CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214460Orig1s000
214461Orig1s000

SUMMARY REVIEW

Combined Cross-Discipline Team Leader and Division Director Review

Date	
From	Kimberly Struble and Debra Birnkrant
Subject	Cross-Discipline Team Leader and Division Director Review
NDA/BLA #	NDA 214460 and 214461
Applicant	Chimerix
Date of Submission	October 7, 2020
PDUFA Goal Date	Original 4/7/2021, major amendment and PDUFA goal date extension granted on February 18, 2021. New PDUFA goal date is 7/7/2021
Proprietary Name / Non-Proprietary Name	TEMBEXA Brincidofovir (BCV)
Dosage form(s) / Strength(s)	10 mg/mL oral suspension and 100 mg oral tablet
Applicant Proposed Indication(s)/Population(s)	TEMBEXA® is indicated for the treatment of human smallpox disease caused by variola virus in adult and pediatric patients.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	TEMBEXA® is indicated for the treatment of human smallpox disease caused by variola virus in adult and pediatric patients, including neonates.

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. Brincidofovir (BCV), an orally bioavailable antiviral drug, was developed by the Applicant, Chimerix, 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, BCV 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 BCV using two well-characterized, lethal animal models of non-variola, surrogate orthopoxviruses: rabbitpox model (New Zealand White rabbits infected with rabbitpox virus) and the mousepox model (BALB/c mice infected with ectromelia virus). 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), the safety profile of BCV is acceptable based on risk mitigating labeling which includes a Box Warning, and several WARNINGS and PRECAUTIONS. Available human data with BCV are obtained from randomized, double-blind, placebo-controlled, multicenter, clinical trials that evaluated non-smallpox indications. The most common adverse reactions experienced in the first 2 weeks of dosing were diarrhea and nausea. The risk of increased mortality observed in a CMV trial for dosing durations greater than two weeks is adequately conveyed in product labeling. The safety database for BCV is sufficient for the proposed indication under FDA's Animal Rule.

The overall benefit-risk profile of BCV is favorable for the treatment of smallpox disease. BCV fills an important unmet medical and has some advantages over the currently approved tecovirimat. Specifically, BCV and tecovirimat have distinct mechanisms of action and BCV does not rapidly select for resistance whereas tecovirimat has a low genetic barrier to resistance. BCV has a lower pill burden compared to tecovirimat and an oral solution is available for those who cannot swallow tablets, including data to support use via enteral or nasogastric tubing. The oral solution is also available for dosing down to neonates; whereas, tecovirimat does not have a pediatric formulation and only has dosing down to 13 kg. While the overall safety profile of BCV is acceptable, some safety concerns such as GI and hepatoxicity were identified. However, these safety concerns are adequately described in product labeling along with risk mitigation strategies.

In our decision to approve BCV, we considered the available safety and efficacy data. All review disciplines recommended approval and we (the Cross-Discipline Team Leader and Division Director) agree with the review team's assessment and recommend approval. BCV was not eligible to receive a medical counter measure priority review voucher (MCM PRV) because BCV contains the same active moiety as that previously approved in NDA 20638 for Vistide (cidofovir, CDV) in 1996. As a result, the request for a MCM PRV was denied.

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%. 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. 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 is a serious and life-threatening disease. Most of the U.S. population is susceptible to smallpox. Smallpox remains a high risk to national security and public health due to its bio-threat potential.
Current Treatment Options	Tecovirimat is currently the only approved antiviral treatment regimen for patients with human smallpox disease caused by variola virus.	Due to concerns regarding potential biothreat uses of variola virus, the theoretical potential to create an antiviral drug-resistant variola virus bioweapon, and the potential for drug resistance to emerge

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		with the use of antiviral treatment, a specific unmet medical need exists for multiple effective antiviral regimens for subjects who develop smallpox disease caused by variola virus because only one approved regimen is currently available.
Benefit	BCV 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 BCV using two well-characterized, lethal animal models of non-variola, surrogate orthopoxviruses: rabbits infected with rabbitpox virus and mice infected with ectromelia virus. In the rabbit/RPXV model, fever, which consistently occurs by Day 4 post-challenge, was selected as a trigger for initiation of BCV treatment. A statistically significant treatment benefit over placebo for the primary endpoint of mortality (90% survival for BCV vs 29% for PBO) was demonstrated when BCV was dosed at 20/5/5 mg/kg (administered every 48 hours for 3 doses) starting at day 4 after virus inoculation. The fully effective dose of BCV defined by the Animal Rule guidance is 20/5/5 mg/kg. In the mouse/ECTV model, a clinically evident sign of disease could not be identified to use as a trigger to initiate treatment; therefore, various time-points during peak disease were evaluated. A statistically significant treatment benefit over placebo for the primary endpoint of mortality (78% survival for BCV vs 13% for PBO) was demonstrated when BCV was dosed at 10/5/5 mg/kg (administered every 48 hours for 3 doses) starting at day 4 after virus inoculation. The fully effective dose of BCV defined by the Animal Rule guidance is 10/5/5 mg/kg.	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 demonstrated using two lethal animal models of non-variola orthopoxvirus infection with disease characteristics relevant to human smallpox.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	In determining the human dose, the PK of BCV was compared between humans and animal models. The exposures in humans using 200 mg once weekly for two doses on Days 1 and 8 were higher than those associated with the fully effective doses in the animal model data. Due to the limitations outlined above, the effectiveness of BCV has not been determined in humans.	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. The Applicant agreed to a Post Marketing Requirement (PMR) 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 identified GI and hepatic toxicities, both of which were seen in human trials evaluating non-smallpox indications. Based on the clinical data submitted in support of this NDA, BCV has an acceptable safety profile with appropriate risk mitigation strategies outlined in product labeling. In trials evaluating non-smallpox indications, 392 adult subjects received the to be approved dose of BCV and 208 subjects received placebo. The safety database is considered adequate to support approval. GI events and hepatoxicity were the major safety findings. Diarrhea, nausea and vomiting were the most commonly reported adverse drug reactions (ADR). The population which composes the safety database (most of which are immunosuppressed) may differ considerably from the general population which could receive BCV in the setting of a smallpox emergency.	GI and hepatotoxicity were the major safety signals identified in trials. BCV demonstrated an acceptable 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	BCV has an acceptable safety profile for the intended patient population. A Box Warning and Warning in section 5 of labeling includes text to indicate BCV is not indicated for use in other disease other than human smallpox because an increase in mortality was observed in another disease. As a result, BCV should not be used for a duration longer than the recommended dosage on Days 1 and 8 and should also not be used off-label for other indications. Section 5 of labeling also includes warnings and risk mitigation strategies regarding risk of transaminase and total bilirubin elevations, risk of diarrhea and other GI events, embryo-fetal toxicity and testicular toxicity which may irreversibly impair fertility based on nonclinical studies, and to warn that BCV is considered a potential human carcinogen.	Safety concerns associated with BCV are adequately addressed in product labeling. 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, BCV 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 BCV was submitted in 2005. Milestone regulatory events included the granting of Fast Track designation in 2005 and Orphan Drug designation in 2018, an FDA Public Workshop in 2009, an Antiviral Drugs Advisory Committee meeting in 2011, and the granting of Rolling Review in 2020.(4,5) From the time of the IND submission, the Agency has worked closely with the Applicant to guide and foster BCV's development program.

The NDAs, submitted by Chimerix, on October 7, 2020, contains information to support the approval of TEMBEXA (brincidofovir, BCV) for the treatment of human smallpox disease caused by variola virus. BCV is an antiviral agent that interferes with critical steps in the replication cycle of variola virus. BCV would be the second antiviral agent approved in the U.S. for the treatment of smallpox.

This document presents the major findings and key issues from each discipline's review. For a more comprehensive assessment, the reader is referred to the specific discipline reviews for the BCV NDA.

3. Product Quality

NDA 214460 and 214991 was recommended for approval from the Product Quality perspective by the review team led by Dr. Erika Englund. 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 NDAs and amendments are adequate to assure that the composition, manufacturing processes, and specifications for BCV are acceptable. The expiration dating period for (b) (4) tablets (b) (4) is 48 months when stored at 15°C to 30°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.

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. Mark Seaton, David McMillan and L. Peyton Myers recommended approval of these NDAs 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

Single and repeat-dose general toxicology studies with BCV were conducted in mice, rats, rabbits and cynomolgus monkeys. BCV-related nonclinical toxicities tended to affect rapidly dividing cell populations of the gastrointestinal epithelium, spermatogonia, and sebaceous glands (after IV administration). Gastroenteropathy was dose limiting in rats and monkeys following daily oral dosing at systemic exposures less than the expected human exposure based on the to be approved dose. Gastric adverse events we also seen in humans. Subsequently repeat-dose studies in rats (6 months) and monkeys (9 months) were dosed twice weekly to avoid the gastric toxicity. In these studies, the primary toxicity was on the reproductive organs.

Increases in ALT were seen in rodent and non-rodent species. ALT increases were more prominent in monkeys compared to mice followed by rats. The ALT increases were not correlated with exposure and reversed after cessation of dosing. Additionally, no gross or microscopic hepatic changes correlated with ALT increases. ALT and bilirubin increases were also seen in humans.

Reproductive toxicology

Nonclinical reproductive assessments demonstrated that BCV should be considered a potential teratogen and may affect male fertility. In rats, depletion of spermatogenesis

and epididymal hypospermia were noted. In monkeys, testicular atrophy, epididymal and seminal vesicle/prostate changes were seen. Reductions in mating and fertility and reduced maternal and fetal weights along with decreased embryo viability were seen in rats. In rabbits, effects on intrauterine growth, survival and morphology, including external malformations and visceral and skeletal developmental variations were observed. These reproductive toxicities were seen at systemic exposures in rats and rabbits that are less than the expected human exposure.

Genetic toxicology and carcinogenicity

Repeat-dose general toxicology studies demonstrated the tumorigenic effect of BCV in rats. Consequently, BCV is considered a potential carcinogen. Palpable tissue masses were seen in rats and were considered malignant mammary gland adenocarcinomas and squamous cell carcinomas. These findings were seen at exposures less than the expected human exposure.

BCV was negative for mutagenicity in the Ames test, negative for clastogenicity in the mouse micronucleus test, and was weakly positive for increased structural aberrations in the absence of metabolic activation in the chromosome aberrations assay.

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 Timothy Bensman for additional details. Please also 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 IV administration of BCV, the time to maximum plasma concentration (T_{max}) is 3 hours. The intracellular active metabolite, cidofovir diphosphate (CDV-PP), reaches T_{max} at 47 hours, with a mean half-life of 113 hours. BCV is approximately > 99.9% bound to human plasma proteins.

BCV is metabolized by hydrolysis of the phosphoester bond to form CDV. CDV is subsequently phosphorylated to form CDV-PP. BCV is also carboxylated at the terminal carbon by Cytochrome P450 (CYP) 4F2, followed by subsequent CYP-mediated oxidations and multiple cycles of fatty acid beta-oxidation. The major inactive metabolites formed via these pathways are CMX103 (3 hydroxypropyl ester of CDV) and CMX064 (4-(3-propoxy)butanoic acid ester of CDV). The unchanged drug as metabolites is eliminated in the urine (51%) and feces (40%).

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

No clinically meaningful differences in the pharmacokinetics of BCV were observed based on age, sex, race, reduced activity in the CYP4F2 enzyme, hepatic impairment (Child Pugh Class B or C), and renal impairment including end stage renal disease with and without dialysis.

Drug-drug interactions

Clinical drug interaction studies were conducted with midazolam, dabigatran etexilate and cyclosporine.

No clinically significant differences in the PK of midazolam or dabigatran etexilate were observed when administered concomitantly with BCV. Clinically significant increases in BCV AUC and C_{max} were seen following a single 600 mg oral dose of cyclosporine. Mean BCV AUC and C_{max} increased by 374% and 269%, respectively. This interaction led to the clinical recommendations regarding inhibitors for OATP1B1 and 1B3 (such as clarithromycin, cyclosporine, erythromycin, gemfibrozil, HIV and HCV protease inhibitors, and rifampin) in section 7 of product labeling. Specifically, where possible, consider alternative medications that are not OATP1B1 or 1B3 inhibitors. If concomitant use with TEMBEXA is necessary, increase monitoring for adverse reactions associated with TEMBEXA (elevations in transaminases and bilirubin, diarrhea, or other GI adverse events) and postpone the dosing of OATP1B1 or 1B3 inhibitors for at least 3 hours after TEMBEXA administration.

Of note, in vitro, BCV is a direct and reversible inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP4F2. In vitro, BCV is an inhibitor of Breast Cancer Resistance Protein (BCRP), multidrug resistance-associated protein 2 (MRP2), bile salt export pump (BSEP), Organic Anion Transporter 1 (OAT1), and OAT3. However, these in vitro results in combination with clinical PK data indicate a low DDI potential and were not evaluated clinically.

Pediatrics:

BCV was studied in 23 hemotopoietic stem cell transplant pediatric subjects aged 7 months to 17 years in a randomized, placebo-controlled trial. An additional 166 pediatric subjects aged 3 months to 18 years of age received TEMBEXA from uncontrolled studies and expanded access. PK simulation was used to derive dosing regimens that are predicted to provide pediatric patients, including neonates, with exposures comparable to the observed exposures in adults receiving BCV tablets. Please refer to the Human Dose Selection subsection for the pediatric dosing rationale.

QT assessment:

A thorough QT study was conducted for BCV and reviewed by the QT-Interdisciplinary Review Team (IRT). No significant QTc prolongation was observed in the study for a single dose of 200 mg and 350 mg BCV. The largest upper bounds of the 2-sided 90% CI for the mean difference between CMX001 (200 mg and 350 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. In conclusion, BCV does not prolong QTc to any clinically relevant extent.

6. Clinical Microbiology

Drs. Patrick Harrington and Eric Donaldson recommended approval of these NDAs 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.

BCV is a lipid conjugate of CDV, which is an acyclic nucleotide analog of (deoxy)cytidine monophosphate. Once inside cells, the lipid ester linkage of BCV is cleaved to liberate CDV, which is then phosphorylated to produce the active triphosphate, referred to as CDV diphosphate (CDV-PP). CDV-PP is an inhibitor of orthopoxvirus replication by inhibiting viral DNA synthesis mediated by the E9L (vaccinia virus [VACV] nomenclature) viral DNA polymerase. In cell culture assays, BCV demonstrated broad antiviral activity and similar potency against orthopoxviruses, including variola virus, rabbitpox virus, ectromelia virus, cowpox, camelpox virus and monkeypox virus.

Drug resistance analyses in cell culture studies identified amino acid substitutions in the viral DNA polymerase that reduce BCV and CDV antiviral activity. Due to the potential threat of variola virus being developed as a biological weapon, the specific BCV 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, BCV 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, Chimerix conducted pivotal efficacy studies of BCV using two lethal animal models of non-variola, surrogate orthopoxviruses: rabbits infected with RPXV and mice infected with ECTV. 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. Mark Seaton and David McMillan, and the Statistical Review by Dr. Yu Cao. For additional details on human dose selection, please refer to the Clinical Pharmacology review by Drs. Su-Young Choi and Timothy Bensman.

Study designs and key efficacy results

Rabbit/RPXV Efficacy Studies

In the rabbit/RPXV efficacy studies, 13-16-week-old New Zealand white rabbits were challenged intradermally with a target of 600 plaque-forming units (PFU) of the RPXV Utrecht strain. As stated in the clinical virology review, the challenge dose was deemed acceptable and would provide a high degree of lethality. Disease in this model is rapid and consistent with what is known about variola virus infection of humans, and only a very low viral challenge dose is required to cause severe disease (e.g., LD_{50} estimated to be < 10 PFU for 9-week-old animals). 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 BCV treatment that would be relevant to treatment of human smallpox.

Using the rabbit/RPXV model, the Applicant completed a placebo-controlled study CMX001-VIR-106. The treatment groups included BCV 20/5/5 mg/kg initiated at Day 3, 4, 5 and 6 post inoculation (PI) (n=29 per group) vs placebo (n=28). A statistically significant treatment benefit over placebo for the primary endpoint of mortality was demonstrated when BCV was dosed at 20/5/5 mg/kg (administered every 48 hours for 3 doses) starting at Days 3, 4, 5 or 6. Table 1 summarizes the results. The 20/5/5 mg/kg dose 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.

Table 1: Study VIR-106 Primary Efficacy Results (ITT)

Dose Regimen (mg/kg)	Treatment Initiation Day	Survival % (# survived/n)		Survival Rate Difference (95% CI)[a]	p-value[b]
		Placebo	Brincidofovir		
Rabbitpox[c]					
Study 1	Day 3	29% (8/28)	100% (29/29)	71.4% (51%, 87%)	<0.001
	Day 4		90% (26/29)	61% (36%, 79%)	<0.0001
	Day 5		69% (20/29)	40% (12%, 63%)	0.0014
	Day 6		69% (20/29)	40% (12%, 63%)	0.0014

a. Survival percentage with brincidofovir-treated animals minus survival percentage in placebo-treated animals. Exact confidence intervals are presented.
b. P-value is from 1-sided Boschloo test compared with placebo.
c. 20/5/5 mg/kg (fully effective dose in the rabbitpox model)
Source: Adapted from clinical and statistical review

Mouse/ECTV Efficacy Studies

In the mouse/ECTV efficacy study, 8-week-old BALB/c mice were challenged intranasally with 200 PFU of the ECTV strain Moscow. In the mouse/ECTV model, a clinically evident sign of disease could not be identified to use as a trigger to initiate treatment. Consequently, treatment initiation at various time-points during peak disease were evaluated. Day 4 PI was used as the primary efficacy outcome in the Applicant's mouse/ECTV studies. The primary efficacy endpoint was the 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.

Using the mouse/ECTV model, the Applicant completed a placebo-controlled, double-blind study CMX001-VIR-044. The treatment groups included BCV 10/5/5 mg/kg initiated at Day 4, 5 and 6 and 20/5/5/ mg/kg initiated at Day 4, 5, 6 and 7 post inoculation (n=32 per group) vs placebo (n=32). A statistically significant treatment benefit over placebo for the primary endpoint of mortality was demonstrated when BCV was dosed at 10/5/5/ mg/kg and 20/5/5 mg/kg (administered every 48 hours for 3 doses) starting at Day 4 post inoculation. Table 2 summarizes the results. The 10/5/5 mg/kg dose 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.

Table 2: Study VIR-044 Primary Efficacy Results (ITT)

Dose Regimen (mg/kg)	Treatment Initiation Day	Survival % (# survived/n)		Survival Rate Difference (95% CI)[a]	p-value[b]
		Placebo	Brincidofovir		
Mousepox[c]					
Study 2	Day 4	13% (4/32)	78% (25/32)	66% (44%, 82%)	<0.0001
	Day 5		66% (21/32)	53% (29%, 72%)	<0.0001
	Day 6		34% (11/32)	22% (1%, 43%)	0.0233[d]

a. Survival percentage with brincidofovir-treated animals minus survival percentage in placebo-treated animals. Exact confidence intervals are presented.
b. P-value is from 1-sided Boschloo test compared with placebo.
c. 10/5/5 mg/kg (fully effective dose in the mousepox model)
d. P-value is not significant at the one-sided alpha of 0.0125.
Source: Adapted from clinical and statistical review

Human Dose Selection

Human PK data with BCV, combined with PK and PD data obtained in the pivotal animal efficacy trials, 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 rabbit/RPXV and mouse/ECTV studies. Healthy adult human PK of plasma BCV and intracellular (PBMC) CDV-PP PK was collected following a single dose of 200 mg BCV tablets or oral suspension. Plasma BCV PK data were also collected in adults and pediatrics (down to 3 months of age) with non-orthopoxvirus infections. The healthy adult plasma BCV exposures following 200 mg tablets were used as reference for smallpox patients as they represent the most conservative exposure measure in humans. As stated previously, 20/5/5 mg/kg/Q48h in the rabbit/RPXV and 10/5/5 mg/kg in the mouse/ECTV model were selected as the fully effective doses in animal models for human dose selection. The effective 20/5/5 mg/kg Q48 dose in rabbits was used to define the reference plasma BCV and intracellular (PBMC) CDV-PP exposures needed to translate to an effective human dose for treatment of smallpox. The rabbit model was the more conservative model for estimating the needed plasma BCV drug exposures. The BCV exposures in healthy adults receiving 200 mg tablets were higher than those associated with the fully effective doses in either rabbit/RPXV or mouse/ECTV models and provides intracellular CDV-PP exposures that are in excess or similar to those in rabbit/RPXV and mouse/ECTV model (Appendix 1). Based on these PK results, the acceptable safety profile of BCV (see Section 8), a human dosing regimen of 200 mg, given as two 100 mg tablets or 20 mL oral solution, once weekly on Days 1 and 8 was selected for patents weighing at least 48 kg.

Originally, the Applicant proposed (b) (4)
However, the clinical pharmacology team noted patients weighing < 10 kg (including neonates) were expected to have lower exposures (AUC) (b) (4) compared to

adults receiving 200 mg tablets. Based on modeling and simulation, a 6 mg/kg once weekly oral suspension dose for patients weighing less than 10 kg is expected to provide plasma BCV exposures that are more comparable to adults receiving 200 mg tablets and ensure that most pediatric patients have plasma BCV exposures greater than the geometric mean fully effective exposures for the infected rabbit model. For patients weighing 10 kg to less than 48 kg, the recommended dose is 4 mg/kg oral suspension once weekly on Days 1 and 8. Both the tablets and oral suspension should be taken on an empty stomach.

Conclusions on Effectiveness

Treatment efficacy was clearly demonstrated using two lethal 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 the proposed to-be-approved dose and duration (200 mg once weekly for 2 doses on Days 1 and 8) from studies in other viral diseases. The trials to support safety are derived from:

- Phase 3 trial (CMX001-301, NCT0176970), a randomized, double-blind, placebo-controlled trial in cytomegalovirus R+ hemotopoietic stem cell transplant (CMV R+ HSCT) adults (303 BCV vs 149 PBO)
- Phase 2 trial (CMX001-201, NCT00942305), a randomized, double-blind, placebo-controlled trial in CMV R+ HSCT adults (303 BCV vs 59 PBO)
- Phase 2 trial (CMX001-202, NCT01241344) a randomized, double-blind, placebo-controlled trial in HSCT ($\geq$ 3 months to $\leq$ 75 years; 30 BCV vs 18 PBO)
- Phase 1 trial (CMX001-120) a randomized, open-label, drug-drug interaction trial in adults (26 BCV)

Data from the 100 mg BIW, 200 mg QW, and placebo cohorts in CMX001-201 and CMX001-301 were pooled to form the integrated safety (ISS) population. For a complete description of the Agency's safety assessment for BCV, 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 submissions included 392 adult subjects from the ISS population who had been exposed to BCV at the proposed dose and

duration. It is important to note, the safety data for BCV were generated in immunocompromised patients and not healthy volunteers which supported the approval of tecovirimat. We agree with Dr. Chan-Tack's assessment that the ISS population meets the FDA's recommendation for a minimum of 300 subjects to support an indication for treatment of smallpox. Given BCV's restricted indication, Orphan Drug designation, and acceptable safety profile, the Agency deemed the safety database adequate.

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

ISS population

The ISS population comprises safety data from the 100 mg BIW, 200 mg QW, and placebo cohorts in CMX001-201 and CMX001-301 and includes a total of 600 subjects (392 BCV and 208 PBO). The safety data presented below was limited to 2 weeks dosing.

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

Overall, the safety profile of BCV was acceptable. 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 are displayed in Table 3. Most of the adverse reactions reported were mild to moderate in severity.

Table 3: Treatment-emergent ADRs Reported in ≥ 2% of Subjects, All Grade, ISS

Dictionary Derived Term	BCV 100 mg BIW 2 weeks N=353	BCV 200 mg QW 2 weeks N=39	Total BCV 2 Weeks N=392	PBO 2 Weeks N=208
Total subjects with ADR	54 (15.3%)	5 (12.8%)	59 (15.1%)	17 (8.2%)
Diarrhea*	31 (8.8%)	1 (2.6%)	32 (8.2%)	6 (2.9%)
Nausea	17 (4.8%)	2 (5.1%)	19 (4.8%)	2 (1.0%)
Vomiting‡	13 (3.7%)	2 (5.1%)	15 (3.8%)	2 (1.0%)
Abdominal pain§	11 (3.1%)	0 (0%)	11 (2.8%)	4 (1.9%)

*Includes diarrhea, bowel movement irregularity, defecation urgency, fecal incontinence, frequent bowel movements.
‡Includes vomiting, retching.
§Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal distension, abdominal discomfort, gastrointestinal pain.

Source: ISS ADAE dataset and clinical review

In the ISS population, 4 deaths in the BCV group and 2 subjects in the PBO group had an adverse event within the first 2 weeks of dosing that resulted in a fatal outcome. We agree with Dr. Chan-Tack's assessment that all deaths were unrelated to drug study. The deaths in both groups were related to acute graft versus host disease, recurrent acute myeloid leukemia or transplant failure.

Overall, more subjects in the BCV group compared to PBO (20% vs 15%) experienced a serious adverse event (SAE). The majority of the SAEs were not treatment related. No subjects in the PBO group had a treatment related SAE whereas, 6 subjects (1.5%) receiving BCV had a treatment related SAE which included diarrhea (5), nausea (1), enteritis (1) and ALT increased (1).

Discontinuations due to AEs occurred in 9% of subjects in the BCV group and 4% of subjects in the PBO group. Most of these events were assessed by investigators as not related to study drug. The most commonly BCV related events leading to discontinuation included, diarrhea (10), followed by nausea (3).

Selected treatment-emergent laboratory values occurring during the first 2 weeks of treatment with BCV are presented in Table 4. During the first 2 weeks of BCV therapy in 392 subjects, ALT elevations >3x the upper limit of normal were reported in 7% of subjects and bilirubin elevations >2x the upper limit of normal were reported in 2% of subjects; these elevations in hepatic laboratory tests were generally reversible and did not require discontinuation of BCV.

Table 4: Frequencies of Selected Laboratory Abnormalities

Laboratory Parameter Abnormality[a]		**TEMBEXA 200 mg N=392**	**Placebo N=208**
Alanine aminotransferase (ALT)[b]	N	382	203
	Grade 2 (>3 to 5x ULN)	3%	2%
	Grade 3 (>5 to 20x ULN)	2%	1%
	Grade 4 (>20x ULN)	0%	0%
Aspartate aminotransferase (AST)[c]	N	380	201
	Grade 2 (>3 to 5x ULN)	2%	1%
	Grade 3 (>5 to 20x ULN)	1%	0%
	Grade 4 (>20x ULN)	0%	0%
Total bilirubin	N	382	203
	Grade 2 (>1.5 to 3x ULN)	3%	2%
	Grade 3 (>3 to 10x ULN)	1%	<1%
	Grade 4 (>10x ULN)	0%	0%
Serum creatinine	N	383	205
	Grade 2 (>1.5 to 3x ULN)	4%	4%
	Grade 3 (>3 to 6x ULN)	<1%	0%
	Grade 4 (>6x ULN)	0%	0%

Adapted from clinical review

ULN = upper limit of normal
[a.] Frequencies are based on treatment-emergent laboratory abnormalities. Graded per Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 toxicity grading criteria.
[b.] ALT >10x ULN occurred in one subject in the TEMBEXA group and no subjects in the placebo group.
[c.] No subjects reported AST >10x ULN.

Submission-specific safety issues

As previously noted, non-clinical toxicology studies demonstrated GI and hepatic effects. Similar events were seen across all BCV clinical trials and included diarrhea, nausea, vomiting and abdominal pain. The GI events were also associated with duration of administration. The ability to discern true treatment related events versus underlying disease, effects of conditioning chemotherapeutic regimens, and concurrent GI infections due to transplant specific complications was challenging. Notably, transplant and immunosuppressed patients are predisposed to GI and hepatic toxicities that also occur with BCV. Nevertheless, BCV treatment was associated with numerically higher GI ADRS compared to placebo. Diarrhea was the predominant Grade 3/4 GI AE and occurred in 16 subjects (4.1%) in the BCV group and 3 subjects (1.4%) in the PBO group. Additionally, most of the Grade 3/4 ADRs occurred in the BCV group compared to PBO (4% vs 0%) and included a GI related event. GI related SAEs (diarrhea (5), nausea (1), enteritis (1)) were seen in 5 BCV treated subjects compared to no GI related SAEs in the placebo group. Thirteen subjects had GI ADRs that lead to discontinuation and diarrhea was the predominant cause (n=10), followed by nausea (3). As noted previously, the GI events are associated with duration and the GI toxicities are less prominent over 2 weeks of treatment compared to longer durations of treatment. Therefore, the safety profile with respect to GI events was deemed acceptable. The product labeling contains a Warning for diarrhea and other GI adverse events.

With respect to hepatic events, the majority were laboratory related changes as noted in the laboratory abnormality section above. The hepatic events were largely coded as ALT, bilirubin or transaminase increased or liver function test abnormal. The protocol did not provide guidance to investigators as to when to code laboratory abnormalities as adverse events. Therefore, the laboratory data is the most objective assessment of hepatoxicity as shown above.

An independent hepatic safety expert (b) (4) reviewed and adjudicated all the events thatmet any criteria for possible drug induced liver injury (DILI). Overall, 82 cases with ALT/AST > 3 times the upper limit of normal and total bilirubin greater than 2 times the upper limit of normal were observed, of which 21 occurred within the first 2 weeks of treatment, 40 cases on treatment but after day 14 and 21 cases post-treatment. Only one case was possibly related to BCV and this subject developed concurrent transaminase and bilirubin increases on Day 43. No clear evidence of DILI cases was seen within the first 2 weeks of treatment.

Like GI events, the hepatic events were associated with duration and the hepatic events are less prominent over 2 weeks of treatment. The safety profile with respect to hepatic related events or laboratory abnormalities is acceptable. A Warning is included in

product labeling regarding elevations in hepatic transaminases and bilirubin. Hepatic laboratory testing is recommended for all patients before starting treatment and while receiving treatment as clinically appropriate. If persistent ALT levels > 10 times upper limit of normal occur and are accompanied by clinical signs and symptoms of liver inflammation, the second and final dose of BCV should not be administered.

Other submission specific safety issues including cardiac events, neuropsychiatric disorders (seizure, migraines, dysgeusia, depression) rash, rhabdomyolysis, pancreatitis and pancytopenia were evaluated in detail by Dr. Chan-Tack. No cases of seizures, migraines, rhabdomyolysis, pancreatitis or pancytopenia were reported in the ISS population. The frequency of other neuropsychiatric events was low, and no unexpected safety signal was noted. Of note dysgeusia is included in product labeling under less common adverse reactions (<2%) and adverse reactions leading to discontinuation (n=1). Related rash events were low (1% vs 0%) and not considered a significant safety signal. Rash is included under less common adverse reaction section in the product labeling.

No clinically significant differences in adverse events was seen for age, gender or race. Of note some of these subgroups were small to make any definitive conclusions.

Pediatric Safety Assessment

The safety profile in pediatric subjects (n=23 ages 7 months to 17 years) from a randomized, placebo-controlled trial was similar to adults. An additional 166 pediatric subjects ages 3 months to 18 years received BCV in either uncontrolled studies or expanded access. No new or unexpected findings were noted in pediatric subjects.

In the pediatric trial, no pediatric deaths were reported in the first two weeks of BCV dosing. The four SAEs in pediatric subjects (3 BCV vs 1 PBO) were not considered related to study drug. One pediatric subject prematurely discontinued treatment due to diarrhea. No differences with respect to Grade 3 or 4 ADRs were seen between BCV (n=1) and placebo (n=2).

9. Advisory Committee Meeting

An Advisory Committee meeting was not convened for this application because the acceptability of the animal models was discussed at the 2011 Antiviral Drugs Advisory Committee and Chimerix closely followed FDA's recommendations for developing BCV under Animal Rule. Further, the results from two animal models demonstrated a statistically significant survival benefit.

10. Pediatrics

The pharmacokinetics of BCV suspension were evaluated in pediatric individuals. Pharmacokinetic simulation was used to derive dosing regimens that are predicted to provide pediatric patients, including neonates, with exposures comparable to the

observed exposure in adults receiving BCV tablets. Please refer to Pediatric Safety Assessment and Dosing subsection for more details.

BCV has orphan drug status and is therefore exempt from Pediatric Research Equity Act (PREA) requirements. However, product labeling includes dosing for those who weigh less than 10 kg.

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 BCV. 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*

Please refer to the OSI Consult Review for further details. No data integrity issues were found inthe five clinical trial sites inspected. One site was cited for unreported AEs (a total of 46 AEs from 14 subjects across 2 trials). The Applicant subsequently obtained the data from the study investigator and all AEs were not related to BCV. Of note only 7 AEs were observed within the first 2 weeks of treatment. The overall safety assessment was not affected.

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

OSIS also inspected the pivotal rabbit/RPXV and mouse/ECTV 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:

Limitations of use were included to reflect BCV is not indicated for the treatment of diseases other than the human smallpox disease

- DOSAGE AND ADMINISTRATION section:

Dosing recommendations for pediatric patients weighing < 10 kg were included in labeling based on modeling and simulation analyses. Additionally, instructions for administration of the oral suspension by enteral tube was added.

- WARNING AND PRECAUTIONS

We agreed with the Applicant's proposal to include a GI and hepatotoxicity warning and added additional edits.

The review team added a Box Warning and Warning to state BCV is not indicated for use in disease other than human smallpox because an increase in mortality was observed in another disease.

The review team deleted (b) (4) Where possible, consider alternative medications that are not OATP1B1 or 1B3 inhibitors. If concomitant use with BCV is necessary, increase monitoring for adverse reactions, specifically transaminases and bilirubin, diarrhea, or other GI adverse events and postpone the dosing of OATP1B1 or 1B3 inhibitors for at least 3 hours after BCV administration

The Warning about concomitant use with CDV was expanded upon to describe coadministration is not recommended because BCV is intracellularly converted to CDV.

The review team agreed with the embryo toxicity and male infertility Warnings and included recommendations to use effective contraception during treatment and for at least 2 months after the last dose. Advise individuals of reproductive potential with partners of childbearing potential to use condoms during treatment and for at least 4 months after the last dose.

- 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). Specifically, Table 3 and less common adverse reaction section was revised based on this guidance.

Reference to (b) (4) were removed (b) (4) (b) (4)

- DRUG INTERACTIONS and CLINICAL PHARMACOLOGY sections:

See comment above about addition of concomitant use with OATP1B1 and 1B3 inhibitors

Text was added by the review team to state, based on in vitro data, mutations in the sphingomyelin phosphodiesterase 1 gene may reduce the ability to convert brincidofovir to CDV and CDV-PP.

A statement was included that co-administration of BCV 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.

- USE IN SPECIFIC POPULATIONS section

The Division of Pediatrics and Maternal Health was consulted for product labeling with respect to pregnancy, lactation and females and males of reproductive potential. Please refer to review by Dr. Wenjie Sun.

See comment above regarding added text regarding use in females and males of reproductive potential.

With regard to lactation, the review team added text to state, breastfeeding is not recommended because of the potential for variola virus transmission through direct contact with the infant.

- 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)

Please refer to the review by Dr. Naomi Boston, Office of Medication Error Prevention and Risk Management, Office of Surveillance and Epidemiology for further details. In summary, a REMS was not needed because the safety concerns associated with BCV are adequately addressed in product labeling. One concern was the increased risk for mortality, as observed in a non-orthopoxvirus trial, when used for a longer duration than the recommended dose on Days 1 and 8. BCV is packaged into blister cards with a total of four film-coated tablets and constitutes a complete regimen (two 100 mg tablets taken on Days 1 and 8). Similarly, the oral suspension formulation delivers 65 mL of BCV and an adult dose is 20 mL on Days 1 and 8. The product overage for adults and pediatric patients is considered acceptable and did not add to the concern for longer

duration of dosing. Additionally, the Applicant states the intent is for BCV to be delivered to the Strategic National Stockpile and distribution by CDC, further limiting the concerns for off-label and longer duration of use. The label also states BCV is not indicated for the treatment of diseases other than human smallpox disease.

Postmarketing Requirements (PMRs) and Postmarketing Commitments (PMCs)

The following PMR was issued and the virology PMC was agreed upon by the Applicant.

Clinical PMR

Field Study to evaluate the clinical response, drug concentrations, and safety profile of BCV when used for the treatment of human smallpox disease due to variola virus infection. This trial should evaluate BCV vs. standard-of-care (i.e. active control) vs. BCV as an add-on-therapy to standard-of-care.

Virology PMC

Conduct cell culture studies to characterize BCV antiviral activity against recombinant orthopoxviruses (vaccinia virus or ectromelia virus) encoding specific amino acid substitutions that emerged in ectromelia virus in BCV-treated animals in mouse study CMX001-VIR-044.

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.

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Appendix 1: Simulated or Observed Plasma BCV PK Parameters After First and Last BCV Dose In Healthy Human Adults (≥ 48 kg) and Rabbitpox-Infected Rabbits

Species	First Dose	BCV		CDV-PP	
		Cmax (ng/mL)	AUC_{tau} (hr·ng/mL)	Cmax (pg/10^6 cells)	AUC_{tau} (hr·pg/10^6 cells)
Healthy human adult	200 mg QW Simulated	480 (70%) [240-950]	3400 (58%) [1900-6300]	9.7 (75%) [4.8-20]	1200 (75%) [560-2400]
RPXV/ Rabbit	20/5/5 mg/kg Simulated	237 (47) [66.7-649]	1490 (46.6) [408-4110]	5.2(38.8) [3.17-10.4]	186 (36.4) [114-391]
Healthy human adult	200 mg QW Observed	Fast: 622 (37.8) Fed: 305 (34.5)	Fast: 3307 (38.8) Fed: 2183 (41.6)	Fast: 11.7 (50.8) Fed: 12 (55.2)	Fast:1323 (70.5) Fed: 1188 (48.7)
RPXV/ Rabbit	20/5/5 mg/kg Observed	185 (40.3)	709 (31.4)	6.9 (32)	362 (28)
Ratio (after first dose) Human:Rabbit		Simulated: 2 Observed: 3.4 / 1.6	Simulated: 2.3 Observed: 4.7 / 3.1	Simulated: 1.9 Observed: 1.7 / 1.7	Simulated: 6.5 Observed: 3.7 / 3.3

Species	Last Dose	BCV		CDV-PP	
		Cmax (ng/mL)	AUC_{tau} (hr·ng/mL)	Cmax (pg/10^6 cells)	AUC_{tau} (hr·pg/10^6 cells)
Healthy human adult	200 mg QW Simulated	480 (70%) [240-950]	3400 (58%) [1900-6300]	14 (75) [6.8-29]	1800 (76) [860-3700]
RPXV/ Rabbit	20/5/5 mg/kg Simulated	60.8(48.2) [16.8-173])	437 (54.5) [109-1530]	4.07 (30.1) [2.7-9.03]]	170 (31.2) [116-386])
Healthy human adult	200 mg QW Observed	NA	NA	NA	NA
RPXV/ Rabbit	20/5/5 mg/kg Observed	15.2 (59.8)	74.3 (67.3)	6.2 (56)	413 (50)
Ratio (after last dose) Human:Rabbit		Simulated: 7.9 Observed: 31.6	Simulated: 7.8 Observed: 45.8	Simulated: 3.4 Observed: 2.3	Simulated: 10.6 Observed: 4.4

Abbreviations: AUC = area under the concentration-time curve; BCV = brincidofovir; CDV-PP = cidofovir diphosphate; and Cmax = maximum concentration; NCA = noncompartmental analysis; PopPK = population PK; Fed = A single dose of 200 mg BCV tablet administered with a low-fat meal; Fast = A single dose of 200 mg BCV tablet administered under fasting conditions.
20/5/5 mg/kg regimen dosed every 48 h

Values are presented as geometric mean (%CV)[90% prediction interval] for human simulations and rabbit simulations and geometric mean (%CV) for study CMX001-114 in healthy adults or arithmetic mean (%CV) for study CMX001-VIR-122 in rabbits.

AUC for humans and rabbits for the dosing interval (168 h interval in humans and 48 h interval for rabbits) or AUC_{tau}

For PopPK model simulations human virtual population distribution was 1:1 male:female; 1:1 fed:fasted; all received TEMBEXA tablet.

Blue band denotes the reference human exposures following 200 mg BCV tablet or rabbit exposures associated with the effective rabbit dose.

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