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APPLICATION NUMBER:

208627Orig1s000

SUMMARY REVIEW

Combined Cross-Discipline Team Leader and Division Director Review

Date	June 15, 2018
From	Adam Sherwat and Debra Birnkrant
Subject	Cross-Discipline Team Leader and Division Director Review
NDA/BLA #	NDA 208627
Applicant	SIGA Technologies, Inc.
Date of Submission	December 8, 2017
PDUFA Goal Date	August 8, 2018
Proprietary Name / Non-Proprietary Name	TPOXX™ Tecovirimat
Dosage form(s) / Strength(s)	200 mg capsule
Applicant Proposed Indication(s)/Population(s)	Treatment of adult and pediatric patients who have been infected with (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of adult and pediatric patients (weighing greater than 13 kg) with human smallpox disease caused by variola virus

1. Benefit-Risk Assessment

We agree with the detailed Benefit-Risk Assessment provided by Dr. Kirk Chan-Tack in his Clinical Review. The following abbreviated Benefit-Risk Assessment highlights the key issues.

Benefit-Risk Summary and Assessment

Smallpox is a serious and life-threatening disease caused by infection with variola virus, an orthopoxvirus. Historic mortality in variola major, the more common and serious form of smallpox, has been commonly cited at 30%. As a result of an intense global vaccination campaign, the disease was declared eradicated from the world in 1980. However, smallpox remains a high risk to national security and public health due to the bio-threat potential of variola virus. As routine smallpox vaccination in the U.S. ended in the 1970s, most of the U.S. population is susceptible to smallpox. Therefore, medical countermeasures, including antiviral therapies, are critically needed in the event of a smallpox outbreak. Tecovirimat, an orally bioavailable antiviral drug, was developed by the Applicant, SIGA Technologies, Inc., for the treatment of human

smallpox.

The development of antiviral drugs for smallpox presents significant challenges. Because smallpox is a potentially serious and life-threatening disease but does not occur naturally, clinical efficacy trials are not feasible, and human challenge studies in healthy subjects are unethical. Therefore, tecovirimat was developed under the Animal Rule (21 CFR part 314, subpart I), which supports a regulatory approval pathway in which studies using suitable animal models contribute directly to drug approval.

The Applicant conducted pivotal efficacy studies of tecovirimat using two well-characterized, lethal animal models of non-variola, surrogate orthopoxviruses: non-human primates (NHPs) infected with monkeypox virus (MPXV), and rabbits infected with rabbitpox virus (RPXV). Treatment efficacy was clearly demonstrated using these animal models, which have disease characteristics relevant to human smallpox. Clinical pharmacokinetic (PK) and non-clinical PK/pharmacodynamic (PD) data were used to establish a human dosing regimen anticipated to be effective for the treatment of human smallpox in accordance with FDA's Guidance for Industry for Product Development Under the Animal Rule.

Based on the clinical data submitted in support of this New Drug Application (NDA), tecovirimat has a favorable safety profile. In the pivotal safety trial (Study 246-008), most adverse events (AEs) were mild in severity, and AE rates were similar in the tecovirimat and placebo trial arms. There were no deaths or serious AEs (SAEs) judged to be related to tecovirimat. The safety database for tecovirimat is sufficient for the proposed indication under FDA's Animal Rule.

The overall benefit-risk profile of tecovirimat is favorable for the treatment of smallpox disease. In our decision to approve tecovirimat, we considered the available safety and efficacy data, the recommendation for approval by all review disciplines, and the unanimously favorable vote of the Antimicrobial Drugs Advisory Committee.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Smallpox is a disease caused by infection with variola virus. The historic mortality rate for variola major, the more common and serious form of smallpox, was variable but commonly cited at 30%.	Smallpox is a serious and life-threatening disease.
	Because of an intense global vaccination campaign, no cases of human smallpox have occurred since 1978, and the disease was declared eradicated from the world in 1980. Routine smallpox vaccination in the U.S. ended in the 1970s.	Most of the U.S. population is susceptible to smallpox.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Despite the eradication of naturally acquired smallpox, variola virus is categorized by the National Institute of Allergy and Infectious Diseases (NIAID) as a Category A priority pathogen.	Smallpox remains a high risk to national security and public health due to its bio-threat potential.
Current Treatment Options	There are no approved treatments for human smallpox.	An unmet medical need exists for treatment options for human smallpox disease in the event of accidental exposure to or intentional release of variola virus.
Benefit	Tecovirimat was developed under the Animal Rule which supports a regulatory approval pathway in which studies using suitable animal models contribute directly to drug approval. The Applicant conducted pivotal efficacy studies of tecovirimat using two well-characterized, lethal animal models of non-variola, surrogate orthopoxviruses: NHPs infected with MPXV and rabbits infected with RPXV. In the NHP/MPXV model, the appearance of skin lesions, which occurs by Day 4 post-viral challenge, was selected as a trigger for initiation of tecovirimat treatment. A statistically significant treatment benefit over placebo for the primary endpoint of mortality was demonstrated when tecovirimat was dosed at 3, 10, or 20 mg/kg/day for 14 days starting at Day 4 after virus inoculation. In the rabbit/RPXV model, fever, which consistently occurs by Day 4 post-challenge, was selected as a trigger for initiation of tecovirimat treatment. A statistically significant treatment benefit over placebo for the primary endpoint of mortality was demonstrated when tecovirimat was dosed at 20, 40, 80, or 120 mg/kg/day for 14 days starting at day 4 after virus inoculation. Treatment regimens of 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 dosing regimens for human dose selection. In determining the human dose, the PK of tecovirimat was compared between humans and animal models. The exposures in healthy humans using 600 mg BID x 14 days were higher than	Because smallpox is a serious and life-threatening disease but does not occur naturally, clinical efficacy trials are not feasible, and human challenge studies in healthy subjects are unethical. Treatment efficacy was clearly demonstrated using two lethal, well-characterized animal models of non-variola orthopoxvirus infection with disease characteristics relevant to human smallpox. Clinical PK and non-clinical PK/PD data were used to establish a human dosing regimen anticipated to be effective for the treatment of human smallpox.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	those associated with the fully effective doses in either NHP/MPXV or rabbit/RPXV. Studies in immunocompromised animal models have demonstrated reduced efficacy of tecovirimat. Due to the limitations outlined above, the effectiveness of tecovirimat has not been determined in humans.	 Efficacy may be reduced in immunocompromised patients. A Postmarketing Requirement (PMR) will be issued for the applicant to conduct a clinical trial to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical
Risk	Nonclinical toxicology studies demonstrated a neurologic safety signal (e.g., convulsions, tremors, ataxia) which led to the adoption of a maximum allowable exposure level in clinical trials. Based on the clinical data submitted in support of this NDA, tecovirimat has a favorable safety profile. In the pivotal safety trial, 359 healthy subjects received tecovirimat and 90 subjects received placebo. Most AEs were mild in severity, and AE rates were similar in the tecovirimat and placebo trial arms. There were no deaths or SAEs judged to be related to tecovirimat. No seizures or other significant neurological events were reported. The healthy population which composes the safety database may differ considerably from the general population which could receive tecovirimat in the setting of a smallpox emergency.	A neurologic safety signal was demonstrated in nonclinical toxicology studies. Tecovirimat demonstrated a favorable safety profile in clinical trials. A database of at least 300 individuals allows for reasonably reliable detection of adverse reactions occurring at a rate of 1% or greater. The safety database is sufficient for the proposed indication under FDA's Animal Rule.
Risk Management	Tecovirimat has a favorable safety profile.	Safety risks have not been identified that require risk management beyond standard pharmacovigilance in the event of drug use.

2. Background

Smallpox is caused by infection with variola virus, a member of the orthopoxvirus genus of viruses. Historic mortality in variola major, the more common and serious form of smallpox, was commonly cited at 30% but reported to vary widely among outbreaks, ranging from 5% to 40% or higher.(1)

Because of an intense global vaccination campaign, no cases of human smallpox have occurred since 1978, and the disease was declared eradicated from the world in 1980. Despite the eradication of naturally acquired smallpox, variola virus is categorized by the NIAID as a Category A priority pathogen.(2) Category A pathogens are those organisms/biological agents that pose the highest risk to national security and public health. Due to the discontinuation of routine vaccination in the U.S. in the 1970s, most of the U.S. population is now immunologically susceptible to smallpox. Therefore, medical countermeasures, including antiviral therapies, could be of critical importance in the event of a variola (smallpox) virus outbreak.

Because smallpox is a serious and life-threatening disease but does not occur naturally, clinical efficacy trials are not feasible, and human challenge studies in healthy subjects are unethical. Therefore, tecovirimat was developed under the Animal Rule (21 CFR part 314, subpart I), which supports a regulatory approval pathway in which studies using suitable animal models contribute directly to drug approval.(3)

The original Investigational New Drug Application (IND) for tecovirimat was submitted in 2005. Milestone regulatory events included the granting of Fast Track designation in 2005 and Orphan Drug designation in 2006, an FDA Public Workshop in 2009, an Antiviral Drugs Advisory Committee meeting in 2011, and the granting of Rolling Review in 2017. From the time of the IND submission, the Agency has worked closely with the Applicant to guide and foster tecovirimat's development program.

The NDA, submitted by SIGA Technologies Inc. on December 8, 2017, contains information to support the approval of TPOXX (tecovirimat) for the treatment of human smallpox disease caused by variola virus. Tecovirimat is an orally bioavailable antiviral drug that inhibits efficient viral spread to uninfected cells by targeting an orthopoxvirus protein (VP37) involved in the production of extracellular enveloped virus. Tecovirimat would be the first antiviral agent approved in the U.S. for the treatment of smallpox.

This review will present the major findings and key issues from the NDA review of tecovirimat. For a more comprehensive assessment, the reader is referred to the specific discipline reviews for the tecovirimat NDA.

3. Product Quality

NDA 208627 was recommended for approval from the Product Quality perspective by the review team headed by Dr. Stephen Miller. There are no unresolved product quality issues that

would preclude approval at this time. For additional details, please refer to the multi-disciplinary Quality Assessment review.

General product quality considerations

Per the Quality Assessment review, the data presented in the NDA and amendments are adequate to assure that the composition, manufacturing processes, and specifications for tecovirimat are acceptable. The expiration dating period of 84 months when stored at 20°C to 25°C is supported by adequate data. Further extension of the expiration dating may be possible given the high stability of the product. No product quality microbiology issues were identified. The dissolution method and dissolution acceptance criterion were deemed acceptable, and the bridging for the different formulations used in clinical studies was acceptable.

Facilities review/inspection

All facilities inspections have been completed and the Office of Pharmaceutical Quality and Office of Compliance have determined these facilities to be acceptable.

4. Nonclinical Pharmacology/Toxicology

Drs. David McMillan and L. Peyton Myers recommended approval of this NDA based on their review of the nonclinical safety information provided in the submission. Please refer to the Pharmacology/Toxicology review for additional details.

General nonclinical pharmacology/toxicology considerations

Repeat-dose general toxicology studies with tecovirimat were conducted in mice, rats, dogs and monkeys. No adverse drug-related findings were observed in the pivotal 3- month studies in mice or monkeys up to the highest doses tested, and the findings in a 12-day rat study were limited to decreased body weight and food consumption, and mild liver toxicity. Exposure multiples at the no-observed-adverse-effect-levels (NOAELs) in the 3-month mouse and monkey studies were 24.3- and 2.7-fold, respectively, relative to the proposed clinical dose. Phototoxicity and dedicated safety pharmacology studies were negative.

In a 7-day toxicology study in Beagle dogs, adverse findings at the high dose of 300 mg/kg included convulsions, tremors, ataxia, stereotypic walk, excessive blinking, face-twitching, and jerky head movements. Electroencephalography (EEG) findings during the observed convulsions were consistent with seizure activity. The findings at the 300 mg/kg dose correspond to a C_{max} of 16,500 ng/mL in humans. Findings at the mid-dose of 100 mg/kg included tremors and face-twitching; however, no convulsions or seizure activity on EEG were reported. The findings at the 100 mg/kg dose correspond to a C_{max} of 5,575 ng/mL in humans. Drug was detectable in the brain and cerebrospinal fluid at all dose levels, indicating that tecovirimat crosses the blood-brain barrier in this species. Based on these data, a C_{max} of 5,575 ng/mL was selected as the maximum allowable exposure level for humans in clinical trials.

Reproductive toxicology

No adverse findings were observed in females in a mouse fertility and early embryonic development study (exposure multiple = 23.8). However, male reproductive toxicities (increased abnormal sperm counts, decreased sperm motility), and associated decreases in fertility and fecundity indices, were observed in this study at 1000 mg/kg/dose (exposure multiple = 23.8). In an embryofetal development study in rabbits, no fetal toxicities were observed, but maternal toxicities consisting of mortality, seizures, weight loss, premature delivery, total implant loss, increased resorptions, and decreased live fetuses and gravid uterine weights were reported (exposure multiples = 0.1 and 0.4 for maternal and fetal toxicity, respectively). No adverse findings were observed in either an embryofetal development study in mice (exposure multiple = 23.0 for both maternal and fetal toxicity), or in a pre/postnatal development study in mice (exposure multiple = 23.8 for both maternal and fetal toxicity).

Genetic toxicology and carcinogenicity

Genotoxicology studies were negative. Carcinogenicity studies with tecovirimat were not required given the proposed treatment duration of less than 6 months.

5. Clinical Pharmacology

The Office of Clinical Pharmacology reviewed the clinical pharmacology information submitted, and considers the NDA approvable from their perspective. Please refer to the Clinical Pharmacology review by Drs. Su-Young Choi and Ruojing Li for additional details. Please refer to Section 7 for a discussion human dose selection.

General clinical pharmacology/biopharmaceutics considerations, including absorption, food effects, metabolism, half-life, and excretion

Following oral administration of tecovirimat, the time to maximum plasma concentration (T_{max}) is 4-6 hours. The mean C_{max} and AUC_{24} values were higher by 31% and 41%, respectively, under fed conditions as compared to fasted conditions following the administration of tecovirimat twice daily. Tecovirimat is approximately 80% bound to plasma proteins.

The major route of metabolism is amide hydrolysis; primary and secondary glucuronidation is a minor route. The major metabolites in plasma are M4, M5, and TFMBA (4-trifluoromethyl benzoic acid). None of the metabolites is pharmacologically active. The apparent elimination half-life in healthy volunteers is 21 hours. The unchanged drug is mainly eliminated in feces; the metabolites are mainly eliminated in urine.

Critical intrinsic factors potentially affecting elimination: age, sex, race, hepatic impairment, and renal impairment

No clinically significant differences in the pharmacokinetics of tecovirimat were observed based on age, sex, race, hepatic impairment (Child Pugh A, B, or C), or mild to severe renal impairment (not requiring renal replacement therapy).

In subjects with end-stage renal disease requiring hemodialysis, C_{max} and AUC_{inf} values were 33% and 48% lower 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. The etiology of this phenomenon is unclear, although altered drug absorption due to an unexpected drug interaction (e.g., with phosphate binders) is a possibility. While lower exposures were observed in subjects with ESRD requiring hemodialysis, no dose increase is recommended at this time. A dose increase would result in significant accumulation of major metabolites, specifically TFMBA, potentially impacting safety. Meanwhile, a 50% lower tecovirimat exposure in humans is still comparable to exposures observed in NHPs at 10 mg/kg/day where maximal efficacy (survival) was observed. Post-marketing studies will be requested to investigate the etiology of this finding and to ensure proper dosing for this patient population.

Body weight was a significant covariate for the clearance of tecovirimat within the range observed in Study 246-008 (54 kg to 145 kg) and thus lower exposures are predicted in patients with higher body weight. Post-marketing studies in subjects with high body weight will be requested to inform appropriate dosing for this population.

Drug-drug interactions

Tecovirimat is a substrate of UGT1A1/4, and tecovirimat exposures can be increased or decreased by the concomitant use of UGT1A1/4 inhibitors or inducers, respectively.

Tecovirimat is a weak inducer of CYP3A and a weak inhibitor of CYP2C8 and CYP2C19. Based on the anticipated magnitude of interaction and the recommended duration of treatment with tecovirimat, no clinically relevant effect on drug exposure is expected for most substrates of CYP3A, CYP2C8 or CYP2C19.

A drug interaction study performed with repaglinide (a sensitive substrate of CYP2C8) in healthy, non-diabetic subjects, demonstrated mild to moderate hypoglycemia in 10 of 30 subjects administered repaglinide with tecovirimat. Hypoglycemia was not reported in subjects who received repaglinide alone. Of note, blood glucose levels were determined only in subjects who had symptoms due to hypoglycemia. Therefore, it is possible that some subjects had subclinical hypoglycemia that was not captured as blood glucose levels were not measured. Given the relatively small magnitude of the interaction (<30% increase in repaglinide concentrations) it is unlikely that a drug interaction was solely responsible for apparent imbalance in hypoglycemia cases. However, the United States Prescribing Information (USPI) will include a Warning summarizing the study results and recommending blood glucose monitoring if repaglinide and tecovirimat are co-administered.

Pediatrics:

Tecovirimat has not been studied in children. Due to ethical concerns, a PK study cannot be conducted in healthy children, thus pediatric dosing regimens were determined based on modeling and simulation conducted by the clinical pharmacology review team. Modeling generated dosing recommendations across all pediatric weight bands, but the USPI will initially

only include dosing recommendations for pediatric patients weighing ≥ 13 kg. Dosing of pediatric patients less than 13 kg would require dose increments less than 200 mg (i.e., less than 1 capsule). (b) (4)

QT assessment:

A thorough QT study was conducted for tecovirimat, which was reviewed by the QT-Interdisciplinary Review Team (IRT). No significant QTc prolongation was observed in the study for a single dose of 1000 mg tecovirimat, which corresponds to the therapeutic exposure of tecovirimat. However, significant accumulation is expected for three metabolites (2 to 5-fold) and the exposure after a single dose of 1000 mg of tecovirimat does not cover the expected steady-state exposure of these metabolites. Therefore, QT-IRT also reviewed electrocardiographic data from the pivotal safety study (Study 246-008). Based on their review of the results of the thorough QT study combined with their review of Study 246-008, QT-IRT concluded that small mean increases (i.e., 10 ms) in the QTc interval can be excluded at the therapeutic exposure for tecovirimat.

6. Clinical Microbiology

Drs. Patrick Harrington and Eric Donaldson recommended approval of this NDA based on their reviews of the virology and next generation sequencing data provided in the submission. Please refer to the Virology Reviews by Drs. Harrington and Donaldson for a detailed assessment of the virology and next generation sequencing data.

Tecovirimat is a small molecule antiviral drug that targets the highly conserved orthopoxvirus VP37 protein within an infected cell to block a viral envelope wrapping step, resulting in inhibition of viral spread to uninfected cells. In cell culture assays, tecovirimat demonstrated broad antiviral activity and similar potency against orthopoxviruses, including variola virus, monkeypox virus, rabbitpox virus and vaccinia virus.

Tecovirimat resistance could be selected in multiple different orthopoxviruses in cell culture, and was associated with the emergence of amino acid substitutions in VP37. There are several potential independent pathways for the generation of orthopoxviruses with high-level phenotypic resistance to tecovirimat, which in many cases require only a single amino acid substitution. Due to the potential threat of variola virus being developed as a biological weapon, the specific tecovirimat resistance pathways will not be described in this review.

7. Clinical/Statistical- Efficacy

Background

As previously noted, smallpox is a potentially serious threat but does not occur naturally; therefore, clinical efficacy trials are not feasible, and human challenge studies in healthy subjects are unethical. For these reasons, tecovirimat was developed under the Animal Rule (21 CFR part

314, subpart I), which supports a regulatory approval pathway in which studies using suitable animal models contribute directly to drug approval.

In theory, the ideal animal model for smallpox would involve infection of animals directly with variola virus, but natural variola virus infection and smallpox disease are specific to humans. Current lethal NHP models using variola virus are not consistently reproducible and do not mimic what is known about human smallpox disease. Furthermore, studies of variola virus present numerous feasibility challenges due to the worldwide restriction of variola virus research to two maximum containment laboratories.

Because of the unique complexities of drug development in this area, extensive discussion with multiple stakeholders has taken place, including an FDA public workshop in 2009 and an FDA public Advisory Committee meeting in 2011.[4,5] During the 2011 Antiviral Drugs Advisory Committee meeting, the advisory committee agreed with the FDA's assessment of the scientific and practical limitations of the available variola virus/NHP model. Furthermore, the FDA and advisory committee concluded that a combination of other lethal animal models using surrogate orthopoxviruses could be used to evaluate the efficacy of antiviral drugs for smallpox, provided the drug target is conserved across different orthopoxviruses. 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 predictive of human response to the treatment of smallpox.

Guided by the above recommendations, SIGA conducted pivotal efficacy studies of tecovirimat using two well-characterized, lethal animal models of non-variola, surrogate orthopoxviruses: NHPs infected with MPXV and rabbits infected with RPXV. The Applicant and the Division reached consensus on key study design and study conduct parameters prior to the initiation of the studies. Mortality, based on prospectively defined criteria for euthanasia, was the primary efficacy endpoint in these studies.

This section will briefly review the results of the pivotal studies supporting the proposed indication, and will summarize the basis for dose selection in humans. For additional details on the animal efficacy studies, please refer to the Clinical Review by Dr. Chan-Tack, the Virology Review by Drs. Patrick Harrington and Eric Donaldson, the Pharmacology/Toxicology review by Drs. David McMillan and L. Peyton Myers, and the Statistical Review by Dr. Wen Zeng. For additional details on human dose selection, please refer to the Clinical Pharmacology review by Drs. Su-Young Choi and Ruojing Li.

Study designs and key efficacy results

NHP/MPXV Efficacy Studies

In the NHP/MPXV efficacy studies, cynomolgus macaques were challenged intravenously with a high viral challenge dose of 5×10^7 plaque-forming units (PFU) of the MPXV Zaire '79 strain. This strain was originally collected from a severely ill child survivor during a 1978-1979 MPXV outbreak in Zaire (now Democratic Republic of Congo) in which there was high mortality.

Disease in this model is rapid, resulting in a systemic viremia and disease signs such as fever, rash and skin lesions that resemble features of human smallpox. Mortality is nearly universal, with a mean time to death or moribund disease requiring humane euthanasia at approximately 14 days post-challenge. The appearance of skin lesions, which occurs by Day 4 post-viral challenge in this model, was selected as a trigger for initiation of tecovirimat treatment that would be relevant to the treatment of human smallpox.

Using the NHP/MPXV model, the Applicant completed four studies in which tecovirimat was started at the time of lesion onset. All four studies were randomized and placebo-controlled; three of four were double-blinded. A statistically significant treatment benefit over placebo for the primary endpoint of mortality was demonstrated when tecovirimat was dosed at 3, 10, or 20 mg/kg/day for 14 days starting at Day 4 after virus inoculation (Appendix 1). 10 mg/kg/day was selected as the fully effective dose to ensure that drug levels used to determine the effective human dose would exceed the minimally effective dose in this model.

Rabbit/RPXV Efficacy Studies

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

Using the rabbit/RPXV model, the Applicant completed two randomized studies in which tecovirimat was started at the time of fever onset. The pivotal efficacy study was placebo-controlled; the PK study was not. A statistically significant treatment benefit over placebo for the primary endpoint of mortality was demonstrated when tecovirimat was dosed at 20, 40, 80, or 120 mg/kg/day for 14 days starting at day 4 after virus inoculation (Appendix 2). 40 mg/kg/day was selected as the fully effective dose to ensure that drug levels used to determine the effective human dose would exceed the minimally effective dose in this model.

Human Dose Selection

Human PK data of the investigational agent, combined with PK and PD data obtained in the same animal models that were used to demonstrate animal efficacy, were used to identify an efficacious dose in humans under the Animal Rule. The dosing regimen for humans was selected to provide exposures that exceeded those associated with the fully effective dose in animals, as recommended under FDA's Animal Rule Guidance.

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 human dosing regimen, 600 mg BID under fed conditions, were also collected in healthy volunteers in 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. In determining the human dose, the PK of tecovirimat was compared between humans and animal models. The exposures in healthy humans using 600 mg BID x 14 days were higher than those associated with the fully effective doses in either NHP/MPXV or rabbit/RPXV (Appendix 3). Based on these PK results, the favorable safety profile of tecovirimat as demonstrated in Study 246-008 (see Section 8), and the limitations on human exposure based on the toxicology findings (see Section 4), a human dosing regimen of 600 mg BID x 14 days was selected.

Conclusions on Effectiveness

Treatment efficacy was clearly demonstrated using two lethal, well-characterized animal models of non-variola orthopoxvirus infection with disease characteristics relevant to human smallpox. Clinical PK and non-clinical PK/PD data were used to establish a human dosing regimen anticipated to be effective for the treatment of human smallpox.

As required by the Code of Federal Regulations [21CFR314.610], a PMR will be issued for the applicant to conduct a clinical trial to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical (see Section 13).

8. Safety

This section will provide a summary of safety focusing on Study 246-008, the pivotal clinical safety and PK trial using the proposed treatment regimen. As no unique safety signals were demonstrated in the earlier clinical trials, the safety profile of tecovirimat as demonstrated in Study 246-008 is illustrative of the overall safety profile of the product. For a complete description of the Agency's safety assessment for tecovirimat, please refer to the Clinical Review performed by Dr. Kirk Chan-Tack.

Adequacy of the safety database, Applicant's safety assessments, and submission quality

The safety database at the time of the NDA submission included 788 subjects who had been exposed to tecovirimat (at any dose and for any duration) across the entire development program. A total of 437 healthy adult subjects received the proposed dosing regimen of 600 mg BID x 14 days: 78 subjects during Phase 1 and 359 subjects in Study 246-008. Given tecovirimat's restricted indication, Orphan Drug designation, and favorable safety profile, the Agency deemed the safety database to be adequate.

The Applicant provided a basic assessment of safety as a component of the NDA submission. No substantive issues with data integrity were identified.

Study design

The pivotal safety trial, Study 246-008, was a double-blind, randomized, placebo-controlled, multi-center trial that assessed the safety, tolerability, and pharmacokinetics of tecovirimat

administered orally for 14 days to healthy subjects. A total of 452 subjects were enrolled, and 449 of these subjects were randomized to treatment groups and received at least one dose of study medication. These 449 subjects were included in the safety population: 359 in the tecovirimat group and 90 in the placebo group.

Key safety results, including deaths, serious adverse events (SAEs), discontinuations due to AEs, and results of laboratory tests

The safety profile of tecovirimat was favorable. Common adverse drug reactions (ADRs, i.e., adverse events assessed as reasonably associated with the use of the drug) that occurred in greater than 2% of subjects in Study 246-008 are displayed in Table 1. Most of the adverse reactions reported in Study 246-008 were mild in severity.

Table 1: Treatment-emergent ADRs Reported in ≥ 2% of Subjects, All Grade, Study 008

Adverse Reaction	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%)

*Includes abdominal pain, abdominal pain upper, abdominal distension, abdominal discomfort, abdominal pain lower, epigastric pain.
Table adapted from the FDA Clinical Review

There was only one death in Study 246-008; this event was also the only SAE in the trial. The death was due to pulmonary embolism and occurred in a 46-year-old female with a history of lower extremity deep venous thrombosis (DVT) and concomitant use of Depo-Provera. Seven days post-completion of her 14 day tecovirimat regimen, she developed acute shortness of breath and chest pain at home. She subsequently developed pulseless electrical activity in route to the hospital and died. Her autopsy revealed extensive pulmonary embolism with no other significant gross or microscopic abnormalities. Toxicology results were negative. The AE of pulmonary embolism was considered not related to study drug by the investigator and the Applicant. Based on the subject's history of DVT, concomitant Depo-Provera use, and the absence of an anticipated drug interaction with tecovirimat, the Agency agrees with the investigator's assessment.

Six subjects stopped study drug due to an AE in Study 246-008. These events are summarized in the Table 2 below. Most of these events were mild in severity and all events resolved without sequelae.

Table 2: AEs Leading to Discontinuation of Tecovirimat

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

Table adapted from the FDA Clinical Review

Laboratory analyses did not reveal any significant safety concerns. Graded laboratory abnormalities occurred with a similar frequency in the tecovirimat and placebo arms.

Submission-specific safety issues

As previously noted, non-clinical toxicology studies in dogs demonstrated neurological effects (e.g., tremors, seizures) at higher than anticipated clinical exposures of tecovirimat. As a precaution, electroencephalograms (EEGs) were assessed in a cohort of subjects (65 in the tecovirimat arm, 16 in the placebo arm) in Study 246-008. No seizure events were reported, but one asymptomatic subject (displayed in Table 2 above) discontinued tecovirimat due to an abnormal EEG. The clinical significance of this finding is unknown.

9. Advisory Committee Meeting

An Advisory Committee meeting was convened for this application on May 1, 2018. 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.

The regulatory considerations (including the requirements of FDA's Animal Rule as outlined in the Code of Federal Regulations [21CFR 314.610]), safety, efficacy, and pharmacokinetic data were presented and discussed. 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. Pediatrics

No pediatric trials were submitted in support of this NDA. Please refer to Section 5 (Clinical Pharmacology) for a discussion of pediatric dose selection based on modeling and simulation. Tecovirimat has orphan drug status and is therefore exempt from Pediatric Research Equity Act (PREA) requirements.

11. Other Relevant Regulatory Issues

- *Financial disclosures*

Financial disclosures were provided and reviewed for investigators involved in the relevant clinical trials. There were no financial disclosures of significant concern, individually or collectively. The financial disclosures do not impact the approvability of TPOXX. Please refer to the Clinical Review for additional details.

- *Other Good Clinical Practice (GCP) issues*

The clinical trials discussed in this review were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Counsel (ICH) Good Clinical Practice (GCP) guidelines.

- *Office of Scientific Investigations (OSI) audits*

Three U.S. clinical sites from Trial 246-008 were selected for inspection. Factors considered when selecting sites included high enrollment, protocol deviations and screen failure rate. The Applicant (SIGA Technologies, Inc.) was also inspected.

Per OSI's assessment, no regulatory violations were found during inspections at two of the three clinical investigator (CI) sites, and no regulatory violations were found during the inspection of the Applicant. These inspections are classified as No Action Indicated (NAI). Regulatory violations were found during the inspection of one CI site (Site #103) for failure to follow the investigational plan and failure to prepare or maintain accurate case histories with respect to data pertinent to the investigation. However, per OSI's assessment, these findings do not appear to impact the validity of the data at the site. Therefore, the data from the CI sites and the Applicant in support of the pending application are acceptable, and the study was conducted adequately to support approval.

Please refer to the OSI Consult Review for further details.

- *Office of Study Integrity and Surveillance (OSIS) audits*

OSIS inspected two CI sites that participated in evaluating the pharmacokinetics of tecovirimat in Study 246-008. No objectionable conditions were observed and the final inspection classification for both sites was NAI. OSIS concluded that the clinical data generated by the two inspected sites are reliable and should be accepted for further Agency review.

OSIS also inspected the pivotal NHP/MPXV and rabbit/RPXV efficacy studies. Their inspection confirmed the data integrity of these studies.

Please refer to OSIS' Consult Reviews for further details.

12. Labeling

Prescribing Information

The summary that follows reflects the major changes to the Applicant's labeling that have been proposed by the Agency and accepted by the Applicant. Please refer to the individual FDA reviews from each of the review disciplines for additional details.

- INDICATIONS AND USAGE section:

The indication for tecovirimat was narrowed from the Applicant's proposed indication to one limited to the treatment of human smallpox disease caused by variola virus.

Limitations of use were included to reflect that the effectiveness of TPOXX has not been determined in humans, and that efficacy may be reduced in immunocompromised patients.

- DOSAGE AND ADMINISTRATION section:

Dosing recommendations for pediatric patients weighing at least 13 kg were included in labeling based on modeling and simulation analyses.

- ADVERSE REACTIONS section:

In accordance with FDA guidance, the listing of adverse events was limited to those events for which there was at least a possible causal relationship with the drug (i.e., adverse reactions).

- DRUG INTERACTIONS and CLINICAL PHARMACOLOGY sections:

A statement was included that no clinically relevant effects on drug exposure are expected for most substrates of CYP3A, CYP2C8 or CYP2C19, even though tecovirimat is a weak inducer of CYP3A and a weak inhibitor of CYP2C8 and CYP2C19.

A statement was included that co-administration of TPOXX at the same time as live smallpox vaccine may reduce the immune response to the vaccine, and that the clinical impact of this interaction on vaccine efficacy is unknown.

The Microbiology sub-section was revised to remove (b) (4)

- USE IN SPECIFIC POPULATIONS section

A statement was included to indicate that clinical studies of TPOXX did not include sufficient numbers of subjects aged 65 and over to determine whether the safety profile of TPOXX is different in this population compared to younger subjects.

- NONCLINICAL TOXICOLOGY section:

A statement was included to indicate that decreased male fertility associated with testicular toxicity (increased percent abnormal sperm and decreased sperm motility) was observed in male mice at 1000 mg/kg/day (approximately 24 times the human exposure at the recommended human dose).

Information was included describing the neurologic findings in dogs (see Section 4).

- CLINICAL STUDIES section:

In accordance with FDA guidance, this section was limited to describing the animal efficacy studies that used the to-be-recommended treatment duration.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Based on the overall safety profile of tecovirimat, a REMS is not recommended.

Postmarketing Requirements (PMRs) and Postmarketing Commitments (PMCs)

To date, the Agency has determined that the following should be issued:

Clinical PMR

- Conduct a clinical trial to evaluate the clinical response, drug concentration, and safety profile of tecovirimat when used in the treatment of subjects with variola virus infection.

Clinical Pharmacology PMCs

- Conduct a study to determine the pharmacokinetics of tecovirimat in subjects with high body weight (>120 kg) and determine the necessity of a change in dosing regimen in those subjects.

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

Virology PMC

- Conduct cell culture studies to characterize tecovirimat antiviral activity against an expanded panel of variola virus isolates and recombinant vaccinia viruses. These studies should capture the known VP37 amino acid heterogeneity in variola viruses, as well as a common orthopoxvirus VP37 polymorphism, and should also include multiple independent isolates with identical VP37 amino acid sequences, when feasible.

Product Quality PMC

- Conduct and submit a risk assessment for elemental impurities when new batches of the drug product are manufactured.

General PMC

- Conduct a human factors validation study to demonstrate that representative users (e.g. healthcare providers and lay users) can safely and effectively prepare and administer tecovirimat to pediatric patients requiring less than a 200 mg dose (i.e. less than 1 full capsule) under simulated use conditions that are representative of realistic use conditions.

14. References

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

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

3. Guidance for Industry. Product Development Under the Animal Rule. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm399217.pdf.

4. Materials for the 2009 FDA Public Workshop are available at: https://www.federalregister.gov/documents/2009/08/18/E9-19781/development-of-antiviral-products-for-treatment-of-smallpox-and-related-poxvirus-infections-public.

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

15. Appendices

Appendix 1: Summary of selected NHP/MPXV studies with tecovirimat

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

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

Appendix 2: Summary of selected rabbit/RPXV studies with tecovirimat

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

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

Appendix 3: Tecovirimat pharmacokinetic parameters in healthy volunteers, NHP/MPXV, and rabbit/RPXV

		Cmax (ng/mL)	AUC24 (ng/mL·hr)	Cmin (ng/mL)
Day1	Human (N=48)	1516 (761-3290, 32%)	20879 (10627-45733, 35%)	477 (143-2020, 65%)
	NHP (N=6)	749 (378-1320, 42%)	7629 (4577-13294, 39%)	134 (37.3-339, 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)
- PK in human: tecovirimat 600 mg BID under fed conditions for 14 days in healthy volunteers (Study 008).
- PK in NHP: tecovirimat 10 mg/kg/day for 14 days (FY 10-087)
- PK in rabbits: tecovirimat 40 mg/kg/day for 14 days (SR14-008)
- Steady state PK data: 14^{th} day dosing for human and NHP and 7^{th} day dosing for rabbits. As the PK of tecovirimat in rabbits were lower on Day 14 as compared to Day 7, comparisons were made using Day 7 data as a conservative assessment for human dose selection.

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/s/

ADAM I SHERWAT
06/15/2018

DEBRA B BIRNKRANT
06/15/2018
I am in agreement with the conclusions reached by the multidisciplinary review team that the benefits of tecovirimat outweigh any risks of tecovirimat for the treatment of smallpox infection.