was non-functional.
- Animal 4 (1 mg/kg) was euthanized on Study Day 11 (11 Dec 2009). Euthanasia criteria called for euthanasia when an animal was prostrate for 4 hours. This animal was leaning against the side of the cage, but fell over when prodded and was unable to rise. The entire oral cavity was sloughed off, it was bleeding from the face, palms and feet were sloughed, eyes were swollen shut, and trachea was almost swollen shut.
- Animal 17 (1 mg/kg) was euthanized on Study Day 15 (16 March 2010). The animal had sloughing of the mouth and edema, and the animal was not eating.

Reviewer Comment: These narratives were reviewed and discussed with Dr. L. Peyton Myers. Please refer to Dr. L. Peyton Myers' nonclinical review for complete details; I agree with Dr. Myers' assessment that these six NHPs were moribund, had MPXV-related disease, and that the decision to euthanize prior to meeting the euthanasia criteria was made by the Study Director for humane reasons.

Virology

Overall trends in whole blood viral DNA levels showed dose-related decreases (i.e. increasing tecovirimat doses correlated with lower viral DNA levels in blood). Whole blood viral DNA showed a statistically significant difference in the 3 and 10 mg/kg groups compared to placebo.

Viral DNA levels in tissues collected at necropsy were higher in animals that died or were euthanized due to moribund condition, relative to animals that survived to the pre-specified end-of-study.

For the three tecovirimat-treated NHPs whose deaths were assessed by investigators as not attributed solely to MPXV infection, 2 of these 3 NHPs had blood viral DNA levels >10,000 copies/mL (>LLOQ) at the last measurement prior to death, although the viral DNA levels throughout the infection trended similar or lower than those observed for other NHPs in the same tecovirimat dosing groups. In these three tecovirimat-treated NHPs, MPXV viral DNA was detected above the limit of quantitation in some tissues.

For these three tecovirimat-treated NHPs, the blood viral DNA levels at the last measurement prior to death, and the virology necropsy findings, are summarized below:

- Animal 19 (1 mg/kg; died on Day 27 PI): MPXV blood viral DNA was 1,024,000 copies/mL on Day 23 PI; at necropsy, MPXV viral DNA above the limit of quantitation was detected in 3/18 tissues.

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- Animal 27 (3 mg/kg; died on Day 5 PI): MPXV blood viral DNA was 76,200 copies/mL on Day 3 PI; at necropsy, MPXV viral DNA above the limit of quantitation was detected in 6/16 tissues.
- Animal 21 (10 mg/kg; died on Day 11 PI): MPXV blood viral DNA was 10,000 copies/mL on Day 9 PI; at necropsy, MPXV viral DNA above the limit of quantitation was detected in 6/17 tissues.

Reviewer Comment: Please refer to Dr. Patrick Harrington's virology review for complete details; I agree with Dr. Harrington's assessment that NHPs had virologic evidence of MPXV infection and tecovirimat treated NHPs in the 3 and 10 mg/kg groups had lower whole blood viral DNA levels, fewer histopathology tissues with detectable MPXV viral DNA, and lower MPXV viral DNA histopathology levels than placebo NHPs.

Pathology

- In all seven placebo NHPs, investigators assessed the major histopathologic findings as due to MPXV disease. Additionally, 3 of these 7 placebo NHPs had evidence of concurrent bacterial infection.
- The four NHPs in the 0.3 mg/kg cohort that were euthanized when moribund had major histopathologic findings assessed by investigators as due to MPXV disease. Additionally, 3 of these 4 NHPs had evidence of concurrent bacterial infection.
- All five NHPs in the 1 mg/kg cohort had major histopathologic findings assessed by investigators as due to MPXV disease. Additionally, 2 NHPs had evidence of concurrent bacterial infection. Animal 19 died under anesthesia on Day 27 PI. Investigators assessed the timing of death as unusual for MPXV disease, and the animal had no skin lesions at the time of death. Necropsy showed a complicating secondary bacterial infection, as well as other lesions that investigators assessed as unusual for MPXV. Investigators assessed these lesions as likely due to a combination of factors, including MPXV and bacterial infection.
- In the 3 mg/kg cohort, Animal 27 died on Day 5 PI. Although this NHP had histologic evidence of MPXV infection, the investigators stated that it is unusual for NHPs to die due to MPXV this early in the disease course. This NHP had a subdural hematoma, which was likely associated with the animal's death, and death was assessed by investigators as unrelated to MPXV infection.
 - Subdural hematoma was noted grossly and confirmed histologically, and was not considered to be related to MPXV infection. Although this may have been associated with the cause of death, there was no evidence of an underlying cause; the reason for this hemorrhage could not be determined histologically. Additionally, this animal died after undergoing anesthesia and, although it underwent anesthesia on previous occasions during the study, the investigators postulated that it is possible that death was associated to this particular anesthetic event. In cases of an anesthesia-related death, the investigators stated that there is often a lack of histopathologic evidence because acute hypoxia and/or metabolic abnormalities cause the animal to die before there is

enough time for any lesions to develop that can be detected by routine light microscopy.

- In the 10 mg/kg cohort, the investigators stated the cause of death of Animal 21 is unknown as the clinicopathologic findings attributed to MPXV were relatively mild in comparison to the other animals that succumbed at Day 11 PI. This animal died after undergoing anesthesia and, although it underwent anesthesia on previous occasions during the study, the investigators postulated that it is possible that death was associated to this particular anesthetic event. In cases of an anesthesia-related death, the investigators stated that there is often a lack of histopathologic evidence because acute hypoxia and/or metabolic abnormalities cause the animal to die before there is enough time for any lesions to develop that can be detected by routine light microscopy. The investigators stated that the histologic lesions interpreted to be related to MPXV in this animal were unusual in character. On Day 11 PI, the investigators stated that lesions attributed to MPXV infection are usually necrotizing; however, the lesions in this animal were subacute to chronic and very mild in severity. The investigators stated that it is possible that the test article altered the disease course in this animal, allowing for the development of atypical lesions (less severe and non-necrotizing) at this time point post-infection.
- Four out of five (4/5) animals in the 10 mg/kg group, 4/5 animals in the 3 mg/kg group, and 1/5 animals in the 0.3 mg/kg group survived to Day 42 PI. According to investigators, tecovirimat-treated animals that survived and were euthanized at the end of the study (n=9) had chronic lesions often observed in NHPs that survive MPXV infection.

Reviewer Comment: Please refer to Dr. L. Peyton Myers' nonclinical review for complete details; I agree with Dr. Myers' assessment that, unless specified otherwise, these pathology findings are consistent with MPXV-related disease.*

**Although there were three tecovirimat-treated NHPs [Animal 19 (1 mg/kg); Animal 27 (3 mg/kg); Animal 21 (10 mg/kg)] whose deaths were assessed by investigators as not attributed solely to MPXV infection, I agree with the assessment that it is difficult to definitively exclude a contribution of MPXV to these animals' morbidity that eventually resulted in deaths. Therefore, the primary efficacy analysis was performed using the intent-to-treat population as this approach provides the most conservative estimate of efficacy (Tables 7 and 8).*

Reviewer Summary: In Study AP-09-026G, it was determined that skin lesions were a consistent and reproducible trigger for treatment initiation at the onset of clinically evident illness. In the subsequent NHP-MPXV studies (Sections 6.2-6.4), Day 4 PI (i.e. time-point when NHPs developed skin lesions) was used for treatment initiation. This approach for treatment initiation based on the onset of clinically evident illness is consistent with the Animal Rule.

In Study AP-09-026G, it was determined that the fully effective dose of tecovirimat, when initiated on the day of lesion onset in each animal, was 3 mg/kg. In the subsequent NHP-MPXV studies (Sections 6.2-6.4), 10 mg/kg was selected to provide exposures that are several-fold

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higher than the exposures associated with the fully effective dose. This approach for dose selection is consistent with the Animal Rule.

6.2. Study SR10-037F

6.2.1. Study Design

Overview and Objectives

Study SR10-037F was a randomized, double-blind, placebo-controlled study assessing the effect of delayed tecovirimat treatment on efficacy following intravenous (IV) MPXV challenge. The trial began on July 23, 2010 and was completed on January 4, 2011. Study SR10-037F was conducted at (b) (4)

Trial Design

Twenty-one (21) randomly selected healthy male and female cynomolgus monkeys were assigned to four groups according to weight and sex.

Cynomolgus monkeys negative for poxvirus antigens were intravenously infected with 5.0×10^7 PFU of Zaire strain (V79-I-005; NR-523) of MPXV on Day 0. Group 1 received placebo. Groups 2, 3, and 4 received tecovirimat (10 mg/kg) once daily by orogastric gavage for 14 consecutive days beginning on Days 4, 5, and 6 PI, respectively. To accommodate blinding, Groups 2, 3, and 4 were administered placebo on non-tecovirimat dose days during the treatment period.

Reviewer Comment: In Study SR10-037F, 10 mg/kg was selected to provide exposures that are several-fold higher than the exposures associated with the fully effective dose. The study objective was to identify the maximum delay post-viral inoculation at which tecovirimat (10 mg/kg/day x 14 days) was effective at preventing mortality. Treatment initiated at Day 4 PI (Group 2) corresponds to the time-point when NHPs develop skin lesions; treatment initiated at Day 5 PI (Group 3) and Day 6 PI (Group 4) correspond to delayed treatment in the NHP-MPXV model.

Blood levels of tecovirimat were collected. Survival was evaluated to Day 56 PI. Viral DNA levels, skin lesions, clinical observations (vital signs, body weights, food consumption, and signs of illness), hematology and clinical chemistry, and gross and microscopic anatomic pathology were evaluated.

Please refer to Dr. L. Peyton Myers' nonclinical review and Dr. Patrick Harrington's virology review for complete details.

Study Endpoints

The primary efficacy endpoint is the proportion of animals that survived until Day 56 PI.

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Mortality was assessed as unscheduled euthanasia prior to the pre-specified end-of-study. Mortality was based on prospectively defined criteria for euthanasia. Euthanasia was based on clinical criteria that included significant weight loss, numerous skin lesions, elevated body temperature, anorexia, inability to eat or drink, dehydration, and lethargy. The decision to euthanize a given animal prior to scheduled termination (Day 56 PI) was determined through consultation between the Study Director and the veterinary staff and was based on the severity of the clinical observations in combination with significant weight loss, severity of skin lesions, elevated body temperature, and anorexia.

The pre-specified primary endpoint, survival at Day 56 PI, was used in this reviewer’s efficacy analyses (Table 9) and in Dr. Wen Zeng’s efficacy analyses (Table 10).

Statistical Analysis Plan

Statistical Analysis Plan for this study described analysis through Day 56 PI. This review focuses on the analysis of the primary efficacy endpoint (i.e. proportion of animals that survived until Day 56 PI).

Please refer to Dr. Wen Zeng’s statistics review for complete details.

Protocol Amendments

Three protocol amendments were made. None of these changes significantly impact the conduct of the trial.

6.2.2. Study Results

Efficacy Results - Primary Endpoint

Table 9 summarizes the proportion of animals that survived until Day 56 PI.

Table 9. Study SR10-037F Primary Efficacy Results (ITT)

| Group | Tecovirimat regimen* | ID# | Date of death (Days PI) | Death rationale | Survival at Day 56 PI |
|-------|--|------|-------------------------|---|-----------------------|
| 1 | Placebo | 4762 | 7 | Euthanized in moribund condition; typical MPXV disease apparent | 0/3 (0%) |
| | | 4763 | 7 | Found dead; typical MPXV disease apparent | |
| | | 4765 | 10 | Euthanized in moribund condition; typical MPXV disease apparent | |
| 2 | 10 mg/kg/day x 14 days; Initiated at Day 4 PI | 4756 | Survived | N/A | 5/6 (83%) |
| | | 4757 | Survived | N/A | |
| | | 4760 | Survived | N/A | |
| | | 4767 | Survived | N/A | |
| | | 4768 | 12 | Found dead; typical MPXV disease apparent | |
| | | 4769 | Survived | N/A | |
| 3 | 10 mg/kg/day | 4758 | Survived | N/A | 5/6 (83%) |

| | | | | | |
|---|--|------|----------|--|-----------|
| | x 14 days; Initiated at Day 5 PI | 4759 | Survived | N/A | |
| | | 4761 | Survived | N/A | |
| | | 4766 | Survived | N/A | |
| | | 4771 | Survived | N/A | |
| | | 4773 | 8 | Euthanized in moribund condition; typical MPXV disease apparent | |
| 4 | 10 mg/kg/day x 14 days; Initiated at Day 6 PI | 4754 | Survived | N/A | 3/6 (50%) |
| | | 4755 | Survived | N/A | |
| | | 4764 | 12 | Found dead; typical MPXV disease was not apparent | |
| | | 4770 | 11 | Euthanized in moribund condition; typical MPXV disease apparent | |
| | | 4772 | 8 | Euthanized in moribund condition; typical MPXV disease apparent | |
| | | 4774 | Survived | N/A | |

Mortality is assessed as unscheduled euthanasia prior to the end-of-study.

PFU, plaque forming units; PI, post-inoculation; NHP, non-human primate; MPXV, monkeypox virus (MPXV strain ZAI 1979-005; inoculum per animal = 5×10^7 PFU; administered via IV inoculation); N/A not applicable. Day 4 PI corresponds to onset of skin lesions.

Reviewer Comment: A statistically significant treatment benefit over placebo for the primary endpoint of survival was shown for tecovirimat dosed at 10 mg/kg/day for 14 days starting at Day 4 or Day 5 after virus inoculation (Table 10).

Table 10. Study SR10-037F Primary Efficacy Results (10 mg/kg) by Treatment Initiation date

| Group (Treatment Initiation, Days PI) | Survival rate % (n/N) | Rate diff and exact 95% CI of (tecovirimat – placebo) | Boschloo's 1-sided P-value | Barnard's 1-sided P-value |
|---------------------------------------|-----------------------|---|----------------------------|---------------------------|
| 1 - Placebo | 0% (0/3) | | | |
| 2 - Day 4 PI | 83% (5/6) | 83.3% (7.5%, 99.6%) | 0.0151 | 0.0151 |
| 3 - Day 5 PI | 83% (5/6) | 83.3% (7.5%, 99.6%) | 0.0151 | 0.0151 |
| 4 - Day 6 PI | 50% (3/6) | 50% (-28.3%, 90.2%) | 0.1231 | 0.1723 |

Source: Analysis performed by Dr. Wen Zang, Statistics Reviewer

Additional analyses for animals that died or underwent euthanasia

Overall, 8 NHPs died or were euthanized at an unscheduled interval prior to the pre-specified end-of-study. The most common finding prior to death or euthanasia was moderate to severe dehydration, which was seen in all 8 animals. All 8 animals were also observed to have mild to severe depression, described as a lack of responsiveness, and mildly to severely reduced food consumption. Other findings included weakness (manifested as trembling or incoordination), dyspnea, and nasal or ocular discharge.

Clinical Review
Kirk Chan-Tack, MD
NDA 208627
TPOXX (tecovirimat)

Reviewer Comment: These narratives were reviewed and discussed with Dr. L. Peyton Myers. Please refer to Dr. L. Peyton Myers' nonclinical review for complete details; I agree with Dr. Myers' assessment that these NHPs were moribund and had MPXV-related disease at the time of death (regardless of whether the animal was found dead [n=2] or met the euthanasia criteria [n=6]).

Virology

Overall trends showed that treated groups, especially when initiated at Day 4 or Day 5 PI, had lower whole blood viral DNA levels compared to placebo.

Consistent with the results from Study AP-09-026G, viral DNA levels in tissues collected at necropsy were higher in animals that died or were euthanized due to moribund condition, relative to animals that survived to the pre-specified end-of-study.

Reviewer Comment: Please refer to Dr. Patrick Harrington's virology review for complete details; I agree with Dr. Harrington's assessment that NHPs had virologic evidence of MPXV infection and that, when initiated at Day 4 or Day 5 PI, tecovirimat treated NHPs had lower whole blood viral DNA levels, fewer histopathology tissues with detectable MPXV viral DNA, and lower MPXV viral DNA histopathology levels than placebo NHPs.

Reviewer Comment: Please refer to Dr. L. Peyton Myers' nonclinical review for complete details; I agree with Dr. Myers' assessment that the pathology findings are consistent with MPXV-related disease.

6.3. Study SR10-038F

6.3.1. Study Design

Overview and Objectives

Study SR10-038F was a randomized, double-blind, placebo-controlled study assessing the effect of duration of tecovirimat treatment on efficacy following intravenous (IV) MPXV challenge. The trial began on October 8, 2010 and was completed on January 4, 2011. Study SR10-038F was conducted at (b) (4)

Trial Design

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

Cynomolgus monkeys negative for poxvirus antigens were intravenously infected with 5.0×10^7 PFU of Zaire strain (V79-I-005; NR-2324) of MPXV on Day 0. Group 1 received placebo. Groups 2, 3, and 4 received tecovirimat (10 mg/kg) once daily by orogastric gavage for 3, 5, 7, or 10 consecutive days beginning on Day 4 PI. To accommodate blinding, Groups 2, 3, and 4 were administered placebo on non-tecovirimat dose days during the treatment period.

Clinical Review
Kirk Chan-Tack, MD
NDA 208627
TPOXX (tecovirimat)

Reviewer Comment: The study objective was to identify the minimum treatment duration at which tecovirimat (10 mg/kg/day, initiated at Day 4 PI) was effective at preventing mortality. As a 14-day treatment duration was shown to be effective in Study AP-09-026G and Study SR10-037F, the duration of treatment evaluated in Study SR10-038F ranged from 3 to 10 days.

Blood levels of tecovirimat were collected. Survival was evaluated to Day 28 PI. Viral DNA levels, skin lesions, clinical observations (vital signs, body weights, food consumption, and signs of illness), hematology and clinical chemistry were evaluated. Gross and microscopic anatomic pathology were not collected. Necropsies were not performed and tissues were not saved for histopathology or for assessing viral DNA in tissues.

Please refer to Dr. L. Peyton Myers' nonclinical review and Dr. Patrick Harrington's virology review for complete details.

Study Endpoints

The primary efficacy endpoint is the proportion of animals that survived until Day 28 PI.

Mortality was assessed as unscheduled euthanasia prior to the pre-specified end-of-study. Mortality was based on prospectively defined criteria for euthanasia. Criteria for euthanasia included significant weight loss, numerous skin lesions, elevated body temperature, anorexia, inability to eat or drink, dehydration, and lethargy. The decision to euthanize a given animal prior to scheduled termination (Day 28 PI) was determined through consultation between the Study Director and the veterinary staff and was based on the severity of the clinical signs.

The pre-specified primary endpoint, survival at Day 28 PI, was used in this reviewer's efficacy analyses (Table 11) and in Dr. Wen Zeng's efficacy analyses (Table 12).

Statistical Analysis Plan

Statistical Analysis Plan for this study described analysis through Day 28 PI. This review focuses on the analysis of the primary efficacy endpoint (i.e. proportion of animals that survived until Day 28 PI).

Please refer to Dr. Wen Zeng's statistics review for complete details.

Protocol Amendments

Two protocol amendments were made. None of these changes significantly impact the conduct of the trial.

6.3.2. Study Results

Efficacy Results - Primary Endpoint

Table 11 summarizes the proportion of animals that survived until Day 28 PI.

Table 11: Study SR10-038F Primary Efficacy Results (ITT)

| Group | Tecovirimat regimen* | ID# | Date of death (Days PI) | Death rationale | Survival at Day 28 PI |
|-------|------------------------|------|-------------------------|--|-----------------------|
| 1 | Placebo | 4803 | 13 | Euthanized in moribund condition; typical MPXV disease apparent | 1/4 (25%) |
| | | 4814 | Survived | N/A | |
| | | 4815 | 10 | Euthanized in moribund condition; typical MPXV disease apparent | |
| | | 4821 | 11 | Euthanasia was intended (due to moribund condition; typical MPXV disease apparent) but NHP died under anesthesia for terminal blood collection | |
| 2 | 10 mg/kg/day x 3 days; | 4801 | Survived | N/A | 2/4 (50%) |
| | | 4808 | 16 | Euthanized in moribund condition; typical MPXV disease apparent | |
| | | 4812 | Survived | N/A | |
| | | 4818 | 14 | Euthanized in moribund condition; typical MPXV disease apparent | |
| 3 | 10 mg/kg/day x 5 days | 4799 | Survived | N/A | 6/6 (100%) |
| | | 4805 | Survived | N/A | |
| | | 4809 | Survived | N/A | |
| | | 4816 | Survived | N/A | |
| | | 4817 | Survived | N/A | |
| | | 4823 | Survived | N/A | |
| 4 | 10 mg/kg/day x 7 days | 4800 | Survived | N/A | 6/6 (100%) |
| | | 4802 | Survived | N/A | |
| | | 4806 | Survived | N/A | |
| | | 4807 | Survived | N/A | |
| | | 4811 | Survived | N/A | |
| | | 4822 | Survived | N/A | |
| 5 | 10 mg/kg/day x 10 days | 4804 | Survived | N/A | 4/5 (80%) |
| | | 4810 | Survived | N/A | |
| | | 4813 | Survived | N/A | |
| | | 4819 | 11 | Euthanized in moribund condition; typical MPXV disease apparent | |
| | | 4820 | Survived | N/A | |

Mortality is assessed as unscheduled euthanasia prior to the end-of-study.

PFU, plaque forming units; PI, post-inoculation; NHP, non-human primate; MPXV, monkeypox virus (MPXV strain ZAI 1979-005; inoculum per animal = 5×10^7 PFU; administered via IV inoculation); N/A not applicable.

*Treatment was initiated on Day 4 PI; Day 4 PI corresponds to onset of skin lesions.

Reviewer Comment: A statistically significant treatment benefit over placebo for the primary endpoint of survival was shown for tecovirimat dosed at 10 mg/kg/day for 5 or 7 days starting at Day 4 after virus inoculation.

Reviewer Comment: A statistically significant treatment benefit over placebo for the primary endpoint of survival was shown for tecovirimat dosed at 10 mg/kg/day for 5 or 7 days starting at Day 4 after virus inoculation (Table 12).

Table 12: Study SR10-038F Primary Efficacy Results (10 mg/kg) by Treatment Duration (ITT)

| Group (Treatment Duration) | Survival rate % (n/N) | Rate diff and exact 95% CI of (tecovirimat – placebo) | Boschloo’s 1-sided P-value | Barnard’s 1-sided P-value |
|----------------------------|-----------------------|---|----------------------------|---------------------------|
| 1 - Placebo | 25% (1/4) | | | |
| 2 - 3 days | 50% (2/4) | 25% (-51.0%, 83.0%) | 0.3633 | 0.3633 |
| 3 - 5 days | 100% (6/6) | 75% (8.1%, 99.4%) | 0.0133 | 0.0133 |
| 4 - 7 days | 100% (6/6) | 75% (8.1%, 99.4%) | 0.0133 | 0.0133 |
| 5 - 10 days | 80% (4/5) | 55% (-20.9%, 93.7%) | 0.0962 | 0.0962 |

Source: Analysis performed by Dr. Wen Zang, Statistics Reviewer

Additional analyses for animals that died or underwent euthanasia

Overall, 6 NHPs died or were euthanized at an unscheduled interval prior to the pre-specified end-of-study. The most common findings prior to death or euthanasia were dehydration, dyspnea, depression (described as a lack of responsiveness), weakness (manifested as decreased activity and/or uncontrolled trembling), edema, nasal discharge, and reduced food consumption.

Reviewer Comment: These narratives were reviewed and discussed with Dr. L. Peyton Myers. Please refer to Dr. L. Peyton Myers’ nonclinical review for complete details; I agree with Dr. Myers’ assessment that these NHPs were moribund and had MPXV-related disease at the time of death (regardless of whether the animal met the euthanasia criteria [n=5] or died under anesthesia [n=1]).

Virology

Overall, trends in blood viral DNA levels indicated that tecovirimat treatment duration longer than 3 days showed more antiviral activity; blood viral DNA levels over time were similar in the 5-day, 7-day, and 10- day groups, and were lower than those in the placebo and 3-day groups. Across all groups, there was also a trend toward higher viral DNA levels in NHPs that underwent early euthanasia compared to those that survived to the end of the study.

Reviewer Comment: Please refer to Dr. Patrick Harrington’s virology review for complete details; I agree with Dr. Harrington’s assessment that NHPs had virologic evidence of MPXV infection and that, overall, tecovirimat treated NHPs in the 5, 7, and 10-day groups had lower whole blood viral DNA levels than placebo NHPs.

6.4. Study FY10-087

6.4.1. Study Design

Overview and Objectives

Study FY10-087 was a randomized, placebo-controlled study assessing tecovirimat PK parameters in NHPs, infected intravenously with MPXV. Tecovirimat (3, 10, or 20 mg/kg) or placebo was initiated on Day 4 PI. The trial began on August 6, 2010 and was completed on October 17, 2010. Study FY10-087 was conducted at [REDACTED] (b) (4)

Trial Design

Twenty-eight (28) healthy male and female cynomolgus monkeys were assigned to four groups according to weight and sex.

Cynomolgus monkeys negative for poxvirus antigens were intravenously infected with 5.0×10^7 PFU of Zaire strain (V79-I-005; NR-2324) of MPXV on Day 0. Monkeys received tecovirimat at 0 (placebo), 3, 10, and 20 mg/kg once daily by orogastric gavage beginning on Day 4 PI and continued every 24 ± 2 hours for 14 consecutive days. This study was not blinded.

Reviewer Comment: The study objective was to evaluate the pharmacokinetics of tecovirimat, including evaluating doses that exceeded the fully effective dose (3 mg/kg) by several-fold.

Blood levels of tecovirimat were collected. Survival was evaluated to Day 28 PI. Viral DNA levels, skin lesions, clinical observations (vital signs, body weights, food consumption, and signs of illness), hematology and clinical chemistry were evaluated. Gross and microscopic anatomic pathology were not collected. Necropsies were not performed and tissues were not saved for histopathology or for assessing viral DNA in tissues.

Please refer to Dr. L. Peyton Myers' nonclinical review and Dr. Patrick Harrington's virology review for complete details.

Study Endpoints

The primary efficacy endpoint is the proportion of animals that survived until Day 28 PI.

Mortality was assessed as unscheduled euthanasia prior to the pre-specified end-of-study. Mortality was based on prospectively defined criteria for euthanasia. Euthanasia due to moribund conditions included the following: (1) demonstrating seizures, severe depression or coma; (2) respiratory distress or severe dyspnea; (3) persistent recumbency and weakness; (4) unresponsiveness to touch or external stimuli; (5) body weight loss >20% over a 7-day period, or; (6) any combination of these observations. The study director was responsible for making decisions regarding euthanasia of moribund NHPs.

Clinical Review
 Kirk Chan-Tack, MD
 NDA 208627
 TPOXX (tecovirimat)

The pre-specified primary endpoint, survival at Day 28 PI, was used in this reviewer’s efficacy analyses (Table 13) and in Dr. Wen Zeng’s efficacy analyses (Table 14).

Statistical Analysis Plan

Statistical Analysis Plan for this study described analysis through Day 28 PI. This review focuses on the analysis of the primary efficacy endpoint (i.e. proportion of animals that survived until Day 28 PI).

Please refer to Dr. Wen Zeng’s statistics review for complete details.

Protocol Amendments

Three protocol amendments were made. In amendment 1, the location for implanting the temperature transponders was changed from the back of each shoulder to each thigh. None of these changes significantly impact the conduct of the trial.

6.4.2. Study Results

Efficacy Results - Primary Endpoint

Table 13 summarizes the proportion of animals that survived until Day 28 PI.

Table 13. Study FY10-087 Primary Efficacy Results (ITT)

| Group | Tecovirimat regimen* | ID# | Date of death (Days PI) | Death rationale | Survival at Day 28 PI |
|-------|------------------------|------|-------------------------|---|-----------------------|
| 1 | Placebo | 1001 | 12 | Euthanized in moribund condition; typical MPXV disease apparent | 0/6 (0%) |
| | | 1002 | 12 | Euthanized in moribund condition; typical MPXV disease apparent | |
| | | 1003 | 13 | Euthanized in moribund condition; typical MPXV disease apparent | |
| | | 1004 | 16 | Euthanized in moribund condition; typical MPXV disease apparent | |
| | | 1005 | 12 | Euthanized in moribund condition; typical MPXV disease apparent | |
| | | 1006 | 14 | Euthanized in moribund condition; typical MPXV disease apparent | |
| 2 | 3 mg/kg/day x 14 days | 2001 | Survived | N/A | 6/6 (100%) |
| | | 2002 | Survived | N/A | |
| | | 2003 | Survived | N/A | |
| | | 2004 | Survived | N/A | |
| | | 2005 | Survived | N/A | |
| | | 2006 | Survived | N/A | |
| 3 | 10 mg/kg/day x 14 days | 3001 | Survived | N/A | 6/6 (100%) |
| | | 3002 | Survived | N/A | |
| | | 3003 | Survived | N/A | |
| | | 3004 | Survived | N/A | |

| | | | | | |
|---|---------------------------|------|----------|-----|------------|
| | | 3005 | Survived | N/A | |
| | | 3006 | Survived | N/A | |
| 4 | 20 mg/kg/day x 14 days | 4001 | Survived | N/A | 6/6 (100%) |
| | | 4002 | Survived | N/A | |
| | | 4003 | Survived | N/A | |
| | | 4004 | Survived | N/A | |
| | | 4005 | Survived | N/A | |
| | | 4006 | Survived | N/A | |

Mortality is assessed as unscheduled euthanasia prior to the end-of-study.

PFU, plaque forming units; PI, post-inoculation; NHP, non-human primate; MPXV, monkeypox virus (MPXV strain ZAI 1979-005; inoculum per animal = 5×10^7 PFU; administered via IV inoculation); N/A not applicable.

*Treatment was initiated on Day 4 PI; Day 4 PI corresponds to onset of skin lesions.

Reviewer Comment: A statistically significant treatment benefit over placebo for the primary endpoint of mortality was shown for all treatment arms with tecovirimat dosed at 3, 10, or 20 mg/kg/day for 14 days starting at Day 4 after virus inoculation (Table 14).

Table 14. Study FY10-087 Primary Efficacy Results by Dose (ITT)

| Group (Dose) | Survival rate % (n/N) | Rate diff and exact 95% CI of (tecovirimat – placebo) | Boschloo's 1-sided P-value | Barnard's 1-sided P-value |
|--------------|-----------------------|---|----------------------------|---------------------------|
| 1 - Placebo | 0% (0/6) | | | |
| 2 - 3 mg/kg | 100% (6/6) | 100% (47.1%, 100%) | 0.0002 | 0.0002 |
| 3 - 10 mg/kg | 100% (6/6) | 100% (47.1%, 100%) | 0.0002 | 0.0002 |
| 4 - 20 mg/kg | 100% (6/6) | 100% (47.1%, 100%) | 0.0002 | 0.0002 |

Source: Analysis performed by Dr. Wen Zang, Statistics Reviewer

Additional analyses for animals that underwent euthanasia

Overall, 6 NHPs were euthanized at an unscheduled interval prior to the pre-specified end-of-study. The most common findings prior to unscheduled euthanasia included unresponsiveness, respiratory distress, rectal body temperature < 33.3°C, decreased food consumption, no feces, no urine output, and dehydration.

Reviewer Comment: These narratives were reviewed and discussed with Dr. L. Peyton Myers. Please refer to Dr. L. Peyton Myers' nonclinical review for complete details; I agree with Dr. Myers' assessment that these NHPs were moribund and had MPXV-related disease at the time of euthanasia.

Virology

Overall trends showed that treated groups had lower whole blood viral DNA levels compared to placebo. Group 1 (placebo) NHPs showed increases in blood viral DNA levels from Day 6 PI until end of life. All tecovirimat treatment groups (Groups 2-4) had gradual decreases in blood viral DNA levels from Day 6 PI onward; the rate of decline was not dose-dependent.

Reviewer Comment: Please refer to Dr. Patrick Harrington's virology review for complete details; I agree with Dr. Harrington's assessment that NHPs had virologic evidence of MPXV infection and that, overall, tecovirimat treated NHPs had lower whole blood viral DNA levels than placebo NHPs.

6.5. Study SR14-008F

6.5.1. Study Design

Overview and Objectives

Study SR14-008F was a randomized, double-blind, placebo-controlled study assessing the dose-response relationship between tecovirimat plasma exposure and efficacy in New Zealand White (NZW) rabbits intradermally-infected with a lethal dose of rabbitpoxvirus (RPXV). The trial began on February 20, 2015 and was completed on May 12, 2016. Study SR10-038F was conducted at (b) (4)

Trial Design

Fifty healthy (50) 16-week old NZW rabbits were randomized into five groups of 10 animals based on weight and sex.

All animals were challenged intradermally with RPXV (rabbitpox virus, Utrecht strain, Lot #090314-RPXV) at a target dose of 1,000 PFU on Day 0. Animals received tecovirimat at 0 (placebo), 20, 40, 80, and 100 mg/kg once daily by orogastric gavage beginning on Day 4 PI and for 14 consecutive days.

Reviewer Comment: In the rabbit-RPXV model, the development of fever was determined to be a consistent and reproducible trigger for treatment initiation. In the natural history study, fever occurred in all animals by Day 4 PI and therefore Day 4 PI was used in the Applicant's treatment studies as this time-point is consistent with treatment initiation following the onset of clinically evident illness.

Blood levels of tecovirimat were collected. Survival was evaluated to Day 30 PI. Viral DNA levels, skin lesions, clinical observations (vital signs, body weights, food consumption, and signs of illness), hematology and clinical chemistry were evaluated. Spleen and lung tissue were removed for PCR viral load, not for pathology examination. Microscopic anatomic pathology was not evaluated.

Please refer to Dr. L. Peyton Myers' nonclinical review and Dr. Patrick Harrington's virology review for complete details.

Study Endpoints

The primary efficacy endpoint is the proportion of animals that survived until Day 30 PI.

Mortality was assessed as unscheduled euthanasia prior to the pre-specified end-of-study. Mortality was based on prospectively defined criteria for euthanasia. Animals meeting any of the following 4 criteria were considered candidates for euthanasia:

1. Open mouth breathing.
2. Moribund/Persistent prostration and unresponsive to gentle prodding or noxious stimuli.
3. Weight loss greater than 20% from pre-challenge weight
4. At least 2 of the following:
 - o A respiration rate 75% lower or higher than the average rate observed during the pre-study acclimation period (confirmed by a second observation within 1 hour).
 - o Body temperature less than 37.2°C (99°F) (confirmed by a second reading 1 hour (±10 min.) later).
 - o Weight loss of greater than 15% from pre-challenge weight.

The decision to euthanize a given animal was determined by assessment of the severity of clinical signs and through consultation between the Study Director and the Veterinarian or qualified designee.

The pre-specified primary endpoint, survival at Day 30 PI, was used in this reviewer's efficacy analyses (Table 15) and in Dr. Wen Zeng's efficacy analyses (Table 16).

Statistical Analysis Plan

Statistical Analysis Plan for this study described analysis through Day 30 PI. This review focuses on the analysis of the primary efficacy endpoint (i.e. proportion of animals that survived until Day 30 PI).

Please refer to Dr. Wen Zeng's statistics review for complete details.

Protocol Amendments

Seven protocol amendments were made. None of these changes significantly impact the conduct of the trial.

6.5.2. Study Results

Efficacy Results - Primary Endpoint

Table 15 summarizes the proportion of animals that survived until Day 30 PI.

Table 15. Study SR14-008F Primary Efficacy Results (ITT)

| Group | Tecovirimat regimen* | ID# | Date of death (Days PI) | Death rationale | Survival at Day 30 PI |
|-------|----------------------|-----|-------------------------|---|-----------------------|
| 1 | Placebo | 934 | 7 | Found dead; typical RPXV disease apparent | 0/10 (0%) |

| | | | | | |
|---|-------------------------------|-----|----------|---|------------|
| | | 937 | 8 | Euthanized; typical RPXV disease apparent | |
| | | 951 | 10 | Found dead; typical RPXV disease apparent | |
| | | 952 | 6 | Found dead; typical RPXV disease apparent | |
| | | 953 | 6 | Euthanized; typical RPXV disease apparent | |
| | | 963 | 7 | Found dead; typical RPXV disease apparent | |
| | | 968 | 8 | Euthanized; typical RPXV disease apparent | |
| | | 972 | 7 | Euthanized; typical RPXV disease apparent | |
| | | 987 | 9 | Euthanized; typical RPXV disease apparent | |
| | | 990 | 5 | Found dead ^a | |
| 2 | 20 mg/kg/day x 14 days | 938 | Survived | N/A | 9/10 (90%) |
| | | 941 | Survived | N/A | |
| | | 957 | 14 | Euthanized; typical RPXV disease apparent | |
| | | 960 | Survived | N/A | |
| | | 962 | Survived | N/A | |
| | | 966 | Survived | N/A | |
| | | 973 | Survived | N/A | |
| | | 975 | Survived | N/A | |
| | | 979 | Survived | N/A | |
| | | 986 | Survived | N/A | |
| 3 | 40 mg/kg/day x 14 days | 935 | Survived | N/A | 9/10 (90%) |
| | | 936 | Survived | N/A | |
| | | 940 | Survived | N/A | |
| | | 944 | Survived | N/A | |
| | | 959 | 12 | Euthanized; typical RPXV disease apparent | |
| | | 970 | Survived | N/A | |
| | | 971 | Survived | N/A | |
| | | 974 | Survived | N/A | |
| | | 982 | Survived | N/A | |
| | | 983 | Survived | N/A | |
| 4 | 80 mg/kg/day x 14 days | 943 | Survived | N/A | 8/10 (80%) |
| | | 946 | Survived | N/A | |
| | | 947 | Survived | N/A | |
| | | 949 | Survived | N/A | |
| | | 950 | Survived | N/A | |
| | | 964 | Survived | N/A | |
| | | 976 | 9 | Euthanized; typical RPXV disease apparent | |
| | | 978 | Survived | N/A | |
| | | 985 | Survived | N/A | |
| | | 989 | 13 | Found dead ^b | |
| 5 | 120 mg/kg/day x 14 days | 939 | Survived | N/A | 8/10 (80%) |
| | | 942 | Survived | N/A | |
| | | 945 | 12 | Euthanized; typical RPXV disease apparent | |
| | | 956 | Survived | N/A | |
| | | 961 | Survived | N/A | |
| | | 967 | Survived | N/A | |

| | | | | | |
|--|--|-----|----------|---|--|
| | | 969 | Survived | N/A | |
| | | 977 | Survived | N/A | |
| | | 981 | Survived | N/A | |
| | | 984 | 9 | Euthanized; typical RPXV disease apparent | |

PFU, plaque forming units; PI, post-inoculation; ID, intradermal; RPXV, rabbitpox virus (Utrecht strain, Lot #090314-RPXV; inoculum per animal = 1000 PFU; administered via ID inoculation); N/A, not applicable.

*Treatment was initiated on Day 4 PI; Day 4 PI corresponds to onset of fever.

End-of-Study (i.e. scheduled euthanasia) was Day 30-31 PI; FD, found dead.

^aDeath assessed by study investigators as due possibly to complications from blood collection procedures.

^bCause of death inconclusive, but assessed by study investigators as unlikely to be severe RPXV disease.

Reviewer Comment: A statistically significant treatment benefit over placebo for the primary endpoint of mortality was shown for all treatment arms with tecovirimat dosed at 20, 40, 80, or 120 mg/kg/day for 14 days starting at Day 4 after virus inoculation. There was no statistical difference in the survival rate across treatment group (Table 16).

Table 16. Study SR14-008F Primary Efficacy Results by Dose (ITT)

| Group (Dose) | Survival rate % (n/N) | Rate diff and exact 95% CI of (tecovirimat – placebo) | Boschloo's 1-sided P-value | Barnard's 1-sided P-value |
|---------------|-----------------------|---|----------------------------|---------------------------|
| 1 - Placebo | 0% (0/10) | | | |
| 2 - 20 mg/kg | 90% (9/10) | 90% (50.3%, 99.8%) | 0.0 | 0.0 |
| 3 - 40 mg/kg | 90% (9/10) | 90% (50.3%, 99.8%) | 0.0 | 0.0 |
| 4 - 80 mg/kg | 80% (8/10) | 80% (41.4%, 97.5%) | 0.0001 | 0.0001 |
| 5 - 120 mg/kg | 80% (8/10) | 80% (41.4%, 97.5%) | 0.0001 | 0.0001 |

Source: Analysis performed by Dr. Wen Zang, Statistics Reviewer

Additional analyses for animals that were found dead or underwent euthanasia

Overall, 16 animals were found dead or euthanized at an unscheduled interval prior to the pre-specified end-of-study. The most common findings prior to death or euthanasia were depression/weakness (described as a lack of responsiveness and/or decreased activity), hunched posture, reduced water consumption, reduced food consumption, dehydration, changes in stool condition, decreased or fecal output, reaction at the inoculation sites, secondary lesions on the ears and the back, ocular or nasal discharge, increased lung sounds, dyspnea, increased respiration rate, hyperthermia or hypothermia, and weight loss.

The two animals (ID #990 [placebo], ID# 989 [80 mg/kg]) whose deaths were assessed by investigators as not attributed to RPXV infection are discussed below:

- Animal 990 (placebo): Death was assessed by study investigators as due possibly to complications from blood collection procedures. This animal had blood viral DNA levels >4,000 copies/mL (>LLOQ) at the last measurement prior to death, and viral DNA was detected above the limit of quantitation in lung and spleen.

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- Animal 989 (80 mg/kg): Cause of death was inconclusive, but assessed by study investigators as unlikely to be severe RPXV disease. This animal had blood viral DNA levels <4,000 copies/mL (<LLOQ) at the last measurement prior to death, and viral DNA was below the limit of quantitation in lung and spleen.

Reviewer Comment: These narratives were reviewed and discussed with Dr. L. Peyton Myers. Please refer to Dr. L. Peyton Myers' nonclinical review for complete details; I agree with Dr. Myers' assessment that, unless specified otherwise, these animals had RPXV-related disease at the time of euthanasia (regardless of whether the animal was found dead [n=6] or met the euthanasia criteria [n=10]).*

**Although there were two animals [Animal 990 (placebo); Animal 989 (80 mg/kg)] whose deaths were assessed by investigators as not attributed due to RPXV infection, the primary efficacy analysis was performed using the intent-to-treat population as this approach provides the most conservative estimate of efficacy.*

Virology

Overall trends showed that treated groups had lower whole blood viral DNA levels compared to placebo. The rate of decline was not dose-dependent.

Viral DNA levels in lung and spleen tissues collected at necropsy were lower among tecovirimat treated animals compared to placebo animals.

Reviewer Comment: Please refer to Dr. Patrick Harrington's virology review for complete details; I agree with Dr. Harrington's assessment that rabbits had virologic evidence of RPXV infection and that, overall, tecovirimat treated rabbits had lower whole blood viral DNA levels and lower tissue viral DNA levels than placebo rabbits.

Reviewer Summary: In Study SR14-008F, it was assessed that the fully effective dose of tecovirimat, when initiated on the day of fever onset in each animal, was 20 mg/kg. In the subsequent rabbit-RPXV study SR13-025F (Section 6.6), doses above 20 mg/kg were evaluated to provide exposures that are several-fold higher than the exposures associated with the minimum effective dose. This approach for dose selection is consistent with the Animal Rule.

The high survival rates across treatment groups precluded showing a dose-response relationship in this animal model.

6.6. Study SR13-025F

6.6.1. Study Design

Overview and Objectives

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Study SR13-025F was a randomized, double-blind, placebo-controlled study assessing the impact of rabbitpox virus (RPXV) infection on oral pharmacokinetics (PK) of tecovirimat in male and female New Zealand White (NZW) rabbits intradermally-infected with a lethal dose of rabbitpoxvirus (RPXV). The trial began on April 17, 2015 and was completed on May 11, 2016. Study SR10-025F was conducted at (b) (4)

Trial Design

Twenty four healthy (24) 16-week old NZW rabbits were randomized into three groups of 8 animals based on weight and sex.

All animals were challenged intradermally with RPXV (rabbitpox virus, Utrecht strain, Lot #090314-RPXV) at a target dose of 1,000 PFU on Day 0. Animals received tecovirimat at 40, 80, and 100 mg/kg once daily by orogastric gavage beginning on Day 4 PI and for 14 consecutive days.

Reviewer Comment: The study objective was to evaluate the pharmacokinetics of tecovirimat, including evaluating doses that exceeded the minimum effective dose (20 mg/kg) by several-fold.

Blood levels of tecovirimat were collected. Survival was evaluated to Day 18 PI. Viral DNA levels, skin lesions, clinical observations (vital signs, body weights, food consumption, and signs of illness), hematology and clinical chemistry were evaluated. Spleen and lung tissue were removed for PCR viral load, not for pathology examination. Microscopic anatomic pathology was not evaluated.

Please refer to Dr. L. Peyton Myers' nonclinical review and Dr. Patrick Harrington's virology review for complete details.

Study Endpoints

The primary efficacy endpoint is the proportion of animals that survived until Day 18 PI.

Mortality was assessed as unscheduled euthanasia prior to the pre-specified end-of-study. Mortality was based on prospectively defined criteria for euthanasia. The study protocol pre-specified that animals meeting any of the following 3 criteria would be euthanized:

1. Open mouth breathing.
2. Moribund/Persistent prostration and unresponsive to gentle prodding or noxious stimuli.
3. At least 2 of the following:
 - o A respiration rate 75% lower or higher than the average rate observed during the pre-study acclimation period (confirmed by a second observation within 1 hour).
 - o Body temperature less than 37.2°C (99°F) (confirmed by a second reading 1 hour (±15 min.) later).

- o Weight loss of greater than 15% from pre-challenge weight.

The decision to euthanize a given animal was determined by assessment of the severity of clinical signs and through consultation between the Study Director and the Veterinarian or qualified designee.

The pre-specified primary endpoint, survival at Day 18 PI, was used in this reviewer's efficacy analyses (Table 17) and in Dr. Wen Zeng's efficacy analyses (Table 18).

Statistical Analysis Plan

Statistical Analysis Plan for this study described analysis through Day 18 PI. This review focuses on the analysis of the primary efficacy endpoint (i.e. proportion of animals that survived until Day 18 PI).

Please refer to Dr. Wen Zeng's statistics review for complete details.

Protocol Amendments

Five protocol amendments were made. None of these changes significantly impact the conduct of the trial.

6.6.2. Study Results

Efficacy Results - Primary Endpoint

Table 17 summarizes the proportion of animals that survived until Day 18 PI.

Table 17. Study SR13-025F Primary Efficacy Results (ITT)

| Group | Tecovirimat regimen* | ID# | Survival at Day 18 PI |
|-------|-------------------------|---|-----------------------|
| 1 | 40 mg/kg/day x 14 days | 992, 994, 1001, 1005, 1011 ^a , 1012, 1017, 1022 | 7/8 (87.5%) |
| 2 | 80 mg/kg/day x 14 days | 993 ^b , 1000, 1002, 1006, 1014, 1019, 1020, 1023 | 7/8 (87.5%) |
| 3 | 120 mg/kg/day x 14 days | 995, 996, 999, 1003, 1015, 1016, 1018, 1021 | 8/8 (100%) |

PFU, plaque forming units; PI, post-inoculation; ID, intradermal; RPXV, rabbitpox virus (Utrecht strain, Lot #090314-RPXV; inoculum per animal = 1000 PFU; administered via ID inoculation); N/A, not applicable.

*Treatment was initiated on Day 4 PI; Day 4 PI corresponds to onset of fever.

End-of-Study (i.e. scheduled euthanasia) was Day 18 PI; FD, found dead.

^aAnimal 1011 (Group 1) was found dead (FD) on Day 16 PI; ^bAnimal 993 (Group 2) was found dead (FD) on Day 17 PI; all other animals survived until Day 18 PI.

Reviewer Comment: High survival rates occurred across all treatment arms with tecovirimat dosed at 40, 80, or 120 mg/kg/day for 14 days starting at Day 4 after virus inoculation. There was no statistically significant difference in the survival rate across treatment groups, regardless of whether analyses of the primary efficacy endpoint used the intent-to-treat population (survival: 88% vs. 88%. vs. 100%; see Tables 17 and 18) or used a population that excluded the 2 animals that died due to study conduct issues (survival: 100% vs. 100%. vs. 100%).

Table 18. Study SR13-025F Primary Efficacy Results by Dose (ITT)

| Group (Dose) | Survival rate % (n/N) | Exact 95% CI Two-sided Fisher exact P-value |
|---------------|--------------------------|--|
| 1 - 40 mg/kg | 87.5% (7/8) | 87.5% (47.4%, 99.7%) |
| 2 - 80 mg/kg | 87.5% (7/8) | 87.5% (47.4%, 99.7%) |
| 3 - 120 mg/kg | 100% (8/8) | 100% (63.1%, 100%) |

Source: Analysis performed by Dr. Wen Zang, Statistics Reviewer

Virology

All treatment groups appeared to reduce whole blood viral DNA levels; overall trends were not statistically different across treatment groups.

Viral DNA levels in lung and spleen tissues collected at necropsy were overall similar across treatment groups.

Reviewer Comment: Please refer to Dr. Patrick Harrington's virology review for complete details; I agree with Dr. Harrington's assessment that rabbits had virologic evidence of RPXV infection and that, overall, tecovirimat treated rabbits had reductions in whole blood viral DNA levels, as was observed in Study SR14-008F.

Reviewer Summary: In Study SR13-025F, the high survival rates across treatment groups precluded showing a dose-response relationship in this animal model.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The primary efficacy endpoint was proportion of animals that survived to the pre-specified end-of-study, as survival is clearly related to the desired benefit in humans and satisfies one of the tenets of the Animal Rule. As displayed in the tables below, survival in treated animals overall ranged from 80-100% when treatment was initiated at day 4 after virus inoculation.

Results from the NHP/MPXV efficacy studies are summarized describing survival rates by treatment arm (Table 19). A 14 day course of tecovirimat (10 mg/kg) is effective when treatment was initiated at day 4 after virus inoculation (i.e. the time-point when all animals had developed skin lesions). No placebo animals survived in these 3 studies.

Table 19. NHP/MPXV studies with tecovirimat 10 mg/kg x 14 days: Survival by Treatment Arm n (%)

| Study | Treatment Initiation (# of days after viral inoculation) | Tecovirimat x 14 days | Placebo x 14 days |
|------------|---|--------------------------|----------------------|
| AP-09-026G | Day 4 | 4/5 (80%) | 0/7 (0%) |
| SR10-037F | Day 4 | 5/6 (83%) | 0/3 (0%) |
| | Day 5* | 5/6 (83%) | |
| | Day 6* | 3/6 (50%) | |
| FY10-087 | Day 4 | 6/6 (100%) | 0/6 (0%) |

*These cohorts evaluated the effect of delayed treatment initiation on efficacy and were done for exploratory purposes.

Results from the rabbit/RPXV are summarized are summarized describing survival rates by treatment arm (Table 20). A 14 day course of tecovirimat (40 mg/kg) is effective when treatment was initiated at day 4 after virus inoculation (i.e. the time-point when all animals had developed fever). No placebo animals survived.

Table 20. Rabbit/RPXV studies with tecovirimat 40 mg/kg x 14 days: Survival by Treatment Arm n (%)

| Study | Treatment Initiation (# of days after viral inoculation) | Tecovirimat x 14 days | Placebo x 14 days |
|-----------|---|--------------------------|----------------------|
| SR14-008F | Day 4 | 9/10 (90%) | 0/10 (0%) |
| SR13-025F | Day 4 | 7/8 (88%) | - |

7.1.2. Secondary and Other Endpoints

Secondary endpoints from these animal efficacy studies are not discussed as the clinical significance of extrapolating these exploratory secondary endpoints from animal studies to human disease is unclear.

7.1.3. Subpopulations

Subpopulation analyses from these animal efficacy studies are not discussed as the clinical significance of extrapolating such analyses from animal studies to human disease is unclear.

7.1.4. Dose and Dose-Response

Dose-ranging studies were conducted in both NHP/MPXV and rabbit/RPXV animal models to identify the fully effective dose, i.e. the dose that achieved maximum efficacy (survival) and above which, no further increases in survival were observed.

In NHP/MPXV, 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 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.

In rabbit/RPXV, 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 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.

7.1.5. **Onset, Duration, and Durability of Efficacy Effects**

The goal of treatment of human smallpox is reduction in mortality. Therefore, in the Applicant's NHP/MPXV and rabbit/RPXV studies, mortality (based on prospectively defined euthanasia criteria) was 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 when tecovirimat was initiated at the onset of clinically established disease (i.e. at day 4 after virus inoculation) in these animal models.

7.2. **Additional Efficacy Considerations**

7.2.1. **Considerations on Benefit in the Postmarket Setting**

If there was a smallpox event – whether natural re-emergence, accidental or deliberate release of live variola virus, or created through synthetic biology – tecovirimat would be the first antiviral treatment regimen for patients with human smallpox disease caused by variola virus.

7.2.2. **Other Relevant Benefits**

Not applicable.

7.3. **Integrated Assessment of Effectiveness**

The efficacy of tecovirimat for the treatment of human smallpox infection under the Animal Rule has been established by the results from the six pivotal animal efficacy studies discussed in Section 6: four using the NHP/MPXV model (Study AP-09-026G, Study SR10-037F, Study SR10-038F, and Study FY10-087), and two using the rabbit/RPXV model (Study SR14-008F and Study SR13-025F).

Because smallpox is a potentially serious threat but does not occur naturally, clinical 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.^{5,6}

Because of the unique complexities of drug development in this area, extensive discussion with multiple stakeholders has occurred, including an FDA public workshop in 2009 and an FDA public Advisory Committee meeting in 2011.^{7,8} During the 2011 Antiviral Drugs Advisory Committee (AVDAC) meeting, the advisory committee agreed with the FDA's assessment that current lethal NHP models using variola virus are not consistently reproducible and do not mimic what is known about human smallpox disease. 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 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) 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.

Based on multiple discussions with stakeholders (including the aforementioned 2011 Antiviral Drugs Advisory Committee), the FDA 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 single orthopoxvirus animal model is known to be the best predictor of human responses to treatments for smallpox.

The Applicant focused on the NHP/MPXV animal model and the rabbit/RPXV animal model. In these animal studies, key study design issues were discussed by the Applicant and the Division and consensus was reached before these studies were conducted. The Agency concludes that the Applicant closely followed the FDA's recommendations and demonstrated a mortality benefit in the NHP/MPXV animal model and in the rabbit/RPXV animal model. In these NHP and rabbit studies, mortality (based on euthanasia criteria) was evaluated as the primary endpoint since mortality has been assumed to be the principal outcome of interest for human smallpox. Evaluation of the specific euthanasia criteria used in each study was done to help assure the clinical significance of a mortality-based primary endpoint.

For the NHP/MPXV model, the Applicant completed studies (randomized, placebo-controlled, double-blinded [in 3 of 4 studies], two of which were performed under Good Laboratory Practices [GLP]) in which tecovirimat was started at the time of lesion onset. 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 the NHP/MPXV model. 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

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10 mg/kg/day for 14 days. These studies also underwent evaluation by the Office of Scientific Investigations (OSI); OSI's inspection confirmed the data integrity of these studies. The Agency assessed that the NHP/MPXV model is sufficiently characterized for scientific regulatory purposes. The Agency also assessed that the studies summarized in this review constitute completion of the Applicant's NHP/MPXV program.

For the rabbit/RPXV model, the Applicant completed studies (randomized, placebo-controlled [in 1 of 2 studies], double-blinded, performed under GLP) in which tecovirimat was started at the time of fever onset. 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 Scientific Investigations (OSI); OSI's inspection confirmed the data integrity of these studies. The Agency assessed that the rabbit/RPXV model is sufficiently characterized for scientific regulatory purposes. The Agency also assessed that the studies summarized in this review constitute completion of the Applicant's rabbit/RPXV program.

The Applicant's NHP/MPXV and rabbit/RPXV studies evaluated and confirmed statistically significant treatment benefit using a primary efficacy endpoint that is clearly related to the desired benefit in humans.

Due to concerns regarding potential bioterror uses of variola virus, a specific unmet medical need exists for effective antiviral regimens for subjects who develop smallpox disease caused by variola virus because no approved regimens are available. Approval of tecovirimat would provide the first antiviral to address this unmet medical need.

I recommend approval of tecovirimat for the treatment of smallpox under the FDA's Animal Rule for treatment of human smallpox disease caused by variola virus infection. However, the uncertainties inherent to drug approval under the Animal Rule (e.g., that survival rates observed in the animal studies cannot be directly compared between studies and may not reflect the rates observed in clinical practice) should be clearly described in labeling.

8 Review of Safety

8.1. **Safety Review Approach**

The safety review focused on Study 008 as this Phase 3 clinical trial in healthy adults principally comprises the safety database for the proposed dose and duration. Unless otherwise specified, the analyses presented in this section were performed using the analysis datasets for Study 008. Data were analyzed with JMP software. Discrepancies between the FDA analyses and the Applicant's analyses were relatively minor and attributable to variable methods of pooling and subgroup analyses.

Seizure events were a focus of scrutiny during the safety review, prompted by the nonclinical signal in dogs. The safety review also focused on adverse drug reactions of interest, including rash, hepatic events, neuropsychiatric events, rhabdomyolysis, and pancreatitis.

Compliance with Good Clinical Practices

The pivotal Phase 3 safety trial was conducted under a US IND application and in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312).

The trial protocol, amendments and informed consent forms were reviewed and approved by independent ethics committees (IEC) or institutional review boards (IRB) before trial initiation. Investigators (or designees) were responsible for obtaining written informed consent from each individual prior to undertaking any study-related procedures. The FDA OSIS inspected selected clinical sites but the inspection reports were not available at the time this review was finalized (See Section 4.1). A detailed discussion of the OSI audit will be available in the Clinical Inspection Summary by Sharon Gershon.

Data Quality and Integrity: Sponsor's Assurance

The review team considered the Applicant's methods for assuring data quality and integrity to be adequate. These methods included investigator and study center staff training on the trial protocols and study-specific procedures, study site monitoring in accordance with ICH GCP guidelines, compliance audits of investigative sites, use of electronic case report forms (eCRFs), and use of data validation specifications along with manual data review. The Applicant reviewed eCRF data to verify protocol and GCP adherence, and to verify the data against source documentation. The Applicant confirmed that missing data, selected protocol deviations and other data inconsistencies were addressed prior to database finalization. Clinical laboratory data were transferred electronically to the Applicant using defined transfer specifications. The Applicant's lead clinical data associate completed the database.

Overview and Objectives

Study 008 (SIGA-246-008) is a completed Phase 3, randomized, double-blind, placebo-controlled, multicenter, trial assessing the antiviral safety, tolerability, and pharmacokinetics of

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14 days of tecovirimat (600 mg BID) treatment compared with 14 days of placebo treatment in healthy adults. The primary objectives of the trial are to evaluate the safety and tolerability of treatment with 14 days of tecovirimat (600 mg BID) in healthy adults.

The trial began on June 29, 2015 and completed on August 24, 2016. The last subject observation included in the NDA submission was made on June 5, 2017, at which point the database was finalized for safety analysis. Subjects were enrolled across 12 study sites in the US.

Trial Design

Healthy adults were randomized in a 4:1 ratio in a double-blind manner to receive either tecovirimat or matching placebo for 14 days. A placebo-controlled trial design was chosen to provide a clear assessment of tecovirimat's safety profile.

Men and non-pregnant/non-lactating women ≥ 18 years of age in good general health, without clinically significant medical history, and had not been hospitalized for a chronic medical condition in the last 2 years at screening were eligible for participation.

Subjects were ineligible if they had HIV, HBV or HCV infection, significant cardiac, pulmonary or psychiatric disease, bleeding disorder, angioedema in the past 3 years, seizure disorder, family history of idiopathic seizures, abnormal electroencephalogram, clinically significant electrocardiogram abnormality, malignancy, current drug or alcohol abuse in the past year, received immunizations/vaccines administered starting from 4 days before study drug dosing at Day 1 through Day 14, current clinically significant acute bacterial, fungal, or mycobacterial infection requiring systemic antibiotics, known chronic bacterial, mycobacterial, fungal, parasitic, or protozoal infection with the exception of clinically insignificant dermal infections, current clinically significant viral infection, known clinically significant chronic viral infection (e.g., human T-cell lymphotropic Virus I or II), received treatment with > 20 mg prednisone or equivalent dose or any immunosuppressant or immunomodulatory medication within the 3 months before Screening, or previously enrolled in any clinical study involving tecovirimat.

Subjects were also ineligible if they had been currently (as defined in the protocol) using any of the following: insulin, anticoagulants, anticonvulsants, methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan, atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, dronedarone, eplerenone, felodipine, nisoldipine, ticagrelor, vardenafil, sildenafil, budesonide, conivaptan, darifenacin, eletriptan, fluticasone, sirolimus, tolvaptan, triazolam, dihydroergotamine, ergotamine, probenecid, or quinidine.

Additionally, subjects were excluded if they had any of the following laboratory test results within 14 days before the first dose of study drug:

- **For Lead-in cohort only:** Estimated serum creatinine clearance (Cockcroft-Gault) < 80 mL/min
- Estimated serum creatinine clearance (Cockcroft-Gault) < 30 mL/min

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- Creatinine in males > 1.7 mg/dL and in females > 1.4 mg/dL (1.3 x ULN, central laboratory reference range)
- Hemoglobin ≤ 10% x LLN, central laboratory reference range
- White blood cell count not within the central laboratory reference range
- Absolute neutrophil count < 1,000 cells/mm³
- Platelets not within ± 10% of central laboratory reference range
- Alanine aminotransferase > 2 x ULN, central laboratory reference range
- Aspartate aminotransferase > 2 x ULN, central laboratory reference range
- Alkaline phosphatase > 20% above the upper central laboratory reference range
- For all subjects, hemoglobin A1c ≥ 7.0% (for diabetic subjects, this included those whose diabetes was diet controlled or who were taking oral hypoglycemics)
- Cholesterol ≥ 300 mg/dL and low-density lipoprotein ≥ 190 mg/dL

Study Endpoints

The primary endpoint was safety. The primary safety analysis was performed using the full analysis set (FAS), which included all subjects who received at least one dose of study medication.

Statistical Analysis Plan

There is no formal sample size calculation for this Phase 3 safety trial. The target enrollment of at least 422 subjects (338 subjects to receive tecovirimat and 84 subjects to receive placebo) met FDA’s recommendation for a minimum of a 300 subject safety database for treatment of patients with smallpox.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 21 describes the overall exposure to tecovirimat in the 12 studies that contribute to the primary safety database.

Table 21. Safety Population, Size and Denominators

| Primary Safety Database for Tecovirimat Individuals exposed to tecovirimat for the indication under review N= 2017 | | |
|--|-------------------------------------|--------------------|
| Clinical Trial Groups | Tecovirimat ^a (n=788) | Placebo (n=119) |
| Phase 1: Healthy Volunteers | 338 | 13 |
| Phase 2: Healthy Volunteers | 91 | 16 |
| Phase 3: Healthy Volunteers | 359 | 90 |

^a Total numbers include subjects who received lower than the to-be-marketed dose

Overall, a total of 437 healthy adult subjects received the proposed dose and duration of tecovirimat: 78 subjects in the Phase 1 drug-drug interaction (DDI) study 015 and 359 subjects in the Phase 3 safety study 008.

Reviewer Comment: See Section 8.5 for discussion of Study 015 findings. Pooling of this Phase 1 DDI study with the Phase 3 safety study was not done because the trial design and conduct of these studies were different.

8.2.2. Relevant characteristics of the safety population

Baseline characteristics for Study 008 are described below.

Table 22. Baseline Demographic Characteristics, Study 008

| Demographic Parameters | Tecovirimat (N=359) n (%) | Placebo (N=90) n (%) | Total (N=449) n (%) |
|-----------------------------------|---------------------------------|----------------------------|---------------------------|
| Sex | | | |
| Male | 148 (41%) | 36 (40%) | 184 (41%) |
| Female | 211 (59%) | 54 (60%) | 265 (59%) |
| Age | | | |
| Mean years (SD) | 40 (15.7) | 42 (15.9) | 41 (15.7) |
| Median (years) | 38 | 41 | 39 |
| Min, max (years) | 18, 79 | 18, 80 | 18, 80 |
| Age Group | | | |
| < 65 years | 323 (90%) | 79 (88%) | 402 (90%) |
| ≥ 65 years | 36 (10%) | 11 (12%) | 47 (10%) |
| Race | | | |
| White | 249 (69%) | 62 (69%) | 311 (69%) |
| Black | 101 (28%) | 26 (29%) | 127 (28%) |
| Asian | 3 (1%) | 1 (1%) | 4 (1%) |
| Other ¹ | 6 (2%) | 1 (1%) | 7 (2%) |
| Ethnicity: Hispanic/Latino | | | |
| Yes | 43 (12%) | 5 (6%) | 48 (11%) |
| No | 315 (88%) | 85 (94%) | 400 (89%) |
| Not disclosed | 1 (<1%) | 0 | 1 (<1%) |

¹Includes American Indian/Alaska Native, Hawaiian or Pacific Islander and other

Source: ADSL dataset

Reviewer Comment: The two treatment arms are well balanced with respect to age, race, sex, and ethnicity. Study 008 was conducted entirely in the US, which makes the data readily applicable to the US population. Subgroup analyses based on demographic factors will be presented in Section 8.6 of this review.

8.2.3. Adequacy of the safety database

The safety database is adequate to assess the safety of tecovirimat for the proposed dosage regimen and duration of treatment. Study 008 evaluated 359 subjects treated at the proposed dose and duration of tecovirimat. Study 008 meets FDA’s recommendation for a minimum of a 300 subject safety database for treatment of patients with smallpox. A database of at least 300

individuals is needed to rule out a 1% rate of a specific adverse reaction if that specific adverse reaction did not occur in the population studied.⁵

Patient Disposition

Of the 452 enrolled subjects, 449 were randomized to treatment groups and received at least one dose of study medication and were included in the safety population: 359 in the tecovirimat group and 90 in the placebo group (Table 23). Thirty subjects (7%) prematurely discontinued study treatment. Twenty five of the 30 subjects were in the tecovirimat group, and the reasons for premature discontinuation were AE (6 subjects), subject request (4 subjects), lost to follow up (6 subjects), protocol violation (4 subjects), inability to complete study procedures (1 subject), and other (4 subjects). In the placebo group, the reasons for premature discontinuation were AE (2 subjects), inability to complete study procedures (1 subject), and other (1 subject).

Table 23. Treatment-emergent AEs Reported in \geq 2% of Subjects, All Grade and All Causality, Study 008

| | Tecovirimat | Placebo |
|--|-------------|-----------|
| Randomized | 361 | 91 |
| Treated | 359 (100%) | 90 (100%) |
| Completed treatment | 334 (93%) | 85 (94%) |
| Discontinued treatment | | |
| Adverse event | 6 (2%) | 2 (2%) |
| Subject request | 4 (1%) | 0 |
| Lost to follow up | 6 (2%) | 0 |
| Protocol violation | 4 (1%) | 0 |
| Inability to complete study procedures | 1 (<1%) | 1 (1%) |
| Other* | 4 (1%) | 1 (1%) |

*Includes positive drug test at screening, non-compliance with study drug, sponsor request to withdraw subject

Source: ADSL, ADAE datasets

Reviewer Comment: Completion rates were high (\geq 93%) and comparable across treatment groups.

Protocol Violations/Deviations

A total of 97 important protocol deviations occurred in 92 subjects during the study. Six subjects had 2 deviations and the remainder had a single deviation. Dosing/Compliance (missed doses, diary and drug accountability discrepancies) were the most common deviations (n=62), followed by delayed signing of revised informed consent forms (n=10), receipt of prohibited concomitant medications (n=8), violations of inclusion/exclusion criteria (n=6), management not according to protocol (n=6), positive drug screen (n=4), and missed visit (n=1). These protocol violations had no bearing on the interpretability of the trial results.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No data quality or data integrity issues were identified. For Study 008, all narratives for deaths, SAEs, and treatment discontinuations were reviewed and compared to the Applicant's summary and assessment.

8.3.2. Categorization of Adverse Events

No issues were identified with respect to recording, coding, and categorizing AEs. The Applicant categorized AEs and SAEs in accordance with standard regulatory definitions.

AEs were graded using the Division of AIDS (DAIDS) toxicity grading criteria. The clinical reviewer verified the Applicant's translation of verbatim terms to preferred terms for events reported in Study 008.

8.3.3. Routine Clinical Tests

In Study 008, routine clinical evaluation and laboratory testing occurred at pre-specified intervals:

- Lead-in cohort or PK subset of the expanded study: Screening, Day -1, Day 1 (Randomization/Pre-Dose, Post-Dose 1, and Post-Dose 2), Day 2, Day 5 (± 1 day), Day 6 (± 1 day), Day 13, Day 14, Day 15, and Day 28 (± 2 days). For subjects enrolled in the lead-in cohort only, additional study visits for PK sample collection occurred on Days 16, 17, 18, 19, and 20.
- Non-PK subset of the expanded study: Screening, Day 1 (Randomization/Pre-Dose and Post-Dose 1), Day 6 (± 1 day), Day 15, and Day 28 (± 2 days).

Telephone contact occurred on Days 3 and 10 for all subjects. Telephone contact or follow-up visit occurred on Day 45 (± 2 days) for any subjects with unresolved AEs/SAEs at Day 28. The frequency and scope of this testing was deemed adequate. Safety assessments primarily included clinical evaluation of AEs, vital sign measurement, physical examinations, 12-lead ECGs, EEGs, and standard laboratory safety tests. Additional testing occurred as indicated or deemed clinically necessary by the investigator during the trial.

8.4. Safety Results

Each subsection in this section presents the results from Study 008. Any notable safety issues that were not observed in, or differed from Study 008, are presented where applicable.

The Safety Analysis Set (SAS) was used for all analyses unless otherwise specified; all subjects who received at least one dose of study medication were included in the SAS. Treatment-emergent events were defined in the Phase 3 trial and in this review as any AE with onset date on or after study drug start date and no later than 30 days after permanent study drug discontinuation, or any AE leading to premature study drug discontinuation. For all analyses, subjects who experienced the same treatment-emergent AE on more than once occasion are counted only once, at the highest toxicity grade reported. When a "total" value is included for

a column, it represents the total number of subjects included the analysis, rather than the total number of events.

An overall summary of safety events in Study 008 is presented in Table 24.

Table 24. Grade 3 or higher 4 AEs, Study 008

| Subjects Experiencing Event n (%) | Tecovirimat 14 Days N=359 | Placebo 14 Days 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 |

*Not related to study drug

Source: ADAE, ADSL datasets

Reviewer Comment: Adverse events occurred at similar frequency across treatment groups. The majority of AEs were Grade 1 in severity. Serious adverse events (SAEs), AEs leading to study drug discontinuation, and Grade 3/4 AEs were infrequent across treatment groups. Related Grade 3/4 AEs were infrequent and there were no related SAEs.

8.4.1. Deaths

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 (b) (6). 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.

Reviewer Comment: The clinical narrative was reviewed and this event was discussed with the Pharmacology/Toxicology reviewers (Drs. Myers and McMillan) and Clinical Pharmacology reviewer (Dr. Choi). We agree with the investigator's assessment that these events (SAE, death) were unrelated to study medication. Our rationale is summarized below:

- *Subject had pre-existing risk factors (history of deep venous thrombosis; concomitant oral contraceptive use) for pulmonary embolism. Depo-Provera is contraindicated in subjects with a current or past history of thromboembolic disorders.*
- *No thrombotic signal was observed in the tecovirimat nonclinical studies.*
- *The active component of Depo-Provera, medroxyprogesterone, is mainly metabolized by CYP3A4. Based on in vitro studies as well as a DDI study (evaluating the effects of tecovirimat at 600 mg BID on the PK of index substrates [see Section 4.5.3]), tecovirimat (and its metabolites) did not inhibit CYP3A4 at clinically relevant concentrations. Therefore, tecovirimat (and its metabolites) is not expected to increase medroxyprogesterone concentrations. In fact, tecovirimat may decrease medroxyprogesterone concentrations due to enzyme induction by metabolites of tecovirimat.*

8.4.2. Serious Adverse Events

Please see Section 8.4.1 of this review for complete details.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Discontinuations due to AEs were infrequent, occurring in 6 subjects (2%) in the tecovirimat group and 2 subjects (2%) in the placebo group (Table 25). The narratives were reviewed and those from the tecovirimat group are briefly summarized below.

- Subject (b) (6) was a 21-year-old Caucasian male with a history of myopia and no concomitant medications. He received his first dose of study drug on the morning of (b) (6) and his last dose on the evening of (b) (6) at the Day 2 visit after Dose 3, he was noted to have an abnormal electroencephalogram (EEG) result (grade E3 on the EEG grading scale, *please see Section 8.5.3 of this review for complete details on the EEG grading scale*), which was reported as an adverse event. The subject was clinically asymptomatic. The EEG result remained at grade 3 on the EEG grading scale at the Day 6 post-dose visit. Study drug was discontinued on (b) (6) because of this event. On (b) (6) the subject experienced nausea, which resolved the following day (approximately 13.5 hours later). On (b) (6), the subject experienced fatigue, which resolved the following day. The abnormal EEG result returned to baseline levels, and the event was considered resolved on (b) (6) at the Day 14 post-dose visit. The investigator considered the events of abnormal EEG result, nausea, and fatigue to be mild in intensity and possibly related to study drug.

Reviewer Comment: This event was discussed with the Clinical Pharmacology reviewer (Dr.

Choi). Subject (b) (6) was assigned to the fasted group and PK results are summarized below:

*- On Day 1: Subject (b) (6)'s Cmax and AUC: 1640 ng/mL, 19666 ng*hr/mL.*

*In comparison, mean (min-max) Cmax and AUC of the fasted group (Day 1): 1178 ng/mL (581-2480 ng/mL), 13997 (6735 – 24086) ng*hr/mL.*

*Mean (min-max) Cmax and AUC of the fed group (Day 1): 1516 ng/mL (761-3290 ng/mL), 20879 (10627 – 45733) ng*hr/mL.*

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Based on Day 1 data, Subject (b) (6)'s tecovirimat concentrations were higher (but not the highest) among fasted subjects. Similar results were noted for all three metabolites (M4, M5, and TFMBA). It should be noted that there were many other subjects with higher concentrations of tecovirimat and its metabolites in the fed group.

- There were no notable PK findings for the Day 2 PK data.

- The Applicant also collected PK data after discontinuation (b) (6)

(b) (6) There were no notable PK findings (i.e. within the range of expected values) and these PK data showed the predicted elimination for a drug with a half-life of ~ 20 hours.

- Based on the above clinical and PK data for this clinically asymptomatic subject, the primary review team concludes that the abnormal EEG did not correlate with elevated C_{max}.

- Subject (b) (6) was a 60-year-old Caucasian female with a history of food allergy (possible soy allergy) and no concomitant medications. She received her first dose of study drug on the morning of (b) (6) and her last dose on the evening of (b) (6). She completed the Day 6 post-dose visit on (b) (6), she experienced slight upset stomach, dry mouth, dysphoria, and decreased concentration. She discontinued study drug after her evening dose that day because of the events. On (b) (6), the events of slight upset stomach, dry mouth, and dysphoria resolved, and the event of decreased concentration resolved the next day. The investigator considered the events of slight upset stomach, dry mouth, dysphoria, and decreased concentration to be mild in intensity and possibly related to study drug.

- Subject (b) (6) was a 47-year-old Caucasian male with a history of tension headache, allergy to animal (cat), house dust (mite) allergy, seasonal allergy, sinus headache, cardiac murmur, and bilateral deafness (hearing loss). Concomitant medications included oxymetazoline 2 sprays PRN and menthol cough drops 1 lozenge PRN. He received his first dose of study drug on the morning of (b) (6) and his last dose on the morning of (b) (6). He completed the Day 6 post-dose visit on (b) (6), the subject experienced fever, diarrhea, nausea, and headache. He took aspirin 650 mg BID beginning on (b) (6) for the events of fever and headache; this prohibited concomitant medication was considered a major protocol deviation. The event of fever resolved on (b) (6), and the remaining events resolved on (b) (6). The investigator considered the events of fever and nausea to be mild, the event of diarrhea to be moderate, and the event of headache to be severe. All of the events were considered by the investigator to be definitely related to study drug.

- Subject (b) (6) was a 58-year-old Caucasian female with a history of depression and hyperthyroidism. Concomitant medications included levothyroxine 50 µg QD and sertraline hydrochloride 50 mg QD. She received her first dose of study drug on the morning of (b) (6) and her last dose on the evening of (b) (6). She completed the Day 14 post-dose visit on (b) (6) she experienced palpable purpura, described by the investigator as a raised non-pruritic rash of mild intensity that started after the third dose of

study drug. The rash started on both legs and then progressed to the torso. No photographs were taken. No skin biopsy was done. She was instructed by the investigator to discontinue study drug. Other than stopping study drug, no other intervention was made. The investigator advised the subject to take Benadryl if needed. Subject did not want or feel like she needed to take any medication for this AE. On physical examination on Day 15, the investigator noted a fading rash/palpable purpura, and the event resolved on (b) (6). The only laboratory abnormality was an isolated Grade 2 AST on Day 15. The investigator considered the event of palpable purpura to be mild in intensity and definitely related to study drug.

- Subject (b) (6) was a 56-year-old Caucasian male with a history of hypertension and anxiety. Concomitant medications included amlodipine 10 mg QD and lorazepam 1 mg PRN. He received his first dose of study drug on the morning of (b) (6) and his last dose on the morning of (b) (6). On (b) (6) the subject experienced nausea and discontinued study drug. On (b) (6), he experienced chills and fever. All of the events resolved on (b) (6). The investigator considered the events of nausea, chills, and fever to be mild in intensity, the event of nausea to be definitely related to study drug, and the events of chills and fever to be unlikely related to study drug.

Reviewer Comment: Agree with the investigators' assessments that tecovirimat was related to the AEs experienced in the above five subjects.

- Subject (b) (6) was a 37-year-old Caucasian female with a history of ulcerative colitis and no concomitant medications. She received her first dose of study drug on the morning of (b) (6) and her last dose on the evening of the same day. On (b) (6) she experienced facial redness, pruritus, and facial swelling before taking study drug. The patient diary recorded the AE as "woke up with swelling throughout my body especially around and under my eyes. Skin felt itchy and burning." These symptoms were noticed when the patient woke from sleep, at approximately 8 AM. The investigator assessed this AE as not related to study drug, but as a precaution, advised the subject to discontinue study drug. At an unscheduled visit on (b) (6), the investigator noted facial redness and swelling and pruritus on the PE. The events resolved on (b) (6). Other than stopping study drug, no other intervention was made. The investigator considered the events of facial redness, pruritus, and facial swelling to be mild in intensity and not related to study drug. During a follow-up phone call on (b) (6), the subject stated that she handles chemicals working as a house cleaner and stated that she was not sure if the facial redness and swelling might be due to contact with a chemical.

Reviewer Comment: For Subject (b) (6) (facial erythema, pruritus, facial swelling), although the individual AEs were only Grade 1, the constellation of symptoms and the timing is concerning for an allergic reaction (e.g. angioedema). Although there is a potential confounder (exposure to household chemical cleaner), based on the timing of events, this reviewer assesses these AEs to be drug-related. Additionally, the investigator assessment that these AEs were not related to study drug is inconsistent with the investigator decision to discontinue drug due to these AEs.

Table 25. Adverse Events Leading to Study Drug Discontinuation, Study 008

| Treatment Arm | Dictionary-Derived Term | Day, Start of AE | Day, End of AE | Last Day of study drug | SAE | Grade | Outcome | Related§ |
|--------------------|--------------------------|------------------|----------------|------------------------|-----|----------|----------|----------|
| Tecovirimat | | | | | | | | |
| (b) (6) | Abnormal EEG | 2 | 14 | 5 | No | 1 | Resolved | Yes |
| | Abdominal discomfort | 3 | 5 | 3 | No | 1 | Resolved | Yes |
| | Dry mouth | 3 | 5 | | No | 1 | Resolved | Yes |
| | Dysphoria | 3 | 5 | | No | 1 | Resolved | Yes |
| | Disturbance in attention | 3 | 6 | | No | 1 | Resolved | Yes |
| | Fever | 2 | 4 | 3 | No | 1 | Resolved | Yes |
| | Diarrhea | 2 | 4 | | No | 2 | Resolved | Yes |
| | Nausea | 2 | 4 | | No | 1 | Resolved | Yes |
| | Headache | 2 | 6 | | No | 3 | Resolved | Yes |
| | Palpable purpura | 2 | 16 | 2 | No | 1 | Resolved | Yes |
| | Nausea | 8 | 13 | 8 | No | 1 | Resolved | Yes |
| | Chills | 12 | 13 | | No | 1 | Resolved | No |
| | Fever | 12 | 13 | | No | 1 | Resolved | No |
| | Erythema | 2 | 5 | 1 | No | 1 | Resolved | No* |
| | Pruritus | 2 | 5 | | No | 1 | Resolved | No* |
| Facial swelling | 2 | 5 | No | | 1 | Resolved | No* | |
| Placebo | | | | | | | | |
| (b) (6) | Nausea | 1 | 3 | 2 | No | 2 | Resolved | Yes |
| | Fatigue | 10 | 10 | 8 | No | 1 | Resolved | Yes |

§ = Investigator assessment of causality; *FDA reviewer assessed AEs as related to study drug

Source: ADAE, ADSL datasets

Overall Assessment: No clear safety signal emerges from the review of AEs leading to study drug discontinuation. Routine pharmacovigilance will be in place to detect post-marketing signals.

8.4.4. Significant Adverse Events

This section describes Grade 3 or higher events that occurred in the treatment emergent period. Adverse events (AEs) are treatment emergent and all cause. Adverse drug reactions (ADRs) are treatment emergent and at least possibly related by investigator. One of these events was a SAE with fatal outcome; hence, there is some overlap between events reported in this section and sections 8.4.1 and 8.4.2.

Grade 3 or higher AEs were infrequent, occurring in 1% of subjects in the tecovirimat group and 1% of subjects in the placebo group, as summarized below (Table 26). Other than Subject (b) (6) (see Section 8.4.3), the other 4 subjects with ≥Grade 3 AEs completed the pre-specified 14 days of dosing.

Table 26. Grade 3 or higher 4 AEs, Study 008

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| Treatment Arm | Dictionary-Derived Term | Day, Start of AE | Day, End of AE | SAE | Grade | Outcome | Related§ |
|--------------------|--------------------------|------------------|----------------|-----|-------|----------|----------|
| Tecovirimat | | | | | | | |
| (b) (6) | Pulmonary embolus | 21 | 21 | Yes | 5 | Died | No |
| (b) (6) | Headache | 2 | 6 | No | 3 | Resolved | Yes |
| (b) (6) | Headache | 24 | 25 | No | 3 | Resolved | Yes |
| (b) (6) | Osteoarthritis | 9 | 13 | No | 3 | Resolved | Yes |
| Placebo | | | | | | | |
| (b) (6) | Hidradenitis suppurativa | 16 | 16 | No | 3 | Resolved | No |

§ = Investigator assessment of causality; *See Section 8.4.1 for details; **See Section 8.4.3 for details

Source: ADAE, ADSL datasets

In the tecovirimat group: 2 subjects experienced a severe headache, 1 subject experienced severe osteoarthritis, and 1 subject experienced a fatal PE. Study investigators assessed PE as not related to study drug (see Section 8.4.1), the AEs of headache as definitely related (b) (6) and probably related (b) (6) and the AE of osteoarthritis (b) (6) as possibly related.

In the placebo group: 1 subject experienced severe hidradenitis and was considered by study investigators as unlikely to be related to study drug.

Reviewer Comment: In the tecovirimat group, both subjects with headache (b) (6) and the subject with worsening osteoarthritis (b) (6) required concomitant medication (NSAID) use for relief - this may have contributed to the investigators considering these 3 AEs to be related. For Subject (b) (6) I agree with the investigator assessment that tecovirimat was related to the headache. For Subject (b) (6), the timing of the headache (i.e. onset at 11 days post-completion of dosing) does not closely correlate with causal relationship to study drug. For Subject (b) (6) the AE of worsening osteoarthritis might not be drug related.

Overall Assessment: As noted, some of these events have been discussed in prior sections. No clear safety signal emerges from the review of Grade 3 and 4 events.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most common AEs reported were headache, nausea, abdominal pain, and diarrhea. Table 27 summarizes common AEs irrespective of severity and causality.

Table 27. Treatment-emergent AEs Reported in $\geq 2\%$ of Subjects, All Grade and All Causality, Study 008

| Dictionary Derived Term | Tecovirimat N=359 | Placebo N=90 |
|-------------------------|----------------------|-----------------|
| Headache | 61 (17%) | 13 (14%) |
| Nausea | 20 (6%) | 5 (6%) |
| Abdominal pain* | 12 (3%) | 1 (1%) |
| Diarrhea | 11 (3%) | 3 (3%) |
| Vomiting | 9 (3%) | 0 (0%) |
| Dizziness | 9 (3%) | 3 (3%) |
| Total Subjects with AE | 134 (37%) | 30 (33%) |

*Includes abdominal pain, abdominal pain upper, abdominal distension, abdominal discomfort, abdominal pain lower, epigastric pain.

Source: ADAE, ADSL datasets

The majority of events were Grade 1 in severity. The three most commonly reported AEs in each group were:

- Tecovirimat: headache (17%), nausea (6%), abdominal pain (3%)
- Placebo: headache (14%), nausea (6%), diarrhea (3%)

Reviewer Comment: The Applicant displayed the following preferred terms separately under the MedDRA Gastrointestinal Disorders SOC: abdominal pain, abdominal pain upper, abdominal distension, abdominal discomfort, abdominal pain lower, epigastric pain. FDA analyses of abdominal pain (Tables 27 and 28) pooled these preferred terms as there is overlap in these clinical symptoms.*

Headache (17% vs. 14%), abdominal pain (3% vs. 1%), and vomiting (3% vs. 0%) were the only TEAEs with a $\geq 2\%$ risk difference between tecovirimat and placebo.*

Table 28 summarizes related adverse events (hereafter referred to adverse drug reactions [ADR]), irrespective of severity. The investigator's determination of causality is the basis for classification. The inaccuracies and biases of this type of classification are acknowledged.

Table 28: Treatment-emergent ADRs Reported in $\geq 2\%$ of Subjects, All Grade, Study 008

| Dictionary Derived Term | Tecovirimat N=359 | Placebo N=90 |
|-------------------------|----------------------|-----------------|
| Headache | 44 (12%) | 7 (8%) |
| Nausea | 16 (5%) | 4 (4%) |
| Abdominal pain* | 7 (2%) | 1 (1%) |
| Vomiting | 7 (2%) | 0 (0%) |
| Diarrhea | 7 (2%) | 2 (2%) |
| Total subjects with ADR | 71 (20%) | 15 (15%) |

*Includes abdominal pain, abdominal pain upper, abdominal distension, abdominal discomfort, abdominal pain lower, epigastric pain.

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Source: ADAE, ADSL datasets

Most ADRs were mild or moderate severity. The three most commonly reported ADRs in each group were:

- Tecovirimat: headache (12%), nausea (5%), abdominal pain (2%)
- Placebo: headache (8%), nausea (4%), diarrhea (2%)

Reviewer Comment: Both analyses (all AEs and ADRs) yield similar results, affirming that headache, nausea, and abdominal pain are the most frequently reported AEs with tecovirimat. Adverse reactions in subjects receiving tecovirimat with $\geq 2\%$ greater frequency were headache, nausea, abdominal pain, vomiting, and diarrhea.

Headache (12% vs. 8%) and vomiting (2% vs. 0%) were the only treatment-emergent ADRs with a $\geq 2\%$ risk difference between tecovirimat and placebo.

Reviewer Summary: Product labeling will display ADR results for headache, nausea, abdominal pain and vomiting from Table E as these ADRs occurred in greater frequency compared to placebo.

8.4.6. **Laboratory Findings**

The tables in this section display treatment-emergent graded laboratory abnormalities for chemistry and hematology parameters in Study 008. These analyses represent the worst change from baseline per subject.

Grade 3 abnormalities occurred infrequently and at a similar rate in subjects treated with tecovirimat relative to placebo. No Grade 4 abnormalities were reported. Laboratory analyses did not reveal any new significant safety concerns. Graded chemistry results are summarized in Table 29, and hematology results in Table 30.

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Table 29: Liver Function Tests and Other Chemistry Lab Results, All Grade, Study 008

| Parameter and max Analysis Toxicity Grade | Tecovirimat N=359 | Placebo N=90 |
|--|----------------------|-----------------|
| LIVER FUNCTION TESTS | | |
| Increased Alanine Aminotransferase (U/L) | | |
| Grade 1 (1.25 to 2.5 × ULN) | 11 (3%) | 3 (3%) |
| Grade 2 (2.5 to 5 × ULN) | 1 (<1%) | 0 (0%) |
| Grade 3 (>5 to 10 × ULN) | 0 (0%) | 0 (0%) |
| Grade 4 (>10 × ULN) | 0 (0%) | 0 (0%) |
| Increased Aspartate Aminotransferase (U/L) | | |
| Grade 1 (1.25 to 2.5 × ULN) | 5 (1%) | 1 (1%) |
| Grade 2 (>2.5 to 5 × ULN) | 0 (0%) | 0 (0%) |
| Grade 3 (>5 to 10 × ULN) | 0 (0%) | 0 (0%) |
| Grade 4 (>10 × ULN) | 0 (0%) | 0 (0%) |
| Increased Total Bilirubin (mg/dL) | | |
| Grade 1 (>1 to 1.5 × ULN) | 2 (<1%) | 1 (1%) |
| Grade 2 (>1.5 to 2.5 × ULN) | 0 (0%) | 0 (0%) |
| Grade 3 (>2.5 to 5 × ULN) | 0 (0%) | 0 (0%) |
| Grade 4 (>5 × ULN) | 0 (0%) | 0 (0%) |
| Increased Alkaline Phosphatase (U/L) | | |
| Grade 1 (1.25 to 2.5 × ULN) | 2 (<1%) | 1 (1%) |
| OTHER CHEMISTRY LABS | | |
| Increased Creatinine (mg/dL) | | |
| Grade 1 (>1.5 to 2 mg/dL) | 1 (<1%) | 0 (0%) |
| Grade 2 (>2 to 3 mg/dL) | 3 (1%) | 0 (0%) |
| Increased Creatinine Clearance (mL/min/1.73 m ²) | | |
| Grade 1 (NA) | 0 (0%) | 0 (0%) |
| Grade 2 (<90 to 60 ml/min/1.73 m ²) | 13 (4%) | 3 (3%) |
| Grade 3 (<60 to 30 ml/min/1.73 m ²) | 2 (<1%) | 0 (0%) |
| Grade 4 (<30 ml/min/1.73 m ²) | 0 (0%) | 0 (0%) |
| Increased Glucose (mg/dL) | | |
| Grade 1 (116 to 160 mg/dL) | 37 (10%) | 10 (11%) |
| Grade 2 (>160 to 250 mg/dL) | 9 (3%) | 3 (3%) |
| Grade 3 (>250 to 500 mg/dL) | 0 (0%) | 0 (0%) |
| Decreased Glucose (mg/dL) | | |
| Grade 1 (55 to 64 mg/dL) | 8 (2%) | 2 (2%) |
| Grade 2 (40 to <55 mg/dL) | 6 (2%) | 0 (0%) |
| Grade 3 (30 to <40 mg/dL) | 0 (0%) | 0 (0%) |
| Decreased Phosphate (mg/dL) | | |
| Grade 1 (2.0 to <LLN) | 0 (0%) | 0 (0%) |
| Grade 2 (1.4 to <2.0) | 11 (3%) | 1 (1%) |
| Grade 3 (1.0 to <1.4) | 1 (<1%) | 0 (0%) |

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 NA, not applicable
 Source: ADLB dataset

Reviewer Comment: Grade 3 laboratory abnormalities were uncommon across treatment groups. Grade 4 laboratory abnormalities were not observed. No clear safety signal emerges from the review of laboratory abnormalities.

Given the low frequency of chemistry abnormalities and the similarities in laboratory profile between tecovirimat and placebo, chemistry laboratory parameters are not recommended for inclusion in product labeling.

Table 30. Hematology Laboratory Results, All Grade, Study 008

| Parameter and max Analysis Toxicity Grade | Tecovirimat N=359 | Placebo N=90 |
|---|-------------------|--------------|
| Decreased Hemoglobin (g/dL) | | |
| Grade 1 (10 to < 10.9 g/dL OR any decrease 2.5 to < 3.5 g/dL from baseline) | 2 (<1%) | 3 (3%) |
| Grade 2 (9 to < 10 g/dL OR any decrease 3.5 to < 4.5 g/dL from baseline) | 0 (0%) | 0 (0%) |
| Grade 3 (7 to < 9 g/dL OR any decrease ≥ 4.5 g/dL from baseline) | 0 (0%) | 0 (0%) |
| Decreased Neutrophils, Segmented (cells/mm³) | | |
| Grade 1 (1000 to 1300/mm ³) | 1 (<1%) | 0 (0%) |
| Grade 2 (750 to < 1000/mm ³) | 0 (0%) | 0 (0%) |
| Grade 3 (500 to < 750/mm ³) | 0 (0%) | 0 (0%) |
| Grade 4 (<500/mm ³) | 0 (0%) | 0 (0%) |
| Decreased Lymphocytes (cells/mm³) | | |
| Grade 1 (600 to 650/mm ³) | 0 (0%) | 0 (0%) |
| Grade 2 (500 to < 600/mm ³) | 1 (<1%) | 0 (0%) |
| Grade 3 (350 to < 500/mm ³) | 1 (<1%) | 0 (0%) |
| Grade 4 (< 350/mm ³) | 0 (0%) | 0 (0%) |
| Decreased Platelets (cells/mm³) | | |
| Grade 1 (100,000 to < 125,000/mm ³) | 1 (<1%) | 0 (0%) |
| Grade 2 (50,000 to < 100,000/mm ³) | 0 (0%) | 0 (0%) |
| Grade 3 (25,000 to < 50,000/mm ³) | 0 (0%) | 0 (0%) |

Source: ADLB dataset

Reviewer Comment: Grade 3 laboratory abnormalities were uncommon across treatment groups. Grade 4 laboratory abnormalities were not observed. No clear safety signal emerges from the review of laboratory abnormalities. Given the low frequency of hematologic abnormalities and the similarities in laboratory profile between tecovirimat and placebo, hematologic laboratory parameters are not recommended for inclusion in product labeling.

8.4.7. Vital Signs

Treatment-emergent AEs due to vital sign changes were overall infrequent and occurred only in tecovirimat recipients. Treatment-emergent AEs due to changes from baseline systolic or diastolic blood pressure or heart rate were infrequent, mild, clinically asymptomatic, did not require intervention, and did not result in study drug discontinuation. Treatment-emergent pyrexia was infrequent (1%).

8.4.8. Electrocardiograms (ECGs)

ECGs were assessed at the following time-points:

- For subjects in the PK cohort: Screening, Day -1 Check-in visit pre-Dose 1, Day 2 visit after Dose 3, Day 6 visit after AM dose, and Day 15 visit after study drug dosing is complete.
- For non-PK subjects: Screening, Day 1 visit pre-Dose 1, Day 6 visit after AM dose, and Day 15 visit after study drug dosing is complete.

Other than screening, ECGs were done in triplicate at the above study time-points.

Twelve subjects (tecovirimat [n=9] vs. placebo [n=3]) had ECG interpretations that were noted to be abnormal clinically significant by the central reader at 1 or more time points. No TEAEs related to the ECG findings were reported for any of these subjects. One tecovirimat recipient (b) (6) experienced a TEAE of ventricular extrasystoles that began and ended on Day 15. This event was mild and considered by the investigator as not related to study drug. On Day 15, the triplicate ECG interpretations for this subject were abnormal not clinically significant for 2 readings and normal for the third.

Reviewer Comment: This subject was the only cardiac AE reported in Study 008. There were no cardiac SAEs. The primary review team concludes that the available reported ECG data do not require specific safety labeling.

8.4.9. QT

A thorough QT (TQT) study was conducted to evaluate the potential of tecovirimat to prolong the QT interval. Study SIGA-246-010 was a randomized, partial-blinded placebo- and positive-controlled, 3-period, single-dose crossover study of 48 healthy subjects who received tecovirimat (1000 mg), placebo, and moxifloxacin 400 mg. The results were reviewed by the Interdisciplinary Review Team (IRT), who concluded the following:

While no significant QTc prolongation was observed after a single dose of 1000 mg tecovirimat with food in this study, the exposure to metabolites (M4, M5 and TFMBA) is not adequate; thereby limiting the interpretation of the study findings. At steady state, the exposure to all the major metabolites are 2 to 5-fold higher than the exposures observed in this study, and the plasma concentrations of some of the metabolites could be further increased in patients with impaired renal function. In addition, the preclinical assessment of risk for QTc prolongation is limited to a hERG assay for only tecovirimat and ECG assessment in monkeys had similar or lower exposures of the major metabolites compared to humans. As a result, the data described in this review are not adequate to exclude a 10-ms mean increase in the QTc interval at therapeutic doses.

IRT recommended that the Applicant collect safety ECGs (at baseline and periodically at steady state) in their late phase clinical trials. IRT reviewed Study 008 and evaluated if the steady-state ECG data from Study 008 could characterize the three major metabolites (M4, M5 and TFMBA).

Table 31. Plasma exposure for tecovirimat and metabolites (M4, M5, TFMBA) in fed subjects on Day 1 and 14

| | C_{max} (ng/mL) | | AUC ₀₋₂₄ (h•ng/mL) | | | |
|-------------|-------------------|---------|-------------------------------|---------------------|-----------|---------------------|
| | Day 1 | Day 14 | Day 1 | % of Total Exposure | Day 14 | % of Total Exposure |
| Tecovirimat | 1591.00 | 2208.75 | 25875.94 | 24.0 | 30632.18 | 13.5 |
| M4 | 906.96 | 1289.52 | 13634.28 | 12.6 | 23486.76 | 10.4 |
| M5 | 109.11 | 665.48 | 929.11 | 0.9 | 13066.87 | 5.8 |
| TFMBA | 5135.63 | 7955.83 | 67597.04 | 62.6 | 159582.68 | 70.4 |

- Study 008 PK data suggest that steady-state levels are reached by Day 14 and that little fluctuation is expected between the last dose and the timing of the ECG collection.
- Additionally, the PK data suggests that the M4 and M5 metabolites are minor metabolites and the C_{max} of TFMBA, the most abundant metabolite, is ~1.87-fold higher than what was observed in the TQT study.
- Overall, the data collected in the TQT study and in Study 008 support the absence of small mean increases (i.e. 10 ms) on the QTc interval at therapeutic exposure.

In conclusion, tecovirimat does not prolong QTc to any clinically relevant extent. Please refer to the QT-IRT review by Lars Johannesen for additional details (IND 69019, August 15, 2017; NDA 208627, February 1, 2018).

8.4.10. Immunogenicity

Because tecovirimat is a small molecule and not a peptide, immunogenicity was not anticipated and therefore not specifically evaluated in clinical trials.

8.5. Analysis of Submission-Specific Safety Issues

This section includes analyses conducted to address safety concerns such as seizure, as well as issues of interest, such as cardiac events, rash, neuropsychiatric events, and elevations of creatine kinase and lipase.

Analyses were conducted by organ system to identify possible safety concerns that were not apparent in the routine AE and laboratory analyses presented in prior sections. Analyses were performed using the relevant SOC or High Level Group Term (HLGT).

8.5.1. Hepatotoxicity

There were no cases of hepatotoxicity. There were no Grade 3/4 ALT or AST values.

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Reviewer Comment: The primary review team concludes that the available reported data do not require specific safety labeling for hepatotoxicity. Routine pharmacovigilance will be in place to detect post-marketing signals.

8.5.2. Cardiac Disorders

Please see Section 8.4.8 of this review for complete details.

Overall Cardiac Assessment: The primary review team concludes that the available reported cardiac data do not require specific safety labeling. Routine pharmacovigilance will be in place to detect post-marketing signals.

8.5.3. Neuropsychiatric Disorders

Seizure

As discussed in Section 4.4, nonclinical toxicology studies in dogs demonstrated neurological effects (e.g., tremors, seizures) at higher than anticipated clinical exposures of tecovirimat.

To evaluate for potential epileptiform activity and possible seizures associated with tecovirimat, Study 008 included electroencephalogram (EEG) testing for subjects in the lead-in cohort and in the PK subset of the expanded study. EEG were assessed at Screening, Day 2 visit after Dose 3, Day 6 visit after AM dose, and Day 14 visit after AM dose. All EEGs done post-study drug dosing should be done at 4 hours \pm 30 minutes post-dose to enable evaluation at both the maximum plasma concentration and steady state.

The following EEG safety grading scale was used:

E0: Normal

E1: Less than 3 focal epileptiform abnormalities or non-epileptiform abnormalities

E2: 3-10 focal discharges, 2-10 multifocal or generalized discharges

E3: Sharp/slow complex, runs of epileptiform discharges (>1s), more than 10 epileptiform discharges

E4: Seizure

A total of 81 subjects (tecovirimat [n=65] vs. placebo [n=16]) had EEGs. The findings are summarized below:

- At Screening, all subjects had EEG readings that were graded E0 (95%) or E1 (5%).
- At the Day 2 visit after Dose 3, a grade E3 reading was noted for 1 subject: Subject (b) (6) in the tecovirimat group; this subject also had a grade E3 reading at the Day 6 Post-dose visit. Subject (b) (6) was discontinued from study drug due to this event. Subject (b) (6) was also withdrawn from the study. Please see Section 8.4.3 of this review for complete details.
- At the Day 14 Post-dose visit, all subjects had EEG readings that were graded E0 (89%) or E1 (10%).

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Reviewer Comment: All subjects, including the small proportion with mild EEG abnormalities, were clinically asymptomatic. The primary review team concludes that the available reported EEG data do not require specific safety labeling.

Migraines

Migraines were infrequent in Study 008, occurring in 1% of subjects in the tecovirimat group and 0% of subjects in the placebo group. All events were Grade 1 in severity. There were no discontinuations due to migraines.

Reviewer Comment: There is no clear signal for increased risk of migraines with tecovirimat.

Depression

Analyses of depression and/or suicidal events were performed to evaluate a potential causal association with tecovirimat using pooled terms from the MedDRA High Level Group Terms (HLGT) “Depressed Mood Disorders and Disturbances” and “Suicidal and Self-Injurious Behaviours NEC.”

Depression events were infrequent in Study 008, occurring in <1% of subjects in the tecovirimat group and 0% of subjects in the placebo group. All events were Grade 1 in severity. There were no suicide attempts. There were no discontinuations due to neuropsychiatric events.

Neuropsychiatric events that were considered related occurred in <1% of subjects in the tecovirimat group and 0% of subjects in the placebo group.

Reviewer Comment: There is no clear signal for increased risk of depression events with tecovirimat.

In order to determine whether there is a trend toward tolerability issues caused by anxiety events, an analysis was performed using the High Level Group Term “Anxiety Disorders and symptoms.” There were no anxiety events in Study 008.

Reviewer Comment: No anxiety events were identified in Study 008.

For completeness of the neuropsychiatric evaluation, additional analyses were performed using the High Level Group Terms “Schizophrenia and other psychotic disorders” and “Sleep Disorders.” No events were found in these analyses.

Overall Assessment: The frequency and severity of neuropsychiatric events occurring in tecovirimat subjects was low. Although no specific safety signal was detected for neuropsychiatric events with tecovirimat, product labeling is recommended for this adverse event of special interest. Any potential signals of neuropsychiatric events associated with tecovirimat use will be closely monitored in the postmarketing setting.

8.5.4. **Rash**

Analyses of rash events were performed to evaluate a potential causal association with tecovirimat. Analyses of rash events pooled the following preferred terms under the MedDRA Skin and Soft Tissue Body SOC: rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, and palpable purpura.

Rash events were infrequent in Study 008, occurring in 1% of subjects in the tecovirimat group and 0% of subjects in the placebo group. All events were Grade 1 in severity. There was one discontinuation due to rash (b) (6) palpable purpura, see Section 8.4.3) and no Grade 3 or 4 events were observed. No events of Stevens Johnson Syndrome, toxic epidermal necrolysis or erythema multiforme were reported.

Approximately half of the rash events were assessed by investigators as unrelated to study drug. Rash events that were considered related occurred in <1% of subjects in the tecovirimat group and 0% of subjects in the placebo group.

Overall Assessment: The frequency and severity of rash events occurring in tecovirimat subjects was low. Although no specific safety signal was detected for serious rash events with tecovirimat, product labeling is recommended for this adverse event of special interest. Any potential signals of serious rash events associated with tecovirimat use will be closely monitored in the postmarketing setting.

8.5.5. **Rhabdomyolysis**

There were no cases of rhabdomyolysis in Study 008. Of note, creatine kinase (CK) was not measured in Study 008.

Reviewer Comment: Rhabdomyolysis was not an adverse event of specific concern during the tecovirimat development program. Routine pharmacovigilance will be in place to detect post-marketing signals.

8.5.6. **Pancreatitis**

There were no cases of pancreatitis in Study 008. There were no Grade 3/4 triglyceride elevations. Of note, amylase and lipase were not measured in Study 008.

Reviewer Comment: Pancreatitis was not an adverse event of specific concern during the tecovirimat development program. Routine pharmacovigilance will be in place to detect post-marketing signals.

8.5.7. **Pancytopenia**

There were no cases of pancytopenia in Study 008. There were no Grade 3/4 decreases in white blood cells, hemoglobin, or platelets.

Reviewer Comment: The primary review team concludes that the available reported data do not require specific safety labeling for pancytopenia. Routine pharmacovigilance will be in place to detect post-marketing signals.

8.5.8. **Safety Profile Among Subjects with concomitant use of blood glucose-lowering drugs**

In a cohort of the open-label DDI study (SIGA-246-015), 30 healthy adults received:

- Single oral dose of repaglinide 2 mg (AM, on Day 1)
- Followed by a washout period (Days 2 through 7)
- Then tecovirimat 600 mg BID x 15 days (Days 8 through 22); a single oral dose of repaglinide 2 mg was co-administered with AM dose of tecovirimat on Day 22

Hypoglycemia occurred in 10 subjects (mild-6; moderate-4) following co-administration of repaglinide (2 mg) and tecovirimat (at steady state). After a meal (and oral glucose for subjects with finger-stick glucose < 50 mg/dL), symptoms resolved in 9 subjects. In 1 subject, symptoms resolved the following morning.

Concomitant use of antidiabetic drugs was infrequent in Study 008, occurring in <1% of subjects in the tecovirimat group (present at start of study) and 0% of subjects in the placebo group. There were no hypoglycemia events in Study 008.

Reviewer Comment: Section 5 of the label will include information from Study 015 that co-administration of repaglinide and tecovirimat may cause mild-to-moderate hypoglycemia. We will continue to monitor closely in the postmarketing setting for any potential serious safety signals of hypoglycemia when administering tecovirimat with blood glucose-lowering drugs.

8.6. **Safety Analyses by Demographic Subgroups**

Consistent with the approach for the overall safety review, the impact of age, sex, and race on the frequencies of adverse events were assessed for Study 008. Overall, we did not find any demographic subgroups at substantially higher risk for serious or severe AEs. This section contains a brief summary of the findings, organized by demographic variable. The discussion is limited to Study 008 subjects treated with tecovirimat.

Age

Subjects <65 years of age (n=323) were compared to subjects ≥65 years old (n=36). The older cohort comprised 10% of the tecovirimat population. Differences between age groups were difficult to assess due to the predominance of subjects <65 years in the study population.

There was one death/SAE (46 year old, see Sections 8.4.1 and 8.4.2). The percentage of subjects with Grade 3/4 AEs was 1% and 0% respectively. All-cause AEs of any severity occurred in 37% and 44% respectively; this observation is driven primarily by differences in the percentages of subjects <65 years and subjects ≥65 years with headache (17% vs. 25%) and dizziness (2% vs.

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8%). Graded laboratory abnormalities occurred in 52% of subjects <65 years and 78% of subjects ≥65 years.

Reviewer Comment: It is possible that the differences may be less notable had there been more equal representation between age groups. Given the similarities in the types of AEs reported between men and women and the predominance of Grade 1 and 2 events, the relatively higher rate of AEs among subjects aged ≥65 years do not appear clinically significant.

Gender

Women comprised 59% of the tecovirimat population (211/359). There was one death/SAE (46 year old woman, see Sections 8.4.1 and 8.4.2). Grade 3/4 events occurred in 1% of women and 1% of men. All-cause AEs of any severity occurred in 41% of women and 32% of men; this observation is driven primarily by differences in the percentages of women and men with headache (19% vs. 14%) and abdominal pain (5% vs. 1%). Graded laboratory abnormalities occurred in 56% of women and 52% of men.

Reviewer Comment: Given the similarities in the types of AEs reported between men and women and the predominance of Grade 1 and 2 events, the relatively higher rate of AEs among women do not appear clinically significant.

Race

Differences between racial groups were difficult to assess due to the predominance of white subjects in the study population. Analyses of black (28%) and non-black (72%) subjects in the tecovirimat group are summarized. There was one death/SAE (subject of White and American Indian or Alaska native descent, see Sections 8.4.1 and 8.4.2). Grade 3/4 AEs occurred in 0% of black subjects and 2% of non-black subjects. All-cause AEs of any severity occurred in 25% of black subjects and 42% of non-black subjects; this observation is driven primarily by differences in the percentages of black subjects and non-black subjects with headache (10% vs. 20%), nausea (2% vs. 7%), abdominal pain (2% vs. 4%), and diarrhea (1% vs. 4%). Graded laboratory abnormalities occurred in 52% of black subjects and 55% of non-black subjects.

Reviewer Comment: It is possible that the differences may be less notable had there been more equal representation between racial groups.

Overall Demographic Safety Analysis Conclusion: Adverse events occurred with similar frequency and severity across all demographic groups. No clinically significant patterns were identified to suggest a higher risk for specific events in any population.

8.7. Specific Safety Studies/Clinical Trials

No additional trials have been conducted to evaluate specific safety concerns.

8.8. Additional Safety Explorations

8.8.1. **Human Carcinogenicity or Tumor Development**

The relatively short duration of tecovirimat treatment (14 days) and follow-up (45 days in Study 008) in clinical trials limits the assessment for oncologic events. There were no treatment-emergent oncologic events in Study 008.

Reviewer Comment: Based on the available data from the Phase 3 trial, there is no clinical evidence of carcinogenicity for tecovirimat.

8.8.2. **Human Reproduction and Pregnancy**

Pregnant and lactating women were excluded from participation for all clinical trials. No pregnancies have been reported during the tecovirimat development program.

8.8.3. **Pediatrics and Assessment of Effects on Growth**

On December 27, 2006, the Applicant was granted Orphan Designation for the treatment of smallpox. Consequently, the Applicant's drug development program for the treatment of smallpox is exempt from the PREA requirements, an agreed to Pediatric Study Plan (PSP) was not required prior to the submission of an NDA, and no meetings were held with the Pediatric Review Committee (PeRC). The Applicant used pharmacokinetic simulation to propose dosing regimens that are predicted to provide pediatric patients with exposures comparable to the observed exposure in adults receiving 600 mg twice daily.

8.8.4. **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

The potential for drug abuse, withdrawal, or rebound with tecovirimat was not evaluated but is not anticipated. In the event of an overdose, hemodialysis is unlikely to remove a significant amount of tecovirimat because it is highly plasma protein bound.

8.9. **Safety in the Postmarket Setting**

8.9.1. **Safety Concerns Identified Through Postmarket Experience**

The Animal Rule stipulates that all drugs approved using the Animal Rule should be evaluated for efficacy and safety through clinical trials if circumstances arise in which that would be feasible and ethical. Therefore, smallpox drug approval under the Animal Rule will include a requirement to conduct one or more human postmarketing trials if a smallpox outbreak occurs, and the marketing application must include a plan or approach to meet this requirement (21 CFR part 314, subpart I). The drug approval letter will include a time frame for submission of the final clinical protocol, ready for implementation should the need arise.

The Applicant proposed the following clinical protocol to assess the safety and efficacy of the investigational drugs in the event of a human smallpox outbreak:



(b) (4)

Reviewer Comment:

(b) (4)

Negotiations on this required post-marketing study were ongoing at the time of finalization of this review.

8.9.2. Expectations on Safety in the Postmarket Setting

Safety analyses and conclusions in this review are primarily based upon data from the submitted Phase 3 trial in healthy adults. 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 outbreak. Additionally, tecovirimat has not been studied in pediatric subjects, pregnant women, or lactating women. Emergence of new safety signals can be managed by routine pharmacovigilance activities.

8.10. Additional Safety Issues From Other Disciplines

All relevant safety issues from other disciplines are included elsewhere in this review.

8.11. Integrated Assessment of Safety

No major safety issues or concerns specifically related to tecovirimat were identified in this review. Section 5 of the label will include information from DDI Study 015 that co-administration of repaglinide and tecovirimat may cause mild to moderate hypoglycemia. In the Study 008 population, headache, nausea, abdominal pain and vomiting were the most common ADRs reported and will be included in Section 6 of the label as these ADRs occurred in greater frequency with tecovirimat compared to placebo. Section 6 of the label will also display Less Common Adverse Reactions, including ADRs of interest such as rash, palpable purpura, abnormal electroencephalogram, and depression.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was convened for this application on May 1, 2018. The regulatory considerations, animal efficacy and pharmacokinetic data from the NHP/MPXV and rabbit/RPXV studies, and human safety and pharmacokinetic data summarized in this review were discussed. The Advisory Committee was 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.

As a key component of the FDA's presentation, the following requirements of FDA's Animal Rule as outlined in the Code of Federal Regulations (21CFR 314.610) were summarized along with the Agency's perspective as to whether these requirements were successfully met by the Applicant for tecovirimat:

Tenet 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.

Tenet 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.

Tenet 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.

Tenet 4: Issues Related to Pharmacokinetics and Dosing

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, 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.

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

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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.

Issues Related to Clinical Safety

The Animal Rule requires clinical safety to be established for the new drug product. Tecovirimat administered to healthy adults at the proposed dosing regimen of 600 mg BID for 14 days was demonstrated to be safe and well tolerated.

Reviewer Comment: The Advisory Committee agreed with the Agency's assessment of the collective evidence of tecovirimat efficacy for the treatment of human smallpox:

- (1) The mechanism of action of tecovirimat is well established, and the drug target is highly conserved across all orthopoxviruses.*
- (2) Tecovirimat was demonstrated to have broad and consistent antiviral activity in cell culture assays against 7 different orthopoxviruses, including several independent isolates of variola virus.*
- (3) Treatment efficacy was clearly demonstrated using two lethal, well-studied animal models of non-variola orthopoxvirus infection, with several disease characteristics in each of these models being relevant to human smallpox.*
- (4) PK and PD data from these animal studies enabled selection of an effective human dose.*

The Advisory Committee also agreed with the Agency's assessment of the collective evidence of tecovirimat safety. The Advisory Committee voted unanimously (17-0) that based on the available data, the risk-benefit profile of tecovirimat is acceptable for the treatment of human smallpox.

10 Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling negotiations are ongoing. Below are general clinical recommendations for proposed labeling. Major labeling recommendations or changes will be further summarized in a clinical review addendum as warranted.

1 INDICATIONS AND USAGE

The review team concludes that the approval of tecovirimat under the FDA's Animal Rule for treatment of human smallpox disease caused by variola virus infection is fully supported by the available evidence of efficacy and safety.

2 DOSAGE AND ADMINISTRATION

The review team recommends that the dosage for adult and pediatric patients weighing at least 40 kg is three capsules by mouth twice daily for 14 days. The review team recommends the following doses for pediatric patients in other weight bands:

- 25 kg to < 40 kg: two capsules by mouth twice daily for 14 days
- 13 kg to < 25 kg: one capsule by mouth twice daily for 14 days

5 WARNINGS AND PRECAUTIONS

The label will describe the Study 015 findings that co-administration of repaglinide and tecovirimat may cause mild-to-moderate hypoglycemia, and include that blood glucose should be monitored when administering tecovirimat with repaglinide. (See Section 8.5.8)

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

- Table (b) (4) adverse reactions (i.e. adverse events assessed as reasonably associated with the use of the drug), all grades, and occurring at higher rates with tecovirimat compared to placebo. (See Section 8.4.5)
- Table (b) (4) a pooled term for abdominal pain generated by pooling the following adverse reactions (ARs): abdominal pain, abdominal pain upper, abdominal distension, abdominal discomfort, abdominal pain lower, epigastric pain. (b) (4)
- Table (b) (4) will be revised to (b) (4)
- (b) (4) less common adverse reactions (i.e. adverse events assessed as reasonably associated with the use of the drug), all grades, and occurring at higher rates with tecovirimat compared to placebo. This section will likely include abnormal EEG, depression and rash. (See Sections 8.5.3 and 8.5.4)

7 DRUG INTERACTIONS

(b) (4)
The following changes are proposed to Table (b) (4)

- The review team is discussing the appropriate clinical recommendations for the interactions between tecovirimat and CYP3A, CYP2C8, or CYP2C19 substrates. Based on the magnitude of interactions, as well as risk-benefit assessments, the review team aims to develop practical recommendations applicable to a broad range of CYP3A, CYP2C8 or CYP2C19 substrates (b) (4). (See Section 4.5.3)

8 USE IN SPECIFIC POPULATIONS

- The review team has concluded that the Applicant's methodology for determining pediatric dosing regimens is not acceptable. The recommended dosing regimen has

been provided by the review team based on the population pharmacokinetic analysis and simulation. (See Section 4.5.2)

12 CLINICAL PHARMACOLOGY

12.4 Microbiology

- The review team has had further internal discussions (b) (5)

14 CLINICAL STUDIES

- Additional wording will be added to more clearly describe the uncertainties inherent to drug approval under the Animal Rule (e.g., that survival rates observed in the animal studies cannot be directly compared between studies and may not reflect the rates observed in clinical practice).
- In Table (b) (4) NHP/MPXV Study 3 (SR10-037F; tecovirimat initiated at Day 4 PI, Day 5 PI, and Day 6 PI) should be revised to include all study arms since 10 mg/kg x 14 days was evaluated in all treatment arms.
- NHP/MPXV Study 4 (SR10-038F) should be removed from Section 14 as these durations are shorter than the proposed treatment duration and labeling should not imply that a shorter duration could be used.

10.2. Patient Labeling

Patient labeling will be updated in accordance with the final agreed upon prescribing information in the Package Insert. Because negotiations pertaining to prescribing information were ongoing at the time of completion of this review, patient labeling was not yet updated.

10.3. Nonprescription Drug Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

No issues were identified to necessitate REMS.

12 Postmarketing Requirements and Commitments

Post-marketing requirements and commitments were still under discussion at the time this review was completed. This section includes PMRs and PMCs that will be proposed by the clinical review team.

- A PMR will be issued for a trial to assess the safety and efficacy of tecovirimat for 14

days in the event of a smallpox outbreak due to variola virus.

Additional postmarketing requirements or commitments may be proposed at a later time based on ongoing labeling and review discussions.

13 Appendices

13.1. References

1. Breman JG, Henderson DA. Diagnosis and management of smallpox. *N Engl J Med*. 2002;346(17):1300-1308.
2. World Health Organization. Smallpox. <http://www.who.int/csr/disease/smallpox/en/>
3. NIAID Emerging Infectious Diseases/Pathogens. Available at: <https://www.niaid.nih.gov/research/emerging-infectious-diseases-pathogens>
4. World Health Organization. Smallpox Preparedness and Response. <http://www.who.int/csr/disease/smallpox/preparedness/en/>
5. Guidance for Industry Product Development Under the Animal Rule. (October 2015) <https://www.fda.gov/downloads/drugs/guidances/ucm399217.pdf>
6. Guidance for Industry Smallpox (Variola Virus Infection): Developing Drugs for Treatment or Prevention (Draft Guidance November 2007) <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071179.pdf>
7. Development of Antiviral Products for Treatment of Smallpox and Related Poxvirus Infections; Public Workshop. (September 2009) <https://www.federalregister.gov/documents/2009/08/18/E9-19781/development-of-antiviral-products-for-treatment-of-smallpox-and-related-poxvirus-infections-public>
8. 2011 Antiviral Drugs Advisory Committee. (December 2011) <https://wayback.archive-it.org/7993/20170404145348/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/ucm247236.htm>.
9. Lederman E, Davidson W, Groff H, et al. Progressive Vaccinia: Case description and laboratory-guided therapy with vaccinia immune globulin, tecovirimat, and CMX001. *J Infect Dis*. 2012;206(9):1372-1385.
10. Vora S, Damon I, Fulginiti V, et al. Severe Eczema Vaccinatum in a Household Contact of a Smallpox Vaccinee. *Clin Infect Dis*. 2008;46(10):1555-1561.

13.2. Financial Disclosure

There were no financial disclosures of significant concern, individually or collectively. The financial disclosures described below do not affect approvability of tecovirimat.

Covered Clinical Study (Name and/or Number):

SIGA-246-001, SIGA-246-002, SIGA-246-004, SIGA-246-005, SIGA-246-006, SIGA-246-008, SIGA-246-009, SIGA-246-010, SIGA-246-013, SIGA-246-015, SIGA-246-018

| | | |
|--|---|--|
| Was a list of clinical investigators provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from |
|--|---|--|

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| | | Applicant) |
| Total number of investigators identified: <u>176 Overall: 29 Principal Investigators, 147 Sub-investigators</u> | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u> | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u> | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): | | |
| Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> | | |
| Significant payments of other sorts: <u>0</u> | | |
| Proprietary interest in the product tested held by investigator: <u>0</u> | | |
| Significant equity interest held by investigator in Sponsor of covered study: <u>0</u> | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u> | | |
| Is an attachment provided with the reason: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request explanation from Applicant) |

The Applicant adequately examined financial disclosure information from all clinical investigators for the covered clinical trials, as recommended in the *Guidance for Industry: Financial Disclosure by Clinical Investigators*. The Applicant certified in Form FDA 3454 that, as the sponsor of the submitted studies, the Applicant has not entered into any financial arrangement with the listed clinical investigators (list was included in the submission) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. The Applicant further certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Those investigators who are participating or have participated in the clinical trials and who have financial interest or arrangements as described in 21 CFR 54.4(a)(3) are noted in the above template. There are no investigators with a financial interest.

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In conclusion, the likelihood that trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

13.3. **Expanded Access**

In the United States (US), tecovirimat has been provided via Emergency Investigational New Drug applications (EINDs) to 4 patients with complications of smallpox vaccination (live vaccinia virus). There was also one ex-US case of keratoconjunctivitis possibly due to cowpoxvirus. 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, and/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.⁹ Please see Appendix for a summary description of these cases.

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Appendix: 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 (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 <i>(Vaccination occurred ~ 2 weeks before being diagnosed with acute myelogenous leukemia; had undergone induction chemotherapy when PV developed)</i> | (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) | 400 mg/day x 14 days (b) (6) | Topical corticosteroids (b) (6) | Applicant assessed that it is possible that CPXV infection had resolved prior to the start of |

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| subsequently tested positive by viral culture, PCR and electron microscopy, for cowpox virus [CPXV]) | | Systemic corticosteroids (b) (6) [redacted] Topical ophthalmic idoxuridine (b) (6) [redacted] | tecovirimat in (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.

^aTopical tecovirimat is an investigational drug; no human data are available other than in the EIND described above.

^bCMX001 (oral, lipid conjugate of cidofovir) is an investigational drug with activity in cell culture against orthopoxviruses.

^cBaits 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).

^dPrior to CPXV diagnosis, patient received topical and systemic corticosteroids, intravenous immunoglobulins, broad-spectrum systemic antibiotics, and topical trifluridine.

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/s/

KIRK M CHAN-TACK
05/05/2018

ADAM I SHERWAT
05/05/2018