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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

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Submission Date	October 7th, 2020
PDUFA Goal Date	June 7th, 2021
Submission Type	505(b)1, NDA, priority review
Brand Name	TEMBEXA
Generic Name	Brincidofovir
Dosage Form and Strength	Tablet 100 mg Suspension 10 mg/mL
Route of Administration	Oral ingestion
Proposed Indication	Treatment of human smallpox disease in adults and pediatric patients
Applicant	Chimerix
Associated IND	067681
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OCP Final Signatory	Kellie Reynolds, Pharm.D. Director, Division of Infectious Disease Pharmacology

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1 EXECUTIVE SUMMARY

The Applicant is seeking approval of TEMBEXA (brincidofovir) for the treatment of smallpox infection. Naturally occurring, smallpox was deemed eradicated in 1980 by the World Health Organization and vaccination is no longer routinely conducted. However, there is the potential for the accidental or deliberate release of the live virus which would be serious threat to public health. Since conducting an efficacy trial for smallpox treatment in humans is neither feasible nor ethical, the product was developed under the Animal Rule (21 CFR part 314, subpart I).

The effectiveness of TEMBEXA in smallpox infected adult and pediatric patients, including neonates, is based solely on efficacy studies in two animal models with surrogate orthopoxvirus disease mentioned in the FDA's 2019 guidance on *Smallpox (Variola Virus) Infection: Developing Drugs for the Treatment or Prevention*: Rabbits infected with the rabbitpox virus (RPXV/rabbits) and Mice infected with the ectromelia virus (ECTV/mice). The safety of TEMBEXA is based on adults and pediatrics (down to 0.3 years of age) in Phase 2 and 3 randomized, placebo-controlled clinical trials of another indication.

The Applicant's proposed TEMBEXA dosing regimen is 200 mg in adults (4 mg/kg in pediatrics) once weekly for two doses (short course therapy). The translation of the effective animal to human dose was based on the efficacy studies demonstrating a survival benefit in animals and higher exposures in humans as compared to those associated with the identified fully effective dose in animals with the proposed human dosing regimens.

1.1 Recommendation

The clinical pharmacology information in this NDA supports approval of TEMBEXA [established name brincidofovir (BCV)] tablets and oral suspension for the treatment of human smallpox disease caused by variola virus in adult and pediatric patients, including neonates.

The review team's recommendations for two important issues identified during the review are below:

(1) Pediatric dosing recommendations. The review team noted that there is an increased risk of underexposure in all patients weighting <10 kg (including neonates) with the Applicant's proposed weight-based dose (b) (4) Therefore, we recommended a more optimal weight-based dosage within weight-bands in the pediatric population, including neonates as follows (Table 1-1):

Table 1-1: (Review Team) Recommended Dosages of BCV for Adult and Pediatric Patients with Smallpox Disease

	TEMBEXA	
Weight (kg)	**Oral Suspension**	**Tablets**
< 10 kg	6 mg/kg once weekly	Not recommended
≥ 10 kg to < 48 kg	4 mg/kg once weekly	Not recommended
≥ 48 kg	200 mg (20 mL) once weekly	200 mg (2 100 mg tablets) once weekly

The Applicant proposed (b) (4) See PEDIATRICS in Section 3.3.3 for further discussion.

(2) Concomitant use of TEMBEXA and OATP1B1 and 1B3 inhibitors. We recommend where possible, use of alternative medications that are not OATP 1B1 or 1B3 inhibitors. If concomitant use of OATP1B1

or 1B3 inhibitors with TEMBEXA is necessary, there should be increased monitoring for adverse reactions associated with TEMBEXA and postponed dosing of OATP1B1 or 1B3 inhibitors to at least 3 hours after TEMBEXA administration. Coadministration in a dedicated BCV-cyclosporine (CsA) DDI study (600 mg CsA) increased BCV exposure (AUC) approximately 5-fold. The Applicant's proposed recommendation was [redacted] (b) (4) when co-administered with CsA based on an uncontrolled BCV-CsA interaction population PK analysis. See Section 3.3.4 for further discussion.

1.2 Post-Marketing Requirements and Commitments

There are no Clinical Pharmacology requested Post-Marketing Requirements or Commitments.

2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Clinical Pharmacology and Clinical Pharmacokinetics

Table 2-1: Summary of Brincidofovir, Cidofovir, and Cidofovir Diphosphate Pharmacokinetics in Humans Following Oral Administration of TEMBEXA

Bridge between the To-Be-Marketed and clinical trial formulations	The To-Be-Marketed TEMBEXA tablet and suspension formulations was not the same as the "other indication" Phase 2/3 trial tablet and suspension formulations used to provide sufficient evidence of PK and safety. However, PK bridging studies demonstrated similar relative bioavailability for the two formulations. Therefore, from a clinical pharmacology perspective, it is reasonable to extrapolate the PK and safety finds made with the "other indication" Phase 2/3 trial formulations to the To-Be-Marketed formulations. Three tablet formulations and 2 oral suspension formulations were used to obtain human PK data used for comparison to animal PK data. Comparative bioavailability studies demonstrated similar relative bioavailability between the different formulations of the same drug product. See *Comparison Between Dosage Forms Across Clinical Development Formulations and To-Be-Marketed Formulations*.
Drug product formulations and administration instructions	TEMBEXA tablets can be taken on an empty stomach or with a low-fat meal (approximately 400 calories, 25% fat). The effect of a high-fat meal on bioavailability has not been studied. TEMBEXA oral suspension is to be taken on an empty stomach.
Absorption	Tmax: 3 hr (2 to 8) for both TEMBEXA tablets and oral suspension Food decrease the absorption of BCV (↓ C_{max} by 49% and ↓ $AUC_{0\text{-}inf}$ by 31%) but not CDV-PP (the active drug).
Distribution	BCV Vp/F: The geomean (%GCV) estimate is 1230 (43.8) L. Fraction of BCV bound to plasma protein is > 0.999
Metabolism	Major: hydrolysis by intracellular phospholipases such as ASM (BCV to CDV) and hydroxylation by CYP4F2 (BCV to CMX103 and CMX064). CDV is subsequently phosphorylated, intracellularly, to form cidofovir diphosphate. The major inactive metabolites formed via these pathways are CMX103 and CMX064.

Elimination	BCV CL/F: The geomean (%GCV) estimate is 44.1 (41.1) L/h. BCV apparent elimination half-life: 19.3 h CDV-PP apparent elimination half-life: 133 h No unchanged BCV detected in feces or urine. Metabolites were eliminated to similar extent in both feces and urine.
Potential for drug interactions	BCV is a substrate of OATP1B1 or 1B3 membrane uptake transporters. BCV exposures can be increased by the concomitant use of OATP1B1 or 1B3 inhibitors.

ASM = acid sphingomyelinase; CDV = cidofovir; BCV = brincidofovir; Vp/F = apparent volume of distribution; CL/F = apparent clearance

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The Applicant's proposed dosage regimens for the treatment of smallpox are acceptable for the general population weighing ≥ 10 kg based on the nonhuman animal efficacy studies demonstrating a survival benefit and higher exposures in humans as compared to those associated with the identified fully effective dose in rabbits with the proposed human dosing regimens (see Sections 3.3.1, 3.3.2, and 3.3.3).

The fully effective dose in rabbitpox virus infection in rabbits (RXPV/rabbits) is 20/5/5 mg/kg/Q48h, a total of 3 doses. The plasma BCV and PBMC CDV-PP exposure information in RXPV/rabbits at this dose comes primarily from study CMX001-VIR-122, but was assessed in 8 healthy or RXPV infected rabbit studies at multiple dose levels (Table 2-2). Population PK (PopPK) modeling was conducted by the Applicant to characterize the PK of plasma BCV and intracellular (PBMC) CDV-PP in both healthy rabbits and RXPV/rabbits to establish reference plasma BCV and PBMC CDV-PP exposures associated with the fully effective dose in RXPV/rabbits (See Section 3.3.2).

Table 2-2: Overview of Rabbit Studies Included in the Population PK Model

Study CMX001-	BCV	CDV-PP	Rabbitpox-Infected	Dosing Regimen
NCA-030	Y	N	N	4 mg/kg QD PO for 7 days 20 mg/kg q48h PO for 5 days 4 mg/kg single dose IV
NCA-043	Y	Y[a]	N	5 mg/kg single dose PO 20 mg/kg single dose PO
NCA-061	Y	Y[a]	N	20/5/5 mg/kg q48h PO
NCA-121	Y	Y	N	20/5/5 mg/kg q48h PO
NCA-123	Y	Y	N	20/5/5 mg/kg q48h PO
VIR-058	Y	Y[a]	Y	20/5/5 mg/kg q48h PO; dosing initiated on PID 4.
VIR-106	Y	N	Y	20/5/5 mg/kg q48h PO; dosing initiated on PID 3, 4, 5, or 6.
VIR-122	Y	Y	Y	20/5/5 mg/kg q48h PO; dosing initiated on PID 4.

[a]CDV-PP PK data excluded due to the use of a different methodology for PBMC isolation
Abbreviations: BCV = brincidofovir; CDV-PP = cidofovir diphosphate; N = no: PID = post inoculation day; PO = per oral administration; q48h = every 48 hours; QD = once a day; Y = yes
Source: Human dose justification report. Table 4.3, pg. 23.

For selection and justification of the Applicant's proposed human dose regimen, healthy adult human PK for plasma BCV and PBMC CDV-PP comes from 7 Phase 1 clinical pharmacology studies (6 studies had PBMC CDV-PP data). Studies include CMX001-114, CMX001-115 (plasma BCV only), CMX001-123, CMX001-124, CMX001-125, CMX001-126, and CMX001-127. A PopPK model was developed using a parent-metabolite approach, which jointly described the PK time courses for plasma BCV and intracellular (PBMC) CDV-PP in healthy adults (See Section 3.3.2).

For Pediatric dosing of BCV for the smallpox indication, human PK for plasma BCV comes from 5 Phase 2/3 studies in adults and pediatrics (down to 0.3 years of age) with non-orthopoxvirus infections. Studies included CMX001-202, CMX001-304, CMX001-350, CMX001-201, and CMX001-301. A PopPK model was developed to describe the PK time course for plasma BCV in adults and pediatrics with non-orthopoxvirus infections (See PEDIATRICS in Section 3.3.3).

Dose in Pediatric Patients < 10 kg

The review team noted that there is an increased risk of underexposure in pediatric patients weighing <10 kg with the Applicant's proposed dose (b) (4) for pediatric patients (b) (4) The Agency's recommended pediatric dosing regimen is expected to produce BCV exposures that are comparable to those in adults based on a POPPK modeling and simulation approach. Hence, we recommend the following dosing regimen (Table 2-3). See PEDIATRICS in Section 3.3.3 for the Agency's assessments and basis for the Agency's dose recommendation.

Table 2-3: Agency Recommended Dosage in Pediatric and Adult Patients

Patient's Weight (kg)	TEMBEXA Oral Suspension (10 mg/mL)	TEMBEXA Tablet (100 mg)
Less than 10 kg	6 mg/kg once weekly for 2 doses (on Days 1 and 8)	
Less than 48 kg	4 mg/kg once weekly for 2 doses (on Days 1 and 8)	
48 kg and above	200 mg (20 mL) once weekly for 2 doses (on Days 1 and 8)	200 mg (two 100 mg tablets) once weekly for 2 doses (on Days 1 and 8)

The Applicant proposed (b) (4) the review team recommends that TEMBEXA oral suspension be taken on an empty stomach (See FOOD-DRUG INTERACTIONS in Section 3.3.4)

2.3 Outstanding Issues

There are no outstanding issues.

3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Brincidofovir (BCV) is a novel, lipid-modified acyclic nucleotide with antiviral activity against orthopoxviruses. Mimicking a natural phospholipid (lysophosphatidylcholine), BCV gains intracellular delivery via endogenous lipid uptake pathways. Once inside the cell, BCV undergoes hydrolysis of the phosphoester to release cidofovir, which is subsequently phosphorylated to the active antiviral cidofovir diphosphate. Cidofovir diphosphate exerts its antiviral effects against orthopoxviruses by acting as an alternate substrate (nucleotide analog) that blocks DNA chain elongation inhibiting viral DNA synthesis during viral replication.

BCV was developed for the treatment of smallpox. Smallpox is an infectious disease caused by the variola virus. It is highly contagious and lethal (mortality rates as high as 30%). Naturally occurring, smallpox was deemed eradicated in 1980 by the World Health Organization and vaccination is no longer routinely conducted. However, there is the potential for the accidental or deliberate release of the live virus which would be serious threat to public health. Since smallpox does not naturally occur and is a life-threatening disease, conducting an efficacy trial in humans is neither feasible nor ethical. Therefore, the product was developed under the Animal Rule (21 CFR part 314, subpart I). Note, BCV was also being developed under a different clinical program for other double-stranded (ds) DNA viral infections, mostly in recipients of organ transplants. Therefore, PK and safety (based on 2-week data) analyses from that program were available and incorporated for clinical decision making of the smallpox dose regimen.

Tecovirimat is the only antiviral drug approved by the FDA (2018) for the treatment of smallpox infection. However, tecovirimat is associated with a low barrier to resistance, with single point mutations conferring high-level drug resistance. Therefore, additional effective smallpox treatments with varying mechanisms of action are needed to ensure readiness in the event of a smallpox outbreak. Tecoviromat was also developed under the Animal Rule.

There have been extensive discussions between the Applicant and the FDA regarding the animal models utilized, including the design of the efficacy studies in each model and the primary endpoint of mortality. The Agency also provided guidance on other key aspects of the development program, including the clinical studies supporting safety and the methodology utilized for human dose selection. The Applicant chose to use two non-human animal models of smallpox, ectromelia virus infection in mice (ECTV/mice) and rabbitpox virus infection in rabbits (RXPV/rabbits), to determine BCV efficacy.

A comprehensive clinical pharmacology program was completed for TEMBEXA tablet and oral suspension. In healthy adults, this included Phase 1 studies to characterize the PK of BCV and CDV in plasma, and the intracellular PK of CDV-PP (active drug) in PBMCs. Formulation development studies (relative bioavailability, absolute bioavailability) were also conducted, along with special population and safety studies (renal and hepatic impairment, thorough QT), and multiple drug-drug interaction (DDI) studies. All studies in healthy adults were single dose studies. In adult and pediatric (down to 0.3 years of age) organ transplant recipients with a non-orthopoxvirus infection, this included Phase 2/3 trials in which serial or sparse blood sampling was obtained to characterize the PK of BCV in plasma for pediatric dose scaling.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Table 3-1. Summary of Pharmacologic Activity and Clinical Pharmacology

Characteristic	Drug Information
Pharmacologic Activity	
Mechanism of action	TEMBEXA is an antiviral drug. As an alternate substrate for orthopoxvirus DNA polymerase, it blocks further viral DNA synthesis inhibiting orthopoxvirus replication.
Active moiety	The nucleotide analog CDV-PP is the active antiviral of TEMBEXA. BCV hydrolysis is required for conversion to CDV and subsequent phosphorylations by cellular enzymes to form CDV-PP.
QT prolongation	No significant QTc prolongation effect of BCV (200 mg [C_{max} of 802 ng/mL] and 350 mg [C_{max} of 1482 ng/mL]) was detected in a TQT study using moxifloxacin (400mg) as positive control.
General Information	
Bioanalysis	Validated HPLC/MS/MS methods were used to determine the concentrations of BCV, CDV, CDV-PP, CMX064, CMX103, and co-administered drugs in various biological matrices as applicable to individual studies.
Healthy versus patients	Not studied in patients with Smallpox. However, the BCV AUC is slightly higher (approx. 30%) in organ transplant patients with other double-stranded (ds) DNA viral infections relative to a healthy population (See Section 4.4.3).
PK following TEMBEXA Tablet	Simulated Plasma BCV and intracellular (PBMC) CDV-PP Exposures in Healthy Adults after 200 mg BCV Tablet QW

Parameter	Week 1		Week 2	
	$AUC_{0\text{-}168}$ (h·ng/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}168}$ (h·ng/mL)	C_{max} (ng/mL)
BCV				
200 mg Tablet	3400 (58) [1900-6300]	480 (70) [240-950]	3400 (58) [1900-6300]	480 (70) [240-950]
CDV-PP				
200 mg Tablet	1200 (75) [560-2400]	9.7 (75) [4.8-20]	1800 (76) [860-3700]	14 (75) [6.8-29]

Data are presented as Geomean (GCV%)[90% prediction interval].
PBMC = peripheral blood mononuclear cells; QW = once weekly. $AUC_{0\text{-}168}$ = area under the concentration-time curve from the time of drug administration (0 hours) to time before the next dose (168 hours); C_{max} = maximum concentration; BCV = brincidofovir; CDV-PP = cidofovir diphosphate; CV% = coefficient of variation expressed as a percent; Geomean = geometric mean
Source: CMX001-MS-104 Report. Table 14; page 48.

<table>
<tr><td>Maximally tolerated dose or exposure</td><td>Healthy adults tolerated single doses of BCV up to 350 mg PO (tablet) and 50 mg IV and multiple doses (total of 4) of BCV up to 20 mg IV. Higher doses have not been studied.
Average BCV exposures following single and multiple administration in healthy adults were:
• Single dose
PO 350 mg - 1482 ng/mL (Cmax); 6938 ng*hr/mL (AUC0-last)
IV 50 mg (2 h infusion) - 2950 ng/mL (Cmax); 5921 ng*hr/mL (AUC0-last)
• Multiple dose (Once weekly dosing [4 doses])
IV 20 mg (1 h infusion) - 1820 ng/mL (Cmax); 3030 ng*hr/mL (AUC0-last)
The maximally tolerated dosing in a transplant recipient population receiving multiple doses for greater than 2 weeks is 100 mg PO BIW or 200 mg PO QW (tablet or suspension).</td></tr>
<tr><td>Dose proportionality</td><td>BCV C_{max} and AUC increased approximately dose proportionally
Dose Range: 100 mg – 350 mg (Tablet), 100 mg – 200 mg (Suspension), 0.025 to 2 mg/kg (solution). See Section 4.3.3</td></tr>
<tr><td>Accumulation</td><td>Accumulation ratio (assessed by AUC) was 1 and 1.5 for BCV and CDV-PP, respectively based on population PK modeling.</td></tr>
<tr><td>Absorption</td><td></td></tr>
<tr><td>Bioavailability (BA)</td><td>Absolute BA is 16.8% and 13.4% for suspension and tablet respectively</td></tr>
<tr><td>Food-Effect (FE)</td><td>The ratio of PK parameters (Fed/Fasted) following administration of BCV tablets: Geomean (90% CI)
<table><tr><th>$AUC_{0\text{-}inf}$</th><th>C_{max}</th><th>T_{max}</th></tr><tr><td>0.687 (0.60 to 0.78)</td><td>0.51 (0.45 to 0.58)</td><td>No change</td></tr><tr><td colspan="3">Fed state = 30 min from completion of low fat (25%) breakfast</td></tr></table></td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>Apparent Volume of distribution (L)</td><td>BCV: The geomean (%GCV) estimate is 1230 (43.8).</td></tr>
<tr><td>Plasma protein binding</td><td>> 99.9% of BCV is bound to human plasma proteins</td></tr>
<tr><td>Blood to Plasma Ratio</td><td>0.48 to 0.61 in healthy adults</td></tr>
<tr><td>Elimination</td><td></td></tr>
<tr><td>Mass balance results</td><td>Following PO BCV administration, 50.7% and 40.4% of total radioactivity was recovered in urine and feces, respectively. The fraction metabolized through the hydrolysis pathway (Acid sphingomyelinase (ASM) contribution) to form CDV represented ca. 43% of the dose. The fraction metabolized through the CYP4F2 pathway with subsequent biotransformation to form the other identified metabolites (CMX103 and CMX064) represented ca. 49% of the dose. Unchanged BCV was not detected in urine or feces.

Plasma AUC / total blood AUC radioactivity-ng equivalents ratios:
• CMX103 (0.32), BCV (0.22), CMX064 (0.23), CDV (0.05)</td></tr>
<tr><td>Apparent Clearance (L/h)</td><td>BCV: The geomean (%GCV) estimate is 44.1 (41.1).</td></tr>
<tr><td>Terminal elimination half-life (h)</td><td>BCV: The geomean (%GCV) estimate is 19.3 (40.6).
CDV-PP: The geomean (%GCV) estimate is 113 (34.2).</td></tr>
</table>

Primary metabolic pathway(s)	Hydrolysis (ASM contribution) and CYPF42 pathway
Drug Interaction Liability (Drug as Perpetrator or Substrate)	
As substrate of transporters	BCV is a substrate of OATP1B1 and 1B3 efflux transporters.
Inhibition/induction of CYP metabolism or transporter systems	BCV and its associated metabolites are not expected to inhibit or induce drug metabolizing enzymes or membrane transporters

IV= intravenous; Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; AUC_{inf} = area under the concentration-time curve from time 0 to infinity after drug administration; AUC_{last} = area under the plasma concentration-time curve from. time zero to time of last measurable concentration; C_{max} = maximum plasma concentration of drug; $T_{1/2}$ = half-life; CI = confidence interval; PK = pharmacokinetic; ASM = acid sphingomyelinase; BCV = brincidofovir; CDV = cidofovir; CDV-PP = cidofovir diphosphate; CYP = cytochrome P450 enzymes; OATP = organic anion transporting polypeptide

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Clinical pharmacology information provides pivotal evidence of effectiveness because the translation of the effective animal to human dose relied on PK comparisons. This approach required accounting for factors such as PK differences in uninfected and infected animals, differences in ADME between animals and humans, PK variability, and effects of intrinsic and extrinsic factors. See section 3.3.2 (below) for additional details.

Effectiveness of TEMBEXA for the treatment of smallpox infection is provided by two well-characterized, lethal, nonhuman animal models of non-variola orthopoxvirus infection; the intradermal rabbitpox model in NZW rabbits and the intranasal mousepox ECTV model in BALB/c mice.

The applicant completed 1 dose-response study in rabbits (CMX001-VIR-039), 1 efficacy study in rabbits (CMX001-VIR-106), and 1 dose-response/efficacy study in mice (CMX001-VIR-044). The primary endpoint of efficacy was survival and this review focuses on the dose survival relationship to determine an effective dose for humans. Secondary endpoints such as viral DNA levels and total pox lesions were reviewed by clinical virology and pharm/tox review teams.

Briefly, brincidofovir (BCV) demonstrated statistically significant survival (primary endpoint) as compared to placebo in RPXV/rabbits and ECTV/mice when oral (PO) BCV was administered at the time of fever/viremia development for rabbits and viremia development for mice (Day 4 post challenge) and later disease progression timepoints. Key findings are presented in Table 3-2 and Table 3-3 in Section 3.3.2.

PK studies in rabbits and mice provided plasma BCV concentrations and peripheral blood mononuclear cell (PBMC) CDV-PP concentrations associated with the fully effective dose in animal models.

Refer to Section 3.3.2 for details.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, we agree with the Applicant, the proposed dosage regimen, 200 mg once weekly (QW) for 2 days, is appropriate for the general adult patient population. Doses higher than 200 mg BCV to treat smallpox were not considered. A longer-term dosage regimen of 200 mg total weekly for up to 14 weeks (either as 200 mg once weekly or 100 mg twice weekly) was associated with safety concerns (e.g., enterotoxicities) in Phase 2/3 clinical trial patients with other ds-DNA viral infections and led the Applicant to discontinue clinical development programs (not variola virus [smallpox]; mostly recipients of organ transplants). Note, the proposed dosing regimen for the full pediatric patient population will be discussed in Section 3.3.3 as an alternative dosing regimen is recommend for a subpopulation of the pediatric population based on body-weight.

Under the Animal Rule, there are several approaches to determine an effective dose in humans depending on the availability of previously established PK/PD for other relevant indications, qualified biomarkers, and acceptable target PK values. For BCV and the treatment of smallpox infection, the review team agrees with the Applicant's "conservative" approach to human dose selection with the assumption of a similar exposure-response relationship between animal models and humans. A conservative approach here is defined as selection of human dosing regimens to provide exposures that exceed those associated with the fully effective dose in animals, ideally by several-fold, if the drug's safety profile allows such dosing.

To select an effective dose in humans, fully effective doses were determined in RPXV/rabbits and ECTV/mice (Table 3-2). In RPXV/rabbits, efficacy was observed starting at 5/5/5 mg/kg/Q48h for a total of 3 doses and 20/5/5 mg/kg/Q48h was chosen as the fully effective dose. The survival rate in RPXV/rabbits receiving 20/5/5 mg/kg/Q48h was 100% or 90% on post-inoculation day (PID) 42 when BCV treatment was started on PID 3 or 4 respectively. The delayed start to dosing is based on the consistent development of fever by this timepoint. In ECTV/mice, efficacy was observed starting at 10/5/5 mg/kg/Q48h, which was selected as the fully effective dose.

Table 3-2: BCV Dose-Response Relationship for Survival in Animal Models

RPXV/Rabbits (total of 3 doses; CMX001-VIR-039)	Survival
Placebo	25% (4/16)
5/5/5 mg/kg Q48h	47% (7/15)
20/5/5 mg/kg Q48h	73% (11/15)
20/20/20 mg/kg Q48h	80% (12/15)
ECTV/Mice (total of 3 doses; CMX001-VIR-044)	Survival
Placebo	13% (4/32)
10/5/5 mg/kg Q48h	78% (25/32)
20/5/5 mg/kg Q48h	84% (27/32)

Treatment initiated on Day 4 (fever/viremia onset (rabbits) or viremia onset (mice). Rabbits were intradermally challenge with RPXV and mice intranasally challenged with ECTV.

Source: Human dose justification report: Table 20, pg. 63 and Table 22, pg. 65.

Table 3-3: Fully Effective BCV Dose Survival Rates in RPXV/Rabbits and ECTV/mice Models

	Treatment Initiation Day	Survival % (# survived/n)	
		Placebo	Brincidofovir
RPXV/Rabbits Dose Regimen of 20/5/5 mg/kg			
VIR-106	Day 4	29% (8/28)	90% (26/29)
	Day 5		69% (20/29)
	Day 6		69% (20/29)
ECTV/Mice Dose Regimen of 10/5/5 mg/kg			
VIR-044	Day 4	13% (4/32)	78% (25/32)
	Day 5		66% (21/32)
	Day 6		34% (11/32)

Treatment with oral BCV resulted in statistically significant improvement in survival relative to placebo, except when the 10/5/5 mg/kg regimen was initiated at Day 6 post-challenge in the mousepox study

Source: Human dose justification report: Table 21, pg. 64 and Table 22, pg. 65.

To justify selection of the human dose, the key exposure comparisons between species included assessing the C_{max}, and AUC_{tau} values. Consideration of the full concentration-time profile was also made.

The effective 20/5/5 mg/kg/Q48 dose in RPXV/rabbits was used to define the reference plasma BCV and intracellular PBMC CDV-PP exposures needed to translate to an effective human dose for treatment of smallpox (Table 3-4, blue box). The RPXV/rabbit model compared to the ECTV/mouse model was the more conservative model for estimating the needed plasma BCV drug exposures. This is consistent with the difference in the effective dose determined in RXPV/rabbits compared to ECTV/mice (20/5/5 mg/kg vs 10/5/5 mg/kg) (studies CMX001-VIR-122 and VIR-121). Also, rabbits compared to mice have a larger total circulating blood volume allowing for serial blood sampling from individual rabbits to measure plasma BCV and PBMC CDV-PP concentrations and make more confident PK assessments; especially in regard to CDV-PP. It should be noted that currently, the relevant site of drug action to treat smallpox, or the relative contribution of tissue versus PBMC CDV-PP drug concentrations to smallpox efficacy, have not been established. Additionally, no separate assessment was done accounting for difference in the unbound BCV concentrations between species as BCV is highly protein bound across all species (> 99%) and prevented the analytical detection of the unbound (free) BCV.

The Applicant used a multi-stage PopPK modeling and simulation approach for plasma BCV and intracellular (PBMC) CDV-PP cross-species PK comparisons and human dose justification. At a human dose of 200 mg BCV tablet QW for two doses, the mean predicted healthy human plasma BCV and PBMC CDV-PP C_{max} and AUC_{tau} values are generally greater than 2-fold compared to RPXV/rabbit plasma BCV and PBMC CDV-PP C_{max} and AUC_{tau} values based on simulated exposure comparisons between humans and rabbits (Table 3-4). The mean predicted healthy human plasma BCV $AUC_{0\text{-}7days}$ is also greater than the RPXV/rabbit plasma BCV $AUC_{0\text{-}7days}$ (3400 h·ng/mL vs 2364 h·ng/mL). These conclusions are not different based on observed exposure comparisons between humans and rabbits (Table 3-4).

Also, simulated plasma BCV and PBMC CDV-PP human concentration-time profiles following the proposed dosing regimen are equal or greater than that in rabbits following the 20/5/5 mg/kg dosing regimen (Figure 3-1). Importantly, throughout the proposed dosing interval (168 h) in humans the PBMC CDV-PP concentrations (active drug) in humans are higher than in rabbits despite the more frequent

dosing interval (48 h) in rabbits resulting in additional BCV plasma peaks (Figure 3-1). That is, healthy human PBMC CDV-PP C_{max}, AUC, and C_{min} are greater than RXPV/rabbit PBMC CDV-PP C_{max}, AUC, and C_{min}. This observation is due to the long half-life of the intracellular active metabolite CDV-PP and lower maintenance dose in rabbits (5 mg/kg) compared to humans (200 mg). Additionally, study CMX001-VIR-039 demonstrated that the 20 mg/kg loading dose is crucial to efficacy (Table 3-2). There was no substantial improvement in survival (1 animal difference) with a 20/20/20 dosing regimen compared to the 20/5/5 dosing regimen. Furthermore, when rabbit efficacy studies were pooled, data suggest that even a single 20 mg/kg dose demonstrated a statistically significant survival benefit compared to placebo (source: Applicant's Clinical Overview; Figure 3, pg. 32; data not shown). In summary, considering all this, once weekly dosing with 200 mg is reasonable despite undetectable concentrations of plasma BCV beyond 24 hours post-dose in humans.

Table 3-4: Simulated or Observed Plasma BCV PK Parameters After First and Last BCV Dose in Healthy Human Adults (≥48 kg) and Rabbitpox-Infected Rabbits

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

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

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

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

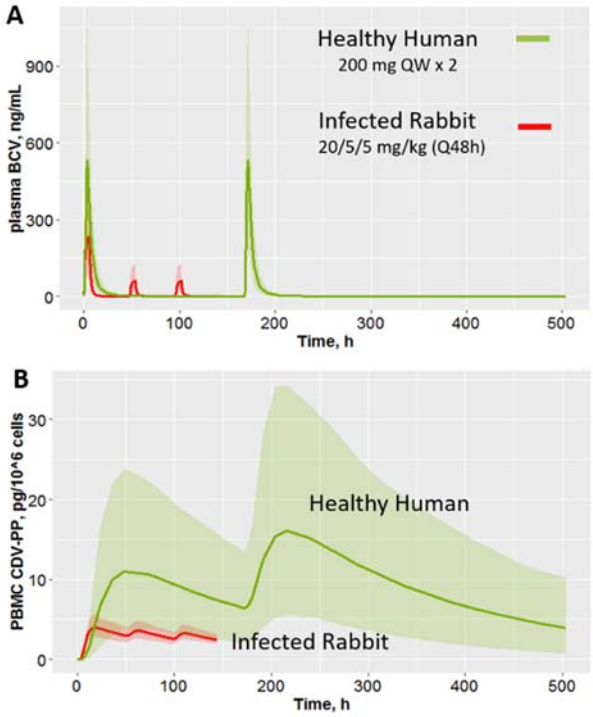
AUC for humans and rabbits for the dosing interval (168 h interval in humans and 48 h interval for rabbits) or AUC_{tau}

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

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

Source: Human dose justification report Tables 5 and 7 (CMX001-VIR-122 RPXV/Rabbit PK) pgs. 26-27, BCV-MS-104 healthy adult PK report Tables 15 and 16 (healthy adult PopPK) pgs. 44-45, and Study report CMX001-114 Table 8 and 11(Phase 1 health adult observed PK) pg. 51 and54.

Figure 3-1: Simulated Concentration-Time Profiles in Healthy Adults (≥48 kg) Following 200 mg QW BCV Tablet and in Infected Rabbits Following 20/5/5 mg/kg/Q48h. Solid lines represent geometric mean concentration-time profiles; shaded area represents 90% prediction interval. Virtual patient population distribution for POPK simulations was 1:1 fed to fasting, male to female.

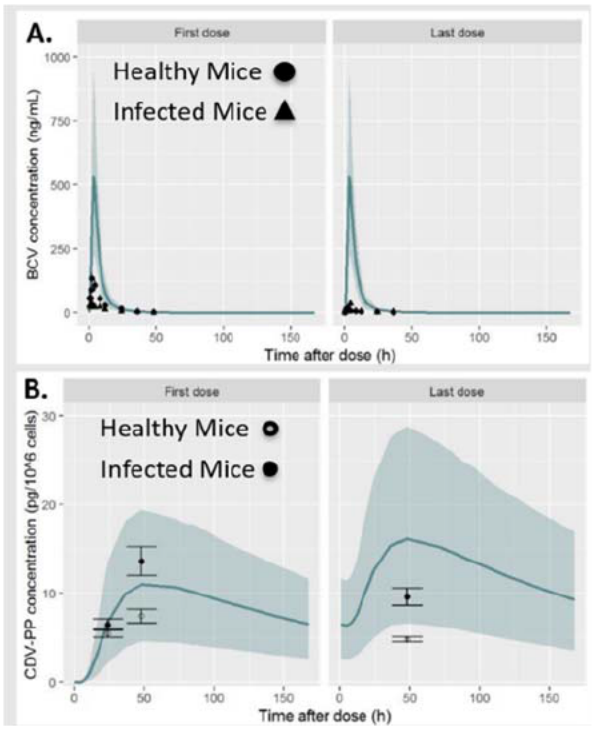


The Applicant's POPPK modeling and simulation strategy to define human plasma BCV and PBMC CDV-PP concentration-time profiles as well as, define RXPV/rabbit effective exposure targets was deemed adequate by the pharmacometrics reviewers (See Sections 4.4.2 and 4.4.1). Human POPPK simulations were necessary to account for important factors such as bodyweight, sex, and food-effects expected in the indicated (unstudied) patient population that are not well reflected in individual Phase 1 studies. It also allowed for estimation of CDV-PP accumulation following administration of TEMBEXA as no multiple-dose studies in healthy adults were conducted. No accumulation of BCV in plasma is expected based on its half-life in humans and multiple-dose PK data from non-orthopoxvirus infection Phase 2/3 trials. Considering individuals with smallpox will experience severe flu-like-symptoms making consuming food difficult, it is possible that many patients will take TEMBEXA in a fasted state, although the label will indicate it should be taken with food. Therefore, the virtual patient population consists of 50% fed and 50% fasted individuals for human plasma BCV PK simulations (healthy adult BCV PopPK model) that inform clinical pharmacology assessments and therapeutic decision making.

Technical factors associated with total blood volume requirements and bioanalytical methods/quantification thresholds limit the ability to assess individual plasma BCV and PBMC CDV-PP PK and between-subject variability in ECTV/Mice administered the 10/5/5 mg/kg dosing regimen. In particular, PBMC CDV-PP concentrations were difficult to interpret given the wide-range of average

values (6.31 to 27.9 pg/10^6 cells) reported from each of the 'pooled' units (up to 5 mice/unit). A constraint of the 'pooled' units arithmetic averaging strategy is that it can overestimate the central tendency measure when underlying individual C_{max} data is log normally distributed (typical for PK data). Even so, the typical population values of the PBMC CDV-PP C_{max} were similar between healthy adult humans and ECTV/mice (median 12.45 pg/10^6 cells [VIR-121] vs median of 11.7 pg/10^6 cells [CMX001-114]). The typical healthy adult PBMC CDV-PP C_{max} was approximately 1.8-fold the healthy mice CDV-PP C_{max} (median 11.7 pg/10^6 cells [CMX001-114] and 6.4 pg/10^6 cells [CMX001-NCA-106]). The ratio of the PBMC CDV-PP C_{max} in mice with and without infection was approximately 2. Suggesting, infection-induced disease produced higher PBMC CDV-PP concentrations - a trend also observed in rabbits but to a smaller degree. Lastly, plasma BCV concentrations in healthy adults are greater than those in mice at all time points(Figure 3-2).Taken together, the PBMC CDV-PP and plasma BCV concentrations in healthy adult humans are similar or greater than those observed in mice at the efficacious dose of 10/5/5 mg/kg.

Figure 3-2: Plasma BCV (A) and Intracellular (PBMC) CDV-PP (B) Concentration Profiles in Healthy Subjects Following BCV 200 mg QW Doses and in Healthy and Mousepox-Infected Mice After 10/5/5 mg/kg q48h BCV Doses



Solid line and shaded area represent the simulated geometric mean 90% prediction interval values for humans weighing ≥ 48 kg. Human virtual population distribution was 1:1 male:female; 1:1 fed:fasted; all received TEMBEXA tablet.

Filled (infected; VIR-121 study report) and open (healthy; NCA-106 study report) circles are the observed arithmetic mean and standard deviation values for mice.

Source: Human dose justification report Figure 13 pg 52.

It should be noted that the Applicant's dose selection strategy is "conservative" in that: **(i)** dose selection is based on drug exposures following tablet administration, which are lower than those following suspension administration (study CMX001-114); **(ii)** that higher BCV exposures were observed

in a Phase 2/3 patient population with non-orthopoxvirus infections (BCV-MS-02 report); **(iii)** that the EC_{50} value against variola virus is approximately 10-fold lower than RPXV or ECTV (study CMX001-VIR-107); and **(iv)** that in vitro data show immune activation results in higher CDV-PP conversion in human PBMCs (study CMX001-VIR-109).

Taken as a whole, we find a dose of 200 mg BCV QW in humans reasonably likely to produce clinical benefit from a clinical pharmacology standpoint as it provides plasma BCV exposures that are in excess of those in both non-human animal models and provides intracellular (PBMC) CDV-PP exposures that are in excess or similar of those in RPXV/rabbit and ECTV/mice.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Yes, we have identified an "at risk" pediatric subpopulation and have an optimized pediatric dosing recommendation that differs from the Applicant's recommendation Therefore, pediatric dosing for the full pediatric population are discussed here.(See details at the end of this section).

No dose adjustment are required for subpopulations based on the following intrinsic factors: age, sex, race/ethnicity, reduced activity in CYP4F2 enzyme, renal impairment including end stage renal disease (ESRD) with or without dialysis (based on estimated GFR), or hepatic impairment (Child-Pugh B, C).

RENAL IMPAIRMENT

The plasma PK of BCV and CDV have been evaluated in adults with severe renal impairment and ESRD receiving dialysis. The plasma BCV $AUC_{0\text{-}inf}$ was unchanged in severe renal impairment (eGFR <30 mL/min/1.73m^2) and was approximately 1.43-fold higher in adults with ESRD compared to adults with normal renal function. The effect of renal impairment (including ESRD receiving dialysis) had no effect on plasma BCV C_{max}. Plasma concentrations of CDV were significantly elevated in severe renal impairment (approximately 5-fold C_{max} and 10-fold $AUC_{0\text{-}last}$) and ESRD (approximately 10-fold C_{max} and 25-fold $AUC_{0\text{-}last}$) compared to adults with normal renal function. In patients requiring hemodialysis, the AUC and C_{max} of BCV and its metabolite CDV were comparable between subjects whether on- or off-dialysis. TEMBEXA was well tolerated in subjects with severe renal impairment and ESRD.

Assuming linear PK, the projected plasma CDV C_{max} and AUC in ESRD following 200 mg BCV is approximately 272 to 294 ng/mL and 25,804 to 26,616 ng·h/mL, respectively. The reported CDV C_{max} and AUC following a 5 mg/kg IV injection of CDV is 11,500 ng/mL and 28,300 ng·h/mL, respectively (Vistide US Prescribing Information). Although the projected plasma CDV AUC in ESRD is approaching the values reported for Vistide, the projected plasma CDV C_{max} in ESRD is significantly lower (2.5% of IV CDV C_{max}). CDV nephrotoxicity is postulated to be concentration-driven with OAT1 mediated uptake of plasma CDV (but not BCV or other metabolites) into kidney cells leading to accumulation and subsequent nephrotoxicity.

Considering the substantially lower plasma CDV C_{max} observed in adults with ESRD relative to IV CDV, the limited treatment duration for the smallpox indication (2 doses in 2 weeks), and that a dose reduction increases the loss-of efficacy risk in patients with renal impairment, we agree with the Applicant that no dose adjustment is necessary in patients with renal impairment or ESRD.

HEPATIC IMPAIRMENT

BCV PK were evaluated in adults with moderate (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C). Administration of TEMBEXA to subjects with moderate hepatic impairment resulted in similar mean $AUC_{0\text{-}inf}$ and 20% lower mean C_{max} values compared with subjects with normal hepatic function. Subjects with severe hepatic impairment showed approximately 30% higher $AUC_{0\text{-}inf}$ and 22% lower C_{max} compared with subjects with normal hepatic function. Note the plasma BCV C_{max} reduction in individuals with hepatic impairment is not considered clinically relevant as the expected typical C_{max} in adults with hepatic impairment is still greater than the C_{max} target/thresholds associated with the fully effective dose in RXPV/rabbits.

We agree with the Applicant that no dose adjustment is necessary in patients with hepatic impairment.

REDUCED CYP4F2 ACTIVITY

BCV PK were investigated in healthy adults with various levels of Cytochrome P450 (CYP) 4F2 activity as defined by the presence of variant T allele for rs2108622. CYP4F2 genotype data were generated and analyzed from healthy subjects in six Phase 1 studies utilizing tablet (N=100), suspension (N=161), or IV formulations (N=49). Individuals with the CYP4F2 T/T genotype (lowest enzymatic activity) had higher dose/weight normalized $AUC_{0\text{-}inf}$ and C_{max} following the administration of BCV as compared to individuals with the CYP4F2 C/C genotype (reference wild type). Following tablet, suspension, and IV administration, the CYP4F2 T/T genotype had 36%, 20%, and 10% higher dose/weight normalized $AUC_{0\text{-}inf}$, in comparison to the CYP4F2 C/C wild type.

We agree with the Applicant that the genetic polymorphism leading to reduced activity of CYP4F2 does not have a clinically significant impact on BCV exposures.

ACID SPHINGOMYELINASE DEFICIENCY

Acid sphingomyelinase (ASM) deficiency is a rare lysosomal storage disease in humans caused by autosomal recessive mutations of the sphingomyelin phosphodiesterase 1 (SMPD1) gene and characterized by a primary deficiency of ASM activity.

A principle BCV metabolic pathway is hydrolysis of the phosphoester bond to form CDV. CDV is subsequently phosphorylated to form CDV-PP. Genetic and chemical inhibition of ASM enzyme activity in multiple human cell lines (n=5) demonstrate ASM plays a major role in the hydrolysis of BCV to CDV and CDV-PP and thus antiviral activity in these cell lines. For example, the average relative reduction for CDV-PP concentrations was 78% (ASM knockout vs ASM wildtype). This translated to an average 2,138% relative increase for the antiviral half-maximal effect concentration (EC_{50}; ASM knockout vs ASM wildtype).

Based on these findings, [redacted] (b) (4) based on in vitro data, mutations in SMPD1 may reduce the ability to convert BCV to CDV and CDV-PP and thus antiviral activity. No clinical data are available in patients with ASM deficiency. The birth prevalence of ASM deficiency is estimated at 1/100,000 (Geberhiwot, Moro et al. 2018).

PEDIATRICS

The PK of TEMBEXA Suspension has been studied in pediatric patients down to 0.3 years of age enrolled in Phase 2/3 trials with non-orthopoxvirus infection. A PopPK modeling and simulation approach was used to derive dosing regimens that are predicted to provide pediatric patients, including neonates, with exposures comparable to the observed exposure in adults receiving TEMBEXA tablets.

The Applicant's literature review suggests a lack of difference in OATP1B1 function, inconclusive data on OATP1B3 function, and sparse data on CYP4F2 function when assessed for differences across ages ranging from neonates to adults. We agree that these findings negate the use of a maturation function with age within the BCV PopPK model and support the use of the BCV PopPK model that describes BCV clearance by weight-based allometric scaling (with the estimated exponent) in projecting the exposures in pediatric patients age birth to 0.3 years.

Applicant's simulations show that the simulated plasma BCV exposures are lowest in the age group of 0 to < 0.3 years compared to the older age groups, following a 4 mg/kg QW for 2 weeks dose regimen (Table 4-47. in Section 4.4.4). FDA reviewer's independent simulations performed by body weight groups (Figure 3-3) reproduce this trend, finding noticeably lower plasma BCV exposure in the lowest body weight groups (<10 kg). The geometric mean plasma BCV AUC_{tau} in pediatric patients weighing <10 kg is lower than the geometric mean plasma BCV AUC_{tau} (3400 ng·h/mL) in healthy adults receiving the 200 mg weekly tablet dosage. More than 25% of pediatric patients weighing <5 kg are predicted to have a plasma BCV AUC_{tau} below the geometric mean plasma BCV AUC_{tau} associated with the fully effective dose in infected rabbits (1410 ng·h/mL). For patients weighing > 10 kg, the plasma BCV AUC_{tau} across weight-bands were similar or greater than the geometric mean plasma BCV AUC_{tau} (3400 ng·h/mL) in healthy adults receiving the 200 mg weekly tablet dosage. The reference plasma BCV exposure values for healthy adults and fully effective rabbit plasma BCV exposures can be found in Table 3-4 and Table 4-42 respectively. See Section 4.4.1 for more details.

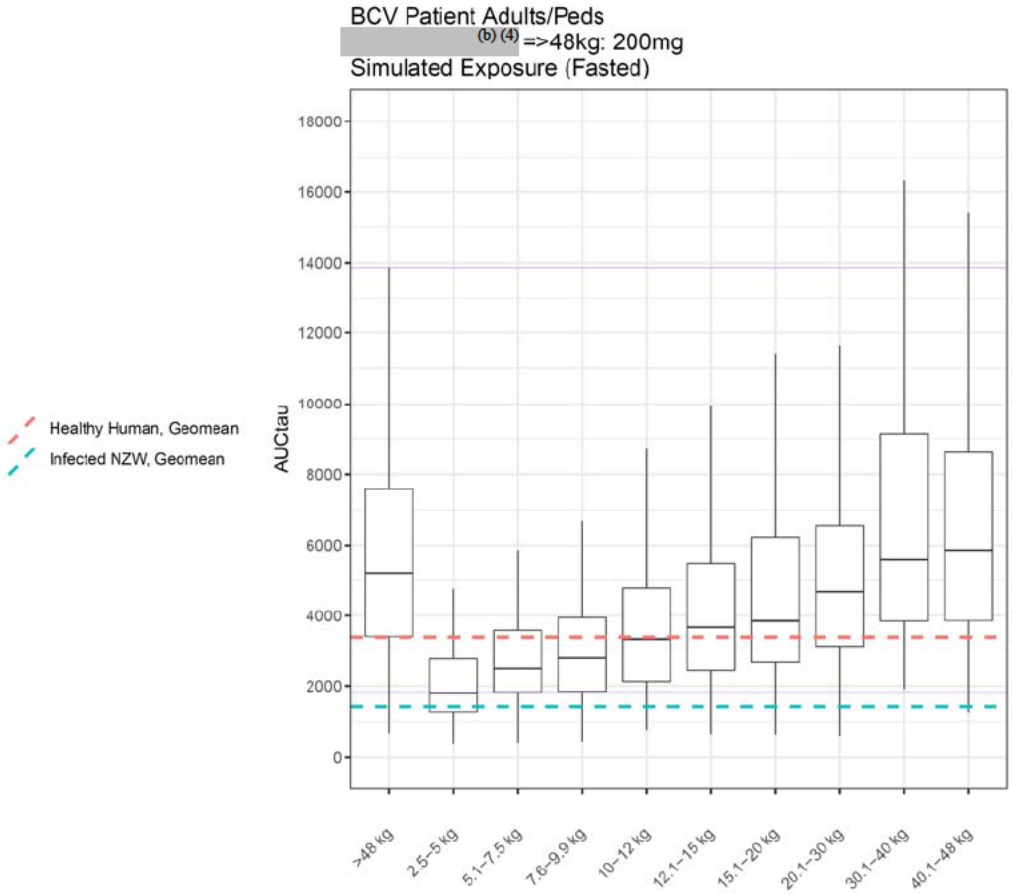
In addition, the Applicant's PopPK analyses show that plasma BCV exposures are expected to be higher in this Phase 2/3 adult patient population with non-orthopoxvirus infection compared to healthy adults, which poses an additional uncertainty in the projected pediatric exposures which were derived for Phase 2/3 pediatric patients. Therefore, we cannot rule out the possibility that plasma BCV exposure in smallpox-infected pediatric patients could be lower than the PopPK -predicted pediatric exposures. As such, the FDA's dose decision making criteria was two-fold: **(i)** to provide the pediatric patients a comparable exposure to adult plasma BCV exposures (healthy subjects and Phase 2/3 patients with non-orthopoxvirus infection) and **(ii)** to ensure that most pediatric patients have exposures greater than the geometric mean fully effective exposures for the infected rabbit model. As body weight is a significant covariate impacting PK of plasma BCV, the dose selection approach was applied across the body weight bands.

Based on the above, we judged there was an increased risk of underexposure in pediatric patients weighing <10 kg with the Applicant's currently proposed dose (b) (4) Subsequently, Agency reviewers conducted additional PK simulations with weight-band guided dosing that address the suboptimal pediatric exposures/dosing described above (Figure 3-4). Based on our findings, we recommend the following pediatric dosing regimen (Table 3-5). See Section 4.4 for more details regarding the Agency's pharmacometrics review and independent analyses.

Table 3-5: Agency's Pediatric Dosing Recommendation

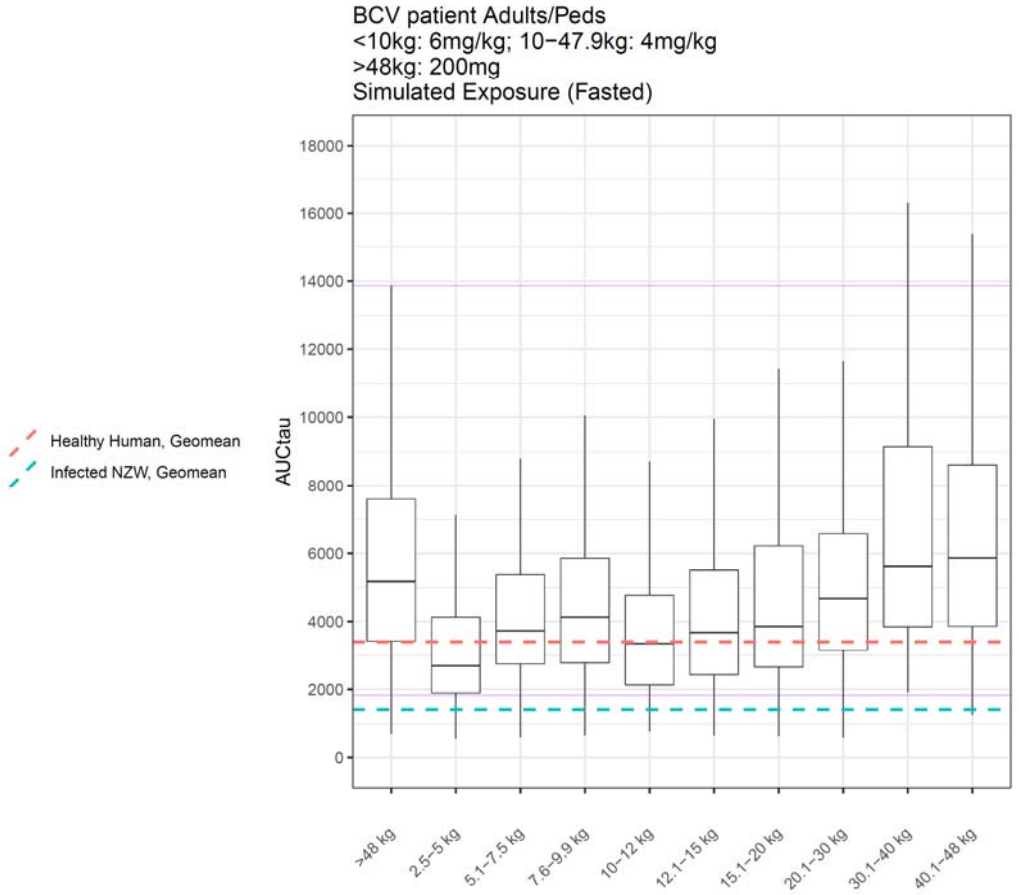
Weight	Dose
<10 kg	6 mg/kg
10 kg to < 48 kg	4 mg/kg
48 kg and above	200 mg

Figure 3-3: Plasma BCV AUC_{tau} by Body Weight Bands in Patients with Non-Orthopoxvirus Infections Following Applicant's Proposed Dosage



Source: FDA reviewer's analysis using the patients PopPK model (BCV-MS-02). Purple lines denote upper and lower bounds of 90% prediction interval of simulated patient adult exposure. Dashed orange line represents the geometric mean AUC_{tau} (3,400 ng*h/mL) for healthy adults. Dashed blue line represents the geometric mean AUC_{tau} (1410 ng*h/mL) for the rabbit model.

Figure 3-4: Plasma BCV AUC_{tau} by Body Weight Bands in Patients with Non-Orthopoxvirus Infections Following Agency's Proposed Dosage



Source: FDA reviewer's analysis using the patients PopPK model (BCV-MS-02). Purple lines denote upper and lower bounds of 90% prediction interval of simulated patient adult exposure. Dashed orange line represents the geometric mean AUC_{tau} (3,400 ng*h/mL) for healthy adults. Dashed blue line represents the geometric mean AUC_{tau} (1410 ng*h/mL) for the rabbit model.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Yes, there are PK food-drug and PK drug-drug interactions (DDI) that potentially pose a clinically significant risk (efficacy loss or adverse events) for TEMBEXA.

FOOD-DRUG INTERACTIONS

TEMBEXA Tablet

BCV, but not CDV-PP, exposures are lower under fed conditions compared to fasted conditions (Crossover Study CMX001-114). A single 200 mg dose of oral BCV tablets was administered under two fed conditions (6% of total calories fat and 22% of total calories fat) and fasted conditions. Plasma BCV mean $AUC_{0\text{-}inf}$ values were 29% and 31% lower after a breakfast containing 6% fat or 22% fat compared to a fasted state, respectively. However, PBMC CDV-PP mean $AUC_{0\text{-}144}$ values were unchanged (1079 pg·h/10^6 cells or 1111 pg·h/10^6 cells) compared to the fasted state (1181 pg·h/10^6 cells). Plasma BCV T_{max} was unchanged in the presence of food.

The Applicant's TEMBEXA tablet administration instructions (b) (4) is generally acceptable considering: **i)** the reduction in plasma BCV is not considered clinically relevant as C_{max} and AUC under the fed state are still greater than the C_{max} and AUC targets/thresholds associated with the fully effective dose in RXPV/rabbits (C_{max}: 330 vs 237 ng/mL and AUC: 2650 vs 1490 ng·h/mL)(source: Clinical Response IR2 – Simulations, submitted 01/29/2021); **ii)** PBMC CDV-PP (the active drug) concentrations were unchanged when TEMBEXA tablets were co-administered with a meal. There will be a slight modification to the label specifying a low-fat meal (approx. 25% of total calories) as the effect of higher fat content meals on BCV or CDV-PP bioavailability is unknown and would represent the worst-case scenario.

TEMBEXA Suspension

No dedicated food-drug interaction study was conducted with the BCV oral suspension formulation. The mechanism of the food-drug interaction found for the Tablet is unknown.

The Applicant originally proposed the BCV oral suspension (b) (4) (b) (4) In the absence of food-drug interaction data regarding the Suspension (potential efficacy loss) and considering the short duration and infrequent dosing schedule of TEMBEXA, we recommended drug administration instructions on an empty stomach. The Applicant agreed.

DRUG-DRUG INTERACTIONS

Summary of In Vitro DDI Studies

The potential of BCV or its metabolites as a substrate, inhibitor, or inducer of membrane transporters and CYP450 metabolism was assessed through in vitro studies consistent with the 2020 FDA In Vitro DDI Guidance. The results suggest BCV is: (i) a substrate of CYP4F2 enzymes and OATP1B1 and OATP1B3 transporters; (ii) an inhibitor of CYP3A enzymes and P-gp transporters in the gut. The Applicant subsequently conducted clinical DDI studies with TEMBEXA to address clinical DDI concerns.

Summary of Clinical PK DDI Studies with TEMBEXA

Effects of other drugs on BCV

- OATP1B1 or 1B3 inhibitor:

In a dedicated Phase 1 DDI study, a single dose of PO 600 mg cyclosporine (CsA; inhibitor) increased the mean BCV C_{max} and $AUC_{0\text{-}inf}$ by 269% and 374%, respectively, when co-administered with TEMBEXA. 600 mg CsA is considered the highest clinical dose (loading dose) and used to determine the likely maximum effects of OATP1B1/3 inhibition on BCV PK.

In an uncontrolled CsA-BCV population PK analysis in Phase 2/3 participants with non-orthopoxvirus infection the final BCV population PK model estimates an increase in the BCV AUC by 43% when BCV is co-administered with various maintenance doses of CsA compared to administration of BCV alone. (b) (4)

- Gastric acid pH modulators (Acid reducing agents; ARA):

BCV is a free acid and exhibits pH-dependent solubility and dissolution (BCV solubility increases as pH increases). Co-administration of BCV with an ARA (e.g., proton pump inhibitor; PPI) theoretically could increase either the rate of absorption or extent of absorption or both resulting in either a higher BCV C_{max} or AUC or both. However, a potential ARA DDI with TEMBEXA is judged not to be clinically important based on TEMBEXA's acceptable safety profile determined from a non-orthopoxvirus infected patient population with 90% receiving PPI therapy with TEMBEXA as well as experience to date, suggesting the magnitude of pH-dependent DDIs for immediate-release products of weak-acid drugs is modest and likely within those experienced in the clinical development program.

Effects of BCV on other drugs

- BCV as CYP3A4 inhibitor: The effect of BCV on the disposition of PO and IV midazolam (CYP3A4 substrate) was minimal (i.e., <12% increase in midazolam exposure).
- BCV as P-gp inhibitor: The effect of BCV on the disposition of PO dabigatran etexilate (P-gp substrate) was minimal (i.e., <14% decrease in total dabigatran exposure).

OVERALL DDI SUMMARY

The review team does not agree with the Applicant (b) (4) Rather, the risk management approach should be "Where possible, consider alternative medication that are not OATP 1B1 or 1B3 inhibitors. If concomitant use with (b) (4) is necessary, increase monitoring for adverse reactions associated with TEMBEXA and postpone the dosing of OATP1B1 or 1B3 inhibitors at least 3 hours after TEMBEXA administration". This approach (b) (4) is judged to be clinically practical given the short duration and infrequent dosing schedule of TEMBEXA.

The following serve as the basis for our position:

(b) (4)

3.3.5 Questions on clinically relevant specifications

Comparison Between Dosage Forms Across Clinical Development Formulations and To-Be-Marketed Formulations

Tablet

Clinical safety data was obtained using a different tablet formulation than the To-Be-Marketed formulation. Therefore, the effect of tablet formulation changes on relative bioavailability between the previous "other indication" Phase 2/3 clinical trials tablet formulation (b) (4) and the final To-Be-Marketed tablet formulation (PCI)was conducted (study CMX001-126). The results from this assessment demonstrated relative bioavailability between the (b) (4) tablet formulation and To-Be-Marketed tablet formulation were similar (90% confidence interval for exposure ratio within the 80% to 125% range). Therefore, PK bridging has been established between the To-Be-Marketed PCI formulation and the previous (b) (4) tablet formulation.

The Applicant's plasma BCV and PBMC CDV-PP PopPK model in healthy adults used human plasma BCV and PBMC CDV-PP concentrations obtained following administration of different clinical development tablet formulations ((b) (4) and the To-Be-Marketed PCI)(Section 4.4.2). The influence of these differences in tablet formulation on bioavailability was not accounted for in the Applicant's models used for human dose selection. This is reasonable, considering that bioavailability was similar across the clinical development tablet formulations. Similar relative bioavailability between the previous (b) (4) tablet formulation and a previous clinical pharmacology (b) (4) tablet formulation was demonstrated (90% confidence interval for exposure ratio within the 80% to 125% range)(study CMX001-115) as well as between the (b) (4) tablet formulation and To-Be-Marketed tablet formulation described above.

Suspension

Clinical PK and safety data were obtained using a different oral suspension formulation than the To-Be-Marketed formulation. Therefore, the effect of oral suspension formulation changes on relative bioavailability between the previous "other indication" Phase 2/3 clinical trials oral suspension formulation (b) (4) and the final To-Be-Marketed oral suspension formulation (b) (4) was conducted (study CMX001-124). The results from this assessment demonstrated similar relative bioavailability between the (b) (4) oral suspension formulation and To-Be-Marketed oral suspension formulation (90% confidence interval for exposure ratio within the 80% to 125% range). Therefore, PK bridging has been established between the To-Be-Marketed PCI formulation and the previous (b) (4) tablet formulation. Note, plasma BCV and PBMC CDV-PP concentration data obtained following administration of these two different oral suspension formulations described above were included in the Applicant's plasma CDV and CDV-PP PopPK model in healthy adults used for human dose selection (Section 4.4.2).

4 APPENDICES

4.1 Summary of Bioanalytical Methods and Validation

HPLC-MS/MS bioanalytical methods were used for quantification of brincidofovir (BCV) and its metabolites in study samples. Methods were adequately validated and included dilution linearity and extraction efficiency (recovery) when applicable. Concentrations were precisely and accurately measured with samples stored and processed in the time frame supported by stability data. Bioanalytical methods and validation results are summarized in Table 4-1.

Table 4-1: Summary of Bioanalytical Method Validation for Brincidofovir and its metabolites

Study No.	CMX001-102	CMX001-103 / 112	CMX001-106 / 108 CMX001-201 /202 / 350
Drug	BCV, CDV, CMX064	BCV, CDV, CMX064	BCV, CDV
Biological Matrix	Plasma		
Anticoagulant	K_2EDTA		
Extraction Methods	acetonitrile/formic acid + SPE		
Internal Standard	$[^2H_6]$BCV, $[^{13}C_2,^{15}N_3]$CDV, $[^2H_6]$CMX064		$[^2H_6]$BCV, $[^{13}C_2,^{15}N_3]$CDV
Validation Range (ng/mL)	BCV: 0.1 to 50 CDV: 2 to 600 CMX064: 1 to 300	BCV: 1 to 300 CDV: 0.5 to 150 CMX064: 1 to 300	BCV: 5 to 1500 CDV: 2.18 to 653
QC Levels (ng/mL)	BCV: 0.1, 0.25, 3, 40 CDV: 2, 5, 50, 480 CMX064: 1, 2.5, 25, 240	BCV: 1, 2.5, 25, 240 CDV: 0.5,1.2 5,12.5, 120 CMX064: 1, 2.5, 25, 240	BCV: 5, 12.5, 125, 1200 CDV: 2.18, 5.4, 54.4, 5223
Inter-day Accuracy (RE%)	BCV: 1.5 to 3 CDV: -6 to -0.6 CMX064: -3.2 to 2	BCV: -2.5 to 2.8 CDV: -1.6 to 9.4 CMX064: -1.2 to 1.6	BCV: -4 to 0 CDV: -3.9 to 11.5
Inter-day Precision (CV%)	BCV: 1.9 to 7.2 CDV: 4.4 to 8 CMX064: 3.5 to 11.7	BCV: 3 to 7.1 CDV: 4.7 to 6.5 CMX064: 2.5 to 6.6	BCV: 2 to 9.5 CDV: 3.1 to 8.1
Validation Report	CMX001-BAN-VAL-010.01	CMX001-BAN-VAL-009.01	CMX001-BAN-VAL-109.01
Study No.	CMX001-113 / 114 / 115 CMX001-301	CMX001-117 CMX001-304	CMX001-116 / 123 / 124 CMX001-125 / 126 / 127
Drug	BCV, CDV		
Biological Matrix	Plasma		
Anticoagulant	K_2EDTA		
Extraction Methods	acetonitrile		

Internal Standard	$[^2H_6]$BCV, $[^{13}C_2,^{15}N_3]$CDV		
Validation Range (ng/mL)	BCV: 1 to 1500 CDV: 2.5 to 750	BCV: 1 to 1000 CDV: 2.5 to 750	BCV: 1 to 750 CDV: 2.5 to 75
QC Levels (ng/mL)	BCV: 1, 3, 125, 1200 CDV: 2.5, 6.25, 62.5, 600	BCV: 1, 3, 75, 750 CDV: 2.5, 7.5, 100, 500	BCV: 1, 2.5, 8, 30, 100, 580 CDV: 2.5, 5, 7, 15, 25, 60
Inter-day Accuracy (RE%)	BCV: -5.4 to 9 CDV: -0.3 to 8	BCV: -1 to 0.3 CDV: -5.6 to 2.6	BCV: -8.35 to -0.13 CDV: -9.76 to -0.51
Inter-day Precision (CV%)	BCV: 2.1 to 14 CDV: 3.8 to 12	BCV: 1.4 to 3.4 CDV: 2 to 9.2	BCV: 2.47 to 9.46 CDV: -3.81 to 7.98
Validation Report	CMX001-BAN-VAL-113.02	BIO-VIR-0163-1358.03	AIUG4 with Addenda

Study No.	CMX001-106	CMX001-118
Drug	BCV	
Biological Matrix	Plasma	
Anticoagulant	K_2EDTA	
Extraction Methods	acetonitrile	
Internal Standard	$[^2H_6]$BCV	
Validation Range (ng/mL)	BCV: 0.5 to 150	BCV: 0.5 to 500
QC Levels (ng/mL)	BCV: 0.5, 1.25, 7.5, 75, 120	BCV: 0.5, 1, 5 ,200, 375
Inter-day Accuracy (RE%)	BCV: -3.9 to 3.4	BCV: -2.8 to 0.46
Inter-day Precision (CV%)	BCV: 1.3 to 3.1	BCV: 2 to 3.3
Validation Report	CMX001-BAN-VAL-114.01	AJKW2

Study No.	CMX001-123 / 124 / 125 CMX001-126 / 210	CMX001-114 CMX001-350	CMX001-102 / 112
Drug	BCV, CDV-PP	BCV, CDV, CDV-PP	BCV, CDV, CMX064
Biological Matrix	PBMC lysate		Urine
Extraction Methods	70/30 methanol water		Acetonitrile/formic acid+SPE
Internal Standard	$[^2H_6]$BCV, $[^{13}C_3,^{15}N_2]$CDV-PP	$[^2H_6]$BCV, $[^{13}C_2,^{15}N_3]$CDV $[^{13}C_3,^{15}N_2]$CDV-PP	$[^2H_6]$BCV, $[^{13}C_2,^{15}N_3]$CDV, $[^2H_6]$CMX064
Validation Range (ng/mL)	BCV: 100 to 10,000[a] CDV-PP: 45.5 to 4550[a]	BCV: 100 to 10,000[a] CDV: 810 to 40,500[a] CDV-PP:45.5 to 4.550[a]	BCV: 1 to 512 CDV: 5 to 1500 CMX064: 5 to 1500
QC Levels (pg/mL)	BCV: 300, 3000, 8500[a] CDV-PP: 136, 1360, 3870[a]	BCV: 100, 300, 3000, 8500[a] CDV: 810, 1220, 12200, 34,400[a] CDV-PP: 45.5, 136, 1360, 3870[a]	BCV: 1.02, 2.56, 51.2, 410 CDV: 5, 15, 250, 1250 CMX064: 5, 15, 250, 1250
Inter-day Accuracy (RE%)	BCV: -3.1 to 8 CDV-PP: -1.5 to 7	BCV: -3.4 to 0 CDV: -4.7 to 1 CDV-PP: 1 to 2	BCV: 0.5 to 11.1 CDV: -2.8 to 6.7 CMX064: -3.4 to 9.3
Inter-day Precision (CV%)	BCV: 5.9 to 10 CDV-PP: 8.2 to 12	BCV: 4.6 to 7.4 CDV: 7.8 to 10 CDV-PP: 5.4 to 11	BCV: 2.3 to 2.8 CDV: 2.9 to 5.1 CMX064: 1.9 to 5.4
Validation Report	#3182	CMX001-BAN-VAL-105.01	CMX001-BAN-VAL-006.02

Study No.	CMX001-NCA-121 /123, CMX001-VIR-122	NCA-123, VIR-122
Drug	BCV, CDV-PP	CDV-PP
Biological Matrix	Plasma, PBMC lysate	PBMC lysate
Anticoagulant	K_2EDTA	--
Extraction Methods	BCV: acetonitrile, CDV-PP:70/30 methanol H_2O	70/30 methanol water
Internal Standard	$[^2H_6]$BCV, $[^{13}C_3,^{15}N_2]$ CDV-PP	$[^{13}C_3,^{15}N_2]$ CDV-PP
Validation Range (ng/mL)	BCV: 1 to 1000; CDV-PP: 45.5 to 4550[a]	45.6 to 2600[a]
QC Levels (ng/mL)	BCV: 3, 75, 750; CDV-PP:135, 773, 3870[a]	137, 912, 2280[a]
Inter-day Accuracy (RE%)	BCV: -1.4 to 4.9; CDV-PP: -1.8 to 11	-2.6 to -1.5
Inter-day Precision (CV%)	BCV: 6.2 to 6.7; CDV-PP: 6.6 to 11	2.2 to 6.8
Validation Report	BAM.0605 STM2310	BAN-VAL-3666

[a] pg/mL

CV% = co-efficient of variation expressed as percent; SPE= solid phase extraction; BCV= brincidofovir; CDV= cidofovir; CDV-PP = cidofovoir diphosphate; PBMC = peripheral blood mononuclear cells; QC = quality control; RE% = relative error expressed as percent.

4.2 Nonclinical Studies

4.2.1 Protein binding

Brincidofovir (BCV) plasma protein binding (PPB) has been studied in CD-1 mouse, Sprague-Dawley rat, New Zealand white rabbit, beagle dog, minipig, cynomolgus monkey, and human plasma (Studies CMX001-NCA-118 and 006: *in vitro* assay) and human plasma (Studies CMX001-106 and 118 *ex vivo* assays). PPB was determined by equilibrium dialysis methods.

BCV was highly bound to plasma proteins (> 99.9%) after equilibrium dialysis against plasma obtained from cynomolgus monkeys or humans at concentrations of 0.1 and 1 µg/mL (Study CMX001-NCA-006). In a separate study (Study CMX001-NCA-108), the estimated percent bound in CD-1 mouse, Sprague-Dawley rat, New Zealand white rabbit, beagle dog, minipig, cynomolgus monkey, and human plasma indicated similar PPB of BCV across species.

In the clinical renal (CMX001-106) and hepatic (CMX001-118) impairment studies, PPB results were consistent with those described above. Relative PPB differences due to organ impairment were not detected. However, preventing a definitive assessment, BCV concentrations in post-dialysis buffer samples were below the limit of quantification (BLQ; 0.5 ng/mL) in all samples.

4.2.2 In vitro metabolism

BCV metabolism has been studied in vitro or ex vivo using human biomaterials. BCV metabolism studies include pooled liver and intestinal microsomes (Study CMX001-NCA-040), hepatocytes (Study CMX001-NCA-037), lung epithelial carcinoma cells, foreskin or lung fibroblast cells (Study CMX001-VIR-077), and recombinant human cytochrome P450 (CYP450) enzymes including CYPs involved in metabolism of medium and long-chain fatty acids (e.g., CYP 4F2) (Studies CMX001-NCA-049 and Study CMX001-NCA-056).

Reviewer's Conclusion

BCV is extensively metabolized via 2 primary pathways: oxidation and hydrolysis (Study CMX001-NCA-037 and Study CMX001-NCA-012). BCV metabolism or stability was concentration-dependent in a pooled hepatocytes model (BCV recovery at 4 h: 48% at 0.56 mcg/mL and 77% at 5.6 mcg/mL) (Study CMX001-NCA-012; Tables 1 and 2, pgs 18 and 19).

BCV hydroxylation is CYP-mediated by the CYP 4F2 isozyme, with subsequent CYP-mediated oxidations, followed by fatty acid β-oxidation (Study CMX001-NCA-049 and Study CMX001-NCA-056). Major circulating human metabolites (CMX103 and CMX064) are thought to be formed through this pathway (Study CMX001-NCA-012). Hepatocytes have greater propensity for BCV metabolism based on 5-fold increase in intrinsic clearance in liver compared to intestinal microsomes (Study CMX001-NCA-040; Table 1, pg 8).

BCV hydrolysis to cidofovir (CDV) is mediated by cleavage at the lipid ester through as yet unidentified esterases (Studies CMX001-NCA-012 and CMX001-NCA-037). Partial involvement by acid sphingomyelinase (ASM) is suggested by in vitro human fibroblast (HFF, MRC-5, HAP1) and human lung epithelial carcinoma (A549) cell systems whereby genetic and chemical inhibition studies demonstrated that the ASM enzyme was critical for conversion of BCV to CDV and antiviral activity via CDV-PP concentrations (CMX001-VIR-077). In particular, CDV and CDV-PP concentrations were reduced by approximately 75% in ASM knockout HAP1 cells compared to parent cell CDV and CDV-PP concentrations. Leading to a significant reduction in antiviral activity against adenovirus (an orthopoxvirus) as measured by the 2,138% increase in the concentration necessary for half-maximal antiviral activity (EC_{50}) in knockout HAP1 cells compared to parent cells. In addition, concentration-

dependent activity was demonstrated with chemical inhibition studies in multiple cell types MRC-5 (lung fibroblasts), HFF (foreskin fibroblasts), and A549 (lung epithelia) that further support ASM's critical role in BCV conversion to CDV. Phospholipase C is not thought to be involved with metabolism of BCV to CDV (Study CMX001-NCA-035).

Intracellular conversion of CDV to the anti-viral moiety CDV-diphosphate (CDV-PP), is postulated to occur via intracellular kinases. No studies were conducted to identify these enzymes.

See Table 4-2 for BCV stability (%) and substrate potential of CYP 450 enzymes.

4.2.3 Evaluation of CYP enzyme-mediated drug-drug interactions

The Applicant conducted in vitro enzyme-mediated drug-drug interaction (DDI) studies providing cytochrome P450 (CYP) inhibition and induction potentials of BCV and its major metabolites CDV, CMX064, and CMX103.

BCV (Studies CMX001-NCA-038 and CMX001-111) and metabolites (Study CMX001-NCA-054) inhibition studies were conducted with pooled human liver microsomes.

BCV and metabolites induction studies were conducted with human donor hepatocyte cultures (Study CMX-NCA-053).

Reviewer's Conclusion:

Based on the 2020 FDA In Vitro DDI Guidance document, in vivo thresholds were determined for BCV as either a victim or perpetrator of potentially significant clinical DDIs (See Table 4-2.). A clinical study was conducted to further evaluate BCV as an inhibitor of the intestinal CYP 3A4 enzyme (See Section 4.3.6). A pharmacogenetic assessment of CYP 4F2 variants on the PK of BCV was conducted showing no dose adjustment necessary (Report CMX001-CP-101 data not shown).

There was no evidence of CDV, CMX 064, and CMX 103 as direct or time-dependent inhibitors (IC_{50} > 100 µM). Lack of an in vivo metabolite-dependent induction potential could not be confirmed as in vitro concentrations of CMX 103 (190 ng/mL) were only 0.73-fold that of systemic plasma concentrations achieved clinically following administration of 200 mg oral BCV. Because of the short duration of dosing this is not a concern.

Model assumptions were as follows: **(i)** dose 200 mg BCV tablet; **(ii)** BCV $C_{max,}$= 561 ng/mL or 1 µM; **(iii)** CDV C_{max} = 28 ng/mL or 100 nM; **(iv)** CMX 064 C_{max} = 180 ng/mL or 425 nM; **(v)** CMX 103 C_{max} = 260 ng/mL or 771 nM; **(vi)** $f_{u,\,p}$ =0.1 based on in vitro plasma protein binding data worst case; **(vii)** nominal in vitro drug concentrations (e.g., IC_{50}). Refer to the 2020 FDA In Vitro DDI Guidance for all equations and other default parameter specifics.

Table 4-2. In Vitro Assessment of BCV as Substrate, Inhibitor, or Inducer of CYP Metabolism

		In Vitro Findings			In Vivo Potential		Applicant Action
Drug	**Enzyme**	% Drug Consumed After Incubation[a]	IC_{50}[b,c] [μM]	Induction FC[d]	Rationale/ Interpretation Reviewer Analysis	Substrate/ Inhibitor/ Inducer	
BCV	CYP1A2	0.6	28	<2	R_1 = 1 < 1.02	---	
	CYP2B6	---	11	<2	R_1 = 1 < 1.02	---	
	CYP2C8	---	4.7		R_1 = 1 < 1.02		
	CYP2C9	---	22		R_1 = 1 < 1.02	---	
	CYP2C19	---	26		R_1 = 1 < 1.02	---	
	CYP2D6	8	24		R_1 = 1 < 1.02	---	
	CYP2J2	---				---	
	CYP3A4/5	---	12	<2	R_1 = 1 < 1.02 $R_{1,gut}$[e] = 238 > 11	Inhibitor	Clinic (M)
	CYP4A11	---				---	
	CYP4F2	35.7	45		>25% consumed R_1 = 1 < 1.02	Substrate	Clinic PG
	CYP4F3a4/5	7.4				---	
	CYP4F3b	10				---	
	CYP4F12	7.1				---	

[a] human recombinant CYP450 Isoenzymes (Study CMX001-NCA-049)
[b] human liver microsome (pooled; n≥16) (Studies CMX001-NCA-038 and CMX001-NCA-111)
[c] no evidence of time-dependent metabolism ($IC_{50,\ 30\ min\ incubation}$ / $IC_{50,\ 30\ min\ incubation\ +\ NADPH}$ < 2)
[d] human hepatocytes (mRNA expression); 3 cell lots up to 1 μM BCV (expected hepatic BCV concentration = 0.3 μM) (Study CMX001-NCA-053)
[e] $[I]_g$ = Dose/250 mL =0.8 mg/mL or 142 μM
IC_{50} = half-maximal inhibitory concentration; FC = fold change; (---) = not significant; R_1 = ratio using basic model of reversable inhibition in liver; $R_{1,gut}$ = ratio using basic model of reversible inhibition in gut; M = midazolam; PG = pharmacogenetic analysis; Clinic = clinical study

4.2.4 Evaluation of Transporter-mediated drug-drug interactions

The Applicant conducted in vitro transporter-mediated drug-drug interaction (DDI) studies providing hepatic and renal transporter substrate and inhibition potentials of BCV and its major metabolites CDV, CMX064, and CMX103.

Studies evaluated OATP1 B1/B3, OAT 1/3, P-gp, and BCRP mediated transport of BCV or BCV metabolites in overexpressing cell culture monolayers or membrane vesicles (Studies CMX001-NCA-039, CMX001-NCA-045, CMX001-NCA-046, CMX001-NCD-055b, and CMX001-NCA-058).

Studies evaluated OATP1 B1/B3, OAT 1/3, P-gp, BCRP, MRP2, BSEP, OCT2, MATE1, and MATE2-K transport inhibition by BCV or BCV metabolites in in overexpressing cell culture monolayers or membrane vesicles (Studies CMX001-NCA-045, CMX001-NCA-046, CMX001-NCA-112, CMX001-NCA-055a,

Reviewer's Conclusion:

Based on the 2020 FDA In Vitro DDI Guidance document, in vivo thresholds were determined for BCV as either a victim or perpetrator of potentially significant clinical DDIs (Table 4-3). A clinical study was conducted to further evaluate BCV as an inhibitor of the intestinal P-gp transporter (See Section 4.3.6).

Consistent with prior knowledge, CDV was found to be a substrate of OAT1 (net flux ratio 8.5) but not OAT3 (net flux ratio < 2). CDV, CMX 064, and CMX 103 were not found to be substrates or inhibitors of

membrane drug transporters studied (< 2-fold flux rate ratio and generally no inhibition observed at 20 µM; max 26%).

Model assumptions were as follows: **(i)** dose 200 mg BCV tablet; **(ii)** BCV $C_{max,}$= 561 ng/mL or 1 µM; **(iii)** CDV C_{max} = 28 ng/mL or 100 nM; **(iv)** CMX 064 C_{max} = 180 ng/mL or 425 nM; **(v)** CMX 103 C_{max} = 260 ng/mL or 771 nM; **(vi)** $f_{u,\ p}$ =0.1 based on in vitro plasma protein binding data worst case; **(vii)** k_a = 0.84 hr^{-1}; **(viii)** F_a = 0.92; **(ix)** F_g = 0.2; **(x)** nominal in vitro drug concentrations (e.g., IC_{50}). Refer to the 2020 FDA In Vitro DDI Guidance for all equations and other default parameter specifics. The BCV F_a, and F_g were predicted from the BCV human mass balance study (Section 4.3.1). BCV k_a and F_h values were obtained from study reports BCV-MS-02 and CMX001-127.

Table 4-3: In Vitro Assessment of BCV as Substrate or Inhibitor of Human Uptake and Efflux Transporters

	In Vitro Findings				
Transporter	Max Flux Rate Ratio	IC_{50} [µM]	**In Vivo Potential Substrate/Inhibitor**	**Rationale/Interpretation Reviewer Analysis**	**Applicant Action**
BCRP	---	20.2	Inhibitor	I_{gut} / IC_{50} =72 ≥ 10[c]	
P-gp	---	11.1	Inhibitor	I_{gut} / IC_{50} =129 ≥ 10[c]	Clinical (D)
MRP2	NT	81.4	---	[b]	
BSEP	NT	73.4	---	[b]	
OATP1B1	3.8	20.9	Substrate	ER > 2 R = 1.00 < 1.1[d]	
OATP1B3	6.3	>30	Substrate	ER > 2 R = 1.00 < 1.1[d]	
OAT1	---	122	---	$I_{max,\ u}$ / IC_{50} < 0.00 < 0.1	
OAT3	---	12.3	---	$I_{max,\ u}$ / IC_{50} < 0.00 < 0.1	
OCT2	NT[a]	>30	---	$I_{max,\ u}$ / IC_{50} < 0.00 < 0.1	
MATE1	NT[a]	>30	Inhibitor	$I_{max,\ u}$ / IC_{50} < 0.00 < 0.1	
MATE2	NT[a]	>30	---	$I_{max,\ u}$ / IC_{50} < 0.00 < 0.1	

[a] renal clearance <25% of total BCV clearance
[b] Not specified in FDA in vitro DDI guidance
[c] $[I]_g$ = Dose/250 mL =0.8 mg/mL or 142 µM
[d] $[I]_{in,\ max}$ = 1 µg/mL or 1.8 µM; estimated max plasma concentration of inhibitor at the inlet to the liver.
IC_{50} = half-maximal inhibitory concentration; $I_{max,\ u}$ = maximum unbound plasma concentration of interacting drug at steady-state; FC = fold change; (---) = not significant; NT = not tested; R = ratio using basic model of reversable inhibition in liver and $[I]_{in,\ max}$; D = dabigatran etexilate

4.2.5 Pharmacokinetics

4.2.5.1 New Zealand White Rabbits

Healthy Rabbits

Study NCA-121 was a PK study conducted in healthy rabbits to measure plasma BCV and peripheral blood mononuclear (PBMC) cell CDV-PP concentrations following BCV solution administration via oral syringe. Healthy rabbits were 16 weeks old and weighed between 2.5 kg and 3 kg at the initiation of dosing.

Study Groups:

- Group 1 = 20 mg/kg BCV on Day 1 (n=6; 3 female)
- Group 2 = 20 mg/kg BCV on Day 1, 5 mg/kg BCV on Day 3, and 5 mg/kg BCV on Day 5 (n=6; 3 female)

(K_2) EDTA anticoagulated blood was collected for each healthy rabbit via vascular access port to measure plasma BCV concentrations at 5 in-series time points (30 min to 12 hr) on Day 1 for Group 1 and at 6 in-series time points (pre-dose to 12 hr) on Day 5 for Group 2.

Sodium citrate anticoagulated blood was collected for each healthy rabbit via vascular access port to measure PBMC CDV-PP concentrations at 5 in-series time points (12 hr to 120 hr) on Day 1 for Group 1 and at 5 in-series time points (pre-dose to 120 hr) on Day 5 for Group 2. Non-compartmental PK analyses were performed.

Table 4-4: PBMC CDV-PP PK Parameters after BCV administration

Exposure / PK Parameter	Group 1 (n=6) 20 mg/kg BCV	Group 2 (n=5) 5 mg/kg BCV[a]
C_{max} (pg/10^6 cells)	4.57 (40%) [1.78, 6.66]	3.86 (36%) [2.74, 6.28]
T_{max} (hr)	24 [12, 48]	24[b] [24, 24]
AUC_{last} (hr·pg/10^6 cells)	279 (52%) [86, 36]	235 (41%) [152, 400]

Data presented as arithmetic mean (%CV) [min, max], except T_{max} and T_{last} reported as median [min, max]
[a]Exposure / PK parameters in 20/5/5 mg/kg group are related to the last 5 mg/kg dose
[b]24 hr was the first time point in this group

Table 4-5: Plasma BCV PK Parameters after BCV administration

Exposure / PK Parameter	Group 1 (n=6) 20 mg/kg BCV	Group 2 (n=6) 5 mg/kg BCV[a]
C_{max} (ng/mL)	361 (19%) [273, 456]	53.5 (46%) [20.3, 95.3]
T_{max} (hr)	1 [1, 2]	1 [1, 2]
AUC_{last} (hr·ng/mL)	1178 (12%) [988, 1414]	220 (47%) [43.1, 352]

Data presented as arithmetic mean (%CV) [min, max], except T_{max} and T_{last} reported as median [min, max]
[a]Exposure / PK parameters in 20/5/5 mg/kg group are related to the last 5 mg/kg dose
[b]12 hr was the first time point in this group

Study NCA-123 was a PK study conducted in healthy rabbits to measure plasma BCV and peripheral blood mononuclear (PBMC) cell CDV-PP concentrations following BCV solution administration via oral syringe. Healthy rabbits were 16 weeks old and weighed between 2.2 kg and 3 kg at the initiation of dosing.

Study Groups:

- Group 1 = 20 mg/kg BCV on Day 1 (n=12; 6 female)
- Group 2 = 20 mg/kg BCV on Day 1, 5 mg/kg BCV on Day 3, and 5 mg/kg BCV on Day 5 (n=12; 6 female)

(K_2) EDTA anticoagulated blood was collected for each healthy rabbit via vascular access port to measure plasma BCV concentrations at 5 in-series time points (30 min to 12 hr) on Day 1 for Group 1 and at 6 in-series time points (pre-dose to 12 hr) on Day 5 for Group 2.

Sodium citrate anticoagulated blood was collected for each healthy rabbit via vascular access port to measure PBMC CDV-PP concentrations at 5 in-series time points (12 hr to 120 hr) on Day 1 for Group 1 and at 5 in-series time points (pre-dose to 120 hr) on Day 5 for Group 2. Non-compartmental PK analyses were performed.

Table 4-6: PBMC CDV-PP PK Parameters after BCV administration

Exposure / PK Parameter	Group 1 (n=11) 20 mg/kg BCV	Group 2 (n=6) 5 mg/kg BCV[a]
C_{max} (pg/10^6 cells)	4.95 (35%) [2.27, 7.52]	3.25 (39.2%) [1.77, 5.05]
T_{max} (hr)	24 [24, 72]	24 [0, 24]
AUC_{last} (hr·pg/10^6 cells)	195 (38.9%) [70.8, 341]	149 (43.1%) [77.3, 257]

Data presented as arithmetic mean (%CV) [min, max], except T_{max} reported as median [min, max]
[a]Exposure / PK parameters in 20/5/5 mg/kg group are related to the last 5 mg/kg dose

Table 4-7: Plasma BCV PK Parameters after BCV administration

Exposure / PK Parameter	Group 1 (n=12) 20 mg/kg BCV	Group 2 (n=12) 5 mg/kg BCV[a]
C_{max} (ng/mL)	527 (49.3%) [163, 921]	84.2 (59.2%) [34.5, 227]
T_{max} (hr)	1 [1, 4]	1 [1, 4]
AUC_{last} (hr·ng/mL)	1810 (34.2%) [644, 2570]	310 (45.1%) [79.7, 586]

Data presented as arithmetic mean (%CV) [min, max], except T_{max} reported as median [min, max]
[a]Exposure / PK parameters in 20/5/5 mg/kg group are related to the last 5 mg/kg dose

The average trough CDV-PP concentration following the second 5 mg/kg oral BCV dose was 2.15 [range: 1.06 to 3.83 pg/10^6 cells in all 12 mice supporting the reported results for Group 2 in Table 4-6 above following the last maintenance dose of 5 mg/kg oral BCV.

Rabbitpox (Utrecht Virus Strain)
Study VIR-122 was a PK study conducted in intradermally inoculated rabbits with rabbitpox virus (600 PFU) to measure plasma BCV and peripheral blood mononuclear (PBMC) cell CDV-PP concentrations following BCV solution administration via oral syringe. Infected rabbits were 16 weeks and 5 days old and weighed between 2.05 kg and 2.6 kg at baseline to establish doses.
Study Groups were as follows:

- Group 1 = 20 mg/kg BCV on post-inoculation Day 4 (n=12; 6 female)
- Group 2 = 20 mg/kg BCV on Day 1, 5 mg/kg BCV on Day 3, and 5 mg/kg BCV on post-inoculation Day 4 (n=12; 6 female)

(K_2) EDTA anticoagulated blood was collected for each healthy rabbit via vascular access port to measure plasma BCV concentrations at 5 in-series time points (30 min to 12 hr) on Day 1 for Group 1 and at 6 in-series time points (pre-dose to 12 hr) on Day 5 for Group 2.

Sodium citrate anticoagulated blood was collected for each healthy rabbit via vascular access port to measure PBMC CDV-PP concentrations at 5 in-series time points (12 hr to 120 hr) on Day 1 for Group 1 and at 5 in-series time points (pre-dose to 120 hr) on Day 5 for Group 2. Non-compartmental PK analyses were performed.

Table 4-8: PBMC CDV-PP PK Parameters after BCV administration

Exposure / PK Parameter	Group 1 (n=12) 20 mg/kg BCV	Group 2 (n=12) 5 mg/kg BCV[a]
C_{max} (pg/10^6 cells)	6.86 (32.7%) [3.23, 12]	6.17 (56.6%) [2.96, 15.5]
T_{max} (hr)	12 [12, 48]	24 [0, 24]
AUC_{last} (hr·pg/10^6 cells)	362 (28.2%) [229, 533]	413 (49.9%) [173, 928]

Table 4-9: Plasma BCV PK Parameters after BCV administration

Exposure / PK Parameter	Group 1 (n=12) 20 mg/kg BCV	Group 2 (n=12) 5 mg/kg BCV[a]
C_{max} (ng/mL)	185 (40.3%) [97.1, 342]	15.2 (59.8%) [2.62, 31.1]
T_{max} (hr)	2 [1, 4]	2 [0.5, 4]
AUC_{last} (hr·ng/mL)	709 (31.4%) [462, 1210]	74.3 (67.3%) [11.2, 183]

Data presented as arithmetic mean (%CV) [min, max], except T_{max} reported as median [min, max]
[a]Exposure / PK parameters in 20/5/5 mg/kg group are related to the last 5 mg/kg dose

Table 4-10: Viral Blood Burden measured by Whole Blood qPCR

Study Group	Prior to First Treatment Viral Load (Viral HA gene copies/mL)
Group 1	1.34×10^4 (99%) [134, 4.39×10^4]
Group 2	1.11×10^4 (78.3%) [426, 2.79×10^4]
Combined	1.23×10^4 (90%) [134, 4.39×10^4]

Data presented as arithmetic mean (%CV) [min, max]

One animal from Group 1 (20 mg/kg BCV x 1) died. This animal had the largest viral load prior to first treatment (4.39×10^4 copies/mL). The rest survived till the end of study (Day 14).

4.3 Clinical Studies

4.3.1 ADME

Mass Balance

Study CMX001-112 was a single, oral dose of ^{14}C-radiolabeled BCV in six healthy male subjects 22 to 34 years of age. Oral drug (40 mL solution [197 mg (~100 µCi)]) was administered with 240 mL of water after an overnight fast of ≥ 8 hr.

Blood, urine, and fecal samples were collected up to 336 hr postdose to measure total radioactivity (whole blood, plasma, urine, and feces), BCV and metabolites CDV, CMX064, CMX103, CMX104, CMX105, CMX106 concentrations (plasma and urine) and metabolic profiles (plasma, urine, and feces). Percentages described below refer to % of dose.

- Mean radioactive recoveries in total excreta (urine+feces), urine, and feces
  - 91.1% (min to max: 90.1% to 92.4%), 50.7%, and 40.4% respectively
- The blood to plasma ratio ranged from 0.479 to 0.609
- Circulating plasma radioactivity (plasma AUC/ blood AUC radioactivity-ng equivalents)
  - CMX103 (32%), BCV (22%), CMX064 (23%), CDV (5%)
- Parent/Metabolite profiling and identification in excreta (urine or feces)
  - No parent BCV was detected in excreta
    - 43% metabolized through ASM hydrolysis pathway to form CDV
    - 49% metabolized through CYP4F2 pathway to form other identified metabolites
  - Major BCV-derived metabolites in urine: CMX103 (21%), CDV (10%), CMX064 (10%)
  - Major BCV-derived metabolites in feces: CDV (32%) and CMX103 (6%)
- Median terminal half-life
  - BCV: 21.7 hr
  - CDV: 64.1 hr

4.3.2 Single Ascending Dose

Study CMX001-102 was a randomized, double-blind, placebo-controlled, single-dose and limited multidose, dose escalation study to evaluate the safety and PK of BCV in 54 (n=18 placebo, 36 BCV) healthy males approximately 30.7 (range: 19 to 50) years of age and weighing approximately 82 (range: 55 to 103) kg.

There were 4 subjects in 9 BCV dosing cohorts of an oral solution formulation as follows: 25 µg/kg [~2.1 mg], 50 µg/kg [~4.0 mg], 100 µg/kg [~8.6 mg], 200 µg/kg [~16.5 mg], 400 µg/kg [~31.0 mg], 600 µg/kg [~50.2 mg], 1000 µg/kg [~84.7 mg], 1500 µg/kg [~117.3 mg], and 2000 µg/kg [~161.6 mg].

Table 4-11: PK Parameters [Geo Mean (%GCV)] of plasma BCV

Dose (mg/kg)	C_{max} (ng/mL) n=4	AUC_{last} (ng·h/mL) n=4
0.025	2.34 (21.9)	16.5 (17.6)
0.05	4.81 (23.2)	33.6 (14.5)
0.1	9.82 (20.5)	126 (20)
0.2	24.2 (7)	223 (8.8)
0.4	62.7 (22.2)	514 (11.5)
0.6	111 (13.4)	687 (14.8)
1	246 (24.3)	1220 (23.4)
1.5	340 (21)	2080 (23.7)
2	330 (18.7)	2580 (7.5)

Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; AUC_{last} = area under the plasma concentration-time curve from. time zero to time of last measurable concentration; C_{max} = maximum plasma concentration of drug; PK = pharmacokinetic; BCV = brincidofovir
Source: Study report CMX001-102 – Table 14.2.5 (pg 94-98) and dataset CMX001-102-PP (reviewer's calculation of %GCV).

Table 4-12: BCV Dose Proportionality (ANOVA)

Exposure Parameter	Dose Range (mg/kg)	P-value[a]	Dose-Proportional
Ln C_{max} / dose	0.025 to 2	0.0251	No
	0.025 to 0.4	0.4701	Yes
	0.4 to 2	0.5875	Yes
Ln AUC_{last} / dose	0.025 to 2	0.0605	Yes
	0.025 to 0.05	0.9492	Yes
	0.1 to 2	0.9858	Yes

AUC_{last} = area under the plasma concentration-time curve from time zero to time of last measurable concentration; C_{max} = maximum plasma concentration of drug; BCV = brincidofovir
[a] Probability of dose-effect (F-Test, $\alpha = 0.05$)
Source: Study report CMX001-102 – Table 15 (pg 54).

Table 4-13: BCV Dose Proportionality (Power Model)

Exposure Parameter	Dose Range (mg/kg)	Estimated Slope	95% CI of Slope		P-value[a]	Dose-Proportional
			Lower	Upper		
Ln C_{max} / dose	0.025 to 2	1.217	1.116	1.318	0.0001	No
	0.025 to 0.4	1.182	0.98	1.384	0.074	Yes
	0.4 to 2	1.098	0.733	1.464	0.578	Yes
Ln AUC_{last} / dose	0.025 to 2	1.151	1.064	1.238	0.0012	No
	0.1 to 2	1.03	0.894	1.166	0.6511	Yes

AUC_{last} = area under the plasma concentration-time curve from. time zero to time of last measurable concentration; C_{max} = maximum plasma concentration of drug; BCV = brincidofovir
[a] Probability of dose-effect (F-Test, $\alpha = 0.05$; H_o: Slope =1)
Source: Study report CMX001-102 – Table 16 (pg 54).

Reviewer's Conclusion:

There are limitations to the classical hypothesis test with the power model, which the Applicant used to assess dose proportionality. The method is limited by estimator imprecision/ variability that leads to large confidence intervals of the estimated slope. Based on this reviewer's independent dose proportionality analysis with a decision criterion, an approximate dose proportionality is observed (Table 4-14).

Table 4-14: Reviewer's Independent Dose Proportionality Analyses (Power Model)

Exposure Parameter	Dose Range (mg/kg)	Estimated Slope	90% CI of Slope		Equivalent Limits[a]		Dose-Proportional
			Lower	Upper	Lower	Upper	
Ln C_{max} / dose	0.025 to 2	1.22	1.13	1.30	0.699	1.3	Yes
Ln AUC_{last} / dose	0.025 to 2	1.15	1.08	1.22	0.699	1.3	Yes

AUC_{last} = area under the plasma concentration-time curve from. time zero to time of last measurable concentration; C_{max} = maximum plasma concentration of drug; BCV = brincidofovir
Method: Data were log transformed. The equation for the power model used for the log Cmax or log AUC = log (μ) + β log dose +ε; where log(μ) and β are the intercept and slope, respectively.
[a] Pre-defined equivalents criterion values of 0.5 and 2 were used to calculate the slope equivalent limits.

4.3.3 Dose Proportionality (Also discussed above)

Applicant states an increase in exposure, following an increase in dose, was demonstrated at clinical doses in both the suspension and tablet formulations (Table 4-15). Based on these general trends the Applicant states that the BCV exposure was generally dose proportional from 100 to 350 mg. Differences in exposures across studies may be related to differences in formulation and demographics (e.g., males versus females and body weight) between studies, as these factors were shown to impact BCV PK.

Table 4-15: Plasma BCV Exposures Across Doses by Product Formulation

	BCV Tablet						BCV Suspension	
	100 mg		200 mg			350 mg	100 mg	200 mg
Parameter	Study 115	Study 126	Study 106	Study 108	Study 114	Study 108	Study 124	Study 127
AUC_{inf} (ng·h/mL)	1380 (40.7)	2828 (35.7)	3985 (30.4)	3616 (35.9)	3307 (38.8)	7263 (26.6)	2908 (42.1)	4536 (41.1)
C_{max} (ng/mL)	258 (42.3)	534 (37.4)	820 (31.5)	802 (38.3)	622 (33.7)	1482 (34)	493 (35.7)	814 (40.9)

Data are presented as geometric mean with geometric coefficient of variation expressed as percent.
AUC_{inf} = area under the concentration-time curve from time 0 to infinity after drug administration; AUC_{last} = area under the plasma concentration-time curve from. time zero to time of last measurable concentration; C_{max} = maximum plasma concentration of drug; PK = pharmacokinetic; BCV = brincidofovir
Source: Summary of Clinical Pharmacology Studies; Table 15; pg 49.

Reviewer's Conclusions:

To better explore and quantify dose proportionality trends the Reviewer conducted his own analysis using the power model on the exposure parameters in the above studies. For the purposes of this review a general dose-proportional PK trend is reasonable to assume based on the data below in addition to linear elimination kinetics determined from population PK modeling (See Section 4.4.2). For the tablet, the BCV C_{max} and AUC increased approximately dose proportionally (Table 4-16). For the

suspension, a dose increase of 100% resulted in an increase in BCV C_{max} and AUC of approximately 0.7 (slightly less than proportional to dose) (Table 4-17). The reviewer agrees that the sub-proportional increase in the BCV suspension may be the result of an imbalance of males to females. Body weight affects BCV PK (see Section 4.4). Greater body weight results in lower BCV exposures. Males generally display greater body weight and thus lower exposures compared to females. Study CMX001-124 consisted of 44 females and 2 males. Study CMX001-127 consisted of 24 males and no females.

Table 4-16: Reviewer's Independent Dose Proportionality Analyses (Power Model) for BCV Tablet

Exposure Parameter	Dose Range (mg/kg)	Estimated Slope	90% CI of Slope		Equivalent Limits[a]		Dose-Proportional
			Lower	Upper	Lower	Upper	
Ln C_{max} / dose	100 to 350	1.14	1.05	1.22	0.699	1.3	Yes
Ln AUC_{last} / dose	100 to 350	1.04	0.96	1.13	0.699	1.3	Yes

AUC_{last} = area under the plasma concentration-time curve from. time zero to time of last measurable concentration; C_{max} = maximum plasma concentration of drug; BCV = brincidofovir

[a] Pre-defined equivalents criterion values of 0.5 and 2 were used to calculate the slope equivalent limits.

Source: datasets CMX001-115-PP, CMX001-126-PP, CMX001-106-PP, CMX001-108-PP, CMX001-114-PP

Method: Data were log transformed. The equation for the power model used for the log C_{max} or log AUC = log (μ) + β log dose +ε; where log(μ) and β are the intercept and slope, respectively.

Table 4-17: Reviewer's Independent Dose Proportionality Analyses (Power Model) for BCV Suspension

Exposure Parameter	Dose Range (mg/kg)	Estimated Slope	90% CI of Slope		Equivalent Limits[a]		Dose-Proportional
			Lower	Upper	Lower	Upper	
Ln C_{max} / dose	100 to 200	0.7	0.47	0.93	0.699	1.3	No
Ln AUC_{last} / dose	100 to 200	0.72	0.48	0.96	0.699	1.3	No

AUC_{last} = area under the plasma concentration-time curve from. time zero to time of last measurable concentration; C_{max} = maximum plasma concentration of drug; BCV = brincidofovir

[a] Pre-defined equivalents criterion values of 0.5 and 2 were used to calculate the slope equivalent limits.

Source: datasets CMX001-124-PP, CMX001-127-PP

Method: Data were log transformed. The equation for the power model used for the log C_{max} or log AUC = log (μ) + β log dose +ε; where log(μ) and β are the intercept and slope, respectively.

4.3.5 Bioavailability

Absolute Bioavailability

Study CMX001-127 was an open-label, randomized, single-dose, two-period, crossover study evaluating the absolute bioavailability of BCV (b) (4) Suspension compared to BCV IV.

Part A: 200 mg BCV oral suspension compared to 20 mg BCV IV infused over 2 hours to 24healthy adults weighing 81.8 (range: 57 to 108) kg and 34 (range: 19 to 52) years of age.

Individuals were fasted overnight for ca. 10 hr before drug administration. Fasting continued ca. 4 hr postdose. The washout period between periods was at least 21 days between doses. Plasma BCV and CDV (data not shown) and PBMC CDV-PP PK samples were collected up to 96 hr postdose.

Table 4-18: Part A BCV PK Parameters After Single PO Administration of 200 mg BCV (b) (4) Suspension and IV Administration of 20 mg BCV infused over 2 hours.

Parameter	(b) (4) Suspension (T) Geo Mean (%GCV)	IV (R) Geo Mean (%GCV)	T/R GeoMean Ratio (%) (90% CI)
AUC_{inf} (ng·hr·mL^{-1})	4536 (41.1)[a]	2807 (24.8)[b]	NC
C_{max} (ng·mL^{-1})	814 (40.9)[a]	1070 (19.7)[b]	NC
$T_{1/2}$ (h)	19.3 (40.6)[a]	5.9 (36.1)[b]	NC
Dose-normalized AUC_{inf} (ng·hr·mL^{-1}/ mg)	23.6[c]	140[c]	16.8 (15.2 to 18.5)

[a]n =24
[b]n =22
[c]Geometric mean %
Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; AUC_{inf} = area under the concentration-time curve from time 0 to infinity after drug administration; C_{max} = maximum plasma concentration of drug; $T_{1/2}$ = half-life; CI = confidence interval; NC = not calculated; PK = pharmacokinetic; BCV = bincidofovir
Source: Study Report CMX001-127. Tables 12 (pg. 74) and 15 (pg. 78).

Table 4-19: Part A CDV PK Parameters After Single PO Administration of 200 mg BCV (b) (4) Suspension and IV Administration of 20 mg BCV infused over 2 hours.

Parameter	(b) (4) Suspension Geo Mean (%GCV)	IV Geo Mean (%GCV)
AUC_{last} (ng·hr·mL^{-1})	1506 (22.9)[a]	131 (78.4)[b]
C_{max} (ng·mL^{-1})	35.8 (21.9)[a]	4.87 (25.3)[b]
$T_{1/2}$ (h)	47.19 (21.2) [a]	28.44 (28.6) [b]

[a]n =24
[b]n =22
[c]Geometric mean %
Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; AUC_{last} = area under the plasma concentration-time curve from. time zero to time of last measurable concentration; C_{max} = maximum plasma concentration of drug; $T_{1/2}$ = half-life; CI = confidence interval; NC = not calculated; PK = pharmacokinetic; BCV = bincidofovir
Source: Study Report CMX001-127. Tables 16 (pg. 84) and 18 (pg. 87).

Table 4-20: Part A CDV-PP PK Parameters After Single PO Administration of 200 mg BCV (b) (4) Suspension and IV Administration of 20 mg BCV infused over 2 hours.

Parameter	(b) (4) Suspension Geo Mean (%GCV)	IV Geo Mean (%GCV)
AUC_{last} (pg·hr·10^6 cells^{-1})	2052 (35.2)[a]	717 (43.5)[b]
C_{max} (pg·10^6 cells^{-1})	16.6 (45)[a]	7.45 (72.9)[b]
T_{max} (h)[c]	47.3 (22.6 to 310.8)[a]	23.4 (22.5 to 71.5)[b]
$T_{1/2}$ (h)	112.9 (34.2)	86.2 (20.1)

[a]n =24
[b]n =13
[c] T_{max} presented as median (range)
Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; AUC_{lastf} = area under the plasma concentration-time curve from. time zero to time of last measurable concentration; C_{max} = maximum plasma concentration of drug; T_{max} = time to maximum observed concentration; $T_{1/2}$ = half-life; NC = not calculated; PK = pharmacokinetic; CDV-PP = cidofovir diphosphate
Source: Study Report CMX001-127. Tables 14 (pg. 77)

Food Effect and Relative Bioavailability (BA)

Study CMX001-114 was an open-label, randomized, four-period, single-dose, crossover study in 24 enrolled healthy subjects (24; 100% male) 20 to 51 years of age.

The washout time between periods was at least 21 days. Eighteen BCV and CDV plasma PK samples were collected up to 312 hr postdose. Six PBMC BCV and CDV-PP PK samples were collected up to 144 hr postdose (dose period 1-3) or 312 hr postdose (dose period 4).

Table 4-21: Study Design

Treatment Sequence	Dose Period 1	Dose Period 2	Dose Period 3	Dose Period 4
1	A	B	C	D
2	B	D	A	C
3	C	A	D	B
4	D	C	B	A

Treatment A = Single 200 mg dose of BCV administered as 2 x 100 mg tablets under fasting condition (≥10 hr prior to dosing and 4 hr after)
Treatment B = Single 200 mg dose of BCV administered as 2 x 100 mg tablets after a 6%-fat meal (total caloric content)
Treatment C = Single 200 mg dose of BCV administered as 2 x 100 mg tablets after a 22%-fat meal (total caloric content)
Treatment D = Single 200 mg dose of BCV administered as 20 mL (10 mg/mL) (b) (4) suspension (≥10 hr prior to dosing and 4 hr after)

Table 4-22. PK Parameters [Geo Mean (%GCV)] After a Single 200 mg Oral BCV Dose and by Treatment

	Treatment			
Parameter	**A (n=15)**	**B (n=12)**	**C (n=15)**	**D (n=14)**
Plasma BCV				
AUC_{inf} (ng·h/mL)	3307 (38.8)	2213 (49.2)[a]	2183 (41.6)[a]	3419 (52.1)[b]
C_{max} (ng/mL)	622 (33.7)	399 (49.3)	305 (34.5)	657 (42.5)
T_{max} (h)	4 (3 to 6)	5 (3 to 6)	4 (3 to 8)	3 (2 to 6)
Plasma CDV				
AUC_{last} (ng·h/mL)[c]	1437 (16.1)	1237 (23.9)	1213 (19.5)	1645 (13.1)
C_{max} (ng/mL)	28.5 (9.6)	23.6 (18.3)	22.7 (15.3)	31.9 (13)
T_{max} (h)	12 (8 to 12)	12 (10 to 16)	12 (8 to 16)	12 (8 to 12)
	A (n=15)	**B (n=16)**	**C (n=18)**	**D (n=21)**
PBMC BCV				
AUC_{last} (pg·h/10^6 cells)[c]	1204 (46.8)	1180 (43.5)	1042 (61.8)	1399 (52.1)
C_{max} (pg/10^6 cells)	28.4 (55.9)	24.2 (47.1)	22.2 (49.7)	31.2 (39.1)
T_{max} (h)	24 (24 to 48)	24 (24 to 48)	24 (24 to 48)	24 (24 to 24)
PBMC CDV-PP				
AUC_{last} (pg·h/10^6 cells)[c]	1323 (70.5)	1135 (62.9)	1188 (48.7)	2099 (43.4)
C_{max} (pg/10^6 cells)	11.7 (50.8)	12 (55.2)	11.2 (38)	16.1 (42.7)
T_{max} (h)	72 (48 to 144)	72 (48 to 144)	72 (48 to 144)	72 (48 to 145)

Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; AUC_{inf} = area under the concentration-time curve from time 0 to infinity after drug administration; AUC_{last} = area under the plasma concentration-time curve from. time zero to time of last measurable concentration; C_{max} = maximum plasma concentration of drug; PK = pharmacokinetic;
[a]n=11
[b]n=13
[c]AUC_{last} was used because concentration-time profiles did not allow for estimation of terminal elimination phase
Treatment A = Single 200 mg dose of BCV administered as 2 x 100 mg tablets under fasting condition
Treatment B = Single 200 mg dose of BCV administered as 2 x 100 mg tablets after a low-fat meal
Treatment C = Single 200 mg dose of BCV administered as 2 x 100 mg tablets after a low-fat meal
Treatment D = Single 200 mg dose of BCV administered as 20 mL (10 mg/mL) suspension
Source: Study report CMX001-114; Table 8 (pg. 51), Table 9 (pg. 52), Table 10 (pg. 53), and Table 11 (pg. 54)

Table 4-23. Statistical Comparisons [Geo Mean ratio % (90% CI)] of Plasma BCV Exposure Measures by Treatment (Relative BA)

	Treatment		
Parameter	**B / A**	**C / A**	**D / A**
BCV			
AUC_{inf}	71 (58.3, 86.4)	68.7 (60.3, 78.3)	117.2 (104.9, 130.8)
C_{max}	68.4 (56.3, 83.0)	51 (44.9, 57.9)	112.9 (99.6, 128.0)

Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; AUC_{inf} = area under the concentration-time curve from time 0 to infinity after drug administration; AUC_{last} = area under the plasma concentration-time curve from. time zero to time of last measurable concentration; C_{max} = maximum plasma concentration of drug; PK = pharmacokinetic;
[a]AUC_{last} was used because concentration-time profiles did not allow for estimation of terminal elimination phase
Treatment A = Single 200 mg dose of BCV administered as 2 x 100 mg tablets under fasting condition
Treatment B = Single 200 mg dose of BCV administered as 2 x 100 mg tablets after a low-fat meal
Treatment C = Single 200 mg dose of BCV administered as 2 x 100 mg tablets after a low-fat meal
Treatment D = Single 200 mg dose of BCV administered as 20 mL (10 mg/mL) suspension
Source: Study report CMX001-114 – PK report; Table 11 (pg 49)

Treatment group imbalances were the result of early subject withdrawal attributed to ALT/AST elevations ≤ 2.5 x upper limit of normal.

4.3.6 Relative bioavailability studies

Tablet

Study CMX001-115 was an open-label, randomized, single-dose, two-period, crossover study evaluating the bioequivalence (BE) of BCV (b) (4) 100 mg tablet and (b) (4) 100 mg tablet in 52 healthy adults (1 Female) weighing 81.8 (range: 57 to 108) kg and 34 (range: 19 to 52) years of age.

Individuals were fasted overnight for ca. 10 hr before study drug administration. Fasting continued ca. 4 hr postdose. The washout period between periods was at least 21 days between doses. BCV and CDV (data not shown) plasma PK samples were collected up to 312 hr postdose.

Table 4-24: BCV PK Parameters After Single PO Administration of 100 mg (b) (4) BCV and 100 mg (b) (4) BCV.

Parameter	**(b) (4) Tablet (T) Geo Mean (%GCV)**	**(b) (4) Tablet (R) Geo Mean (%GCV)**	**T/R GeoMean Ratio (%) (90% CI)**
AUC_{inf} (ng·hr·mL^{-1})	1300 (43.7)[a]	1380 (40.7)[b]	94.5 (88.8 to 100)
C_{max} (ng·mL^{-1})	250 (45.9)[a]	258 (42.3)[b]	96.9 (89.4 to 105)
T_{max} (h)[c]	2.52 (1.5 to 10)	3.5 (1.5 to 10)	NC

[a]n =51
[b]n =52
[c] T_{max} presented as median (range)
Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; AUC_{inf} = area under the concentration-time curve from time 0 to infinity after drug administration; C_{max} = maximum plasma concentration of drug; T_{max} = time to maximum observed concentration; CI = confidence interval; NC = not calculated; PK = pharmacokinetic; BCV = bincidofovir
Source: Study Report CMX001-115. Tables 8 (pg. 46) and 10 (pg. 47).

Study CMX001-126 was an open-label, randomized, single-dose, two-period, crossover study evaluating the bioequivalence (BE) of BCV Penn Pharmaceuticals Limited 100 mg tablet (PCI; to-be marketed formulation) and (b) (4) 100 mg tablet in 50 healthy adults (45 Female) weighing 73.2 (range: 54.7 to 95.3) kg and 50 (range: 36 to 65) years of age.

Individuals were fasted overnight for ca. 10 hr before study drug administration. Fasting continued ca. 4 hr postdose. The washout period between periods was at least 14 days between doses. Plasma BCV and

CDV (data not shown) and peripheral blood mononuclear cell CDV-PP PK samples were collected up to 96 hr postdose.

Table 4-25: BCV PK Parameters After Single PO Administration of 100 mg PCI BCV and 100 mg (b) (4) BCV.

Parameter	PCI Tablet (T) Geo Mean (%GCV)	(b) (4) Tablet (R) Geo Mean (%GCV)	T/R GeoMean Ratio (%) (90% CI)
AUC_{inf} (ng·hr·mL^{-1})	2694 (39.8)[a]	2828 (35.7)[b]	95.7 (89.6 to 102.2)
C_{max} (ng·mL^{-1})	501 (41.8)[a]	534 (37.4)[b]	95.9 (88.2 to 104.3)
T_{max} (h)[c]	3.03 (2 to 8)	3.3 (2 to 6)	NC

[a] n =48
[b] n =50
[c] T_{max} presented as median (range)
Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; AUC_{inf} = area under the concentration-time curve from time 0 to infinity after drug administration; C_{max} = maximum plasma concentration of drug; T_{max} = time to maximum observed concentration; CI = confidence interval; NC = not calculated; PK = pharmacokinetic; BCV = bincidofovir
Source: Study Report CMX001-126. Tables 8 (pg. 64) and 11 (pg. 67).

Table 4-26: CDV-PP PK Parameters After Single PO Administration of 100 mg PCI BCV and 100 mg (b) (4) BCV.

Parameter	PCI Tablet (T) Geo Mean (%GCV)	(b) (4) Tablet (R) Geo Mean (%GCV)
AUC_{last} (pg·hr·10^6 cells^{-1})	1384 (70.2)[a]	1534 (60.4)[b]
C_{max} (pg·10^6 cells^{-1})	8.86 (52.3)[a]	9.79 (42.1)[b]
T_{max} (h)[c]	72 (47.9 to 192.5)	72 (24 to 168)
$T_{1/2}$ (h)	132 (19)	121 (12.7)

[a] n =29
[b] n =30
[c] T_{max} presented as median (range)
Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; AUC_{inf} = area under the concentration-time curve from time 0 to infinity after drug administration; C_{max} = maximum plasma concentration of drug; T_{max} = time to maximum observed concentration; $T_{1/2}$ = half-life; CI = confidence interval; NC = not calculated; PK = pharmacokinetic; CDV-PP = cidofovir diphosphate
Source: Study Report CMX001-126. Tables 10 (pg. 66)

Suspension

Study CMX001-116 was an open-label, randomized, single-dose, two-period, crossover study evaluating the bioequivalence (BE) of BCV (b) (4) 100 mg suspension and (b) (4) 100 mg suspension in 104 healthy adults (14 Female) weighing 82.5 (range: 61 to 121) kg and 37 (range: 18 to 55) years of age.

Individuals were fasted overnight for ca. 10 hr before study drug administration. Fasting continued ca. 4 hr postdose. The washout period between periods was at least 14 days between doses. BCV and CDV (data not shown) plasma PK samples were collected up to 144 hr postdose.

Table 4-27: BCV PK Parameters After Single PO Administration of 100 mg (b) (4) BCV and 100 mg (b) (4) BCV.

Parameter	(b) (4) Suspension (T) Geo Mean (%GCV)	(b) (4) Suspension (R) Geo Mean (%GCV)	T/R GeoMean Ratio (%) (90% CI)
AUC_{inf} (ng·hr·mL^{-1})	1833 (43.1)[a]	2059 (37.1)[b]	89.5 (86.3 to 92.7)
C_{max} (ng·mL^{-1})	347 (44.2)[a]	384 (40.3)[b]	91.1 (87.5 to 94.8)
T_{max} (h)[c]	3 (1.5 to 5.0)	3 (1.5 to 6)	NC

[a] n =102
[b] n =101
[c] T_{max} presented as median (range)
Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; AUC_{inf} = area under the concentration-time curve from time 0 to infinity after drug administration; C_{max} = maximum plasma concentration of drug; T_{max} = time to maximum observed concentration; CI = confidence interval; NC = not calculated; PK = pharmacokinetic; BCV = bincidofovir
Source: Study Report CMX001-116. Tables 10 (pg. 47) and 12 (pg. 48).

Study CMX001-124 was an open-label, randomized, single-dose, two-period, crossover study evaluating the bioequivalence (BE) of BCV Cambrex Pharmaceuticals 100 mg suspension (b) (4) (to be marketed formulation) and (b) (4) 100 mg suspension in 24 healthy adults (23 Female) weighing 73.2 (range: 55.2 to 97.1) kg and 48 (range: 27 to 59) years of age.

Individuals were fasted overnight for ca. 10 hr before study drug administration. Fasting continued ca. 4 hr postdose. The washout period between periods was at least 14 days between doses. Plasma BCV and CDV (data not shown) and peripheral blood mononuclear cell CDV-PP PK samples were collected up to 168 hr postdose.

Table 4-28: BCV PK Parameters After Single PO Administration of 100 mg (b) (4) BCV and 100 mg (b) (4) BCV.

Parameter	(b) (4) Suspension (T) Geo Mean (%GCV)	(b) (4) Suspension (R) Geo Mean (%GCV)	T/R GeoMean Ratio (%) (90% CI)
AUC_{inf} ($ng \cdot hr \cdot mL^{-1}$)	2908 (42.1)[a]	2997 (35.8)[b]	95.8 (85.5 to 107.4)
C_{max} ($ng \cdot mL^{-1}$)	493 (35.7)[a]	524 (35.9)[b]	92.4 (80.9 to 105.6)
T_{max} (h)[c]	3 (2 to 6)	3.25 (2 to 5)	NC

[a] n =24
[b] n =22
[c] T_{max} presented as median (range)
Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; AUC_{inf} = area under the concentration-time curve from time 0 to infinity after drug administration; C_{max} = maximum plasma concentration of drug; T_{max} = time to maximum observed concentration; CI = confidence interval; NC = not calculated; PK = pharmacokinetic; BCV = bincidofovir
Source: Study Report CMX001-124. Tables 8 (pg. 62) and 12 (pg. 48).

Table 4-29: CDV-PP PK Parameters After Single PO Administration of 100 mg (b) (4) BCV.

Parameter	(b) (4) Suspension (T) Geo Mean (%GCV)
AUC_{last} ($pg \cdot hr \cdot 10^6\ cells^{-1}$)	1414 (49.6)[a]
C_{max} ($pg \cdot 10^6\ cells^{-1}$)	8.7 (50.9)[a]
T_{max} (h)[c]	71 (46 to 170.8)
$T_{1/2}$ (h)	117 (13.3)

[a] n =29
[c] T_{max} presented as median (range)
Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; AUC_{inf} = area under the concentration-time curve from time 0 to infinity after drug administration; C_{max} = maximum plasma concentration of drug; T_{max} = time to maximum observed concentration; $T_{1/2}$ = half-life; CI = confidence interval; NC = not calculated; PK = pharmacokinetic; CDV-PP = cidofovir diphosphate
Source: Study Report CMX001-124. Tables 11 (pg. 65)

4.3.7 Drug-drug interactions

Effect of Cyclosporine (CSA) on Brincidofovir (BCV) and Cidofovir (CDV) Exposure
Study CMX001-120 was a single-center, randomized, two-period, cross-over study in 26 healthy subjects (20 males) 26 to 51 years of age.

Treatment sequence:

- Dose period 1: (BCV 100 mg) then Treatment B (BCV 100 mg + cyclosporine 600 mg)

Dose period 2: Treatment B then Treatment A

Individuals were fasted overnight for ca. 10 hr before study drug administration. Fasting continued ca. 4 hr postdose. The washout period between periods was at least 14 days. BCV and CDV plasma PK samples were collected up to 144 hr postdose.

Table 4-30. BCV PK Parameters After Single PO Administration of 100 mg BCV With and Without 600 mg PO CSA.

Parameter	BCV+CSA (T) Geo Mean (%GCV)	BCV (R) Geo Mean (%GCV)	T/R GeoMean Ratio (%) (90% CI)
AUC_{inf} (ng·hr·mL^{-1})	6417 (40)[a]	1394 (39)[b]	474 (411-548)[c]
C_{max} (ng·mL^{-1})	910 (41.7)[b]	251 (41.5)[b]	369 (317-431)[d]
$T_{1/2}$ (h)	13.1 (67.9)	8.68 (38.6)	NC

[a]n =24
[b]n =25
[c]n =23
[d]n =24
Source: Study Report CMX001-120. Tables 10 (pg. 46) and 13 (pg. 48)

Table 4-31. CDV PK Parameters After Single PO Administration of 100 mg BCV With and Without 600 mg PO CSA.

Parameter	BCV+CSA (T) Geo Mean (%CGV)	BCV (R) Geo Mean (%GCV)	T/R GeoMean Ratio (%) (90% CI)
AUC_{inf} (ng·hr·mL^{-1})	1244 (30)[a]	1111 (26)[b]	115 (107-125)[c]
C_{max} (ng·mL^{-1})	21.5 (24.5)[b]	18.6 (20.3)[b]	116 (109-124)[d]

[a]n =24
[b]n =25
[c]n =23
[d]n =24
Source: Study Report CMX001-120. Tables 11 (pg. 47) and 14 (pg. 49)
Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; AUC_{inf} = area under the concentration-time curve from time 0 to infinity after drug administration; C_{max} = maximum plasma concentration of drug; $T_{1/2}$ = terminal half-life; CI = confidence interval; NC = not calculated; PK = pharmacokinetic; CSA = cyclosporine; BCV = bincidofovir; CDV = cidofovir

BCV is a clinical substrate of OATP1B 1/3. There is a clinically significant impact on BCV exposures, but not CDV exposures, when oral 100 mg BCV is administered with oral 600 mg CSA based on a default no-effect boundary (80-125%) assessment.

Effect of BCV on Midazolam (MDZ) Exposure
Study CMX001-113 was an open-label, randomized, 2-sequence, 2-period cross-over study in 20 healthy participants (3-females) 23 to 55 years of age.

Treatment sequence 1:

Dose period 1: 1 mg MDZ IV (Treatment A) on study day 1 then 1 mg MDZ IV + 200 mg BCV PO (Treatment B) on study day 2.

Dose period 2: 2.5 mg MDZ oral (PO) (Treatment C) on study day 1 then 2.5 mg MDZ PO + 200 mg BCV PO (Treatment D) on study day 2.

Treatment sequence 2:

Dose period 1: Treatment C on study day 1 then Treatment D on study day 2.

Dose period 2: Treatment A on study day 1 then Treatment B on study day 2.

Participants fasted overnight ca. 8 hr prior to dosing and ca. 4 hr postdose. MDZ plasma PK samples were collected up to 24 hr on Days 1 and 2 The washout period between periods was at least 14 days. BCV and CDV plasma PK samples were collected up to 216 hr postdose. MDZ and its metabolite 1-OH MDZ plasma PK samples were collected up to 14 hr postdose.

Table 4-32. MDZ PK Parameters After Single IV Administration of 1 mg With and Without 200 mg PO BCV

Parameter	BCV+MDZ (T) Geo Mean (%GCV)	MDZ alone (R) Geo Mean (% GCV)	T/R GeoMean Ratio (%) (90% CI)
AUC_{inf}(ng*hr/mL)	49.1 (23.6)[a]	48.8 (23.1)[b]	104.9 (102.5-107.5)[c]
C_{max} (ng/mL)	36.5 (48.3)[a]	49.1 (23.6)	NR

[a]n =19
[b]n =19
[c]n =19
Source: Study Report CMX001-113. Tables 4 (pg. 52) and 13 (pg. 66)

Table 4-33. MDZ PK Parameters After Single PO Administration of 2.5 mg With and Without 200 mg PO BCV

Parameter	BCV+MDZ (T) Geo Mean (%GCV)	MDZ alone (R) Geo Mean (%GCV)	T/R Geo Mean Ratio (%) (90% CI)
AUC_{inf} (ng*hr/mL)	40.2 (45.8)[a]	35.8 (37.9)[a]	112.1 (107.6-116.8)[b]
C_{max} (ng/mL)	11.5 (31.6)	10.8 (25.9)	105.6 (97.2-114.7)

[a]n =19
[b]n =19
Source: Study Report CMX001-113. Tables 5 (pg. 53) and 12 (pg. 66)

Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; AUC_{inf} = area under the concentration-time curve from time 0 to infinity after drug administration; C_{max} = maximum plasma concentration of drug; CI = confidence interval; SD = standard deviation; PK = pharmacokinetic; MDZ = midazolam; BCV = bincidofovir; CDV = cidofovir; NR = not reported

Systemic exposures of the primary metabolite of MDZ (1-hydroxymidazolam) were also comparable either when administered MDZ alone (both PO and IV) or in combination with BCV.
BCV is not a clinically relevant inhibitor of gastrointestinal or hepatic CYP3A.

Effect of BCV on Dabigatran Exposure
Study CMX001-117 was an open-label, 2-period, single-sequence study in 30 healthy subjects (4-female) 18 to 55 years of age.

Treatment A: Single 150 mg dabigatran etexilate capsule

Treatment B: Single 200 mg BCV tablet followed 1 h later by a single 150 mg dabigatran (DBG) etexilate capsule.

Subjects were fasted for ca. 10 hrs before morning dosing. Total and free dabigatran, as well as BCV and CDV plasma PK samples (period 2 only), were collected up to 48 h post-dose and then on Day 7.

Table 4-34. Total Dabigatran (TDBG) PK Parameters Following Single Oral Administration of 150 mg DBG With or Without 200 mg BCV Tablet

Parameter	TDBG+BCV (T) Geo Mean (%GCV)	TDBG alone (R) Geo Mean (%GCV)	T/R Geo Mean Ratio (%) (90% CI)
AUC_{inf} (ng*hr/mL)	920 (45)	1043[a] (54)	86.6 (73.9–101)
C_{max} (ng/mL)	107 (45.4)	107 (45.4)	89.4 (74.8–107)
$T_{1/2}$ (hr)	9.91 (14.5)	9.3 (15.3)	NC

[a] n =29
Source: Study Report CMX001-117. Tables 8 (pg. 51) and 12 (pg. 53)

Table 4-35. Active Dabigatran (DBG) PK Parameters Following Single Oral Administration of 150 mg DBG With or Without 200 mg BCV Tablet

Parameter	DBG+BCV (T) Geo Mean (%GCV)	DBG alone (R) Geo Mean (%GCV)
AUC_{inf} (ng*hr/mL)	826 (49)	904 (53)
C_{max} (ng/mL)	93.9 (46.6)	105 (58.3)
$T_{1/2}$ (hr)	9.91 (15.6)	9.67 (15.1)

Source: Study Report CMX001-117. Tables 9 (pg. 51)

Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; $AUC_{0\text{-}inf}$ = area under the concentration-time curve from time 0 to infinity after drug administration; C_{max} = maximum plasma concentration of drug; $T_{1/2}$ = half-life; PK = pharmacokinetic; NC = not calculated; BCV = brincidofovir

BCV is not a clinically relevant inhibitor of gastrointestinal P-gP.

4.3.8 Intrinsic factors

4.3.8.1 Hepatic Impairment

Study CMX001-106 was an open label study to determine the safety and PK of BCV in hepatically impaired individuals. Eight individuals with moderate hepatic impairment (Child-Pugh Scores 7 to 9) and 8 individuals with severe hepatic impairment (Child-Pugh Scores 10 to 12) were enrolled together with age-, gender-, and weight-matched individuals with normal hepatic function (n=8). Individuals were 44 to 63 years of age, 19.1 to 35.7 kg, and majority male -3 females with severe hepatic impairment. Individuals received a single 200 mg BCV tablet dose. Blood samples were collected predose and up to 120 hr postdose for determination of plasma BCV and CDV PK. Plasma protein binding of BCV was determined from two plasma samples; between 3 hr to 4 hr postdose (T_{max}) and 24 hr post-dose.

Table 4-36. BCV PK Parameters [Geo Mean (%GCV)] After Single Dose Administration in Individuals With Different Hepatic Function

Parameter	Severe Impairment	Moderate Impairment	Normal Function
BCV			
AUC_{inf} (ng·h/mL)	4991 (24.6)	3993.2 (68.7)	3850.3 (27.6)
C_{max} (ng/mL)	613.2 (23.4)	633.6 (82)	788.3 (30)
$T_{1/2}$ (hr)	9.1 (26.4)	6.8 (31.4)	5.2 (21.2)
CDV			
AUC_{inf} (ng·h/mL)	1935 (31.8)	2064.7 (35.7)	1914.5 (23.4)
C_{max} (ng/mL)	27.1 (27.2)	31.5 (27.7)	27.6 (19.1)
$T_{1/2}$ (hr)	47 (13)	48.7 (21.4)	50.8 (20.2)

Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; AUC_{inf} = area under the concentration-time curve from time 0 to infinity after drug administration; C_{max} = maximum plasma concentration of drug; $T_{1/2}$ = half-life; PK = pharmacokinetic; BCV = brincidofovir; CDV = cidofovir
Source: Study Report CMX001-106-pharmacokinetic, Table 4-2 (pg 21) and Table 4-5 (pg 25).

Table 4-37. Statistical Comparisons [Geo Mean ratio % (90% CI)] of BCV and CDV Exposure Measures

Parameter	Moderate/Healthy Control	Severe/Healthy
BCV		
AUC_{inf}	103.7 (72.5, 148.3)	129.6 (90.6, 185.4)
C_{max}	80.4 (53.8, 120.1)	77.8 (52.1, 116.3)
CDV		
AUC_{inf}	107.8 (83.3, 139.6)	101.1 (78.1, 130.8)
C_{max}	114 (92.2, 140.8)	98.1 (79.4, 121.3)

AUC_{inf} = area under the concentration-time curve from time 0 to infinity after drug administration; C_{max} = maximum plasma concentration of drug; $T_{1/2}$ = half-life; CI = confidence interval; BCV = brincidofovir; CDV = cidofovir
Source: Study Report CMX001-106-pharmacokinetic, Table 4-3 (pg 21) and Table 4-6 (pg 25).

Similar trends were observed when C_{max} and AUC_{inf} values were normalized by weight (mg/kg) (data not shown).

BCV is highly plasma protein bound (PPB; estimated to be > 0.99) across study groups as determined by equilibrium dialysis. The fraction of BCV unbound was estimated to be < 0.009 (T_{max} collection timepoint). Caution is needed in the use and interpretation of PPB results for this very strongly bound drug with very small absolute unbound fraction values as it is the relative change in the unbound fraction that is most clinically meaningful but not reportable. See **Section 4.2.1** for specifics regarding in vitro / ex vivo plasma protein binding studies.

Overall, moderate or severe hepatic impairment did not clinically significantly influence the PK of BCV or CDV.

4.3.8.2 Renal Impairment

Study CMX001-118 was an open-label safety and PK study of a single oral BCV dose (100 mg tablet). In this study, the BCV and CDV PK in individuals with severe renal impairment (eGFR ≤ 30 mL/min/1.73 m^2 not on dialysis: n=8; MDRD equation) and individuals on hemodialysis (HD: pre-HD n=8; post HD n=9) were compared with age-, gender-, and weight-matched individuals with normal renal function (creatinine clearance (CLcr); n=8). Individuals were 27 to 77 years of age, 65.4 to 110.4 kg total body weight, and majority male (n= 21/25; 84%). K_2EDTA anticoagulated blood and dialysate samples were collected predose and up to 312 hr postdose for determination of plasma BCV and CDV PK and hemodialysis clearance (CL_d). Plasma protein binding of BCV was determined from one plasma sample; 4 hr postdose (T_{max}).

Table 4-38. BCV and CDV PK Parameters [Geo Mean (%GCV)] After a Single 100 mg Oral BCV Dose in Individuals With Different Renal Function

		Hemodialysis		Normal Renal
Study Drug/Parameter	**Severe Impairment**	**On Dialysis**	**Off Dialysis**	**Function**
BCV				
AUC_{inf} (ng·h/mL)	1014 (61.2)	1609 (61.2)	1466 (44.5)	1023 (28.4)
C_{max} (ng/mL)	193 (80.6)	307 (60.8)	235 (51)	213 (40.1)
$T_{1/2}$ (hr)	5.50 (64.1)	4.81 (41.3)	7.13 (51.3)	7.3 (45.0)
CDV				
AUC_{inf} (ng·h/mL)	8687 (60.4)	---	---	889 (11.4)
AUC_{last} (ng·h/mL)	7933 (64.3)	16155 (22.5)	16963 (41.3)	676 (15.4)
C_{max} (ng/mL)	67.6 (39.1)	147 (13.8)	136 (27.9)	13.5 (20.4)
$T_{1/2}$ (hr)	72 (18.2)	---	---	47.3 (16)
CL_d (mL/min)	---	236 (101)	---	---

Geo = geometric; %GCV = geometric coefficient of variation expressed as a %; AUC_{inf} = area under the concentration-time curve from time 0 to infinity after drug administration; AUC_{last} = area under the plasma concentration-time curve from. time zero to time of last measurable concentration; C_{max} = maximum plasma concentration of drug; CL_d = hemodialysis clearance from plasma; $T_{1/2}$ = half-life; PK = pharmacokinetic; --- = not reported; On and Off periods were separated by 14 days.
Severe: Subjects with severe renal impairment (BCV 100 mg).
On Dialysis: Subjects with ESRD (BCV 100 mg 1 hour before HD).
Off Dialysis: Subjects with ESRD (BCV 100 mg 3 hours after HD).
Normal: Subjects with normal renal function (BCV 100 mg).
Source: Study report CMX001-118 – Clinical Study; Table 12 (pg 56) and Table 14 (pg 58)

Table 4-39. Statistical Comparisons [Geo Mean ratio (90% CI)] of BCV and CDV Exposure Measures

Parameter	Severe/Normal	Off dialysis/Normal	On Dialysis / Off Dialysis
BCV			
AUC_{inf}	0.99 (0.68, 1.44)	1.43 (0.99, 2.06)	1.14 (0.78, 1.66)
C_{max}	0.90 (0.57, 1.44)	1.10 (0.7, 1.73)	1.24 (0.84, 1.85)
CDV			
AUC_{inf}	9.77 (6.85, 13.9)	25.1 (17.6, 35.7)[a]	0.85 (0.69, 1.05)[a]
C_{max}	5.01 (3.9, 6.44)	10.1 (7.89, 12.9)	1.04 (0.87, 1.24)

[a]AUC_{last} was used due to influence of subsequent dialysis treatments on terminal elimination phase
AUC_{inf} = area under the concentration-time curve from time 0 to infinity after drug administration; AUC_{last} = area under the plasma concentration-time curve from. time zero to time of last measurable concentration; C_{max} = maximum plasma concentration of drug; $T_{1/2}$ = half-life; CI = confidence interval; BCV = brincidofovir; CDV = cidofovir
Severe: Subjects with severe renal impairment (BCV 100 mg).
On Dialysis: Subjects with ESRD (BCV 100 mg 1 hour before HD).
Off Dialysis: Subjects with ESRD (BCV 100 mg 3 hours after HD).
Normal: Subjects with normal renal function (BCV 100 mg).
Source: Study Report CMX001-118-pharmacokinetic, Table 16 (pg 60) and Table 17 (pg 61).

BCV was very highly plasma protein bound (PPB). The fraction of BCV unbound was estimated to be between <0.0024 to <0.037. The Applicant states that "the extent of protein binding was not obviously different across groups." However, all BCV concentrations for post-equilibrium dialysis samples were below limit of quantification (BLQ; 0.5ng/mL). Caution is needed in the use and interpretation of PPB results for this very strongly bound drug with very small absolute unbound fraction values as it is the relative change in the unbound fraction that is most clinically meaningful but not reportable. See Section 4.2.1 for specifics regarding in vitro / ex vivo plasma protein binding studies.

The PK of BCV was not significantly different in subjects with severe renal impairment or ESRD compared with subjects with normal renal function. The PK of CDV was significantly different in subjects with severe renal impairment and subjects with ESRD compared with normal subjects, indicating higher CDV exposure. However, the increases in CDV exposures across groups, as measured by C_{max}, remain well-below the C_{max} following IV CDV administration (Vistide drug label).

4.4 Pharmacometrics

Review Summary:

Pharmacometrics reviewer evaluated the population PK (PopPK) analyses submitted by the Applicant to support the approval of TEMBEXA (Brincidofovir, BCV) and human dose translation under Animal Rule. The Applicant utilized PopPK analyses 1) to simulate the fully efficacious exposures in the animal model (NZW rabbits), 2) to predict exposures for BCV and PBMC CDV-PP in healthy adult subjects for dose selection in human for smallpox indication, and 3) to predict exposures for BCV to guide dose selection for pediatric patients for smallpox indication.

The submitted PopPK analyses include:

(1) PopPK model for Plasma BCV and PBMC CDV-PP in New Zealand White (NZW) rabbits ("Rabbit PopPK model") based on the data collected from non-clinical studies conducted with NZW rabbits (Report No. CMX001-MS-103)
(2) PopPK model for Plasma BCV and PBMC CDV-PP in Healthy Adults ("Healthy PopPK model") based on the PK data collected from Phase 1 clinical studies (Report No. CMX001-MS-104)
(3) PopPK model for Plasma BCV in Non-orthopoxvirus Infected Patients ("Patient PopPK model") based on PK data collected from clinical studies conducted in patients infected with non-orthopoxvirus which included both adults and pediatric patients (Report No. BCV-MS-02)

The rabbit PopPK model adequately describes the PK of plasma BCV and PBMC CDV-PP observed in NZW rabbits and is acceptable to be used to simulate the efficacious exposures associated with fully effective dose (20/5/5 mg/kg) which is subsequently used as target exposures for plasma BCV and PBMC CDV-PP to support a dosing regimen for humans for smallpox indication.

The healthy adult PopPK model provides acceptable model fits to the PK data of plasma BCV and PBMC CDV-PP in healthy adults. This model tends to slightly underpredict the concentrations of PBMC CDV-PP following oral administration of BCV; however, the underpredictions would provide more conservative (lower) predictions in PBMC CDV-PP exposures when assessing human dose translation.

The patient PopPK model reasonably described the PK data of plasma BCV observed in clinical studies. Particularly, this model was informed by PK data collected from pediatric patients down to 3.6 months. The model diagnostics supports the use of this PopPK model to project plasma BCV exposures in pediatric population. However, this model is not suitable to quantify the magnitude of covariate effects (i.e., concomitant CsA use, food status) on BCV PK.

The reviewer's independent analyses revealed that pediatric patients weighing less than 10 kg (including neonates weighing as low as 2.5 kg) are at risk of underexposure of BCV with the Applicant's proposed weight-based dose (b) (4) The review team recommends the following dose regimen:

1) patients weighing <10 kg receive 6 mg/kg once weekly
2) patients weighing at or above 10 kg and below 48 kg receive 4 mg/kg once weekly
3) patients weighing at or above 48 kg receive 200 mg once weekly.

4.4.1 PopPK analysis for plasma BCV and PBMC CDV-PP in New Zealand White (NZW) rabbits

Data: A PopPK analysis for NZW rabbit model (herein referred to as "Rabbit PopPK model") was performed based on the plasma BCV data collected from 8 studies (NCA-030, NCA-043, NCA-061, NCA-121, NCA-123, VIR-058, VIR-106, VIR-122) and PBMC CDV-PP data collected from 3 studies (NCA-121, NCA-123, VIR-122). For the descriptions of study objectives, dose regimen, and PK sampling scheme, refer to Applicant's report (CMX001-MS-103, Table 1 on pages 15-19). The rabbit PopPK dataset contains 2088 PK observations total (after excluding BLQs), with 1046 PK observations for plasma BCV, 810 for plasma CDV, and 232 for PBMC CDV-PP.

Base models: The base BCV model was a 2-compartment PK model with sequential zero- then first-order absorption and linear CL. PK parameters for clearance and volumes of distribution were allometrically scaled based on median body weight of 2.4 kg with fixed exponents (0.75 for CL and Q2, and 1 for V2 and V3). Subsequently, the BCV model was used as the input for the PopPK model development for PBMC CDV-PP. Base model for PBMC CDV-PP was a 1-compartment model with linear CL parameterized from central compartment. The conversion of oral BCV to CDV (intermediate metabolite) was fixed at 0.42 based on the human ADME study, and combining with the 2-step phosphorylation, the pathway to PBMC CDV-PP was modeled using 3 transit compartments.

Between subject variability (BSV) was modelled for Ka, CL, and V (peripheral) in BCV model and CL and V (central) in CDV-PP model with a multiplicative form, assuming log-normal distribution. Residual variability of plasma BCV observation was modeled as additive and proportional on the dependent variables.

Covariate analysis: In the BCV model development, baseline age, health status and sex were tested on CL, Q2 (between central and peripheral), V2 (central), and V3 (peripheral). Only health status (infected or not) on Q2 was significant ($p<0.05$) and was retained in the final model. In the CDV-PP model, baseline age, health status, sex and body weight were tested on CL and V (central). No covariates were selected during the final covariate analysis step.

Final Model: The final BCV PK model was 3-compartment model by adding the third compartment to the base model, which improved the model predictions for the terminal phase of the BCV PK profile. The parameter estimates for the final model for plasma BCV and PMBC CDV-PP are listed in **Table 4-40.** and **Table 4-41.** The goodness-of-fit (GOF) plots for the final covariate model are shown in **Figure 4-15** and **Figure 4-16**. The Visual Predictive Checks (VPCs) plots for the final covariate model are shown in **Figure 4-17** and **Figure 4-18**.

Table 4-40. BCV PK Parameter Estimates and %RSE for the Final Model

Parameter	Value	%RSE
CL (L/h)	5	9.9
V_2 (L)	0.59	11
Q_2 (L/h) (infected)	3.8	9.9
Q_2 (L/h) (healthy)	1.37	9.9
V_3 (L)	4.9	11
K_a (1/h)	1.8	9.8
D_1 (h)	5.7	4.4
F_1	0.18	12
Q2STAT1	-0.64	7.4
Q_3 (L/h)	1.3	24
V_4 (L)	250	49
BW effect on CL and Q_2	0.75	Fixed
BW effect on V_2 and V_3	1	Fixed
IIV (SD) K_a	0.94	8.9
IIV (SD) CL	0.77	11
IIV (SD) CL_V3	0.92	2.5
IIV (SD) V3	1.3	8.5
Shrinkage IIV K_a	41	-
Shrinkage IIV CL	14	-
Shrinkage IIV V3	17	-
Proportional RE (SD) BCV	0.48	5.4
Additive RE (SD) BCV	0.93	25

Abbreviations: %RSE=percentage relative standard error; BW=bodyweight; CL=clearance; D_1=duration of absorption F_1=bioavailability; IIV=inter-individual variability K_a=first-order absorption rate constant; Q_2 and Q_3=inter-compartmental flows; POPPK=population pharmacokinetic; RE=residual error; SD=standard deviation; Shrink=Shrinkage; V_2=volume of central compartment; V_3 and V_4=volume of the peripheral compartments.

Source: Applicant's CMX001-MS-103 report. Table 11. Page 41.

Table 4-41. CDV-PP PK Parameter Estimates and %RSE for the Final Model

Parameter	Estimate	%RSE
CL_m	6.5	5.6
V_5	580	12
MTT	4.8	34
IIV (SD) CL_m	0.34	16
IIV (SD) V_5	0.51	16
Shrinkage IIV CL_m	21	-
Shrinkage IIV V_5	20	-
Proportional RE (SD) CDV-PP	0.34	5.4

Abbreviations: %RSE=percentage relative standard error; CDV-PP=cidofovir diphosphate; CL_m=PMBC CDV-PP clearance; IIV=inter-individual variability; Ktr=transit rate; MTT=mean transit time; PBMC=peripheral blood mononuclear cell; POPPK=population pharmacokinetic; RE=residual error; SD=standard deviation; Shrink=shrinkage; V_5= volume of PBMC CDV-PP central compartment.

Source: Applicant's CMX001-MS-103 report. Table 12. Page 46.

Using the individual parameter estimates derived from the final rabbit popPK model, plasma BCV and PBMC CDV-PP exposures in healthy and infected rabbits at the fully effective dose (20/5/5 mg/kg every 48-hour) were simulated and summarized in below.

Table 4-42. Simulated Plasma BCV and PBMC CDV-PP after 20/5/5 mg/kg Q48h Dosing in NZW Rabbits

Health Status	Dose (mg/kg)	BCV		CDV-PP	
		C_{max} (ng/mL)	AUC_{tau} (h*ng/mL)	C_{max} (pg/1×10^6 cells)	AUC_{tau} (h*pg/1×10^6 cells)
Healthy	20	237 (47) [66.7-649]	1490 (46.6) [408-4110]	4.31 (38.6) [1.89-7.41]	154 (33) [73.7-237]
Healthy	5	60.8 (48.2) [16.8-173]	437 (54.5) [109-1530]	3.34 (22.9) [2.25-5.05]	138 (26.2) [77.2-217]
Infected	20	225 (68) [30-691]	1410 (62.2) [231-4410]	5.2 (38.8) [3.17-10.4]	186 (36.4) [114-391]
Infected	5	57.7 (69.5) [7.61-186]	417 (73) [61.6-1700]	4.07 (30.1) [2.7-9.03]	170 (31.2) [116-386]

Note: Simulations for 5 mg/kg performed for the last dose in the 20/5/5 mg/kg regimen.
Note: AUC_{tau} was calculated from time zero to 48 hours after dose
Note: Data are presented as geometric mean (%CV geometric mean) [range].
Abbreviations: %CV=percentage coefficient of variation; AUC_{tau}=area under the concentration-time profile from time zero to time before next dose; BCV=brincidofovir; CDV-PP=cidofovir diphosphate; C_{max}=maximum concentration; PBMC=peripheral blood mononuclear cell; Q48h=every 48 hours; RPXV=rabbitpox virus.

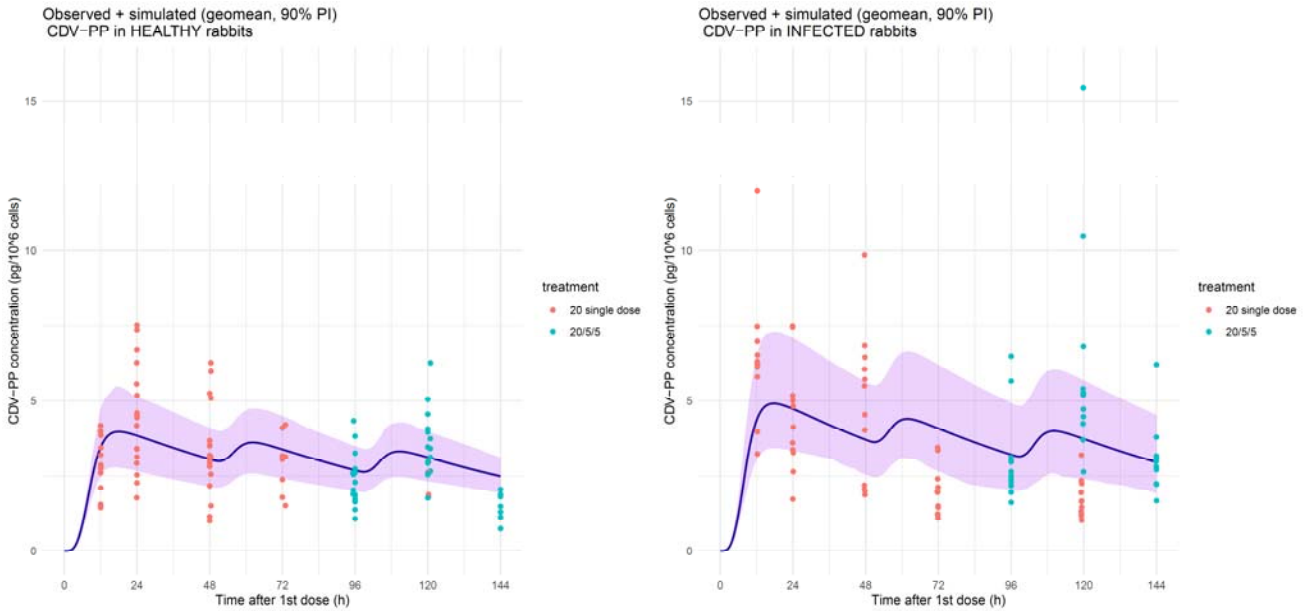
Source: Applicant's CMX001-MS-103 report. Table 15. Page 55.

Reviewer's Assessment of NZW rabbit PopPK analysis

For BCV final PK model, the reviewer was not able to reproduce the %RSE with Applicant's model file; however, all PK parameters (except for V4) and objective function values (OFV) were reproducible. Thus, the reviewer did not pursue error in %RSE estimates in the model minimization step. ETA Shrinkages were acceptable for CL (14%) and V3 (18%); however, Ka exhibited relatively high shrinkage (41%), and this could be explained by the imbalance of BCV being administered via IV or PO routes in study subjects. Of note, most subjects received BCV orally in the non-clinical studies. This relatively high shrinkage % is also consistent with the observed base model Ka (36%). The covariate analysis was adequate, and the covariate-ETA plots all centered around x=0. The final covariate model is acceptable. Based on reproducibility of final pop PK model parameters and diagnostic plots, the reviewer did not notice obvious misspecification or bias of the final model. For the CDV-PP final PK model, the reviewer was able to reproduce the results regarding final PK parameters with acceptable precisions and ETA shrinkages (approximately 20%).

Given there were relatively limited observations in CDV-PP PK data, the reviewer conducted independent simulations and compared the simulated exposures with observed CDV-PP concentrations ***Figure 4-1****. In general, the central tendency (geometric means) of the simulated CDV-PP concentration are in acceptable agreement with the observed CDV-PP data.*

Figure 4-1. Observed and Simulated CDV-PP Concentration-Time Profiles by Infection Status



Source: Reviewer's figure. Note: blueline, geometric mean of simulated values; purple shade, 90% prediction interval of simulated values; orange and green dots, observed data stratified by dosing regimen

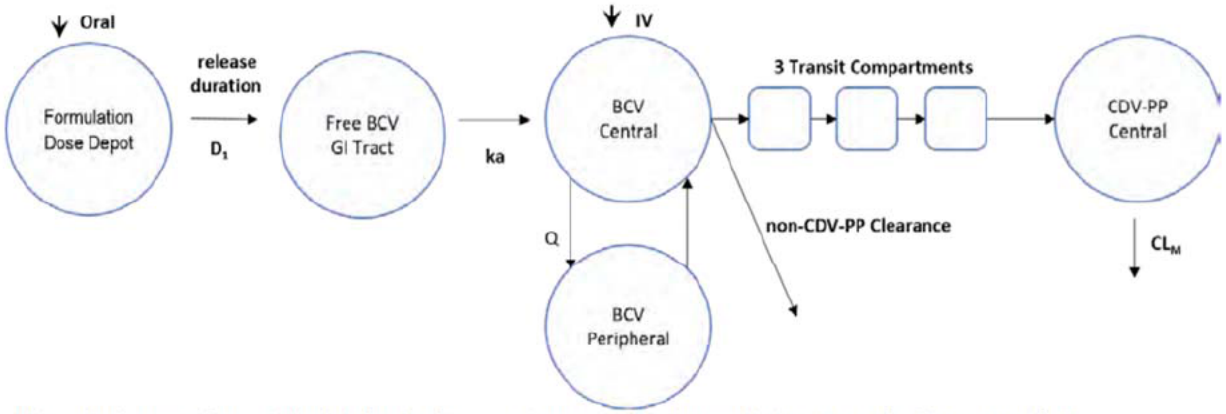
Overall, the final BCV PK model and the final CDV-PP PK model are acceptable in describing the NZW rabbit PK data based on the model fits and diagnostic plots. In addition, the simulated exposure profiles of CDV-PP align with the observed data. The final models for BCV PK and CDV-PP PK are acceptable to derive the fully efficacious exposure via simulation to support human dose translation.

4.4.2 PopPK Analysis for plasma BCV and PBMC CDV-PP in Healthy Human Subjects

Data: PopPK analyses for healthy human was performed based on the plasma BCV data and CDV-PP PK data observed from 7 Phase 1 studies [CMX001-114, CMX001-115 (BCV only), CMX001-123, CMX001-124, CMX001-125, CMX001-126, and CMX001-127]. The final PopPK dataset contained 6736 (after excluding one observation with high residual) PK observations from 224 healthy adults and 1371 CDV-PP PK observations from 145 healthy adults. Study design, BCV dosing regimen, and PK sampling analytes for each study are presented in **Table 4-51.** Summary statistics of the baseline demographic covariates in the analysis dataset is described in **Table 4-52.**

Base model: The base model structure for **plasma BCV PK** for healthy subjects was a 2-compartment model with linear elimination and zero-order absorption process preceded by a lag compartment (Tlab) and followed by the first-order absorption into the central compartment. Body weight (with fixed standard exponents) was included as a covariate on CL, Q, Vp, and Vc. The effect of food (low- or moderate-fat meal) and formulation (tablet and suspension) on F were also incorporated. BSV was modelled on CL, central and peripheral V, Ka with assuming an exponential distribution for subject level random effects. Residual variability was tested as additive, proportional or both on the dependent variable.

The base model structure of **PBMC CDV-PP** model was a 1-compartment model (preceded by 3 transit compartments) with a linear elimination parameterized from the central compartment. The diagram of the structure of the POPPK model for plasma BCV and PBMC CDV-PP is presented below. For GOF plots for the base models for plasma BCV and PBMC CDV-PP, refer to Applicant's report (CMX001-MS-104), Figure 15-16. Pages 34-35.



Abbreviations: BCV = brincidofovir; CL_M = clearance for intracellular (PBMC) CDV-PP; CDV-PP = cidofovir diphosphate; D1 = duration of zero-order drug release; GI = gastrointestinal; IV = intravenous; ka = first-order absorption rate constant; POPPK = population pharmacokinetic; Q = inter-compartmental clearance for plasma BCV.

Source: Applicant's CMX001-MS-104 report. Figure 14. Page 32.

Covariate analysis: Stepwise covariate modeling was performed. For BCV final PK model, fed state and formulation were significant for absorption rate constant, and sex was significant on CL, Q and Vp. For CDV-PP, only sex was significant on CL.

Final model: The parameter estimates for the final BCV and CDV-PP covariate models are listed in **Table 4-43** and **Table 4-44.** The GOF plots for the final covariate models are shown in **Figure 4-2** and **Figure 4-3**. The VPC plots for the final covariate models with all data are shown in **Figure 4-4** and **Figure 4-5**. The absolute BA for tablet and suspension were estimated as 13.4% and 15.8%, respectively. A low- or moderate-fat meal decreased BCV BA by 30% and decreased Ka by 30% compared to fasted state. Females were found to have 23.4% lower CL and 28.1% lower Q and 23.4% lower Vp than males.

Table 4-43. Final Model Parameter Estimates for BCV Model for Healthy Subjects

PARAMETER	FIXED EFFECTS		BSV CV%		
	Estimate	%RSE	Estimate	%RSE	Shrinkage
Clearance (L/h)	7.14	2.2%	14.0%	9.6%	27.0%
Central volume (L)	4.57	10%	95.8%	6.0%	7.78%
Inter-compartmental clearance (L/h)	0.876	3.2%			
Peripheral volume (L)	17.2	4.4%	24.0%	6.3%	21.6%
First-order absorption rate (1/h)	0.32	2.2%	18%	10%	26.9%
Release duration (h)	2.46	1.1%			
Lag time (h)	0.170	2.2%			
Absolute bioavailability (tablet)	0.134	3.9%	40.7%	6.8%	18.2%
Absolute bioavailability (suspension)	0.158	4.2%			
Formulation effect on Ka	0.178	17%			
Food effect on bioavailability	F1 if fasted; F1 × 70.0% if fed	5.9%			
Food effect on Ka	-0.300	5.5%			
Body weight effect on clearance	$CL \times (\frac{WT}{70})^{0.75}$				
Body weight effect on inter-compartmental clearance	$Q \times (\frac{WT}{70})^{0.75}$				

Body weight effect on central volume	$Vc \times (\frac{WT}{70})^{1.0}$		
Body weight effect on peripheral volume	$Vp \times (\frac{WT}{70})^{1.0}$		
Route of administration effect on peripheral volume	Vp if oral; Vp × 27.0% if IV	1.1%	
Sex effect on clearance	-0.234	14%	
Sex effect on inter-compartmental clearance	-0.281	12%	
Sex effect on peripheral volume	-0.234	23%	
Proportional CV	0.354	0.52%	4.3%
Additive SD (ng/mL)	0.001	FIXED	

Source: Applicant's CMX001-MS-104 report. Table 10. Pages 37-38.

Table 4-44. Final Model Parameter Estimates for CDV-PP Model for Healthy Subjects

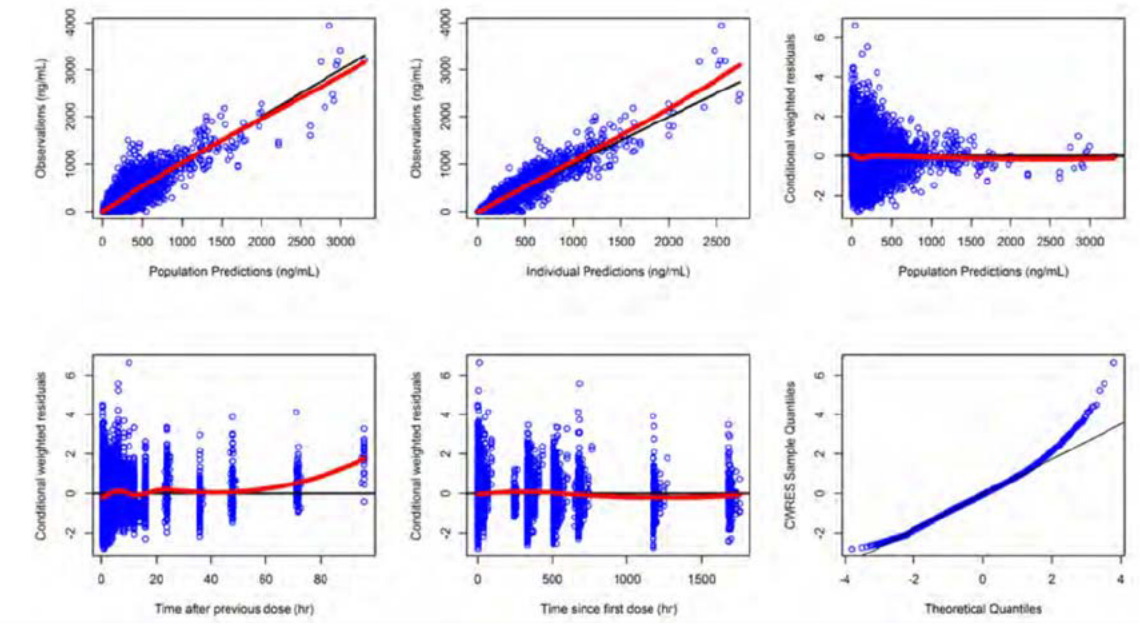
PARAMETERS	FIXED EFFECTS		BSV CV%			
	Estimate	%RSE		Estimate	%RSE	Shrinkage
CLm(10^6 cells/h)	4.98	5.22%	IIV_CLm	66.6%	8.3%	21.7%
			COV_CLm_Vm	82.7%	8.6%	
Vm (10^6 cells)	769	4.83%	IIV_Vm	65.8%	8.0%	24.6%
MTT (h)	18.9	4.06%	IIV_MTT	64.0%	13.3%	38.4%
Sex effect on CLm	-0.276	16.7%				
Route effect on fraction of conversion	If oral, conversion fraction is 0.42[a]; if IV, 0.23	3.37%				
Proportional CV	0.379	2.22%				
Additive SD (ng/mL)	0.001	FIXED				

[a] The fraction of BCV dose converted to CDV-PP was fixed for oral administration using the results from the human ADME study, in which approximately 42% of the oral dose was metabolized via the pathway leading to CDV-PP formation.

Abbreviations: ADME = absorption, distribution, metabolism, and excretion; CDV-PP = cidofovir diphosphate; CLm = clearance for intracellular (PBMC) CDV-PP; IV = intravenous; MTT = mean transit time; PK = pharmacokinetic; Prop = proportional; RSE = relative standard error; SD = standard deviation; Vm = volume for intracellular (PBMC) CDV-PP.

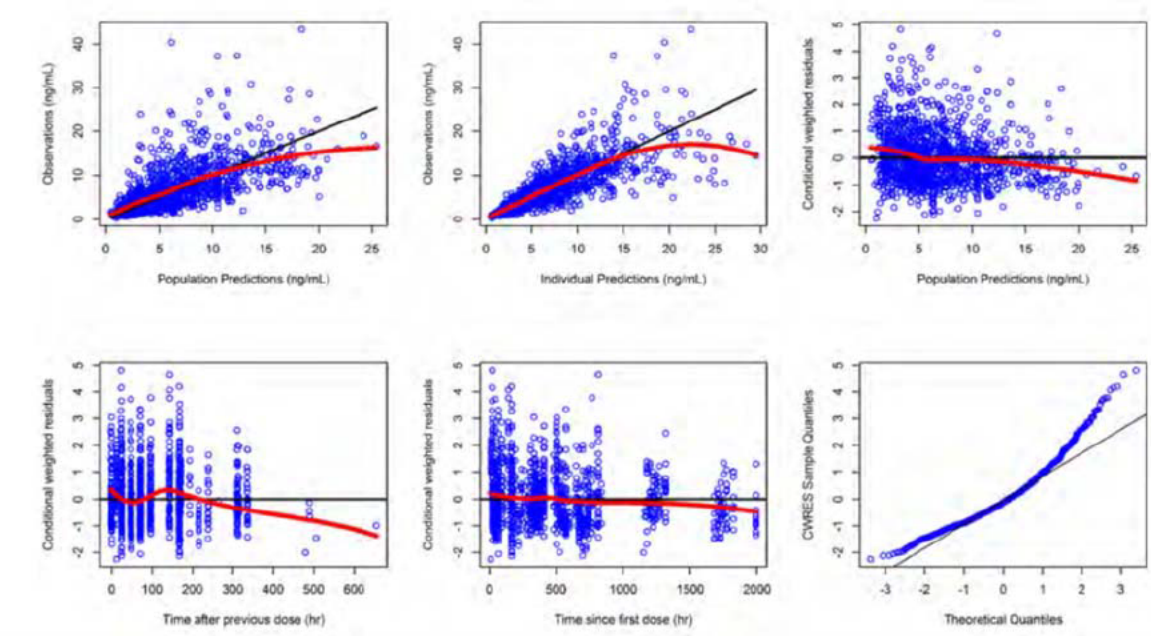
Source: Applicant's CMX001-MS-104 report. Table 11. Pages 38.

Figure 4-2. GOF Plots for Plasma BCV Final Pop PK Model for Healthy Adults



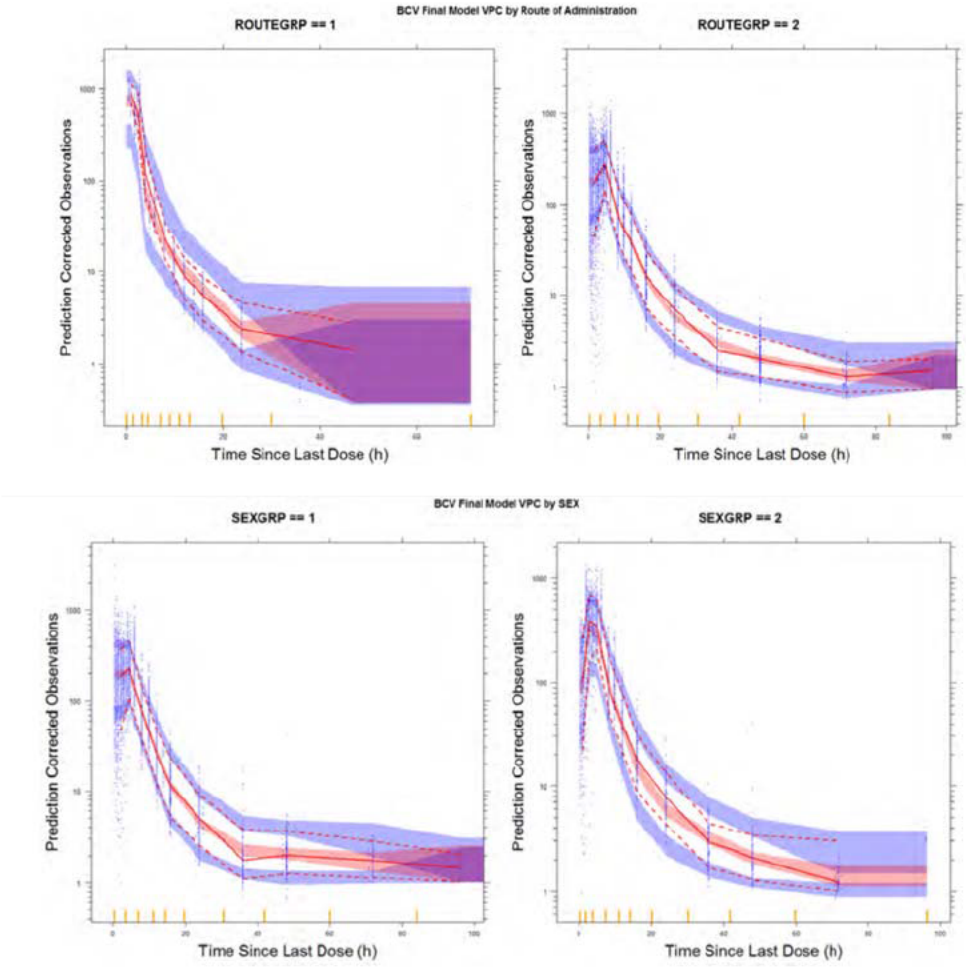
Source: Applicant's CMX001-MS-104 report. Figure 17. Pages 39.

Figure 4-3. GOF Plots for Plasma CDV-PP Final Pop PK Model for Healthy Adults



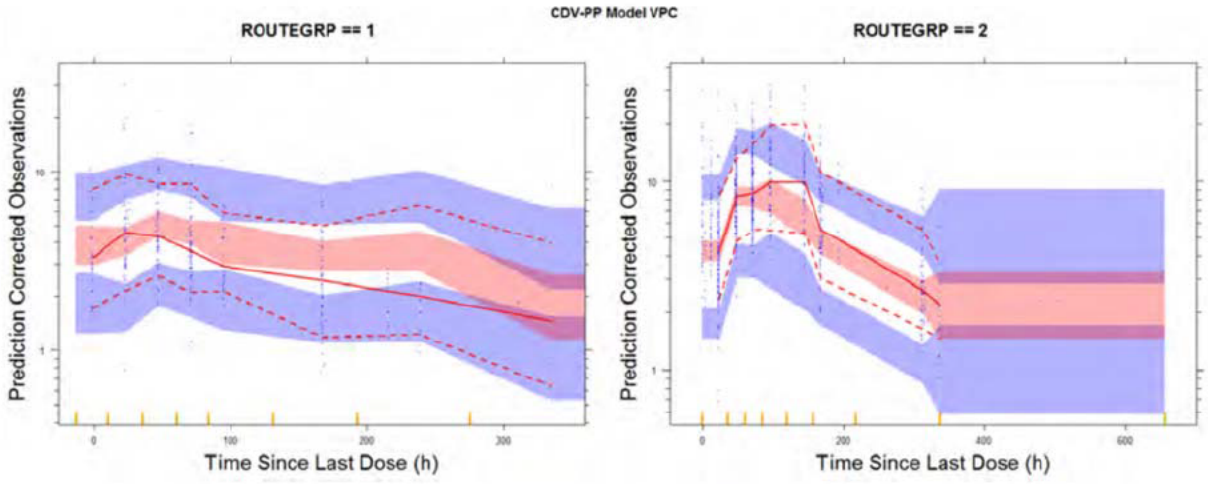
Source: Applicant's CMX001-MS-104 report. Figure 18. Pages 40.

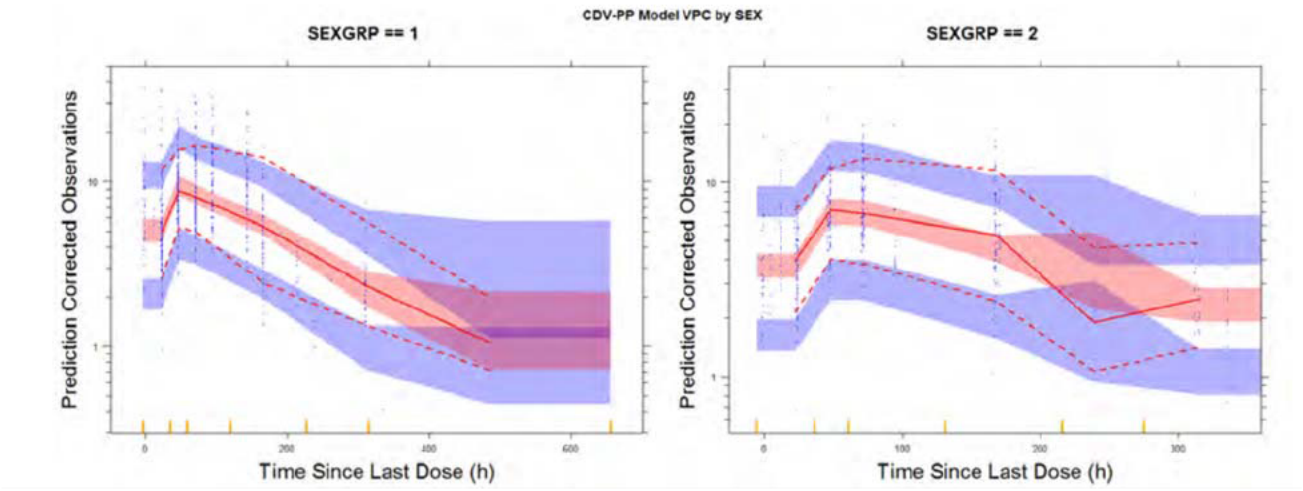
Figure 4-4. VPCs of Plasma BCV for Final Pop PK Model for Healthy Adults



Note: ROUTEGRP==1, IV; ROUTEGRP==2, oral; SEXGRP==1, male; SEXGRP==2, female
Source: Applicant's CMX001-MS-104 report. Figures 19-20. Page 41.

Figure 4-5. VPCs of PBMC CDV-PP for Final Pop PK Model for Healthy Adults





Note: ROUTEGRP==1, IV; ROUTEGRP==2, oral; SEXGRP==1, male; SEXGRP==2, female
Source: Applicant's CMX001-MS-104 report. Figures 21-22. Page 42.

The Applicant performed simulations to derive BCV and PMBC CDV-PP concentration profiles in a virtual population of 1000 subjects following BCV suspension or tablet 200 mg QW. The BCV and PMBC CDV-PP concentration profiles are summarized below.

Table 4-45. Simulated Plasma BCV and PBMC CDV-PP Exposures in Healthy Adult Subjects After 200 mg QW BCV Suspension and Tablet Doses

Analyte	Scenario	First Dose			Last Dose		
		C_{max} (ng/mL)	AUC (hr*ng/mL)	C_{avg} (ng/mL)	C_{max} (ng/mL)	AUC (hr*ng/mL)	C_{avg} (ng/mL)
BCV	Tablet	480 (70) [240-950]	3400 (58) [1900-6300]	20 (58) [11-37]	480 (70) [240-950]	3400 (58) [1900-6300]	20 (58) [11-37]
BCV	Suspension	620 (69) [310-1200]	4000 (57) [2300-7300]	24 (57) [13-43]	620 (69) [310-1200]	4000 (57) [2300-7300]	24 (57) [13-43]
		C_{max} (pg/10^6 cells)	AUC (hr* pg/10^6 cells)	C_{avg} (pg/10^6 cells)	C_{max} (pg/10^6 cells)	AUC (hr* pg/10^6 cells)	C_{avg} (pg/10^6 cells)
CDV-PP	Tablet	9.7 (75) [4.8-20]	1200 (75) [560-2400]	7 (75) [3.4-14]	14 (75) [6.8-29]	1800 (76) [860-3700]	11 (76) [5.1-22]
CDV-PP	Suspension	11 (74) [5.7-23]	1400 (74) [670-2800]	8.2 (74) [4-17]	17 (74) [8.1-34]	2100 (75) [1000-4400]	13 (75) [6-26]

Note: Data are presented as Geomean (CV% geomean) [80% PI].
Abbreviations: AUC_{tau} = area under the concentration-time curve from time zero to time before the next dose; BCV = brincidofovir; C_{avg} = average concentration; CDV-PP = cidofovir diphosphate; C_{max} = maximum concentration; CV = coefficient of variation; Geomean = geometric mean; PBMC = peripheral blood mononuclear cell; PI = prediction interval; QW = once weekly.

Source: Applicant's CMX001-MS-104 report. Table 14. Page 47.

Reviewer's Assessment of Healthy Human PopPK analysis

The final PopPK model parameters for both plasma BCV and PBMC CDV-PP are reproducible. All PK parameters were estimated with acceptable precision with RSE% below 30%. In the BCV model, ETA shrinkages for CL, V (central), V (peripheral), Ka, and F were moderate (8%-27%). While central volume of distribution exhibited a relatively high BSV (>50%), the random effects RSE% was relatively low at 6%. Additionally, the Applicant externally validated the final BCV PK (Refer to Applicant's CMX001-MS-104 report. Section 4.2.5). In the CDV-PP model, ETA shrinkages for CL, V and median transition time (for the 3 transit compartments) are moderate (<38.5%). All parameters and BSV (on CL, V, median transition time) were estimated with acceptable precisions with RSE% below 16.7%. Overall, both final models are adequate to describe plasma BCV and PBMC CDV-PP concentration data in healthy human and it is acceptable to estimate the BCV exposures (both plasma BCV and PBMC CDV-PP) for human dose translation.

The model development of healthy PopPK was not informed by any PK data from pediatric patients. Therefore, the reviewer used this model as sensitivity analyses for pediatric dose selection. (See Section 4.4.4)

The model predicts that food decreases BA and absorption rate by ~30%. It should be noted that this prediction was made based on only 12 subjects from CMX001-114 (Food effect study) who received tablet formation in fed status. The PopPK analysis dataset did not include any data from subjects who received suspension in fed status. Therefore, this model cannot describe/quantify food effect on suspension formulation.

4.4.3 PopPK Analysis for Non-Orthopoxvirus Infected Patients

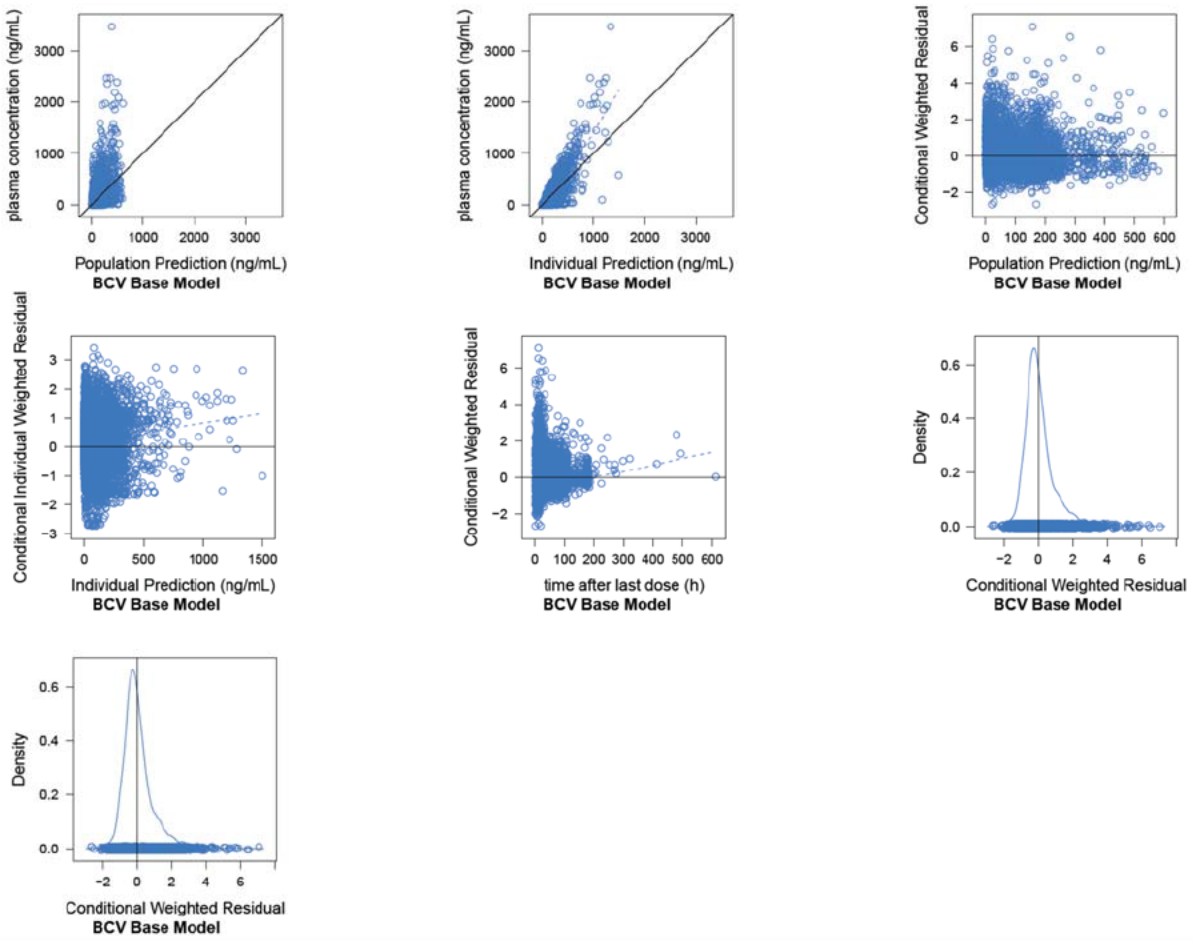
Data: The PopPK model for non-orthopoxvirus infected patients (referred to as "Patient PopPK model" in this review) was developed based on PK data of plasma BCV and plasma CDV observed in pediatric and adult subjects infected with non-orthopoxvirus. The contributing studies included: two randomized, placebo-controlled studies in adult CMV seropositive allogeneic HCT (CMX001-201, CMX001-301), one Phase 2 randomized, placebo-controlled clinical study in pediatric and adult HCT recipients with asymptomatic adenovirus (AdV) viremia (CMX001-202), one open-label Phase 3 clinical study in subjects with disseminated AdV disease or with AdV infection and at risk for progression to disseminated AdV disease (CMX001-304), one expanded access study (CMX001-350), and one Phase 1 study in healthy volunteers (CMX001-115). Refer to Applicant's report (BCV-MS-02, Table 1, Pages 12-13) for additional details for the studies included in PopPK modeling.

The PopPK dataset consists of observations from 941 subjects including 889 patients with or at risk of developing CMV or AdV infection. Of these, 218 were pediatric patients. A total of 15114 quantifiable concentration data for BCV and CDV were available in this data set. For BCV, 6432 observations were included in the final analysis (after exclusions), including 1422 observations from pediatric patients (3 months to 18 years of age). Summary statistics of the baseline demographic covariates in the analysis dataset is described in **Table 4-53.** and **Table 4-54.**

Base Model: Distribution and elimination processes were modeled as first-order processes and parameterized in terms of apparent oral clearance of BCV (CL/F), apparent central volume of BCV (Vc/F),

apparent inter-compartmental clearance of BCV (Q/F), and apparent peripheral volume of BCV (Vp/F). Weight-based allometric scalers as exponents were estimated in the base model. BSV random effects were modeled for CL/F, V/F (central and peripheral), Q/F, and Ka, assuming an exponential distribution. Residual error model was a combined additive and proportional error model.

Figure 4-6. GOF plots for Plasma BCV Base PopPK Model for Non-orthopoxvirus Patients



Source: Applicant's BCV-MS-02 report. Figure 23. Page 86.

Covariate Analysis: Cyclosporine use, food status, diarrhea severity (mild/moderate/severe), healthy volunteer status were tested for covariate inclusion in the final model. The final model included cyclosporine on CL/F, diarrhea on F, food status on F, and healthy volunteer status on CL/F.

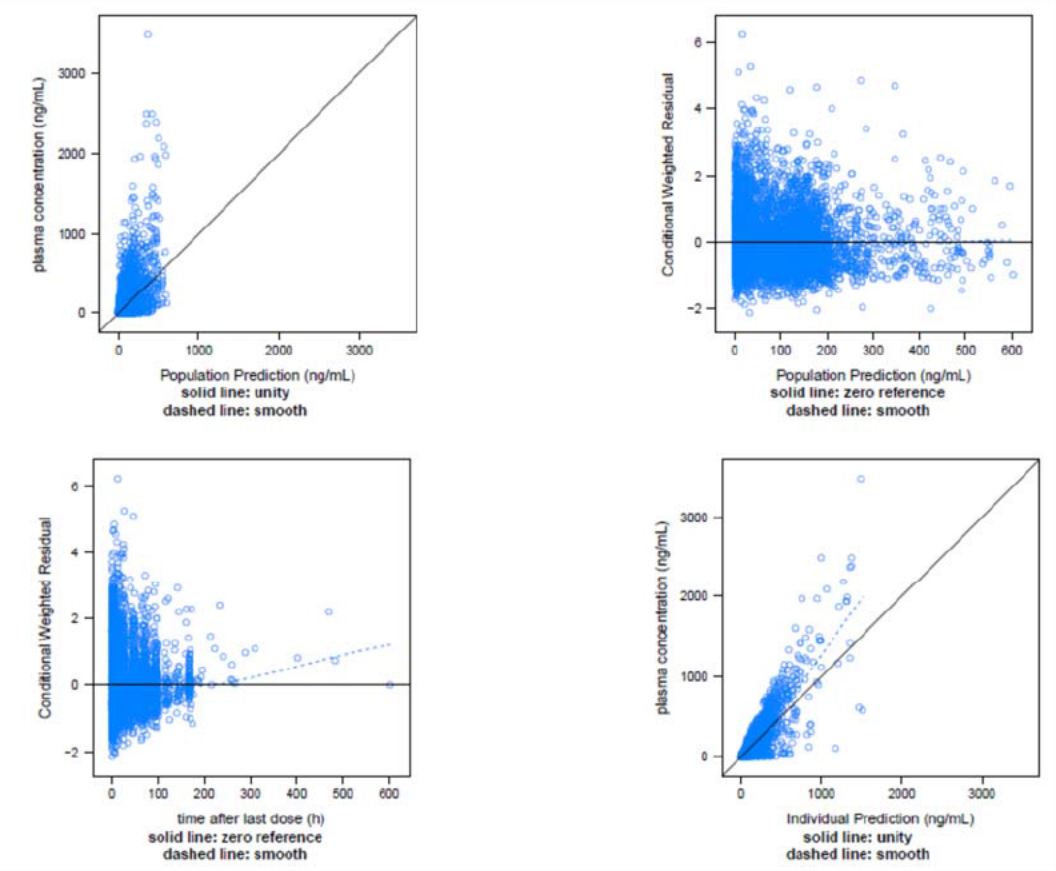
Final Model: The plasma BCV PK in adult and pediatric patients were adequately described by a two-compartment model with zero-order appearance in depot/absorption compartment followed by first order absorption into the central compartment, with first-order elimination and the covariate effects from cyclosporine, diarrhea, food status and healthy volunteer status. Exponents of body weight effects on CL/F and Vc/F were fixed with 0.626, an 0.896 which were estimated from the base model.

Table 4-46. Parameter Estimates for Plasma BCV Final PopPK Model for Non-orthopoxvirus Infected Patients

symbol	label	estimate (%RSE)	variance (%RSE)	bootstrap median (95% CI)
CL/F	Apparent Clearance (L/h)	38 (3.08)	0.401 (5.14)	37.9 (34.7, 40.3)
Vc/F	Apparent Central Volume (L)	323 (3.65)	0.458 (7.95)	323 (293, 362)
Q/F	Apparent Inter-compartmental Clearance (L/h)	6.98 (3.02)	0.781 (11.7)	6.91 (5.54, 7.66)
Vp/F	Apparent Peripheral Volume (L)	359 (2.95)	1.15 (10.6)	358 (282, 437)
KA	Absorption Rate Constant (1/h)	0.835 (9.6)	2.21 (9.07)	0.868 (0.765, 1.24)
D1	Absorption Duration (h)	2.17 (2.29)		2.17 (2.02, 2.47)
ALAG1	Absorption Lag (h)	0.157 (5.59)		0.158 (0.104, 0.207)
WT_CL/F	Effect of Weight on Apparent Clearance	0.626 (fixed)		
WT_Vc/F	Effect of Weight on Apparent Central Volume	0.896 (fixed)		
CICLO1_CL/F	Effect of Ciclosporine on Apparent Clearance	-0.295 (6.78)		-0.295 (-0.388, -0.187)
DIARMM_F1	Effect of Mild/Moderate Diarrhea on Relative Bioavailability	-0.096 (19.6)		-0.0962 (-0.193, -0.0189)
DIARSEV_F1	Effect of Severe Diarrhea on Relative Bioavailability	-0.174 (13.2)		-0.173 (-0.314, -0.0305)
FED_F1	Effect of Food on Relative Bioavailability	-0.207 (9.6)		-0.212 (-0.286, -0.123)
HV_CL/F	Effect of Health Status on Apparent Clearance	0.993 (1.29)		1.06 (0.903, 1.32)
CV_HV	Proportional Error CV Health Status	0.359 (0.967)		0.359 (0.33, 0.389)
CV_PT	Proportional Error CV Patients	0.593 (1.56)		0.592 (0.572, 0.613)

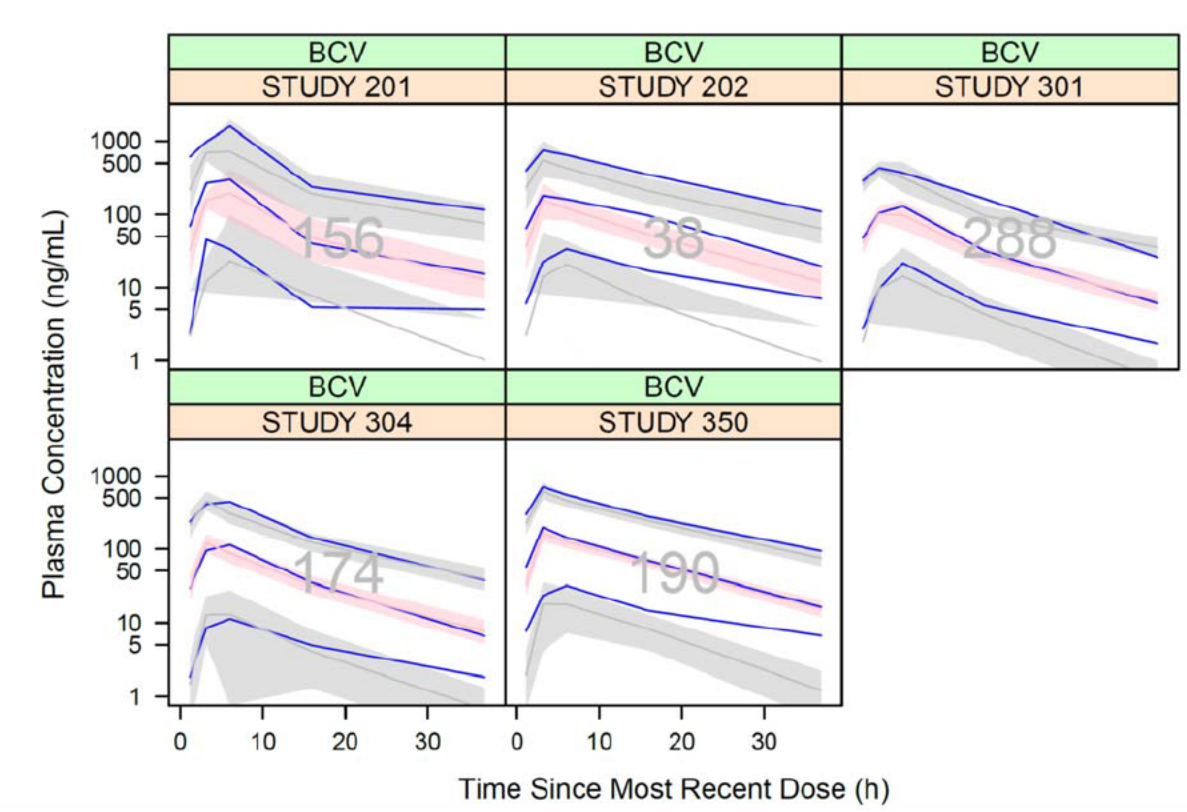
Source: Applicant's BCV-MS-02 report. Table 10. Page 26.

Figure 4-7. GOF Plots for BCV Final Pop PK Model for Non-orthopoxvirus Infected Patients



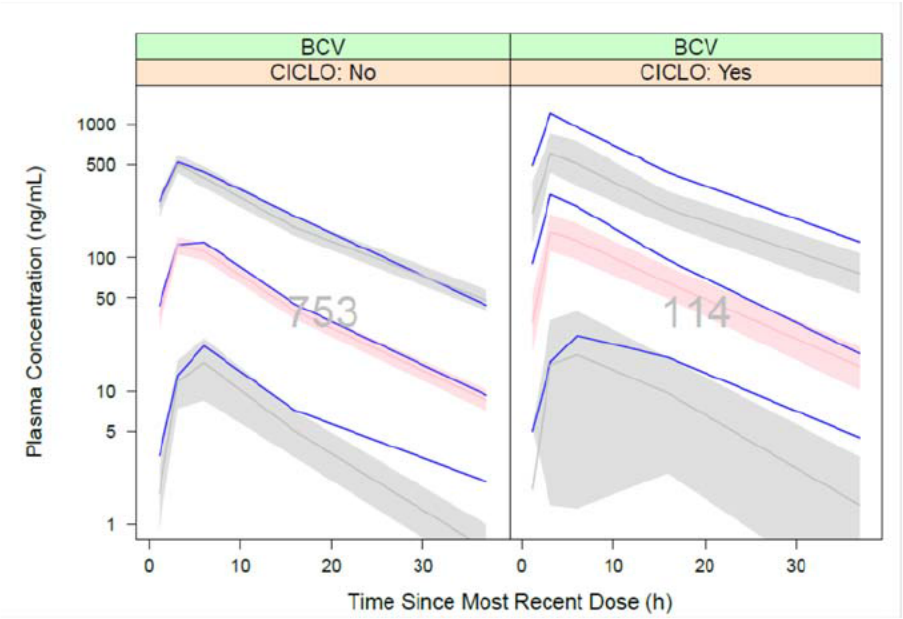
Source: Applicant's BCV-MS-02 report. Figure 3. Page 27.

Figure 4-8. VPCs of BCV Final Pop PK Model by Study for Non-orthopoxivirus Infected Patients



Source: Applicant's BCV-MS-02 report. Figure 4. Page 28.

Figure 4-9. VPCs of BCV Final PK Model by Cyclosporine Status for Non-orthopoxivirus Infected Patients

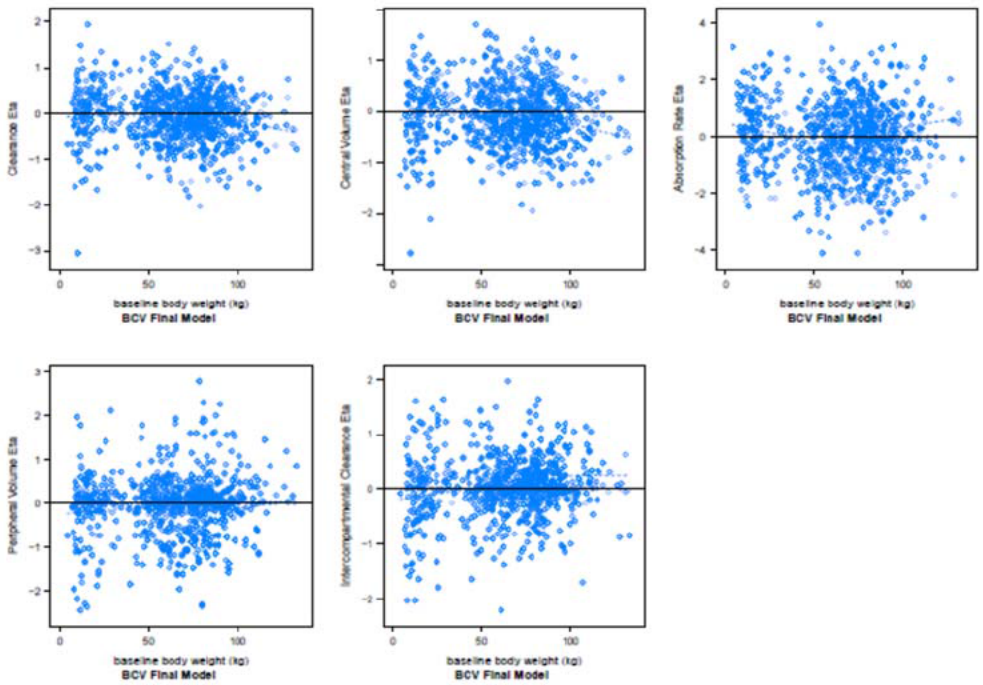


Source: Applicant's BCV-MS-02 report. Figure 28. Page 105.

Reviewer's Assessment of PopPK for Non-orthopoxvirus Infected Patients

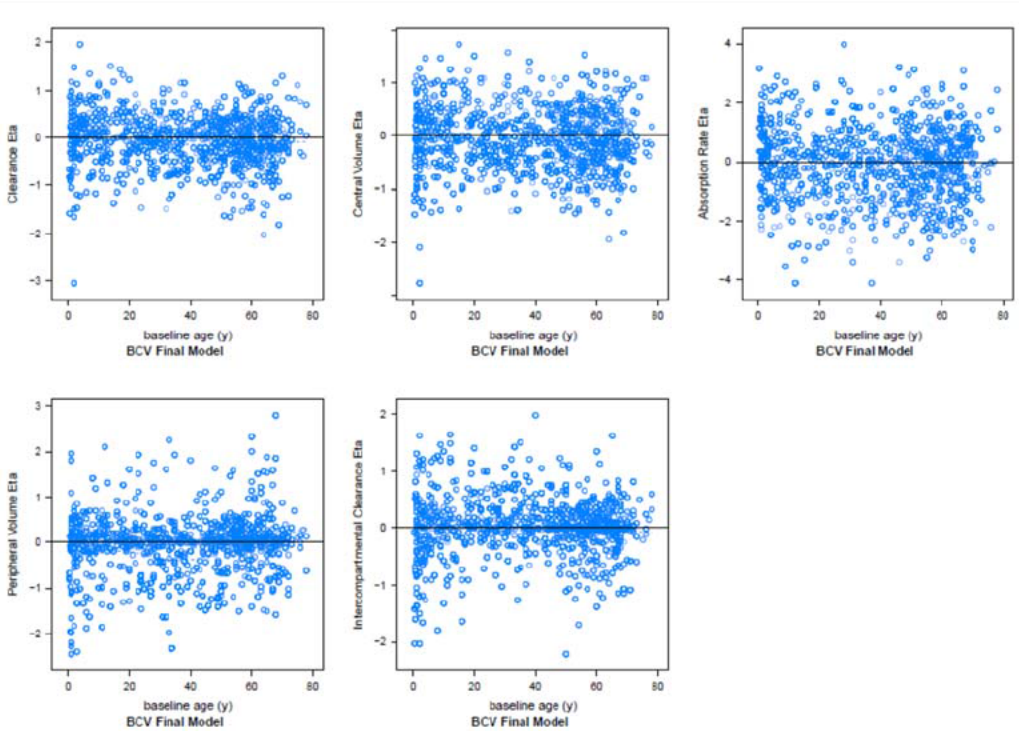
- *Applicant's final BCV model parameters were reproducible with reviewer's independent analysis (<5% deviation from final parameter estimates). Parameter estimates are generally precise with RSE <20%, and GOF plots shows that the final model provides acceptable model fit to the dataset. In ETA-covariate plots (**Figure 4-10** and **Figure 4-11**), ETAs for CL are centered around zero in the studied body weight/age ranges without obvious bias. The effects of body weight and age are generally captured by the final covariate model.*
- *BSV for CL, Vc, Vp, Ka, and Q are high (70-77%) with acceptable shrinkage (14-44%). The high BSVs may be due to the heterogeneity in the studied population with comorbid conditions (transplant, non-orthopoxvirus infections etc.).*
- *The model diagnostics showed underprediction of BCV concentrations in subjects on cyclosporin, hence do not support the utility of this model in estimating the impact of cyclosporine on BCV exposures. Also, there is a considerable discrepancy in the magnitude of cyclosporin effect on BCV exposure between PopPK analysis and the observed in dedicated DDI study. Refer to Section 3.3.4.*
- *Food effect on BCV PK was not estimated separately for the two formulations (tablet and suspension). This model cannot provide quantitative extents of food effect on each formulation.*
- *The development of this model was informed by relative rich PK data pool collected from pediatric patients (> 200 pediatric patients aged 3.6 months to 17 years and serial/intensive PK samples from 66% of these patients). There are no obvious bias or misspecifications noted in model diagnostics in describing the observed PK data from pediatric patients. Also, in the Applicant's sensitivity analysis by fitting a separate model to pediatric data only, the model-derived BCV AUC and Cmax are generally in agreement between those derived from the pediatric sensitivity analysis and the final infected PopPK model (Figure 4-12). The reviewer agrees that this model can be to simulate BCV exposures in pediatric patients to guide dose selection in pediatric population.*

Figure 4-10. ETA-body weight relationship for Patient BCV Final Model



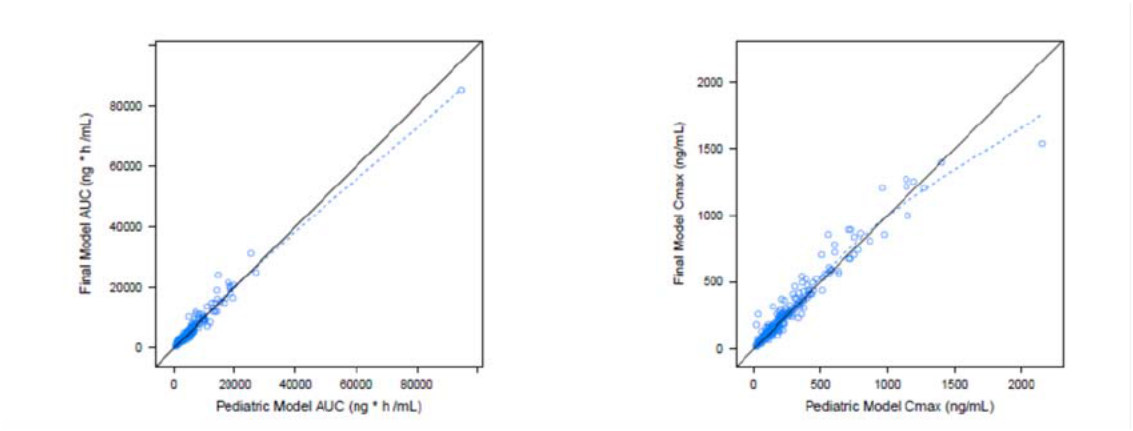
Source: Applicant's BCV-MS-02 report. Figure 56. Page 124.

Figure 4-11. ETA-baseline age relationship for Infected BCV Final Model



Source: Applicant's BCV-MS-02 report. Figure 49. Page 120.

Figure 4-12. Comparison of BCV Final Model and Pediatric Model Exposures (Bayesian) for Pediatric Patients



Source: Applicant's BCV-MS-02 report. Figure 5. Page 29.

4.4.4 Reviewer's Independent Analysis

The review team determined that the proposed dose regimen for adults (200 mg QW x 2 weeks) is appropriate and is expected to provide a similar or greater than the target exposures associated with the fully effective dose for animal models. (b) (4) In evaluation of the dose regimen for pediatric patients, the followings were considered 1) whether the proposed dose can provide pediatric patients comparable drug exposure to adult plasma BCV exposures across ages groups (birth to < 18 years) and body weight groups, and 2) whether most pediatric patients are expected to have BCV exposures greater than the fully effective exposures for the infected rabbit model. Additional key considerations include:

- The pediatric dose selection was made based on the exposures of plasma BCV only. No PBMC CDV-PP data were collected in pediatric patients.
- All pediatric PK data were from those infected with non-orthopoxvirus (0.3 years to < 18 years of age). Therefore, it was assumed that pediatric patients infected with smallpox would exhibit similar PK characteristics as those infected with non-orthopoxvirus. Hence, the patient PopPK was used as the primary model to project the exposures in pediatric patients. The healthy PopPK model was used as the secondary model for sensitivity analyses.
- No PK data for plasma BCV were collected from pediatric patients ages birth to < 0.3 years old. The Applicant's literature review (Applicant's Response to FDA Information Request received on Jan 29, 2021) suggests a lack of difference in OATP1B1 function, inconclusive data on OATP1B3 function, and sparse data on CYP4F2 function assessed across ages ranging from neonates to adults. The review team agreed that incorporating these findings in PopPK modeling/simulation is not feasible, and it is acceptable to use the patient BCV PopPK model which describes BCV clearance by allometric scaling approach in projecting the exposure in pediatric patients age birth to 0.3 years.
- Pediatric dose selection was also guided to ensure that the projected exposures do not exceed the clinical experience of BCV exposure. Therefore, exposure comparisons were performed with the exposures predicted for non-orthopoxvirus infected adults who showed 25% to 47% higher exposures compared to healthy adult subjects.

- As body weight is a significant covariate impacting PK of plasma BCV, the dose selection approach was applied across the body weight bands.

Objectives

- To estimate pediatric BCV exposures by weight groups (birth to 17 years) using the patient PopPK model
- To evaluate whether the Applicant's proposed dosage for pediatric patients is appropriate to provide comparable exposures to those in healthy subjects receiving 200 mg tablet weekly
- To propose an optimal pediatric dose regimen guided by the primary simulation (using the patient PopPK model) and the sensitivity simulations (using the healthy pop PK model)

Methods

The Applicant's simulation dataset included 1573 virtual adult and pediatric subjects. Additional virtual subjects were added for the reviewer's simulation to supplement the relatively small sample size across all weight groups. Applicant's patient PopPK model with the estimated allometric scalers were used as the primary model for simulations. Simulation was performed in R version 3.6.3. Graphical representation of exposure profiles across (adult and pediatric) weight bands were generated using R packages.

In evaluating and optimizing the dose for pediatric subjects, sensitivity analyses were conducted based on the same virtual subjects using the healthy population PK model with fixed allometric scaling to 0.75 (CL) and 1 (V), as well as data-driven allometric scaling exponents estimated from the patient PopPK model.

Results

Simulations of BCV exposures following the Applicant's proposed dosing regimen

Table 4-47 described the exposure profiles (AUCtau, AUC after first dose) across age groups following the Applicant's proposed dosing regimen. The median BCV exposures in the age groups, 0 to <0.3 year and 0.3 to 2 years are observed to be lower than healthy adults AUCtau of 3400 ng*h/mL. The sensitivity analysis (simulations) using the healthy PopPK model (using data-driven allometric scalars or theoretical scalars) shows a similar trend (**Table 4-48** and **Table 4-49**), though the simulations using the theoretical allometric scaling (0.75 and 1) shows overall higher exposures compared to those using the data-driven scalars (0.62 and 0.9). In examining by body weight groups, this trend is the most pronounced with the lowest body weight groups <10 kg: the median BCV exposures were lower than that of healthy adults (**Figure 4-13**). For the lowest body weight group (< 5 kg), more than 25% of pediatric patients are predicted to have exposures below that of the infected rabbits. Interdisciplinary review team determined that a dose escalation for pediatric patients < 10 kg is necessary.

Table 4-47. Simulation for BCV Exposures (Fasted) in Infected Pediatric Subjects using Patient PopPK Model Following Applicant's Proposed Dosage

Fasted, infected subjects: [redacted] (b) (4) **≥ 48 kg: a 200 mg QW x 2 weeks**							
Groups		0 to <0.3 yr (n=53)	0.3 to <2 yr (n=214)	2 to <6 yr (n=265)	6 to <12 yr (n=382)	12 to <18 yr (n=417)	Infected Adult (n=242)
AUCtau (ng*h/mL)	Median	2360	3270	4160	4990	5400	4730
	[5th, 95th]	[950, 4900]	[1240, 6910]	[1360, 10500]	[2010, 12700]	[1940, 14200]	[1850, 12400]
Cmax (ng/mL)	Median	232	314	351	444	392	340
	[5th, 95th]	[42.3, 655]	[72.6, 806]	[78.8, 1040]	[106, 1240]	[103, 1310]	[86.5, 1240]

(Adapted from: Applicant's Response to FDA Information Request received on Jan 29, 2021)

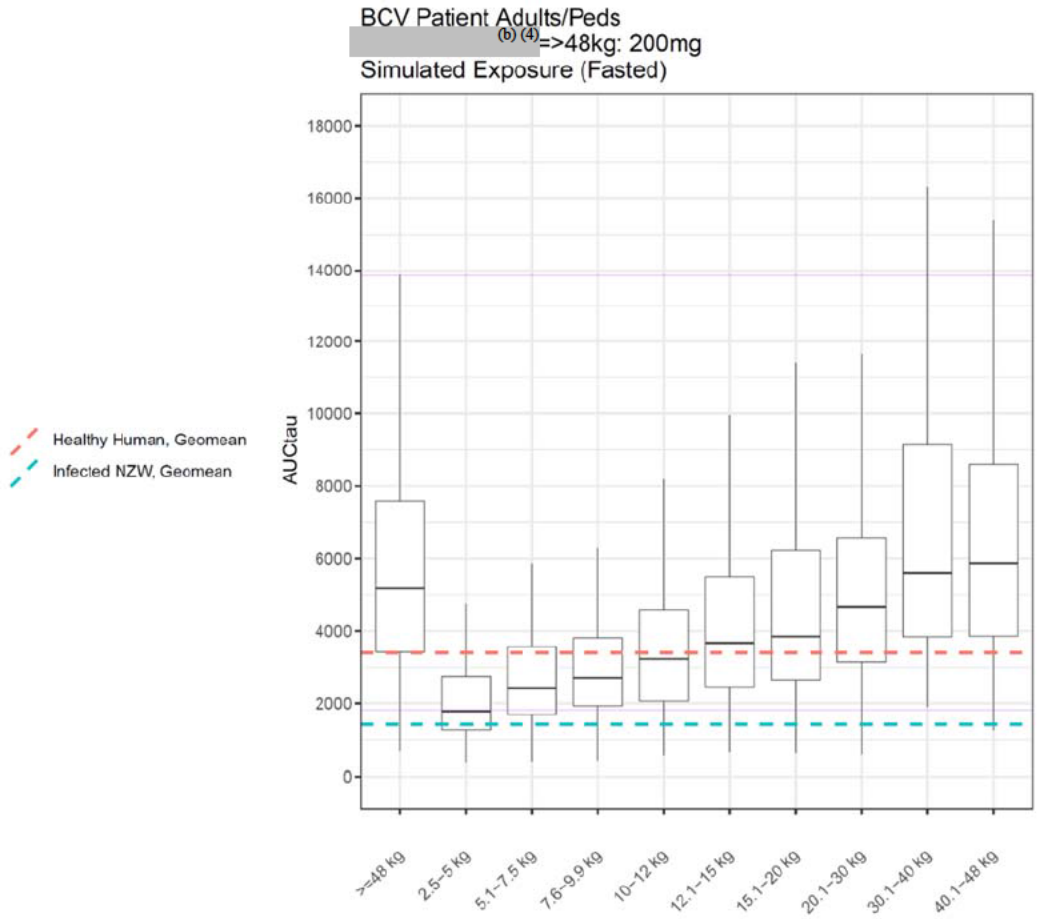
Table 4-48. Reviewer's Simulation for BCV Exposure (Fasted) in Pediatric Subjects Using the Healthy Adults PopPK model (with allometric scalars 0.62 for CL, and 0.9 for V) Following Applicant's Proposed Dosage

Groups		0 to <0.3 yr (n=296)	0.3 to <2 yr (n=587)	2 to <6 yr (n=693)	6 to <12 yr (n=850)	12 to <18 yr (n=559)	Adult (n=242)
AUCtau (ng*h/mL)	Median	2820	3530	4580	5350	4950	3570
	[5th, 95th %tiles]	[1550, 5190]	[1840, 6690]	[2250, 8060]	[2690, 9890]	[2370, 9920]	[1890, 7560]
Cmax (ng/mL)	Median	558	681	838	957	818	554
	[5th, 95th %tiles]	[285, 1010]	[342, 1290]	[412, 1530]	[468, 1880]	[356, 1780]	[266, 1300]

Table 4-49. Reviewer's Simulation for BCV Exposure (Fasted) in Pediatric Subjects Using the Healthy Adults PopPK model (with theoretical allometric scalars 0.75 for CL, and 1 for V) Following Applicant's Proposed Dosage

Groups		0 to <0.3 yr (n=296)	0.3 to <2 yr (n=587)	2 to <6 yr (n=693)	6 to <12 yr (n=850)	12 to <18 yr (n=559)	Adult (n=242)
AUCtau (ng*h/mL)	Median	3770	4220	5010	5560	4610	3600
	[5th, 95th %tiles]	[2080, 6570]	[2460, 7930]	[2350, 8980]	[2850, 10500]	[2140, 8960]	[1850, 7390]
Cmax (ng/mL)	Median	704	806	945	1000	748	555
	[5th, 95th %tiles]	[364, 1350]	[462, 1520]	[405, 1710]	[515, 1940]	[325, 1590]	[260, 1220]

Figure 4-13. Plasma BCV AUCtau Across Body Weight Bands in Patients with Non-Orthopoxvirus Infection Following Applicant's Proposed Dosage (Patient PopPK model)



Source: FDA reviewer's analysis using the patients PopPK model (BCV-MS-02). Purple lines denote upper and lower bounds of 90% prediction interval of simulated patient adult exposure. Dashed orange line represents the geometric mean AUC_{tau} (3,400 ng*h/mL) for healthy adults. Dashed blue line represents the geometric mean AUC_{tau} (1410 ng*h/mL) for the rabbit model.

Simulation of BCV exposures following the review team's recommended dosing regimen

Following the review team's final recommended dosing regimen:

- Weight <10 kg: 6 mg/kg oral suspension under fasted condition
- Weight 10 kg to less than 48 kg: 4 mg/kg oral suspension under fasted condition
- Weight 48 kg and above: 200 mg oral tablet

Table 4-50 outlines the baseline summary for the virtual population dataset for simulation and

Figure 4-14 presents the projected plasma BCV exposure by body weight groups. Following the review team's final recommended dose, the median BCV exposures in pediatric subjects weighing <10 kg is approaching or above the median healthy adult exposure and the median BCV exposures in pediatric

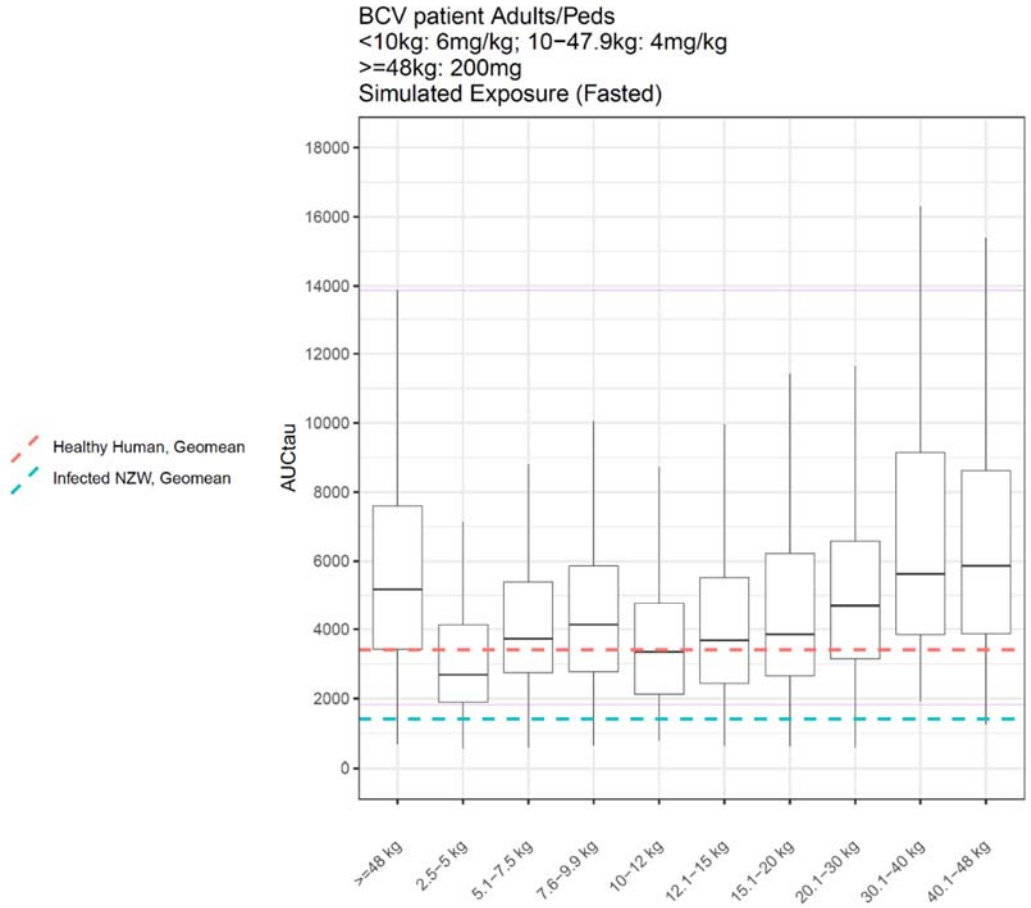
patient weighing <10 kg are expected to be higher than the mean rabbit efficacious exposure. The interquartile range (25th to 75th percentiles) of the predicted exposures across body weight subgroups generally fall within the 90% PI of the simulated exposures for non-orthopoxvirus adult patients.

Table 4-50. Baseline Demographic Summary for Reviewer Revised Virtual Subjects (N=6454)

Weight Bands, kg	>=48	2.5-5	5.1-7.5	7.6-9.9	10-12	12.1-15	15.1-20	20.1-30	30.1-40	40.1-47.9
Subject Count	(n=1322)	(n=400)	(n=426)	(n=448)	(n=490)	(n=608)	(n=704)	(n=1240)	(n=240)	(n=576)
Median Weight, kg	69.2 [max 150]	3.7	6.2	8.7	11.0	13.3	17.6	24.8	34.4	43.8
Median age, years	16.8 [max 71]	0.17	0.25	0.75	1.6	2.7	4.4	8.0	9.8	12.2

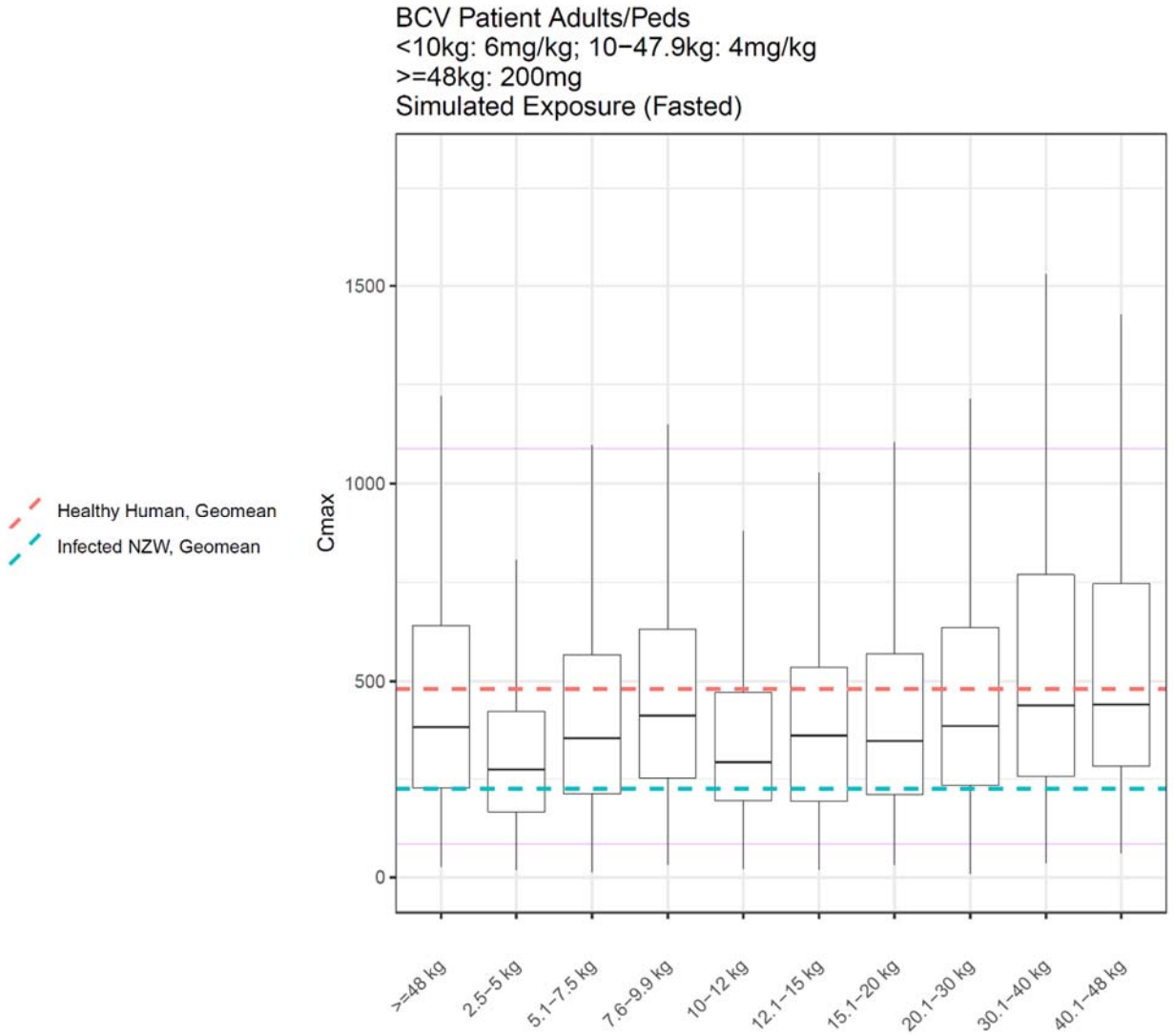
Source: FDA reviewer's analysis.

Figure 4-14. Plasma BCV AUCtau Across Body Weight Bands in Patients With Non-Orthopoxvirus Infection *Following Review Team's Proposed Dosage*



Source: FDA reviewer's analysis using the patients PopPK model (BCV-MS-02). Purple lines denote upper and lower bounds of 90% prediction interval of simulated patient adult exposure. Dashed orange line represents the geometric mean AUCtau (3,400 ng*h/mL) for healthy adults.

Figure 4-15. Plasma BCV Cmax Across Body Weight Bands in Patients with Non-Orthopoxvirus Infection Following Review Team's Proposed Dosage



Source: FDA reviewer's analysis using the patients PopPK model (BCV-MS-02). Purple lines denote upper and lower bounds of 90% prediction interval of simulated adult patient maximal concentration (Cmax) following first dose. Dashed orange line represents the geometric mean Cmax (480 ng/mL) for healthy adults.

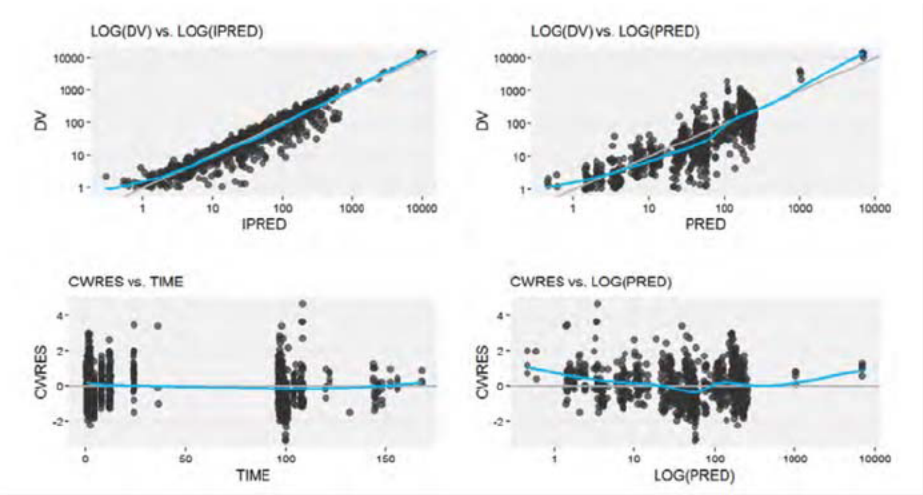
Listing of analyses codes and output files

File Name	Description	Location in \\cdsnas\pharmacometrics\

Revised Virtual Subjects Dataset	Revised peds subject by combining newly generated subjects with originally submitted subjects to increase sample size.	Additional peds subjects: \\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Brincidofovir_NDA214460-61_JLiu\SIM_01292020_after_IR\data\peds_additional.xlsx Original peds subjects: \\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Brincidofovir_NDA214460-61_JLiu\SIM_01292020_after_IR\data\pop_2.csv Summary of age and weight for combined virtual subjects (N=6454): \\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Brincidofovir_NDA214460-61_JLiu\SIM_01292020_after_IR\scripts\VirtualSubjectSummary_FINAL.xlsx
R Script for healthy pop PK simulation (fixed or data-driven allometric scalers)	User specified allometric scaler values are modified in the inputs being parsed to pre-specified ODEs	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Brincidofovir_NDA214460-61_JLiu\SIM_01292020_after_IR\scripts\healthy-sims2_modifiedAllometry.R \\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Brincidofovir_NDA214460-61_JLiu\SIM_01292020_after_IR\scripts\healthy-sims2.R
R Script for patient pop PK simulation (6 mg/kg, 4 mg/kg, 200 mg)	Only run the lines for 6 mg/kg for subgroups	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Brincidofovir_NDA214460-61_JLiu\SIM_01292020_after_IR\scripts\patient-sims.R
NONMEM dataset and model for rabbit animal model		\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Brincidofovir_NDA214460-61_JLiu\NONMEM\popPK_animal\
NONMEM dataset and model for final healthy PopPK model (fixed or data-driven allometric scalers)	Run 2: BCV PopPK, fixed allometric scalers Run 9: BCV PopPK, data-driven allometric scalers from Patient PopPK model	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Brincidofovir_NDA214460-61_JLiu\NONMEM\popPK_Human\runs\
NONMEM dataset and model for final patient PopPK model	BCV PopPK	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Brincidofovir_NDA214460-61_JLiu\NONMEM\popPK_infected_adult_kids\runs\run_9\

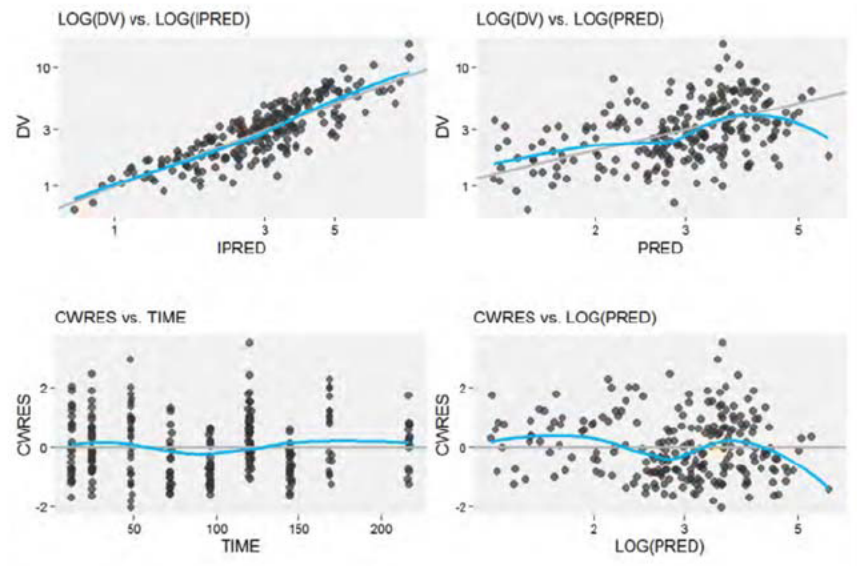
Additional Figures and Tables

Figure 4-15. GOF Plots for Rabbit Final Model for BCV



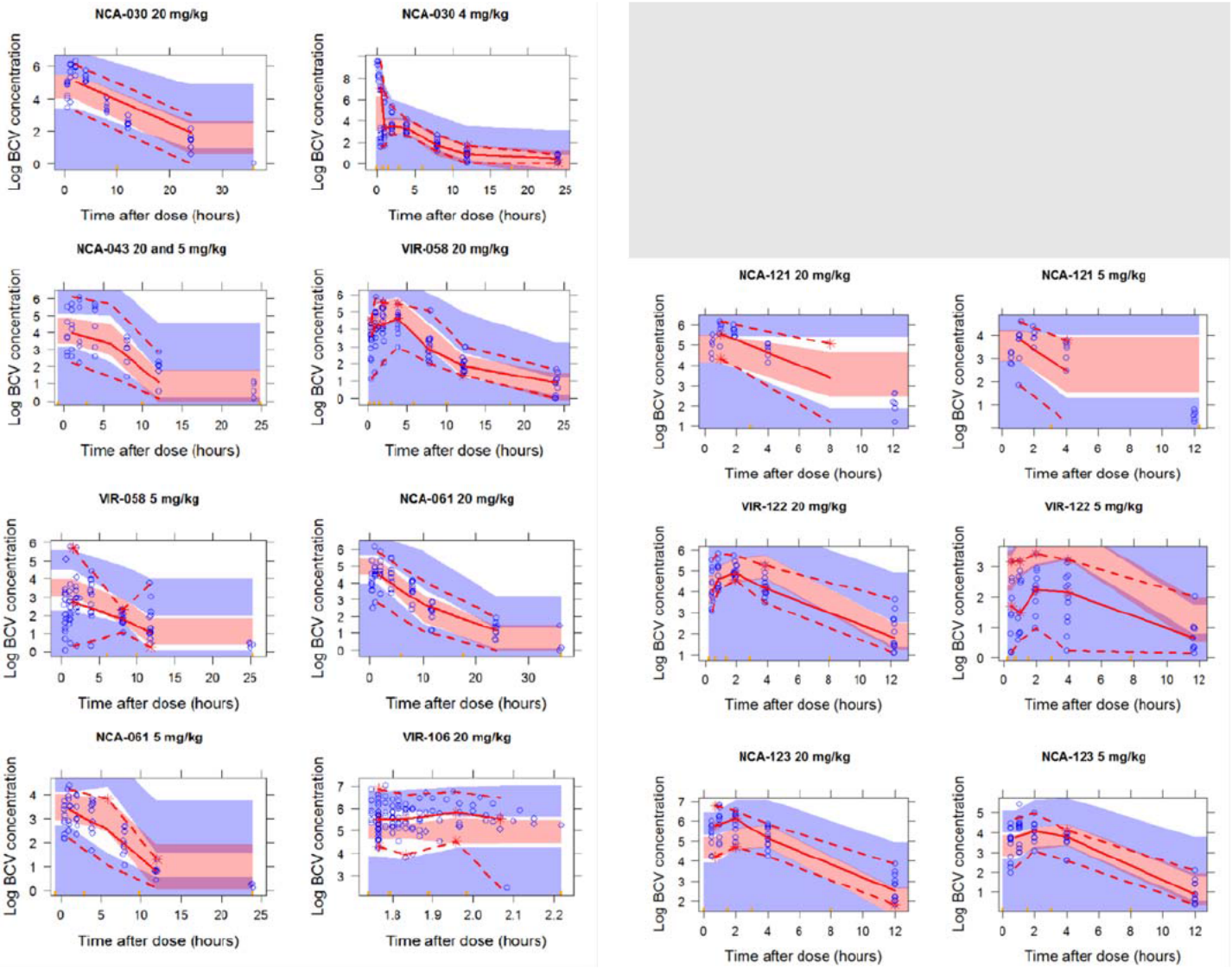
Source: Applicant's CMX001-MS-103 report. Figure 7. Page 42.

Figure 4-16. GOF Plots for Rabbit Final Model for CDV-PP



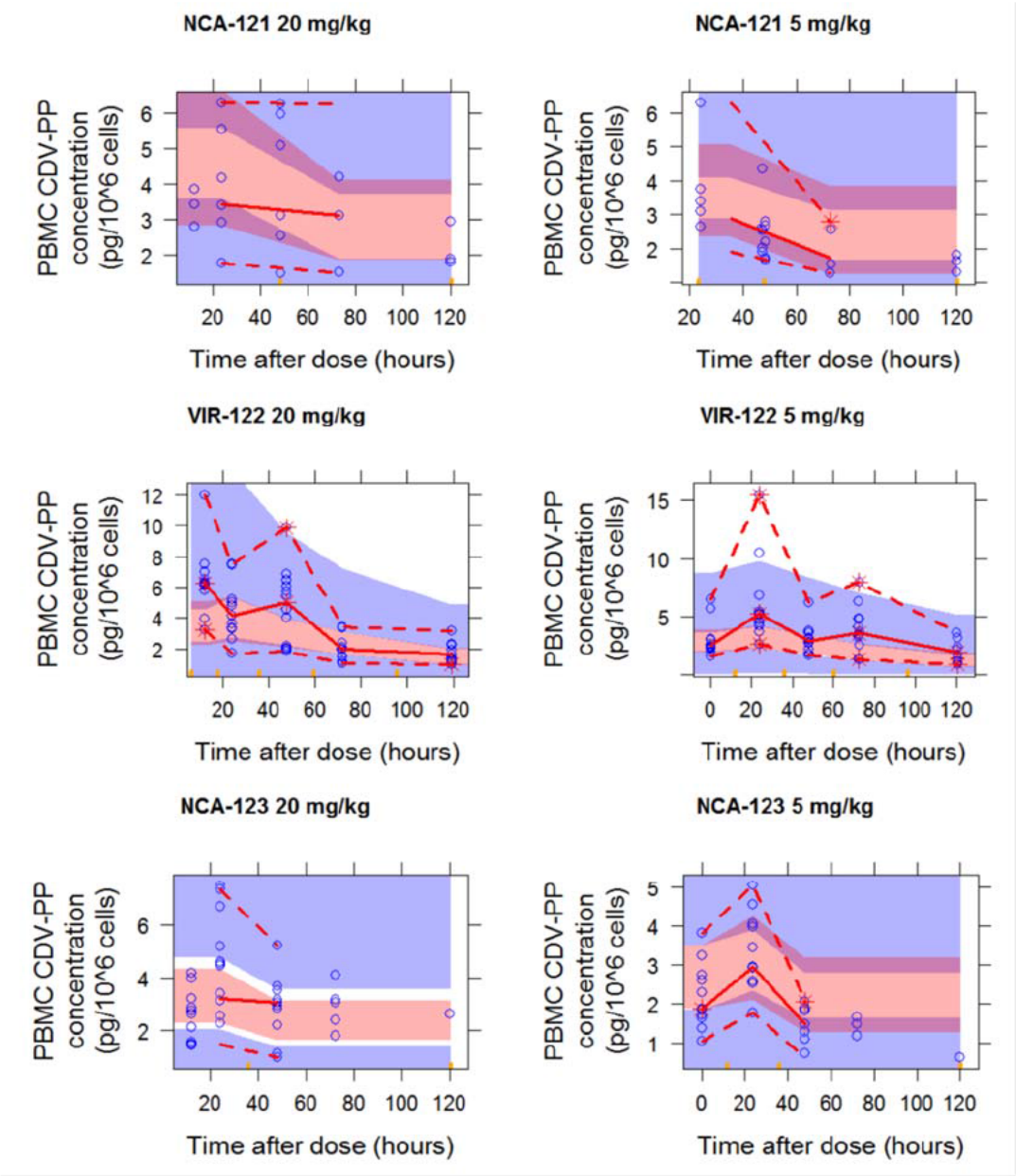
Source: Applicant's CMX001-MS-103 report. Figure 10. Page 46.

Figure 4-17. VPCs for Rabit BCV PK Model



Source: Applicant's report, CMX001-MS-103. Figures 8. Pages 43-44.

Figure 4-18. VPCs for Rabbit CDV-PP PK Model



Source: Applicant's report, CMX001-MS-103. Figures 11. Page 47.

Table 4-51. Clinical Studies Included in the Healthy Human PopPK Analysis

Study Number, Type, Location	Study Design, N	BCV Dose and Regimen[a]	PK Sampling
CMX001-114 Bioequivalence/ Food Effect	Phase 1, open-label, randomized, single-dose, four-period, crossover study in healthy subjects N = 24	200 mg BCV via two 100 mg tablets (fasted and fed [with a low-fat or moderate-fat meal] conditions) 200 mg BCV via 20 mL of a 10 mg/mL liquid suspension (fasted condition)	Plasma BCV PBMC CDV-PP
CMX001-115 Bioequivalence Study	Phase 1, open-label randomized, single-dose, two-period, crossover study in healthy subjects N = 52	100 mg BCV tablet, new formulation 100 mg BCV tablet, current formulation	Plasma BCV
CMX001-123 IV Single Ascending Dose	Phase 1, randomized, double-blind, placebo-controlled study in healthy subjects N = 30	10 mg BCV, 2-hour IV infusion[b] 25 mg BCV, 2-hour IV infusion[b] 50 mg BCV, 2-hour IV infusion 50 mg BCV, 4-hour IV infusion	Plasma BCV PBMC CDV-PP
CMX001-124 Relative Bioavailability/ Bioequivalence	Phase 1, open-label, single-dose, randomized, two-period, crossover study in healthy subjects N = 24	100 mg BCV CMX001-P-SU-(b) (4)-001 suspension 100 mg BCV (b) (4) 150-mL fill suspension	Plasma BCV PBMC CDV-PP (Treatment A only)
CMX001-125 IV Multiple Ascending Dose	Phase 1, randomized, double-blind, placebo-controlled, multiple ascending, dose-escalation study in healthy subjects N = 20	10 mg BCV, 2-hour IV infusion BIW (4 doses) 20 mg BCV, 2-hour IV infusion QW (4 doses) 20 mg BCV, 1-hour IV infusion QW (4 doses)	Plasma BCV PBMC CDV-PP
CMX001-126 Bioequivalence Study	Phase 1, open-label, randomized single dose, two-period, crossover study in healthy subjects N = 50	100 mg BCV tablet, (b) (4) 100 mg BCV tablet, CMX001-P-CTB-PCI-009	Plasma BCV PBMC CDV-PP
CMX001-127 Absolute Bioavailability Study	Phase 1, randomized, single-dose, two-period, crossover study in healthy subjects N = 24	200 mg BCV CMX001-P-SUS-(b) (4) 010 suspension 20 mg BCV, 2-hour IV infusion, CMX001-P-IVS-PPS-003 100 mg BCV CMX001-P-SUS-(b) (4) 010 suspension 10 mg BCV, 2-hour IV infusion, CMX001-P-IVS-(b) (4) 003	Plasma BCV PBMC CDV-PP

Source: Applicant's CMX001-MS-104 report. Table 1 (partial). Page 14.

Table 4-52. Summary of Continuous and Categorical Covariates in Healthy Human PopPK Dataset

Covariate	114 (N = 24)	115 (N = 52)	123 (N = 30)	124 (N = 24)	125 (N = 20)	126 (N = 50)	127 (N = 24)	Total (N = 224)
Age (y)	31.4 (9.84) 29.0 [20.0, 51.0]	34.0 (8.90) 32.5 [19.0, 52.0]	24.5 (6.25) 22.0 [18.0, 46.0]	48.1 (9.71) 50.5 [27.0, 59.0]	53.1 (9.26) 57.0 [29.0, 65.0]	50.2 (8.23) 50.5 [33.0, 65.0]	27.8 (8.89) 25.5 [19.0, 54.0]	38.6 (13.5) 37.0 [18.0,65.0]
BMI (kg/m^2)	27.4 (2.74) 27.2 [22.7, 32.0]	25.9 (2.97) 25.8 [18.6, 31.4]	24.1 (3.17) 23.8 [19.0, 30.5]	27.1 (2.56) 27.3 [21.7, 30.9]	26.3 (2.84) 25.9 [21.4, 31.2]	27.4 (3.05) 27.7 [20.5, 32.3]	24.9 (2.80) 24.9 [19.5, 29.2]	26.2 (3.11) 26.2 [18.6,32.3]
BW (kg)	88.6 (7.92) 87.8 [76.1, 104.0]	82.1 (12.5) 81.2 [56.6, 112.0]	78.7 (10.9) 78.0 [61.5, 104.0]	73.4 (9.80) 72.5 [56.5, 97.6]	77.6 (12.6) 77.3 [59.8, 106.0]	73.6 (11.1) 73.3 [54.7, 101.0]	79.7 (10.9) 80.3 [60.4, 102.0]	78.8 (11.9) 78.5 [54.7, 112.0]

Covariate	Category	114 (N = 24)	115 (N = 52)	123 (N = 30)	124 (N = 24)	125 (N = 20)	126 (N = 50)	127 (N = 24)	Overall (N = 224)
Sex	Male	24 (100%)	51 (98.1%)	30 (100%)	1 (4.17%)	9 (45.0%)	5 (10.0%)	24 (100%)	144 (64.3%)
	Female	0 (0.0%)	1 (1.92%)	0 (0.0%)	23 (95.8%)	11 (55.0%)	45 (90.0%)	0 (0.0%)	80 (35.7%)
Food status	Fed	12 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (5.36%)
	Fasted	12 (50.0%)	52 (100%)	30 (100%)	24 (100%)	20 (100%)	50 (100%)	24 (100%)	212 (94.6%)
Formulation	(b) (4) tablet	18 (75.0%)	26 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	25 (50.0%)	0 (0.0%)	69 (30.8%)
	(b) (4) 150-mL fill suspension	6 (25.0%)	0 (0.0%)	0 (0.0%)	12 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (8.04%)
	(b) (4) tablet	0 (0.0%)	26 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	26 (11.6%)
	Solution (IV)	0 (0.0%)	0 (0.0%)	30 (100%)	0 (0.0%)	20 (100%)	0 (0.0%)	12 (50.0%)	62 (27.7%)
	CMX001-P-SUS-(b) (4) suspension	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (50.0%)	0 (0.0%)	0 (0.0%)	12 (50.0%)	24 (10.7%)
	P-CTB-PCI-009 tablet	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	25 (50.0%)	0 (0.0%)	25 (11.2%)

Source: Applicant's CMX001-MS-104 report. Tables 5 and 6. Pages 30-31.

Table 4-53. Baseline Characteristics of Patients (Categorical) for Infected Patient PopPK Analysis

Characteristic	CMX001-115	CMX001-201	CMX001-202	CMX001-301	CMX001-304	CMX001-350
< 2y	0	0	10.3	0	15.2	6.2
2 to < 6y	0	0	23.1	0	20.1	11.5
6 to < 12y	0	0	23.1	0	15.8	14.1
12 to < 18y	0	0	12.8	0	13.6	5.7
18 to < 65y	100.0	87.7	28.2	75.9	31.0	54.2
>= 65y	0	12.3	2.6	24.1	4.3	8.3
female	1.9	42.7	28.2	46.2	36.4	43.2
male	98.1	57.3	71.8	53.8	63.6	56.8
healthy volunteer	100.0	0	0	0	0	0
patient	0	100.0	100.0	100.0	100.0	100.0
race: White	76.9	90.1	69.2	84.2	73.9	71.4
race: Black or African-American	15.4	1.8	20.5	7.9	12.5	12.5
race: Asian	0	5.8	2.6	5.6	4.3	5.7
race: American Indian or Alsaska Native	0	0	0	0.3	2.2	0.5
race: Other/Multiple/Unknown	3.8	2.3	7.7	1.7	5.4	9.9
race: Native Hawaiian or Other Pacific Islander	3.8	0	0	0	1.6	0
race: missing	0	0	0	0.3	0	0

Source: Applicant's BCV-MS-02 report. Table 5. Pages 22.

Table 4-54. Baseline Characteristics of Patients (Continuous) for Infected Patient PopPK Analysis

covariate	statistic (sd) [range]	CMX001-115	CMX001-201	CMX001-202	CMX001-301	CMX001-304	CMX001-350
AGE	mean	34.0 (8.90)	50.8 (11.9)	16.3 (18.6)	53 (14.3)	18.7 (20.5)	32.1 (23.8)
AGE	median	32.5 [19.0, 52.0]	51.0 [22.0, 71.0]	10.0 [0.600, 70.0]	56.0 [18.0, 77.0]	11.0 [0.400, 69.0]	29.5 [0.300, 78.0]
BCRCL	mean	89.7 (17.1)	79.0 (32.1)	150 (92.7)	97.3 (39.2)	154 (115)	99.8 (76.4)
BCRCL	median	88.4 [65.8, 134]	70.8 [27.8, 179]	130 [32, 424]	88.6 [26.5, 244]	135 [11.6, 820]	79.3 [10.9, 417]
BSA	mean	2.01 (0.179)	1.91 (0.259)	1.17 (0.526)	1.92 (0.237)	1.21 (0.589)	1.49 (0.550)
BSA	median	2.00 [1.58, 2.42]	1.94 [1.33, 2.67]	1.07 [0.440, 2.18]	1.95 [1.33, 2.51]	1.25 [0.340, 2.52]	1.66 [0.240, 2.46]
BWT	mean	82.1 (12.5)	77.4 (17.8)	39.6 (25.5)	78.5 (16.3)	41.9 (28.4)	55.6 (28.4)
BWT	median	81.2 [56.6, 112]	77.7 [40.6, 132]	30.8 [9.70, 98.2]	78.7 [42.2, 122]	41.0 [7.00, 133]	59.7 [4.20, 131]

Source: Applicant's BCV-MS-02 report. Table 7. Pages 23.

4.5 References

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