CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214460Orig1s000
214461Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	214461 and 214460
Priority or Standard	Priority
Submit Date(s)	October 7, 2020
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Division/Office	Division of Antivirals/Office of Infectious Diseases
Reviewer Name(s)	Kirk Chan-Tack, MD
Review Completion Date	May 10, 2021
Established Name	Brincidofovir
(Proposed) Trade Name	Tembexa
Applicant	Chimerix, Inc.
Formulation(s)	100 mg tablet (NDA 214461) 10 mg/mL suspension (NDA 214460)
Dosing Regimen	200 mg (two 100 mg tablets or 20 mL oral suspension for patients who cannot swallow tablets) taken orally once weekly for 2 doses (on Days 1 and 8)
Applicant Proposed Indication(s)/Population(s)	Treatment of adult and pediatric patients with human smallpox disease caused by variola virus
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of adult and pediatric patients with human smallpox disease caused by variola virus

Table of Contents

Table of Tables

Glossary

ADAC	Antiviral Drugs Advisory Committee
ADR	adverse drug reaction
ADV	adenovirus
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCV	brincidofovir
BIW	twice weekly
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDV	cidofovir
CFR	Code of Federal Regulations
CK	creatine kinase
CMC	chemistry, manufacturing, and controls
CMV	cytomegalovirus
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DAV	Division of Antiviral Products
DSMB	Data Safety Monitoring Board
DDI	drug-drug interaction
DILI	drug-induced liver injury
ECG	electrocardiogram
ECI	event of clinical interest
eCTD	electronic common technical document
ECTV	ectromelia virus
eGFR	estimated glomerular filtration rate
EIND	Emergency Investigational New Drug
FAS	full analysis set
FDA	Food and Drug Administration
FU	follow up
GFR	glomerular filtration rate
GLP	Good Laboratory Practices
GVHD	graft-versus-host disease
HSCT	hematopoietic stem cell transplant
ICH	International Conference on Harmonization
ID	intradermal
IND	Investigational New Drug
ISE	integrated summary of effectiveness

ISS	integrated summary of safety
ITT	intent to treat
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NME	new molecular entity
OSI	Office of Scientific Investigation
OSIS	Office of Study Integrity and Surveillance
PBO	placebo
PD	pharmacodynamics
PFU	plaque forming units
PI	post inoculation
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert
PREA	Pediatric Research Equity Act
PT	Preferred Term (aka Dictionary Derived Term)
QW	once weekly
RPXV	rabbitpox virus
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SNS	Strategic National Stockpile
SOC	system organ class
TDD	total daily dose
TEAE	treatment emergent adverse event
TW	treatment week
ULN	upper limit of normal
US	United States
VARV	variola virus
WHO	World Health Organization

1 Executive Summary

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

1.1. Product Introduction

TEMBEXA® (brincidofovir, BCV) is an antiviral agent that interferes with critical steps in the replication cycle of variola virus. BCV is a lipid conjugate of cidofovir, which is a nucleotide analog. The lipid conjugate is designed to mimic a natural lipid, lysophosphatidylcholine, and thereby use endogenous lipid uptake pathways. Once inside cells, the lipid ester linkage of brincidofovir is cleaved to liberate cidofovir, which is then phosphorylated to produce the active antiviral, cidofovir diphosphate. Cidofovir diphosphate inhibits orthopoxvirus replication by inhibiting viral DNA polymerase-mediated synthesis of viral DNA.

The Applicant's proposed indication is treatment of patients with human smallpox disease caused by variola virus. The recommended dosage for adult and pediatric patients weighing at least 48 kg is 200 mg (two 100 mg tablets or 20 mL of suspension) once weekly for 2 doses (on Days 1 and 8). The proposed doses, based on simulation, for pediatric patients in other weight bands is summarized below:

- 10 kg to < 48 kg: 4 mg/kg of suspension once weekly for 2 doses (on Days 1 and 8)
- < 10 kg: 6 mg/kg of suspension once weekly for 2 doses (on Days 1 and 8)

1.2. Conclusions on the Substantial Evidence of Effectiveness

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

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Brincidofovir (BCV) is an oral antiviral with a proposed indication for the treatment of human smallpox infection under the Animal Rule. The mechanism of action of BCV involves inhibiting orthopoxvirus replication by inhibiting viral DNA polymerase-mediated synthesis of viral DNA.

The historical picture of smallpox is that of a human-to-human communicable disease characterized by an asymptomatic incubation period (averaging close to two weeks but with substantial variability), an initial period of nonspecific symptoms lasting a few days (fever, headache, back pain, prostration), then evolution of skin manifestations followed by death or by gradual recovery with varying degrees of scarring. Most of the clinical descriptions are based on variola major, the more serious form that was also more prevalent throughout most of the history of the disease, and that is also the focus of concerns regarding potential biothreat uses of variola virus. Mortality in variola major is commonly cited as about 30% but was reported to vary widely among outbreaks from as little as 5% to 40% or more. In 1980, following an historic global campaign of surveillance and vaccination, the World Health Assembly declared smallpox eradicated – the only infectious disease to achieve this distinction. Despite the eradication of naturally acquired smallpox, the disease remains a threat as variola virus could be developed as a bioterrorism agent. Routine vaccination in the U.S. ended in the 1970s, so most of the population is immunologically susceptible to smallpox. Medical countermeasures, including antiviral therapies, are needed in the event of a variola (smallpox) virus outbreak. Due to the mortality and severe morbidity associated with smallpox, the World Health Organization (WHO) states that preparedness to deal with any kind of smallpox event – whether natural re-emergence, accidental or deliberate release of the live virus, or created through synthetic biology – requires global and national attention.

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

Because of the unique complexities of drug development in this area, extensive discussion with multiple stakeholders has occurred, including an FDA public workshop in 2009 and an FDA public Advisory Committee meeting in 2011. During the 2011 Antiviral Drugs Advisory Committee (ADAC) meeting, the advisory committee agreed with the FDA's assessment that current lethal non-human primate (NHP) models using variola virus are not consistently reproducible and do not mimic what is known about human smallpox disease. Because scientific limitations of the available NHP/variola model preclude definitive efficacy assessments, and uncertainty exists whether an adequate variola model can be developed, the FDA and the advisory committee agreed that data from a combination of other lethal animal models using surrogate orthopoxviruses (e.g. non-human primate studies with monkeypox virus, rabbit studies with rabbitpox virus, mouse studies with ectromelia

virus) could be used as evidence along with, or potentially instead of, animal studies using variola virus. This assumes a mechanistically plausible target for the candidate drug, and the drug target being conserved across different orthopoxviruses.

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

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

For the rabbit/RPXV model, the Applicant completed a randomized, placebo-controlled, double-blinded study, performed under GLP in which BCV was started at the time of fever onset. Development of fever was determined to be a consistent and reproducible trigger for treatment initiation in this animal model. Day 4 after virus inoculation corresponds to the time-point when all animals had developed fever, and this time-point was used as the primary efficacy outcome. A statistically significant treatment benefit over placebo for the primary endpoint of mortality was shown in Study VIR-106 in which BCV was dosed at 20/5/5 mg/kg (administered every 48 hours for 3 doses) starting at day 4 after virus inoculation, and also when BCV was initiated at later time-points (i.e. Days 5 or 6 after virus inoculation). Maximum efficacy was observed with the 20/5/5 mg/kg regimen, thus the fully effective dose of BCV defined by the Animal Rule guidance is 20/5/5 mg/kg. Therefore, for the purpose of human dose selection, the rabbit dose was determined to be 20/5/5 mg/kg. Study VIR-106 also underwent evaluation by the Office of Scientific Investigations (OSI); OSI's inspection confirmed the data integrity of Study VIR-106. The Agency assessed that the rabbit/RPXV

model is sufficiently characterized for scientific regulatory purposes. The Agency also assessed that the studies summarized in this review constitute completion of the Applicant's rabbit/RPXV program.

For the mouse/ECTV model, the Applicant completed a randomized, placebo-controlled, double-blinded study, performed under GLP. 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 after virus inoculation was used as the primary efficacy outcome in the Applicant's mouse/ECTV model. A statistically significant treatment benefit over placebo for the primary endpoint of mortality was shown in Study VIR-044 in which BCV was dosed at 10/5/5 mg/kg (administered every 48 hours for 3 doses) starting at day 4 after virus inoculation, and also when BCV was initiated at a later time-point (i.e. Day 5 after virus inoculation). Maximum efficacy was observed with the 10/5/5 mg/kg regimen, thus the fully effective dose of BCV defined by the Animal Rule guidance is 10/5/5 mg/kg. Therefore, for the purpose of human dose selection, the mouse dose was determined to be 10/5/5 mg/kg. Study VIR-044 also underwent evaluation by the Office of Scientific Investigations (OSI); OSI's inspection confirmed the data integrity of Study VIR-044. The Agency assessed that the mouse/ECTV model is sufficiently characterized for scientific regulatory purposes. The Agency also assessed that the studies summarized in this review constitute completion of the Applicant's mouse/ECTV program.

Safety information to support approval of a smallpox drug can be derived from clinical trials of the same drug for a non-smallpox indication. Available human data with BCV are obtained from randomized, double-blind, placebo-controlled, multicenter, clinical trials that evaluated non-smallpox indications.

The label will include a Warning that BCV is not indicated for use in diseases other than human smallpox. An increase in mortality was observed in a randomized, placebo-controlled Phase 3 trial when BCV was evaluated in another disease. The label will also include a Boxed Warning that an increased risk for mortality was observed when BCV was used for a duration longer than at the recommended dosage on Days 1 and 8. The Warning is included to discourage off label use for longer durations of treatment where the risk may outweigh the benefit.

Gastrointestinal (GI) toxicities and hepatotoxicity were the major safety issues identified in this review. GI toxicities, manifested as diarrhea, nausea, vomiting, and abdominal pain, comprise one of the dose-limiting toxicities for BCV and were clearly demonstrated across all BCV development programs. These GI toxicities are also associated with duration of administration. The Warnings and Precautions section will provide wording that clearly describes the GI toxicities that have been observed for BCV, along with risk mitigation strategies.

A hepatic safety signal, manifested as transaminase and total bilirubin elevations, is the other dose-limiting toxicity for BCV and has been observed across all BCV development programs. The hepatic safety signal is also associated with duration of administration. The Warnings and Precautions section will provide wording that clearly describes the hepatotoxicity safety signal that has been observed for BCV, along with risk mitigation strategies.

Approval of BCV under the FDA's Animal Rule for treatment of human smallpox disease caused by variola virus infection is fully supported by the available evidence of efficacy and safety. Based on thorough analysis of efficacy, safety, pharmacokinetic, and virology data overall, BCV taken orally once weekly for 2 doses (on Days 1 and 8) is recommended for adult and pediatric patients with human smallpox disease caused by variola virus.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The conventional historical picture of smallpox is that of a human-to-human communicable disease characterized by an asymptomatic incubation period (averaging close to two weeks but with substantial variability), an initial period of nonspecific symptoms lasting a few days (fever, headache, back pain, prostration), then evolution of skin manifestations followed by death or by gradual recovery with varying degrees of scarring. The classic dermatologic manifestation was a centrifugally-distributed rash. The rash evolved from macule-to-papule-to-vesicle-to-pustule-to-scab-to-scar, with initial stages of a day or two each, scab evolution and separation over a period of a few weeks, and scarring over a few months' time. • Most of the clinical descriptions are based on variola major, the more serious form that was also more prevalent throughout most of the history of the disease, and that is also the focus of concerns regarding potential biothreat uses of variola virus. Mortality in variola major is commonly cited as about 30% but was reported to vary widely among outbreaks from as little as 5% to 40% or more.	Smallpox is a potentially serious threat but does not occur naturally. When infected with variola virus, patients can experience symptoms that are severe, debilitating, and can be fatal.
Current Treatment Options	• Tecovirimat is currently the only approved antiviral treatment regimen for patients with human smallpox disease caused by variola virus. • Variola virus is categorized by the National Institute of Allergy and Infectious Diseases as a Category A priority pathogen. Category A pathogens are those organisms/biological	Due to concerns regarding potential biothreat uses of variola virus, a specific unmet medical need exists for effective

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	agents that pose the highest risk to national security and public health. • Due to the mortality and severe morbidity associated with smallpox, the WHO Advisory Committee on Variola Virus Research states that preparedness to deal with any kind of smallpox event – whether natural re-emergence, accidental or deliberate release of the live virus, or created through synthetic biology – requires global and national attention.	antiviral regimens for subjects who develop smallpox disease caused by variola virus because only one approved regimen is available.
Benefit	• Because smallpox is a potentially serious threat but does not occur naturally, clinical trials are not feasible and human challenge studies in healthy subjects are unethical. Therefore, animal models may provide important information for the evaluation of treatment effect and may contribute directly to drug approval under 21 CFR part 314, subpart I, if a suitable approach is agreed upon. • Because of the unique complexities of drug development in this area, extensive discussion with multiple stakeholders has occurred, including an FDA public workshop in 2009 and an FDA public Advisory Committee meeting in 2011. During the 2011 Antiviral Drugs Advisory Committee (ADAC) meeting, the advisory committee agreed with the FDA's assessment that current lethal NHP models using variola virus are not consistently reproducible and do not mimic what is known about human smallpox disease. Because scientific limitations of the available NHP/variola model preclude definitive efficacy assessments, and uncertainty exists whether an adequate variola model can be developed, the FDA and the advisory committee agreed that data from a combination of other lethal animal models using surrogate orthopoxviruses (e.g. NHP studies with monkeypox virus, rabbit studies with rabbitpox virus, mouse studies with ectromelia virus) could be used as evidence along with, or potentially instead of, animal studies using variola virus. This assumes a mechanistically plausible target for the candidate drug, and the drug target being conserved across different orthopoxviruses. • Based on multiple discussions with stakeholders (including the aforementioned	Uncertainties inherent in drug development under the Animal Rule have been addressed to the extent possible via animal studies demonstrating a clear, statistically significant mortality benefit in two well-characterized, lethal non-variola orthopoxvirus animal models. These studies have also allowed for the selection of a human dose with an acceptable safety profile and which satisfies the other tenets of the Animal Rule.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	2011 Antiviral Drugs Advisory Committee), the FDA recommended the following: 1) Data from at least two lethal animal models of non-variola orthopoxvirus infection should be obtained to evaluate drug efficacy; 2) Non-variola orthopoxvirus animal models proposed for use in regulatory decision-making (i.e., efficacy studies) must be well-characterized and generate reproducible results that are reasonably expected to predict efficacy in variola virus infected or exposed humans, and; 3) Mortality, based on prospectively defined criteria for euthanasia, should be the primary endpoint for efficacy studies. The recommendation for use of multiple non-variola orthopoxvirus animal models acknowledges the unique challenges and uncertainties associated with this area of drug development, and the fact that no single orthopoxvirus animal model is known to be the best predictor of human responses to treatments for smallpox. • The efficacy of BCV was established in the rabbit/RPXV animal model and the mouse/ECTV animal model. • For the rabbit/RPXV model, efficacy studies evaluated BCV when treatment was started at the time of fever onset. Development of fever was determined to be a consistent and reproducible trigger for treatment initiation in this animal model. Day 4 after virus inoculation corresponds to the time-point when all animals had developed fever. • Maximum efficacy was observed with BCV dosed at 20/5/5 mg/kg (administered every 48 hours for 3 doses), thus the fully effective dose of BCV defined by the Animal Rule guidance is 20/5/5 mg/kg. Therefore, for the purpose of human dose selection, the rabbit dose was determined to be 20/5/5 mg/kg; this dose and duration were evaluated in the randomized, double-blind, placebo-controlled rabbit/RPXV study VIR-106. • For the mouse/ECTV model, efficacy studies evaluated BCV when treatment was started at Day 4 after virus inoculation. In the mouse/ECTV model, a	The studies in these two lethal animal models of non-variola orthopoxvirus infection provide substantial evidence of effectiveness of BCV. The Applicant's rabbit/RPXV and mouse/ECTV studies evaluated and confirmed statistically significant treatment benefit using a primary efficacy endpoint that is clearly related to the desired benefit in humans.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
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.
• Maximum efficacy was observed with BCV dosed at 10/5/5 mg/kg (administered every 48 hours for 3 doses), thus the fully effective dose of BCV defined by the Animal Rule guidance is 10/5/5 mg/kg. Therefore, for the purpose of human dose selection, the mouse dose was determined to be 10/5/5 mg/kg; this dose and duration were evaluated in the randomized, double-blind, placebo-controlled mouse/ECTV study VIR-044.
• The primary efficacy endpoint was proportion of animals that survived to the pre-specified end-of-study, as survival is clearly related to the desired benefit in humans and satisfies one of the tenets of the Animal Rule. As displayed in the tables below, survival in treated animals overall ranged from 80-100% when treatment was initiated at day 4 after virus inoculation.

Rabbit/RPXV study with BCV 20/5/5 mg/kg (administered every 48 hours for 3 doses):
Survival by Treatment Arm n (%)
<table>
<tr><th>Study</th><th>Treatment Initiation
(# of days after viral inoculation)</th><th>BCV</th><th>Placebo</th></tr>
<tr><td rowspan="3">VIR-106</td><td>Day 4</td><td>26/29 (90%)</td><td rowspan="3">8/28 (28%)</td></tr>
<tr><td>Day 5*</td><td>20/29 (69%)</td></tr>
<tr><td>Day 6*</td><td>20/29 (69%)</td></tr>
</table>
*These cohorts evaluated the effect of delayed treatment initiation on efficacy and were done for exploratory purposes.

Mouse/ECTV study with BCV 10/5/5 mg/kg (administered every 48 hours for 3 doses):
Survival by Treatment Arm n (%)
<table>
<tr><th>Study</th><th>Treatment Initiation
(# of days after viral inoculation)</th><th>BCV</th><th>Placebo</th></tr>
</table>
</td><td>
BCV demonstrated a survival benefit in the rabbit/RPXV animal model and in the mouse/ECTV animal model.

BCV fills an important unmet medical need.
- BCV and tecovirimat have distinct mechanisms of action.
- Available data indicate that BCV does not rapidly select for resistance (b)
</td></tr>
</table>

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
<table>
<tr><td>VIR-044</td><td>Day 4</td><td>25/32 (78%)</td><td>4/32 (13%)</td></tr>
<tr><td></td><td>Day 5*</td><td>21/32 (66%)</td><td></td></tr>
<tr><td></td><td>Day 6*</td><td>11/32 (34%)</td><td></td></tr>
</table>
*These cohorts evaluated the effect of delayed treatment initiation on efficacy and were done for exploratory purposes.

• In the rabbit/RPXV model, BCV 20/5/5 mg/kg is effective when treatment was initiated at day 4 after virus inoculation (i.e. the time-point when all animals had developed fever).
• In the mouse/ECTV model, BCV 10/5/5 mg/kg is effective when treatment was initiated at day 4 after virus inoculation.
</td><td>- BCV has an oral solution for those who cannot swallow tablets.
- BCV has dosing down to neonates.
- BCV regimen is 2 doses (two 100 mg tablets or 20 mL suspension), given on Days 1 and 8.
- BCV has data to support use of the suspension via enteral or nasogastric tubing.</td></tr>
<tr><td>Risk</td><td>• The safety database for BCV was primarily based on Studies CMX001-201 and CMX001-301. In these randomized, double-blind, placebo-controlled, multicenter, clinical trials that evaluated non-smallpox indications, a total of 392 adult subjects received the proposed dose of BCV and 208 subjects received placebo (PBO). The safety database is considered adequate.
• Gastrointestinal (GI) reactions and hepatotoxicity were the major safety issues.
• Diarrhea, nausea, and vomiting were the three most commonly reported adverse drug reactions (ADRs).
• In the Phase 1 drug-drug interaction Study 120, co-administration of BCV and cyclosporine resulted in increased BCV exposures and increased serum bilirubin.</td><td>BCV demonstrated an overall acceptable safety profile for the proposed indication. GI toxicities and hepatotoxicity were the major safety issues identified.</td></tr>
<tr><td>Risk Management</td><td>• The BCV prescribing information will include the following safety information:
• Section 5 of the label will include a Warning that BCV is not indicated for use in diseases other than human smallpox. An increase in mortality was observed in a randomized, placebo-controlled Phase 3 trial when BCV was evaluated in another disease. The label will also include a Boxed Warning that an increased risk for mortality was observed when BCV was used for a duration longer than at the recommended dosage on Days 1 and 8. The Warning is included to discourage off</td><td>Safety concerns associated with BCV are adequately addressed in product labeling.</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons

	label use for longer durations of treatment where the risk may outweigh the benefit.
	• Section 5 of the label will include a Warning regarding the risk of transaminase and total bilirubin elevations.
	  o The hepatic safety profile will also be described in Section 6 of the label.
	  o Rates of transaminase and total bilirubin elevations were higher for BCV compared to PBO. Given that these elevations may impact patient management, this information will be described in labeling, outlining that monitoring is recommended while receiving BCV.
	• Section 5 of the label will include a Warning regarding the risk of diarrhea and other GI adverse events.
	  o The GI safety profile will also be described in Section 6 of the label.
	  o Rates of diarrhea, nausea, vomiting, and abdominal pain were higher for BCV compared to PBO. Given that these events may impact patient management, this information will be described in labeling, outlining that monitoring is recommended while receiving BCV.
	• ADRs of interest such as rash, dysgeusia, decreased appetite, muscular weakness, and peripheral edema, will be included under Less Common Adverse Reactions.
	• Section 5 will include a Warning to describe that concomitant use of BCV with IV cidofovir is not recommended because BCV, a lipid-linked derivative of cidofovir, is intracellularly converted to cidofovir.
	• Section 5 will include a Warning to describe that, based on findings from animal reproduction studies, BCV may cause fetal harm when administered to pregnant individuals. Given that these findings may impact patient management, this information will be described in labeling along with risk mitigation strategies outlining that:
	  o Pregnancy testing is recommended in individuals of childbearing potential before initiation of BCV.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	○ Individuals of childbearing potential should avoid becoming pregnant and use effective contraception during treatment with BCV and for 2 months after the last dose. ○ Individuals of reproductive potential with partners of childbearing potential should use condoms during treatment with BCV and for 4 months after the last dose. • Section 5 will include a Warning to describe that, based on findings from animal studies, BCV is considered a potential human carcinogen. Given that these findings may impact patient management, this information will be described in labeling along with risk mitigation strategies outlining that: ○ BCV tablets should not be crushed or divided. ○ Direct contact with broken or crushed tablets or oral suspension should be avoided. If contact with skin or mucous membranes occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with water. • Section 5 will include a Warning to describe that, based on findings of testicular toxicity in animal studies, BCV may irreversibly impair fertility in individuals of reproductive potential. • Section 7 will describe that co-administration of BCV and OATP inhibitors (which includes cyclosporine) resulted in increased BCV exposures and may increase adverse reactions associated with BCV. It will also describe risk mitigation strategies outlining that: ○ Where possible, consider alternative medication that are not OATP inhibitors. If concomitant use with BCV is necessary, increase monitoring for adverse reactions associated with BCV (elevations in transaminases and bilirubin, diarrhea or other GI adverse events) and separate the dose by at least 3 hours.	

1.4. Patient Experience Data

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

Table 1. Patient Experience Data Relevant to this Application

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

2 Therapeutic Context

2.1. Analysis of Condition

The historical picture of smallpox is that of a human-to-human communicable disease characterized by an asymptomatic incubation period (averaging close to two weeks but with substantial variability), an initial period of nonspecific symptoms lasting a few days (fever, headache, back pain, prostration), then evolution of skin manifestations followed by death or by gradual recovery with varying degrees of scarring. Most of the clinical descriptions are based

on variola major, the more serious form that was also more prevalent throughout most of the history of the disease, and that is also the focus of concerns regarding potential biothreat uses of variola virus. Mortality in variola major is commonly cited as about 30% but was reported to vary widely among outbreaks from as little as 5% to 40% or more.[1] In 1980, following an historic global campaign of surveillance and vaccination, the World Health Assembly declared smallpox eradicated – the only infectious disease to achieve this distinction.[2] Despite the eradication of naturally acquired smallpox, the disease remains a threat as variola virus could be developed as a bioterrorism agent. Variola virus is categorized by the National Institute of Allergy and Infectious Diseases (NIAID) as a Category A priority pathogen. Category A pathogens are those organisms/biological agents that pose the highest risk to national security and public health.[3] Routine vaccination in the U.S. ended in the 1970s, so most of the population is immunologically susceptible to smallpox. Medical countermeasures, including antiviral therapies, are needed in the event of a variola (smallpox) virus outbreak. Due to the mortality and severe morbidity associated with smallpox, the World Health Organization (WHO) states that preparedness to deal with any kind of smallpox event – whether natural re-emergence, accidental or deliberate release of the live virus, or created through synthetic biology – requires global and national attention.[4]

Due to concerns regarding potential biothreat uses of variola virus, a specific unmet medical need exists for effective antiviral regimens for subjects who develop smallpox disease caused by variola virus because only one approved regimen is available. Approval of BCV would provide the second antiviral to address this unmet medical need.

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

2.2. Analysis of Current Treatment Options

Tecovirimat is currently the only approved antiviral treatment regimen for patients with human smallpox disease caused by variola virus. Approved in July 2018 under the Animal Rule, tecovirimat is indicated for the treatment of human smallpox disease caused by variola virus in adults and pediatric patients weighing at least 13 kg.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This is the first marketing application for any product containing BCV.

3.2. Summary of Presubmission/Submission Regulatory Activity

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

An Investigational New Drug application (IND) for BCV was submitted on May 12, 2005 by Chimerix, Inc. Fast track designation for BCV for treatment of human smallpox disease caused by variola virus was granted on July 8, 2005. Orphan Designation for treatment of human smallpox disease caused by variola virus was granted on June 5, 2018.

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

During the 2011 Antiviral Drugs Advisory Committee (ADAC) meeting, the advisory committee agreed with the FDA's assessment that current lethal NHP models using variola virus are not consistently reproducible and do not mimic what is known about human smallpox disease. Because scientific limitations of the available NHP/variola model preclude definitive efficacy assessments, and uncertainty exists whether an adequate variola model can be developed, the FDA and the advisory committee agreed that data from a combination of other lethal animal models using surrogate orthopoxviruses (e.g. NHP studies with monkeypox virus [MPXV], rabbit studies with rabbitpox virus [RPXV], mouse studies with ectromelia virus [ECTV]) could be used as evidence along with, or potentially instead of, animal studies using variola virus. This assumes a mechanistically plausible target for the candidate drug, and the drug target being conserved across different orthopoxviruses. The Applicant focused on the rabbit/RPXV animal model and the mouse/ECTV animal model. In these animal studies, key study design issues were discussed by the Applicant and the Division and consensus was reached before these studies were conducted.

FDA granted the Applicant's request for a rolling review of this NDA on March 26, 2020. The details of the milestone meetings can be found in the official meeting minutes archived in the Document Archiving, Reporting and Regulatory Tracking System (DARRTS). All previous reviews can also be accessed in DARRTS for additional information.

3.3. Foreign Regulatory Actions and Marketing History

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

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

4.1. Office of Scientific Investigations and Surveillance (OSIS)

Inspection sites were selected from Studies 201, 202, and 301 as these contributed to the safety database for the proposed indication. A total of 5 sites, 3 with overlapping enrollment in Studies 201 and 301, and 2 with overlapping enrollment in Studies 201, 202, and 301, were selected from the large number of sites per study based on high enrollment and/or protocol deviations and/or screen failure rate. All sites were domestic, and this approach was assessed as appropriate because Studies 201 and 202 were conducted solely in the US, and Study 301 was conducted predominantly in the US.

The final reports from the clinical site inspections were reviewed. The notable inspection finding was one site (site number #25 for both Study 301 and Study 201) with unreported AEs (Study 301-27 AEs in 10 subjects; Study 201-19 AEs in 4 subjects). Following OSI audit, the Applicant obtained these data from the study investigator: all AEs were assessed as not related to BCV; 7 AEs had onset in the first 2 weeks of BCV treatment. These AEs did not change the overall safety assessment for BCV.

4.2. Product Quality

The commercial BCV tablet, 100 mg is an immediate release solid oral dosage form. The inactive ingredients are Colloidal Silicon Dioxide, Crospovidone, FD&C Blue #1/Brilliant Blue FCF Aluminum Lake, FD&C Blue #2/Indigo Carmine Aluminum Lake, Magnesium Stearate, Mannitol, Microcrystalline Cellulose, Polyethylene Glycol, Polyvinyl Alcohol, Purified Water, Silicified Microcrystalline Cellulose, Talc, and Titanium Dioxide.

The commercial BCV oral suspension, 10 mg/mL is an aqueous based, preserved, orally dosed suspension. The inactive ingredients are Citric Acid Anhydrous, Microcrystalline Cellulose and Carboxymethyl Cellulose Sodium, (b) (4) Lemon Lime Flavor, Purified Water, Simethicone 30% Emulsion, Sodium Benzoate, Sucralose, Trisodium Citrate Anyhydrous, and (b) (4) Xanthan Gum.

Please refer to the CMC Reviews by Dr. Peter Guerrieri, Dr. Raymond Frankewich, Dr. Gerlie Gieser, Dr. Naveen Kanthamneni, and Dr. Erika Englund for further details on manufacturing processes, process controls, formulation specifications, and the adequacy of data provided to assure drug stability, strength, purity, and quality for BCV. The final report from the inspection of the production facilities was not available at the time this review was finalized.

4.3. Clinical Microbiology

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

In cell culture assays, BCV has activity against a variety of orthopoxviruses, including five different isolates of VARV, with EC50 values of 0.05-21 µM. *In vivo* antiviral activity was

demonstrated in animal models evaluating different orthopoxvirus infections, including mice (ectromelia, vaccinia, cowpox viruses) and rabbits (rabbitpox virus). Sections 6 and 7 detail the two pivotal animal efficacy trials: one using the rabbit/RPXV model, and one using the mouse/ECTV model.

A brief summary of *in vitro* (i.e., cell culture) and *in vivo* resistance against BCV is provided below:

(b) (3) (A), (b) (3) (B)

- Cross-resistance between BCV and tecovirimat is not expected based on their distinct mechanisms of action. The mechanism of action of tecovirimat involves preventing the production of extracellular enveloped virus necessary for spread of orthopoxvirus infection. BCV targets the viral DNA polymerase and inhibits viral DNA replication. Where tested, orthopoxvirus isolates resistant to tecovirimat have not been resistant to BCV and/or CDV and vice versa. Non-antagonistic antiviral activity of BCV and tecovirimat has been demonstrated in cell culture and animal models.

Please refer to Dr. Patrick Harrington's and Dr. Eric Donaldson's Clinical Virology reviews for additional details.

4.4. Nonclinical Pharmacology/Toxicology

This section summarizes the key findings from the pharmacology/toxicology discipline review. Please see the Pharmacology/Toxicology review by Dr. Mark Seaton for full details.

The oral bioavailability of BCV was 8% in rats, 8% in rabbits, and <1% in NHPs. *In vitro* protein binding was >98% in all species, including human.

Following an oral dose of ^{14}C-BCV in mice and rats, radioactivity was widely distributed. Tissues with the highest concentrations of radioactivity were those comprising the alimentary canal, particularly the small intestine in which high concentrations of BCV-related material were sustained through 24 hours post-dose. The tissue to plasma (T/P) ratio of the AUC radioactivity values after oral administration was greatest in the small intestine (particularly duodenum and

jejunum) and were 3 to 6 times greater than the AUC T/P ratio in any other tissue. Longer term radioactivity was seen in the lymph nodes, bone marrow, and kidneys. Association of BCV-related material with central nervous system (CNS) tissues was low and no preferential association with melanin containing tissues was observed. Qualitatively, the distribution patterns were similar following oral or IV administration to rats.

Dose-limiting GI events, manifested as gastropathy and enteropathy or enteritis, were observed following daily oral administration of BCV in mice, rats, and monkeys. GI events were also observed in clinical studies (see Section 8 of this review).

Increases in ALT (2-5 fold) were observed in both rodent and nonrodent species in nonclinical toxicology studies of orally administered BCV. The changes seen with oral dosing appeared with highest frequency in monkeys, followed by mice and then rats. ALT elevations did not correlate with dose concentration and reversed after cessation of dosing. There were no gross or microscopic hepatic changes that correlated with the ALT increases. ALT elevations were also observed in clinical studies (see Section 8 of this review).

BCV was not associated with clinically relevant adverse effects on CNS, cardiovascular, respiratory or renal endpoints evaluated in safety pharmacology studies.

Nonclinical reproductive assessments demonstrated that BCV should be considered a potential teratogen and may affect male fertility.

Repeat-dose general toxicology studies demonstrated the tumorigenic effect of BCV in rats. Consequently, BCV is considered a potential carcinogen.

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.

4.5. Clinical Pharmacology

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

4.5.1. Mechanism of Action

BCV is a lipid conjugate of cidofovir (CDV), which is a nucleotide analog. The lipid conjugate is designed to mimic a natural lipid, lysophosphatidylcholine, and thereby use endogenous lipid uptake pathways. Once inside cells, the lipid ester linkage of BCV is cleaved to liberate CDV, which is then phosphorylated to produce the active antiviral, CDV-diphosphate. CDV-

diphosphate inhibits orthopoxvirus replication by inhibiting viral DNA polymerase-mediated synthesis of viral DNA.

4.5.2. Human Dose Selection

The results from the two pivotal animal efficacy trials, one using the rabbit/RPXV model (Study VIR-106) and one using the mouse/ECTV model (Study VIR-044) formed the basis for selecting the human dose and duration.

- In the rabbit/RPXV model, maximum efficacy was observed with the 20/5/5 mg/kg regimen (i.e. 20 mg/kg followed by two 5 mg/kg maintenance doses administered at Q48h intervals), thus the fully effective dose of BCV defined by the Animal Rule guidance is 20/5/5 mg/kg. Therefore, for the purpose of human dose selection, the rabbit dose was determined to be 20/5/5 mg/kg.
- In the mouse/ECTV model, maximum efficacy was observed with the 10/5/5 mg/kg regimen (i.e. 10 mg/kg followed by two 5 mg/kg maintenance doses administered at Q48h intervals), thus the fully effective dose of BCV defined by the Animal Rule guidance is 10/5/5 mg/kg. Therefore, for the purpose of human dose selection, the mouse dose was determined to be 10/5/5 mg/kg.
- Exposures from the 20/5/5 mg/kg regimen in the rabbit/RPXV model were compared with exposures from the 10/5/5 mg/kg regimen in the mouse/ECTV model. To achieve the same efficacy of BCV, a higher exposure of BCV is needed in rabbits compared to mice. Therefore, PK data from the 20/5/5 mg/kg regimen in rabbits was primarily used to determine the human dose (Table 2).

Table 2. BCV exposures in rabbits and humans

		Cmax (ng/mL)	$AUC_{0\text{-}168\ h}$ (h*ng/mL)
After 1st dose	Human	480 (240-950, 70%)	3400 (1900-6300, 58%)
	Rabbit	237 (67-649, 47%)	1490 (408-4110, 47%)
	H/R ratio	2.0	2.3
After last dose	Human	480 (240-950, 70%)	3400 (1900-6300, 58%)
	Rabbit	61 (17-173, 48%)	437 (109-1530, 55%)
	H/R Ratio	7.9	7.8

Data are expressed as geometric mean values (range, %CV); H/R, human-to-rabbit
$AUC_{0\text{-}168\ h}$: area under the concentration-time curve from time 0 to 168 h (time before the next dose).

- The exposure-response data from these two animal models allowed for selection of a dosing regimen for humans that would provide exposures that exceed those associated with the fully effective dose in animals.
- Overall, the exposure comparisons show that a BCV dose of 200 mg QW provides BCV exposures that are above the efficacious exposures observed in RPXV-infected rabbits for the duration of the smallpox disease course. Mean BCV plasma C_{max} and AUC following the first 200 mg QW dose in healthy adults were approximately 2-

fold higher than the BCV exposures simulated in rabbits following the 20 mg dose in the 20/5/5 mg/kg dose regimen.

- The above assessments informed the Agency's rationale for recommending 200 mg taken orally once weekly for 2 doses (on Days 1 and 8) as the proposed regimen.

Pediatric dosing regimens

Pediatric dosing regimens were based on comparing BCV exposures in non-orthopoxvirus-infected pediatric subjects to the adult exposures. As BCV has been evaluated in clinical development programs for various non-smallpox indications, BCV has been studied in children aged 3 months to < 18 years of age. From birth to 3 months of age, pediatric dosing regimens have been determined solely based on modeling and simulation.

The Applicant submitted the following pediatric dosing regimen:

(b) (4)

Based on the Office of Clinical Pharmacology (OCP) review team's assessment for the 0 – 0.3 year-old and 0.3 – 2 year-old age groups, the Applicant's proposed dosing regimen would likely result in BCV exposures that are lower than those observed in adult healthy volunteers receiving BCV 200 mg.

Therefore, the OCP review team recommended the following dosing regimen based on their independent population pharmacokinetic analysis and simulation. The proposed doses, based on simulation, for pediatric patients in other weight bands is summarized below:

- 10 kg to < 48 kg: 4 mg/kg of suspension once weekly for 2 doses (on Days 1 and 8)
- < 10 kg: 6 mg/kg of suspension once weekly for 2 doses (on Days 1 and 8)

In OCP analyses, the simulations showed the lowest weight groups (2.5-5 kg, 5-7 kg, 7-9 kg) are expected to have lower area under the concentration-time curve from time 0 to 168 h after drug administration ($AUC_{0–168\ h}$) of BCV with the Applicant's proposed regimen compared to adults receiving 200 mg tablets. Consequently, for pediatric subjects < 10 kg, the best matching exposure is 6 mg/kg based on the available PK data and modeling and simulation. The FDA recommended pediatric dosing regimen is expected to produce BCV exposures that are comparable to those in adults based on a population PK modeling and simulation approach.

4.5.3. Pharmacokinetics

Absorption, Distribution, Metabolism, and Elimination

The pharmacokinetic properties of BCV have been evaluated in healthy subjects:

- BCV is >99.9% bound to human plasma proteins.
- Administration of BCV tablets under fed conditions at 200 mg (i.e., administered within 10 minutes after a low-fat meal) reduces AUC by approximately 31% and reduces plasma BCV Cmax by approximately 49%, relative to fasting. No food-effect studies were conducted with the BCV suspension formulation and the mechanism of the food-BCV interaction is unknown.

BCV tablets should be taken on an empty stomach at least 1 hour before a meal or 2 hours after a meal or with a low-fat meal. BCV suspension should be taken on an empty stomach at least 1 hour before a meal or 2 hours after a meal.

- BCV is metabolized by hydrolysis of the phosphoester bond to form cidofovir (CDV). One enzyme involved in BCV hydrolysis is acid sphingomyelinase. Forty-three percent of the dose is metabolized via this pathway. CDV is subsequently phosphorylated to form CDV-diphosphate (CDV-PP) via intracellular kinases.
    - The Applicant provided in vitro data showing that concentrations of CDV and CDV-PP were reduced by approximately 78% in acid sphingomyelinase (ASM) knockout cells compared to parent cell CDV and CDV-PP concentrations. Although no clinical data are available in patients with ASM deficiency, the absence of clinical data is not unexpected given the birth prevalence of ASM deficiency is estimated at 1/100,000 (https://ojrd.biomedcentral.com/track/pdf/10.1186/s13023-018-0785-7.pdf).

(b) (4)

- BCV is also hydroxylated at the terminal carbon by CYP4F2, followed by subsequent CYP-mediated oxidations and multiple cycles of fatty acid beta-oxidation. Forty-nine percent of the dose is metabolized through this pathway. The major inactive metabolites formed via these pathways are CMX103 (3-hydroxypropyl ester of cidofovir) and CMX064 (4-(3-propoxy)butanoic acid ester of CDV).
- Renal clearance is the major (51%) elimination pathway for the metabolites, followed by biliary excretion (40%).
- Median terminal half-life of BCV and CDV-PP is approximately 19 hours and 133 hours respectively.

Intrinsic Factors

- Renal Impairment

The PK of BCV was studied in adults with normal renal function, severe renal impairment following a single dose of 100 mg, and in subjects with end stage renal disease (ESRD) requiring hemodialysis following a single dose of 100 mg prior to dialysis and following a single dose of 100 mg after dialysis. The PK of BCV were not significantly different in subjects with severe renal impairment or ESRD compared to those with normal renal function.

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

- Hepatic Impairment

The PK of BCV was studied with a single dose of 200 mg in adults with normal hepatic function and in adults with moderate and severe hepatic impairment (Child Pugh Class B and C). The PK of BCV were not significantly different in subjects with moderate (CP-B) and severe (CP-C) hepatic impairment as compared to subjects with normal hepatic function following the administration of a single dose of BCV 200 mg.

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

- Other intrinsic factors

No dose adjustment is needed based on sex (male vs. female) or race (White vs. Non-White). BCV PK parameters (AUC_{inf} and C_{max}) were correlated with body weight. After normalization of AUC_{inf} and C_{max} to doses in mg/kg (dose and weight adjustments), the correlation of body weight with BCV exposures was substantially reduced. Although the correlation to body weight, was reduced, it remained significantly correlated for C_{max} following tablet administration. Body weight effects were incorporated in the POPPK model developed with healthy subject data, which was subsequently applied to support the dose selection. No dose adjustments based on body weight are recommended in adult subjects weighing ≥ 48 kg.

Extrinsic Factors: Drug Interactions
Clinical Studies

● OATP 1B1 and 1B3 Inhibitors: Co-administration of BCV with 600 mg oral cyclosporine (OATP1B1 and 1B3 inhibitor) increased mean BCV $AUC_{0\text{-}inf}$ and C_{max} by 374% and 269%, respectively, compared to administration of BCV alone. In vitro data suggested BCV was a substrate of OATP 1B1 and 1B3.

- Based on these findings, Section 7 of the label will describe that OATP 1B1 and 1B3 inhibitors (which includes cyclosporine) resulted in increased BCV exposures and may increase adverse reactions associated with BCV. It will also describe risk mitigation strategies outlining that:
- Where possible, consider alternative medication that are not OATP 1B1 or 1B3 inhibitors. If concomitant use with BCV is necessary, increase monitoring for adverse reactions associated with BCV (elevations in transaminases and bilirubin, diarrhea or other GI adverse events) and separate the dose by at least 3 hours.

● CYP Substrates: No clinically significant differences in the pharmacokinetics of midazolam (sensitive CYP3A substrate) were observed when administered concomitantly with BCV. In vitro data suggested BCV as a potential inhibitor of CYP 3A4 in the gut.

● P-gp Substrates: No clinically significant differences in the pharmacokinetics of dabigatran etexilate (P-gp substrate) were observed when administered concomitantly with BCV. In vitro data suggested BCV as a potential inhibitor of P-gp in the gut.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically

● CYP Enzymes: BCV is a direct and reversible inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP4F2. BCV is not an inducer of CYP1A2, CYP2B6 or CYP3A.

● Transporter Systems: BCV is an inhibitor of Breast Cancer Resistance Protein (BCRP), multidrug resistance-associated protein 2 (MRP2), bile salt export pump (BSEP), OATP1B1, Organic Anion Transporter 1 (OAT1), and OAT3. BCV is not an inhibitor of OATP1B3, Organic Cation Transporter 2 (OCT2), multidrug and toxin extrusion protein 1 (MATE1), or MATE2-K in vitro.

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 3 contains a summary of the Phase 2/3 trials with the proposed to-be-marketed dose that were submitted with this application.

Table 3. Summary of Relevant Clinical Trials

Trial Identity	Phase	Trial Design	Regimen	Study Population	No. of patients enrolled	Study Endpoint	No. of Centers and Countries
Studies to Support Safety							
Study 301 (NCT01769170)	3	Randomized, double-blind, placebo-controlled trial with 2:1 randomization	BCV (100 mg BIW) or PBO	CMV R+ HSCT adults	452 in total: 303 BCV 149 PBO	Safety	44 sites, 3 countries
Study 201 (NCT00942305)	2	Randomized, double-blind, placebo-controlled, dose-escalation trial with 4:1 randomization	BCV (40 mg QW [n=25]; 100 mg QW [n=27]; 200 mg QW [n=39]; 200 mg BIW [n=30]; 100 mg BIW [n=50]) or PBO	CMV R+ HSCT adults	230 in total: 171 BCV 59 PBO	Safety	26 sites (all US)
Study 202 (NCT01241344)	2	Randomized, double-blind, placebo-controlled trial with 2:1 randomization	Pediatric (< 18 years) BCV 2 mg/kg or PBO BIW[a] BCV 4 mg/kg or PBO QW[b] Adult (≥ 18 years) BCV 100 mg or PBO BIW BCV 200 mg or PBO QW	HSCT (≥3 months to ≤ 75 years)	48 in total[c]: 30 BCV 18 PBO	Safety	17 sites (all US)
Other Studies Pertinent to the Review of Safety							
Study 120	1	Randomized, open-label, two-period, balanced crossover drug-drug interaction (DDI) study	Adult (≥ 18 years) • BCV 100 mg • BCV 100 mg + CsA 600 mg	Healthy adults	26 in total: 26 BCV	Safety	1 site (in US)

[a]Not-to-exceed 100 mg BIW; [b]Not-to-exceed 200 mg QW; [c]Pediatric (BCV [n=23]; PBO [n=12]).
ISS (Study 201 and Study 301): BCV 100 mg BIW (n=353); BCV 200 mg QW (n=39); PBO (n=208).
Tablet formulation was used in Study 301, Study 201 and Study 202 (adult dosing); solution or suspension was used in Study 202 (pediatric dosing).
The Applicant provided datasets, summaries of key safety events, narratives, and case report forms for these studies.

5.2. Review Strategy

The clinical efficacy review is based on the two pivotal animal efficacy trials: one using the rabbit/rabbitpox virus (RPXV) model (Study VIR-106), and one using the mouse/ectromelia virus (ECTV) model (Study VIR-044). The clinical reviewer along with the nonclinical, virology, and statistical reviewers collaborated extensively during the review process, and a number of analyses included in this review were performed by the nonclinical reviewers, Drs. David McMillan and L. Peyton Myers, the virology reviewers, Drs. Patrick Harrington and Eric Donaldson, and the statistical reviewer, Dr. Yu Cao. In addition, there were significant interactions with the clinical pharmacology, pharmacometrics, and chemistry manufacturing and controls reviewers. Their assessments are summarized in this document in the relevant sections, but complete descriptions of their findings are available in their respective discipline reviews.

For treatment studies to support animal efficacy under the Animal Rule, the preference is to evaluate a therapeutic intervention when it is initiated at the onset of clinically evident illness. In the rabbit/RPXV model, the development of fever was determined to be a consistent and reproducible trigger for treatment initiation. In the mouse/ECTV model, a clinically evident sign of disease could not be identified to use as a consistent and reproducible trigger for treatment initiation. Consequently, treatment initiation at various time-points during peak disease were evaluated. In both animal models, initiation of the drug at other later time-points was also evaluated in the Applicant's treatment studies.

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

The clinical safety review was primarily based on Studies CMX001-201 and CMX001-301. 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. Pooling of these studies was appropriate because the trial design and conduct of these studies were similar and the trial populations were comparable in terms of underlying disease severity.

The safety review also included CMX001-202 as this randomized, double-blind, placebo-controlled, multicenter trial comprises the pediatric data that will be described in labeling. Pooling of Study 202 with Studies 201 and 301 was not done because the trial design and conduct of these studies were different. Any notable findings that were not observed in, or differed from the ISS population, are presented where applicable.

In addition, data from the Phase 1 drug-drug interaction (DDI) study 120 that evaluated the effect of cyclosporine on the PK of BCV were reviewed. Pooling of this Phase 1 DDI study with Studies 201 and 301 was not done because the trial design and conduct of these studies were different. Any notable findings that were not observed in, or differed from the ISS population, are presented where applicable (see Section 8.5.9). JMP software was used to conduct the safety analyses presented in this review; any analyses performed by the Applicant or other members of the FDA review team will be labeled as such.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study VIR-106

6.1.1. Study Design

Overview and Objective
Study VIR-106 was a randomized, double-blind, placebo-controlled study assessing the efficacy of oral BCV in New Zealand White (NZW) rabbits intradermally challenged with rabbitpox virus (RPXV) strain Utrecht. The trial began on September 28, 2018 and the final study report was completed on February 19, 2020. Study VIR-106 was conducted at (b) (4) (b) (4) and was conducted in accordance with Good Laboratory Practices (GLP).

Trial Design
One hundred and fifty healthy (150) 16-week old NZW rabbits were randomized (1:1:1:1:1 to one of 4 BCV groups or placebo) into five groups of 30 animals based on weight and sex.

All animals were challenged intradermally with RPXV (Utrecht strain, Lot #050310-ALS) at a target dose of 600 PFU on Day 0. In the BCV groups, BCV was administered as 20/5/5 mg/kg (i.e. 3-dose regimen, with each dose separated by 48 hours, where the first dose was 20 mg/kg and the second and third doses were 5 mg/kg). The treatment groups are summarized below:

- BCV 20/5/5 mg/kg, treatment initiated at Day 3 PI
- BCV 20/5/5 mg/kg, treatment initiated at Day 4 PI
- BCV 20/5/5 mg/kg, treatment initiated at Day 5 PI
- BCV 20/5/5 mg/kg, treatment initiated at Day 6 PI
- Placebo (PBO)

Six animals were excluded or not challenged, of which 3 were euthanized because the inclusion criteria were not met, 1 died prior to challenge, 1 was euthanized after being found with a broken leg, and 1 was found dead. The final numbers of animals analyzed per group were 29 for each of the BCV groups and 28 in the PBO group.

Reviewer Comment: In the rabbit/RPXV model, the development of fever was determined to be a consistent and reproducible trigger for treatment initiation. In the natural history study, fever occurred in all animals by Day 4 PI and therefore Day 4 PI was used as the primary efficacy outcome in the Applicant's rabbit/RPXV studies as this time-point is consistent with treatment initiation following the onset of clinically evident illness. The Applicant included the Day 3 PI cohort for exploratory purposes as clinical signs of disease were evident in some animals at Day 3 PI in the natural history study. The Day 5 PI and Day 6 PI cohorts evaluated the effect of delayed treatment initiation on efficacy and were included for exploratory purposes.

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.

Blood levels of BCV were collected. Survival was evaluated to Day 42 PI. Viral DNA levels, skin lesions, clinical observations (vital signs, body weights, food consumption, and signs of illness), hematology and clinical chemistry, and gross anatomic pathology were evaluated.

Please refer to Dr. David McMillan's nonclinical review and Dr. Patrick Harrington's virology review for complete details.

Study Endpoints
The primary efficacy endpoint is the proportion of animals that survived until Day 42 PI.

Mortality was assessed as unscheduled euthanasia prior to the pre-specified end-of-study. Mortality was based on prospectively defined criteria for euthanasia. To meet the criteria for euthanasia, an animal must meet any of the following three criteria:
1) Severe respiratory distress, as assessed by clinical observations or morbidity and moribundity checks including open mouth breathing and/or forced abdominal respirations, *OR*
2) Moribund, persistent prostration, seizures, and/or unresponsive to external stimuli (e.g., gentle prodding by hand, *OR*
3) Animal(s) with 2 or more of the following objective signs:
• Respiration rate 75% lower or higher than the average observed during the baseline period (confirmed by second respiration rate measurement 1 hour±10 minutes later)
• Body temperature less than 37.2°C from either chip (confirmed by a second temperature measurement 1 hour ±10 minutes later)
• Weight loss greater than 15% from pre-challenge (Day 0) weight.
Note: For respiration rate and body temperature, the second confirmatory measurement was not required if that was the only euthanasia criteria met at that time point.

Statistical Analysis Plan
Statistical Analysis Plan for this study described analysis through Day 42 PI. This review focuses on the analysis of the primary efficacy endpoint (i.e. proportion of animals that survived until Day 42 PI).

Please refer to Dr. Yu Cao's statistics review for complete details.

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

6.1.2. Study Results

Efficacy Results – Primary Endpoint
Table 4 summarizes the proportion of animals that survived until Day 42 PI.

Table 4. Study VIR-106 Primary Efficacy Results (ITT)

Group (Treatment Initiation, Days PI)	Survival rate % (n/N)	95% CI[a] %	Rate difference[b] and exact 95% CI[c] (BCV – placebo)	Boschloo's 1-sided P-value	
				Unadjusted[d]	Adjusted[e]
BCV 20/5/5 mg/kg at Day 3 PI	100.0 (29/29)	88.1, 100.0	71.4% (51.3%, 86.8%)	<0.0001	<0.0001
BCV 20/5/5 mg/kg at Day 4 PI	89.7 (26/29)	72.7, 97.8	61.1% (35.7%, 79.3%)	<0.0001	<0.0001
BCV 20/5/5 mg/kg at Day 5 PI	69.0 (20/29)	49.2, 84.7	40.4% (12.5%, 62.8%)	0.0014	0.0028
BCV 20/5/5 mg/kg at Day 6 PI	69.0 (20/29)	49.2, 84.7	40.4% (12.5%, 62.8%)	0.0014	0.0028
Placebo	28.6 (8/28)	13.2, 48.7	-		
Cochran-Armitage Trend Test[f]	p = 0.0002				

[a] Clopper-Pearson 95% CI; [b] Difference in survival rate, BCV – placebo; [c] Exact confidence interval for difference in survival rate was based on inverting two one-sided tests in Cytel Studio; [d] P-value was based on a one-sided Boschloo's test with gamma=0 as compared to placebo group; [e] Adjusted p-values using Holm's procedure; [f] Cochran-Armitage trend test across BCV groups.
Source: Analysis performed by Dr. Yu Cao, Statistics Reviewer

Reviewer Comment: The animal narratives were reviewed and discussed with Dr. David McMillan. Please refer to Dr. McMillan's nonclinical review for complete details; I agree with Dr. McMillan's assessment that these animals had RPXV-related disease at the time of death (regardless of whether the animal met the euthanasia criteria or was found dead).

A statistically significant treatment benefit over placebo for the primary endpoint of survival was shown for BCV dosed at 20/5/5 mg/kg (administered every 48 hours for 3 doses) starting at Days 3, 4, 5 or 6 after virus inoculation.

Virology
Overall trends showed that treated groups had modestly lower whole blood viral DNA levels compared to placebo.

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

Pathology
Investigators assessed the major pathology findings as due to RPXV disease.

Reviewer Comment: Please refer to Dr. David McMillan's nonclinical review for complete details; I agree with Dr. McMillan's assessment that the pathology findings are consistent with RPXV-related disease.

6.2. Study VIR-044

6.2.1. Study Design

Overview and Objectives
Study VIR10-044 was a randomized, double-blind, placebo-controlled study assessing the efficacy of oral BCV in BALB/c mice intranasally challenged with ectromelia virus (ECTV) strain Moscow. The trial began on September 28, 2018 and the final study report was completed on February 19, 2020. Study VIR-044 was conducted at (b) (4) and was conducted in accordance with Good Laboratory Practices (GLP).

Trial Design
BALB/c mice aged 8 weeks were randomized (1:1:1:1:1:1:1:1 to one of 7 BCV groups or placebo) into groups of 32 animals based on weight and sex.

All animals were challenged intranasally with ECTV (Moscow strain, Lot #032516- ECTV) at a target dose of 200 PFU on Day 0. The treatment groups are summarized below:
- BCV 10/5/5 mg/kg, treatment initiated at Day 4 PI
- BCV 10/5/5 mg/kg, treatment initiated at Day 5 PI
- BCV 10/5/5 mg/kg, treatment initiated at Day 6 PI
- BCV 20/5/5 mg/kg, treatment initiated at Day 4 PI
- BCV 20/5/5 mg/kg, treatment initiated at Day 5 PI
- BCV 20/5/5 mg/kg, treatment initiated at Day 6 PI
- BCV 20/5/5 mg/kg, treatment initiated at Day 7 PI

- Placebo (PBO)

BCV regimens were administered every 48 hours for 3 doses, initiated at the above time-points.

Reviewer Comment: 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.

Blood levels of BCV were collected. Survival was evaluated to Day 42 PI. Viral DNA levels, skin lesions, clinical observations (vital signs, body weights, food consumption, and signs of illness), hematology and clinical chemistry, and gross and microscopic anatomic pathology were evaluated.

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

Study Endpoints
The primary efficacy endpoint is the proportion of animals that survived until Day 42 PI.

Mortality was assessed as unscheduled euthanasia prior to the pre-specified end-of-study. Mortality was based on prospectively defined criteria for euthanasia. To meet the criteria for euthanasia, an animal must meet either of two criteria:
1) Moribund/persistent prostration and unresponsive to touch or external stimuli, which included a gentle prodding or placing the mouse on its back to determine if the animal could right itself, *OR*
2) Any animal having >25% weight loss (when compared to baseline) along with any concurrent severe sign of illness was euthanized. Animals meeting this level of weight loss but without a severe sign could be euthanized, if deemed necessary for humane reasons, following examination or consultation by the Study Veterinarian or designee. If an animal reached 30% weight loss, regardless of presence or absence of severe clinical signs, it was euthanized.

Statistical Analysis Plan
Statistical Analysis Plan for this study described analysis through Day 42 PI. This review focuses on the analysis of the primary efficacy endpoint (i.e. proportion of animals that survived until Day 42 PI).

Please refer to Dr. Yu Cao's statistics review for complete details.

Protocol Amendments

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

6.2.2. Study Results

Efficacy Results - Primary Endpoint
Table 5 summarizes the proportion of animals that survived until Day 42 PI.

Table 5: Study VIR-044 Primary Efficacy Results (ITT)

Group (Treatment Initiation, Days PI)	Survival rate % (n/N)	95% CI[a] %	Rate difference[b] and exact 95% CI[c] (BCV – placebo)	Boschloo's 1-sided P-value	
				Unadjusted[d]	Adjusted[e]
BCV 10/5/5 mg/kg at Day 4 PI	78.1 (25/32)	60.0, 90.7	65.6% (43.6%, 81.9%)	<0.0001	<0.0001
BCV 10/5/5 mg/kg at Day 5 PI	65.6 (21/32)	46.8, 81.4	53.1% (28.9%, 71.6%)	<0.0001	<0.0001
BCV 10/5/5 mg/kg at Day 6 PI	34.4 (11/32)	18.6, 53.2	21.9% (0.7%, 43.0%)	0.02334[h]	0.02334[h]
Cochran-Armitage Trend Test[f]	0.0003				
BCV 20/5/5 mg/kg at Day 4 PI	84.4 (27/32)	67.2, 94.7	71.9% (50.0%, 86.7%)	<0.0001	<0.0001
BCV 20/5/5 mg/kg at Day 5 PI	75.0 (24/32)	56.6, 88.5	62.5% (40.3%, 79.4%)	<0.0001	<0.0001
BCV 20/5/5 mg/kg at Day 6 PI	46.9 (15/32)	29.1, 65.3	34.4% (10.6%, 54.6%)	0.0014	0.0028
BCV 20/5/5 mg/kg at Day 7 PI	37.5 (12/32)	21.1, 56.3	0.25% (3.2%, 45.8%)	0.0118	0.0118
Placebo	12.5 (4/32)	3.5, 29.0	-	-	-
Cochran-Armitage Trend Test[f]	<0.0001				

[a] Clopper-Pearson 95% CI; [b] Difference in survival rate, BCV – placebo; [c] Exact confidence interval for difference in survival rate was based on inverting two one-sided tests in Cytel Studio; [d] P-value was based on a one-sided Boschloo's test with gamma=0 as compared to placebo group; [e] Adjusted p-values using Holm's procedure; [f] one-sided Cochran-Armitage trend test across groups with BCV 10/5/5 mg/kg; [g] one-sided Cochran-Armitage trend test across groups with BCV 20/5/5 mg/kg; [h] p-value is not significant at the one-sided alpha of 0.0125.
Source: Analysis performed by Dr. Yu Cao, Statistics Reviewer

Reviewer Comment: A statistically significant treatment benefit over placebo for the primary endpoint of survival was shown for BCV dosed at 10/5/5 mg/kg (administered every 48 hours for 3 doses) or 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 was 10/5/5 mg/kg (Table 7).

A statistically significant treatment benefit over placebo for the primary endpoint of survival was shown for BCV dosed at 10/5/5 mg/kg (administered every 48 hours for 3 doses) starting at Days 4 or 5 after virus inoculation.

A statistically significant treatment benefit over placebo for the primary endpoint of survival was shown for BCV dosed at 20/5/5 mg/kg (administered every 48 hours for 3 doses) starting at Days 4, 5, 6 or 7 after virus inoculation.

Given the similarity in efficacy between 10/5/5 mg/kg and 20/5/5 mg/kg, 10/5/5 mg/kg was determined to be the fully effective dose.

Reviewer Comment: The animal narratives were reviewed and discussed with Dr. L. Peyton Myers. Please refer to Dr. Myers' nonclinical review for complete details; I agree with Dr. Myers' assessment that these animals had ECTV-related disease at the time of death (regardless of whether the animal met the euthanasia criteria or was found dead).

Virology

Virologic data in the efficacy analysis mouse groups were not sufficient to assess the impact of BCV treatment on viral replication since only terminal samples were collected from these mice. However, limited data from the resistance analysis groups provide some indication of BCV antiviral activity.

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

Pathology

Investigators assessed the major histopathologic findings as due to ECTV disease.

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

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The primary efficacy endpoint was proportion of animals that survived to the pre-specified end-of-study, as survival is clearly related to the desired benefit in humans and satisfies one of the tenets of the Animal Rule. As displayed in the tables below, survival in treated animals overall ranged from 78-90% when treatment was initiated at day 4 after virus inoculation.

Results from the rabbit/RPXV efficacy study VIR-106 are summarized describing survival rates by treatment arm (Table 6). BCV (dosed at 20/5/5 mg/kg, administered every 48 hours for 3 doses) is effective when treatment was initiated at day 4 after virus inoculation (i.e. the time-point when all animals had developed fever).

Table 6. Rabbit/RPXV studies with BCV: Survival by Treatment Arm n (%)

Study	Treatment Initiation (# of days after viral inoculation)	BCV	Placebo
VIR-106	Day 4	26/29 (90%)	8/28 (28%)
	*Day 5**	*20/29 (69%)*	
	*Day 6**	*20/29 (69%)*	

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

Results from the mouse/ECTV efficacy study VIR-044 are summarized describing survival rates by treatment arm (Table 7). BCV (dosed at 10/5/5 mg/kg, administered every 48 hours for 3 doses) is effective when treatment was initiated at day 4 after virus inoculation.

Table 7. Mouse/ECTV studies with BCV: Survival by Treatment Arm n (%)

Study	Treatment Initiation (# of days after viral inoculation)	BCV	Placebo
VIR-044	Day 4	25/32 (78%)	4/32 (13%)
	*Day 5**	21/32 (66%)	
	*Day 6**	11/32 (34%)	

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

7.1.2. Secondary and Other Endpoints

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

7.1.3. Subpopulations

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

7.1.4. Dose and Dose-Response

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

In the rabbit/RPXV model, maximum efficacy was observed with BCV dosed at 20/5/5 mg/kg (administered every 48 hours for 3 doses), thus the fully effective dose of BCV defined by the Animal Rule guidance is 20/5/5 mg/kg. Therefore, for the purpose of human dose selection, the rabbit dose was determined to be 20/5/5 mg/kg.

In the mouse/ECTV model, maximum efficacy was observed with BCV dosed at 10/5/5 mg/kg (administered every 48 hours for 3 doses), thus the fully effective dose of BCV defined by the Animal Rule guidance is 10/5/5 mg/kg. Therefore, for the purpose of human dose selection, the mouse dose was determined to be 10/5/5 mg/kg.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

The goal of treatment of human smallpox is reduction in mortality. Therefore, in the Applicant's rabbit/RPXV and mouse/ECTV studies, mortality (based on prospectively defined euthanasia criteria) was evaluated as the primary endpoint since mortality has been assumed to be the principal outcome of interest for human smallpox. Statistically significant treatment benefit over placebo for the primary endpoint of mortality was observed in the Applicant's rabbit/RPXV and mouse/ECTV studies when BCV was initiated at day 4 after virus inoculation in these animal models.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

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

Other benefits that should be factored into an assessment of benefit are summarized below:
(1) BCV and tecovirimat have distinct mechanisms of action.

(2) Available data indicate that BCV does not rapidly select for resistance.

(3) BCV has an oral solution for those who cannot swallow tablets. BCV oral solution can also be administered via enteral or nasogastric tubing for those who cannot swallow tablets or suspension.
• For those who cannot swallow tecovirimat capsules, tecovirimat capsules can be administered by carefully opening the capsule and mixing the entire contents in 30 mL of liquid (e.g., milk, chocolate milk) or soft food (e.g., apple sauce, yogurt). The entire mixture should be administered within 30 minutes of its preparation.

(4) BCV has dosing down to neonates. Tecovirimat dosing goes down to 13 kg.

(5) BCV regimen is 2 doses, given on Days 1 and 8.
• For tecovirimat, the adult dose is 600 mg (3 x 200 mg capsules) twice daily for 14 days, i.e. a total of 84 capsules.

7.2.2. Other Relevant Benefits

Not applicable.

7.3. Integrated Assessment of Effectiveness

The efficacy of BCV for the treatment of human smallpox infection under the Animal Rule has been established by the results from the two pivotal animal efficacy studies discussed in Section 6: Study VIR-106 using the rabbit/RPXV model and Study VIR-044 using the mouse/ECTV model.

Because smallpox is a potentially serious threat but does not occur naturally, clinical trials are not feasible and human challenge studies in healthy subjects are unethical. Therefore, animal models may provide important information for the evaluation of treatment effect and may contribute directly to drug approval under 21 CFR part 314, subpart I, if a suitable approach is agreed upon.[5,6]

Because of the unique complexities of drug development in this area, extensive discussion with multiple stakeholders has occurred, including an FDA public workshop in 2009 and an FDA public Advisory Committee meeting in 2011.[7,8] During the 2011 Antiviral Drugs Advisory Committee (ADAC) meeting, the advisory committee agreed with the FDA's assessment that current lethal NHP models using variola virus are not consistently reproducible and do not mimic what is known about human smallpox disease. Because scientific limitations of the available NHP/variola model preclude definitive efficacy assessments, and uncertainty exists whether an adequate variola model can be developed, the FDA and the advisory committee agreed that data from a combination of other lethal animal models using surrogate orthopoxviruses (e.g. NHP studies with monkeypox virus, rabbit studies with rabbitpox virus, mouse studies with ectromelia virus) could be used as evidence along with, or potentially instead of, animal studies using variola virus. This assumes a mechanistically plausible target for the candidate drug, and the drug target being conserved across different orthopoxviruses.

Based on multiple discussions with stakeholders (including the aforementioned 2011 Antiviral Drugs Advisory Committee), the FDA recommended the following: 1) Data from at least two lethal animal models of non-variola orthopoxvirus infection should be obtained to evaluate drug efficacy; 2) Non-variola orthopoxvirus animal models proposed for use in regulatory decision-making (i.e., efficacy studies) must be well-characterized and generate reproducible results that are reasonably expected to predict efficacy in variola virus infected or exposed humans, and; 3) Mortality, based on prospectively defined criteria for euthanasia, should be the primary endpoint for efficacy studies. The recommendation for use of multiple non-variola orthopoxvirus animal models acknowledges the unique challenges and uncertainties associated

with this area of drug development, and the fact that no single orthopoxvirus animal model is known to be the best predictor of human responses to treatments for smallpox.

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

For the rabbit/RPXV model, the Applicant completed a randomized, placebo-controlled, double-blinded study, performed under GLP in which BCV was started at the time of fever onset. Development of fever was determined to be a consistent and reproducible trigger for treatment initiation in this animal model. Day 4 after virus inoculation corresponds to the time-point when all animals had developed fever, and this time-point was used as the primary efficacy outcome. A statistically significant treatment benefit over placebo for the primary endpoint of mortality was shown in Study VIR-106 in which BCV was dosed at 20/5/5 mg/kg (administered every 48 hours for 3 doses) starting at day 4 after virus inoculation, and also when BCV was initiated at later time-points (i.e. Days 5 or 6 after virus inoculation). Maximum efficacy was observed with the 20/5/5 mg/kg regimen, thus the fully effective dose of BCV defined by the Animal Rule guidance is 20/5/5 mg/kg. Therefore, for the purpose of human dose selection, the rabbit dose was determined to be 20/5/5 mg/kg. Study VIR-106 also underwent evaluation by the Office of Scientific Investigations (OSI); OSI's inspection confirmed the data integrity of Study VIR-106. The Agency assessed that the rabbit/RPXV model is sufficiently characterized for scientific regulatory purposes. The Agency also assessed that the studies summarized in this review constitute completion of the Applicant's rabbit/RPXV program.

For the mouse/ECTV model, the Applicant completed a randomized, placebo-controlled, double-blinded study, performed under GLP. 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 after virus inoculation was used as the primary efficacy outcome in the Applicant's mouse/ECTV model. A statistically significant treatment benefit over placebo for the primary endpoint of mortality was shown in Study VIR-044 in which BCV was dosed at 10/5/5 mg/kg (administered every 48 hours for 3 doses) starting at day 4 after virus inoculation, and also when BCV was initiated at a later time-point (i.e. Day 5 after virus inoculation). Maximum efficacy was observed with the 10/5/5 mg/kg regimen, thus the fully effective dose of BCV defined by the Animal Rule guidance is 10/5/5 mg/kg. Therefore, for the purpose of human dose selection, the mouse dose was determined to be 10/5/5 mg/kg. Study VIR-044 also underwent evaluation by

the Office of Scientific Investigations (OSI); OSI's inspection confirmed the data integrity of Study VIR-044. The Agency assessed that the mouse/ECTV model is sufficiently characterized for scientific regulatory purposes. The Agency also assessed that the studies summarized in this review constitute completion of the Applicant's mouse/ECTV program.

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

Due to concerns regarding potential biothreat uses of variola virus, a specific unmet medical need exists for effective antiviral regimens for subjects who develop smallpox disease caused by variola virus because only one approved regimen is available. Approval of BCV would provide the second antiviral to address this unmet medical need.

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

8 Review of Safety

8.1. Safety Review Approach

The safety review focused on CMX001-201 and CMX001-301 as these two randomized, double-blind, placebo-controlled, multicenter trials comprise the adult data that will be described in labeling.[9,10] Data from CMX001-201 and CMX001-301 were pooled to form the integrated safety (ISS) population. Pooling of these studies was appropriate because the trial design and conduct of these studies were similar and the trial populations were comparable in terms of underlying disease severity. Unless otherwise specified, the analyses presented in this section were performed using the analysis datasets for CMX001-201 and CMX001-301. Data from CMX001-201 and CMX001-301 were pooled to form the integrated safety (ISS) population.

The safety review also included CMX001-202 as this randomized, double-blind, placebo-controlled, multicenter trial comprises the pediatric data that will be described in labeling.[11]

These trials evaluating BCV for prevention of CMV in CMV-seropositive (R+) HSCT recipients (CMX001-201 and CMX001-301), or for prevention of adenovirus (ADV) disease following HSCT, support the safety assessment detailed in this section at the proposed dose and duration for the following reasons:
- Exposures in humans with 200 mg dose exceed the fully effective dose in animals as recommended for Animal rule.

- Given the mortality imbalance observed with longer durations of BCV and since the proposed dose is two doses, the review presents data through Week 2 from the completed trials referenced.

Data were analyzed with JMP software. Discrepancies between the FDA analyses and the Applicant's analyses were relatively minor and attributable to variable methods of pooling and subgroup analyses.

Gastrointestinal (GI) and hepatic events were a focus of scrutiny during the safety review, prompted by the dose-limiting GI and hepatic toxicities that were observed throughout all BCV programs and also observed in animal studies. These GI and hepatic toxicities are also associated with duration of administration.

GI safety signals can be difficult to detect in trials with hematopoietic stem cell transplant (HSCT) recipients due to underlying disease, conditioning chemotherapeutic regimens resulting in mucositis, multiple concomitant medications known to cause diarrhea (e.g. antibiotics, magnesium, methotrexate and mycophenolate mofetil), other comorbidities, concurrent GI infections (e.g. *C. difficile*), and transplant-specific complications such as acute GI GVHD.

Hepatic safety signals can also be difficult to detect in trials with HSCT recipients due to underlying disease, chemotherapeutic regimens and/or other concomitant medications, other comorbidities, and transplant-specific complications such as graft-versus-host disease (GVHD) and/or veno-occlusive liver disease (VOD). To facilitate detection of possible safety concerns, the Applicant had an independent hepatic safety expert review possible cases of DILI. The independent hepatic safety expert reviewed all cases of reviewed all cases of BCV subjects from completed clinical studies who experienced hepatic laboratory events meeting biochemical criteria for potential Hy's Law cases. In addition, a thorough hepatic safety review was conducted by the clinical reviewers and the conclusions reached by FDA reviewers were compared to those of the independent hepatic safety expert.

The safety review also focused on adverse drug reactions of interest for nucleotide analogs, including rash, neuropsychiatric events, rhabdomyolysis, and pancreatitis.

Compliance with Good Clinical Practices
Studies CMX001-201, CMX001-202, and CMX001-301 were conducted under a US IND application and in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312).

The trial protocols, amendments and informed consent forms were reviewed and approved by independent ethics committees (IEC) or institutional review boards (IRB) before trial initiation.

Investigators (or designees) were responsible for obtaining written informed consent from each individual prior to undertaking any study-related procedures. The FDA OSIS inspected selected clinical sites but the inspection reports were not available at the time this review was finalized (See Section 4.1 for information on AE reporting at one site and the steps taken that adequately resolved said inspection finding). A detailed discussion of the OSI audit will be available in the Clinical Inspection Summary.

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

Study 201
Overview and Objectives
Study 201 (CMX001-201) is a completed Phase 2, randomized, double-blind, placebo-controlled, dose-escalation study evaluating the safety, tolerability, and ability of BCV to prevent or control CMV infection in CMV-seropositive (R+) HSCT recipients. The primary safety objectives of the trial are to evaluate the safety and tolerability of BCV in HSCT recipients and to select the dose of BCV to be evaluated in subsequent studies.

The trial began on December 24, 2009 and completed on November 15, 2011. Subjects were enrolled across 26 study sites in the US.

Trial Design
Adult (R+) HSCT recipients were randomized in a 4:1 ratio in a double-blind manner to receive either BCV or matching placebo (PBO). A placebo-controlled trial design was chosen to provide a clear assessment of BCV's safety profile. Study 201 consisted of a screening evaluation, a blinded treatment phase of 9 to 13 weeks' duration posttransplant (depending on when treatment was initiated relative to the date of transplant), followed by an 8-week follow-up phase. The following doses were evaluated:
• 40 mg once weekly (QW)
• 100 mg QW
• 200 mg QW
• 200 mg twice weekly (BIW); this dose was reduced to 200 mg QW for ongoing subjects following the April 2011 Data and Safety Monitoring Board (DSMB) recommendation that was based on the identification of dose-limiting GI toxicities. No new subjects were enrolled into

this cohort following DSMB's recommendation to reduce the dose.

• 100 mg BIW

Men and non-pregnant/non-lactating women ≥ 18 years of age, (R+) HSCT recipients who were up to and including 30 days post qualifying transplant, and must have had evidence of engraftment before randomization were eligible for participation.

Subjects were ineligible if they had any of the following: active CMV disease diagnosed within 6 months prior to enrollment or had CMV DNAemia requiring antiviral therapy at the time of enrollment; ALT/AST >5 times the upper limit of normal (ULN); direct bilirubin >2.5 times ULN; GFR < 30 mL/min; Grade 3/4 GVHD of the GI tract; HIV, HBV or HCV infection; malignancy; automimmune disease; significant cardiac, pulmonary or psychiatric disease; current diagnosis of hypotony, uveitis, or retinitis or any intraocular pathology; one or more episodes of hyperglycemic coma or diabetic ketoacidosis in the past 6 months.

Subjects were also ineligible if they had been using any of the following: high dose acyclovir (> 2,000 mg PO total daily dose [TDD] or > 5 mg/kg IV 3x daily) or valacyclovir (> 3,000 mg TDD) at the time of dosing; ganciclovir, valganciclovir, foscarnet, or cidofovir within 14 days prior to enrollment; any anti-CMV therapy following transplantation; any CMV vaccine; or any investigational drug within 14 days prior to enrollment.

Study Endpoints
The safety endpoints included adverse events (AEs) and serious adverse events (SAEs). The primary safety analysis was performed using the full analysis set (FAS), which included all subjects who received at least one dose of study medication.

Statistical Analysis Plan
There is no formal sample size calculation for safety analyses in this trial.

Protocol Amendments
Six protocol amendments were made. Key changes in these amendments are summarized below. None of the other changes significantly impact the conduct of the trial.

<u>Amendment 3 (dated August 11, 2011)</u>

• Dosage for the 200 mg BIW cohort was reduced to 200 mg QW per DSMB's recommendation due to an imbalance in SAEs of severe diarrhea with BCV compared to PBO.
• 100 mg BIW cohort was added.

Reviewer Comment: In April 2011, FDA placed all BCV INDs on partial clinical hold based on the serious adverse event (SAE) reports of severe diarrhea associated with gastrointestinal graft-versus-host disease (GVHD) that led to the independent DSMB's recommendation to discontinue the 200 mg BIW dosing cohort, and that all patients who were still receiving 200 mg BIW undergo dose reduction to 200 mg QW. FDA also identified some reports of hepatotoxicity,

including hepatic failure, with fatal outcome in one case, among subjects receiving the higher doses of BCV. Based on the available data, FDA assessed the risk/benefit profile was not acceptable for adult doses of BCV above 200 mg QW or pediatric doses above 4 mg/kg QW at this time. The April 2011 hold letter also specified that: all adult subjects who were currently receiving BCV at 200 mg BIW or higher should have their dose decreased to 200 mg QW; all pediatric subjects who were currently receiving BCV at 4 mg/kg BIW or higher should have their dose decreased to 4 mg/kg QW. Study 201 protocol was revised accordingly. Additionally, across all BCV INDs, the following revisions were made to the maximum doses allowed for subjects:

- *200 mg QW (adult) or 4 mg/kg QW (pediatric)*
- *100 mg BIW (adult) or 2 mg/kg BIW (pediatric)*

Study 301

Overview and Objectives

Study 301 (CMX001-301) is a completed Phase 3, randomized, double-blind, placebo-controlled, parallel-group study evaluating the safety, tolerability, and efficacy of BCV for the prevention of CMV infection in CMV-seropositive (R+) HSCT recipients. The primary safety objective of the trial is to evaluate the safety and tolerability of BCV in HSCT recipients.

The trial began on August 22, 2013 and completed on November 12, 2015. Subjects were enrolled across 39 study sites in the US, 3 study sites in Canada, and 2 study sites in Belgium.

Trial Design

Adult (R+) HSCT recipients were randomized in a 2:1 ratio in a double-blind manner to receive either BCV (100 mg BIW) or matching PBO. A placebo-controlled trial design was chosen to provide a clear assessment of BCV's safety profile. Study 301 consisted of a screening evaluation, a blinded treatment phase of 10 to 14 weeks' duration posttransplant (depending on when treatment was initiated relative to the date of transplant), followed by a 10-week post-treatment phase (to Week 24 post-transplant).

Men and non-pregnant/non-lactating women ≥ 18 years of age, (R+) HSCT recipients who were up to and including 30 days post qualifying transplant and must have had evidence of engraftment before randomization, were eligible for participation.

Subjects were ineligible if they had any of the following: positive CMV viremia at any time between transplant and the first dose day (FDD); possible, probable, or definitive CMV disease diagnosed within 6 months prior to FDD; ALT/AST >5x ULN; total bilirubin >2x ULN; direct bilirubin >1.5x ULN; GFR < 15 mL/min or requiring hemodialysis; Grade 2 or higher GVHD of the GI tract or any other GI disease; HIV, HBV or HCV infection; malignancy.

Subjects were also ineligible if they had been using any of the following: high dose acyclovir (> 2,000 mg PO TDD or > 15 mg/kg IV TDD) or valacyclovir (> 3,000 mg TDD) or leflunomide on the FDD; ganciclovir, valganciclovir, foscarnet, or cidofovir within 14 days prior to FDD; any anti-

CMV therapy following transplantation; any CMV vaccine; any investigational drug within 14 days prior to FDD; digoxin or ketoconazole on FDD or who were anticipated to need either digoxin or ketoconazole during the treatment phase (through Week 14); any prior BCV use.

Study Endpoints
The safety endpoints included AEs, SAEs, and AEs leading to discontinuation. The primary safety analysis was performed using the full analysis set (FAS), which included all subjects who received at least one dose of study medication.

Statistical Analysis Plan
There is no formal sample size calculation for safety analyses in this trial.

Protocol Amendments
One protocol amendment was made. None of these changes significantly impact the conduct of the trial.

Reviewer Comment: Overall Study 201 and 301 (392 subjects to receive BCV and 208 subjects to receive placebo) met FDA's recommendation for a minimum of a 300 subject safety database at the proposed dose and duration to support an indication for treatment of patients with smallpox.

Study 202
Overview and Objectives
Study 202 (CMX001-202) is a completed Phase 2, randomized, double-blind, placebo-controlled, dose-escalation study evaluating the safety and efficacy of pre-emptive treatment with BCV for the prevention of adenovirus (ADV) disease following HSCT. The primary safety objective of the trial is to evaluate the safety and tolerability of BCV in HSCT recipients.

The trial began on June 29, 2011 and completed on February 28, 2013. Subjects were enrolled across 17 study sites in the US.

Trial Design
HSCT recipients were randomized in a 2:1 ratio in a double-blind manner to receive either BCV or matching PBO. A placebo-controlled trial design was chosen to provide a clear assessment of BCV's safety profile. Study 202 consisted of a screening evaluation, a blinded treatment phase of 6 to 12 weeks' duration posttransplant (depending on when treatment was initiated relative to the date of transplant), an open-label BCV phase of up to 12 weeks (if needed), and a 4-week post-treatment follow-up phase. The following doses were evaluated:
- 4 mg/kg BIW (pediatric) or 200 mg BIW (adult)
- 4 mg/kg QW (pediatric) or 200 mg QW (adult)
- 2 mg/kg BIW (pediatric) or 100 mg BIW (adult)

Male or female, ≥ 3 months to ≤ 75 years of age, HSCT recipients who had serum ADV PCR ≥ 100 copies/mL were eligible for participation.

Subjects were ineligible if they had any of the following: possible, probable, or definitive ADV disease; definitive ADV disease diagnosed within 6 months prior to randomization; ALT/AST >5x ULN; total bilirubin >2x ULN; direct bilirubin >1.5x ULN; GFR < 30 mL/min; hypotony, uveitis, or retinitis or any intraocular pathology; significant cardiac, pulmonary or central nervous system disease; HIV, HBV or HCV infection; CDV, ribavirin, or leflunomide within 14 days prior to randomization; currently receiving digoxin or anticipated to need digoxin during the treatment phase; any prior BCV use.

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

Statistical Analysis Plan
There is no formal sample size calculation for safety analyses in this trial.

Protocol Amendments
Five protocol amendments were made. Key changes in these amendments are summarized below. None of the other changes significantly impact the conduct of the trial.

Amendment 3 (dated August 23, 2011) – revisions made for consistency with Study 201
• 4 mg/kg BIW (pediatric) cohort was removed*.
• 200 mg BIW (adult) cohort was removed*.
*These changes occurred in April 29, 2011 and communicated via a Dear Investigator Letter.

Reviewer Comment: Study 202 (23 subjects to receive BCV and 12 subjects to receive placebo) provided randomized clinical trial data in pediatric subjects and will be described in labeling.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 8 describes the overall exposure to BCV in the studies that contribute to the primary safety database.

Table 8. Safety Population, Size and Denominators

Primary Safety Database for BCV (controlled data) Individuals exposed to BCV for the indication under review N=1090		
Clinical Trial Groups	BCV[a] (n=1090)	PBO (n=254)
Phase 1: Healthy Volunteers[b]	586	28

Phase 2: HSCT recipients[b]	201	77
Phase 3: HSCT recipients	303	149

[a]Total numbers include subjects who received lower than the to-be-marketed dose
[b]Phase 1 and Phase 2 studies include dose-ranging studies evaluating BCV.
ISS (Study 201 and Study 301): BCV 100 mg BIW (n=353); BCV 200 mg QW (n=39); PBO (n=208).

Overall, a total of 392 adult subjects received the proposed dose and duration of BCV: 89 subjects in Study 201 and 303 subjects in Study 301.

Reviewer Comment: See Section 8.5.9 for discussion of Study 120 findings. Pooling of this Phase 1 DDI study with the Phase 2/3 studies was not done because the trial design and conduct of these studies were different.

8.2.2. Relevant characteristics of the safety population

Baseline characteristics for the ISS population are described below.

Table 9. Baseline Demographic Characteristics, ISS

Demographic Parameters	BCV 100 mg BIW (N=353) n (%)	BCV 200 mg QW (N=39) n (%)	Total BCV (N=392) n (%)	PBO (N=208) n (%)
Sex				
Male	189 (54%)	22 (56%)	211 (54%)	132 (63%)
Female	164 (46%)	17 (44%)	181 (46%)	76 (37%)
Age				
Mean years (SD)	52.4 (14.1)	49.5 (12.8)	52.1 (14.0)	51.4 (14.4)
Median (years)	55	51	41	53
Min, max (years)	18, 77	23, 70	18, 77	20, 75
Age Group				
< 65 years	273 (77%)	36 (92%)	309 (79%)	158 (76%)
≥ 65 years	80 (23%)	3 (8%)	83 (21%)	50 (24%)
Race				
White	299 (85%)	35 (90%)	334 (85%)	176 (85%)
Black	27 (8%)	0 (0%)	27 (7%)	18 (9%)
Asian	19 (5%)	3 (8%)	22 (6%)	12 (6%)
Other[1]	8 (2%)	1 (3%)	9 (2%)	2 (1%)
Ethnicity: Hispanic/Latino				
Yes	33 (9%)	5 (13%)	38 (10%)	20 (10%)
No	316 (90%)	34 (87%)	350 (89%)	187 (90%)
Not disclosed	4 (1%)	0 (0%)	4 (1%)	1 (<1%)

[1]Includes American Indian/Alaska Native, Hawaiian or Pacific Islander and other
Source: ISS ADSL dataset

Reviewer Comment: The two treatment arms are well balanced with respect to age, race, sex, and ethnicity. Studies 201 and 301 (i.e. ISS population) were predominantly conducted in the US,

which makes the data readily applicable to the US population. Subgroup analyses based on demographic factors will be presented in Section 8.6 of this review.

Baseline characteristics for the Study 202 pediatric population are described below.
Table 10. Baseline Demographic Characteristics, Study 202 Pediatric Population

Demographic Parameters	BCV 100 mg BIW[1] (N=11) n (%)	BCV 200 mg QW[2] (N=12) n (%)	Total BCV (N=23) n (%)	PBO (N=12) n (%)
Sex				
Male	7 (64%)	10 (83%)	17 (74%)	8 (67%)
Female	4 (36%)	2 (17%)	6 (46%)	4 (33%)
Age				
Mean years (SD)	6.5 (4.7)	6.7 (3.4)	6.6 (4.0)	7.5 (5.2)
Median (years)	7	6	7	7
Min, max (years)	0, 13	2, 12	0, 13	1, 17
Age Group				
< 2 years	3 (27%)	0 (0%)	3 (13%)	1 (8%)
2 to < 6 years	2 (18%)	6 (50%)	8 (35%)	4 (33%)
6 to < 12 years	4 (36%)	5 (42%)	9 (39%)	4 (33%)
12 to < 18 years	2 (18%)	1 (8%)	3 (13%)	3 (25%)
Race				
White	6 (55%)	8 (67%)	14 (61%)	12 (100%)
Black	2 (18%)	4 (33%)	6 (26%)	0 (0%)
Asian	1 (9%)	0 (0%)	1 (4%)	0 (0%)
Other[3]	2 (18%)	0 (0%)	2 (9%)	0 (0%)
Ethnicity: Hispanic/Latino				
Yes	1 (9%)	2 (17%)	3 (13%)	4 (33%)
No	10 (91%)	10 (83%)	20 (87%)	8 (67%)

[1]BIW dosing includes 100 mg BIW or 2 mg/kg BIW, depending on subject's ability to swallow tablets.
[2]QW dosing includes 200 mg QW or 4 mg/kg QW, depending on subject's ability to swallow tablets.
[3]Includes American Indian/Alaska Native, Hawaiian or Pacific Islander and other
Source: Study 202 ADSL dataset

Reviewer Comment: Study 202 was conducted entirely in the US, which makes the data readily applicable to the US population. The age of pediatric subjects ranged from 7 months to 17 years. Given the small pediatric sample size in Study 202, safety analyses by demographic subgroups were not feasible.

8.2.3. Adequacy of the safety database

The safety database is adequate to assess the safety of BCV for the proposed dosage regimen and duration of treatment. The ISS population encompassed 392 adult subjects treated at the proposed dose and duration of BCV. The ISS population meets FDA's recommendation for a minimum of a 300 subject safety database to support an indication for treatment of patients with smallpox. A database of at least 300 individuals is needed to rule out a 1% rate of a specific

adverse reaction if that specific adverse reaction did not occur in the population studied.[5]

Patient Disposition
In the ISS population, 600 subjects were randomized to treatment groups and received at least one dose of study medication and were included in the safety population: 392 in the BCV group and 208 in the placebo group (Table 11). Eighty-five subjects (14%) prematurely discontinued study treatment. Fifty nine of the 85 subjects were in the BCV group, and the reasons for premature discontinuation were AE (34 subjects), subject request (14 subjects), protocol violation (10 subjects), and physician request (1 subject). In the placebo group, the reasons for premature discontinuation were AE (9 subjects), subject request (5 subjects), protocol violation (10 subjects), and physician request (2 subjects).

Table 11. Treatment Duration, ISS

	BCV	PBO
Treated	392 (100%)	208 (100%)
Received ≥ 2 weeks	333 (85%)	182 (88%)
Discontinued treatment		
Adverse event	34 (9%)	9 (4%)
Subject request	14 (4%)	5 (2%)
Protocol violation	10 (3%)	10 (5%)
Physician request	1 (<1%)	2 (1%)

Receipt of prohibited concomitant medications
Source: ADSL, ADAE datasets

Reviewer Comment: Two-week treatment duration was overall tolerable; completion rates were high (≥85%) and comparable across treatment groups. The reported protocol violations had no bearing on the interpretability of the trial results.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No data quality or data integrity issues were identified. For Studies 201, 301, and 202, all narratives for deaths, SAEs, and treatment discontinuations were reviewed and compared to the Applicant's summary and assessment.

8.3.2. Categorization of Adverse Events

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

AEs were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 toxicity grading criteria.[12] The clinical reviewer verified the Applicant's translation of verbatim terms to preferred terms for events reported in Studies 201, 301, and 202.

8.3.3. Routine Clinical Tests

In Studies 201, 301, and 202, routine clinical evaluation and laboratory testing occurred at pre-specified intervals:

- Study 201: Screening; Day 0 (pre-Dose 1, defined as Baseline); Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11; Follow-Up on post-treatment Weeks 1, 2, 4, and 8.
- Study 301: Screening; Day 0 (pre-Dose 1, defined as Baseline); Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 (on-treatment); Weeks 15, 18, 21, and 24 (post-treatment).
- Study 202: Screening; Day 0 (pre-Dose 1, defined as Baseline); Days 3, 7, 10, 14, 21; Weeks 5, 6, 7, 8, 9, 10, 11, 12; Follow-Up on post-treatment Weeks 1, 2, and 4.

For these trials, the frequency and scope of this testing was deemed adequate. Safety assessments primarily included clinical evaluation of AEs, vital sign measurement, physical examinations, and standard laboratory safety tests. Additional testing occurred as indicated or deemed clinically necessary by the investigator during the trials.

8.4. Safety Results

Each subsection in this section presents the results for the ISS population (Study 201 and Study 301) and from Study 202.

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

An overall summary of ISS safety events is presented in Table 12.

Table 12. Overview of Adverse Events, ISS

Subjects Experiencing Event n (%)	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
Any AE	323 (92%)	33 (85%)	356 (91%)	177 (85%)
Grade 2, 3, or 4 AE	230 (65%)	20 (51%)	250 (64%)	115 (55%)
Grade 3 or 4 AE	120 (34%)	10 (26%)	130 (33%)	35 (17%)
Related AE	54 (15%)	5 (13%)	59 (15%)	17 (8%)
Related Grade 3 or 4 AE	15 (4%)	0	15 (4%)	0
SAE	73 (21%)	6 (15%)	79 (20%)	32 (15%)
Related SAE	6 (2%)	0	6 (2%)	0
Death*	4 (1%)	0	4 (1%)	2 (1%)

Study drug discontinuation due to AE	31 (9%)	3 (8%)	34 (9%)	9 (4%)
D/c of study drug due to related AEs	14 (4%)	0	14 (4%)	0

*Not related to study drug
Source: ISS ADAE dataset

Reviewer Comment: Higher rates of SAEs, AEs, Grade 3/4 AEs, and AEs leading to discontinuation were observed with BCV compared to PBO. The majority of AEs were Grade 2 or higher in severity. Related Grade 3/4 AEs, related SAEs, and related AEs leading to discontinuation were infrequent and there were no related deaths.

8.4.1. Deaths

ISS population
A total of 4 subjects (1%) in the BCV group and 2 subjects (1%) in the PBO group experienced AEs with onset in the first 2 weeks of treatment that resulted in fatal outcomes (Table 13).

Table 13. Deaths, ISS

Treatment Arm	Dictionary-Derived Term	Day, Start of AE	Day of death	Last Day of study drug	# of doses	Related
BCV						
301-0007-029	Acute myeloid leukemia recurrent	14	19	14	5	No
301-0025-032	Acute GVHD	11	53	20	6	No
301-0129-002	Acute GVHD	4	41	11	4	No
301-0129-006	Acute GVHD	5	43	18	3	No
PBO						
201-038-3026	Acute GVHD	4	25	1	1	No
301-0031-003	Transplant failure	14	32	22	7	No

Source: ISS ADAE dataset

Reviewer Comment: All of the deaths were assessed as unrelated to study drug by the study investigators. The clinical narratives were reviewed and I agree with the investigators' assessments that these deaths were unrelated to study medication.

Study 202 pediatric population
There were no deaths in BCV recipients in the first 2 weeks of BCV dosing.

Overall Assessment: No specific drug-related safety concern has been identified from the deaths reported in during the first 2 weeks of BCV dosing. There were no treatment-related deaths.

8.4.2. Serious Adverse Events

ISS population
SAEs occurred in 20% of subjects in the BCV group and 15% of subjects in the PBO group. The majority of these SAEs were assessed by investigators as not related to study drug. Table 14 provides a summary of SAEs by system organ class (SOC) and Preferred Term (PT).

Table 14. Treatment-emergent SAEs by System Organ Class (SOC) and Preferred Term (PT), ISS

SOC PT	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	73 (20.7%)	3 (15.4%)	79 (20.2%)	32 (15.4%)
Gastrointestinal disorders (SOC)	13 (3.7%)	1 (2.6%)	14 (3.6%)	2 (1.0%)
Abdominal pain	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Diarrhea	10 (2.8%)	1 (2.6%)	11 (2.8%)	2 (1.0%)
Enteritis	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Ileus	2 (0.6%)	0 (0%)	2 (0.5%)	0 (0%)
Nausea	1 (0.3%)	1 (2.6%)	2 (0.5%)	0 (0%)
Hepatobiliary disorders (SOC)	3 (0.8%)	0 (0%)	3 (0.8%)	0 (0%)
Hepatic steatosis	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Hepatitis acute	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Veno-occlusive liver disease	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Investigations (SOC)	5 (1.4%)	0 (0%)	5 (1.3%)	4 (1.9%)
ALT increased	2 (0.6%)	0 (0%)	2 (0.5%)	0 (0%)
AST increased	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Citrobacter test positive	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
QT prolonged	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Enterococcus test positive	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Escherichia test positive	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Klebsiella test positive	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Polyomavirus test positive	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Pseudomonas test positive	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Staphylococcal test positive	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Cardiac disorders (SOC)	3 (0.8%)	0 (0%)	3 (0.8%)	1 (0.5%)
Atrial fibrillation	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.5%)
Cardiac failure congestive	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Supraventricular tachycardia	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Blood and lymphatic system disorders (SOC)	4 (1.1%)	0 (0%)	4 (1.0%)	2 (1.0%)
Febrile neutropenia	4 (1.1%)	0 (0%)	4 (1.0%)	1 (0.5%)
Microangiopathic hemolytic anemia	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Injury, poisoning and procedural complications (SOC)	2 (0.6%)	0 (0%)	2 (0.5%)	3 (1.4%)
Delayed engraftment	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.5%)
Fall	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Joint dislocation	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Transplant failure	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Vascular disorders (SOC)	4 (1.1%)	0 (0%)	4 (1.0%)	3 (1.4%)
Hematoma	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Hypertension	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Hypotension	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Jugular vein thrombosis	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Orthostatic hypotension	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)

Thrombophlebitis	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Thrombosis	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Nervous system disorders (SOC)	2 (0.6%)	0 (0%)	2 (0.5%)	1 (0.5%)
Arachnoiditis	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Headache	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Seizure	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
General disorders and administration site conditions (SOC)	7 (2.0%)	1 (2.6%)	8 (2.0%)	5 (2.4%)
Multi-organ failure	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Pyrexia	6 (1.7%)	1 (2.6%)	7 (1.8%)	5 (2.4%)
Psychiatric disorders (SOC)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Substance induced psychotic disorder	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Musculoskeletal and connective tissue disorders (SOC)	5 (1.4%)	0 (0%)	5 (1.3%)	0 (0%)
Back pain	2 (0.6%)	0 (0%)	2 (0.5%)	1 (0.5%)
Chondrocalcinosis pyrophosphate	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Musculoskeletal pain	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Pain in extremity	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Immune system disorders (SOC)	29 (8.2%)	3 (7.7%)	32 (8.2%)	5 (2.4%)
Acute GVHD	29 (8.2%)	3 (7.7%)	32 (8.2%)	5 (2.4%)
Metabolism and nutrition disorders (SOC)	4 (1.1%)	1 (2.6%)	5 (1.3%)	1 (0.5%)
Dehydration	2 (0.6%)	0 (0%)	2 (0.5%)	1 (0.5%)
Failure to thrive	1 (0.3%)	1 (2.6%)	2 (0.5%)	0 (0%)
Hypophagia	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Neoplasms (SOC)	2 (0.6%)	0 (0%)	2 (0.5%)	0 (0%)
AML recurrent	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Leukemia recurrent	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Renal and urinary disorders (SOC)	3 (0.8%)	0 (0%)	3 (0.8%)	3 (1.4%)
Acute kidney injury	3 (0.8%)	0 (0%)	3 (0.8%)	3 (1.4%)
Infections and infestations (SOC)	16 (4.5%)	2 (5.1%)	18 (4.6%)	12 (5.8%)
Bacteremia	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
BK virus infection	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Bronchiolitis	0 (0%)	1 (2.6%)	1 (0.3%)	0 (0%)
Cellulitis	0 (0%)	1 (2.6%)	1 (0.3%)	1 (0.5%)
C difficile infection	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
C difficile colitis	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Coronavirus infection	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Encephalitis	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Enterovirus infection	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.5%)
EBV infection	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Gastroenteritis norovirus	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
HHV6 infection	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Influenza	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Pneumonia	4 (1.1%)	0 (0%)	4 (1.0%)	2 (1.0%)
Pneumonia bacterial	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)

Pneumonia RSV	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Rhinovirus infection	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Rotavirus infection	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Sinusitis	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Soft tissue infection	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Staphylococcal bacteremia	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Staphylococcal infection	0 (0%)	0 (0%)	0 (0%)	2 (1.0%)
Staphylococcal sepsis	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Stenotrophomonas infection	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Systemic candida	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Toxoplasmosis	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Urinary tract infection	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Viral hemorrhagic cystitis	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders (SOC)	7 (2.0%)	3 (1.4%)	7 (1.8%)	3 (1.4%)
Dyspnea	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Hypoxia	3 (0.8%)	0 (0%)	3 (0.8%)	1 (0.5%)
Pulmonary edema	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Pulmonary embolism	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Respiratory distress	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Respiratory failure	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.5%)

Source: ISS ADAE dataset

Reviewer Comment: Higher rates of SAEs occurred in the BCV group compared to the PBO group. The clinical narratives were reviewed and I agree with the investigators' assessments that most of these SAEs are unlikely to be related to study medication.

Related SAEs were reported in 6 (1.5%) subjects in the BCV group and no subjects in the PBO group (Table 28; see Section 8.4.3). Two subjects had two adverse reactions; the other subjects had one reaction each. These adverse reactions were diarrhea (n=5), nausea (n=1), enteritis (n=1), ALT increased (n=1).

Reviewer Comment: The clinical narratives were reviewed and I agree with the investigators' assessments that these SAEs are related to study medication.

Study 202 pediatric population
SAEs occurred in 3 subjects (13%) in the BCV group and 1 subject (8.3%) in the PBO group:

- BCV: sinus tachycardia (n=1), upper GI hemorrhage (n=1), infusion-related reaction (n=1)
- PBO: psychotic disorder (n=1)

These SAEs were assessed by investigators as not related to study drug.

Reviewer Comment: The narratives were reviewed and I agree with the investigators' assessments. Review of the pediatric data did not uncover new concerns.

Overall Assessment: Review of SAEs identified GI toxicities (predominantly diarrhea) as the most notable drug-related safety concern from the broad range of SAEs reported in Studies 201, 301 and Study 202. All narratives were reviewed and did not uncover new concerns. The reviewer assessments and conclusions are similar to the Applicant's.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

ISS population

Discontinuations due to AEs occurred in 9% of subjects in the BCV group and 4% of subjects in the PBO group (Table 15). The majority of these events were assessed by investigators as not related to study drug.

Table 15. Adverse Events Leading to Study Drug Discontinuation by System Organ Class (SOC) and Preferred Term (PT), ISS

SOC PT	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	31 (8.8%)	3 (7.7%)	34 (8.7%)	9 (4.3%)
Gastrointestinal disorders (SOC)	16 (4.5%)	1 (2.6%)	17 (4.3%)	2 (1.0%)
Diarrhea	11 (3.1%)	0 (0%)	11 (2.8%)	0 (0%)
Dyspepsia	0 (0%)	1 (2.6%)	1 (0.3%)	0 (0%)
Enteritis	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Nausea	3 (0.8%)	0 (0%)	3 (0.8%)	2 (1.0%)
Vomiting	2 (0.6%)	0 (0%)	2 (0.5%)	0 (0%)
Investigations (SOC)	2 (0.6%)	0 (0%)	2 (0.5%)	0 (0%)
ALT increased	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
GGT increased	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Immune system disorders (SOC)	9 (2.5%)	0 (0%)	9 (2.3%)	4 (1.9%)
Acute GVHD	9 (2.5%)	0 (0%)	9 (2.3%)	4 (1.9%)
Blood and lymphatic system disorders (SOC)	0 (0%)	2 (5.1%)	2 (0.5%)	0 (0%)
Neutropenia	0 (0%)	2 (5.1%)	2 (0.5%)	0 (0%)
Cardiac disorders (SOC)	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Atrial fibrillation	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Cardiac failure congestive	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
General disorders and administration site conditions (SOC)	2 (0.6%)	0 (0%)	2 (0.6%)	0 (0%)
Mucosal inflammation	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Multi-organ failure	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Renal and urinary disorders (SOC)	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Acute kidney injury	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Infections and infestations (SOC)	2 (0.6%)	0 (0%)	2 (0.5%)	3 (1.4%)
Adenovirus infection	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
C difficile colitis	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Encephalitis	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Gastroenteritis norovirus	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
HHV6 infection	0 (0%)	0 (0%)	0 (0%)	2 (1.0%)

Renal and urinary disorders (SOC)	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Acute kidney injury	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)

Source: ISS ADAE dataset

Reviewer Comment: Higher rates of AEs leading to discontinuation occurred in the BCV group compared to the PBO group. The clinical narratives were reviewed and I agree with the investigators' assessments that most of these SAEs are unlikely to be related to study medication.

A total of 15 subjects (4%) discontinued due to AEs that were assessed by investigators as related to BCV (Table 16). Two subjects had two adverse reactions; the other subjects had one reaction each. These adverse reactions were diarrhea (n=10), nausea (n=3), vomiting (n=1), enteritis (n=1), dyspepsia (n=1), ALT increased (n=1).

Table 16. Adverse Events Leading to Study Drug Discontinuation assessed as related to BCV, ISS

ID#	Dictionary-Derived Term	Day, Start of AE	Day, End of AE	Last Day of study drug	# of doses	SAE	Grade	Outcome
(b) (6)	Vomiting	1	27	12	4	No	2	Resolved
	Dyspepsia	8	29	15	3	No	2	Resolved
	Diarrhea	12	31	15	5	No	2	Resolved
	Nausea	11	36	18	6	No	2	Resolved
	Diarrhea	5	36	4	2	No	3	Resolved
	Diarrhea	4	26	4	2	No	3	Resolved
	Diarrhea	14	36	11	4	Yes	3	Resolved
	Diarrhea	3	20	4	2	Yes	3	Resolved
	Enteritis	7	20	4	2	Yes	2	Resolved
	Diarrhea	2	24	4	2	Yes	3	Resolved
	ALT increased	10	34	11	4	Yes	3	Resolved
	Diarrhea	12	36	12	4	Yes	1	Resolved
	Diarrhea	12	28	15	5	No	2	Resolved
	Diarrhea	8	87	4	2	Yes	3	Resolved
	Nausea	8	108	4	2	Yes	3	Resolved
	Nausea	10	21	12	4	No	2	Resolved
	Diarrhea	11	23	18	6	No	3	Resolved

Source: ISS ADAE dataset

Reviewer Comment: The narratives were reviewed and I agree with the investigators' assessments.

Study 202 pediatric population
Discontinuations due to AEs occurred in 1 subject in the BCV group. This AE (diarrhea) was assessed by investigators as not related to study drug.

Reviewer Comment: The narrative was reviewed and I agree with the investigators' assessment.

Review of the pediatric data did not uncover new concerns.

Overall Assessment: Review of AEs leading to study drug discontinuation identified GI toxicities (predominantly diarrhea) as the most notable drug-related safety concern.

8.4.4. Significant Adverse Events

This section describes Grade 3 or higher events that occurred in the treatment emergent period. Adverse events (AEs) are treatment emergent and all cause. Adverse drug reactions (ADRs) are treatment emergent and at least possibly related by investigator.

ISS population

Grade 3 or higher AEs occurred in 33% of subjects in the BCV group and 17% of subjects in the PBO group, as summarized below (Table 17).

Table 17. Grade 3 or higher AEs by System Organ Class (SOC) and Preferred Term (PT), ISS

SOC PT	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	120 (34.0%)	10 (25.6%)	130 (33.2%)	35 (16.8%)
Gastrointestinal disorders (SOC)	18 (5.1%)	1 (2.6%)	19 (4.8%)	3 (1.4%)
Abdominal pain	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Diarrhea	15 (4.2%)	1 (2.6%)	16 (4.1%)	3 (1.4%)
Ileus	2 (0.6%)	0 (0%)	2 (0.5%)	0 (0%)
Nausea	1 (0.3%)	1 (2.6%)	2 (0.5%)	0 (0%)
Stomatitis	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Vomiting	1 (0.3%)	1 (2.6%)	2 (0.5%)	0 (0%)
Hepatobiliary disorders (SOC)	6 (1.7%)	0 (0%)	6 (1.5%)	1 (0.5%)
Cholangitis	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Hepatic steatosis	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Hepatitis acute	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Hyperbilirubinemia	3 (0.8%)	0 (0%)	3 (0.8%)	0 (0%)
Veno-occlusive liver disease	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Investigations (SOC)	27 (7.6%)	0 (0%)	27 (6.9%)	7 (3.4%)
ALT increased	5 (1.4%)	0 (0%)	5 (1.3%)	1 (0.5%)
AST increased	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.5%)
Blood bilirubin increased	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
QT prolonged	2 (0.6%)	0 (0%)	2 (0.5%)	0 (0%)
Enterococcus test positive	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Escherichia test positive	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
GGT increased	2 (0.6%)	0 (0%)	2 (0.5%)	0 (0%)
Hepatic enzyme increased	2 (0.6%)	0 (0%)	2 (0.5%)	0 (0%)
Klebsiella test positive	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Liver function test abnormal	2 (0.6%)	0 (0%)	2 (0.5%)	1 (0.5%)
Lymphocyte count decreased	2 (0.6%)	0 (0%)	2 (0.5%)	0 (0%)

Neutrophil count decreased	3 (0.8%)	0 (0%)	3 (0.8%)	1 (0.5%)
Platelet count decreased	4 (1.1%)	0 (0%)	4 (1.0%)	0 (0%)
Polyomavirus test positive	0 (0%)	0 (0%)	0 (0%)	2 (1.0%)
Pseudomonas test positive	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
RSV test positive	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Staphylococcal test positive	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.5%)
Stenotrophomonas test positive	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Streptococcus test positive	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Transaminases increased	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Weight decreased	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Cardiac disorders (SOC)	5 (1.4%)	0 (0%)	5 (1.3%)	2 (1.0%)
Angina pectoris	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Atrial fibrillation	2 (0.6%)	0 (0%)	2 (0.5%)	1 (0.5%)
Cardiac failure congestive	2 (0.6%)	0 (0%)	2 (0.5%)	0 (0%)
Pericardial effusion	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Sinus tachycardia	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Supraventricular tachycardia	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Blood and lymphatic system disorders (SOC)	18 (5.1%)	2 (5.1%)	20 (5.1%)	7 (3.4%)
Anaemia	6 (1.7%)	1 (2.6%)	7 (1.8%)	0 (0%)
Febrile neutropenia	4 (1.1%)	0 (0%)	4 (1.0%)	2 (1.0%)
Hemolysis	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Hemolytic anemia	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Microangiopathic hemolytic anemia	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Neutropenia	2 (0.6%)	2 (5.1%)	4 (1.0%)	2 (1.0%)
Pancytopenia	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Thrombocytopenia	5 (1.4%)	0 (0%)	5 (1.3%)	1 (0.5%)
Thrombotic microangiopathy	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Injury, poisoning and procedural complications (SOC)	2 (0.6%)	0 (0%)	2 (0.5%)	2 (1.0%)
Delayed engraftment	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.5%)
Fall	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Transplant failure	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Vascular disorders (SOC)	6 (1.7%)	1 (2.6%)	7 (1.8%)	2 (1.0%)
Hematoma	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Hypertension	2 (0.6%)	1 (2.6%)	3 (0.8%)	1 (0.5%)
Hypotension	2 (0.6%)	0 (0%)	2 (0.5%)	1 (0.5%)
Jugular vein thrombosis	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Orthostatic hypotension	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Nervous system disorders (SOC)	2 (0.6%)	0 (0%)	2 (0.5%)	3 (1.4%)
Headache	0 (0%)	0 (0%)	0 (0%)	2 (1.0%)
Seizure	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.5%)
Syncope	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
General disorders and administration site conditions (SOC)	17 (4.8%)	2 (5.1%)	19 (4.8%)	6 (2.9%)
Asthenia	0 (0%)	1 (2.6%)	1 (0.3%)	0 (0%)

Fatigue	4 (1.1%)	0 (0%)	4 (1.0%)	0 (0%)
Generalized edema	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Inflammation	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Mucosal inflammation	10 (2.8%)	0 (0%)	10 (2.6%)	3 (1.4%)
Multi-organ failure	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Pyrexia	2 (0.6%)	1 (2.6%)	3 (0.8%)	2 (1.0%)
Psychiatric disorders (SOC)	2 (0.6%)	0 (0%)	2 (0.5%)	1 (0.5%)
Agitation	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Anxiety	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Confusional state	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Substance induced psychotic disorder	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Musculoskeletal and connective tissue disorders (SOC)	6 (1.7%)	0 (0%)	6 (1.5%)	0 (0%)
Arthralgia	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Back pain	2 (0.6%)	0 (0%)	2 (0.5%)	0 (0%)
Chondrocalcinosis pyrophosphate	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Musculoskeletal pain	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Pain in extremity	2 (0.6%)	0 (0%)	2 (0.5%)	0 (0%)
Immune system disorders (SOC)	29 (8.2%)	2 (5.1%)	31 (7.9%)	7 (3.4%)
Acute GVHD	29 (8.2%)	2 (5.1%)	31 (7.9%)	6 (2.9%)
Engraftment syndrome	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Metabolism and nutrition disorders (SOC)	21 (5.9%)	2 (5.1%)	23 (5.9%)	7 (3.4%)
Decreased appetite	7 (2.0%)	0 (0%)	7 (1.8%)	1 (0.5%)
Dehydration	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.5%)
Failure to thrive	0 (0%)	1 (2.6%)	1 (0.3%)	0 (0%)
Fluid overload	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Hyperglycemia	0 (0%)	1 (2.6%)	1 (0.3%)	2 (1.0%)
Hypernatremia	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Hyperuricemia	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Hypoalbuminemia	3 (0.8%)	0 (0%)	3 (0.8%)	1 (0.5%)
Hypokalemia	1 (0.3%)	0 (0%)	1 (0.3%)	3 (1.4%)
Hypomagnesemia	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.5%)
Hyponatremia	4 (1.1%)	0 (0%)	4 (1.0%)	1 (0.5%)
Hypophagia	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Hypophosphatemia	3 (0.8%)	0 (0%)	3 (0.8%)	2 (1.0%)
Malnutrition	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Neoplasms (SOC)	2 (0.6%)	0 (0%)	2 (0.5%)	0 (0%)
AML recurrent	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Leukemia recurrent	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Renal and urinary disorders (SOC)	3 (0.8%)	0 (0%)	3 (0.8%)	3 (1.4%)
Acute kidney injury	3 (0.8%)	0 (0%)	3 (0.8%)	3 (1.4%)
Infections and infestations (SOC)	18 (5.1%)	2 (5.1%)	20 (5.1%)	11 (5.3%)
Bacteremia	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
BK virus infection	0 (0%)	0 (0%)	0 (0%)	3 (1.4%)

Bronchiolitis	0 (0%)	1 (2.6%)	1 (0.3%)	0 (0%)
Bronchopneumonia	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Cellulitis	0 (0%)	1 (2.6%)	1 (0.3%)	0 (0%)
C difficile infection	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Coronavirus infection	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Encephalitis	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Enterovirus infection	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.5%)
Escherichia sepsis	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Gastroenteritis norovirus	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
HHV6 infection	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Influenza	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Pneumonia	4 (1.1%)	0 (0%)	4 (1.0%)	1 (0.5%)
Pneumonia bacterial	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Pneumonia HSV	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Pneumonia parainfluenza virus	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Pneumonia RSV	2 (0.6%)	0 (0%)	2 (0.5%)	0 (0%)
RSV infection	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Rhinovirus infection	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Skin infection	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Staphylococcal bacteremia	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Staphylococcal infection	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Staphylococcal sepsis	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Stenotrophomonas infection	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Systemic candida	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Toxoplasmosis	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Urinary tract infection enterococcal	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Viral hemorrhagic cystitis	0 (0%)	0 (0%)	0 (0%)	3 (1.4%)
Respiratory, thoracic and mediastinal disorders (SOC)	9 (2.5%)	0 (0%)	9 (2.3%)	4 (1.9%)
Epistaxis	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Hiccups	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Hypoxia	3 (0.8%)	0 (0%)	3 (0.8%)	1 (0.5%)
Pulmonary embolism	2 (0.6%)	0 (0%)	2 (0.5%)	0 (0%)
Pulmonary hemorrhage	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Pulmonary edema	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Respiratory distress	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Respiratory failure	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.5%)
Wheezing	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Skin and subcutaneous tissue disorders (SOC)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Erythema	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Pruritus	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)

Source: ISS ADAE dataset

Reviewer Comment: Higher rates of Grade 3/4 AEs occurred in the BCV group compared to the PBO group. The clinical narratives were reviewed and I agree with the investigators' assessments that most of these AEs are unlikely to be related to study medication.

Grade 3/4 AEs considered related to study drug by the study investigators (i.e. ADRs) occurred in 15 (3.8%) subjects in the BCV group and 0% of subjects in the PBO group. One subject had two ADRs; the other subjects had one ADR each. These Grade 3/4 ADRs were diarrhea (n=9), nausea (n=1), ALT increased (n=1), LFT increased (n=1), anemia (n=1), decreased appetite (n=2), hypophosphatemia (n=1). These cases are briefly summarized in the below table.

Table 18. Grade 3/4 ADRs, ISS

ID#	Dictionary-Derived Term	Day, Start of AE	Day, End of AE	Last Day of study drug	# of doses	D/c due to AE	SAE	Grade	Outcome
(b) (6)	Diarrhea	12	25	42	9	No	No	3	Resolved
	Diarrhea	5	36	4	2	Yes	No	3	Resolved
	Diarrhea	3	17	15	5	No	No	3	Resolved
	Diarrhea	4	26	4	2	Yes	No	3	Resolved
	Diarrhea	14	36	11	4	Yes	Yes	3	Resolved
	Diarrhea	3	20	4	2	Yes	Yes	3	Resolved
	Diarrhea	2	24	4	2	Yes	Yes	3	Resolved
	ALT increased	10	34	11	4	Yes	Yes	3	Resolved
	Anemia	7	7	25	8	No	No	3	Resolved
	Diarrhea	8	87	4	2	Yes	Yes	3	Resolved
	Nausea	8	108	4	2	Yes	Yes	3	Resolved
	Decreased appetite	9	39	84	19	No	No	3	Resolved
	Hypophosphatemia	12	Ongoing	58	15	No	No	3	Ongoing
	Diarrhea	11	23	18	6	Yes	No	3	Resolved
	LFT increased	10	26	40	9	No	No	3	Resolved
	Decreased appetite	4	Ongoing	63	17	No	3	No	Ongoing

Source: ISS ADAE dataset

Reviewer Comment: The narratives were reviewed and I agree with the investigators' assessments.

Study 202 pediatric population
Grade 3/4 AEs occurred in 6 subjects (26.1%) in the BCV group and 5 subjects (41.7%) in the PBO group. Grade 3/4 ADRs occurred in 1 subject (diarrhea) in the BCV group and 2 subjects (diarrhea; acute GVHD) in the PBO group.

Reviewer Comment: The narratives were reviewed and I agree with the investigators' assessments. Review of the pediatric data did not uncover new concerns.

Overall Assessment: Review of Grade 3/4 AEs and Grade 3/4 ADRs identified GI toxicities (predominantly diarrhea) as the most notable drug-related safety concern.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

ISS population
Treatment-emergent AEs occurred in 92% of subjects in the BCV group and 85% of subjects in the PBO group. Table 19 summarizes TEAEs occurring with ≥2% frequency in either group.

Table 19. Treatment-emergent AEs Reported in ≥ 2% of Subjects, All Grade and All Causality, by System Organ Class (SOC) and Preferred Term (PT), ISS

SOC PT	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	323 (91.5%)	33 (84.6%)	356 (90.8%)	177 (85.1%)
Gastrointestinal disorders (SOC)	200 (56.7%)	11 (28.2%)	211 (53.8%)	85 (40.9%)
Diarrhea*	112 (31.7%)	4 (10.3%)	116 (29.6%)	37 (17.8%)
Nausea	62 (17.6%)	6 (15.4%)	68 (17.3%)	21 (10.1%)
Abdominal pain§	63 (17.8%)	2 (5.1%)	65 (16.6%)	25 (12.0%)
Vomiting‡	52 (14.7%)	4 (10.3%)	56 (14.3%)	17 (8.2%)
Dyspepsia	14 (4.0%)	1 (2.6%)	15 (3.8%)	2 (1.0%)
Constipation	10 (2.8%)	0 (0%)	10 (2.6%)	7 (3.4%)
Dry mouth	9 (2.5%)	0 (0%)	9 (2.3%)	7 (3.4%)
Hemorrhoids	9 (2.5%)	0 (0%)	9 (2.3%)	2 (1.0%)
Hepatobiliary disorders (SOC)	12 (3.4%)	2 (5.1%)	14 (3.6%)	3 (1.4%)
Hyperbilirubinemia	7 (2.0%)	1 (2.6%)	8 (2.0%)	1 (0.5%)
Immune system disorders (SOC)	72 (20.4%)	7 (17.9%)	79 (20.2%)	35 (16.8%)
Acute GVHD	65 (18.4%)	7 (17.9%)	72 (18.4%)	28 (13.5%)
Investigations (SOC)	84 (23.8%)	5 (12.8%)	89 (22.7%)	34 (16.3%)
Blood creatinine increased	17 (4.8%)	2 (5.1%)	19 (4.8%)	6 (2.9%)
ALT increased	11 (3.1%)	1 (2.6%)	12 (3.1%)	4 (1.9%)
AST increased	10 (2.8%)	1 (2.6%)	11 (2.8%)	6 (2.9%)
Hepatic enzyme increased	3 (0.8%)	3 (7.7%)	6 (1.5%)	0 (0%)
Liver function test abnormal	3 (0.8%)	0 (0%)	3 (0.8%)	1 (0.5%)
Transaminases increased	8 (2.3%)	0 (0%)	8 (2.0%)	1 (0.5%)
Blood and lymphatic system disorders (SOC)	41 (11.6%)	6 (15.4%)	47 (12.0%)	24 (11.5%)
Febrile neutropenia	14 (4.0%)	0 (0%)	14 (3.6%)	10 (4.8%)
Anemia	8 (2.3%)	2 (5.1%)	10 (2.6%)	2 (1.0%)
Neutropenia	6 (1.7%)	3 (7.7%)	9 (2.3%)	6 (2.9%)
Cardiac disorders (SOC)	21 (5.9%)	1 (2.6%)	22 (5.6%)	8 (3.8%)
Sinus tachycardia	6 (1.7%)	0 (0%)	6 (1.5%)	1 (0.5%)
Tachycardia	8 (2.3%)	0 (0%)	8 (2.0%)	3 (1.4%)
Eye disorders (SOC)	31 (8.8%)	1 (2.6%)	32 (8.2%)	13 (6.3%)
Dry eye	8 (2.3%)	0 (0%)	8 (2.0%)	5 (2.4%)
Vision blurred	8 (2.3%)	0 (0%)	8 (2.0%)	2 (1.0%)
General disorders and administration site conditions (SOC)	113 (32.0%)	9 (23.1%)	122 (31.1%)	64 (30.8%)

Mucosal inflammation	32 (9.1%)	0 (0%)	32 (8.2%)	15 (7.2%)
Fatigue	28 (7.9%)	4 (10.3%)	32 (8.2%)	17 (8.2%)
Pyrexia	21 (5.9%)	1 (2.6%)	22 (5.6%)	16 (7.7%)
Edema peripheral	17 (4.8%)	1 (2.6%)	18 (4.6%)	11 (5.3%)
Asthenia	11 (3.1%)	2 (5.1%)	13 (3.3%)	2 (1.0%)
Pain	7 (2.0%)	1 (2.6%)	8 (2.0%)	2 (1.0%)
Chills	6 (1.7%)	1 (2.6%)	7 (1.8%)	7 (3.4%)
Infections and infestations (SOC)	68 (19.3%)	4 (10.3%)	72 (18.4%)	34 (16.3%)
BK virus infection	7 (2.0%)	1 (2.6%)	8 (2.0%)	3 (1.4%)
C difficile colitis	10 (2.8%)	1 (2.6%)	11 (2.8%)	2 (1.0%)
Metabolism and nutrition disorders (SOC)	97 (27.5%)	9 (23.1%)	106 (27.0%)	44 (21.2%)
Decreased appetite	29 (8.2%)	2 (5.1%)	31 (7.9%)	11 (5.3%)
Hypomagnesemia	21 (5.9%)	2 (5.1%)	23 (5.9%)	11 (5.3%)
Hyperglycemia	13 (3.7%)	1 (2.6%)	14 (3.6%)	10 (4.8%)
Dehydration	12 (3.4%)	0 (0%)	12 (3.1%)	4 (1.9%)
Hypokalemia	9 (2.5%)	0 (0%)	9 (2.3%)	4 (1.9%)
Hyponatremia	6 (1.7%)	3 (7.7%)	9 (2.3%)	2 (1.0%)
Hyponalbuminemia	6 (1.7%)	0 (0%)	6 (1.5%)	5 (2.4%)
Musculoskeletal and connective tissue disorders (SOC)	45 (12.7%)	6 (15.4%)	51 (13.0%)	28 (13.5%)
Back pain	11 (3.1%)	0 (0%)	11 (2.8%)	4 (1.9%)
Pain in extremity	9 (2.5%)	2 (5.1%)	11 (2.8%)	4 (1.9%)
Neck pain	1 (0.3%)	0 (0%)	1 (0.3%)	5 (2.4%)
Nervous system disorders (SOC)	66 (18.7%)	4 (10.3%)	70 (17.9%)	36 (17.3%)
Headache	16 (4.5%)	0 (0%)	16 (4.1%)	17 (8.2%)
Dizziness	13 (3.7%)	1 (2.6%)	14 (3.6%)	7 (3.4%)
Dysgeusia	12 (3.4%)	1 (2.6%)	13 (3.3%)	4 (1.9%)
Tremor	10 (2.8%)	0 (0%)	10 (2.6%)	5 (2.4%)
Burning sensation	7 (2.0%)	1 (2.6%)	8 (2.0%)	1 (0.5%)
Psychiatric disorders (SOC)	32 (9.1%)	2 (5.1%)	34 (8.7%)	22 (10.6%)
Insomnia	13 (3.7%)	1 (2.6%)	14 (3.6%)	4 (1.9%)
Anxiety	8 (2.3%)	1 (2.6%)	9 (2.3%)	7 (3.4%)
Depression	8 (2.3%)	0 (0%)	8 (2.0%)	2 (1.0%)
Confusional state	2 (0.6%)	0 (0%)	2 (0.5%)	6 (2.9%)
Renal and urinary disorders (SOC)	38 (10.8%)	2 (5.1%)	40 (10.2%)	28 (13.5%)
Pollakiuria	11 (3.1%)	2 (5.1%)	13 (3.3%)	5 (2.4%)
Acute kidney injury	10 (2.8%)	0 (0%)	10 (2.6%)	6 (2.9%)
Dysuria	5 (1.4%)	1 (2.6%)	6 (1.5%)	4 (1.9%)
Nocturia	4 (1.1%)	0 (0%)	4 (1.0%)	4 (1.9%)
Respiratory, thoracic and mediastinal disorders (SOC)	53 (15.0%)	2 (5.1%)	55 (14.0%)	35 (16.8%)
Cough	17 (4.8%)	0 (0%)	17 (4.3%)	14 (6.7%)
Oropharyngeal pain	9 (2.5%)	1 (2.6%)	10 (2.6%)	3 (1.4%)
Dyspnea	7 (2.0%)	1 (2.6%)	8 (2.0%)	1 (0.5%)
Dyspnea exertional	8 (2.3%)	0 (0%)	8 (2.0%)	2 (1.0%)
Epistaxis	6 (1.7%)	0 (0%)	6 (1.5%)	6 (2.9%)
Skin and subcutaneous tissue disorders (SOC)	79 (22.4%)	8 (20.5%)	87 (22.2%)	53 (25.5%)
Rash[@]	43 (12.2%)	5 (12.8%)	48 (12.2%)	32 (15.4%)
Pruritus	20 (5.7%)	3 (7.7%)	23 (5.9%)	10 (4.8%)
Dry skin	15 (4.2%)	0 (0%)	15 (3.8%)	4 (1.9%)

Erythema	6 (1.7%)	0 (0%)	6 (1.5%)	5 (2.4%)
Vascular disorders (SOC)	38 (10.8%)	4 (10.3%)	42 (10.7%)	17 (8.2%)
Hypertension	18 (5.1%)	3 (7.7%)	21 (5.4%)	12 (5.8%)
Hypertension	11 (3.1%)	0 (0%)	11 (2.8%)	3 (1.4%)

*Includes diarrhea, bowel movement irregularity, defecation urgency, fecal incontinence, frequent bowel movements.
§Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal distension, abdominal discomfort, gastrointestinal pain.
‡Includes vomiting, retching.
@Includes rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic.
Source: ISS ADAE dataset

TEAEs occurring with ≥10% frequency in each group were:

- BCV: diarrhea (30%), acute GVHD (18%), nausea (17%), abdominal pain (17%), vomiting (14%)
- PBO: diarrhea (18%), acute GVHD (14%), abdominal pain (12%), nausea (10%)

Reviewer Comment: The Applicant displayed the following preferred terms separately under the MedDRA Gastrointestinal Disorders SOC: diarrhea, bowel movement irregularity, defecation urgency, fecal incontinence, frequent bowel movements. FDA analyses of diarrhea (Tables 19 and 20) pooled these preferred terms as there is overlap in these clinical symptoms.

The Applicant displayed the following preferred terms separately under the MedDRA Gastrointestinal Disorders SOC: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal distension, abdominal discomfort, gastrointestinal pain. FDA analyses of abdominal pain (Tables 19 and 20) pooled these preferred terms as there is overlap in these clinical symptoms.

The Applicant displayed the following preferred terms separately under the MedDRA Gastrointestinal Disorders SOC: retching, vomiting. FDA analyses of vomiting (Tables 19 and 20) pooled these preferred terms as there is overlap in these clinical symptoms.

Diarrhea (30% vs. 18%), acute GVHD (18% vs. 14%), abdominal pain (17% vs. 12%), nausea (17% vs. 10%), and vomiting (14% vs. 8%) were the TEAEs with a ≥2% risk difference between BCV and PBO.

Table 20 summarizes related adverse events (hereafter referred to adverse drug reactions [ADR]), irrespective of severity. The investigator's determination of causality is the basis for classification. The inaccuracies and biases of this type of classification are acknowledged.

Table 20: 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

The three most commonly reported ADRs in each group were:
- BCV: diarrhea (8%), nausea (5%), vomiting (4%)
- PBO: diarrhea (3%), abdominal pain (2%), nausea/vomiting (1% each)

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

Diarrhea (8% vs. 3%), nausea (5% vs. 1%) and vomiting (4% vs. 2%) were the only treatment-emergent ADRs with a ≥2% risk difference between BCV and PBO.

Study 202 pediatric population
TEAEs occurred in 16 subjects (69.6%) in the BCV group and 10 subjects (83.3%) in the PBO group. The three most commonly reported TEAEs in each group were:
• BCV: diarrhea (6 subjects, 26.1%), acute GVHD (5 subjects, 21.7%), epistaxis (3 subjects, 13%)
• PBO: diarrhea (2 subjects, 16.7%), acute GVHD (3 subjects, 25%), epistaxis (1 subject, 8.3%)

ADRs occurred in 5 subjects (21.7%) in the BCV group and 3 subjects (25%) in the PBO group. Diarrhea was the only ADR that occurred in more than one BCV-treated subject:
- BCV: diarrhea (5 subjects, 21.7%)
- PBO: diarrhea (1 subject, 8.3%)

Reviewer Comment: Review of the pediatric data did not uncover new concerns.

Overall Assessment: Product labeling will display ADR results for diarrhea, nausea, vomiting, and abdominal pain as these ADRs occurred with greater frequency compared to PBO.

8.4.6. Laboratory Findings

The tables in this section display treatment-emergent graded laboratory abnormalities for chemistry and hematology parameters in the ISS population and the Study 202 pediatric

population. These analyses represent the worst change from baseline per subject.

ISS population
Graded chemistry results are summarized in Table 21, and hematology results in Table 22.

Table 21: Liver Function Tests and Other Chemistry Lab Results, All Grade, ISS

OTHER CHEMISTRY LABS				
Parameter and max Analysis Toxicity Grade	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
LIVER FUNCTION TESTS				
Increased Alanine Aminotransferase (U/L)				
Grade 1 (>ULN to 3 × ULN)	56 (16.2%)	9 (24.3%)	65 (17.0%)	26 (12.8%)
Grade 2 (>3 to 5 × ULN)	13 (3.8%)	0 (0%)	13 (3.4%)	4 (2.0%)
Grade 3 (>5 to 20 × ULN)*	6 (1.7%)	1 (2.7%)	7 (1.8%)	3 (1.4%)
Grade 4 (>20 × ULN)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Increased Aspartate Aminotransferase (U/L)				
Grade 1 (>ULN to 3 × ULN)	77 (22.4%)	6 (16.2%)	83 (21.8%)	20 (10.0%)
Grade 2 (>3 to 5 × ULN)	4 (1.2%)	2 (5.4%)	6 (1.6%)	2 (1.0%)
Grade 3 (>5 to 20 × ULN)§	3 (0.9%)	0 (0%)	3 (0.8%)	0 (0%)
Grade 4 (>20 × ULN)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Increased Total Bilirubin (mg/dL)				
Grade 1 (>ULN to 1.5 × ULN)	8 (2.3%)	2 (5.4%)	10 (2.6%)	7 (3.4%)
Grade 2 (>1.5 to 3 × ULN)	11 (3.2%)	0 (0%)	11 (2.9%)	4 (2.0%)
Grade 3 (>3 to 10 × ULN)	4 (1.2%)	0 (0%)	4 (1.0%)	1 (0.5%)
Grade 4 (>10 x ULN)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Increased Alkaline Phosphatase (U/L)				
Grade 1 (>ULN to 2.5 × ULN)	28 (8.1%)	2 (5.4%)	30 (7.8%)	10 (4.9%)
Grade 2 (>2.5 to 5 × ULN)	5 (1.4%)	0 (0%)	5 (1.3%)	0 (0%)
Grade 3 (>5 to 20 × ULN)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade 4 (>20 × ULN)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Increased Creatinine (mg/dL)				
Grade 1 (>ULN to 1.5 × ULN)	38 (11.0%)	6 (16.2%)	44 (11.5%)	15 (7.3%)
Grade 2 (>1.5 to 3 × ULN)	13 (3.8%)	1 (2.7%)	14 (3.7%)	8 (3.9%)
Grade 3 (>3 to 6 × ULN)	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Grade 4 (>6 × ULN)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Increased Glucose (mg/dL)				
Grade 1 (>ULN to 160 mg/dL)	61 (17.7%)	8 (21.6%)	69 (18.1%)	39 (19.2%)
Grade 2 (>160 to 250 mg/dL)	35 (10.1%)	5 (13.5%)	40 (10.5%)	19 (9.4%)
Grade 3 (>250 to 500 mg/dL)	8 (2.3%)	0 (0%)	8 (2.1%)	3 (1.5%)
Grade 4 (>500 mg/dL)	1 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)
Decreased Potassium (mmol/L)				
Grade 1 (<LLN to 3.0 mmol/L)	30 (8.7%)	2 (5.4%)	32 (8.4%)	12 (5.9%)
Grade 2 (<3.0 mmol/L)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade 3 (2.5 to <3.0 mmol/L)	10 (2.9%)	0 (0%)	10 (2.6%)	4 (2.0%)
Grade 4 (<2.5 mmol/L)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)

Decreased Phosphorus (mg/dL)				
Grade 1 (<LLN to 2.5 mg/dL)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade 2 (2 to <2.5 mg/dL)	8 (2.7%)	0 (0%)	8 (2.7%)	9 (6.1%)
Grade 3 (1.0 to <2.0 mg/dL)	3 (1.0%)	0 (0%)	3 (1.0%)	3 (1.5%)
Grade 4 (<1.0 mg/dL)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Grades for laboratory parameters utilized CTCAE v4.03.[12]; §No subjects reported AST >10x ULN.
*ALT >10x ULN occurred in one subject in the BCV group and no subjects in the PBO group.
Source: ISS ADLB dataset

Reviewer Comment: Higher rates of ALT/AST elevations occurred in the BCV group compared to the PBO group. Given that these hepatic laboratory abnormalities comprised one of the dose-limiting toxicities for BCV and have been observed across the BCV development program, these chemistry laboratory parameters will be described in product labeling.

Bilirubin elevations may be a consequence of competition by BCV for bilirubin uptake by transporter proteins (BCV is a substrate of OATP1B1 and OATP1B3). Although the rates of bilirubin elevations are slightly higher in the BCV group compared to the PBO group, these data will be displayed in product labeling to provide the most complete picture of the key hepatic laboratory findings that have been observed to date with BCV.

The other notable chemistry laboratory abnormality was the higher rate of creatinine elevation in the BCV group compared to PBO group, and this imbalance will also be described in product labeling.

Table 22. Hematology Laboratory Results, All Grade, ISS

Parameter and max Analysis Toxicity Grade	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
Decreased WBC (cells/mm^3)				
Grade 1 (<LLN to 3000/mm^3)	12 (3.5%)	3 (8.1%)	15 (4.0%)	7 (3.4%)
Grade 2 (2000 to < 3000/mm^3)	11 (3.2%)	1 (2.7%)	12 (3.2%)	8 (3.9%)
Grade 3 (1000 to < 2000/mm^3)	6 (1.8%)	4 (10.8%)	10 (2.6%)	7 (3.4%)
Grade 4 (<1000/mm^3)	5 (1.5%)	0 (0%)	5 (1.3%)	3 (1.5%)
Decreased Lymphocytes (cells/mm^3)				
Grade 1 (<LLN to 800/mm^3)	2 (0.6%)	1 (2.7%)	3 (0.8%)	4 (2.0%)
Grade 2 (500 to < 800/mm^3)	19 (5.6%)	3 (8.1%)	22 (5.8%)	9 (4.4%)
Grade 3 (200 to < 500/mm^3)	18 (5.3%)	5 (13.5%)	23 (6.1%)	16 (7.8%)
Grade 4 (<200/mm^3)	8 (2.3%)	2 (5.4%)	10 (2.6%)	7 (3.4%)
Increased INR				
Grade 1 (>1 to 1.5 × ULN)	23 (8.2%)	0 (0%)	23 (8.2%)	9 (6.3%)
Grade 2 (>1.5 to 2.5 × ULN)	3 (1.1%)	0 (0%)	3 (1.1%)	2 (1.4%)
Grade 3 (>2.5 × ULN)	1 (0.4%)	0 (0%)	1 (0.4%)	0 (0%)

Source: ISS ADLB dataset

Reviewer Comment: No clear safety signal emerges from the review of hematologic laboratory abnormalities. Given the similarities in laboratory profile between BCV and PBO, hematologic laboratory parameters are not recommended for inclusion in product labeling.

Study 202 pediatric population
Graded laboratory results are summarized in Table 23.

Table 23. Laboratory data, Study 202 Pediatric Population

Parameter and max Analysis Toxicity Grade	BCV 100 mg BIW[1] 2 weeks N=11	BCV 200 mg QW[2] 2 weeks N=12	Total BCV 2 weeks N=23	PBO 2 weeks N=12
Increased Alanine Aminotransferase (U/L)				
Grade 1 (>ULN to 3 × ULN)	1 (11%)	3 (27%)	4 (20%)	1 (8%)
Grade 2 (>3 to 5 × ULN)	1 (11%)	2 (18%)	3 (15%)	2 (17%)
Grade 3 (>5 to 20 × ULN)*	0 (0%)	1 (9%)	1 (5%)	2 (17%)
Grade 4 (≥20 × ULN)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Increased Aspartate Aminotransferase (U/L)				
Grade 1 (>ULN to 3 × ULN)	1 (10%)	3 (27%)	4 (19%)	4 (33%)
Grade 2 (>3 to 5 × ULN)	0 (0%)	0 (0%)	0 (0%)	2 (17%)
Grade 3 (>5 to 20 × ULN)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade 4 (≥20 × ULN)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Increased Total Bilirubin (mg/dL)				
Grade 1 (>ULN to 1.5 × ULN)	0 (0%)	0 (0%)	0 (0%)	1 (8%)
Grade 2 (>1.5 to 3 × ULN)	1 (10%)	1 (9%)	2 (10%)	0 (0%)
Grade 3 (>3 to 10 × ULN)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade 4 (≥10 x ULN)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Increased Creatinine (mg/dL)				

Grade 1 (>ULN to 1.5 × ULN)	1 (10%)	4 (36%)	5 (24%)	1 (8%)
Grade 2 (>1.5 to 3 × ULN)	2 (20%)	0 (0%)	2 (10%)	0 (0%)
Grade 3 (>3 to 6 × ULN)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade 4 (≥6 × ULN)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Increased Glucose (mg/dL)				
Grade 1 (>ULN to 160 mg/dL)	2 (20%)	5 (45%)	7 (33%)	7 (58%)
Grade 2 (>160 to 250 mg/dL)	1 (10%)	0 (0%)	1 (5%)	0 (0%)
Grade 3 (>250 to 500 mg/dL)	1 (10%)	2 (18%)	3 (14%)	1 (8%)
Grade 4 (≥500 mg/dL)	0 (0%)	1 (9%)	1 (5%)	0 (0%)
Decreased Potassium (mmol/L)				
Grade 1 (<LLN to 3.0 mmol/L)	1 (10%)	2 (18%)	3 (14%)	7 (58%)
Grade 2 (<3.0 mmol/L)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade 3 (2.5 to <3.0 mmol/L)	2 (20%)	0 (0%)	2 (10%)	1 (8%)
Grade 4 (<2.5 mmol/L)	1 (10%)	0 (0%)	1 (5%)	0 (0%)
Decreased Phosphorus (mg/dL)				
Grade 1 (<LLN to 2.5 mg/dL)	3 (30%)	1 (9%)	4 (19%)	2 (17%)
Grade 2 (2 to <2.5 mg/dL)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade 3 (1.0 to <2.0 mg/dL)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade 4 (<1.0 mg/dL)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Decreased WBC (cells/mm^3)				
Grade 1 (<LLN to 3000/mm^3)	0 (0%)	1 (9%)	1 (5%)	0 (0%)
Grade 2 (2000 to < 3000/mm^3)	4 (40%)	2 (18%)	6 (29%)	1 (8%)
Grade 3 (1000 to < 2000/mm^3)	1 (10%)	1 (9%)	2 (10%)	0 (0%)
Grade 4 (<1000/mm^3)	0 (0%)	2 (18%)	2 (10%)	1 (8%)
Decreased Lymphocytes (cells/mm^3)				
Grade 1 (<LLN to 800/mm^3)	0 (0%)	1 (9%)	1 (5%)	0 (0%)
Grade 2 (500 to < 800/mm^3)	0 (0%)	0 (0%)	0 (0%)	1 (8%)
Grade 3 (200 to < 500/mm^3)	1 (10%)	3 (27%)	4 (19%)	1 (8%)
Grade 4 (<200/mm^3)	1 (10%)	3 (27%)	4 (19%)	2 (17%)

[1]BIW dosing includes 100 mg BIW or 2 mg/kg BIW, depending on subject's ability to swallow tablets.
[2]QW dosing includes 200 mg QW or 4 mg/kg QW, depending on subject's ability to swallow tablets.
*ALT >5x-10x ULN occurred in one subject in the BCV group and one subject in the PBO group; ALT >10x ULN occurred in one subject in the PBO group and no subjects in the BCV group.
Source: Study 202 ADLB dataset

Reviewer Comment: Given the small pediatric sample size, no clinically significant patterns were definitively identified. Overall, review of the pediatric laboratory data did not uncover new concerns.

8.4.7. Vital Signs

No clinically meaningful changes in vital signs were observed in association with BCV use.

8.4.8. Electrocardiograms (ECGs)

In Study 201, ECGs were assessed at Screening, pre-Dose 1, post-Dose 1, Week 20 (end-of-study). ECGs were not assessed in Studies 202 and 301 unless clinically indicated. The Applicant reports that 3 subjects developed a treatment-emergent abnormal ECG but was assessed as not related to study drug; these narratives are briefly summarized:

• Subject ID# (b) (6) 68-year-old White, Non-Hispanic female with medical history notable for non-ST segment elevation myocardial infarction (since Apr 2014), QTc prolongation (since (b) (6)). On Day 2 (i.e. one day after the initiation of BCV), the subject experienced the SAEs of worsening prolonged QTc and poor oral intake; subject was hospitalized for monitoring of her QTc interval. Levofloxacin was considered a suspect drug; following levofloxacin discontinuation on the day of admission, the prolonged QTc interval improved. No change was made to study drug dosing. The investigator considered the event as resolved on Day 6. The investigator assessed the event of worsening prolonged QTc as Grade 3 (severe) in intensity, a SAE due to requiring hospitalization, and not related to study drug. The investigator considered the event due to the concomitant medication levofloxacin.

Reviewer Comment: I agree with the investigator that the subject described above had pre-existing conditions of cardiac disease and baseline QT prolongation, and had concurrent medications that confounded assessment. No change was made to BCV dosing due to the event of QT prolongation and the subject received a total of 5 doses over 15 days.

• Subject ID# (b) (6) 54-year-old White Non-Hispanic female with medical history notable for QTc prolonged – intermittent (since (b) (6)). Concomitant medications included haloperidol, amiodarone, voriconazole, prochlorperazine. On Day 3 (i.e. 2 days after the initiation of BCV), the subject experienced the non-serious AEs of dehydration (Grade 2), fatigue (Grade 2), and intermittent QTc prolongation (Grade 3). All three AEs remained ongoing throughout study participation, and were considered by the investigator as not related to study drug. Study drug dosing was continued and the subject received a total of 9 doses over 36 days.

Reviewer Comment: I agree with the investigator that the subject described above had pre-existing history of intermittent QT prolongation, and had concurrent medications (haloperidol, amiodarone, voriconazole, prochlorperazine) that confounded assessment.

• Subject ID# (b) (6) 55-year-old White female with medical history notable for hypertension (since 1995), coronary artery disease (since (b) (6)). Concomitant medications included levofloxacin, fluconazole, prochlorperazine. On Day 8 (i.e. 7 days after initiation of BCV) the subject experienced the non-serious AE of Electrocardiogram QT prolonged (Grade 1). The event of QT prolongation resolved the same day (i.e. Day 8) and was considered by the investigator as probably not related to study drug. Study drug dosing was continued and the subject received a total of 17 doses over 50 days.

Reviewer Comment: I agree with the investigator that the subject described above had pre-existing cardiac risk factors for QT prolongation, and had concurrent medications (haloperidol, amiodarone, voriconazole, prochlorperazine) that confounded assessment.

Reviewer Comment: The primary review team concludes that the available reported ECG data do not require specific safety labeling.

8.4.9. QT

A thorough QT (TQT) study was conducted to evaluate the potential of BCV to prolong the QT interval. Study CMX001-108 was a randomized, double-blind, four-period, single-dose, crossover study to evaluate the potential ECG effects of BCV 200 mg and 350 mg, as compared to PBO and the positive control moxifloxacin, in 86 healthy subjects. The results were reviewed by the Interdisciplinary Review Team (IRT), who concluded the following:

> No significant QTc prolongation of CMX001 (200 mg and 350 mg) was detected in this TQT study. 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.

Based on these assessments, IRT and the primary review team concurred with the Applicant's proposal to collect safety ECGs as clinically indicated in Study 301.

Table 24. Study 108, Geometric mean (%CV) Summary PK parameters

BCV	N	Cmax (ng/mL)	Tmax[a] (h)	AUC_{last} (h*ng/mL)	AUC_{0-24} (h*ng/mL)
200 mg	63	802 (38.3)	4.00 (2.00-8.02)	3744 (34.7)	3823 (32.7)[b]
350 mg	70	1482 (34.0)	4.00 (2.00-6.01)	6938 (31.1)	6937 (31.1)

[a] Median (minimum - maximum); [b] N = 61; %CV = percent coefficient of variation.

In conclusion, BCV does not prolong QTc to any clinically relevant extent. Please refer to the QT-IRT review (entered into DARRTS by Qianyu Dang on August 26, 2013) for additional details.

8.4.10. Immunogenicity

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

8.5. Analysis of Submission-Specific Safety Issues

This section includes analyses conducted to address safety concerns such as GI toxicity, hepatotoxicity, as well as issues of interest for nucleotide analogs, such as cardiac events, rash, and elevations of creatine kinase and lipase.

8.5.1. Gastrointestinal Disorders

A gastrointestinal (GI) safety signal, manifested as diarrhea, nausea, vomiting, and abdominal pain, is one of the dose-limiting toxicities for BCV and has been observed across all BCV development programs and also observed in animal studies. These GI toxicities are also associated with duration of administration.

GI safety signals can be difficult to detect in trials with HSCT recipients due to underlying disease, conditioning chemotherapeutic regimens resulting in mucositis, multiple concomitant medications known to cause diarrhea (including antibiotics, magnesium, methotrexate and

mycophenolate mofetil), other comorbidities, concurrent GI infections (e.g. *C. difficile*), and transplant-specific complications such as acute GI GVHD.

ISS population

- GI AEs (all causality) occurred in 54% (211 of 392 subjects) in the BCV group and 41% (85 of 208 subjects) in the PBO group (see Section 8.4.5). GI events that occurred in at least 5% of either group are summarized below:
    - BCV: diarrhea (30%), acute GVHD (18%), nausea (17%), abdominal pain (17%), vomiting (14%)
    - PBO: diarrhea (18%), acute GVHD (14%), abdominal pain (12%), nausea (10%)
- The three most commonly reported GI ADRs in each group were:
    - BCV: diarrhea (8%), nausea (5%), vomiting (4%)
    - PBO: diarrhea (3%), nausea (1%), vomiting (2%)
- Grade 3/4 GI ADRs occurred in 9 subjects (2.3%) in the BCV group and no subjects in the PBO group (see Section 8.4.4). Diarrhea was the predominant Grade 3/4 GI ADR:
    - Diarrhea was the predominant Grade 3/4 GI ADR and occurred in 9 subjects (2.3%) in the BCV group and no subjects in the PBO group
- Related GI SAEs were reported in 5 (1.3%) subjects in the BCV group and no subjects in the PBO group (see Section 8.4.2 and Section 8.4.3 [Table 28]). Two subjects had two adverse reactions; the other subjects had one reaction each. These adverse reactions were diarrhea (n=5), nausea (n=1), enteritis (n=1).
- GI AEs that led to discontinuation occurred in 17 subjects (4.3%) in the BCV group and two subjects (1.0%) in the PBO group (see Section 8.4.3). Events that occurred in ≥2 subjects are noted below:
    - BCV: diarrhea (n=11), nausea (n=3), vomiting (n=2)
    - PBO: nausea (n=2)
- A total of 13 subjects (3.3%) had GI ADRs that led to discontinuation (see Section 8.4.3). Two subjects had two adverse reactions; the other subjects had one reaction each. These adverse reactions were diarrhea (n=10), nausea (n=3), vomiting (n=1), enteritis (n=1).

Reviewer Comment: Given the GI toxicities are also associated with duration of administration, the GI toxicities are less prominent in the 2-week course for the treatment of smallpox compared to other BCV development programs.

Overall Assessment: GI toxicities were noted in early clinical development and led to dosing restrictions due to drug-related toxicity. Studies 201, 301 and 202 (that evaluated the dosing regimens up to 14 weeks for other, non-smallpox development programs) showed that the observed risk of GI toxicities associated with BCV is also related to duration of drug exposure.

Based on all available information, the Warnings and Precautions section will provide wording that clearly describes the GI safety signal that has been observed for BCV and outline risk mitigation strategies for health care providers to consider:

• *Monitor patients for GI adverse events including diarrhea and dehydration, provide supportive care, and if necessary, do not give the second and final dose of BCV.*

8.5.2. Hepatotoxicity

A hepatic safety signal, manifested as transaminase and total bilirubin elevations, is one of the dose-limiting toxicities for BCV and has been observed across all BCV development programs and also observed in animal studies. The hepatic safety signal is also associated with duration of administration.

ISS population

The majority of hepatic AEs were laboratory events. Consequently, the laboratory data provide the most objective assessment of hepatotoxicity in the trials.

- Hepatic AEs (all causality) occurred in 13% (51 of 392 subjects) in the BCV group and 5% (11 of 208 subjects) in the PBO group (see Section 8.4.5). Hepatic events that occurred in at least 2% of either group are summarized below:
    - BCV: AST increased (3%), ALT increased (3%), hyperbilirubinemia (2%), hepatic enzymes increased (2%), transaminases increased (2%)
    - PBO: AST increased (3%), ALT increased (2%)
- Grade 3/4 hepatic ADRs occurred in 2 subjects (0.5%) in the BCV group and no subjects in the PBO group (see Section 8.4.4):
    - BCV: ALT increased (n=1), liver function test abnormal (n=1)
- One hepatic SAE (ALT increased) was assessed as related to BCV (see Section 8.4.2).
- Hepatic AEs that led to discontinuation occurred in 2 subjects (0.5%) in the BCV group and no subjects in the PBO group (see Section 8.4.3):
    - BCV: ALT increased (n=1), GGT increased (n=1)
- Hepatic ADRs that led to discontinuation were ALT increased (n=1). (see Section 8.4.3).
- Rates of Grade 3/4 ALT elevations were 2% in the BCV group compared to 1% in the PBO group. Rates of Grade 3/4 AST elevations were 1% in the BCV group compared to 0% in the PBO group (see Section 8.4.6).

Reviewer Comment: Given the hepatic safety signal is also associated with duration of administration, the hepatic abnormalities are less prominent in the 2-week course for the treatment of smallpox compared to other BCV development programs.

DILI assessment

The independent hepatic safety expert (James H. Lewis, MD; Professor of Medicine; Director of Hepatology, Georgetown University Hospital) reviewed all cases of BCV subjects from completed clinical studies who met any of the following criteria for potential DILI:
• ALT and/or AST >3x ULN and Total bilirubin >2x ULN; or
• ALT and/or AST >10x ULN

No cases meeting the above criteria occurred in the healthy volunteer Phase 1 studies.

Of 924 subjects exposed to BCV in Phase 2/3 clinical studies (Studies 201, 202, and 301 [randomized, double-blind, placebo-controlled clinical trials]; Study 304 [open-label, single arm trial]; Study 350 [expanded access]), a total of 113 cases were identified:
• 82 cases with ALT/AST >3x ULN and Total bilirubin >2x ULN
- Occurred within the first 2 weeks of BCV (n=21)
- Occurred on treatment, but after Day 14 (n=40)
- Occurred post-treatment (defined as ≥8 days after the last dose) (n=21)

The adjudicator assessed 81 cases as unrelated or unlikely related to BCV. The adjudicator assessed one case (ID# (b) (6)) as possibly related to BCV; this subject had elevated bilirubin (2.1 mg/dL; normal range: 0.2 to 1.2 mg/dL) at baseline and developed concurrent elevations of transaminases and bilirubin on Day 43 of BCV. The adjudicator assessed the LFT abnormalities as possibly related to BCV, however also indicated that the pharmacologic interaction between BCV and cyclosporine may have contributed to the bilirubin elevation. The adjudicator also noted the presence of GVHD and use of concomitant antibiotics as other potential confounders.

Reviewer Comment: The narratives were reviewed and I agree with the independent hepatic safety expert's assessments.

• 31 cases with ALT/AST >10x ULN
- Occurred within the first 2 weeks of BCV (n=2)
- Occurred on treatment, but after Day 14 (n=22)
- Occurred post-treatment (defined as ≥8 days after the last dose) (n=7)

Two cases (ID# (b) (6); ID# (b) (6)) had ALT/AST >10x ULN during the first 2 weeks. Both cases were assessed by the adjudicator as unlikely related to BCV.

The adjudicator assessed 5 cases as possibly related to BCV. Four cases (ID# (b) (6); ID# (b) (6)1; ID# (b) (6); ID# (b) (6)) occurred after Day 14. One case (ID# (b) (6) (b) (6)) occurred post-treatment. All 5 cases had potential confounders (concomitant medications, GVHD, sepsis) as alternate etiologies for these LFT abnormalities.

Reviewer Comment: The narratives were reviewed and I agree with the independent hepatic safety expert's assessments.

Reviewer Summary of DILI Assessment: The possibility of drug-related hepatic toxicity has been evaluated independently by an independent hepatic safety expert and the clinical review team, and both parties have found no clear evidence of DILI with two weeks of BCV exposure.

Overall Assessment: Hepatotoxicity was noted in early clinical development and led to dosing restrictions due to drug-related toxicity. Studies 201, 301 and 202 (that evaluated the dosing

regimens up to 14 weeks for other, non-smallpox development programs) showed that the observed risk of hepatotoxicity associated with BCV is also related to duration of drug exposure.

Based on all available information, the Warnings and Precautions section will provide wording that clearly describes the hepatotoxicity safety signal that has been observed for BCV and outline risk mitigation strategies for health care providers to consider:
• Hepatic laboratory testing should be performed in all patients before starting BCV and while receiving BCV, as clinically appropriate. Patients who develop abnormal hepatic laboratory tests during BCV should be monitored for the development of more severe hepatic injury. Consider discontinuing BCV if ALT levels remain persistently >10x the upper limit of normal. Do not give the second and final dose of BCV on Day 8 if ALT elevation is accompanied by clinical signs and symptoms of liver inflammation or increasing direct bilirubin, alkaline phosphatase, or International Normalized Ratio (INR).

Product labeling will also display hepatic laboratory data in Section 6.

8.5.3. Cardiac Disorders

Please see Section 8.4.8 of this review for complete details.

Overall Cardiac Assessment: The primary review team concludes that the available reported cardiac data do not require specific safety labeling.

8.5.4. Neuropsychiatric Disorders

Seizure
Seizure events were infrequent in the ISS population, occurring in 1 subject (0.3%) in the BCV group and 1 subject (0.5%) in the PBO group. Both events were Grade 3 in severity and both were assessed by investigators as not related to study drug. There were no discontinuations due to seizures.

Reviewer Comment: There is no clear signal for increased risk of seizures with BCV.

Migraines
Migraines were infrequent in the ISS population, occurring in 2 subjects (<1%) in the BCV group and no subjects in the PBO group. One event was Grade 1 in severity; the other event was Grade 2 in severity. Both events were assessed by investigators as not related to study drug. There were no discontinuations due to migraines.

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

Dysgeusia
In the ISS population, dysgeusia events occurred in 13 subjects (3%) in the BCV group and 4 subjects (2%) in the PBO group. Events were Grade 1 (BCV [n=11]; PBO [n=3]) or Grade 2 (BCV

[n=2]; PBO [n=1]) in severity. Both events were assessed by investigators as not related to study drug. There were no discontinuations due to dysgeusia.

Overall, the majority of dysgeusia events were assessed by investigators as unrelated to study drug. Dysgeusia events that were considered related occurred in 1% of subjects in the BCV group and 0% of subjects in the PBO group.

Reviewer Comment: There is no clear signal for increased risk of dysgeusia with BCV.

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

Depression events were infrequent in the ISS population, occurring in 9 (2%) of subjects in the BCV group and 2 (1%) of subjects in the PBO group. Events were Grade 1 (BCV [n=3]) or Grade 2 (BCV [n=6]; PBO [n=2]) in severity. All events were assessed by investigators as not related to study drug. There were no suicide attempts. There were no discontinuations due to neuropsychiatric events.

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

In order to determine whether there is a trend toward tolerability issues caused by anxiety events, an analysis was performed using the High Level Group Term "Anxiety Disorders and symptoms." Anxiety events were infrequent in the ISS population, occurring in 9 (2%) of subjects in the BCV group and 7 (3%) of subjects in the PBO group. Events were Grade 1 (BCV [n=6]; PBO [n=4]), Grade 2 (BCV [n=3]; PBO [n=2]), or Grade 3 (PBO [n=1]) in severity. All events were assessed by investigators as not related to study drug. There were no discontinuations due to anxiety events.

Reviewer Comment: There is no clear signal for increased risk of anxiety events with BCV.

For completeness of the neuropsychiatric evaluation, additional analyses were performed using the High Level Group Terms "Schizophrenia and other psychotic disorders" and "Sleep Disorders." One event in the PBO group was found in these analyses.

Overall Assessment: The frequency and severity of neuropsychiatric events occurring in BCV subjects was low. Although no specific safety signal was detected for neuropsychiatric events with BCV, product labeling is recommended for dysgeusia.

8.5.5. Rash

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

In the ISS population, rash events occurred in 12% of subjects in the BCV group and 15% of subjects in the PBO group. No Grade 3/4 events, and no events of Stevens Johnson Syndrome, toxic epidermal necrolysis or erythema multiforme were reported. There were no discontinuations due to rash.

Overall, the majority of rash events were assessed by investigators as unrelated to study drug. Rash events that were considered related occurred in 1% of subjects in the BCV group and 0% of subjects in the PBO group.

Overall Assessment: The frequency and severity of rash events occurring in BCV subjects was low. Although no specific safety signal was detected for serious rash events with BCV, product labeling is recommended for this adverse event of special interest and is included in the less common adverse reaction subsection of section 6.

8.5.6. Rhabdomyolysis

There were no cases of rhabdomyolysis in the ISS population.

Reviewer Comment: Rhabdomyolysis was not an adverse event of specific concern during the BCV development program.

8.5.7. Pancreatitis

There were no cases of pancreatitis in the ISS population.

Reviewer Comment: Pancreatitis was not an adverse event of specific concern during the BCV development program.

8.5.8. Pancytopenia

There were 3 cases of pancytopenia (BCV [n=1], PBO [n=2]) in the ISS population. All events were assessed by investigators as not related to study drug. There were no discontinuations due to pancytopenia.

Reviewer Comment: The primary review team concludes that the available reported data do not require specific safety labeling for pancytopenia.

8.5.9. Safety Profile Among Subjects with concomitant use of cyclosporine

Study 120 was an open-label, two-period, balanced crossover study to evaluate the effect of cyclosporine (CsA) on the PK of BCV.

Table 25. Study 120

Treatment Sequence	N	Period 1, Day 1	Period 2, Day 1
1	13	BCV 100 mg	BCV 100 mg + CsA 600 mg
2	13	BCV 100 mg + CsA 600 mg	BCV 100 mg

Washout of ≥14 days between Periods.

Co-administration of CsA 600 mg (a potent OATP1B1 and OATP1B3 inhibitor) with BCV 100 mg markedly increased plasma BCV exposure, C_{max} 269% and $AUC_{0\text{-}inf}$ 374%, on average, in healthy volunteers. All-cause AEs of any severity occurred in 84% of subjects with BCV + CsA compared to 28% of subjects with BCV; this observation is driven primarily by differences in the frequencies of nausea (44% vs. 11%), abdominal pain (16% vs. 4%), diarrhea (12% vs. 8%), headache (20% vs. 4%), and dizziness (16% vs. 0%).

Reviewer Comment: Population PK modeling estimated a 30% lower plasma BCV apparent clearance in patients receiving CsA and BCV (41% increase in plasma BCV AUC) compared to patients receiving BCV but not CsA. BCV is a victim drug of CsA based on this uncontrolled cyclosporine-brincidofovir interaction population PK analysis. Study 120 was conducted to further characterize this DDI. Of note, Study 120 was conducted after Studies 201, 202, and 301.

At the time of Study 301 initiation, definitive data was lacking regarding BCV as a perpetrator (inhibitor or inducer) of PK interactions with immunosuppressant medications. The protocol recommended that investigators conduct immunosuppressant therapeutic drug monitoring according to local or institutional practice. Therefore, co-administration of immunosuppressant medication with BCV was allowed.

In the ISS population, concomitant use of CsA occurred in 16% of subjects in the BCV group and 15% of subjects in the PBO group.

Among ISS subjects treated with BCV, subjects who received CsA (n=62) were compared to those who did not (n=330). The percentage of subjects with SAEs was 26% and 19% respectively. The percentage of subjects with Grade 3/4 AEs was 45% and 31% respectively. All-cause AEs of any severity occurred in 95% and 90% respectively; this observation is driven primarily by differences in the frequencies of acute GVHD (27% vs. 17%) and hyperbilirubinemia (10% vs. 1%). Graded increases in total bilirubin occurred in 13% and 5% respectively.

Reviewer Comment: The safety profile of concomitant use of BCV and CsA is overall acceptable in transplant populations. It is possible that the numerical differences observed in the ISS subjects may be influenced by the relatively small proportion (approximately 19%) of subjects with concomitant use of BCV and CsA. Section 7 of the label will describe that concomitant use

of BCV with OATP 1B1 and 1B3 inhibitors (which includes cyclosporine) resulted in increased BCV exposures and may increase adverse reactions associated with BCV. Section 7 of the label will also describe risk mitigation strategies outlining that:
• Where possible, consider alternative medication that are not OATP 1B1 or 1B3 inhibitors. If concomitant use with BCV is necessary, increase monitoring for adverse reactions associated with BCV (elevations in transaminases and bilirubin, diarrhea or other GI adverse events) and separate the dose by at least 3 hours co-administration of BCV and CsA has resulted in increased BCV exposures and increased serum bilirubin.

8.6. Safety Analyses by Demographic Subgroups

Consistent with the approach for the overall safety review, the impact of age, sex, and race on the frequencies of adverse events were assessed for the ISS population. Overall, these analyses did not find any demographic subgroups at substantially higher risk for serious or severe AEs. This section contains a brief summary of the findings, organized by demographic variable. The discussion is limited to the ISS subjects treated with BCV (100 mg QW and 200 mg QW pooled).

Age
Subjects <65 years of age (n=309) were compared to subjects ≥65 years old (n=83). The older cohort comprised 21% of the BCV population. Differences between age groups were difficult to assess due to the predominance of subjects <65 years in the study population.

The percentage of subjects with SAEs was 21% and 17% respectively. The percentage of subjects with Grade 3/4 AEs was 33% and 34% respectively. All-cause AEs of any severity occurred in 91% and 90% respectively. The frequencies of selected AEs of interest were as follows: diarrhea (29% vs. 31%), nausea (17% vs. 21%), vomiting (15% vs.13%), abdominal pain (18% vs. 13%), and acute GVHD (22% vs. 6%).

Reviewer Comment: It is possible that the differences (particularly in GVHD) may be less notable had there been more equal representation between age groups. Otherwise, no clear safety differences were apparent between subjects aged ≥65 years and younger subjects.

Gender
Women comprised 46% of the BCV ISS population (181/392). SAEs occurred in 23% of women and 18% of men. Grade 3/4 events occurred in 36% of women and 31% of men. All-cause AEs of any severity occurred in 93% of women and 89% of men. The frequencies of selected AEs of interest were as follows: diarrhea (34% vs. 26%), nausea (22% vs. 13%), vomiting (17% vs.12%), abdominal pain (20% vs. 14%), and acute GVHD (23% vs. 14%).

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

Race

Differences between racial groups were difficult to assess due to the predominance of white subjects in the study population. Analyses of non-white (15%) and white (85%) subjects in the BCV group are summarized. SAEs occurred in 26% of non-white subjects and 19% of white subjects. Grade 3/4 AEs occurred in 40% of non-white subjects and 32% of white subjects. All-cause AEs of any severity occurred in 97% of non-white subjects and 90% of white subjects. The frequencies of selected AEs of interest were as follows: diarrhea (38% vs. 28%), nausea (20% vs. 17%), vomiting (19% vs.13%), abdominal pain (28% vs. 15%), and acute GVHD (17% vs. 18%).

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

Overall Demographic Safety Analysis Conclusion: No clinically significant patterns were identified to suggest a higher risk for specific events in any age, race or gender subgroup.

8.7. Specific Safety Studies/Clinical Trials

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

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Positive carcinogenicity findings were observed in rats with systemic exposures lower than the expected human exposure based on the proposed dose of BCV.

The following treatment-emergent oncologic events occurred in the ISS population:
- BCV: AML recurrent (n=1), leukemia recurrent (n=1)
- PBO: skin papilloma (n=1)

The Applicant undertook Study 333 (an optional registry for previous subjects who completed Studies 301, 303, 304, and 307) to develop a database to assess long-term effects of BCV on the incidence of specified events, including malignancies. Subjects who agreed to participate were to be followed for a period of approximately 10 years following each subject's completion of the qualifying clinical study. Study 333 was initiated on March 17, 2014 and ended on June 21, 2019 after the Applicant decided to discontinue development of BCV for non-orthopoxvirus indications. Of the 660 subjects who received at least 1 dose of study drug in a qualifying study, a total of 303 subjects (BCV [n=219]; PBO [n=79]; active control [n=5]) agreed to participate in the registry. The malignancy findings are summarized below:
- Of 219 subjects who were previously exposed to BCV, 49 subjects (22%) reported new malignancies and 30 subjects (14%) reported relapsed malignancy.
- Of 79 subjects who received PBO, 25 subjects (32%) reported new malignancies and 22 subjects (28%) reported relapsed malignancy
- Of 5 subjects who received active control, 1 subject reported new malignancy.

Reviewer Comment: Because enrollment in the registry was voluntary, and duration of follow-up

was variable, it is not possible to reliably estimate the frequency of these events or establish a causal relationship to drug exposure. Additionally, the HSCT population is at increased risk for malignancy due to chemotherapeutic regimens and, potentially, due to other comorbidities.

Overall Assessment: Although BCV has the potential for carcinogenicity, the benefit/risk assessment of a 2-week course for the treatment of smallpox is overall favorable. Although no specific safety signal was detected for malignancies in the clinical safety database with BCV, product labeling is recommended to describe that, based on findings from animal studies, BCV is considered a potential human carcinogen. Product labeling will also provide risk mitigation strategies for subjects using BCV, outlining that:

- *BCV tablets should not be crushed or divided.*
- *Direct contact with broken or crushed tablets or oral suspension should be avoided. If contact with skin or mucous membranes occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with water*.

8.8.2. Human Reproduction and Pregnancy

Pregnant and lactating women were excluded from participation for all clinical trials. Study 333 also assessed for pregnancies: 5 subjects experienced 6 pregnancies (1 in a BCV-treated subject, 1 in a partner of a BCV-treated subject, and 4 pregnancies in partners of 3 subjects treated with PBO). No fatal or life-threatening pregnancy-related SAEs experienced by the mother were reported. No pregnancy-related SAEs experienced by the fetus/child were reported.

Reviewer Comment: Although no specific safety signal was detected for adverse pregnancy-related outcomes in the clinical safety database with BCV, product labeling is recommended to describe that: (1) based on findings from animal reproduction studies, BCV may cause fetal harm when administered to pregnant individuals; (2) based on findings of testicular toxicity in animal studies, BCV may irreversibly impair fertility in individuals of reproductive potential. Product labeling will also provide risk mitigation strategies outlining that:

- *Pregnancy testing is recommended in individuals of childbearing potential before initiation of BCV.*
- *Individuals of childbearing potential should avoid becoming pregnant and use effective contraception during treatment with BCV and for 2 months after the last dose.*
- *Individuals of reproductive potential with partners of childbearing potential should use condoms during treatment with BCV and for 4 months after the last dose.*

8.8.3. Pediatrics and Assessment of Effects on Growth

On June 5, 2018, the Applicant was granted Orphan Designation for the treatment of smallpox. Consequently, the Applicant's drug development program for the treatment of smallpox is exempt from the PREA requirements, an agreed to Pediatric Study Plan (PSP) was not required prior to the submission of an NDA, and no meetings were held with the Pediatric Review Committee (PeRC). The Applicant used pharmacokinetic simulation to propose dosing regimens that are predicted to provide pediatric patients (neonates to 17 years of age and < 10 kg, 10kg to < 48 kg, and 48 kg and above) with exposures comparable to the observed exposure in adults

receiving 200 mg.

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

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

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

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

The Applicant proposed the following clinical protocol to be implemented in the event of a human smallpox outbreak:

(b) (6)

Reviewer Comment: Because the approval of BCV would be the second antiviral treatment regimen for patients with human smallpox disease caused by variola virus, the review team assessed that a factorial study design would be the most informative and interpretable design for the clinical trial. The review team proposed that the Field Study 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. Negotiations on this required post-marketing study were ongoing at the time of finalization of this review.

8.9.2. Expectations on Safety in the Postmarket Setting

Safety analyses and conclusions in this review are primarily based upon data from the submitted Phase 2 and Phase 3 randomized, double-blind, placebo-controlled trials in HSCT recipients. These transplant/immunosuppressed patients are predisposed to GI and hepatic toxicities that occur with BCV. Notably, the HSCT population which composes the safety database may differ considerably from the general population which could receive BCV in the setting of a smallpox outbreak. Additionally, BCV has not been studied in pregnant women or lactating women. Emergence of new safety signals can be managed by routine pharmacovigilance activities.

8.10. Additional Safety Issues From Other Disciplines

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

8.11. Integrated Assessment of Safety

GI toxicities and hepatotoxicity were the major safety issues identified in this review. Both of which can be adequately conveyed in product labeling with appropriate risk mitigation strategies and do not preclude approval.

In the ISS population, higher rates of SAEs, AEs, Grade 3/4 AEs, and AEs leading to discontinuation were observed with BCV compared to PBO. The majority of AEs were Grade 2 or higher in severity. Related Grade 3/4 AEs and related SAEs were infrequent and there were no related deaths.

The notable laboratory abnormalities were the higher rates of ALT/AST elevations and total bilirubin elevations in the BCV group compared to PBO group, and these imbalances will be described in product labeling.

Section 5 of the label will describe that BCV is not indicated for use in diseases other than human smallpox. An increase in mortality was observed in a randomized, placebo-controlled Phase 3 trial when BCV was evaluated in another disease. The label will also include a Boxed Warning outlining that an increased risk for mortality was observed when BCV was used for a duration longer than at the recommended dosage on Days 1 and 8.

Section 5 of the label will describe that, based on findings from animal studies: (1) BCV is considered a potential human carcinogen; (2) BCV may cause fetal harm when administered to pregnant individuals; (3) based on testicular toxicity in animal studies, BCV may irreversibly impair fertility in individuals of reproductive potential. Risk mitigation strategies will be described in product labeling.

Section 6 of the label will also display Less Common Adverse Reactions, including ADRs of interest such as rash, dysgeusia, decreased appetite, muscular weakness, and peripheral edema.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting will not be convened for this application for the following reasons:

• Issues involving antiviral drug approval for treatment of human smallpox disease using FDA's Animal Rule were discussed in the 2011 Antiviral Drugs Advisory Committee.
• The Applicant focused on the rabbit/RPXV animal model and the mouse/ECTV animal model. In these animal studies, key study design issues were discussed by the Applicant and the Division and consensus was reached before these studies were conducted. The Agency concluded that the Applicant closely followed the FDA's recommendations and demonstrated a

statistically significant survival benefit in the rabbit/RPXV animal model and in the mouse/ECTV animal model.

10 Labeling Recommendations

10.1. Prescription Drug Labeling

Below are agreed upon changes for proposed labeling. Labeling was finalized at the time of finalization of this review.

BOXED WARNING

The Boxed Warning will provide wording that clearly describes that an increased risk for mortality was observed when BCV was used for a duration longer than at the recommended dosage on Days 1 and 8.

1 INDICATIONS AND USAGE

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

• The label will include a Limitations of Use that BCV is not indicated for the treatment of diseases other than human smallpox disease.

2 DOSAGE AND ADMINISTRATION

The review team recommends that the dosage for adult and pediatric patients weighing at least 48 kg is 200 mg (two 100 mg tablets or 20 mL of suspension) once weekly for 2 doses (on Days 1 and 8). The review team recommends the following doses for pediatric patients in other weight bands:

- 10 kg to < 48 kg: 4 mg/kg of suspension once weekly for 2 doses (on Days 1 and 8)
- < 10 kg: 6 mg/kg of suspension once weekly for 2 doses (on Days 1 and 8)

5 WARNINGS AND PRECAUTIONS

- The Warnings and Precautions section will provide wording that clearly describes the hepatotoxicity safety signal and gastrointestinal safety signal that have been observed for BCV, along with risk mitigation strategies. *(See Sections 8.5.1 and 8.5.2)*
- The Warnings and Precautions section will provide wording that clearly describes that BCV is not indicated for use in diseases other than human smallpox. An increase in mortality was observed in a randomized, placebo-controlled Phase 3 trial when BCV was evaluated in another disease. *(See Section 11)*
- The Warnings and Precautions section will provide wording that clearly describes that concomitant use of BCV with IV cidofovir is not recommended because BCV, a lipid-linked derivative of cidofovir, is intracellularly converted to cidofovir. *(See Section 4.5)*

- The Warnings and Precautions section will provide wording that clearly describes that, based on findings from animal reproduction studies, BCV may cause fetal harm when administered to pregnant individuals *(See Sections 4.4 and 8.8.2)*. Given that these findings may impact patient management, this information will be described in labeling, outlining that:
    - Pregnancy testing is recommended in individuals of childbearing potential before initiation of BCV.
    - Individuals of childbearing potential should avoid becoming pregnant and use effective contraception during treatment with BCV and for 2 months after the last dose.
    - Individuals of reproductive potential with partners of childbearing potential should use condoms during treatment with BCV and for 4 months after the last dose.
- The Warnings and Precautions section will provide wording that clearly describes that, based on findings from animal studies, BCV is considered a potential human carcinogen *(See Sections 4.4 and 8.8.1)*. Given that these findings may impact patient management, this information will be described in labeling, outlining that:
    - BCV tablets should not be crushed or divided.
    - Direct contact with broken or crushed tablets or oral suspension should be avoided. If contact with skin or mucous membranes occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with water.
- The Warnings and Precautions section will provide wording that clearly describes that, based on findings of testicular toxicity in animal studies, BCV may irreversibly impair fertility in individuals of reproductive potential. *(See Sections 4.4 and 8.8.2)*

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

- Table 3 was revised to display adverse reactions (i.e. adverse events assessed as reasonably associated with the use of the drug), all grades, and occurring at ≥2% frequency and at higher rates with BCV compared to PBO. *(See Section 8.4.5)*
- Less common adverse reactions (i.e. adverse events assessed as reasonably associated with the use of the drug) was revised to display adverse reactions, all grades, that were reported in < 2% of subjects (and also occurred in 2 or more subjects) exposed to BCV and occurred at rates higher than subjects who received PBO. This section will likely include rash, dysgeusia, decreased appetite, muscular weakness, and peripheral edema. *(See Sections 8.5.4 and 8.5.5)*
- Additional wording was added to Table 4 to further describe the CTCAE grading system and clarify key differences between this scale (that is less commonly used in antiviral development programs) and the DAIDS scale, especially the cut-offs used for Grade 3 and Grade 4 in the Laboratory Abnormalities. *(See Section 8.4.6)*
- The pediatric subsection was revised to describe pediatric data from subjects who received BCV in a randomized, placebo-controlled clinical trial. *(See Section 8.4)*

- Removed [redacted] (b) (4)

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on TEMBEXA

- Section 7 will describe that concomitant use of BCV with OATP 1B1 and 1B3 inhibitors (which includes cyclosporine) resulted in increased BCV exposures and may increase adverse reactions associated with BCV. *(See Sections 4.5.3 and Section 8.5.9)*
- Section 7 of the label will also describe risk mitigation strategies outlining that:
  • Where possible, consider alternative medication that are not OATP1B1 or 1B3 inhibitors. If concomitant use with BCV is necessary, increase monitoring for adverse reactions associated with BCV (elevations in transaminases and bilirubin, diarrhea or other GI adverse events) and postpone the dosing of OATP1B1 or 1B3 inhibitors at least 3 hours after BCV administration. *(See Sections 4.5.3 and Section 8.5.9)*

8 USE IN SPECIFIC POPULATIONS

8.2 Lactation

- Revised to clarify that, because of the potential for variola virus transmission through direct contact with the breastfed infant, breastfeeding is not recommended in patients with smallpox.

8.3 Females and Males of Reproductive Potential

- The review team concurred with the Applicant that, based on animal data, BCV may cause fetal harm. *(See Sections 4.4 and 8.8.2)*
- Revised to clarify the following risk mitigation strategies:
  - Pregnancy testing is recommended in individuals of childbearing potential before initiation of BCV.
  - Individuals of childbearing potential should avoid becoming pregnant and use effective contraception during treatment with BCV and for 2 months after the last dose.
  - Individuals of reproductive potential with partners of childbearing potential should use condoms during treatment with BCV and for 4 months after the last dose.
- Revised to clarify that, based on testicular toxicity in animal studies, BCV may irreversibly impair fertility in individuals of reproductive potential. *(See Sections 4.4 and 8.8.2)*

8.4 Pediatric Use

- Revised to clarify that pediatric data was provided from: (1) 23 pediatric subjects who received BCV in a randomized, placebo-controlled clinical trial; (2) 166 pediatric subjects who received BCV for treatment of non-orthopoxviruses under expanded access and from uncontrolled studies. *(See Sections 8.4 and 13.3)*

- The review team has concluded that the Applicant's methodology for determining pediatric dosing regimens would likely result in BCV exposures for pediatric subjects < 10 kg that are lower than those observed in healthy adults receiving BCV 200 mg. The recommended dosing regimen has been provided by the review team based on the population pharmacokinetic analysis and simulation. *(See Section 4.5.2)*

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

- Added wording to outlin (b) (4) *(See Section 4.5.3)*

12.4 Microbiology

- The review team has had further internal discussions regarding the public disclosure of specific BCV resistance pathways (i.e., amino acid substitutions associated with BCV exposure or phenotypic resistance), and for security reasons, the Division currently intends to remove all details related to resistance pathways from labeling and retain only general statements.

14 CLINICAL STUDIES

- Additional wording was added to clarify that:
  - In the rabbit/RPXV model, the timing of BCV dosing was intended to assess efficacy when treatment is initiated after all animals have developed clinical signs of disease, specifically fever in rabbits. *(See Sections 6.1 and 7.1.1)*
  - In the mouse/ECTV model, a clinically evident sign of disease could not be identified to use as a trigger to initiate treatment. *(See Sections 6.2 and 7.1.1)*
- In Table 6, Study 1 (rabbit/RPXV study VIR-106) was revised (b) (4) *(See Sections 6.1 and 7.1.1)*
- In Table 6, Study 2 (mouse/ECTV study VIR-044) was revised (b) (4) *(See Sections 6.2 and 7.1.1)*

10.2. Patient Labeling

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

10.3. Nonprescription Drug Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

The following issues were considered in determining whether a REMS (that includes a safe use condition for the treatment of human smallpox disease prior to shipment) would be needed:

• BCV is not indicated for use in diseases other than human smallpox because increased mortality was observed in Study 301, a randomized, double-blind, placebo-controlled Phase 3 trial when BCV was evaluated in another disease. In Study 301, subjects received BCV or PBO for up to 14 weeks; all-cause mortality at Week 24 was 16% in the BCV group compared to 10% in the PBO group.[10] An increased risk in mortality is possible if BCV is used for a duration longer than at the recommended dosage on Days 1 and 8. Other viral diseases (such as cytomegalovirus, adenovirus, herpes simplex virus, varicella zoster, Epstein-Barr virus, HHV-6, BK virus, JC virus, HPV, molluscum contagiosum) would need longer treatment durations. Other sponsors intend to evaluate BCV for other viral diseases (e.g. adenovirus, BK virus, HHV-6); hence off-label use and longer duration of treatment might be possible.[13] All of these other viral diseases can occur in transplant/immunosuppressed patients and these patients are also predisposed to GI and hepatic toxicities that occur with BCV.

The Applicant stated the intent for BCV in the US is for exclusive manufacturing and delivery to the Strategic National Stockpile (SNS). Applicant has no plan or future intent to manufacture or maintain stockpiles of oral BCV for use or study in other indications. The review team assessed that a REMS was not needed because safety concerns associated with BCV are adequately addressed in product labeling:
• The label will include a Boxed Warning as well as Warnings and Precautions outlining that an increased risk for mortality was observed when BCV was used for a duration longer than at the recommended dosage on Days 1 and 8.
• The label will include a Limitations of Use that BCV is not indicated for the treatment of diseases other than human smallpox disease.

Please refer to the Cross-Discipline Team Leader/Division Director Review for additional details.

12 Postmarketing Requirements and Commitments

Post-marketing requirements and commitments were finalized and are summarized below:

- A PMR will be issued for a 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.
- A PMC will be issued to 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.

13 Appendices

13.1. References

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13.2. Financial Disclosure

There were no financial disclosures of significant concern, individually or collectively. The

financial disclosures described below do not affect approvability of BCV.

(b) (4) (where animal efficacy studies VIR-106 [rabbit/RPXV] and VIR-044 [mouse/ECTV] were conducted) certified that no employees have any financial interests/arrangements.

Covered Clinical Study (Name and/or Number): CMX001-201, CMX001-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 554 Overall: 69 Principal Investigators, 485 Sub-investigators (CMX001-201: 27 Principal Investigators, 169 Sub-investigators; CMX001-301: 42 Principal Investigators, 316 Sub-investigators)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The Applicant adequately examined financial disclosure information from all clinical investigators for the covered clinical trials, as recommended in the *Guidance for Industry: Financial Disclosure by Clinical Investigators*. The Applicant certified in Form FDA 3454 that, as the sponsor of the submitted studies, the Applicant has not entered into any financial arrangement with the listed clinical investigators (list was included in the submission) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any

such interests. The Applicant further certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

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

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

13.3. Expanded Access

In the United States (US), BCV has been provided via Emergency Investigational New Drug application (EIND) to one patient with complications of smallpox vaccination (live vaccinia virus).[14] There were also three ex-US cases of BCV use in patients with cowpoxvirus infection. Information from these cases do not allow conclusions regarding the relative contribution to outcomes of BCV, other investigational or approved specific therapeutics, supportive care, and/or patient immune response (Appendix).[14,15]

The Applicant submitted data on 166 pediatric subjects aged 3 months to 18 years of age who received BCV for treatment of non-orthopoxviruses under expanded access and in uncontrolled studies. The available clinical data from these patients are limited. Due to these limitations, assessments of safety should be based on the randomized controlled trials discussed in this review rather than the expanded access program.

Appendix: Summary of Compassionate Use with BCV in subjects with orthopoxvirus infections (n=4; US [#1]; ex-US [#2-4])

Description	Interventions	Comments
21 year-old immunosuppressed male diagnosed with progressive vaccinia (PV) on 3/3/09 following smallpox vaccination *(Vaccination occurred ~ 2 weeks before being diagnosed with acute myelogenous leukemia; had undergone induction chemotherapy when PV developed)* J Infect Dis. 2012;206(9):1372-1385	Oral tecovirimat 3/5/09 – (b) (6) 400 mg/day x (b) (6) days (b) (6) 800 mg/day x (b) (6) days (b) (6) 1200 mg/day x (b) (6) days	Tecovirimat doses were adjusted due to suboptimal plasma exposure and development of new vaccinia satellite skin lesions (b) (6) while receiving tecovirimat. Genotypic and phenotypic evidence that the viral population became less susceptible to tecovirimat during treatment.
	VIG (14 doses, given over 3/4/09 – (b) (6))	
	Topical tecovirimat[a] (3/6/09 – (b) (6))	
	Oral BCV: 2 mg/kg (3/26/09), then 1 mg/kg (5 doses, given QW over (b) (6))	
	Topical imiquimod (b) (6)	
17 year-old immunosuppressed male, renal transplant recipient, developed disseminated cowpox virus [CPXV]) following exposure to cat Pediatr Nephrol. 2017;32(3):533-536	IV CDV (information on dosage, # of doses, and dates of administration – N/A)	CPXV disease progressed despite the listed interventions and reduction in patient's transplant immunosuppressive regimen. Patient died due to disseminated CPXV, septic shock and multi-organ failure.
	VIG (2 doses; information on dosage and dates of administration – N/A)	
	IV CDV was subsequently changed to BCV 100 mg BIW (# of BCV doses and dates of administration – N/A)	
45 year-old female with chronic kidney disease, developed CPXV following exposure to cat	BCV 100 mg BIW (# of BCV doses and dates of administration – N/A)	Narrative describes pustules on extremities and notes clearance of virus within 3 weeks of BCV administration.
Immunosuppressed female, lung transplant recipient (age – N/A)	BCV 200 mg QW started in (b) (6) (# of BCV doses and dates of administration – N/A)	- Narrative describes viral load became non-detectable in November 2019, but subsequently had intermittent viremia.
	Tecovirimat started ~ 1 week following BCV initiation (information on dosage, # of doses, and dates of administration – N/A)	
	VIG used for ~ 3 weeks, starting in late (b) (6)	(b) (6), (b) (3) (A), (b) (3) (B) - Patient died (b) (6) due to pneumonia and progression of renal failure.

Vaccinia immune globulin (VIG); Intravenous (IV); EIND, Emergency Investigational New Drug application; N/A, not available.
[a]Topical tecovirimat is an investigational drug; no human data are available with topical tecovirimat other than in the EIND described above.

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/s/

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