

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209939Orig1s000

209940Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology Review

NDA or BLA Number	209939 (tablet) 209940 (solution for intravenous injection)
Link to EDR	\\CDSESUB1\evsprod\NDA209940\209940.enx
Submission Date	3/8/2017
Submission Type	Priority
Brand Name	Prevymis
Generic Name	Letermovir
Dosage Form and Strength	Tablet: 240 mg and 480 mg Injection: 240 mg/12mL and 480 mg/24 mL in a single dose vial
Route of Administration	Oral or intravenous infusion
Proposed Indication	Prophylaxis of cytomegalovirus (CMV) infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant
Applicant	Merck
Associated IND	104706
OCP Review Team	Mario Sampson, PharmD, Jeffry Florian, PhD, Christian Grimstein, PhD, Jieli Sun, PhD, Islam Younis, PhD
OCP Final Signatory	John Lazor, PharmD, Division Director, DCPIV

Table of Contents

1. EXECUTIVE SUMMARY	5
1.1 Recommendations	5
1.2 Post-Marketing Requirements and Commitments	6
2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT	6
2.1 Pharmacology and Clinical Pharmacokinetics	6
2.2 Dosing and Therapeutic Individualization	7
2.2.1 General dosing	7
2.2.2 Therapeutic individualization	7
2.3 Outstanding Issues	9
2.4 Summary of Labeling Recommendations	10
3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW	10
3.1 Overview of the Product and Regulatory Background	10
3.2 General Pharmacology and Pharmacokinetic Characteristics	10
3.3 Clinical Pharmacology Review Questions	12
3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?	12
3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?	12
3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?	14
3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?	19
4. APPENDICES	25
4.1 Summary of Bioanalytical Method Validation and Performance	25
4.2 Summary of Phase 1 studies in healthy volunteers	28
4.3 Individual Study Reviews	33
Efficacy and safety studies in HSCT recipients	34
P001- Phase 3 study	34
P020 – Phase 2 study	37
Exposure-response	40

Phase 3 Exposure-response Analysis	40
Population PK	42
Letemovir Population PK Phase 1 Modeling	42
Letemovir Population PK Phase 3 Modeling	47
Physiologically-based PK modeling.....	52
Letemovir SIMCYP® PBPK Modeling.....	52
Prediction of interaction between letemovir (MK-8228) and substrates of CYP2C8	66
Mass balance	72
P021 – mass balance study.....	72
Food effect	78
P029 – food effect study.....	78
Renal impairment	81
P006 – renal impairment PK study	81
Hepatic impairment.....	87
P015 – hepatic impairment PK study.....	87
Pharmacogenomics	91
Human drug-drug interaction studies	94
P003 – DDI cyclosporine and tacrolimus	94
P013 – DDI tacrolimus	100
P016 – DDI midazolam.....	103
P018 part C – DDI digoxin	107
P022 – DDI mycophenolate	110
P023 – DDI atorvastatin.....	113
P025 – DDI voriconazole	118
P032 – DDI cyclosporine	121
P033 – DDI posaconazole	124
P034 – DDI acyclovir	127
P035 – DDI ethinyl estradiol and levonorgestrel	129
P036 – DDI sirolimus.....	132
Human PK studies in healthy volunteers.....	135
P005 – single and multiple ascending IV doses	135
P009 – multiple escalating doses.....	138

P014 – relative bioavailability or tablet formulations FFP2 and PMF1.....	141
P017 – Absolute BA (30 mg), single ascending IV doses.....	143
P018 Part A – PO single and multiple ascending doses	147
P018 Part B – single and multiple IV doses.....	150
P026 – multiple PO and IV doses	154
P028 – relative bioavailability study of 240 mg and 480 mg tablets	158
Human PK studies in healthy Japanese volunteers	160
P027 – single ascending oral and IV doses in healthy Japanese subjects	160
In vitro studies	164
Metabolism characterization.....	164
Protein binding	166
CYP induction.....	167
CYP inhibition.....	169
Transporter studies	171
PK033 - Pgp.....	171
PK001 – OATP1B1, OATP1B3, OAT3, OCT2, BCRP	172
PK027 – Pgp, MRP2, BCRP, BSEP	174
PK028 – OATP1B1, OATP1B3, OATP2B1, OCT1, OAT1.....	176

1. EXECUTIVE SUMMARY

Letermovir is a first-in-class inhibitor of the cytomegalovirus (CMV) DNA terminase complex. The proposed indication is prophylaxis of CMV infection or disease in adult CMV-seropositive recipients of an allogeneic hematopoietic stem cell transplant (HSCT). In a single phase 3 trial (n=325 on letermovir and n=170 on placebo), the proportion of subjects who failed prophylaxis was 37.5% in the letermovir arm and 60.6% in the placebo arm ($p < 0.0001$). Available dosage forms are tablets (240 mg and 480 mg) and single-dose vial for IV infusion (240 mg/12mL and 480 mg/24 mL). The proposed dosing regimens are 480 mg PO or IV QD and 240 mg when given with cyclosporine.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 209939 and 209940. This NDA is approvable from a clinical pharmacology perspective. Selected recommendations/comments are summarized below.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	A single pivotal trial provides primary evidence. The dose-response relationship for antiviral activity in a phase 2 study provides supportive evidence.
General dosing instructions	The proposed dose of 480 mg PO or IV QD (240 mg when given with cyclosporine) is considered to be safe and effective.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Renal impairment (RI): (Refer to Sections 2.2.2 and 3.3.3): ○ No dose adjustment for patients with RI ○ The IV formulation contains hydroxypropyl cyclodextrin, which has been associated with renal toxicity in nonclinical studies. Labeling recommendations for use of IV letermovir in patients with RI have not been finalized. • Hepatic impairment (HI) (Refer to Sections 2.2.2 and 3.3.3): ○ No dose adjustment for mild to moderate HI ○ Use is not recommended in patients with severe HI • Effect of letermovir on coadministered drugs (Refer to Sections 1.2 and 2.2.2): ○ Use of letermovir with pimozide or ergot alkaloids is contraindicated ○ Voriconazole concentrations are significantly reduced when coadministered with letermovir. The labeling recommendation has not been finalized and will be described in an addendum to this review ○ Use of letermovir with CYP3A substrates with a narrow therapeutic range is not recommended unless therapeutic drug monitoring of the CYP3A substrate is available

	○ When used with letermovir, the dose of atorvastatin should not exceed 20 mg ○ Monitor whole blood concentrations of the following drugs because letermovir increases plasma concentrations: cyclosporine, sirolimus, tacrolimus ○ Monitor lab values or adverse events associated with the following drugs because letermovir increases plasma concentrations: statins (myopathy and rhabdomyolysis), repaglinide and rosiglitazone (blood glucose) ○ Monitor drug concentrations or adverse events associated with the following drugs because letermovir may decrease plasma concentrations: phenytoin (drug concentrations), warfarin (INR) • Effect of letermovir in combination with cyclosporine on coadministered drugs ○ Use of letermovir in combination with cyclosporine is not recommended with statins or repaglinide
Bridge between the to-be-marketed and clinical trial formulations	No bridge is needed because the commercial formulation was used in the phase 3 trial.

1.2 Post-Marketing Requirements and Commitments

PMC or PMR	Key issue(s) to be addressed	Rationale	Key considerations for design features
PMC	In vitro induction of CYP2C8 and CYP2C9	In vitro, letermovir was found to induce CYP3A and to not induce CYP2C19. It is recommended that induction of CYP2C8 and CYP2C9 should be evaluated if induction of CYP3A is observed. The results of this study will inform labeling recommendations for use of letermovir with CYP2C8 and CYP2C9 substrates.	

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Letermovir inhibits the CMV DNA terminase complex, which is required for viral DNA replication. Selected letermovir clinical PK data are summarized below:

Absorption: Median T_{max} is 0.75-2.25 hours. Letermovir is a substrate of Pgp. In a food effect study (high-fat meal vs. fasted), letermovir AUC was unchanged. In population PK analyses, absolute bioavailability in healthy adults and patients was estimated at 94% and 35%, respectively.

Distribution: Protein binding is ~99% in vitro. The blood-to-plasma ratio is 0.56. Hepatic uptake is mediated by OATP1B1/3.

Metabolism: Metabolism is a minor elimination pathway.

Excretion: Letermovir is primarily eliminated in feces as unchanged parent. Urinary excretion is <2% of the dose.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing regimen is 480 mg PO or IV QD (240 mg when given with cyclosporine). This was the only dosing regimen evaluated in the phase 3 study and is considered to be safe and effective.

2.2.2 Therapeutic individualization

Renal impairment: In the RI PK study done at a subclinical dose of 120 mg QD, the letermovir total AUC ratio (90% CI) was 1.92 (1.43, 2.58) in subjects with moderate RI (eGFR range of 31-57 mL/min/1.73m²) vs. controls and 1.42 (0.83, 2.43) in subjects with severe RI (12-28 mL/min/1.73m²) vs. controls. Because letermovir disposition is mediated by a saturable elimination process (OATP-mediated hepatic uptake), exposure changes observed at a relatively low dose where saturation has not been achieved may produce greater exposure changes compared to a higher dose where saturation has occurred. Because the observed exposure changes may represent a worst case scenario, we consider the evaluation of the subclinical dose to be acceptable to inform labeling. Because exposure-safety relationships were not identified in the phase 3 study, the <2-fold exposure increase in subjects with moderate or severe RI in the phase 1 study is not of concern. Moreover, in the phase 3 study, there was no association between eGFR and letermovir AUC; this included a sufficient number of subjects with normal renal function, as well as mild and moderate RI. We are unable to explain why a larger exposure increase relative to controls was observed in the moderate RI group vs. the severe RI group, and also unable to explain why RI was only observed to affect the PK of letermovir in the phase 1 study and not in the phase 3 study. We agree with the applicant's proposal that no dose adjustment is necessary for patients with RI.

The IV letermovir formulation contains the excipient hydroxypropyl cyclodextrin. Cyclodextrins have been associated with renal toxicity in nonclinical studies. See the Clinical review for discussion of the safety of IV letermovir in patients with RI. Labeling recommendations for use of IV letermovir in patients with RI have not been finalized and will be discussed in an addendum to this review.

Hepatic impairment: In the HI PK study done at a subclinical dose of 60 mg (moderate HI [Child-Pugh Class B] and 30 mg (severe HI [Child-Pugh Class C]), the letermovir total AUC ratio (90% CI) was 1.59 (0.98, 2.57) in subjects with moderate HI vs. controls and 3.84 (2.94, 4.97) in subjects with severe HI vs. controls. Because letermovir has a saturable elimination process (OATP-mediated hepatic uptake) and exposure changes observed prior to saturation (i.e. at a relatively lower dose) may represent a worst case scenario, the data from the HI can be used to inform labeling. PBPK simulations were consistent with this hypothesis in that reductions in OATP abundance (seen in patients with cirrhosis) had a greater impact on letermovir AUC at a dose of 30 mg vs. 480 mg. Also, PBPK simulations of the HI study at doses of 30 mg and 480 mg predicted slightly higher exposure changes at a dose of 30 mg. We agree with the applicant's proposal that no dose adjustment is necessary for patients with mild to moderate HI, and use in patients with severe HI is not recommended.

Effect of cyclosporine on letermovir: Letermovir is an OATP1B1 substrate and cyclosporine is an OATP1B1 inhibitor. In a phase 1 drug-drug interaction study, cyclosporine increased oral letermovir AUC ~2-fold. In the phase 3 study, 45% of subjects in the letermovir arm used concomitant cyclosporine. The letermovir PO or IV dose was reduced from 480 mg to 240 mg when coadministered with cyclosporine. Although median AUC values in the phase 3 study differed by route of administration and use of cyclosporine (Table 1), exposure-efficacy relationships were flat. We consider the proposed dosing regimen of 480 mg PO or IV QD (240 mg when given with cyclosporine) to be acceptable.

Table 1. Letermovir AUC (ng*h/mL) values in the phase 3 study.

N	Letermovir dose (mg)	Letermovir route of administration	Use of cyclosporine	Median AUC (90% prediction interval)
139	480	PO	No	34,400 (16,900, 73,700)
10	480	IV	No	100,000 (65,300, 148,000)
139	240	PO	Yes	60,800 (28,700, 122,000)
5	240	IV	Yes	70,300 (46,200, 106,000)

Source: Exposure-response dataset (N) and proposed labeling (AUC values).

Effect of letermovir on CYP3A substrates: In the presence vs. absence of a subclinical dose of letermovir 240 mg PO, oral midazolam AUC ratios (90% CI) were 2.25 (2.04, 2.49). We requested that the applicant perform PBPK simulations to predict the effect of letermovir 480 mg PO or IV QD on midazolam exposure (see Section 3.3.4 for more details). Letermovir 480 mg was predicted to be a moderate CYP3A inhibitor as was observed for 240 mg. Also, 480 mg PO letermovir in HSCT recipients was predicted to have a similar effect on midazolam as 240 mg PO letermovir in healthy volunteers. This is consistent with the finding of 3-fold lower C_{max} after oral administration in patients vs. healthy subjects. Based on these results we agree with using the letermovir 240 mg-midazolam study as the basis for labeling recommendations for use of letermovir with CYP3A substrates.

(b) (4)

The combined effect of moderate CYP3A inhibitors letermovir and cyclosporine on CYP3A substrates is unknown. Proposed labeling does not provide a specific recommendation for the use of letermovir and cyclosporine with CYP3A substrates. Instead it states the magnitude of CYP3A-mediated interactions may be different when letermovir is given with cyclosporine, and to consult the cyclosporine labeling. Prior to approval, the effect of letermovir plus cyclosporine on CYP3A substrates will be evaluated by

requesting the applicant to perform a literature search for drug interaction studies of two simultaneously administered moderate CYP3A inhibitors on CYP3A substrates.

Effect of letermovir on CYP2C9/2C19 substrates: Voriconazole is a substrate of CYP2C9, CYP2C19, and CYP3A. In vitro, letermovir was found to induce CYP3A and to not induce CYP2C19; CYP2C9 was not evaluated. In vivo, letermovir is a net inhibitor of CYP3A. When coadministered with letermovir in an interaction study, the voriconazole AUC ratio (90% CI) was 0.56 (0.51, 0.62). This result could be explained by induction of CYP2C9 by letermovir, hence our request for a PMC study to evaluate this in vitro. There is a clinical need for use of voriconazole in the immunosuppressed population. The labeling recommendation has not been finalized and will be described in an addendum to this review.

Effect of letermovir on CYP2C8 substrates: In vitro, letermovir was found to induce CYP3A. Per guidance, induction of CYP2C8 should be evaluated if induction of CYP3A is observed. See section 1.2 for a PMC to determine if letermovir is an inducer of CYP2C8. PBPK predictions were conducted in lieu of a clinical study to evaluate the effect of letermovir on CYP2C8 substrates repaglinide and rosiglitazone (see Section 3.3.4 for more details). A limitation to the modeling was that it is unknown whether letermovir is a CYP2C8 inducer. Coadministration with letermovir was predicted to increase repaglinide AUC by 2-3.5-fold and to increase rosiglitazone AUC by 30-55%. We agree with the applicant's labeling recommendation to monitor glucose more frequently during coadministration of repaglinide or rosiglitazone with letermovir. Because both letermovir and cyclosporine inhibit multiple repaglinide elimination pathways (CYP3A and OATP), we do not recommend coadministration of letermovir in combination with cyclosporine and repaglinide.

Effect of letermovir on statins: Letermovir is an inhibitor of OATP1B1/3 and statins are OATP substrates. In the presence vs. absence of letermovir, the atorvastatin AUC ratio (90% CI) was 3.29 (2.84, 3.82). Proposed labeling states that the atorvastatin dose should not exceed 20 mg when coadministered with letermovir. We agree with this recommendation because it is consistent with atorvastatin labeling for coadministration with other drugs that increase atorvastatin AUC by a similar magnitude.

We agree with the recommendation for other statins, which states that myopathy should be monitored and a dose adjustment may be necessary when coadministered with letermovir.

Because both letermovir and cyclosporine inhibit multiple statin elimination pathways (CYP3A and OATP), we do not recommend use of letermovir and cyclosporine with statins.

2.3 Outstanding Issues

- Whether letermovir is an in vitro inducer of CYP2C8 or CYP2C9
- Whether the combination of moderate CYP3A inhibitors letermovir and cyclosporine results in strong CYP3A inhibition

2.4 Summary of Labeling Recommendations

Below are our clinical pharmacology-related labeling recommendations for instances where we disagree with the applicant's proposed recommendation:

- Effect of letermovir on coadministered drugs
 - CYP2C9/2C19 substrates:
 - See section 1.2 for a PMC to determine if letermovir is an inducer of CYP2C9
 - The labeling recommendation for use of letermovir with voriconazole has not been finalized and will be described in an addendum to this review.
 - CYP2C8 substrates: See section 1.2 for a PMC to determine if letermovir is an inducer of CYP2C8

(b) (4)

- Effect of letermovir plus cyclosporine on coadministered drugs
 - Use of letermovir plus cyclosporine is not recommended with statins or repaglinide
- Safety of the hydroxypropyl cyclodextrin excipient in the IV formulation
 - Cyclodextrins have been associated with renal toxicity in nonclinical studies. See the Clinical review for discussion of the safety of IV letermovir in patients with and without RI. Labeling recommendations for use of IV letermovir in patients with RI have not been finalized and will be discussed in an addendum to this review.
- Pharmacogenomics: remove

(b) (4)

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The letermovir IND (104706) was submitted on 2/18/2009. Letermovir received fast track designation on 5/25/2011, orphan drug designation on 12/12/2011, and breakthrough therapy designation on 2/27/2017.

Letermovir is planned to be available as 240 mg and 480 tablets, as well as 240 mg and 480 mg vials for IV infusion. The indication is CMV prophylaxis in HSCT recipients at a dose of 480 mg QD PO or IV (240 mg when coadministered with cyclosporine). In a single phase 3 trial, the proportion of subjects who failed prophylaxis was 37.5% in the letermovir arm and 60.6% in the placebo arm ($p < 0.0001$).

3.2 General Pharmacology and Pharmacokinetic Characteristics

Selected letermovir clinical pharmacology properties are summarized below (Table 2).

Table 2. Selected letermovir clinical pharmacology properties.

PK	
Exposures in HSCT recipients vs. healthy adults	PO administration: Relative to patients, ~3-fold higher C _{max} and ~2-fold higher AUC in healthy adults IV administration: Relative to patients, similar AUC and ~30% higher C _{max} in healthy adults
Dose proportionality	Letermovir exposures increase more than proportionally with dose. After multiple PO or IV doses of 240 mg and 480 mg, letermovir AUC increased 2.7-fold. After multiple doses of 480 mg and 960 mg IV, letermovir AUC increased 2.8-fold.
Time to steady-state	9-10 days in healthy subjects. Upon multiple doses, letermovir trough concentrations increase from days 2-5 followed by a decline, with steady-state reached by day 9-10.
Accumulation ratio	In healthy subjects, 1.22 for AUC and 1.03 for C _{max}
PK Variability	In the phase 3 study, C _{max} was not reliably estimated. AUC and C _{min} CV% values were 38% and 60%, respectively.
Absorption	
Absolute bioavailability	Absolute bioavailability studies were not conducted. In population PK analyses, absolute bioavailability in healthy adults and patients was estimated at 94% and 35%, respectively.
Median T _{max} (oral)	0.75-2.25 hours
Food effect	The food effect study evaluated exposures after a high-fat (57%), high-calorie (~919 kcal) breakfast compared to fasted. C _{max} and AUC ratios [fed/fasted] (90% CI) were 1.30 (1.04, 1.62) and 1.00 (0.84, 1.17), respectively.
Distribution	
Protein binding	~99%
Volume of distribution	Following IV administration in HSCT recipients, central volume is 3.4 L (IIV not estimated) and peripheral volume is 26 L (IIV = 37%)
Metabolism	
Metabolites make up <4% of drug-related component in plasma. Metabolism is a minor route of elimination. Letermovir is a substrate of UGT1A1, UGT1A3, CYP3A, CYP2D6, and CYP2J2; modulation of these enzymes is not anticipated to significantly alter the disposition of letermovir.	
Elimination	
Mass balance	After oral administration of radio-labeled letermovir, 93% of the dose was recovered in feces (70% as unchanged letermovir) and <2% in urine.
Clearance	4.84 L/hr (IIV = 17%) following IV administration in HSCT recipients
Half-life	After a 480 mg IV dose in healthy adults, the mean apparent terminal half-life is ~12 hours
Drug interactions (in vitro)	
Enzyme inhibition	CYP3A (time-dependent)
Enzyme induction	CYP2B6, CYP3A
Enzyme substrate	Not clinically relevant as metabolism is a minor route of elimination. However, letermovir is a substrate of UGT1A1, UGT1A3, CYP3A, CYP2D6, and CYP2J2
Transporter inhibition ¹	BCRP, BSEP, MRP2, OATP1B1/3

Transporter substrate	OATP1B1/3, Pgp
Other	
QT prolongation	Not detected at a 2-fold supratherapeutic IV dose of 960 mg
Pharmacogenomics	Genetic variants of OATP1B1 or UGT1A1 were not found to impact the PK of letermovir (n=299 subjects)

¹Letermovir is an in vitro inhibitor of Pgp and OAT3 but in vivo studies with digoxin (Pgp) and acyclovir (OAT3) found no effect of letermovir on their PK. IIV = interindividual variability (CV%).

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?

A single pivotal trial P001 provides primary evidence. In a single phase 3 trial (n=325 on letermovir and n=170 on placebo), the proportion of subjects who failed prophylaxis was 37.5% in the letermovir arm and 60.6% in the placebo arm (p<0.0001).

The dose-response relationship for antiviral activity in a phase 2 study of human blood precursor cell transplant recipients provides supportive evidence. In the phase 2 study, the incidence of prophylaxis failure in the letermovir PO QD (60 mg, 120 mg, and 240 mg) and placebo PO QD groups was 49%, 32%, 29%, and 64%, respectively. The incidence of failure between the placebo and treatment groups was significant (p<0.05) for the 120 mg group (p=0.014) and 240 mg group (p=0.007).

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

Yes. In the phase 3 study, the letermovir dosing regimen was considered to be safe and effective in HSCT recipients.

In the applicant's exposure-response analyses, flat relationships for efficacy and safety were observed. These analyses included 325 subjects in the letermovir arm and 170 subjects in the placebo arm of the phase 3 study. A limitation to the exposure-efficacy assessment was the lack of a time-to-event analysis with prophylaxis failure as the event and letermovir concentration as a time-varying covariate. Limitations to the exposure-safety assessment included the inability to accurately predict letermovir C_{max} as well as the use of average exposure over the study (as opposed to exposure on the day prior to the event) for most AEs.

Mean steady-state letermovir AUC in HSCT recipients varied ~3-fold depending on route of administration and on coadministration with cyclosporine (Table 1). Lowest exposures were observed for 480 mg PO without cyclosporine, and highest exposures for 480 mg IV without cyclosporine. The applicant likely predicted that mean exposures would be similar across regimens, given the findings of 94% absolute bioavailability in healthy subjects and ~2-fold higher letermovir AUC in the presence vs. absence of cyclosporine in healthy subjects. Exposures were particularly low for the 480 mg PO without cyclosporine regimen because absolute bioavailability was estimated to be much lower in HSCT recipients (35%). Letermovir 240 mg QD with cyclosporine achieved exposures comparable to 240 mg IV with cyclosporine likely because cyclosporine increases oral absorption. In exposure-response analyses

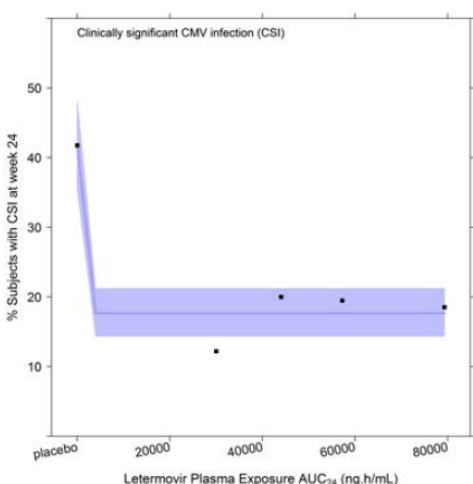
of the phase 3 study, low AUC values were not associated with prophylaxis failure, and high AUC values were not associated with safety concerns. Cmax was not reliably estimated in the phase 3 study.

Given that a large fraction of the phase 3 population successfully used letermovir 480 mg PO without cyclosporine, this suggests that the ~3-fold higher exposures from 480 mg IV are unnecessarily high. We will request that the applicant evaluate lower IV doses in future studies.

Exposure-response for efficacy

The primary efficacy endpoint was risk of clinically significant CMV infection at week 24 post-transplant. Demographic (age, weight, etc) and clinical characteristics (use of immunosuppressants, risk of CMV disease activation) were evaluated as covariates in a logistic regression model and no significant covariates were identified. Letermovir AUC and Cmin were evaluated as exposure metrics. Because many subjects were administered IV and PO letermovir during the study, model-predicted AUC and Cmin values were weighted averages accounting for the number of doses administered by each route during the treatment period. The risk of CMV infection was not associated with AUC (Figure 1) or Cmin.

Figure 1. Observed and predicted rate of clinically significant CMV infection at week 24 post-transplant versus letermovir AUC.



Source: page 32, <\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hgym\04hgym.pdf>.

Exposure-response for safety

In the applicant's initial exposure-safety analysis, various adverse events were evaluated, including cardiac disorders, GI disorders, ear and labyrinth disorders, and renal failure (for a complete list see page 18, <\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hgym\04hgym.pdf>). Letermovir Cmax was not evaluated because it was not reliably estimated in the popPK modeling. Model-predicted exposure on the day of the first event was used for cardiac disorders, GI disorders, renal failure, and ear and labyrinth disorders. For other events, weighted average model-predicted exposures were used. No associations

were found between letermovir AUC and the AEs that were evaluated. Covariates were not evaluated because no significant associations were identified.

The lack of associations between letermovir AUC and arrhythmia or renal failure (full population, or when limited to those with ≥ 1 IV dose) was notable because cardiac disorders (including arrhythmia) were observed in a larger proportion of letermovir subjects compared to placebo subjects in the Clinical review. Cardiac AEs will be described in the Adverse Reactions section of labeling. The phase 3 population used a large number of concomitant medications and the Clinical reviewer found that nearly all subjects with cardiac AEs in the letermovir and placebo arms used at least one medication associated with cardiotoxicity. Also, subjects with a baseline cardiac medical history were more common in the letermovir arm. Renal failure is of interest because the IV formulation contains hydroxypropyl cyclodextrin, and cyclodextrins have been associated with renal toxicity in nonclinical studies. The Clinical reviewer did not find an increased frequency of renal failure among subjects who received IV letermovir. However, an increased frequency of creatinine laboratory abnormalities was observed in the letermovir vs. placebo arm. As this imbalance was seen among the subset of subjects with no IV letermovir therapy, the cyclodextrin does not appear to be driving the increased rate of creatinine abnormalities in the letermovir arm.

In an attempt to assess relationships between letermovir C_{max} and AEs, we asked the applicant to perform exploratory exposure-safety analyses among intensive PK phase 3 subjects (n=75). We asked the applicant to limit the analysis to the intensive PK phase 3 population because presumably C_{max} could be more reliably estimated in this subgroup. Among intensive PK phase 3 subjects, letermovir C_{max} was associated with cardiac disorders, arrhythmias, and renal failure (among the subset of intensive PK subjects with ≥ 1 IV dose). These analyses are exploratory because the associations are potentially confounded by concomitant diseases or medications and may not be applicable to the entire phase 3 population. There will be labeling language to address the potential for cardiac and renal toxicity. When we review future protocols for efficacy studies, we will recommend that sparse samples be collected such that C_{max} can be robustly characterized.

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

Yes. Intrinsic factors for which alternative dosing regimens or management strategies may be required include renal impairment and hepatic impairment.

Renal impairment: The PK of letermovir in subjects with and without moderate or severe RI was evaluated at a subclinical dose of 120 mg QD PO for 8 days. Despite negligible renal elimination of letermovir, total AUC ratio (90% CI) was 1.92 (1.43, 2.58) in subjects with moderate RI vs. controls and 1.42 (0.83, 2.43) in subjects with severe RI vs. controls (Figure 2). Mean letermovir AUC values in subjects with moderate or severe RI were 10,000-11,000 ng*h/mL. Because letermovir has a saturable elimination process (OATP-mediated hepatic uptake) and exposure changes observed prior to saturation (i.e. at a relatively lower dose) may represent a worst case scenario, the data from RI study can be used to inform labeling.

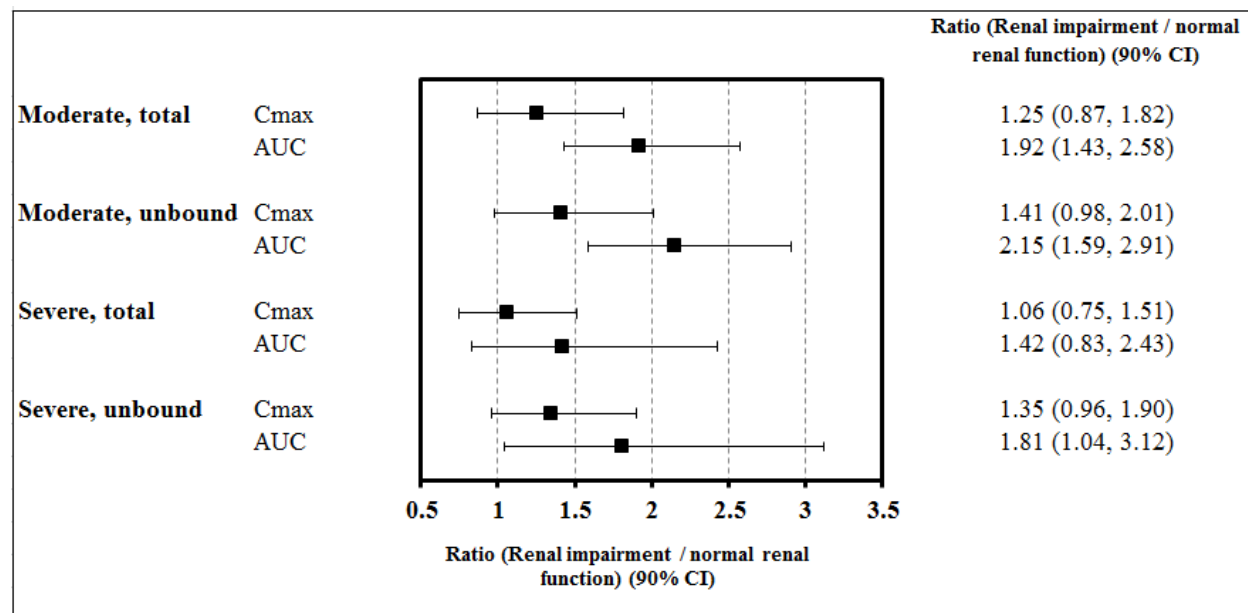
The phase 3 study enrolled subjects with eGFR of ≥ 10 mL/min/1.73m². In the letermovir arm, 230 subjects had normal renal function, 99 had mild RI, 27 had moderate RI, and two had severe RI. In the phase 3 study, there was no association between eGFR and letermovir AUC (Figure 3). Median letermovir AUC was $\sim 49,000$ ng*h/mL in the phase 3 study. The limitation of this analysis is that the phase 3 study population had multiple comorbidities and concomitant medications and is not ideal for identifying the impact of RI on letermovir PK. However, the overlapping distributions of letermovir AUC in phase 3 subjects with and without mild or moderate RI suggests that RI has no major impact on the PK of letermovir at the clinical dose.

We are unable to explain why a larger exposure increase was observed in the moderate RI group vs. the severe RI group, and also unable to explain why letermovir exposure increases as a function of renal impairment were only observed in the phase 1 study and not the phase 3 study. We agree with the applicant's proposal that no dose adjustment is necessary for patients with RI.

Because exposure-safety relationships were not identified in the phase 3 study, the <2 -fold exposure increase in subjects with moderate or severe RI in the phase 1 study is not of concern. The finding of no letermovir AUC increase among subjects in the phase 3 study with mild to moderate RI supports this conclusion.

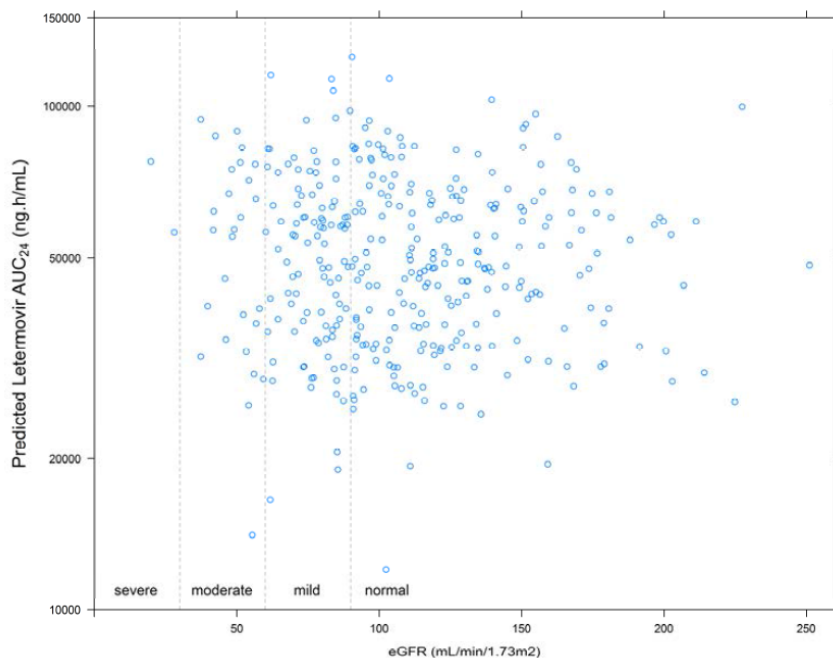
Because RI is not expected to affect the extent of letermovir absorption, it is not expected that RI would have a differential impact on the PK of IV vs. PO letermovir. For this reason the RI labeling recommendations apply to both IV and PO dosing.

Figure 2. Letermovir Cmax and AUC ratios in the RI study (RI/healthy subjects).



Source: prepared by reviewer from data in the study P006 CSR.

Figure 3. Relationship between eGFR and letermovir AUC in phase 3 study P001.



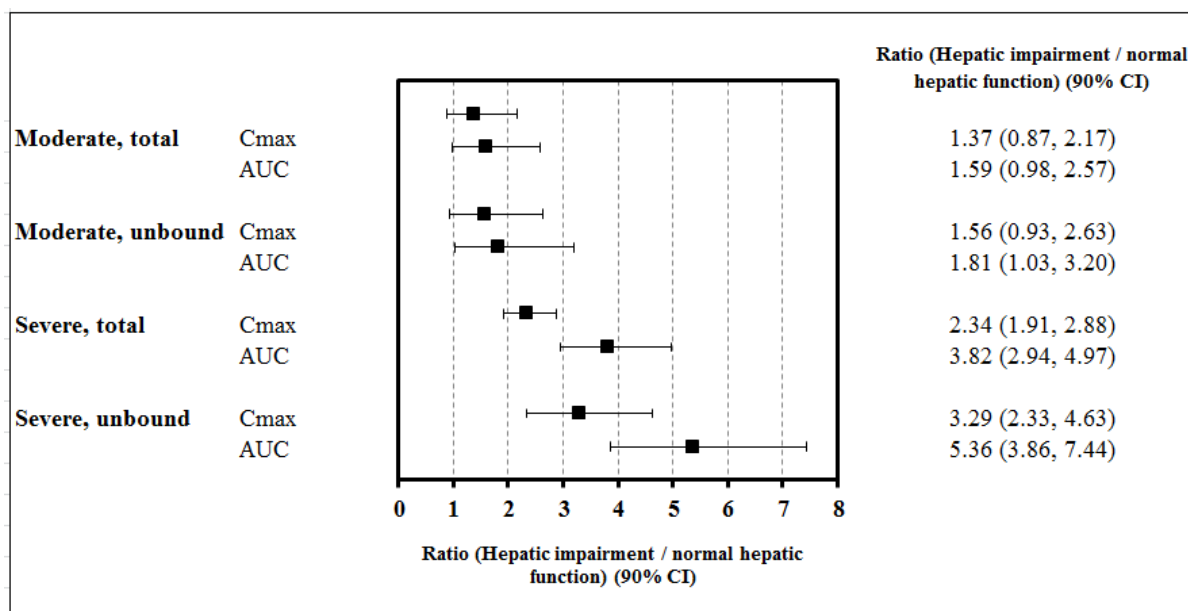
Note: vertical dotted lines represent cut-off values for mild (<90 mL/min/1.73 m²), moderate (<60 mL/min/1.73 m²), and severe (<30 mL/min/1.73 m²) renal impairment

Source: page 1, <\\cdsesub1\evsprod\nda209939\0026\m1\us\efficacy-information-amendment-02aug2017.pdf>.

The IV letermovir formulation contains the excipient hydroxypropyl cyclodextrin. Cyclodextrins have been associated with renal toxicity in nonclinical studies. See the Clinical review for discussion of the safety of IV letermovir in patients with RI. Labeling recommendations for use of IV letermovir in patients with RI have not been finalized and will be discussed in an addendum to this review.

Hepatic impairment: Letermovir is primarily hepatically eliminated. In a study using a subclinical dose of 30-60 mg, letermovir total AUC ratio (90% CI) was 1.59 (0.98, 2.57) in subjects with moderate HI vs. controls and 3.84 (2.94, 4.97) in subjects with severe HI vs. controls (Figure 4). Subjects with mild hepatic impairment were not evaluated.

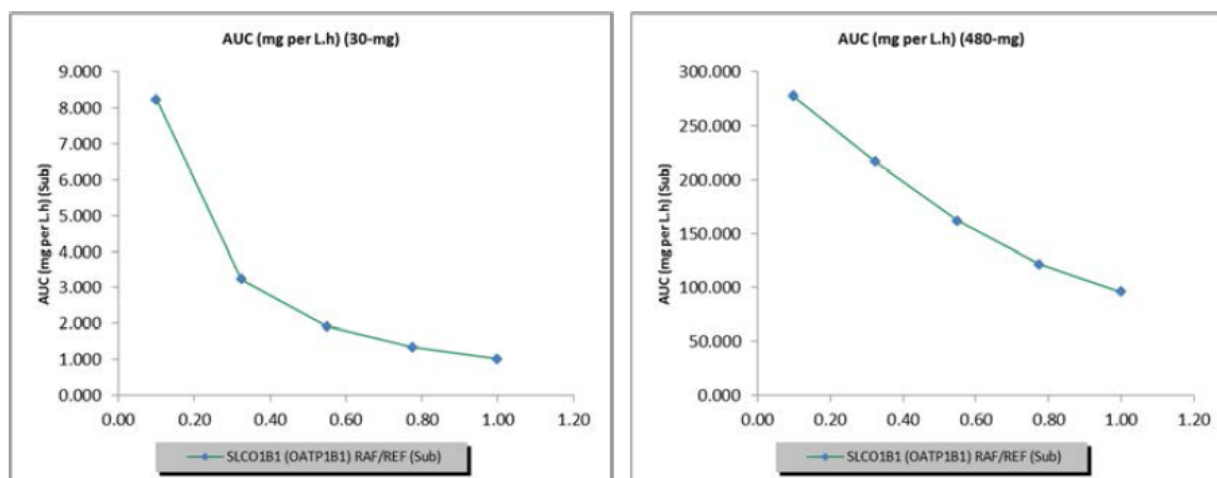
Figure 4. Letemovir Cmax and AUC ratios in the HI study (HI/healthy subjects).



Source: prepared by reviewer from data in the study P015 CSR.

Because letemovir has a saturable elimination process (OATP-mediated hepatic uptake) and exposure changes observed prior to saturation (i.e. at a relatively lower dose) may represent a worst case scenario, the data from HI can be used to inform labeling. PBPK simulations were consistent with this hypothesis in that reductions in OATP abundance (seen in patients with cirrhosis) had a greater impact on letemovir AUC at a dose of 30 mg vs. 480 mg (Figure 5). Also, PBPK simulations of the HI study at doses of 30 mg and 480 mg predicted slightly higher exposure changes at a dose of 30 mg (Table 3).

Figure 5. Impact of OATP1B1 abundance on letemovir AUC following oral administration of multiple once daily doses of letemovir.



Source: Page 9, [\\cdsesub1\evspord\nda209939\0026\m1\us\efficacy-information-amendment-02aug2017.pdf](https://cdsesub1.evspord.nda209939/0026/m1/us/efficacy-information-amendment-02aug2017.pdf).

Table 3. Mean $\pm$ standard deviation observed and SimCYP-predicted pharmacokinetic parameters of letermovir following oral administration of multiple doses of letermovir once daily for 8 days in moderate hepatic impairment patients and matched healthy volunteers (P015).

Dose		Parameters	Moderate Hepatic Impairment Patients	Matched Healthy Volunteers	HI/HV AUC Ratio	Pred./Obs. AUC Ratio
	Observed	f_u	0.01088	0.0095		
60 mg	Observed	C_{max} (ng/mL)	1687 $\pm$ 592.4	1361 $\pm$ 643.3	1.37	
		AUC_{0-24h} (ng*h/mL)	11960 $\pm$ 8164	7121 $\pm$ 3310	1.59	
	Predicted	C_{max} (ng/mL)	1754 $\pm$ 829	1066 $\pm$ 597	1.65	1.20
		AUC_{0-24h} (ng*h/mL)	14839 $\pm$ 12636	7020 $\pm$ 6652	2.11	1.33
480 mg	Predicted	C_{max} (ng/mL)	26234 $\pm$ 9778	19798 $\pm$ 7961	1.33	
		AUC_{0-24h} (ng*h/mL)	381213 $\pm$ 207591	259874 $\pm$ 176899	1.47	

HI = hepatic impairment patients; HV = healthy volunteers; f_u = unbound fraction in plasma

Source: Page 12, \\cdsesub1\evsprod\nda209939\0026\m1\us\efficacy-information-amendment-02aug2017.pdf.

We agree with the applicant's proposal that no dose adjustment is required for patients with mild to moderate HI, and that letermovir is not recommended for patients with severe HI. Based on the lack of exposure-safety relationships identified in the phase 3 study, the 59% exposure increase in subjects with moderate HI in the phase 1 study is not of concern. However, the range of phase 3 exposures is not sufficient to support use in patients with severe HI where 3.8-fold higher exposures would be expected.

Pharmacogenomics: *In vitro* studies indicated that letermovir is both a substrate and an inhibitor of metabolic enzymes and transporters including UGT1A1, UGT1A3, OATP1B1(SLCO1B1), and OATP1B3. An initial exploratory pharmacogenetic (PGx) study based on the pooled data from nine Phase I studies showed that genetic variants of *SLCO1B1* and *UGT1A1* were significantly associated with letermovir PK parameters. As documented in study report 04J9GB, the sponsor further refined the genetic effect estimates for variants in *SLCO1B1* and *UGT1A1* by adding data from three additional Phase I studies to the analysis. Based on pooled data of 12 Phase I studies, the geometric mean of letermovir AUC increased by 18% (95% CI: 6-30%) for subjects carrying one copy of the *SLCO1B1* minor allele (rs4149056) and 42% (95%CI: 10-84%) for subjects carrying two copies of the minor allele when compared to subjects carrying no copies of the minor allele, after adjusting for treatment, race, sex, disease status and weight. The geometric mean of letermovir AUC increased 36% (95% CI: 7-74%) for subjects carrying the *UGT1A1**6 minor allele (rs4148323) compared to subjects carrying no copies of the

minor allele. Other known *SLCO1B1* and *UGT1A1* single copy functional variants did not have a statistically significant impact on letermovir AUC or Cmax.

We agree with the sponsor that based on available data, the effects of the genetic variants (*SLCO1B1* rs4149056 and *UGT1A1**6 rs4148323) on letermovir AUC are unlikely to have a clinically relevant effect on letermovir PK. However, they may account for part of the observed difference in letermovir AUC between Asians and Whites.

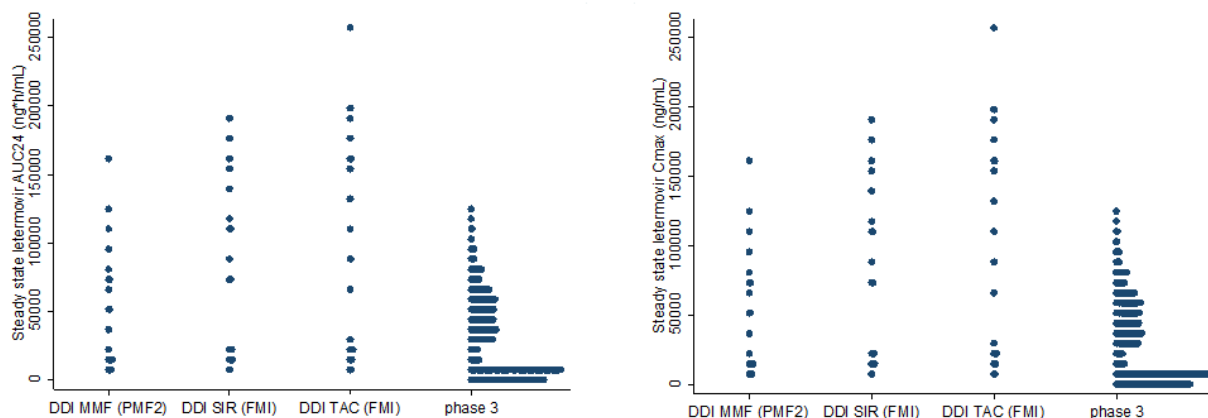
3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Yes, there are clinically relevant drug-drug interactions. Letermovir disposition is affected by OATP inhibitors. Also, letermovir inhibits and/or induces several enzymes and transporters and was found to affect the PK of several drugs. Drug interactions where we disagreed with the applicant's proposed labeling recommendations are discussed in section 2.2.2. Additional issues related to drug interactions are discussed below. Letermovir can be administered without regard to food.

Similarity of letermovir exposures across drug interaction studies and tablet formulations: Several pre-commercial letermovir tablet formulations (FFP2, PMF1, PMF2, and PMF3) were used in drug interaction studies. Exposures of formulations FFP2 and PMF1 were shown to be similar in study P014, PMF1-3 formulations were stated to have similar composition and dissolution according to the applicant, and the PMF3 and FMI formulations differ only by (b) (4)

(b) (4). Relative BA studies comparing the pre-commercial formulations to the commercial tablet formulation FMI were not conducted. Of particular interest were the studies where letermovir was the perpetrator of the interaction, because the magnitude of the interaction may be proportional to exposure of the perpetrator drug. In several of the studies of letermovir as a perpetrator, letermovir exposures were not measured. In studies where letermovir dosing was 480 mg PO and letermovir PK was measured, letermovir exposures were similar to or exceeded exposures seen in the phase 3 study (**Figure 6**). These data are for two of the four pre-commercial formulations of interest. Given that exposures for two of four formulations used in phase 1 studies exceeded phase 3 exposures, exposures in healthy subjects exceed exposures in HSCT recipients, and the applicant's claim of similar composition and dissolution across tablet formulations, it is likely that all of the premarket formulations provided sufficient exposures in interaction studies. Another observation supporting this view is that in drug interaction studies where the letermovir dose ranged from 40 mg BID PO to 480 mg QD PO and where letermovir PK was measured, letermovir AUC and Cmax were not associated with victim drug AUC ratios.

Figure 6. Letermovir Cmax and AUC for a dose of 480 mg QD (240 mg with cyclosporine in phase 3) in phase 1 and phase 3 studies.



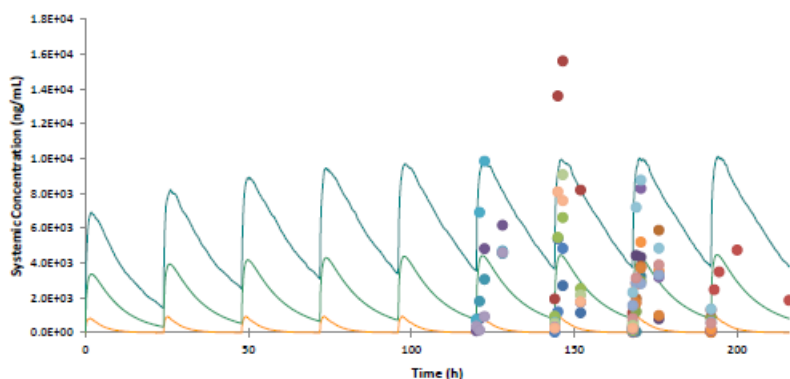
Source: PK parameters submitted by the applicant were plotted by the reviewer. Phase 1 letermovir PK data are in the absence of coadministered drugs. Letermovir was administered PO in the phase 1 studies shown. Phase 3 letermovir exposures shown are for both oral and IV administration. The PMF3 and FMI tablet formulations were used in the phase 3 study. FMI = final market image formulation (i.e. to-be-marketed), MMF = mycophenolate, PMF = premarket formulation, SIR = sirolimus, TAC = tacrolimus.

The effect of letermovir PO vs. IV on the PK of coadministered drugs: In the phase 3 study, IV letermovir resulted in higher exposures versus PO letermovir. However, phase 1 drug interaction studies evaluating the effect of letermovir on other drugs were done using letermovir PO. In the phase 3 study, oral dosing was more common compared to IV dosing (duration of treatment was 100 days and median duration of IV dosing in 99 phase 3 subjects with ≥ 1 IV dose was 12 days). The effect of letermovir on other drugs was evaluated for 12 coadministered drugs in interaction studies. Of the 12 drugs, four are approved for IV use (and could be given IV along with IV letermovir) and their exposures were significantly affected by letermovir: midazolam, digoxin, cyclosporine, and tacrolimus. Drug concentrations of digoxin, cyclosporine, and tacrolimus are routinely monitored and thus we are less concerned over a potential for a greater magnitude interaction for IV vs. PO letermovir. In the case of midazolam, the effect of oral letermovir on midazolam is less for IV midazolam (AUC ratio of 1.47) versus PO midazolam (AUC ratio of 2.25). Also, oral and IV letermovir in HSCT recipients were predicted using PBPK to have similar effects on the exposure of PO midazolam (AUC ratios of ~ 2.5 in both cases). Overall, our conclusion is that the labeling recommendation for use of oral letermovir with CYP3A substrates is also applicable to IV letermovir.

PBPK modeling of the effect of letermovir on CYP3A substrates: The effect of letermovir on midazolam was studied at a subclinical dose of letermovir 240 mg PO. We requested that the applicant perform PBPK simulations to predict the effect of letermovir 480 mg PO or IV QD on midazolam exposure. The applicant's model was able to adequately recover letermovir 480 mg multiple dose PO and IV concentration-time profiles in both healthy subjects and HSCT recipients (Figure 7). The HSCT virtual population was generated from the healthy volunteer virtual population by reducing fraction absorbed

and absorption rate. The applicant's model was also able to adequately recover midazolam AUC values when given with and without letermovir (Table 4). See section 2.2.2 for labeling recommendations for use of letermovir with CYP3A substrates.

Figure 7. Observed and simulated letermovir concentration-time profiles following multiple dosing of 480 mg PO in HSCT recipients.



Source: page 34, <\\cdsesub1\evsprod\nda209939\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hg3\04hg3-addendum.pdf>. Symbols = individual HSCT recipients enrolled in the intensive PK substudy in phase 3 study P001. Lines = 5th percentile, geometric mean, and 95th percentile for a virtual population of N=800 HSCT recipients, respectively.

PBPK modeling of the effect of letermovir on CYP2C8 substrates: PBPK predictions were conducted in lieu of a clinical study to evaluate the effect of letermovir on CYP2C8 substrates repaglinide and rosiglitazone. Repaglinide is a substrate of CYP2C8, CYP3A4, and OATP and rosiglitazone is a substrate of CYP2C8 and CYP2C9 (minor). Letermovir is a net inhibitor of CYP3A4, is an inhibitor of CYP2C8 and OATP, and is not an inhibitor of CYP2C9. The model adequately recovered the effect of letermovir on CYP3A (midazolam DDI study, Table 4) and OATP + CYP3A (atorvastatin DDI study, Table 5). A model limitation is that it is unknown if letermovir is a CYP2C8 inducer. See section 2.2.2 for labeling recommendations for use of letermovir with CYP2C8 substrates.

Table 4. Observed and simulated midazolam PK parameters after a single PO dose of 2 mg midazolam in the presence and absence of letermovir 240 mg PO once daily for six days.

	Observed ^a	Predicted ^b				Predicted/Observed Ratio
Hepatic CYP3A k_{deg} (h^{-1})		0.03	0.0193	0.0193	0.008	
CYP3A induction		-	-	+	+	
AUC _{0-inf} GM (95%CI) MDZ alone (ng/mL*h)	20.59 ± 4.82	23.04 (20.57, 25.80)	23.04 (20.57, 25.80)	23.04 (20.57, 25.80)	23.04 (20.57, 25.80)	1.12
AUC _{0-inf} GM (95%CI) MDZ w/ Letermovir (ng/mL*h)	44.25 ± 13.05	46.71 (41.05, 53.13)	52.76 (46.11, 60.37)	44.53 (38.9, 50.9)	57.3 (49.5, 66.3)	1.06/1.19/1.01/1.29
C _{max} GM (95%CI) MDZ alone (ng/mL)	8.701 ± 1.80	8.68 (7.83, 9.64)	8.68 (7.83, 9.64)	8.68 (7.83, 9.64)	8.68 (7.83, 9.64)	1.00
C _{max} GM (95%CI) MDZ w/ Letermovir (ng/mL)	15.09 ± 3.69	14.42 (13.0, 15.99)	15.21 (13.70, 16.89)	12.89 (11.6, 14.32)	14.25 (12.80, 15.87)	0.96/1.01/0.85/0.94
AUC _{0-inf} GMR (90% CI) ^c	2.25 ^d (2.04, 2.49)	2.03 (1.93, 2.13)	2.29 (2.17, 2.42)	1.93 (1.84, 2.03)	2.49 (2.34, 2.64)	0.91/1.03/0.87/1.12
C _{max} GMR (90% CI) ^c	1.72 (1.55, 1.92)	1.66 (1.61, 1.71)	1.75 (1.69, 1.81)	1.48 (1.44, 1.53)	1.64 (1.59, 1.69)	0.97/1.02/0.86/0.95

^a Arithmetic mean ± standard deviation ^b Geometric mean (GM) ^c LS mean for the observed ratio ^d AUC_{0-inf} -. CYP3A induction was not considered; +, CYP3A induction was considered by applying induction parameters of IndC50 =1.9 and Indmax =8.2 calibrated based on the EC50 and Emax values of letermovir and rifampin estimated from human hepatocyte induction study [Sec. 2.6.5]; GMR = geometric mean ratio, CI= confidence interval. The observed data are from clinical study report PN016 [Ref. 5.3.3.4: P016].

Source: page 25, <\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04kcl7\04kcl7.pdf>.

Table 5. Observed and simulated atorvastatin PK parameters after a single PO dose of 20 mg atorvastatin in the presence and absence of letermovir 480 mg PO once daily for 10 days.

	Observed	Predicted						Predicted/Observed Ratio
OATP1B1 ^a		x 0.5	x 0.2	x 0.2	x 0.2	x 0.1	x 0.1	
Hepatic CYP3A k_{deg} (h^{-1})		0.0193	0.0193	0.0193	0.008	0.0193	0.0193	
CYP3A Induction		-	-	+	+	-	+	
AUC _{0-inf} GM (95%CI) ATV alone (ng/mL*h)	40.2 (29.0, 55.7)	35.8 (31.6, 40.6)	35.8 (31.6, 40.6)	35.8 (31.6, 40.6)	35.8 (31.6, 40.6)	35.8 (31.6, 40.6)	35.8 (31.6, 40.6)	/0.89/
AUC _{0-inf} GM (95%CI) ATV w/ Letermovir (ng/mL*h)	132 (98.0, 178)	91.3 (79.6, 105)	118 (103, 137)	103 (89.3, 120)	106 (91.5, 123)	156 (135, 181)	136 (117, 158)	0.69/0.90/0.79/0.80/1.19/1.03
C _{max} GM (95%CI) ATV alone (ng/mL)	7.12 (5.14, 9.87)	6.05 (5.39, 6.79)	6.05 (5.39, 6.79)	6.05 (5.39, 6.79)	6.05 (5.39, 6.79)	6.05 (5.39, 6.79)	6.05 (5.39, 6.79)	/0.85/
C _{max} GM (95%CI) ATV w/ Letermovir (ng/mL)	15.4 (11.3, 21.0)	17.7 (15.6, 20.0)	22.1 (19.5, 25.1)	18.9 (16.6, 21.5)	19.3 (16.9, 22.0)	27.6 (24.4, 31.3)	23.6 (20.7, 26.9)	1.15/1.44/1.23/1.25/1.80/1.54
AUC _{0-inf} GMR (90% CI)	3.29 (2.84, 3.82)	2.55 (2.43, 2.67)	3.31 (3.13, 3.49)	2.89 (2.74, 3.04)	2.96 (2.81, 3.12)	4.36 (4.10, 4.64)	3.80 (3.58, 4.04)	0.78/1.01/0.88/0.90/1.33/1.16
C _{max} GMR (90% CI)	2.17 (1.76, 2.67)	2.92 (2.79, 3.06)	3.65 (3.46, 3.85)	3.12 (2.97, 3.28)	3.18 (3.03, 3.34)	4.56 (4.31, 4.83)	3.90 (3.70, 4.11)	1.35/1.69/1.44/1.47/2.11/1.80

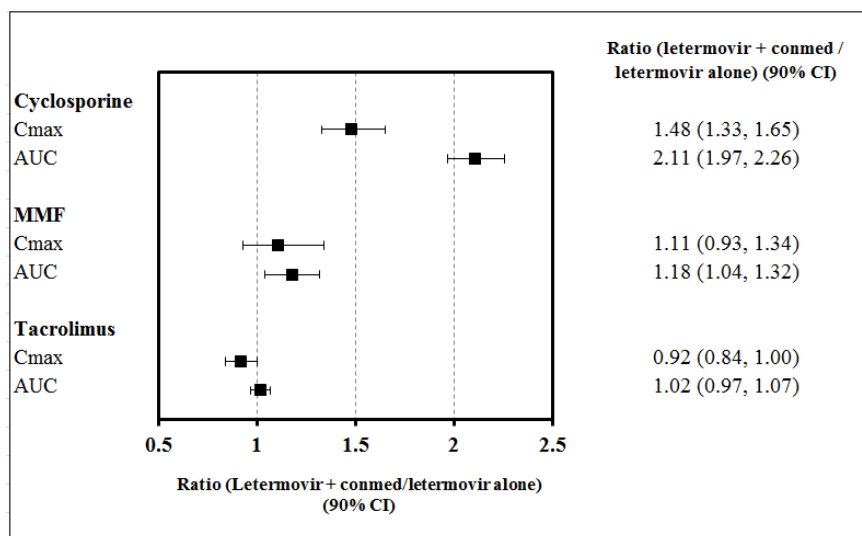
^a Fold change over the K_i value of 1.45 μM estimated from the in vitro experiment [Sec. 2.6.5]; GMR = geometric mean ratio, CI= confidence interval; -, CYP3A induction was not considered; +, CYP3A induction was considered by applying induction parameters of IndC50 =1.9 and Indmax =8.2 calibrated based on the EC50 and Emax values of letermovir and rifampin estimated from human hepatocyte induction study [Sec. 2.6.5]. The observed data are from clinical study report PN023 [Ref. 5.3.3.4: P023].

Source: page 27, <\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04kcl7\04kcl7.pdf>.

Effect of coadministered drugs on the PK of letermovir: No significant change in letermovir PK (i.e. PK parameter ratios and confidence intervals within 0.8-1.25) was observed when coadministered with mycophenolate mofetil or tacrolimus. Cyclosporine increases letermovir AUC by ~2-fold. We agree with proposed labeling (b) (4)

and that the letermovir dose should be reduced from 480 mg to 240 mg when given with cyclosporine.

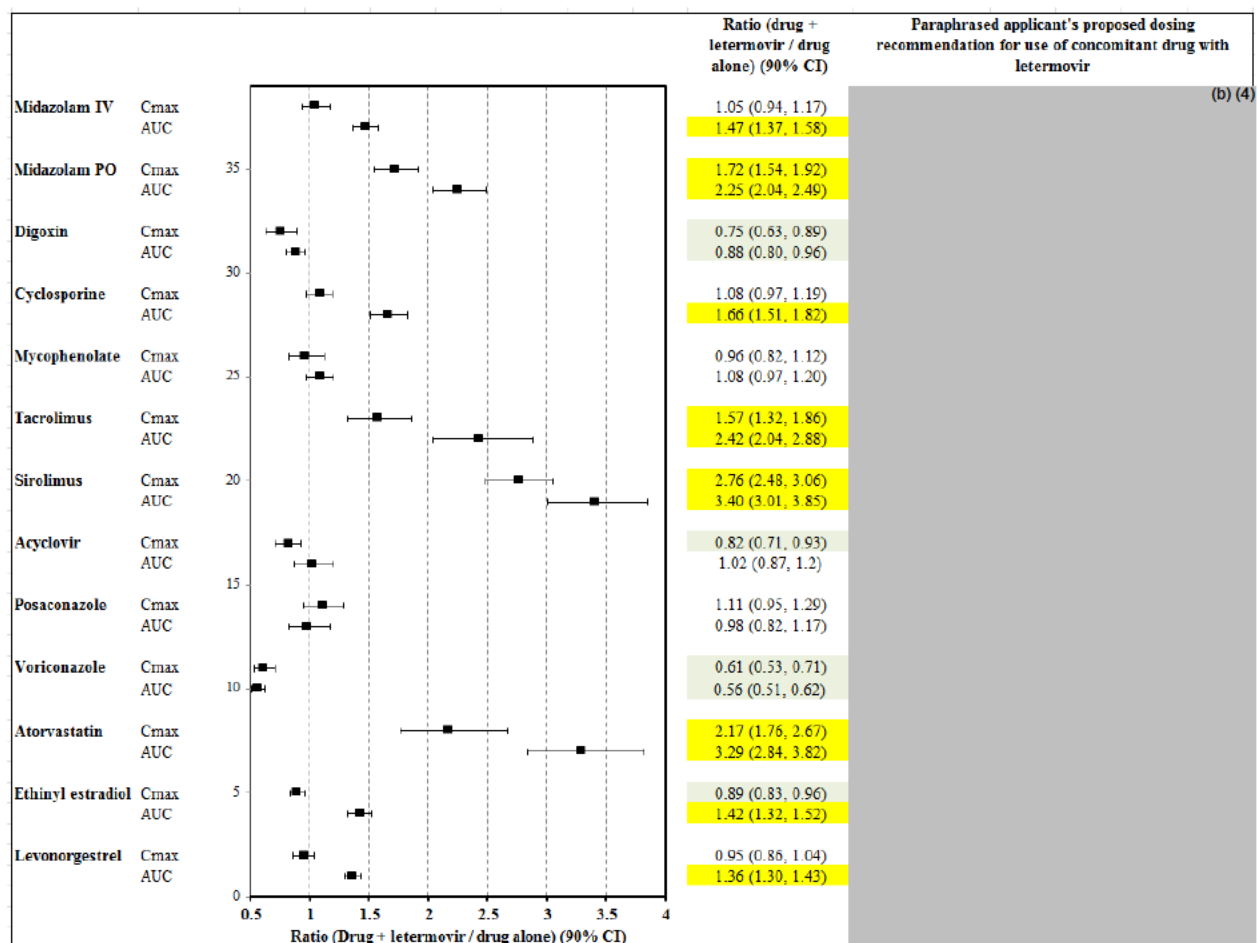
Figure 8. Effect of coadministered drugs on the PK of letermovir.



Source: plotted by reviewer from data in section 12.3 of proposed labeling. MMF = mycophenolate.

Effect of letermovir on the PK of coadministered drugs: Letermovir affected the PK of several drugs evaluated in interaction studies (Figure 9). We agree with the applicant's labeling recommendations for use of these drugs with letermovir except in the case voriconazole and CYP3A substrates with narrow therapeutic ranges (see section 2.2.2). The labeling recommendation for use of letermovir with voriconazole has not been finalized and will be described in an addendum to this review. Letermovir and cyclosporine are likely to be coadministered in this population and both are CYP3A and OATP1B1 inhibitors. The combined effect of these drugs were included in proposed labeling upon our request. Due to inhibition of multiple elimination pathways, we propose that letermovir combined with cyclosporine should not be coadministered with statins or repaglinide (see section 2.2.2). Whether the combination of moderate CYP3A inhibitors letermovir and cyclosporine results in strong CYP3A inhibition is an outstanding issue.

Figure 9. Effect of letermovir on the PK of coadministered drugs.



Source: plotted by reviewer from data in section 12.3 of proposed label. Light green = PK parameter of concomitant drug decreased; yellow = PK parameter of concomitant drug increased.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

We evaluated bioanalytical methods for measurement of letemovir and coadministered drugs in plasma (all LC/MS/MS) in relation to FDA guidance on bioanalytical method validation and found the methods to be acceptable (Table 6, Table 7, Table 8).

Table 6. Summary of letemovir analytical methods.

Method Validation Report	Laboratory	Compound	LLOQ (ng/mL)	Nominal Linear Range (ng/mL)	Matrix
M1210	(b) (4)	Letermovir	0.10	0.10-200.0	Plasma
M1295		Letermovir	1.00	1.00-2000.0	Urine
M1299		Letermovir	0.10	0.10-200.0	Saliva
27AS1438		Letermovir	0.10	0.10-200	Plasma
			5	5-2000	Plasma
			10	10-5000	Plasma
			1	1-2000	Urine
			10	10-5000	Urine
08-061		Letermovir	1.00	1.00-1000	Plasma
09-010		Letermovir	10.0	10.0-10000	Plasma
10-014		Letermovir	1.00	1.00-1000	Alkaline treated Plasma
BP-0032		Letermovir	1.00	1.00-1000	Plasma
(b) (4) 1514-14		Letermovir	1.00	1.00-1000	Plasma

Abbreviations: LLOQ=lower limit of quantification.

(b) (4)

Source: Page 21, <\\cdsesub1\evsprod\nda209939\0000\m2\27-clin-sum\summary-biopharm.pdf>

Table 7. Summary of letermovir analytical methods by study.

Trial	Method	Compounds Analyzed	Matrix	Inter-run Accuracy ^{a,b}	Inter-run Precision %CV ^a
P001	BP-0032	Letermovir	Plasma	94.9 – 103.7	4.7 – 32.5
P003	(b) (4) 1514-14	Letermovir	Plasma	95.1 – 106.2	4.3 – 6.7
P004	BP-0032	Letermovir	Plasma	94.3 – 99.3	4.8 – 37.2
P005	08-061	Letermovir	Plasma	96.4 – 102.8	2.9 – 6.7
P006	08-061	Letermovir	Plasma	98.8 – 105.6	3.2 – 4.3
P007	M1210	Letermovir	Plasma	93.7 – 94.8	3.1 – 5.9
	M1295		Urine	97.0 – 101.0	3.1 – 5.0
	M1299		Saliva	93.3 – 99.7	4.1 – 6.7
P008	M1210	Letermovir	Plasma	95.9 – 98.2	3.4 – 3.7
P009	M1210	Letermovir	Plasma	95.4 – 103.2	4.3 – 10.1
	M1295		Urine	98.6 – 107.2	3.4 – 10.1
P010	M1210	Letermovir	Plasma	89.8 – 97.5	3.6 – 8.9
P011	27AS1438	Letermovir	Plasma	97.3 – 111	2.1 – 9.0
			Urine	97.9 – 102	1.3 – 6.0
P013	27AS1438	Letermovir	Plasma	99.3 – 104	4.4 – 5.0
P014	09-010	Letermovir	Plasma	97.6 – 102.3	6.0 – 7.2
P015	08-061	Letermovir	Plasma	100.5 – 101.7	2.2 – 12.7
	10-014		Plasma (base treated)	99.3 – 105.2	1.3 – 16.7
P016	08-061	Letermovir	Plasma	91.8 – 94.0	Not Calculated
P017	08-061	Letermovir	Plasma	94.1 – 98.4	2.2 – 3.8
P018	08-061	Letermovir	Plasma	93.4 – 98.3	3.5 – 5.5
P019	M1210	Letermovir	Plasma	89.7 – 102.2	1.8 – 11.2
P020	08-061	Letermovir	Plasma	95.5 – 101.9	3.6 – 8.8
P021	08-061	Letermovir	Plasma	96.6 – 99.0	3.6 – 4.1
	09-010			93.2 – 98.3	4.4 – 6.6
P022	BP-0032	Letermovir	Plasma	95.7 – 98.0	3.4 – 9.9
P026	BP-0032	Letermovir	Plasma	89.1 – 100.0	4.4 – 18.9
P027	BP-0032	Letermovir	Plasma	91.1 – 97.5	5.0 – 7.8
P028	(b) (4) 1514-14	Letermovir	Plasma	93.8 – 98.2	5.1 – 9.3
P029	BP-0032	Letermovir	Plasma	90.9 – 97.3	0.2 – 6.4
P032	BP-0032	Letermovir	Plasma	91.5 – 97.0	4.5 – 14.8
P036	(b) (4) 1514-14	Letermovir	Plasma	96.6 – 101.0	3.6 – 5.7
Abbreviations: %CV=percent coefficient of variation; %RE=percent relative error; ISR=incurred sample reproducibility; QC=quality control; SOPs=standard operating procedures.					
a. Statistics based on mean assay performance of low, mid-low, mid-high, high and dilution (if applicable) QC samples from all analytical batches meeting acceptance criteria.					
b. Expressed as [(mean observed concentration/(nominal concentration))] x 100					

Source: Page 22, <\\cdsesub1\evsprod\nda209939\0000\m2\27-clin-sum\summary-biopharm.pdf>

Table 8. Summary of plasma analytical methods for coadministered drugs.

Study	Method	Drug	Calibration range	Inter-run accuracy (%)	Precision (CV%)
P003	55187AECH	Cyclosporine	2-1000 ng/mL	100.4	2.7
P003	125034AFOR	Tacrolimus	0.25-25 ng/mL	99.6	4.0
P013	24XX1081	Tacrolimus	0.47-101 ng/mL	102.0	2.1
P016	011/10-05.MM	Midazolam	0.051-22.538	99.6	6.6
P016	011/10-05.MM	1-hydroxy-midazolam	0.055-5.133	99.6	8.1
P018 part C	11-040	Digoxin	0.04-5.00 ng/mL	93.8-102.9	1.7-4.4
P022	ANI 10415.03	Mycophenolic acid	30-24000 ng/mL	100.8	2.2
P023	(b) (4) 1560-14	Atorvastatin	0.02-20 ng/mL	102.5	7.1
P023	1560-14	2-Hydroxy atorvastatin	0.02-20 ng/mL	105.0	8.0
P023	1560-14	4-Hydroxy atorvastatin	0.02-10 ng/mL	101.5	10.2
P025	85030RQU	Voriconazole	5-2000 ng/mL	99.7	2.4
P033	LCMSC 549	Posaconazole	5-5000 ng/mL	99.7	1.9
P034	65018ALQL	Acyclovir	5-1000 ng/mL	99.8-100.6	2.2-3.4
P035	Ethinyl estradiol	75066AEKE	1-200 pg/mL	99.9	4.2
P035	Levonorgestrel	145017AJPB	10-10000 pg/mL	99.7	5.9
P036	Sirolimus	125035AFOT	100-20000 pg/mL	100.0	2.2

4.2 Summary of Phase 1 studies in healthy volunteers

The majority of phase 1 studies were conducted in healthy white females due to the observation of testicular toxicity in nonclinical studies. A wide range of oral and IV doses were evaluated. Various tablet formulations and two IV formulations were evaluated (Table 9, Table 10, Table 11,

Table 12).

Table 9. Summary of oral letermovir single dose PK studies in healthy volunteers.

Study	Gender	Race	Tablet formulation	Analytical method	Dose (mg)	AUC (ng*h/mL)	AUC type	Cmax (ng/mL)	Central tendency type
P017	Female	White (100%)	PMF1	08-061	30	1802	0-inf	364	Mean
P009	Male	White (100%)	FFP2	M1210	40	2964	0-24h	898	Mean
P009	Male	White (100%)	FFP2	M1210	80	6195	0-12h	1820	Mean
P021 Part 2	Female	White (92%)	FFP2	08-061 09-010	120	11821	0-12h	3715	Mean
P021 Part 2	Male	White (92%)	FFP2	08-061 09-010	120	11200	0-12h	3222	Mean
P021 Part 2	Female	White (92%)	FFP2	08-061 09-010	180	21380	0-12h	6950	Mean
P021 Part 2	Male	White (92%)	FFP2	08-061 09-010	180	14690	0-12h	4358	Mean
P021 Part 2	Female	White (92%)	FFP2	08-061 09-010	240	29640	0-12h	8076	Mean
P021 Part 2	Male	White (92%)	FFP2	08-061 09-010	240	19060	0-12h	5946	Mean
P021 Part 1	Female	White (100%)	FFP2	08-061 09-010	240	34240	0-inf	7340	Mean
P014	Female	White (100%)	FFP2	09-010	240 (12x20)	51940	0-inf	9561	Mean
P014	Female	White (100%)	FFP2	09-010	240 (8x30)	54220	0-inf	9404	Mean
P014	Female	White (100%)	FFP2	09-010	240 (4x60)	49540	0-inf	9097	Mean
P014	Female	White (100%)	FFP2	09-010	240 (2x120)	46890	0-inf	9229	Mean
P014	Female	White (100%)	PMF1	09-010	240	48620	0-inf	9150	Mean
P027	Female	Japanese (100%)	PMF2	BP-0032	240	61791	0-inf	10831	GM
P018 Part A	Female	White (81%)	PMF1	08-061	360	53404	0-inf	9140	Mean
P029	Female	Black (57%)	PMF3	BP-0032	480	86600	0-inf	11800	GM
P022	Female	Black (71%)	PMF2	BP-0032	480	71100	0-inf	12900	GM
P028	Female	White (100%)	PMF3	(b) (4) 1514-14	480 (240x2)	77386	0-inf	11096	GM
P028	Female	White (100%)	PMF2	1514-14	480	84697	0-inf	11880	GM
P032	Female	Japanese-American (100%)	PMF3	BP-0032	480	141000	0-24h	22000	GM
P027	Female	Japanese (100%)	PMF2	BP-0032	480	179574	0-inf	19613	GM
P027	Female	Japanese (100%)	PMF2	BP-0032	720	302584	0-inf	30594	GM
P026	Female	Black (66%)	PMF2	BP-0032	720	104000	0-12h	18000	GM

All studies evaluated letermovir PK in the fasted state with the exception of P029 (food effect study) and P026; for these studies, only PK data for the fasted arm are shown. For drug interaction studies, PK data shown are for when letermovir was administered alone. FFP = fit for purpose; PMF = premarket formulation.

Table 10. Summary of IV letermovir single dose PK studies in healthy volunteers.

Study	Gender	Race	Formulation	Analytical method	Dose (mg)	AUC _{0-inf} (ng*h/mL)	C _{max} (ng/mL)	Central tendency type
P017	Female	White (100%)	(b) (4)	08-061	30	2245	1209	Mean
P017	Female	White (100%)		08-061	60	5436	2953	Mean
P017	Female	White (100%)		08-061	120	12244	6166	Mean
P018 Part B	Female	White (>70%) ^a		08-061	120	18018	5984	Mean
P005	Female	White (100%)	Cyclodextrin	08-061	120	13640	7439	Mean
P018 Part B	Female	White (>70%) ^a	(b) (4)	08-061	240	39158	13180	Mean
P017	Female	White (100%)		08-061	240	31242	14207	Mean
P005	Female	White (100%)	Cyclodextrin	08-061	240	32510	15571	Mean
P027	Female	Japanese (100%)	Cyclodextrin	BP-0032	240	60781	18738	GM
P017	Female	White (100%)	(b) (4)	08-061	480	88569	27328	Mean
P026	Female	Black (66%)		BP-0032	480	101000 ^b	26800	GM
P005	Female	White (100%)	Cyclodextrin	08-061	480	105662	27333	Mean
P027	Female	Japanese (100%)	Cyclodextrin	BP-0032	480	175887	40966	GM
P005	Female	White (100%)	Cyclodextrin	08-061	720	167580	39064	Mean
P027	Female	Japanese (100%)	Cyclodextrin	BP-0032	720	500164	80335	GM
P005	Female	White (100%)	Cyclodextrin	08-061	960	250079	57209	Mean

^aPer protocol, >70% of subjects were to be white. Race was not reported for enrolled subjects. ^bAUC_{0-24h}

Table 11. Summary of oral letermovir multiple dose PK studies in healthy volunteers.

Study	Gender	Race	Tablet formulation	Analytical method	Dose (mg)	Frequency	AUC0-24h (ng*h/mL)	Cmax (ng/mL)	Central tendency type
P015	Female	White (100%)	PMF1	08-061 10-014	30	QD	2732	512	Mean
P009	Male	White (100%)	FFP2	M1210	40	QD	3130	813	GM
P009	Male	White (100%)	FFP2	M1210	40	BID	6226	935	GM
P015	Female	White (100%)	PMF1	08-061 10-014	60	QD	7121	1361	Mean
P009	Male	White (100%)	FFP2	M1210	80	BID	19276	2394	GM
P013	Male	White (100%)	FFP2	27AS1438	80	BID	6640	1709	GM
P006	Female	White (100%)	PMF2	08-061	120	QD	11413	2514	Mean
P021 Part 2	Female	White (92%)	FFP2	08-061 09-010	120	BID	17400	4275	Mean
P021 Part 2	Male	White (92%)	FFP2	08-061 09-010	120	BID	19110	4068	Mean
P021 Part 2	Female	White (92%)	FFP2	08-061 09-010	180	BID	26500	6177	Mean
P021 Part 2	Male	White (92%)	FFP2	08-061 09-010	180	BID	19250	4531	Mean
P003	Female	White (100%)	FMI	(b) (4) 1514-14	240	QD	59599	8160	GM
P021 Part 2	Female	White (92%)	FFP2	08-061 09-010	240	BID	38020	8532	Mean
P021 Part 2	Male	White (92%)	FFP2	08-061 09-010	240	BID	26060	7275	Mean
P018 part C	Female	White (79%)	PMF1	08-061	240	BID	50870	9841	Mean
P018 Part A	Female	White (81%)	PMF1	08-061	240	BID	103946	9721	Mean
P018 Part A	Female	White (81%)	PMF1	08-061	360	QD	55952	7971	Mean
P018 Part A	Female	White (81%)	PMF1	08-061	360	BID	206616	15441	Mean
P003	Female	White (100%)	FMI	(b) (4) 1514-14	480	QD	144000	17600	GM
P022	Female	Black (71%)	PMF2	BP-0032	480	QD	84011	14497	GM
P036	Female	White (86%)	FMI	(b) (4) 1514-14	480	QD	202000	28300	GM
P032	Female	Japanese-American (100%)	PMF3	BP-0032	480	QD	137000	20800	GM
P026	Female	Black (66%)	PMF2	BP-0032	720	BID	143000	24100	GM

AUCtau shown as AUC0-12h x 2 for studies using BID dosing. All studies evaluated letermovir PK in the fasted state with the exception of P029 (food effect study) and P026; for these studies, only PK data for the fasted arm are shown. For drug interaction studies, PK data shown are for when letermovir was administered alone. FFP = fit for purpose; PMF = premarket formulation; FMI = final market image.

Table 12. Summary of IV letermovir multiple dose PK studies in healthy volunteers.

Study	Gender	Race	Formulation	Analytical method	Dose (mg)	Frequency	AUC0-24h (ng*h/mL)	Cmax (ng/mL)	Central tendency type
P018 Part B	Female	White (>70%) ^a	(b) (4)	08-061	120	QD	19869	6014	Mean
P018 Part B	Female	White (>70%) ^a		08-061	240	QD	43914	13972	Mean
P026	Female	Black (66%)	Cyclodextrin	BP-0032	480	QD	123000	28400	GM

4.3 Individual Study Reviews

Electronic resources cited in individual study reviews included the following:

Pharmapendium: <https://www.pharmapendium.com/#/home>

Micromedex: <http://www.micromedexsolutions.com/micromedex2/librarian>

University of Washington Drug Interaction Database Program:

https://www.druginteractioninfo.org/login/?redirect_to=https://didb.druginteractioninfo.org%2f

Dailymed: <https://dailymed.nlm.nih.gov/dailymed/>

Drugs at FDA: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>

FDA list of Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers:

<https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm>

Efficacy and safety studies in HSCT recipients

P001- Phase 3 study

Study #	P001	Study Period	6/20/14-2/16/17
Title	A Phase III Randomized, Placebo-controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-8228 (Letermovir) for the Prevention of Clinically Significant Human Cytomegalovirus (CMV) Infection in Adult, CMV Seropositive Allogeneic Hematopoietic Stem Cell Transplant Recipient		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i> Evaluate the safety and efficacy of letermovir for prevention of CMV infection in HSCT recipients	
<i>Rationale:</i> The proposed indication is (b) (4) Subjects with severe hepatic impairment (Child-Pugh Class C) or eGFR (MDRD) of <10 mL/min were not eligible for the study.	
<i>Study design:</i> Randomized, placebo-controlled, double-blind trial. The primary endpoint is was the proportion of subjects with clinically significant CMV infection through week 24 post-transplant. Subjects were randomized 2:1 to letermovir or placebo. Letermovir treatment was 480 mg PO or IV (60 minute infusion) QD or 240 mg if coadministered with cyclosporine. Treatment duration was through ~100 days post-transplant.	
<i>Population:</i> Adult HSCT recipients seropositive for CMV and within 28 days post-HSCT	
<i>Dose Selection:</i> A letermovir dose of 480 mg was selected so as to exceed exposures associated with failures in a phase 2 study.	
<i>Administration:</i> The protocol did not state how dosing should be administered with regard to timing of meals.	
<i>Formulation:</i> Letermovir 240 mg and 480 mg tablets (PMF3 and FMI formulations) and letermovir for injection (240 mg in 12 mL)	
<i>Excluded concomitant medications:</i> Antiviral drugs used for prevention or treatment of CMV	
<i>PK sampling:</i> Intensive PK was to be performed on day 7 in a subset of ~100 subjects with five samples collected through 24 hours postdose. Pre-dose samples were collected for all subjects on weeks 2, 3, 4, 6, 8, 10, 12,14, and 16.	
<i>Bioanalytical methods:</i> Letermovir method BP-0032	
RESULTS	
Demographics 570 subjects were randomized; 376 received letermovir and 194 received placebo. 295 letermovir subjects and 136 placebo subjects completed the study through week 24 post-transplant. Mean age was 51 years, mean weight was 77 kg, 58% of subjects were male, and 82% of subjects were white.	
Protocol Deviations 47% of randomized subjects had one or more major protocol deviation. The most common major	

deviations were visit out of window ≥ 3 occurrences, eligibility criteria not met (9%), CMV DNA sample not collected (8.5%), and missing ECG (8.0%).

Concomitant medications

The most common concomitant medications by class were systemic antibacterials (97% of subjects), systemic antivirals (98%), and immunosuppressants (98%). In the letermovir arm, common medications included acyclovir (77%), ursodiol (64%), cyclosporine (52%), acetaminophen (50%), and fluconazole (46%).

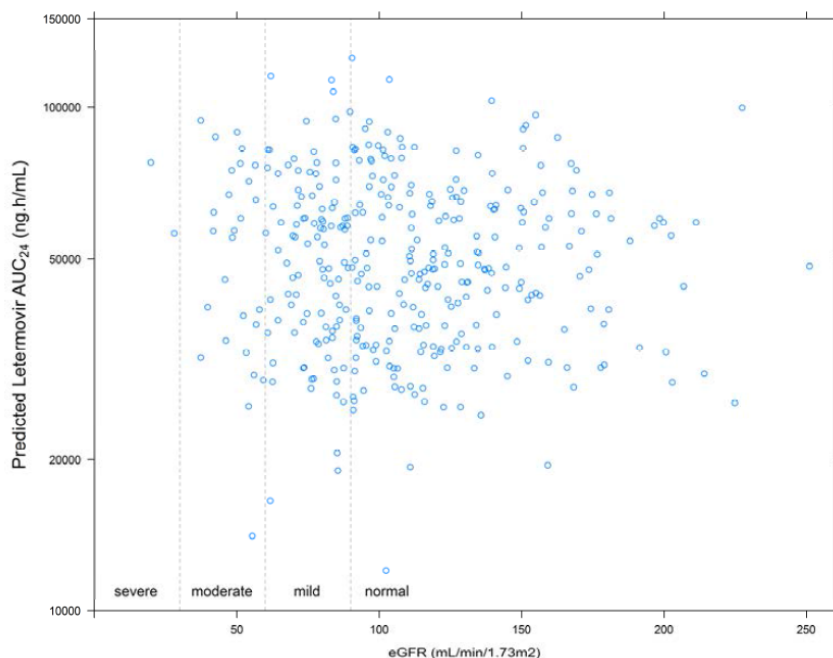
Pharmacokinetics

Letermovir PK findings from this study were described in the phase 3 popPK review.

Renal impairment

The phase 3 study allowed enrollment of subjects with eGFR (MDRD) of ≥ 10 mL/min/1.73m². In the phase 3 population, there was no relationship between eGFR and AUC for subjects with mild to moderate RI; there were an insufficient number of subjects with severe RI to draw a conclusion (Figure 10).

Figure 10. Relationship between eGFR and letermovir AUC in phase 3 study P001.



Note: vertical dotted lines represent cut-off values for mild (<90 mL/min/1.73 m²), moderate (<60 mL/min/1.73 m²), and severe (<30 mL/min/1.73 m²) renal impairment

Source: page 1, <\\cdsesub1\evsprod\nda209939\0026\m1\us\efficacy-information-amendment-02aug2017.pdf>.

Efficacy and safety

See the Biometrics, Clinical Virology, and Clinical reviews for discussions of the safety and efficacy findings.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion	
We reviewed the study design and results only with regard to the PK data. A large number of concomitant medications were used in the letermovir arm. Letermovir exposures are expected to be increased by OATP inhibitors. Reported use of concomitant OATP inhibitors other than cyclosporine included clarithromycin (n=4 subjects), erythromycin (n=6), and rifampin [only an inhibitor after a single dose] (n=2). Based on the 2-fold increased letermovir AUC when given with OATP inhibitor cyclosporine and the lack of exposure-safety relationships identified within a 2-fold AUC range leads us to not be concerned over potentially increased letermovir exposures within a small percentage of the letermovir population. There were major protocol deviations in almost half of the study population. However, these deviations did not appear likely to affect interpretation of the PK results. Based on concerns of whether the renal impairment PK study done at a subclinical dose of 120 mg was applicable to the clinical dose of 480 mg, we evaluated letermovir PK as a function of eGFR in the phase 3 study. The phase 3 study allowed enrollment of subjects with eGFR (MDRD) of ≥ 10 mL/min/1.73m². Ninety-eight percent of phase 3 subjects used concomitant nephrotoxic medications cyclosporine or tacrolimus. The overlapping distributions of exposures in phase 3 subjects with and without RI suggests that RI has no major impact on the PK of letermovir at the clinical dose.	
Labeling Recommendations	
See our review of the phase 3 popPK model for a review of clinical pharmacology labeling statements derived from this study. We agree with the applicants proposal that no dose adjustment is required based on RI. The finding that GFR was not associated with letermovir AUC in this study provided supportive data that there was no significant impact of RI on the PK of letermovir. Primary evidence for the effect of RI on letermovir PK came from RI PK study P006	
Relevant links within the submission	
CSR \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5351-stud-rep-contr\p001v01\p001v01.pdf Bioanalytical report \\cdsesub1\evsprod\nda209939\0011\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\04ktbo\04ktb0.pdf	

P020 – Phase 2 study

Study #	P020	Study Period	3/29/10-10/17/11
Title	A Randomized, Double-Blind, Placebo Controlled Trial to Evaluate the Safety, Tolerability and Antiviral Activity of 12 Weeks' Treatment with a New Antiviral HCMV Drug		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i> Safety and efficacy (primary), as well as PK and exposure-efficacy (secondary)	
<i>Rationale:</i> Determine the dose for future phase 3 trials	
<i>Study design:</i> Multi-center, randomized, double-blind, placebo-controlled, dose-ranging trial. Subjects were randomized to one of four treatment groups: -60 mg QD PO for 84 days -120 mg QD PO for 84 days -240 mg QD PO for 84 days -Placebo QD PO for 84 days	
<i>Population:</i> Male or female allogeneic human blood precursor cell transplant recipients -≥18 years of age -creatinine <2xULN -ALT <3xULN	
<i>Dose Selection:</i> 60 mg was expected to exceed the EC ₉₀ value for 50% of the dosing interval. 240 mg was considered to be the maximum feasible dose.	
<i>Administration with regard to food:</i> Not specified in the protocol	
<i>Formulation:</i> FFP2 60 mg and 120 mg tablets	
<i>Excluded concomitant medications:</i> Certain CYP3A inducers (avasimibe, carbamazepine, phenytoin, rifampicin, and SJW), moderate or strong CYP3A inhibitors, itraconazole	
<i>PK sampling:</i> Trough samples were collected weekly through day 72, and on day 84. In a subset of 25 subjects on day 8 or 15, samples were collected at 0.5, 1, 3, and 8 hours postdose.	
<i>Bioanalytical methods:</i> Letemovir method 08-061	
RESULTS	
Demographics A total of 131 subjects were enrolled (FAS), with 31-34 subjects per group. Mean age was 51 years, 59% of subjects were male, 94% of subjects were Caucasian, and mean weight was 78 kg.	
Protocol Deviations Fourteen subjects had protocol violations. These violations included >7 days between screening CMV sample date and date of randomization (n=2), treatment compliance of <80% (n=3), treatment gap of ≥80 hours (n=6), use of prohibited medication (n=4), and GVHD at randomization (n=1).	
Concomitant medications A large number of medications across various classes were used by ≥25% of the study population (CSR page 89). The effect of cyclosporine, tacrolimus, mycophenolate, acyclovir, valacyclovir, and famciclovir were separately evaluated in population PK modeling for an effect on the PK of letemovir. Cyclosporine was found to affect letemovir PK (43% decrease in letemovir clearance). Also, the effect of letemovir on concomitant immunosuppressant concentrations were evaluated. Increasing doses of letemovir were not found to affect cyclosporine or tacrolimus trough concentrations. There were not enough subjects taking other immunosuppressants to evaluate the effect of letemovir on other immunosuppressants.	

Efficacy

The primary endpoints were incidence and time to onset of CMV prophylaxis failure within the 84 day treatment period. Incidence of failure in the letermovir (60 mg, 120 mg, and 240 mg) and placebo groups was 49%, 32%, 29%, and 64%, respectively. The incidence of failure between the placebo and treatment groups was significant ($p < 0.05$) for the 120 mg group ($p = 0.014$) and 240 mg group ($p = 0.007$). The time to failure between the placebo and treatment groups was significant for the 240 mg group ($p = 0.002$).

Pharmacokinetics

Letermovir C_{max} , AUC, and C_{min} were found to increase approximately proportionally with dose (60-240 mg) (Table 13). However, the confidence intervals for slope estimates were wide due to high variability (CV% of >50%).

Table 13. Model-predicted PK parameters.

Letermovir dose (mg)	C_{max} (ng/mL)	t_{max} (h) ^a	C_{min} (ng/mL)	C_{ss} (ng/mL)	AUC _(0-τ) (ng.h/mL)
60 mg od (N=30)	710.24 (348.84)	1.5 (1.0-1.5)	251.06 (253.79)	442.46 (298.05)	10619.01 (7153.11)
120 mg od (N=29)	1488.63 (714.41)	1.5 (1.5-1.5)	671.11 (477.96)	1028.29 (565.35)	24678.97 (13568.42)
240 mg od (N=31)	3029.53 (2045.73)	1.5 (1.0-2.0)	978.03 (763.41)	1775.77 (954.81)	42618.37 (22915.32)

Abbreviations: AUC_(0-τ) = area under the concentration time curve during a dosing interval; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; C_{ss} = steady-state plasma concentration; od = once a day; POPPKS = population pharmacokinetics set; t_{max} = time to maximum plasma concentration; SD = standard deviation.

^a Presented as median (range).

Source: CSR page 117.

No statistically significant relationship was found between odds of incidence or time to onset of prophylaxis failure and letermovir C_{max} , AUC, or C_{min} .

Safety

Adverse events leading to treatment discontinuation were reported for twenty five (26%) letermovir-treated subjects and 20 subjects (61%) treated with placebo. Serious AEs were reported for forty (41%) letermovir-treated subjects and 16 subjects (49%) treated with placebo. Five subjects died during the trial; two in the 60 mg group (GVHD and AML, respectively), and one in the 120 mg, 240 mg, and placebo groups (all pneumonia).

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion	
This study does not directly impact the clinical pharmacology-related labeling. However, the study was reviewed because it was included in the phase 3 popPK model. The phase 3 model we reviewed is separate from the model used to estimate the PK parameters in Table 13, which we did not review. A large number of concomitant medications were used during the study. OATP inhibitors are of interest because letermovir is an OATP substrate. Use of OATP inhibitors during the study included clarithromycin (n=1 subject) and cyclosporine (n=65). In a drug interaction study, cyclosporine increased letermovir AUC by ~2-fold. In the phase 3 study, the letermovir dose was reduced by half (from 480 mg to 240 mg) when coadministered with cyclosporine. In this study, there was no letermovir dose reduction when given with cyclosporine, but letermovir doses were lower than in the phase 3 study.	
Labeling Recommendations	
This study does not directly impact the clinical pharmacology-related labeling.	
Relevant links within the submission	
CSR \\cdsesub1\evsprod\nda209939\0006\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5351-stud-rep-contr\p020\p020.pdf	
Bioanalytical \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\04jkh4\04jkh4.pdf	

Exposure-response

Phase 3 Exposure-response Analysis

Study #	04HGYM	Report date	1/30/17
Title	Phase 3 Exposure-response Analysis		
STUDY SUMMARY (As Reported by the Applicant)			
METHODS			
<i>Objectives:</i> • Elucidate the therapeutic exposure range for letermovir • Evaluate the clinical bounds for letermovir exposure around the proposed therapeutic dose • Determine clinically relevant covariates and the need for any dose adjustments or restrictions			
<i>Methods:</i> <u>Exposure-efficacy</u> The primary efficacy endpoint was risk of clinically significant CMV infection at week 24 post-transplant. Demographic (age, weight, etc) and clinical characteristics (use of immunosuppressants, risk of CMV disease activation) were evaluated as covariates in a logistic regression model. Letermovir AUC and Cmin were evaluated as exposure metrics. Because many subjects were administered IV and PO letermovir during the study, model-predicted AUC and Cmin values were weighted averages accounting for the number of doses administered by each route during the treatment period. <u>Exposure-safety</u> Various adverse events were evaluated, including cardiac disorders, GI disorders, ear and labyrinth disorders, and renal failure (for a complete list see page 18 of the study report). Additional events and lab values were identified by the Clinical reviewer and we requested analyses of these AEs and lab values. The additional AEs consisted of vertigo, hypokalemia, fluid overload, hyperglycemia, and cough. The laboratory values assessed were blood urea nitrogen, platelets, creatinine, and potassium. Model-predicted exposure on the day of the first event was used for cardiac disorders, GI disorders, renal failure, and ear and labyrinth disorders. For other events, weighted average model-predicted exposures were used.			
RESULTS			
Major findings • The risk of CMV infection was not associated with AUC or Cmin (study report page 32) • In the main analysis, no associations were found between letermovir AUC and the AEs that were evaluated (study report page 41-56) • In analyses of additional events and lab values, clinically insignificant associations were found between exposure (Cmax and AUC) and hypokalemia and fluid overload (report for additional AEs, page 17). In the assessment of lab values, no associations were found (report for additional lab values, page 13) • In exploratory analyses of intensive PK phase 3 subjects, letermovir Cmax was associated with cardiac disorders, arrhythmias, and renal failure (among the subset of intensive PK subjects with ≥1 IV dose) (report for the intensive PK subset, page 26)			

REVIEWER ASSESSMENT
The analysis is acceptable ☒ Yes ☐ No
Discussion and labeling recommendations See the QBR section 3.3.2 for a discussion of the limitations of the exposure-response analyses and labeling recommendations for cardiac and renal adverse reaction. We agree with the following statement in section 12.3 of proposed labeling: (b) (4)
Relevant links within the submission Study report \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hgym\04hgym.pdf Response to Information Requests for additional exposure-response analyses -subjects with prophylaxis failure while on letermovir treatment \\cdsesub1\evsprod\nda209939\0015\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04pn3j\04pn3j.pdf -additional AEs \\cdsesub1\evsprod\nda209939\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hgym\04hgym-additionalaes.pdf -additional lab values \\cdsesub1\evsprod\nda209939\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hgym\04hgym-laboratoryvalues.pdf -intensive PK subset \\cdsesub1\evsprod\nda209939\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hgym\04hgym-intensivepksubset.pdf Exposure-efficacy dataset \\cdsesub1\evsprod\nda209939\0000\m5\datasets\04hgym\analysis\legacy\datasets\eff20170124nmd_ata.csv Dataset and variable definitions \\cdsesub1\evsprod\nda209939\0000\m5\datasets\04hgym\analysis\legacy\datasets\define.pdf

Population PK

Letermovir Population PK Phase 1 Modeling

Study #	04LVRJ	Report date	2/7/17
Title	Letermovir Population PK Phase 1 Modeling		

STUDY SUMMARY (As Reported by the Applicant)

METHODS

Objectives:

- Characterize letermovir PK in healthy volunteers over a broad dose range and variety of dosing regimens
- Evaluate the absolute bioavailability of letermovir
- Evaluate the effect of OATP1B1 and UGT1A1 genetic variants on the PK of letermovir

Studies included in the model:

The applicant's model included PK data from 12 letermovir phase 1 studies in healthy volunteers (Table 14). The PK dataset contained 280 subjects; 254 (91%) were female. Dosing employed was 40-960 mg QD and 40-720 mg BID. PK sampling was intensive in all studies. The dataset contained 9008 non-BQL samples (1.9% of postdose samples were BQL). Population PK modeling was performed by the applicant using NONMEM 7.3 using the first order conditional estimation with interaction method for parameter estimation. The effect of age, weight, gender, race, ethnicity, and genetic variants (OATP1B1 and UGT1A1) were evaluated as covariates for maximal clearance rate and volume of distribution.

Methods:

Model performance was evaluated using diagnostic plots (observed versus predicted concentrations, conditional weighted residuals versus predicted concentrations or time), shrinkage (inter-individual and residual variability parameters), prediction-corrected visual predictive check, and bootstrapping (see section 6.5.1 of the study report).

Table 14. Studies included in the letermovir phase 1 popPK model.

Description of the Clinical Studies Included in Analysis and PK sampling

Study	Study Design	Study Population	N patients	Doses	PK Sampling **
MK-8228-005 (part A and B)	Study to investigate the safety, tolerability and pharmacokinetics of single (part A) and multiple (part B) IV doses of MK-8228	Female subjects	A: 40 B: 10	120,240,480,720,960 mg; part B: 240 mg	extensive day 1 and 14(Part B only)
MK-8228-009	Multiple escalating dose study in healthy male subjects to investigate safety, tolerability and PK of BAY 73-6327	Male subjects	23	40mg QD, 40 mg bid, 80 mg bid	extensive sampling on day 1 and day 7
MK-8228-014	Study to determine the Relative Bioavailability of Solid Oral Formulation of AIC090027	Female subjects	15	240 mg (12x20mg, 8x30mg, 4x60mg, 2x120 mg, 1x240mg)	extensive sampling
MK-8228-017 (part A and B)	Study to investigate the bioavailability of 30 mg MK-8228 (IV vs PO) and the safety, tolerability and PK of single ascending IV doses	Female subjects	A: 12 B: 6/cohort	Part 1: 30 mg (IV and PO) Part B: 60,120,240,480 mg (IV)	extensive sampling
MK-8228-018 (Part A and B)	Study to investigate the safety, tolerability and PK of multiple ascending oral doses (part A) and multiple ascending IV doses	Female subjects	A: 28 B:16	Part A: 240 mg bid, 360mg QD, 360 mg bid; Part B: 120,240 mg IV QD	Part A: extensive sampling on Day 1 and 10; Part B: extensive sampling on day 1 and 7
MK-8228-021 (Part 1 and 2)	Phase I trial to evaluate the safety, tolerability, and pharmacokinetics (PK) of a single oral dose (part 1) or multiple oral doses (part 2)	Male and female subjects	A: 12 B: 12	240 mg SD (part 1) , 120,180, 240 mg bid	extensive sampling on day 1 and 15 (part 2 only)
MK-8228-022	A Pharmacokinetic interaction study between MK-8228 and mycophenolic acid	Female subjects	14	480 mg	extensive sampling on day 5(SD) and 16 (SS, MK-8228 alone)
MK-8228-026	Safety, tolerability and pharmacokinetics of multiple high oral and intravenous doses of MK-8228	Female subjects	24	720 mg bid (PO) or 480 mg QD (IV)	extensive sampling on day 1, 7 (iV) or 14 (PO)
MK-8228-027 (Part 1 and 2)	MK-8228 Single Escalating Dosing Study in Japanese Women	Female subjects	1:6 2: 6	Part 1: 240,480,720 PO; Part 2: 240,480,960 mg IV	extensive sampling
MK-8228-028	A Study to Evaluate the Comparative Bioavailability of One Tablet of 480 mg MK-8228 and Two Tablets of 240 mg MK-8228 Under Fasted Conditions in Healthy Subjects	Male and female subjects	14	480 mg (2x240 vs 1x480)	extensive sampling
MK-8228-029	A Study of the Comparative Fed and Fasted Bioavailability of MK-8228 (Letermovir)	Male and female subject	14	480 mg	extensive sampling
MK-8228-032	A Multiple Dose Study of MK-8228 and a Drug-Drug Interaction Study with MK-8228 and Cyclosporin A in Healthy Japanese Female Subjects	Female subjects	16	480 mg for 7 days, 240 mg for 7 days + CsA on day 8	extensive sampling on day 1,7 and 8

** See individual clinical study reports and protocols for sampling schemes

Source: page 62, study report.

RESULTS**Pharmacokinetics**

The final model had the following characteristics:

- 4-compartment (one central, three peripheral)
- Nonlinear clearance and distribution
- Autoinduction of clearance
- Transit compartment oral absorption
- Covariates included the effect of Japanese race and weight on volume of distribution and the effect of Japanese race on maximal clearance rate.

Model performance was reported to be adequate with the following limitations:

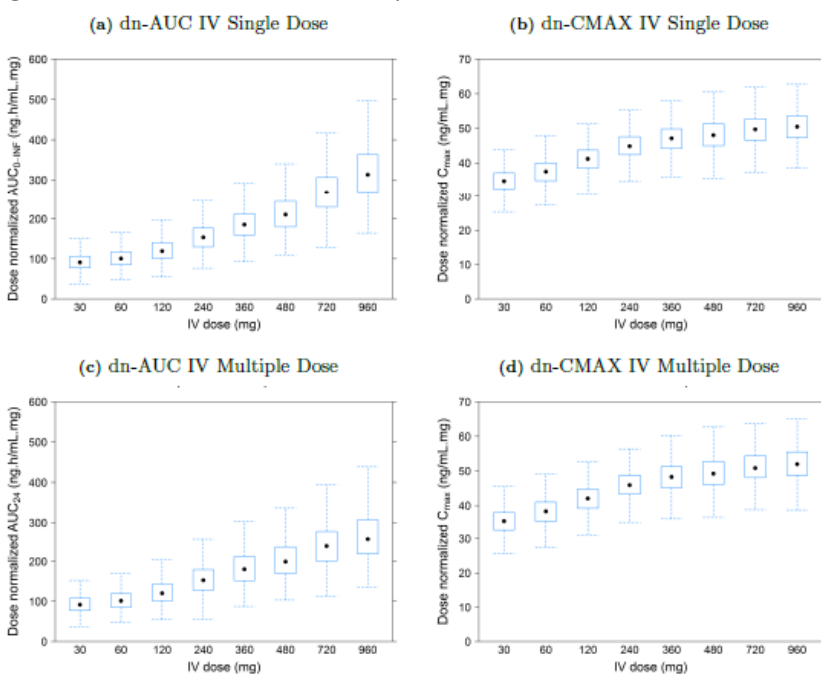
- High shrinkage in volume of distribution inter-individual variability, resulting in an inability to estimate inter-individual differences in C_{max}
- Concentration-time profiles were not adequately described for the lowest (30 mg) and highest (960 mg) doses

Selected findings included the following:

- Estimated letermovir absolute bioavailability was 94%
- With increasing single and multiple PO and IV doses, dose-normalized predicted letermovir AUC increased
- With increasing single and multiple PO doses, dose-normalized predicted C_{max} increased. With increasing single and multiple IV doses, dose-normalized predicted C_{max} did not increase.
- The time for auto-induction of clearance to reach steady-state was 10 days
- At oral doses of 240 mg QD, 480 mg QD, and 720 mg BID, the letermovir clearance increase (steady-state compared to first dose) was 20%, 17%, and 96%
- Polymorphisms of OATP1B1 and UGT1A1 did not have an effect on the exposure of letermovir
- In dedicated studies, compared to non-Japanese subjects observed exposures in Japanese subjects were 1.5-2.5-fold higher. Assuming an identical weight (67 kg) in Japanese and Caucasian subjects, predicted exposures were 10% higher in Japanese. Assuming observed weights of Japanese (57 kg) and Caucasian (67 kg) subjects, predicted exposures were 26% higher in Japanese. There was significant overlap in predicted exposures between Japanese and Caucasian subjects.

Predicted letermovir exposures are shown below.

Figure 11. Predicted letermovir exposures.



Box and whisker plot: The dot is the sample median, the boxes define the interquartile range, the whiskers extend to 1.5 times the interquartile range. AUC represents AUC_∞ for the single dose data and AUC₂₄ for the multiple dose data

Source: CSR, page 53.

Table 15. Predicted letermovir exposures.

		Dose normalized AUC				Dose normalized C _{max}				
Route		Dose (mg)	mean	sd	median	90% CI	mean	sd	median	90% CI
IV	single dose	30 mg	93.7	23.2	91.1	60.8 - 138	34.7	3.47	34.7	28.9 - 40.7
		60 mg	103	25.2	101	66.8 - 147	37.4	3.76	37.4	31.5 - 43.7
		120 mg	123	29.1	119	81.2 - 177	41.1	3.87	41.1	34.8 - 47.4
		240 mg	155	35.6	154	101 - 220	44.9	3.98	44.8	38.5 - 51.4
		360 mg	188	39.6	185	131 - 260	46.9	4.35	47.1	39.5 - 53.9
		480 mg	215	48.1	211	145 - 303	48.1	4.55	48.0	40.9 - 55.3
		720 mg	272	58.7	268	184 - 378	49.6	4.46	49.7	42.4 - 56.7
		960 mg	320	69.3	313	222 - 449	50.3	4.63	50.4	42.4 - 57.4
	multiple dose	30 mg	94.6	24.0	91.8	61.1 - 141	35.5	3.72	35.4	29.5 - 41.9
		60 mg	105	26.6	101	66.6 - 154	38.3	3.99	38.3	32.1 - 45.0
		120 mg	125	31.5	120	80.7 - 185	42.0	4.11	42.0	35.3 - 48.9
		240 mg	157	40.7	153	98.6 - 230	45.9	4.17	45.9	39.1 - 52.7
		360 mg	187	47.3	180	126 - 275	48.1	4.58	48.2	40.5 - 55.3
		480 mg	209	57.6	199	134 - 314	49.4	4.83	49.2	41.9 - 57.6
		720 mg	250	71.7	238	159 - 393	51.2	4.92	50.8	43.4 - 59.5
		960 mg	274	82.3	256	176 - 429	52.1	5.23	51.9	43.4 - 60.5
PO	single dose	30 mg	88.2	29.5	83.5	49.6 - 142	23.6	6.61	22.7	14.3 - 35.7
		60 mg	94.6	30.4	90.7	53.8 - 147	23.8	6.43	22.8	14.8 - 35.4
		120 mg	112	39.3	104	62.8 - 185	25.0	6.88	24.5	15.4 - 37.5
		240 mg	140	51.0	132	73.6 - 231	25.9	7.41	25.2	15.5 - 38.7
		360 mg	169	62.7	158	87.7 - 286	26.4	7.04	25.8	16.2 - 39.2
		480 mg	190	72.1	177	97.9 - 326	25.8	7.01	25.0	15.9 - 38.1
		720 mg	243	99.5	225	117 - 439	26.1	7.04	25.4	16.0 - 39.3
		960 mg	276	107	260	139 - 483	25.0	6.29	24.7	15.9 - 36.6
	multiple dose	30 mg	89.0	30.4	83.9	49.9 - 144	24.3	6.82	23.4	14.7 - 36.7
		60 mg	95.8	31.6	91.5	53.8 - 150	24.5	6.63	23.5	15.2 - 36.5
		120 mg	114	41.9	106	63.1 - 194	26.0	7.17	25.3	15.8 - 38.8
		240 mg	142	54.3	133	73.4 - 241	27.0	7.74	26.2	16.3 - 40.4
		360 mg	170	68.7	157	85.5 - 295	27.7	7.51	27.0	16.8 - 40.2
		480 mg	187	75.3	172	94.9 - 333	27.1	7.49	26.3	16.4 - 40.7
		720 mg	227	96.7	206	109 - 412	27.7	7.83	26.7	16.7 - 42.7
		960 mg	242	100	223	124 - 426	26.5	7.21	25.8	16.3 - 39.3

AUC represents AUC_∞ for the single dose data and AUC₂₄ for the multiple dose data

Source: CSR, page 54.

REVIEWER ASSESSMENT
Study conduct for studies included in the model is acceptable ☒ Yes ☐ No
The model is acceptable ☒ Yes ☐ No
Discussion We reviewed each of the studies included in the model and we found study conduct and results to be acceptable (see individual study reviews). The population PK modeling of phase 1 letermovir studies employed a complex model (autoinduction, nonlinear clearance and distribution, transit compartment absorption) to describe the disposition of letermovir after single and multiple oral and IV doses over a wide dose range in healthy adults. Model performance was overall adequate with good precision of parameter estimates and good fits of concentration-time profiles for individual subjects. One potential limitation not noted by the applicant is an overprediction of variability as observed in the visual predictive check where <5% of observed concentrations appear to lie outside the 95% prediction interval.
Labeling Recommendations We agree with inclusion of the following statement in proposed labeling (section 12.3): (b) (4)
Relevant links within the submission Study report \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04lvrij\04lvrij.pdf Final model 3001 output file \\cdsesub1\evsprod\nda209939\0000\m5\datasets\04lvrij\analysis\legacy\programs\run3001lst.txt Dataset \\cdsesub1\evsprod\nda209939\0000\m5\datasets\04lvrij\analysis\legacy\datasets\intpoppkdata08mp.csv

Letermovir Population PK Phase 3 Modeling

Study #	04KBBP	Report date	1/30/17
Title	Letermovir Population PK Phase 3 Modeling		

STUDY SUMMARY (As Reported by the Applicant)

METHODS

Objectives:

- Characterize the PK of letermovir at steady-state in HSCT recipients
- Determine the effect of covariates on letermovir exposure
- Derive individual subject letermovir exposures for use in exposure-response analyses

Studies included in the model:

Five studies (three phase 1, two phase 2, and one phase 3) were included in the PK dataset (Table 16). Intensive PK samples (>10 samples per subject) were collected in the phase 1 studies. Five samples per subject within a dosing interval were collected in the phase 2 study and in a subset of subjects in the phase 3 study. In the phase 3 study, all subjects had sparse sampling consisting of trough samples on weeks 2, 4, 6, 8, 10, 12, and 14. Because the goal was to characterize steady-state PK, samples were excluded if collected before day 7 of dosing or >72 hours after the last dose. The popPK dataset contained 2888 observations from 399 subjects (Table 17).

Table 16. Studies included in the popPK modeling dataset.

Study	Phase	Dosing	Oral formulation	Analytical method
001	3	480 mg (240 mg with CsA) QD PO or IV	PMF3/FMI	BP-0032
020	2	240 mg QD PO with or without CsA	PMF1	08-061
022	1	480 mg QD PO	PMF2	BP-0032
026	1	480 mg QD IV	PMF2	
032	1	480 mg QD PO	PMF3	

Source: Phase 3 popPK report and Biopharmaceutics Summary.

Table 17. Number of subjects and PK samples in the popPK dataset by study.

Study	N subj	N obs	IV		PO	
			CSA treatment	No CSA treatment	CSA treatment	No CSA treatment
8228-001 Rich PK	74	369	25(5)	64(14)	177(35)	103(22)
8228-001 Sparse PK, rich PK subject	73	416	4(3)	21(14)	212(39)	179(36)
8228-001 Sparse PK	275	1530	43(25)	63(39)	675(132)	749(148)
8228-020	13	129	-	-	129(13)	-
8228-022	14	200	-	-	-	200(14)
8228-026	9	102	-	102(9)	-	-
8228-032	13	142	-	-	-	142(13)
All	399	2888	72(31)	250(66)	1193(186)	1373(212)

Source: Phase 3 popPK report, page 14. Values are number of samples (number of subjects).

Methods:

PK data were modeled using nonlinear mixed effects modeling (NONMEM software). The data were modeled in three steps starting with subsets of the dataset: 1) phase 1 data only; 2) phase 1, phase 2, and intensive phase 3 samples; and 3) all samples. A combined exposure metric was calculated for each subject where the exposure following each combination of treatments was weighted with the number of days with each regimen. Also, in order to explore potential exposure-response for acute effects, the exposure following each regimen for each subject was also reported.

Model performance was evaluated using diagnostic plots (observed versus predicted concentrations, conditional weighted residuals versus predicted concentrations or time), shrinkage (inter-individual and residual variability parameters), prediction-corrected visual predictive check, and bootstrapping (study report pages 27 and 101).

RESULTS

Pharmacokinetics

The final model had two compartments, linear elimination and absorption, and an absorption lag time.

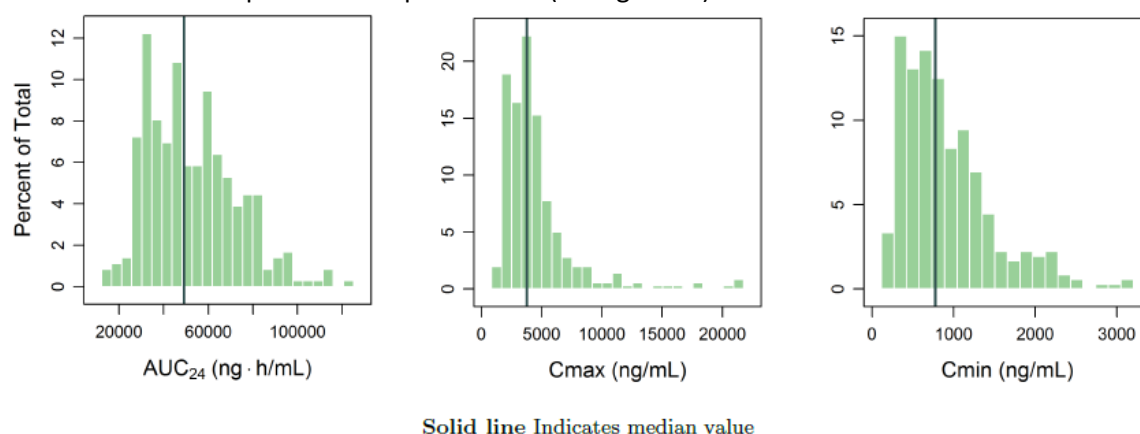
Model performance was reported to be adequate with the following limitations:

- High variability
- Residual and inter-occasion variability was inflated among sparsely sampled subjects, resulting in a possible underprediction of variability in these subjects
- Underprediction of C_{max} (relative to noncompartmental analysis) in the phase 3 study (study report page 36)

Selected findings included the following:

- Lower bioavailability and slower absorption in HSCT recipients vs. healthy volunteers
- Lower letermovir clearance and higher bioavailability when coadministered with cyclosporine
- In HSCT recipients, estimated letermovir bioavailability was 35% when given without cyclosporine and 85% when coadministered with cyclosporine
- 50% lower peripheral volume of distribution in Asian subjects relative to those of other races, resulting in ~50% higher exposures in phase 3 Asian subjects

PK parameters are shown below averaged across all regimens (Table 18) and also subdivided by route of administration, use of cyclosporine, and race (Table 19, Table 20, Table 21).

Table 18. Phase 3 model-predicted PK parameters (all regimens).**Table 12:** Letemovir exposure predictions Phase 3

	Median	90% confidence interval	Minimum	Maximum	Inter quartile range
AUC ₂₄ (ng·h/mL)	49170	(26930-87430)	12050	125200	36380-64980
Cmax (ng/mL)	3786	(1923-10070)	834.7	21750	2682-5042
Cmin (ng/mL)	776.1	(301.4-2094)	115	3204	497.4-1184

Source: CSR page 41.

Table 19. Predicted letemovir AUC24 in HSCT recipients by route of administration, use of cyclosporine, and race.

	Median (ng·h/mL)	90% prediction interval
CSA, 240 mg IV Asian	71490	(47420-108200)
CSA, 240 mg IV Non Asian	70260	(46230-106100)
CSA, 240 mg Oral Asian	61560	(29230-126200)
CSA, 240 mg Oral Non Asian	60770	(28720-121900)
No CSA, 480 mg IV Asian	99680	(64500-145000)
No CSA, 480 mg IV Non Asian	99950	(65320-147800)
No CSA, 480 mg Oral Asian	33850	(15830-69950)
No CSA, 480 mg Oral Non Asian	34430	(16900-73660)

Source: CSR, page 45.

Table 20. Predicted letemovir Cmin in HSCT recipients by route of administration, use of cyclosporine, and race.

	Median (ng/mL)	90% prediction interval
CSA, 240 mg IV Asian	684.2	(217.9-1635)
CSA, 240 mg IV Non Asian	774.3	(302-1689)
CSA, 240 mg Oral Asian	1200	(346.9-3154)
CSA, 240 mg Oral Non Asian	1201	(393.3-3133)
No CSA, 480 mg IV Asian	607.7	(155.5-1482)
No CSA, 480 mg IV Non Asian	767.6	(295.9-1754)
No CSA, 480 mg Oral Asian	506.4	(118.4-1628)
No CSA, 480 mg Oral Non Asian	539.2	(151.9-1552)

Source: CSR, page 45.

Table 21. Predicted letermovir Cmax in HSCT recipients by route of administration, use of cyclosporine, and race.

	Median (ng/mL)	90% prediction interval
CSA, 240 mg IV Asian	11450	(10580-12660)
CSA, 240 mg IV Non Asian	11520	(10650-12720)
CSA, 240 mg Oral Asian	4009	(1783-9085)
CSA, 240 mg Oral Non Asian	3823	(1726-8689)
No CSA, 480 mg IV Asian	21430	(19780-23000)
No CSA, 480 mg IV Non Asian	21570	(19890-23350)
No CSA, 480 mg Oral Asian	2430	(1062-5220)
No CSA, 480 mg Oral Non Asian	2549	(1136-6050)

Source: CSR, page 46.

REVIEWER ASSESSMENT

Study conduct for studies included in the model is acceptable ☒ Yes ☐ No

The model is acceptable ☒ Yes ☐ No

Discussion

We reviewed each of the studies included in the model and we found study conduct and results to be acceptable (see individual study reviews).

The Phase 1 model was intended to predict letermovir exposures prior to steady-state (i.e. before steady-state auto-induction was reached) and across a wide range of doses. In contrast, the simplified phase 3 model is intended to provide steady-state exposures for a dose of 480 mg QD (240 mg QD with CsA). The phase 3 model is suitable for its intended purpose of estimating steady-state letermovir AUC for subjects in phase 3 P001, who received letermovir 480 mg QD (240 mg QD with CsA).

In cross-study comparisons of letermovir PK in healthy Japanese vs. non-Japanese subjects, letermovir exposures were 1.5-2.5-fold higher in Japanese subjects. However, in phase 3 Asian subjects, model-predicted exposures were <50% higher compared to other races. The 50% exposure increase is not clinically relevant.

While there is a significantly lower letermovir absorption and AUC in HSCT recipients not coadministered cyclosporine, no difference in the rate of CMV prophylaxis failure was observed as a function of letermovir AUC in the phase 3 study. Thus we agree with the proposed dosing regimen.

Labeling Recommendations

We agree with inclusion of the following data and statements in proposed labeling (section 12.3):

-
-
-
-

(b) (4)

Relevant links within the submission

Study report

<\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04kbbp\04kbbp.pdf>

Final model 48 control file

<\\cdsesub1\evsprod\nda209939\0000\m5\datasets\04kbbp\analysis\legacy\programs\run48mod.txt>

Final model 48 output file

<\\cdsesub1\evsprod\nda209939\0000\m5\datasets\04kbbp\analysis\legacy\programs\run48lst.txt>

Dataset

<\\cdsesub1\evsprod\nda209939\0000\m5\datasets\04kbbp\analysis\legacy\datasets\nmpkallphases18jan17.csv>

Dataset variable definitions

<\\cdsesub1\evsprod\nda209939\0000\m5\datasets\04kbbp\analysis\legacy\datasets\define.pdf>

Physiologically-based PK modeling

Letermovir SIMCYP® PBPK Modeling

Study #	04HGZ3	Report date	12/19/2016
Title	Letermovir SIMCYP® PBPK Modeling		

STUDY SUMMARY (As Reported by the Applicant)

METHODS

Objectives:

- Mechanistically explain the greater-than-dose-proportional PK of letermovir after IV and PO dosing
- Mechanistically explain the difference in letermovir exposure observed in White and Japanese healthy volunteers
- Generate hypotheses that describe the exposure difference of letermovir observed in white healthy volunteers and HSCT recipients after oral dosing

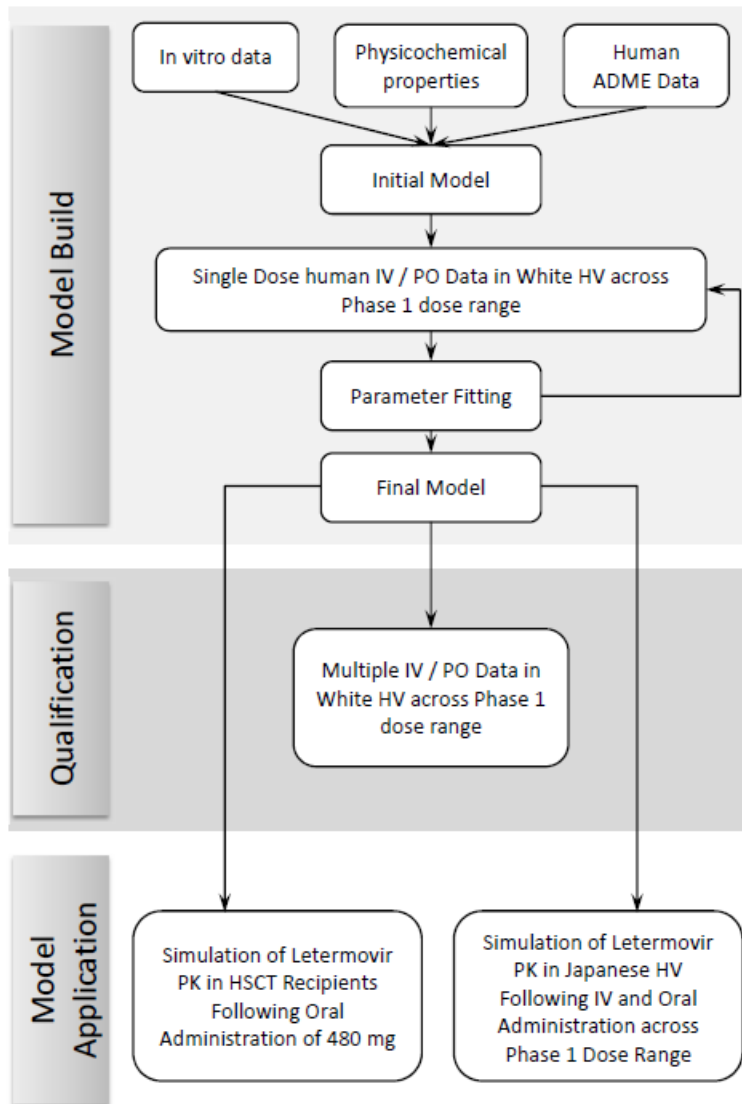
Methods:

Initial model development

Simcyp version 15 (release 1) was used to simulate the PK of letermovir in white and Japanese healthy volunteers (built-in populations) as well as HSCT recipients (not a built-in population). The model was developed using letermovir physicochemical and human ADME data, optimized by fitting parameters to recover single dose PO and IV data in white healthy volunteers, qualified by comparison of simulated PK to observed multiple dose PK data, then utilized for simulations of PK in HSCT recipients and Japanese healthy volunteers (Figure 12, Figure 13).

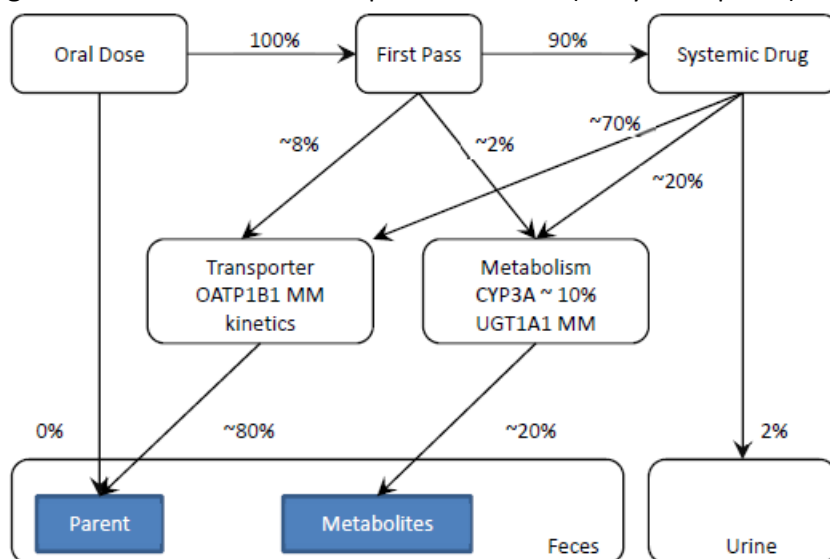
Clinical PK data from studies in HSCT recipients (P001) and healthy volunteers (P005, P011, P018 part 2, P022, P026, P027, P032) were used to qualify the model. Model predictive performance was assessed by graphical comparison of simulated and observed concentration-time profiles and numerical comparison of simulated and observed PK parameters. Adequate predictive performance was defined as a simulated/observed letermovir AUC ratio of 0.5-2. Because efficacy was associated with AUC in a phase 2b study, the model was optimized for simulating AUC most accurately.

Figure 12. Model building workflow.



Source: page 49, <\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hg23\04hg23.pdf>.

Figure 13. Letemovir in vivo disposition scheme (study P021 part 3)



MM: Michaelis-Menten kinetics

Source: page 50, <\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hg3\04hg3.pdf>.

RESULTS

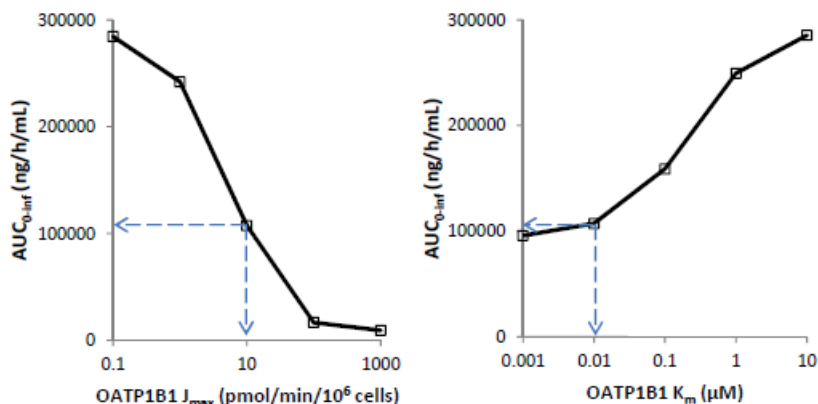
Initial simulations for letemovir PK across a wide dose range

Model description

The model utilized first order absorption, distribution via the full PBPK model with a permeability-limited liver model, hepatic uptake via OATP1B1, and clearance via biliary clearance and UGT1A1 and CYP3A4 metabolism. The initial model based only on physicochemical and ADME data were unable to recover letemovir PK. To improve the predictions, the following parameters were fitted: k_a , K_p scalar, biliary CL_{int} , OATP1B1 J_{max} , OATP1B1 K_m , and $f_{u,lw}$ (Initial PBPK report, page 34).

Sensitivity analyses: In sensitivity analyses, OATP1B1 J_{max} and K_m had the most significant effect on letemovir exposure.

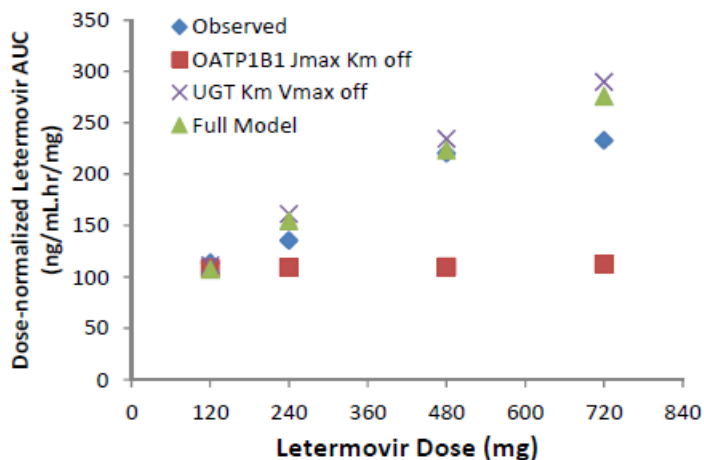
Figure 14. Impact of OATP1B1 Jmax and Km on letermovir AUC.



Source: Page 54, [\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hg3\04hg3.pdf](https://cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hg3\04hg3.pdf). The arrows show the J_{max} and K_m values used in the model.

Role of OATP: Letermovir was found to have greater than dose-proportional PK in human studies. One model assumption was that OATP1B1 and 1B3 are responsible for active hepatic uptake and that active uptake is saturable. This was consistent with simulations where turning off UGT K_m and V_{max} did not affect the ability to recover nonlinear letermovir PK, while turning off OATP1B1 J_{max} and K_m resulted in simulated linear PK (Figure 15).

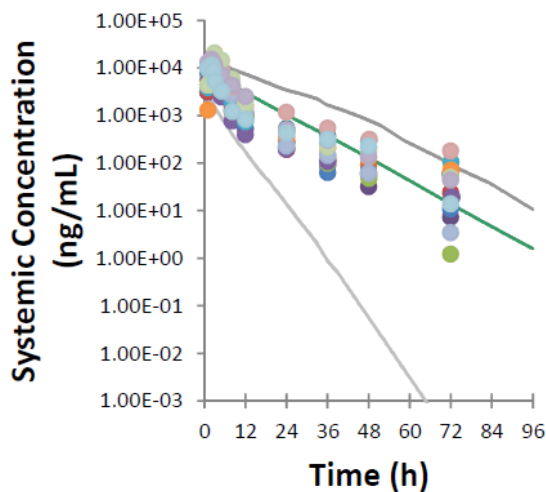
Figure 15. Observed and Simcyp®-simulated dose-normalized AUCs of letermovir following IV administration of single doses (120, 240, 480, 720 mg) of letermovir with and without OATP1B saturation components.



Source: Page 57, [\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hg3\04hg3.pdf](https://cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hg3\04hg3.pdf).

Recovery of observed single-dose PK data: After fitting selected parameters listed above, following IV single doses of 120-720 mg, simulated C_{max} and AUC values were within 20% of observed values. Following oral single doses of 120-240 mg, simulated AUC values were underestimated by 40-50% and were similar to observed values at a dose of 480 mg. C_{max} was underestimated by 2-3-fold for all oral doses (Figure 16). The applicant noted that concentrations >24 hours postdose were not as well predicted, and concluded that given the QD dosing regimen the model was adequate for predicting multiple dose PK.

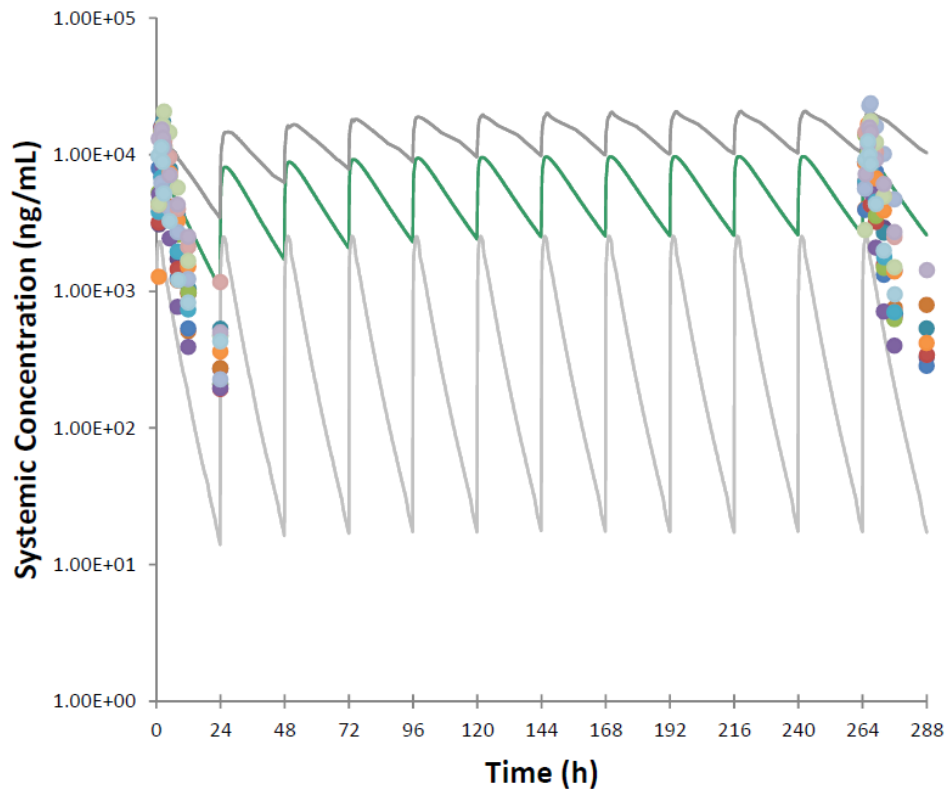
Figure 16. Observed and Simcyp®-simulated plasma concentration-time profiles and dose-normalized AUCs of letermovir following oral administration of a single dose of 480 mg of letermovir in white healthy volunteers.



Source: Page 53, <\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hg3\04hg3.pdf>. See pages 51 and 53 for oral and IV simulations for doses of 120-720 mg.

Recovery of observed multiple-dose PK data: After multiple doses of 480 mg PO and IV, predicted C_{max} and AUC values were within 40% of observed values (Figure 17). The applicant considered simulated and observed concentration-time profiles and PK parameters to be similar.

Figure 17. Observed and Simcyp®- simulated plasma concentration-time profiles of letermovir following oral administration of multiple doses (480 mg) of letermovir in white healthy volunteers.



Source: Page 60, <\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hg23\04hg23.pdf>. See page 58 for multiple dose PK after IV doses of 120-480 mg.

Simulated letermovir PK in Japanese vs. white healthy volunteers: After multiple oral dosing of 480 mg QD, simulated vs. observed C_{max} and AUC ratios were 0.99 and 0.56, respectively. It has been reported that OATP activity/abundance ratio between Japanese and whites is 0.58. When a factor of 0.58 was used, simulated vs. observed C_{max} and AUC ratios were 1.46 and 0.69, respectively. Using an OATP activity/abundance factor of 0.58 in Japanese improved the prediction of C_{max} and AUC ratios in Japanese vs. white healthy volunteers (Table 22).

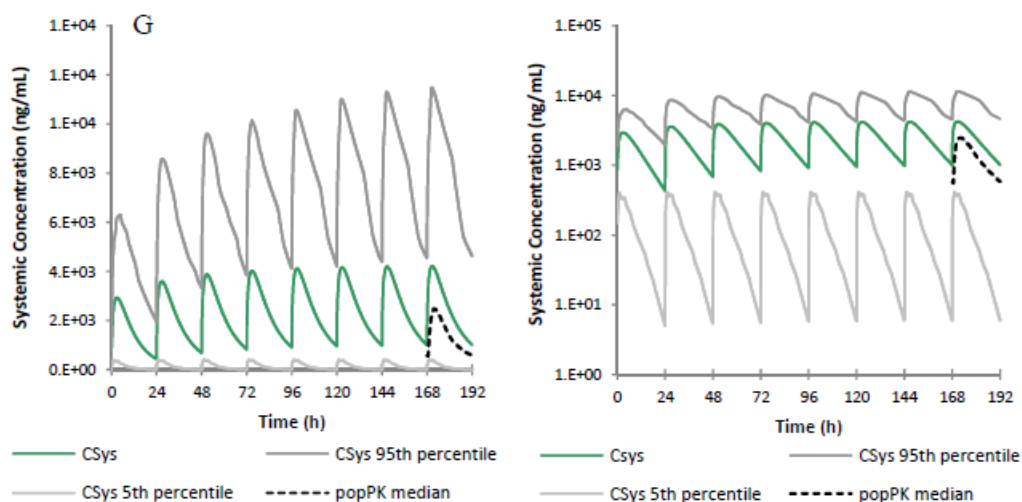
Table 22. Assessment of differences of Simcyp®-simulated pharmacokinetic parameters at steady state following multiple oral administration of letermovir at a dose of 480 mg between white healthy volunteers and Japanese healthy volunteers.

	Parameter	Observed Japanese/Whites GMR	Simulated Japanese/ Whites GMR ¹	Simulated Japanese/ Whites GMR ²
480 mg	C _{max} (ng/mL)	1.6	1.3	1.6
	AUC ₀₋₂₄ (ng•hr/mL)	1.9	1.3	2.1

Source: Page 46, [\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hg3\04hg3.pdf](#). ¹OATP activity/abundance = 1 in Japanese; ²OATP activity/abundance = 0.58 in Japanese.

Simulated letermovir PK in HSCT recipients: Oral letermovir administered without cyclosporine in HSCT recipients results in a ~3-fold lower AUC compared to white healthy volunteers. HSCT recipients are treated with chemotherapy or radiation prior to transplant, and these treatments can cause mucositis. Mucositis has been shown to be a possible contributor to low intestinal absorption of cyclosporine, MMF, and posaconazole in HSCT recipients (page 30, [\\cdsesub1\evsprod\nda209939\0020\m1\us\efficacy-information-amendment-17jul2017.pdf](#)). A HSCT virtual population was generated by reducing the fraction absorbed and rate of absorption. Using $F_a=0.55$ and $k_a=0.45$ (hr⁻¹), predicted vs. observed C_{max} and AUC ratios after an oral dose of 480 mg were 1.2 and 1.0, respectively (Figure 18).

Figure 18. PopPK estimated and Simcyp®-simulated plasma concentration-time profiles of letermovir following oral administration of multiple doses at 480 mg of letermovir in HSCT recipients by modifying F_a and k_a in the Simcyp® model.



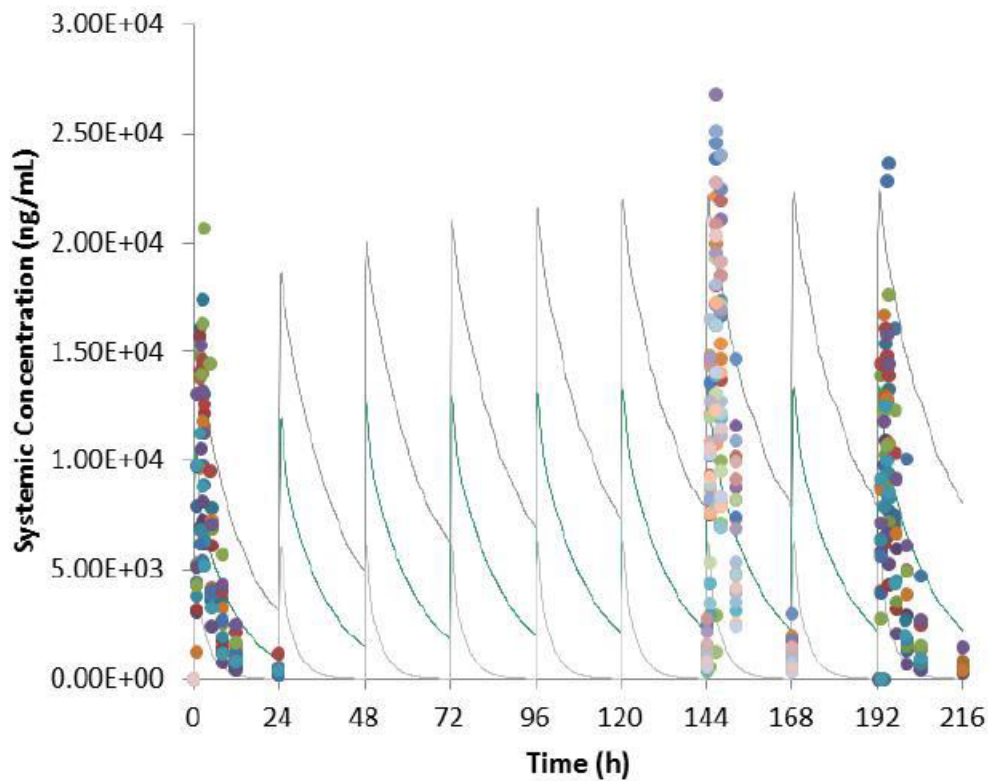
Source: Page 67, <\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hg3\04hg3.pdf>. Left = linear y axis; Right = log y axis.

Additional simulations to improve prediction of letermovir PK at a dose of 480 mg

One of the initial objectives of the initial modeling was to describe the nonlinearity in letermovir PK across a range of doses. Our focus was on the ability to predict PK upon multiple doses of 480 mg. We observed that variability of simulated concentrations was overpredicted compared to observed concentrations after single and multiple doses in healthy volunteers (Figure 16, Figure 17). We asked the applicant to improve the predictions for multiple doses of 480 mg letermovir in healthy volunteers and HSCT recipients. We also asked that the applicant to simulate the effect of 480 mg letermovir (clinical dose) on the PK of midazolam as a subclinical dose of 240 mg was evaluated in the drug interaction study.

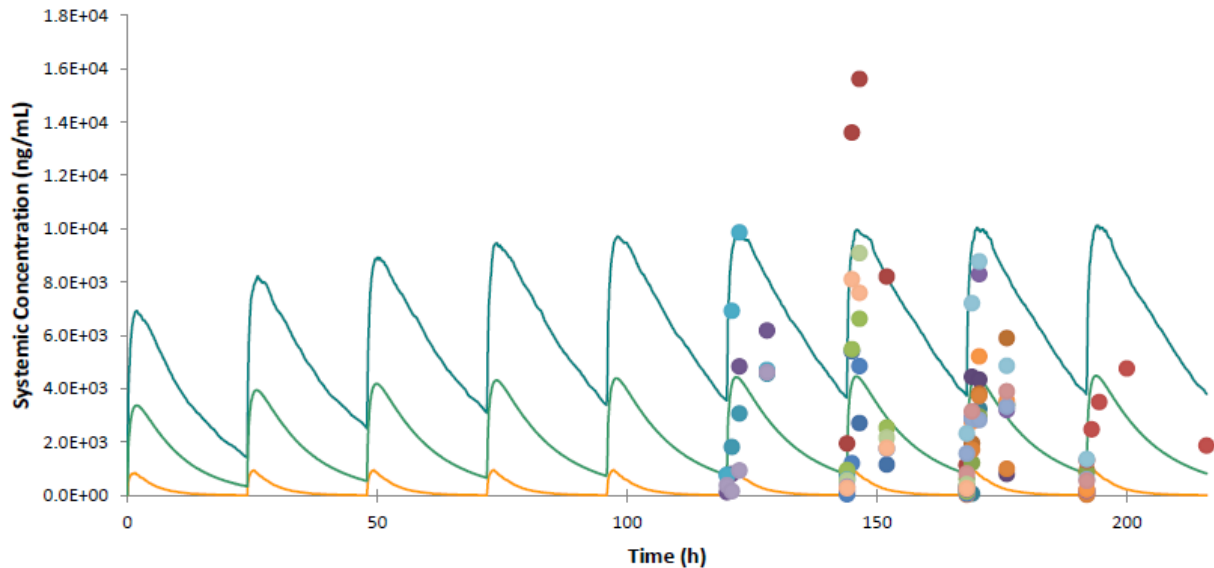
Model alterations: C_{max} was underpredicted upon oral administration in the initial modeling. C_{max} is the most important parameter to optimize for predicting the effect of letermovir on other drugs. To improve C_{max} predictions, the applicant increased k_a from 0.65 to 1.5 hours⁻¹. And to improve the prediction of variability, the sample size for simulations was increased from 10 to 80 subjects per simulated trial. The model with altered C_{max} was qualified in relation to PK data for oral letermovir 480 mg in healthy adults (Figure 19) and HSCT recipients.

Figure 19. Simulated and observed concentration-time profiles following multiple-dose oral administration of 480 mg letermovir once daily in healthy subjects (studies P003, P022, and P036).



Source: Page 32, <\\cdsesub1\evsprod\nda209939\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hg23\04hg23-addendum.pdf>.

Figure 20. Simulated and observed concentration-time profiles following multiple oral administrations of 480 mg letermovir once daily in HSCT recipients.



Source:Page 34, [\\cdsesub1\evsprod\nda209939\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hg3\04hg3-addendum.pdf](#).

Predicted effect of letermovir 480 mg on the PK of midazolam: In vitro, letermovir is an inducer and time-dependent inhibitor of CYP3A. The applicant qualified the CYP3A4 parameters in the letermovir model by simulating the letermovir 240 mg-oral midazolam interaction study (Table 23).

Table 23. Observed and SimCYP-simulated pharmacokinetic parameters of midazolam in healthy females following oral administration of a single oral dose of 2-mg midazolam in the presence and absence of 240-mg oral dose of letermovir once daily for 6 days.

	Observed ^a	Predicted ^b				Predicted/Observed Ratio
Hepatic CYP3A k_{deg} (h^{-1})		0.03	0.0193	0.0193	0.008	
CYP3A induction		-	-	+	+	
AUC _{0-inf} GM (95%CI) MDZ alone (ng/mL*h)	20.59 ± 4.82	23.04 (20.57, 25.80)	23.04 (20.57, 25.80)	23.04 (20.57, 25.80)	23.04 (20.57, 25.80)	1.12
AUC _{0-inf} GM (95%CI) MDZ w/ Letermovir (ng/mL*h)	44.25 ± 13.05	46.71 (41.05, 53.13)	52.76 (46.11, 60.37)	44.53 (38.9, 50.9)	57.3 (49.5, 66.3)	1.06/1.19/1.01/1.29
C _{max} GM (95%CI) MDZ alone (ng/mL)	8.701 ± 1.80	8.68 (7.83, 9.64)	8.68 (7.83, 9.64)	8.68 (7.83, 9.64)	8.68 (7.83, 9.64)	1.00
C _{max} GM (95%CI) MDZ w/ Letermovir (ng/mL)	15.09 ± 3.69	14.42 (13.0, 15.99)	15.21 (13.70, 16.89)	12.89 (11.6, 14.32)	14.25 (12.80, 15.87)	0.96/1.01/0.85/0.94
AUC _{0-inf} GMR (90% CI) ^c	2.25 ^d (2.04, 2.49)	2.03 (1.93, 2.13)	2.29 (2.17, 2.42)	1.93 (1.84, 2.03)	2.49 (2.34, 2.64)	0.91/1.03/0.87/1.12
C _{max} GMR (90% CI) ^c	1.72 (1.55, 1.92)	1.66 (1.61, 1.71)	1.75 (1.69, 1.81)	1.48 (1.44, 1.53)	1.64 (1.59, 1.69)	0.97/1.02/0.86/0.95

^a Arithmetic mean ± standard deviation ^b Geometric mean (GM) ^c LS mean for the observed ratio ^d AUC_{0-inf} - CYP3A induction was not considered; +, CYP3A induction was considered by applying induction parameters of IndC50 = 1.9 and Indmax = 8.2 calibrated based on the EC50 and Emax values of letermovir and rifampin estimated from human hepatocyte induction study [Sec. 2.6.5]; GMR = geometric mean ratio, CI= confidence interval. The observed data are from clinical study report PN016 [Ref. 5.3.3.4: P016].

Source: Page 25, <\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04kcl7\04kcl7.pdf>

The applicant then predicted the effect of 480 mg IV or PO letermovir on the PK of oral midazolam in healthy volunteers and HSCT recipients (Table 24).

Table 24. Simulated drug interactions following coadministration of a single oral dose of 2 mg midazolam with oral doses or 60-minutes IV infusion doses of 480 mg letermovir once daily for 10 days in HSCT recipients and healthy subjects.

	HSCT Recipients (N=800)		Healthy Subjects (N =800)	
Letermovir 480 mg QD	Oral	IV	Oral	IV
Predicted MDZ AUC _{0-inf} GMR (90% CI)	2.56 (2.48, 2.63)	2.48 (2.40, 2.57)	3.44 (3.32, 3.57)	2.48 (2.40, 2.57)
Predicted MDZ C _{max} GMR (90% CI)	1.83 (1.80, 1.86)	1.44 (1.43, 1.46)	2.10 (2.06, 2.14)	1.44 (1.43, 1.46)

GMR = geometric mean ratio, CI= confidence interval

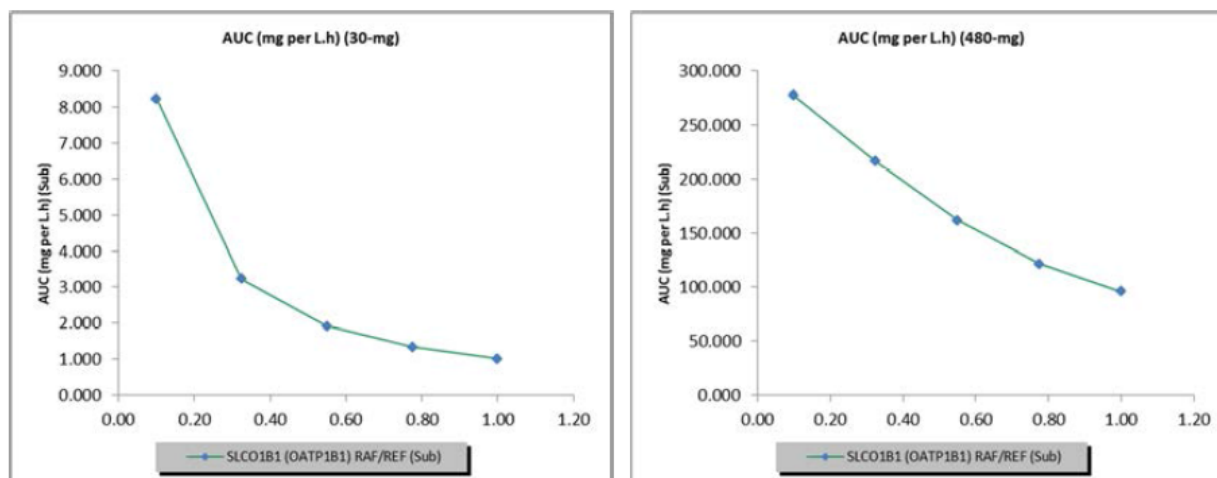
Source: Page 16, <\\cdsesub1\evsprod\nda209939\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hg3\04hg3-addendum.pdf>.

The effect of hepatic impairment (HI) on the PK of 30-60 mg vs. 480 mg letermovir:

Because OATP abundance has been reported to be reduced in cirrhosis (PMID: 27543206), we requested sensitivity analyses of OATP abundance vs. letermovir AUC in healthy volunteers. Also, based on concern over whether the HI PK study done with subclinical letermovir doses was applicable to the clinical dose, we requested PBPK simulations of the HI study at 30-60 mg and 480 mg.

In the sensitivity analysis, a 10-fold reduction of OATP abundance resulted in 8- and 2.8-fold increases in letermovir AUC at 30 mg and 480 mg, respectively (Figure 21).

Figure 21. Impact of OATP1B1 abundance on letermovir AUC following oral administration of multiple once daily doses of letermovir.



Source: Page 9, <\\cdsesub1\evsprod\nda209939\0026\m1\us\efficacy-information-amendment-02aug2017.pdf>.

At a dose of 60 mg in subjects with moderate HI vs. controls, predicted to observed C_{max} and AUC ratios were 1.2 and 1.33, respectively. Predicted letermovir AUC ratios (moderate HI/controls) were slightly larger for a dose of 60 mg vs. 480 mg (Table 25).

Table 25. Mean $\pm$ standard deviation observed and SimCYP-predicted pharmacokinetic parameters of letermovir following oral administration of multiple doses of letermovir once daily for 8 days in moderate hepatic impairment patients and matched healthy volunteers (P015).

Dose		Parameters	Moderate Hepatic Impairment Patients	Matched Healthy Volunteers	HI/HV AUC Ratio	Pred./Obs. AUC Ratio
	Observed	f_u	0.01088	0.0095		
60 mg	Observed	C_{max} (ng/mL)	1687 $\pm$ 592.4	1361 $\pm$ 643.3	1.37	
		AUC_{0-24h} (ng*h/mL)	11960 $\pm$ 8164	7121 $\pm$ 3310	1.59	
	Predicted	C_{max} (ng/mL)	1754 $\pm$ 829	1066 $\pm$ 597	1.65	1.20
		AUC_{0-24h} (ng*h/mL)	14839 $\pm$ 12636	7020 $\pm$ 6652	2.11	1.33
480 mg	Predicted	C_{max} (ng/mL)	26234 $\pm$ 9778	19798 $\pm$ 7961	1.33	
		AUC_{0-24h} (ng*h/mL)	381213 $\pm$ 207591	259874 $\pm$ 176899	1.47	

HI = hepatic impairment patients; HV = healthy volunteers; f_u = unbound fraction in plasma

Source: Page 12, <\\cdsesub1\evsprod\nda209939\0026\m1\us\efficacy-information-amendment-02aug2017.pdf>.

REVIEWER ASSESSMENT

The model is acceptable ☒ Yes ☐ No

Discussion and labeling recommendations

We reviewed the human studies from which observed PK data were obtained and study conduct was acceptable (see individual study reviews).

After altering the model to improve prediction of C_{max} and improving simulation sample size to improve the prediction of variability, the ability to recover oral and IV letermovir for a dose of 480 mg PO or IV in healthy adults and HSCT recipients was acceptable.

Based on the ability to recover the results of the letermovir 240 mg-midazolam drug interaction study, we accept the results for the simulated effect of letermovir 480 mg on the PK of midazolam. Given reduced oral letermovir exposures in HSCT recipients vs. healthy volunteers, the observation of a lower effect of oral letermovir on midazolam was expected for HSCT recipients vs. healthy volunteers. Interestingly, the effect of letermovir on oral midazolam was predicted to be similar for oral and IV letermovir. This can be explained by noting that while letermovir C_{max} is lower upon oral vs. IV administration, oral letermovir inhibits both gut and liver CYP3A while IV letermovir only inhibits gut CYP3A.

We asked that the applicant also simulate letermovir-cyclosporine and letermovir-digoxin interactions. The applicant did not perform these simulations because they did not consider the Simcyp cyclosporine and digoxin compound files to be qualified.

See section 2.2.2 and 3.3.3 for labeling recommendations for use of letermovir in patients with HI.

Relevant links within the submission

Initial PBPK report

<\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hg3\04hg3.pdf>

Simcyp simulation files

<\\Cdsesub4\nonectd\NDA209939\6277839>

7/17/2017 response to FDA request for model improvement, additional simulations, and literature search

-summary response

<\\cdsesub1\evsprod\nda209939\0020\m1\us\efficacy-information-amendment-17jul2017.pdf>

-PBPK report for additional simulations

<\\cdsesub1\evsprod\nda209939\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04hg3\04hg3-addendum.pdf>

PBPK report for the effect of letermovir on CYP2C8 substrates

<\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04kcl7\04kcl7.pdf>

8/2/2017 response to FDA request for PBPK simulations regarding HI

<\\cdsesub1\evsprod\nda209939\0026\m1\us\efficacy-information-amendment-02aug2017.pdf>

Prediction of interaction between letermovir (MK-8228) and substrates of CYP2C8

Study #	04KCL7	Report date	1/10/2017
Title	Prediction of interaction between letermovir (MK-8228) and substrates of CYP2C8		

STUDY SUMMARY (As Reported by the Applicant)

METHODS

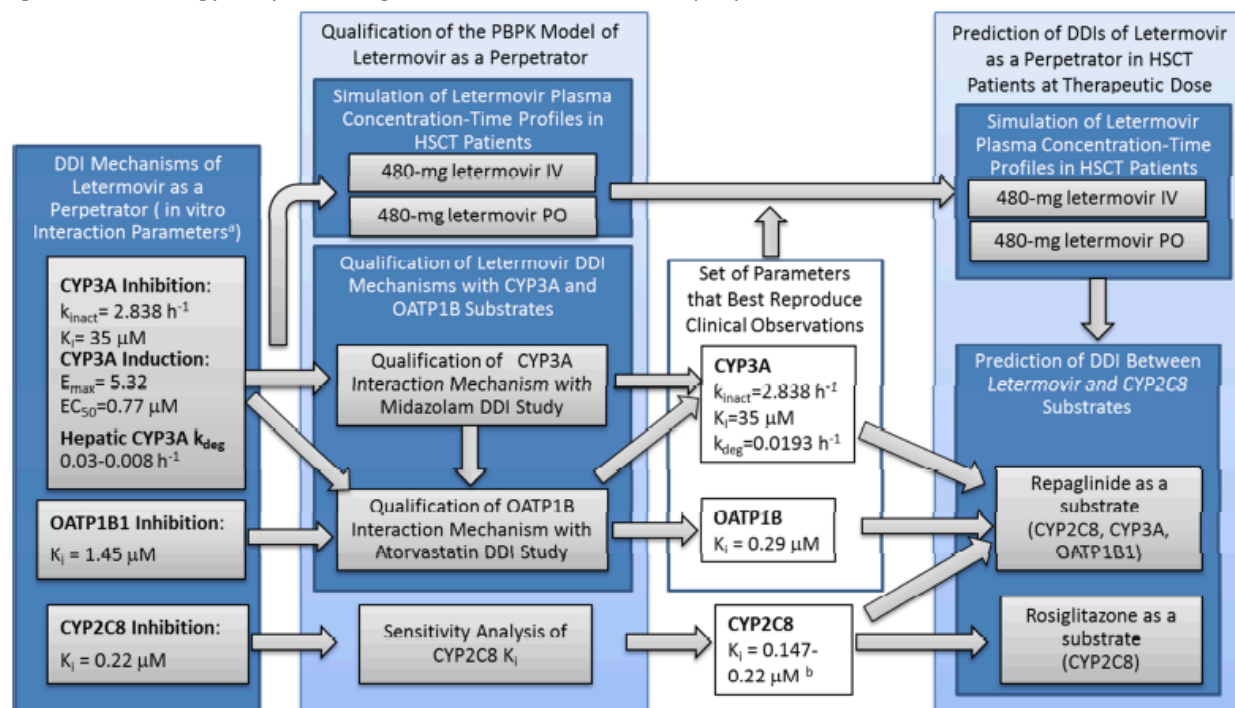
Objectives: Predict the extent of interaction between letermovir and CYP2C8 substrates

Rationale: In vitro, letermovir is a CYP2C8 inhibitor. PBPK simulations were done in lieu of a clinical study.

Methods: PBPK simulations were conducted using Simcyp version 15.

Development of the letermovir PBPK model was described elsewhere (see letermovir PBPK review). The letermovir model was qualified as an inhibitor of CYP3A (midazolam and atorvastatin) and OATP (atorvastatin) before predicting the effect of letermovir on CYP2C8 substrates repaglinide (also a substrate of CYP3A and OATP1B1) and rosiglitazone (also a substrate of CYP2C9 [minor pathway]) (Figure 22). Due to uncertainty, ranges of CYP3A degradation rate constant (k_{deg}), OATP1B1 K_i , and CYP2C8 K_i were evaluated; simulations for the effect of letermovir on midazolam and atorvastatin were conducted with and without CYP3A induction.

Figure 22. Strategy for predicting DDI with letermovir as a perpetrator of CYP2C8.



^a Only parameters that are relevant to this report are shown.

^b Range of parameter values defined by the variability of the K_i value of the positive control in the *in vitro* CYP2C8 inhibition assay.

Source: page 29, <\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04kcl7\04kcl7.pdf>.

The Simcyp built-in repaglinide compound file was qualified via comparison of observed vs. predicted PK from interaction studies with clarithromycin (CYP3A), trimethoprim (CYP2C8), and single dose rifampin (OATP1B1). Atorvastatin, midazolam, and rosiglitazone compound files were stated to have been previously qualified.

RESULTS

Recovery of letermovir PK following administration of 480 mg PO or IV to HSCT recipients: Letermovir model characteristics were described elsewhere (see letermovir PBPK review). Following administration of 480 mg PO or IV to HSCT recipients, simulated/observed C_{max} and AUC ratios were >1 (Table 26).

Table 26. Observed and simulated pharmacokinetic parameters of letermovir in HSCT recipients following IV or oral administration of multiple once daily doses of 480 mg letermovir.

Route of Administration	Oral		IV	
Parameters	AUC _{0-24h} (ng/mL*h)	C _{max} (ng/mL)	AUC _{0-24h} (ng/mL*h)	C _{max} (ng/mL)
Population PK model Predicted ^a	34070 (11520, 99980)	2578 (818.3, 8377)	99960 (65160, 148200)	21570 (19880, 23360)
Simulated ^b	35807 (28467, 45038)	3840 (3251, 4538)	136109 (117866, 157176)	24209 (23115, 25355)
Simulated ^{b, c}	36339 (28897, 45696)	3889 (3292, 4593)	136253 (117985, 157350)	24217 (23121, 25364)
Simulated/Observed Ratio	1.05 (1.07 ^c)	1.49 (1.51 ^c)	1.36 (1.36 ^c)	1.12 (1.12 ^c)

^a Median value (90% confidence interval) ^b geometric mean (95% confidence interval) ^c CYP3A induction parameters were not incorporated in the simulation. The population PK model predicted values are from the report titled Modeling & Simulation Summary: Letermovir Population PK Phase 3 Modeling [Ref. 5.3.5.3: 04KBBP].

Source: Page 24, <\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04kcl7\04kcl7.pdf>.

Recovery of observed CYP3A (midazolam and atorvastatin) and OATP (atorvastatin) substrate PK data: Varying k_{deg} and OATP1B1 K_i values and including or not including CYP3A induction resulted in a range of predicted/observed midazolam and atorvastatin exposure ratios for the presence vs. absence of letermovir; predicted/observed AUC ratios ranged from 0.87-1.12 for oral midazolam and 0.78-1.16 for atorvastatin (Table 27, Table 28).

Table 27. Observed and SimCYP-simulated pharmacokinetic parameters of midazolam in healthy females following oral administration of a single oral dose of 2 mg midazolam in the presence and absence of 240 mg oral dose of letermovir once daily for 6 days.

	Observed ^a	Predicted ^b				Predicted/Observed Ratio
Hepatic CYP3A k_{deg} (h^{-1})		0.03	0.0193	0.0193	0.008	
CYP3A induction		-	-	+	+	
AUC _{0-inf} GM (95%CI) MDZ alone (ng/mL *h)	20.59 ± 4.82	23.04 (20.57, 25.80)	23.04 (20.57, 25.80)	23.04 (20.57, 25.80)	23.04 (20.57, 25.80)	1.12
AUC _{0-inf} GM (95%CI) MDZ w/ Letermovir (ng/mL *h)	44.25 ± 13.05	46.71 (41.05, 53.13)	52.76 (46.11, 60.37)	44.53 (38.9, 50.9)	57.3 (49.5, 66.3)	1.06/1.19/1.01/1.29
C _{max} GM (95%CI) MDZ alone (ng/mL)	8.701 ± 1.80	8.68 (7.83, 9.64)	8.68 (7.83, 9.64)	8.68 (7.83, 9.64)	8.68 (7.83, 9.64)	1.00
C _{max} GM (95%CI) MDZ w/ Letermovir (ng/mL)	15.09 ± 3.69	14.42 (13.0, 15.99)	15.21 (13.70, 16.89)	12.89 (11.6, 14.32)	14.25 (12.80, 15.87)	0.96/1.01/0.85/0.94
AUC _{0-inf} GMR (90% CI) ^c	2.25 ^d (2.04, 2.49)	2.03 (1.93, 2.13)	2.29 (2.17, 2.42)	1.93 (1.84, 2.03)	2.49 (2.34, 2.64)	0.91/1.03/0.87/1.12
C _{max} GMR (90% CI) ^c	1.72 (1.55, 1.92)	1.66 (1.61, 1.71)	1.75 (1.69, 1.81)	1.48 (1.44, 1.53)	1.64 (1.59, 1.69)	0.97/1.02/0.86/0.95

^a Arithmetic mean ± standard deviation ^b Geometric mean (GM) ^c LS mean for the observed ratio ^d AUC_{0-inf}: -, CYP3A induction was not considered; +, CYP3A induction was considered by applying induction parameters of IndC50 = 1.9 and Indmax = 8.2 calibrated based on the EC50 and Emax values of letermovir and rifampin estimated from human hepatocyte induction study [Sec. 2.6.5]; GMR = geometric mean ratio, CI = confidence interval. The observed data are from clinical study report PN016 [Ref. 5.3.3.4: P016].

Source: page 25, <\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04kcl7\04kcl7.pdf>.

Table 28. Observed and SimCYP-simulated pharmacokinetic parameters of atorvastatin following oral administration of a single oral dose of 20-mg atorvastatin in the presence and absence of a 480 mg oral dose of letermovir once daily for 10 days.

	Observed	Predicted						Predicted/Observed Ratio
OATP1B1 ^a		x 0.5	x 0.2	x 0.2	x 0.2	x 0.1	x 0.1	
Hepatic CYP3A k_{deg} (h ⁻¹)		0.0193	0.0193	0.0193	0.008	0.0193	0.0193	
CYP3A Induction		-	-	+	+	-	+	
AUC _{0-inf} GM (95%CI) ATV alone (ng/mL*h)	40.2 (29.0, 55.7)	35.8 (31.6, 40.6)	35.8 (31.6, 40.6)	35.8 (31.6, 40.6)	35.8 (31.6, 40.6)	35.8 (31.6, 40.6)	35.8 (31.6, 40.6)	/0.89/
AUC _{0-inf} GM (95%CI) ATV w/ Letermovir (ng/mL*h)	132 (98.0, 178)	91.3 (79.6, 105)	118 (103, 137)	103 (89.3, 120)	106 (91.5, 123)	156 (135, 181)	136 (117, 158)	0.69/0.90/0.79/0.80/1.19/1.03
C _{max} GM (95%CI) ATV alone (ng/mL)	7.12 (5.14, 9.87)	6.05 (5.39, 6.79)	6.05 (5.39, 6.79)	6.05 (5.39, 6.79)	6.05 (5.39, 6.79)	6.05 (5.39, 6.79)	6.05 (5.39, 6.79)	/0.85/
C _{max} GM (95%CI) ATV w/ Letermovir (ng/mL)	15.4 (11.3, 21.0)	17.7 (15.6, 20.0)	22.1 (19.5, 25.1)	18.9 (16.6, 21.5)	19.3 (16.9, 22.0)	27.6 (24.4, 31.3)	23.6 (20.7, 26.9)	1.15/1.44/1.23/1.25/1.80/1.54
AUC _{0-inf} GMR (90% CI)	3.29 (2.84, 3.82)	2.55 (2.43, 2.67)	3.31 (3.13, 3.49)	2.89 (2.74, 3.04)	2.96 (2.81, 3.12)	4.36 (4.10, 4.64)	3.80 (3.58, 4.04)	0.78/1.01/0.88/0.90/1.33/1.16
C _{max} GMR (90% CI)	2.17 (1.76, 2.67)	2.92 (2.79, 3.06)	3.65 (3.46, 3.85)	3.12 (2.97, 3.28)	3.18 (3.03, 3.34)	4.56 (4.31, 4.83)	3.90 (3.70, 4.11)	1.35/1.69/1.44/1.47/2.11/1.80

^a Fold change over the K_i value of 1.45 μ M estimated from the in vitro experiment [Sec. 2.6.5]; GMR = geometric mean ratio, CI= confidence interval; -, CYP3A induction was not considered; +, CYP3A induction was considered by applying induction parameters of IndC50 =1.9 and Indmax =8.2 calibrated based on the EC50 and Emax values of letermovir and rifampin estimated from human hepatocyte induction study [Sec. 2.6.5]. The observed data are from clinical study report PN023 [Ref. 5.3.3.4: P023].

Source: Page 27, [\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04kcl7\04kcl7.pdf](#).

Predicted effect of letermovir on CYP2C8 substrates repaglinide and rosiglitazone: The applicant did not include CYP3A induction in the letermovir model for the predicted effect upon repaglinide because the effect of CYP3A induction was minimal in the midazolam and atorvastatin simulations. Coadministration with oral or IV letermovir was predicted to increase repaglinide AUC by ~1.9-2.3-fold and ~2.5-3.6-fold, respectively (Table 29). Coadministration with oral or IV letermovir was predicted to increase rosiglitazone AUC by ~1.35-fold and ~1.5-fold, respectively.

Table 29. Predicted drug interactions following coadministration of a single oral dose of 1 mg repaglinide with oral doses or 60 minutes IV infusion doses of 480 mg letermovir once daily for 10 Days in HSCT recipients.

In vitro measurement	Fold Changes in Inhibition Parameters Relative to Measured Values			
OATP1B K_i = 1.45 μ M	x 1	x 1	x 0.2	x 0.2
CYP2C8 K_i = 0.22 μ M	x 1	x 0.67	x 1	x 0.67
Following co-administration with oral letermovir				
Predicted REP AUC_{0-inf} GMR (90% CI)	1.88 (1.79, 1.96)	2.06 (1.96, 2.17)	2.13 (2.02, 2.25)	2.34 (2.21, 2.48)
Predicted REP C_{max} GMR (90% CI)	1.41 (1.38, 1.45)	1.47 (1.43, 1.51)	1.51 (1.47, 1.55)	1.57 (1.52, 1.61)
Following co-administration with i.v. letermovir				
Predicted REP AUC_{0-inf} GMR (90% CI)	2.47 (2.34, 2.61)	2.82 (2.65, 2.99)	3.20 (3.01, 3.41)	3.64 (3.41, 3.89)
Predicted REP C_{max} GMR (90% CI)	1.49 (1.45, 1.52)	1.57 (1.53, 1.61)	1.69 (1.65, 1.74)	1.78 (1.73, 1.83)

GMR = geometric mean ratio, CI= confidence interval

Source: Page 28, <\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04kcl7\04kcl7.pdf>.

Table 30. Predicted drug interactions following coadministration of a single oral dose of 4 mg rosiglitazone with oral doses or 60 minutes IV infusion doses of 480 mg letermovir once daily for 10 Days in HSCT recipients.

Letermovir 480 mg QD	Oral		IV	
CYP2C8 K_i = 0.22 μ M	x 1	x 0.67	x 1	x 0.67
Predicted ROS AUC_{0-inf} GMR (90% CI)	1.32 (1.29, 1.36)	1.40 (1.36, 1.45)	1.46 (1.41, 1.51)	1.55 (1.49, 1.60)
Predicted ROS C_{max} GMR (90% CI)	1.03 (1.02, 1.03)	1.04 (1.03, 1.04)	1.04 (1.04, 1.05)	1.05 (1.04, 1.06)

GMR = geometric mean ratio, CI= confidence interval

Source: page 28, <\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04kcl7\04kcl7.pdf>.

REVIEWER ASSESSMENT
The model is acceptable ☒ Yes ☐ No
Discussion and labeling recommendations The modeling is acceptable in lieu of a clinical study. Predictions for the effect of letermovir PK were conservative in that predicted/observed exposure ratios were >1. Letermovir IV increased the predicted exposure of repaglinide and rosiglitazone more than letermovir PO. This is consistent with higher exposures from IV letermovir and absence of no CYP2C8 in the gut. However, it is anticipated that repaglinide or rosiglitazone would be rarely used with IV letermovir because they have no IV formulation. See section 2.2.2 and 3.3.4 of the QBR for labeling recommendations for use of letermovir with CYP2C8 substrates.
Relevant links within the submission PBPK report \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hsctproph\5353-rep-analys-data-more-one-stud\04kcl7\04kcl7.pdf

Mass balance

P021 – mass balance study

Study #	P021	Study Period	Part 1: 12/8/2008-1/12/2009 Part 2: 11/12/2008-4/6/2009 Part 3: 3/16/2009-4/27/2009
Title	A RANDOMISED, SINGLE CENTRE, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO DETERMINE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF A SINGLE ORAL DOSE OF AIC090027 AND MULTIPLE ASCENDING ORAL DOSES OF AIC090027, AND AN OPEN-LABEL, SINGLE CENTRE TRIAL TO INVESTIGATE THE MASS BALANCE AND METABOLITE PROFILE OF MULTIPLE ORAL DOSES OF AIC090027		

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives:

- Parts 1-2: safety and PK
- Part 3: evaluate mass balance, identify metabolites in plasma, urine, and feces, and identify routes of elimination

Rationale:

- Part 1: safety data were lacking in female subjects
- Part 2: evaluate safety at higher doses
- Part 3: Determine ADME of letermovir

Study design:

- Parts 1-2: randomized, double-blind, placebo-controlled
- Part 3: open-label

Part	Cohort	N treatment / placebo	N male / female	Treatment	Route	Duration
1	1	6/2	0/8	240 mg	PO	Single dose
2	2	12/4	8/8	120 mg PO BID		Days 1-15
	3	12/4	8/8	180 mg PO BID		
	4	12/4	8/8	240 mg PO BID		
3	5	8/0	8/0	80 mg BID 80 mg + 12 kBq (325 nCi) of [14C]-letermovir		Days 1-4 Single dose on day 5

Population:

- Part 1: healthy females aged 18-55 years
- Part 2: healthy males and females aged 18-55 years
- Part 3: healthy males aged 18-55 years

Dose Selection:

- Part 1: Favorable safety was observed for single doses of up to 320 mg and 80 mg BID in males
- Part 2: Exposures from 120 mg BID were thought to be covered by a prior study of 80 mg BID + cyclosporine
- Part 3: The applicant proposed to evaluate 240 mg BID as this was the highest dose that was safe and

well-tolerated. However, after the FDA set a lower NOAEL based on a fertility study in male rats, the dose was reduced to 80 mg BID.
Administration: ☒ Fasted ☐ Fed
Formulation: -FFP2 tablet (Parts 1-3) -capsule containing radiolabeled dose (Part 3)
Excluded concomitant medications: -Parts 1-3: Subjects on medications other than hormonal contraceptives were not eligible for the study. With the exception of hormonal contraceptives, concomitant medications during the trial were not allowed.
PK sampling: <u>Plasma</u> -Part 1: day 1 intensive PK through 72 hours postdose -Part 2: Day 1 intensive PK through 12 hours postdose Day 15 intensive PK through 72 hours postdose -Part 3: For radioactivity in plasma and metabolite identification: day 5 intensive PK through 336 hours postdose <u>Excreta (part 3 only):</u> -Day 5 urine and feces collection in intervals through 336 hours postdose
Bioanalytical Methods: Unlabeled letermovir was measured in plasma using letermovir methods 08-061 and 09-010. Radioactivity in plasma and urine was measured using accelerator mass spectrometry (AMS). Radioactivity in feces was measured using scintillation counting or AMS. Plasma and feces samples were pooled across subjects and measured using HPLC and AMS to generate metabolite profiles.
Results
Demographics Eight subjects were enrolled and all completed the study. Mean age was 29 years, mean weight was 72 kg, and 7/8 subjects were white.
Protocol Deviations -Part 1: Two subjects enrolled without contraception were allowed to enroll because they were sexually abstinent -Part 2: Various deviations were reported (CSR page 48) -Part 3: Three subjects consumed a meal containing a small amount of mustard (prohibited food). Also, PK sampling time deviations were reported.
Concomitant medications -Part 1: The most common concomitant medication was hormonal contraceptives. Several subjects used short term ibuprofen or acetaminophen. One subject used vaginal miconazole during the study and one subject used topical mupirocin before the study. -Part 2: The most common concomitant medications were hormonal contraceptives and short term over-the-counter pain relievers. -Part 3: Short term acetaminophen was used in several subjects in addition to multivitamins (n=1) and topical hydrocortisone (n=1)

Pharmacokinetics (CSR page 43 [part 1], page 67 [part 2], page 48 [part 3])**Part 1**

Part 1 PK parameters are shown below (Table 31).

Table 31. Part 1 PK parameters.

Parameter	Unit	N	Mean	SD
C _{max}	ng/mL	6	7340	1785
t _{max}	h	6	2.00*	1.00-2.50
AUC _{0-last}	ng.h/mL	6	34070	9557
AUC _{0-∞}	ng.h/mL	6	34240	9634
λ _z	1/h	6	0.07449	0.01273
t _{1/2z}	h	6	9.555	1.777
CL/F	L/h	6	7.623	2.680
V _D /F	L	6	103.3	33.54
MRT	h	6	9.775	1.142

* For t_{max}, median (min-max) is presented.

Source: CSR, page 45.

Part 2

One predose sample (subject 47, 240 mg BID, day 5 evening dose) was excluded from the PK analysis due to vomiting. Steady-state concentrations were reached by day 3 for all dose levels (page 2160). Exposures on day 1 and day 15 were dose proportional (pages 2183-2184). Accumulation ratios across dose groups were 1.3-1.6. Day 1 and day 15 C_{max} and AUC variability (CV%) was ~20-30% while C_{min} variability was ~30-50%. Elimination half-life was ~13 hours. Exposures overlapped between genders but were generally higher in females (page 2181). Part 2 PK parameters are shown below (Table 32).

Table 32. Part 2 PK parameters.

Pharmacokinetics of AIC090027 (mean ± SD, t _{max} median [range])	120 mg AIC090027 b.i.d.	180 mg AIC090027 b.i.d.	240 mg AIC090027 b.i.d.
n	12	12 ^a	11 ^b
Day 1			
C _{0,1max} , ng/mL	3469 ± 792.5	5654 ± 1738	7011 ± 1404
t _{max} , h	1.50 (0.75-2.00)	1.50 (1.00-2.50)	1.50 (1.00-2.50)
AUC ₀₋₂₄ , ng.h/mL	11510 ± 2859	18040 ± 4455	24350 ± 6724
Day 2			
C _{0,2} , ng/mL	557.7 ± 233.9	687.4 ± 122.6	862.0 ± 304.5
Day 3			
C _{0,3} , ng/mL	793.2 ± 454.6	864.6 ± 149.8	1085 ± 436.9
Day 4			
C _{0,4} , ng/mL	879.5 ± 510.3	947.9 ± 348.1	1120 ± 490.5
Day 5			
C _{0,5} , ng/mL	886.4 ± 521.6	851.2 ± 285.9	1326 ± 686.9
Day 6			
C _{0,6} , ng/mL	907.7 ± 502.7	892.0 ± 372.4	1358 ± 683.6
Day 7			
C _{0,7} , ng/mL	874.4 ± 398.2	888.7 ± 468.8	1123 ± 502.5
Day 8			
C _{0,8} , ng/mL	733.9 ± 288.5	822.3 ± 351.7	1317 ± 768.3
Day 9			
C _{0,9} , ng/mL	782.9 ± 344.2	839.1 ± 361.3	1156 ± 659.4
Day 10			
C _{0,10} , ng/mL	855.9 ± 482.5	734.0 ± 231.9	1060 ± 368.2

Pharmacokinetics of AIC090027 (mean ± SD, t _{max} median (range))	120 mg AIC090027 b.i.d	180 mg AIC090027 b.i.d	240 mg AIC090027 b.i.d
Day 11			
C _{0h} , ng/mL	772.1 ± 454.8	748.4 ± 345.5	1033 ± 367.6
Day 12			
C _{0h} , ng/mL	849.2 ± 531.8	823.6 ± 289.3	1073 ± 359.0
Day 13			
C _{0h} , ng/mL	789.0 ± 312.7	774.0 ± 250.1	1148 ± 415.0
Day 14			
C _{0h} , ng/mL	780.0 ± 383.4	755.4 ± 275.7	1161 ± 431.7
Day 15			
C _{0h} , ng/mL	705.4 ± 354.6	691.0 ± 299.8	939.2 ± 370.3
C _{min} , ng/mL	614.9 ± 295.4	545.2 ± 176.4	824.7 ± 332.7
C _{12,pm} , ng/mL	4171 ± 888.5	5429 ± 1544	7846 ± 1549
t _{max} , h	1.50 (1.00-2.50)	2.00 (1.50-3.00)	1.50 (0.75-2.50)
AUC ₀₋₂₄ , ng·h/mL	18250 ± 4955	23210 ± 5928	31490 ± 8492
C _{12,pm} , ng/mL	1521 ± 413.2	1932 ± 495.1	2624 ± 707.7
FI, %	242.0 ± 46.51	255.8 ± 69.10	277.8 ± 62.40
t _{1/2} , h	12.44 ± 4.769	14.99 ± 6.062	12.60 ± 5.606
CL/F, L/h	7.036 ± 1.907	8.160 ± 1.769	8.190 ± 2.387
V _{ss} /F, L	125.4 ± 54.21	168.8 ± 59.11	140.0 ± 51.69
MRT, h	12.47 ± 3.075	11.16 ± 3.391	12.28 ± 4.870
RA(C _{max})	1.227 ± 0.2403	0.9855 ± 0.1919	1.165 ± 0.2546
RA(AUC)	1.604 ± 0.2638	1.303 ± 0.2184	1.372 ± 0.3892

^a n=11 for Day 9, Day 11, Day 12, Day 13, Day 14 and Day 15, n=10 for Day 10

^b n=12 for Day 1, n=10 for Day 6

Source: CSR page 73.

Part 3

Mean recovery of total radioactivity was 94.7%. In pooled plasma samples, 96.6% of radioactivity was attributed to letermovir and 3.4% to three uncharacterized metabolites (page 26, [\\cdsesub1\evsprod\nda209939\0000\m2\26-nonclin-sum\pharmkin-written-summary.pdf](#)). The cumulative percentage of dose administered in urine and feces was 1.43% (SD=0.31%) and 93.3% (2.2%), respectively. Of the radioactivity recovered in feces, the percentages of the administered dose attributed to letermovir , acyl-glucuronide, and four uncharacterized metabolites were ~70%, ~6%, and ~16% (4% for each metabolite), respectively (PK summary, page 25). Part 2 PK parameters are shown below.

Table 33. Part 3 PK parameters after administration of 80 mg BID.

<i>Pharmacokinetics of AIC090027</i> (mean ± SD, t _{max} : median [range])	80 mg AIC090027 bid.
n	8
<u>Day 2</u>	
C _{0h} , ng/mL	139.8 ± 74.85
<u>Day 3</u>	
C _{0h} , ng/mL	215.3 ± 117.5
<u>Day 4</u>	
C _{0h} , ng/mL	216.6 ± 134.2
<u>Day 5</u>	
C _{0h} , ng/mL	197.9 ± 94.33
C _{ss,max} , ng/mL	1761 ± 504.7
t _{max} , h	1.50 (1.00-3.00)
AUC _{τ,ss} , ng·h/mL	6845 ± 2236
AUC _{0-last} , ng·h/mL	11020 ± 5258
λ _z , 1/h	0.06852 ± 0.00974
t _{1/2z} , h	10.31 ± 1.555
AUC _{0-∞} , ng·h/mL	11310 ± 5327
CL/F, L/h	12.85 ± 4.228
V _{ss/F} , L	188.3 ± 60.74
MRT, h	11.38 ± 3.415

Source: CSR, page 52.

Table 34. Part 3 PK parameters after administration of a radiolabeled dose.

<i>Pharmacokinetics of Total Radioactivity</i> (mean ± SD, t _{max} : median [range])	Tracer Dose of ¹⁴ C-AIC090027
n	8
<u>Day 5</u>	
C _{max} , ng equi/mL	1800 ± 486.9
t _{max} , h	1.00 (1.00-2.50)
AUC _{0-12h} , ng equi·h/mL	5724 ± 1221
AUC _{0-last} , ng equi·h/mL	8942 ± 2836
t _{1/2} , h	12.33 ± 2.487

Source: CSR, page 52.

Safety

- Part 1: there were no SAEs, discontinuations due to AEs, or deaths
- Part 2: Three subjects discontinued prematurely due to AEs. One was a placebo subject with increased transaminases. One male subject receiving 180 mg discontinued prior to the day 8 evening dose due to abnormal liver function tests. One female subject receiving 240 mg BID discontinued due to vomiting after the morning (moderate) and evening (severe) dose on day 1. There were no deaths or SAEs.
- Part 3: there were no SAEs, discontinuations due to AEs, or deaths

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion and labeling recommendations	
Data obtained in this study are in section 12.3 of the proposed labeling, (b) (4)	
(b) (4). We agree with the statements:	
(b) (4)	
Relevant links within the submission	
CSR	
-part 1	
\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\p021v01\p021v01.pdf	
-part 2	
\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\p021v02\p021v02.pdf	
-part 3	
\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\p021v03\p021v03.pdf	
Bioanalytical sample analysis report	
\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\p021v03\bioanalytical-plan.pdf	

Food effect

P029 – food effect study

Study #	P029	Study Period	10/17/14-10/27/14
Title	A Study of the Comparative Fed and Fasted Bioavailability of MK-8228 (Letermovir) in Healthy Subjects		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i>	Evaluate the effect of food on the PK of letermovir
<i>Rationale:</i>	Not stated
<i>Study design:</i>	Open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover study. In each period, subjects received one of the following two treatments: -Treatment A: letermovir 480 mg PO after the start of a high-fat (57%), high-calorie (~919 kcal) breakfast -Treatment B: letermovir 480 mg PO after an overnight fast of at least 10 hours There was a 7 day washout period.
<i>Population:</i>	Females aged 18-55 years with no clinically significant medical condition
<i>Dose Selection:</i>	480 mg is the recommended dose for CMV prophylaxis
<i>Administration:</i>	☒ Fasted ☒ Fed
<i>Formulation:</i>	PMF3 tablet
<i>Excluded concomitant medications:</i>	Subjects requiring systemic medications or who took enzyme-modifying drugs within 30 days prior to study drug intake were not eligible for the study.
<i>PK sampling:</i>	Blood samples were collected for intensive PK assessment through 72 hours post-dose
<i>Bioanalytical methods:</i>	letermovir method BP-0032
RESULTS	
Demographics	Fourteen subjects were enrolled. All subjects were female, 57% of subjects were black (and 36% were white), and the mean weight was 153 lbs.
Protocol Deviations	One deviation was reported where the 14-day follow-up call for subject # 13 was conducted 6 days late.
Concomitant medications	One subject used acetaminophen during the study.
Pharmacokinetics (CSR page 34)	C _{max} and AUC ratios (fed/fasted) were 1.30 (1.04, 1.62) and 1.00 (0.84, 1.17), respectively. There was one outlier subject (#9) with C _{max} and AUC ratios of ~6 and ~3, respectively. Removal of this subject from the PK analysis resulted in a minimal impact on exposure ratios [C _{max} and AUC ratios of 1.22 (1.15, 1.30) and 0.95 (0.90, 1.01), respectively]. Median T _{max} in the fed and fasted state was 2.5 h and 2.76 h, respectively. PK parameters are shown below (Table 35).

Table 35. PK parameters.

Sbj	Seq	AUC_{0-12h}			AUC_{0-inf}			C_{max}			T_{max}		$t_{1/2}$	
		A	B	A/B	A	B	A/B	A	B	A/B	A	B	A	B
0001	BA	99300	102000	0.97	100000	103000	0.97	16200	10100	1.60	1.50	5.00	13.3	11.7
0002	AB	69700	83900	0.83	69800	84400	0.83	12300	13100	0.94	2.50	3.00	8.86	11.3
0003	BA	73700	73800	1.00	74100	74000	1.00	18100	12200	1.48	2.00	2.00	12.4	9.25
0004	AB	124000	113000	1.10	125000	114000	1.10	19400	15900	1.22	2.00	3.00	12.4	12.4
0005	AB	112000	118000	0.94	112000	119000	0.94	16600	17900	0.93	3.00	2.00	11.9	13.1
0006	BA	76400	90500	0.84	76600	90800	0.84	11600	9780	1.19	5.00	5.00	8.99	10.3
0007	BA	89800	96100	0.93	90800	96800	0.94	17900	13400	1.34	2.00	4.00	15.1	12.3
0008	AB	66900	68700	0.98	67200	70400	0.95	12100	11900	1.02	2.50	2.52	9.64	18.5
0009	BA	74600	27900	2.67	74700	28600	2.61	11700	2020	5.79	3.00	2.50	8.42	13.4
0010	AB	85800	95300	0.90	87200	96300	0.91	21100	17800	1.19	1.50	2.00	22.6	14.1
0011	AB	88000	91100	0.97	88800	91300	0.97	15000	13400	1.12	3.00	2.00	11.3	9.44
0012	BA	69000	70200	0.98	69300	70400	0.98	12900	9170	1.41	1.50	4.00	11.4	10.4
0013	BA	.	195000	.	.	196000	.	.	25400	.	.	3.00	.	10.0
0014	AB	83100	70200	1.18	84400	71000	1.19	13600	12000	1.13	3.00	2.00	22.7	13.6
GeoMean		84100	85900	1.04	84700	86600	1.04	15000	11800	1.35	2.35	2.84	12.3	11.9
ArithMean		85500	92600	1.10	86200	93300	1.10	15300	13100	1.57	2.50	3.00	13.0	12.1
SD		17300	37100	0.48	17600	37100	0.46	3190	5310	1.29	0.957	1.09	4.68	2.43
CV%		20.2	40.1	43.73	20.4	39.8	42.46	20.9	40.4	82.15	38.3	36.4	36.1	20.0
Median		83100	90800	0.97	84400	91100	0.97	15000	12700	1.19	2.50	2.76	11.9	12.0
Minimum		66900	27900	0.83	67200	28600	0.83	11600	2020	0.93	1.50	2.00	8.42	9.25
Maximum		124000	195000	2.67	125000	196000	2.61	21100	25400	5.79	5.00	5.00	22.7	18.5
n		13	14	13	13	14	13	13	14	13	13	14	13	14
Harm.Mean													11.8	11.7
SDjk													3.31	2.08

Treatment A: MK-8228 480 mg Tablets (Fed), Lot No.: WL00059057 (Merck Sharp & Dohme Corp.)
 Treatment B: MK-8228 480 mg Tablets (Fasting), Lot No.: WL00059057 (Merck Sharp & Dohme Corp.)

Source: CSR, page 40.

Safety

Fourteen subjects were enrolled and 13 completed the study. One subject (#13) discontinued due to an AE of emesis. There were no SAEs or deaths.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion	
The only issue with this study was the one outlier subject (#9) who had much higher exposure ratios (fed/fasted) compared to other subjects. This subject had the lowest Cmax and AUC values in the fasted state, and Cmax and AUC values similar to other subjects in the fed state. Low exposures in the fasted state and typical exposures in the fed state would explain the higher exposure ratios for subject #9. It is unclear why subject 9 exposures were low in the fasted state.	
Labeling Recommendations	
We agree with the proposed labeling statement that letermovir can be taken with or without food.	
Relevant links within the submission	
CSR \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\p029\p029.pdf	
Bioanalytical sample analysis \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\p029\publications-based-on-trial.pdf	

Renal impairment

P006 – renal impairment PK study

Study #	P006	Study Period	10/30/2012 – 5/7/2013
Title	An open-label, single-center, non-randomized trial to investigate the pharmacokinetics, safety and tolerability of multiple oral 120 mg letermovir once daily doses in male and female subjects with moderate and severe renal impairment compared to healthy male and female subjects		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i>	Evaluate the PK of letermovir in subjects with moderate and severe renal impairment (RI) in comparison to healthy adults
<i>Rationale:</i>	Not stated
<i>Study design:</i>	Open-label, single-center, non-randomized, multiple dose trial. All subjects received oral letermovir 120 mg QD for 8 days. Subjects enrolled based on eGFR (MDRD) to the following arms: -healthy: eGFR ≥ 90 mL/min/1.73m² -moderate renal impairment: eGFR 30-59 mL/min/1.73m² -severe renal impairment not on dialysis: eGFR < 30 mL/min/1.73m²
<i>Population:</i>	Enrollment was open to male and female Caucasians aged 50-79 years. Subjects with diseases suspected to influence the safety or PK of letermovir were excluded with the exception of renal diseases, which were allowed in the renal impairment group.
<i>Dose Selection:</i>	At the time of the study, the target dose was 240 mg. Because the effect of renal impairment on hepatic transporters involved in letermovir disposition was unknown, 120 mg was selected to ensure safety.
<i>Administration:</i>	☒ Fasted ☐ Fed
<i>Formulation:</i>	120 mg tablets (PMF2 formulation)
<i>Excluded concomitant medications:</i>	Healthy subjects were not eligible if they were treated with any medications within 2 weeks before study dosing (with the exception of hormonal contraceptives and single intake of drugs if deemed not clinically relevant), while subjects with renal impairment could enter the study and continue medications for underlying disease. The following medications were allowed during the study: hormonal contraceptives, acetaminophen, and “personal medication essential to treatment of the underlying disease” (renal impaired subjects only). Prohibited medications (prior to enrollment and during the study) included those that might have interfered with letermovir PK as well as known enzyme/transporter inhibitors or inducers (a list prohibited drugs is not present in the CSR or protocol).

PK sampling:

Plasma

Days 1 and 5-7: pre-dose

Day 8: pre-dose, and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, and 144 hours post-dose

Fraction unbound

Day 8: 1.5 hours post-dose

Bioanalytical Methods: Letemovir method 08-061

RESULTS

Demographics

24 subjects were enrolled and all subjects completed the study. Demographics were comparable between arms (Table 36).

Table 36. Demographics.

	Healthy (n=8)	Moderate RI (n=8)	Severe RI (n=8)
Female	4 (50%)	3 (37.5%)	3 (37.5%)
Caucasian race	8 (100%)	8 (100%)	8 (100%)
Age (years)	64 (59, 68)	74 (64, 76)	71 (51, 76)
BMI (kg/m ²)	25.1 (24.6, 33.2)	27.4 (22.2, 32.5)	26.7 (19.8, 32.5)
eGFR (mL/min/1.73m ²)	97 (93, 112)	37 (31, 57)	21 (12, 28)

Source: CSR, page 70. Values are median (min, max) or N (%).

Protocol Deviations

No major protocol deviations were reported.

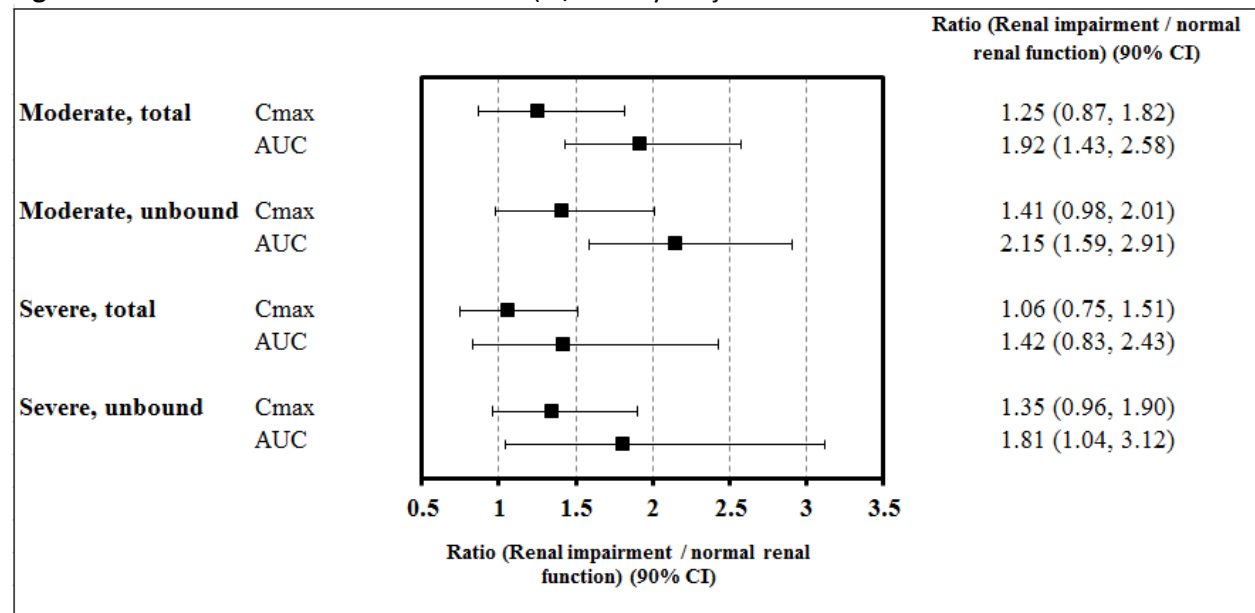
Concomitant medications

No healthy subjects took concomitant medications. The median number of concomitant drugs per subject was four in the moderate RI arm and seven in the severe RI arm. There was no reported use of known OATP inhibitors (as listed in <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-2>).

Pharmacokinetics (CSR page 72)

Fraction bound in all subjects was 98-100% and eGFR was associated with fraction unbound (Table 37). Total and unbound AUC ratios (RI/healthy) and lower 90% CIs were above one with the exception of total AUC for severe RI; total and unbound Cmax ratios were unchanged (Figure 23). Cmax variability was similar or higher in the moderate RI versus severe RI group, while AUC variability was lower in the moderate RI versus severe RI groups. eGFR was not associated with total CL and was weakly associated with unbound CL (Table 37). PK parameters are shown below (Table 38).

Figure 23. Letermovir C_{max} and AUC ratios (RI/healthy subjects).



Source: prepared by reviewer from PK data in the CSR section 11.

Table 37. Linear regression analyses.

Response variable	Explanatory variable	N	Intercept	Slope	R ²	p-value
Fraction unbound	Ln (eGFR [mL/min])	24	0.01713	-0.00174	0.5076	<0.0001
Total letermovir						
Ln (clearance [L/h])	Age (years)	24	5.42413	-0.05054	0.3548	0.0021
Ln (clearance [L/h])	Ln (eGFR [mL/min])	24	1.23895	0.21732	0.0662	0.2249
Unbound letermovir						
Ln (clearance [L/h])	Age (years)	24	9.97916	-0.05049	0.3166	0.0042
Ln (clearance [L/h])	Ln (eGFR [mL/min])	24	5.16811	0.38541	0.1861	0.0353

eGFR=estimated glomerular filtration rate

Source: CSR page 85.

Table 38. Day 8 total letermovir PK parameters.

PK parameter	Healthy	Renal impairment	
		Moderate	Severe
	N=8	N=8	N=8
Mean (SD), t _{max} : median [range]			
Day 8			
C ₀ , ng/mL	82.86 (34.26)	278.5 (165.9)	274.9 (296.5)
C _{min} , ng/mL	80.78 (32.77)	271.5 (161.7)	264.7 (285.7)
C _{ss,max} , ng/mL	2614 (1042)	3301 (1670)	2714 (929.9)
t _{max} , h	1.50 (1.00 - 2.50)	1.51 (1.00 - 2.00)	1.75 (1.00 - 4.00)
AUC _{τ,ss} , ng·h/mL	11,413 (3194)	22,694 (9944)	21,013 (17919)
C _{ss,av} , ng/mL	475.5 (133.1)	945.6 (414.3)	875.4 (746.7)
FI, %	521.8 (116.5)	331.6 (117.7)	410.2 (197.2)
λ _z , 1/h	0.05462 (0.03054)	0.03369 (0.01447)	0.03940 (0.02172)
t _{1/2,z} , h	16.21 (7.705)	25.95 (15.83)	21.69 (9.295)
CL/F, L/h	11.25 (3.090)	6.024 (2.119)	9.929 (7.124)
V _d /F, L	261.4 (148.2)	222.8 (142.4)	314.3 (308.9)

AUC=area under the analyte concentration time curve; av=average; C=concentration; CL/F=apparent clearance following multiple-dose extravascular administration; FI=fluctuation index; max=maximum; min=minimum; ss=steady state; t_{1/2,z}=terminal elimination half-life

Source: CSR page 76.

Safety

There were no discontinuations due to AEs or deaths during the study. One SAE was reported in the severe RI group. The SAE was peripheral ischemia on day 16 (nine days after last letermovir dose) and was resolved and not considered treatment-related. No significant changes in laboratory parameters were reported.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion Despite letermovir being negligibly renally excreted (<2% of dose), unbound letermovir AUC ratios (RI/healthy) were above one. Higher AUC ratios were observed in the moderate versus severe RI groups. Graphically, exposures were comparable between the moderate and severe RI groups with the exceptions of one subject in the severe group with elevated total and unbound AUC (CSR page 77 and 83). Demographics were similar between study arms. Based on the weak association between eGFR and unbound CL and no association with total CL, the applicant suggested that higher exposures in subjects with RI may be due to factors other than renal impairment (CSR page 101). A possible reason for increased exposures in RI despite negligible renal elimination could be an inhibitory effect of uremic toxins on OATP, resulting in higher plasma concentrations. There are in vitro data showing concentration-dependent inhibition of OATP by several uremic toxins (PMID 25579430). This would not seem to explain the greater exposure changes observed in the moderate versus severe RI group. However, it is possible that uremic toxin concentrations were not necessarily higher in the severe group, because in a study of subjects with mild to severe RI, concentrations of uremic retention products other than creatinine were poorly associated with eGFR (PMID 21617084). A large number of concomitant medications were used by subjects with RI. These were mostly for chronic conditions including hypertension, hyperlipidemia, diabetes. None of the concomitant medications were known enzyme or transporter inhibitors or inducers. In this study, letermovir fraction unbound was only assessed at 1.5 hours postdose. In vitro letermovir fraction unbound in human plasma was ~1-2% over a concentration range of ~500-93000 ng/mL (study PK011). Letermovir concentrations in this study ranged from 1-7197 ng/mL, with concentrations at 1.5h postdose being ~2500 ng/mL. As letermovir remained highly (98-99%) bound over a large concentration range, assessment of protein binding at one timepoint in this study was acceptable.	
Labeling recommendations	
See the QBR section 2.2.2 and 3.3.3.	

Relevant links within the submission

Study report

<\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\p006\p006.pdf>

Letermovir bioanalytical method validation report

<\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\04hnr7\04hnr7.pdf>

Letermovir bioanalytical sample analysis report

<\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\04jhbt\04jhbt.pdf>

Determination of fraction unbound

<\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\04jhck\04jhck.pdf>

Hepatic impairment

P015 – hepatic impairment PK study

Study #	P015	Study Period	7/20/10 – 8/4/11
Title	An open-label, parallel group comparison trial to investigate the effect of hepatic impairment on the pharmacokinetics, safety, and tolerability after multiple once daily treatment with 60 mg AIC090027		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i>	Determine the effect of hepatic impairment (HI) on the PK of letermovir
<i>Rationale:</i>	Letermovir is primarily eliminated via OATP-mediated hepatic uptake and biliary excretion. HI may impact this process and letermovir exposure.
<i>Study design:</i>	Open-label, multiple dose, parallel group study. Treatments: -moderate hepatic impairment and matched controls: letermovir 60 mg PO QD for 8 days -severe hepatic impairment and matched controls: letermovir 30 mg PO QD for 8 days. The dose was lowered to 30 mg because of potential drug interactions with concomitant medications after review of safety and PK in subjects with moderate HI.
<i>Population:</i>	-healthy subjects: women aged 18-65 years, BMI of 18-34 kg/m², and lacking any diseases -HI subjects: women aged 18-65 years, BMI of 18-34 kg/m², Child-Pugh B or C HI, and no cardiovascular, renal, or endocrine findings.
<i>Dose Selection:</i>	60 mg in subjects with HI was predicted to provide exposures that would be covered by a prior study in healthy subjects administered 240 mg BID.
<i>Administration:</i>	☒ Fasted ☐ Fed
<i>Formulation:</i>	PMF1 tablet
<i>Excluded concomitant medications:</i>	-any enzyme or transporter inhibitor or inducer within 14 days of enrollment -use of any medication with the exception of treatments of liver disease in the HI group
<i>PK sampling:</i>	-Intensive day 8 PK sampling through 120 hours post-dose -fraction unbound was assessed at 1.5 hours postdose
<i>Bioanalytical methods:</i>	Letermovir methods 08-061 and 10-014. Fraction unbound was determined using equilibrium dialysis.
RESULTS	
Demographics	Thirty three subjects enrolled and completed the study; eight with moderate HI and nine matched controls (one replaced due to protocol violation), and eight with severe HI and eight matched controls. All subjects were Caucasian; age and BMI were similar between HI subjects and controls (CSR page 68).

Protocol Deviations

One major deviation was the enrollment of a “healthy” subject with dyslipidemia. This subject was replaced and was excluded from the PK analysis.

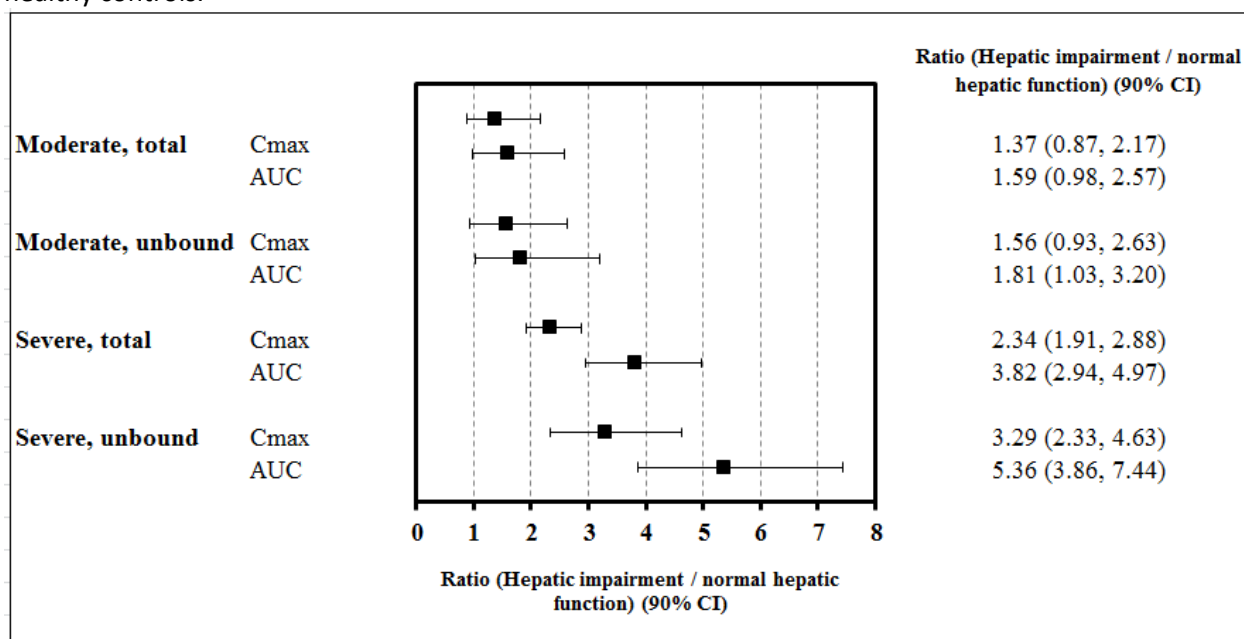
Concomitant medications

The most common medications used prior to or during the study were medications used to treat liver diseases, including spironolactone, lactulose, furosemide, propranolol, and ursodeoxycholic acid (CSR pages 70 and 72).

Pharmacokinetics (CSR page 76)

Compared to healthy controls, total and unbound letermovir exposures were higher in subjects with HI (Figure 24). Total letermovir PK parameters are shown below (Table 39).

Figure 24. Statistical comparison of letermovir PK in subjects with moderate or severe HI relative to healthy controls.



Source: prepared by reviewer from data in the CSR pages 85 and 87.

Table 39. Total letermovir PK parameters.

Parameter (mean $\pm$ SD, t_{max} : median [range])	Treatment group			
	Group 1 (moderate)	Group 2 (healthy matched to moderate)	Group 3 (severe)	Group 4 (healthy matched to severe)
n	8	8	8 ^a	8 ^a
Day 8				
C_{0h} , ng/mL	182.0 $\pm$ 257.8	68.81 $\pm$ 47.38	141.6 $\pm$ 59.53	20.14 $\pm$ 9.226
C_{min} , ng/mL	140.6 $\pm$ 198.3	67.44 $\pm$ 47.55	135.3 $\pm$ 55.97	19.03 $\pm$ 8.435
$C_{ss,max}$, ng/mL	1687 $\pm$ 592.4	1361 $\pm$ 643.3	1206 $\pm$ 326.8	511.5 $\pm$ 111.7
t_{max} , h	2.00 (0.75 to 4.00)	1.50 (1.00 to 2.50)	2.00 (1.00 to 4.00)	1.50 (1.00 to 2.50)
AUC ₀₋₂₄ , ng.h/mL	11960 $\pm$ 8164	7121 $\pm$ 3310	10863 $\pm$ 3986	2732 $\pm$ 525.1
$C_{ss,av}$, ng/mL	498.3 $\pm$ 340.1	296.7 $\pm$ 137.9	452.6 $\pm$ 166.1	113.8 $\pm$ 21.88
FI, %	389.1 $\pm$ 187.0	432.2 $\pm$ 121.0	249.0 $\pm$ 62.32	438.3 $\pm$ 86.05
λ_z , 1/h	0.05542 $\pm$ 0.01563	0.05323 $\pm$ 0.02107	0.03867 $\pm$ 0.01087	0.05807 $\pm$ 0.02355
$t_{1/2z}$, h	13.23 $\pm$ 2.969	14.71 $\pm$ 5.097	19.56 $\pm$ 7.040	13.84 $\pm$ 5.786
CL/F, L/h	6.695 $\pm$ 3.213	10.56 $\pm$ 5.994	3.094 $\pm$ 1.071	11.43 $\pm$ 2.754
V_{ss}/F , L	127.2 $\pm$ 69.09	241.3 $\pm$ 221.1	74.79 $\pm$ 28.08	233.4 $\pm$ 95.57
MRT, h	12.33 $\pm$ 4.006	12.19 $\pm$ 2.916	15.55 $\pm$ 2.914	10.66 $\pm$ 1.582

dosing interval (τ) = 24 h
^a n=6 for λ_z , $t_{1/2z}$, V_{ss}/F , MRT

Source: CSR page 83.

Letermovir glucuronide to letermovir concentration ratios at 1.5 h and 6 h post-dose could not be quantified for some subjects. For this reason the applicant recommends that these ratios should be interpreted with caution. Reported letermovir glucuronide to letermovir concentration ratios at 1.5 h post-dose were similar (6-8%) in moderate HI and control subjects, but differed between severe HI (10-15%) versus control subjects (~3%).

Safety

Thirty-three subjects were included in the safety population. No safety concerns were reported for the moderate or severe HI groups. There were no discontinuations due to AEs, deaths, or SAEs during the study.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion Several concomitant medications used to treat liver diseases were used in many of the subjects with HI, including spironolactone, lactulose, furosemide, propranolol, and ursodeoxycholic acid. Letemovir is primarily eliminated to bile following OATP-mediated hepatic uptake. There are in vitro data showing that spironolactone is an OATP1B1 inhibitor and that furosemide and propranolol are not OATP1B1 inhibitors (PMID 22541068). Also, in a human study, ursodeoxycholic acid was found to inhibit OATP1B1 not by competitive inhibition but via inhibition of the transcription factor HNF1alpha (this factor regulates OATP1B1) (PMID 18443034). Therefore, it is possible that OATP inhibition by concomitant medications may have contributed to the elevated letemovir exposures observed in subjects with HI. Letemovir glucuronide could not be reliably measured in all subjects, metabolite to parent ratios differed between the two control groups, and the applicant recommended the glucuronide data should be interpreted with caution. For these reasons, we did not review the letemovir glucuronide assay or PK results.	
Labeling recommendations	
See the QBR section 2.2.2 and 3.3.3.	
Relevant links within the submission	
CSR \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\p015\p015.pdf	
Bioanalytical sample analysis reports -Letemovir \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\04jhgm\04jhgm.pdf	
-Letemovir glucuronide \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\04jhgd\04jhgd.pdf	
-Protein binding \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\04jhdk\04jhdk.pdf	

Pharmacogenomics

SUMMARY OF STUDY REPORT 04J9GB (LETERMOVIR PHARMACOGENETIC ANALYSIS REPORT)

(Prepared by Dr. Jieli Sun, Genomics and Targeted Therapy reviewer)

Background

Letermovir is both a substrate and an inhibitor of metabolic enzymes and transporters including UGT1A1, UGT1A3, OATP1B1, and OATP1B3. Genetic variants that may affect substrate exposure have been described for these enzymes and transporters. Phase 1 studies (MK-8228 P027 and MK-8228 P032) conducted in Japanese subjects demonstrated 1.5- to 2.5-fold higher observed letermovir AUC in Japanese when compared to historical White subjects. The purpose of this review is to determine if genetic variants have a clinically relevant impact on letermovir PK and to determine if genetic variants contribute to the observed PK difference in letermovir exposure between Asians and Whites.

Contents

In study report 04J9GB, the sponsor submitted subject level exposure data (AUC, Cmax) for genetic variants in *SLCO1B1* and *UGT1A1* from twelve Phase 1 studies. The sponsor proposes the following labeling claim in section 12.5 of the proposed label: (b) (4)

(b) (4)

Methods

The sponsor included 299 unique subjects who were genotyped for three variants in *SLCO1B1* (rs4149056, rs2306283, rs4149032) and two variants in *UGT1A1* (rs4148323 and the TA repeat variants) and were utilized for the statistical analyses. The Axiom Merck Custom Array genotyping platform was used to generate genetic data. *UGT1A1* *28 TA repeat variant was not on the genotyping Axiom Merck Custom Array, and was genotyped using a validated PCR and sequencing based assay. Genotypes for each variant were categorically defined for an individual subject as 0, 1 or 2, depending on the number of copies of the minor allele.

Reviewer comment: The genotyping method and the genetic variant grouping method are acceptable.

Summary of Findings

Letermovir is both a substrate and an inhibitor of metabolic enzymes and transporters including UGT1A1, UGT1A3, OATP1B1 (*SLCO1B1*), and OATP1B3. To evaluate the genetic effect for variants in *SLCO1B1* and *UGT1A1* on letermovir PK parameters, the exposure data (AUC and Cmax) from the 12 Phase I studies was summarized and analyzed using a linear mixed effect model. Statistical analysis was also performed in Asian-only and White-only subgroups. In the pooled data of 12 Phase I studies, the geometric mean of letermovir AUC increased by 18% (95% CI: 6-30%) for subjects carrying one copy of

the *SLCO1B1* minor allele (rs4149056) and 42% (95% CI: 10-84%) for subjects carrying two copies of the minor allele when compared to subjects carrying no copies of the minor allele, after adjusting for treatment, race, sex disease status and weight (Table 40). The geometric mean of letermovir AUC increased 36% (95% CI: 7-74%) for subjects carrying the *UGT1A1* *6 minor allele (rs4148323) compared to subjects carrying no copies of the minor allele (Table 41). Evaluating genetic variants by race, the geometric mean of letermovir AUC increased 42% (95% CI: 2-97%, 1.97) in Asians who carry of one copy of the *SLCO1B1* rs4149056 minor allele relative to non-carriers. This is numerically higher compared to Whites, whose AUC increased 16% ((95% CI:3-29%) in carriers with one copy of the *SLCO1B1* rs4149056 minor allele relative to non-carriers (Table 40).

Reviewer comment: Genetic variants in SLCO1B1 and UGT1A1 are unlikely to have a clinically relevant impact on letermovir PK and may only in part account for the exposure differences between Whites and Asians. The reviewer recommends

(b) (4)

(b) (4)

Table 40. Association Between *SLCO1B1* rs4149056 (minor allele: C) and Letemovir PK Parameters: AUC (h*ng/mL) and Cmax (ng/mL).

	n subj.*	n obs.	GMR (95% CI) [G = 1/G = 0]	GMR (95% CI) [G = 2/G = 0]	p-value
AUC (h*ng/mL)					
All Data	295	445	1.18 (1.06, 1.30)	1.42 (1.10, 1.84)	5.95E-04
Asians-only	30	61	1.42 (1.02, 1.97)	NA	3.67E-02
Whites-only	217	314	1.16 (1.03, 1.29)	1.40 (1.09, 1.81)	3.93E-03
C_{max} (ng/mL)					
All Data	298	530	1.11 (1.03, 1.21)	1.14 (0.92, 1.40)	2.01E-02
Asians-only	30	86	1.17 (0.91, 1.50)	NA	2.18E-01
Whites-only	220	356	1.11 (1.02, 1.21)	1.13 (0.92, 1.38)	5.54E-02

Source: Pharmacogenetic analysis report (04J9GB), page 20, table 5-3)

Table 41. Association Between *UGT1A1**6 (rs4148323, minor allele: A) and Letemovir PK Parameters: AUC (h*ng/mL) and Cmax (ng/mL).

	n subj.*	n obs.	GMR (95% CI) [G = 1/G = 0]	p-value
AUC (h*ng/mL)				
All Data	296	446	1.36 (1.07, 1.74)	1.37E-02
Asians-only	30	61	1.46 (1.07, 1.99)	1.81E-02
Whites-only	218	315	NA	NA
C_{max} (ng/mL)				
All Data	299	531	1.22 (1.01, 1.47)	3.50E-02
Asians-only	30	86	1.26 (1.00, 1.58)	4.56E-02
Whites-only	221	357	NA	NA

Source: Pharmacogenetic analysis report (04J9GB), page 22, table 5-5)

Human drug-drug interaction studies

P003 – DDI cyclosporine and tacrolimus

Study #	P003	Study Period	5/25/16-8/18/16
Title	A Two-Part, One-Way Drug-Drug Interaction Study to Determine the Effect of Multiple Oral Doses of Letemovir on the Pharmacokinetics of Cyclosporine and Tacrolimus in Healthy Adult Female Subjects		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i>	Determine the effect of letemovir on the PK of cyclosporine (CsA) and tacrolimus
<i>Rationale:</i>	Letemovir is likely to be coadministered with immunosuppressants in stem cell transplant recipients
<i>Study design:</i>	Part 1, period 1 CsA 50 mg PO on day 1 10 day washout period Part 1, period 2 CsA 50 mg PO on day 8 Letemovir 240 mg PO QD on days 1-11 Part 2, period 1 Tacrolimus 5 mg PO on days 1 and 8 10 day washout period Part 2, period 2 Letemovir 480 mg PO QD days 1-16 Tacrolimus 5 mg PO on day 8
<i>Population:</i>	Healthy adult females
<i>Dose Selection:</i>	The clinical dose of letemovir was used (480 mg without cyclosporine, 240 mg with cyclosporine). Cyclosporine and tacrolimus doses were selected to be within the range of recommended doses.
<i>Administration:</i>	☒ Fasted ☐ Fed
<i>Formulation:</i>	Letemovir 240 mg and 480 mg FMI tablets, cyclosporine 25 mg capsules, and tacrolimus 5 mg capsules
<i>Excluded concomitant medications:</i>	All medications with the exception of acetaminophen
<i>PK sampling:</i>	Intensive PK samples were collected over 96 hours postdose for cyclosporine on days 1 and 8 of part 1, over 24 hours postdose for letemovir on day 7 of part 1 and part 2, and over 216 hours postdose for tacrolimus on days 1 and 8 of part 2.
<i>Bioanalytical methods:</i>	CsA method 55187AECH, tacrolimus method 125034AFOR, and letemovir

method	(b) (4) 1514-14
RESULTS	
Demographics	
<u>Part 1</u>	
Fourteen subjects were enrolled and all completed the study. In part 1, mean age was 33 years, mean weight was 70 kg, and 11 (79%) subjects were white.	
<u>Part 2</u>	
Fourteen subjects were enrolled and 13 the study. In part 2, mean age was 37 years, mean weight was 67 kg, and 14 (100%) subjects were white. One subject discontinued from part 2 due to vomiting.	
Protocol Deviations	
No deviations were reported.	
Concomitant medications	
Comcomitant medications were diphenhydramine (n=1 subject), acetaminophen (n=2), dextrose plus electrolytes (n=1), loratadine (n=1), and psyllium (n=1).	
Pharmacokinetics (CSR page 71)	
In the presence vs. absence of letermovir, cyclosporine Cmax and AUC ratios (90% CI) were 1.08 (0.97, 1.19) and 1.66 (1.51, 1.82), respectively (Table 42). Geometric mean day 7 letermovir Cmax in part 1 was lower than observed in prior studies of 480 mg QD in healthy volunteers (8,160 ng*h/mL in this study vs. 13,000 ng/mL stated in proposed labeling).	
In the presence vs. absence of letermovir, tacrolimus Cmax and AUC ratios (90% CI) were 1.57 (1.32, 1.86) and 2.42 (2.04, 2.88), respectively (Table 43). Geometric mean day 7 letermovir Cmax in part 2 was comparable to Cmax observed in prior studies of 480 mg QD in healthy volunteers (17,600 ng/mL in this study vs. 13,000 ng/mL stated in proposed labeling).	
Letermovir PK parameters are shown below (Table 44, Table 45).	

Table 42. Cyclosporine PK parameters.

Cyclosporine Pharmacokinetic Parameters	Cyclosporine Alone			Cyclosporine + Letermovir			Cyclosporine + Letermovir/ Cyclosporine Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (ng•hr/mL)	14	838	(691, 1020)	14	1390	(1170, 1650)	1.66	(1.51, 1.82)	14.4
AUC _{0-last} [‡] (ng•hr/mL)	14	810	(667, 984)	14	1350	(1140, 1580)	1.66	(1.51, 1.83)	14.6
AUC ₀₋₁₂ [‡] (ng•hr/mL)	14	752	(633, 893)	14	1140	(988, 1320)	1.52	(1.40, 1.65)	12.6
AUC ₀₋₂₄ [‡] (ng•hr/mL)	14	810	(678, 967)	14	1270	(1090, 1470)	1.56	(1.43, 1.71)	13.2
C _{max} [‡] (ng/mL)	14	305	(264, 353)	14	328	(285, 378)	1.08	(0.97, 1.19)	14.9
C ₁₂ [‡] (ng/mL)	14	8.58	(6.89, 10.7)	14	17.2	(14.2, 20.9)	2.00	(1.77, 2.26)	18.2
C ₂₄ [‡] (ng/mL)	14	2.45	(1.76, 3.40)	14	5.35	(4.49, 6.37)	2.19	(1.80, 2.66)	29.2
T _{max} [§] (hr)	14	1.00	(1.00, 2.50)	14	1.50	(1.49, 2.50)			
Apparent terminal t _{1/2} (hr)	14	6.35	58.5	14	13.23	69.2			
CL/F (L/hr)	14	59.7	34.3	14	36.0	30.1			
Vz/F (L)	14	547	32.0	14	687	40.5			

Cyclosporine Alone: A single oral dose of 50 mg cyclosporine administered on Day 1 in Period 1

Cyclosporine + Letermovir: Multiple oral QD doses of 240 mg letermovir administered on Days 1 - 11 with a single oral dose of 50 mg cyclosporine coadministered on Day 8 of Period 2

[†]Pseudo within-subject %CV = $100 \times \sqrt{(\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares means and confidence intervals from the linear mixed-effects model performed on natural log-transformed values.

[§]Median (Minimum, Maximum) reported for T_{max}.

[‡]Three (3) subjects had C₂₄ below the lower limit of quantification (LLOQ) following cyclosporine alone, and therefore these C₂₄ values were imputed as LLOQ/2. LLOQ = 2.00 ng/mL.

^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}, CL/F, and Vz/F.

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio

Source: CSR, page 10.

Table 43. Tacrolimus PK parameters.

Tacrolimus Pharmacokinetic Parameters	Tacrolimus Alone			Tacrolimus + Letermovir			Tacrolimus + Letermovir/ Tacrolimus Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N [§]	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (ng•hr/mL)	14	287	(231, 358)	13	697	(540, 899)	2.42	(2.04, 2.88)	24.7
AUC _{0-last} [‡] (ng•hr/mL)	14	273	(217, 343)	13	680	(525, 881)	2.49	(2.10, 2.97)	24.8
AUC ₀₋₁₂ [‡] (ng•hr/mL)	14	131	(108, 160)	13	276	(229, 334)	2.10	(1.81, 2.44)	21.4
AUC ₀₋₂₄ [‡] (ng•hr/mL)	14	173	(142, 211)	13	381	(308, 470)	2.20	(1.89, 2.57)	22.3
C _{max} [‡] (ng/mL)	14	32.9	(27.0, 40.0)	13	51.5	(44.2, 60.0)	1.57	(1.32, 1.86)	25.3
C ₁₂ [‡] (ng/mL)	14	4.25	(3.43, 5.28)	13	10.7	(8.22, 13.8)	2.50	(2.07, 3.02)	26.9
C ₂₄ [‡] (ng/mL)	14	2.73	(2.21, 3.37)	13	6.92	(5.19, 9.23)	2.53	(2.12, 3.03)	25.2
T _{max} [§] (hr)	14	1.76	(1.00, 2.50)	13	3.00	(1.00, 5.00)			
Apparent terminal t _{1/2} (hr)	14	30.84	14.8	13	36.78	16.4			
CL/F (L/hr)	14	17.4	39.7	13	7.38	44.0			
Vz/F (L)	14	774	28.4	13	391	35.6			

Tacrolimus Alone: A single oral dose of 5 mg tacrolimus administered on Day 1 in Period 1

Tacrolimus + Letermovir: Multiple oral QD doses of 480 mg letermovir administered on Days 1 - 16 with a single oral dose of 5 mg tacrolimus coadministered on Day 8 of Period 2

[†]Pseudo within-subject %CV = $100 \times \sqrt{(\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares means and confidence intervals from the linear mixed-effects model performed on natural log-transformed values.

[§]Median (Minimum, Maximum) reported for T_{max}.

^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}, CL/F, and Vz/F.

^{||}One (1) subject was discontinued from the study approximately 3 hours following the tacrolimus dose on Day 8 of Period 2.

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio

Source: CSR, page 74.

Table 44. Part 1, day 7 letermovir PK parameters.

Letermovir Pharmacokinetic Parameters				
AN	AUC _τ (ng·hr/mL)	C _{max, ss} (ng/mL)	T _{max, ss} (hr)	Apparent terminal t _{1/2} (hr)
0001	45900	9940	2.50	7.40
0002 ^{†‡}	57600	7730	4.00	.
0003	173000	16700	2.50	7.84
0004	51900	8380	2.50	5.55
0005	74100	8120	2.50	9.02
0006	42800	8610	2.50	6.65
0007 ^{†‡}	46700	5930	4.00	.
0008	88300	11400	2.50	6.52
0009	51500	7170	2.50	6.86
0010 ^{†‡}	42900	5180	4.00	.
0011	61900	8430	2.50	8.61
0012	43600	4430	2.50	9.48
0013	67000	7800	2.50	7.34
0014	56300	10500	2.50	5.71
N	14	14	14	11
AM	64600	8590	2.82	7.36
SD	34000	3020	0.64	1.28
ACV	52.6	35.2	22.6	17.4
Med	54100	8250	2.50	7.34
Min	42800	4430	2.50	5.55
Max	173000	16700	4.00	9.48
GM	59500	8160	2.77	7.26
GCV	39.0	34.2	20.2	17.6

Letermovir Alone: Multiple oral QD doses of 240 mg letermovir administered on Days 1 – 7 in Period 2

[†] Subjects AN 0002, 0007 and 0010 had a terminal phase that could not be characterized. Therefore, apparent terminal t_{1/2} was not determined for these subjects.

[‡] AUC_τ could not be calculated for Subjects AN 0002 and 0007 since their actual 24-hour sampling times were earlier than 24 hours and the terminal phase of their profiles could not be characterized, therefore, AUC_{0-last} was reported as AUC_τ for these subjects. AUC_τ was calculated for Subject AN 0010 based on interpolation since this subject's actual 24-hour sampling time was later than 24 hours.

. = Value missing or not reportable

AN = Allocation number; AM = Arithmetic mean; SD = Standard deviation;

GM = Geometric mean; Med = Median; Min = Minimum; Max = Maximum;

ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: $100 \times (SD/AM)$; GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: $100 \times \sqrt{\exp(s^2) - 1}$, where s^2 is the observed variance on the natural log-scale

Source: CSR, page 118.

Table 45. Part 2, day 7 letermovir PK parameters.

Letermovir Pharmacokinetic Parameters				
AN	AUC _T (ng•hr/mL)	C _{max, ss} (ng/mL)	T _{max, ss} (hr)	Apparent terminal t _{1/2} (hr)
0015	164000	20000	2.50	7.34
0016	162000	23900	2.50	4.79
0017	161000	16200	2.50	6.84
0018 [†]	69000	10000	4.00	.
0019	189000	17200	2.50	6.16
0020 [‡]	151000	16800	4.00	.
0021	134000	22100	2.50	4.94
0022	258000	24600	2.50	6.83
0023 [‡]	174000	21900	4.00	.
0024 [‡]	110000	9990	8.03	.
0025	201000	26800	2.50	5.80
0026	84500	13900	2.50	4.71
0027	88200	10800	2.50	5.98
0028	200000	25100	2.50	4.49
N	14	14	14	10
AM	153000	18500	3.22	5.79
SD	52400	5820	1.52	1.02
ACV	34.2	31.4	47.3	17.6
Med	161000	18600	2.50	5.89
Min	69000	9990	2.50	4.49
Max	258000	26800	8.03	7.34
GM	144000	17600	3.01	5.71
GCV	39.2	35.8	35.6	17.8

Letermovir Alone: Multiple oral QD doses of 480 mg letermovir administered on Days 1 – 7 in Period 2

[†] Subjects AN 0018, 0020, 0023 and 0024 had a terminal phase that could not be characterized. Therefore, apparent terminal t_{1/2} was not determined for these subjects.

[‡] AUC_T could not be calculated for Subjects AN 0018, 0020, 0023, and 0024 since their actual 24-hour sampling times were earlier than 24 hours and the terminal phase of their profiles could not be characterized, therefore, AUC_{0-last} was reported as AUC_T for these subjects.

. = Value missing or not reportable

AN = Allocation number; AM = Arithmetic mean; SD = Standard deviation; GM = Geometric mean; Med = Median; Min = Minimum; Max = Maximum; ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: 100 x (SD/AM); GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: 100 x sqrt(exp(s²) - 1), where s² is the observed variance on the natural log-scale

Source: CSR, page 132.

Safety

There were no discontinuations due to AEs, SAEs, or deaths during the study. One subject who experienced vomiting was discontinued due to potential impact on PK.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion	
Compared to prior studies of 480 mg PO QD in healthy volunteers, relatively low letermovir Cmax was observed in part 1. Cyclosporine increases letermovir exposure, but letermovir PK was assessed on day 7 of part 1 prior to coadministration with cyclosporine on day 8. Thus the letermovir 240 mg exposures are expected to be low compared to letermovir 480 mg.	
Labeling Recommendations	
Based on 66% higher cyclosporine AUC when coadministered with letermovir, proposed letermovir labeling states that cyclosporine concentrations should be frequently monitored when given with letermovir. This is consistent with recommendations for use of cyclosporine with diltiazem and erythromycin, which also increase cyclosporine AUC by 65-80% (recommendations from Micromedex, numerous studies cited). Voriconazole similarly increases cyclosporine AUC, but the recommendation is to reduce the cyclosporine dose to one-half in addition to monitoring concentrations (Voriconazole tablet labeling, last updated 2015). We agree with the proposed letermovir labeling recommendation for use with cyclosporine.	
Based on 2.4-fold increased tacrolimus AUC when given with letermovir, proposed letermovir labeling states that tacrolimus concentrations should be frequently monitored when given with letermovir. Other drugs that similarly increase tacrolimus AUC by ~2.5-fold include amlodipine, ketoconazole, and isavuconazole. Recommendation for use of tacrolimus with amlodipine is to monitor tacrolimus concentrations frequently and dose adjust if appropriate (Micromedex, several FDA labels cited). Use with ketoconazole is not recommended due to increased tacrolimus concentrations and a potential additive effect on QT prolongation (Micromedex, several FDA labels cited). Isavuconazole labeling lacks a specific recommendation for tacrolimus; it only has general language for CYP3A substrates (Micromedex, FDA isavuconazole labelings cited, 2015). We agree with the proposed letermovir labeling recommendation for use with tacrolimus.	
Relevant links within the submission	
CSR \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p003\p003.pdf	
Bioanalytical \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p003\publications-based-on-trial.pdf	

P013 – DDI tacrolimus

Study #	P013	Study Period	7/22/08-8/26/08
Title	Open-label, single centre trial to investigate the interaction of 80mg AIC001 bid oral dosing and a single oral dose of 5 mg tacrolimus		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i> Evaluate the two-way interaction between letermovir and tacrolimus	
<i>Rationale:</i> Letermovir and tacrolimus are likely to be commonly coadministered in transplant recipients	
<i>Study design:</i> Tacrolimus 5 mg PO on Day1 and Day 12 Letermovir 80 mg PO BID on days 8-19	
<i>Population:</i> Healthy male adults	
<i>Dose Selection:</i> At the time of the study, multiple letermovir doses of 80 mg BID had been previously studied. The tacrolimus dose was chosen to be on the lower end of the therapeutic range.	
<i>Administration:</i> ☒ Fasted ☐ Fed	
<i>Formulation:</i> Letermovir 20 mg tablets (FFP2 formulation) and tacrolimus 5 mg capsules	
<i>Excluded concomitant medications:</i> No medications were allowed with the exception of acetaminophen	
<i>PK sampling:</i> -Tacrolimus: intensive plasma sampling through 144 hours postdose on days 1 and 12 -Letermovir: predose samples on days 8-10, and intensive samples through 12 hours postdose on days 11 and 12	
<i>Bioanalytical methods:</i> Letermovir method 27AS1438 and tacrolimus method 24XX1081	
RESULTS	
Demographics Sixteen subjects were enrolled and 14 completed the study. Mean age was 36 years, mean weight was 75 kg, and all subjects were white.	
Protocol Deviations No major deviations were reported.	
Concomitant medications One subject received buscopan and another received antibiotics, electrolyte solution, and antithrombotic agents before being discontinued from the study.	
Pharmacokinetics (CSR page 73) In the presence vs. absence of letermovir, tacrolimus Cmax and AUC ratios (90% CI) were 1.70 (1.28, 2.26) and 1.78 (1.48, 2.13), respectively (Table 46). In the presence vs. absence of tacrolimus, letermovir Cmax and AUC ratios (90% CI) were 0.92 (0.84, 1.00) and 1.02 (0.97, 1.07), respectively (Table 47).	

Table 46. Tacrolimus PK parameters.

Parameter	Day 1 (Tacrolimus alone)			Day 12 (Tacrolimus together with AIC001 80 mg bid)		
	Geom. mean	Geom. CV	Range	Geom. mean	Geom. CV	Range
AUC _{0-24h} (ng*h/mL)	159	106.8%	12.6-385	347	57.9%	115-766
AUC _{0-12h} (ng*h/mL)	273	32.3%	164-417	432	44.8%	157-822
C _{max} (ng/mL)	22.5	66.6%	3.74-42.0	38.1	25.6%	22.5-54.9
T _{max} (h)	1.25*	NA	0.750-2.00	1.25*	NA	0.750-3.00
T _{1/2} (h)	42.0	14.4%	35.2-60.1	44.8	19.4%	36.1-69.8
CL/f (mL/min)	351	40.4%	200-690	210	51.1%	101-547
V _d /f (L)	1277	48.8%	673-3589	813	41.6%	427-1789

*median; geom. = geometric, NA = not applicable

Source: CSR, page 74.

Table 47. Letermovir PK parameters.

Parameter	Day 11 (AIC001 80 mg bid alone)			Day 12 (AIC001 80 mg bid together with Tacrolimus)		
	Geom. mean	Geom. CV	Range	Geom. mean	Geom. CV	Range
AUC _{0-24h} (ng*h/mL)	6640	48.5%	2853-17458	6761	43.8%	3127-14550
C _{max,ss} (ng/mL)	1709	36.3%	872-3480	1568	33.8%	811-2634
T _{max} (h)	1.50*	NA	1.00-2.00	1.00*	NA	0.750-3.00
CL/f (mL/min)	201	48.5%	76.4-467	197	43.8%	91.6-426

*median; geom. = geometric, NA = not applicable

Source: CSR, page 78.

Safety

One subject discontinued the study due to an AE of elevated liver enzymes and another discontinued due to an SAE of urinary tract infection with prostatitis. There was one SAE of urinary tract infection with prostatitis. There were no deaths during the study.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion	
The study design is acceptable for evaluating the effect of tacrolimus on letermovir. Letermovir disposition is primarily modulated by OATP1B1. There are no known inducers of OATP transporters (https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM207267.pdf). For this reason a single dose of tacrolimus was acceptable for evaluating the effect of tacrolimus on letermovir. The study design was not acceptable for evaluating the effect of letermovir on tacrolimus because the proposed clinical dose of letermovir is 480 mg QD and 80 mg BID was studied. The effect of letermovir 480 mg on tacrolimus PK was evaluated in study P003. Chromatograms for at least 5% of subjects (should be submitted per guidance) were not available for tacrolimus or letermovir. The applicant stated that chromatograms were destroyed after the ownership changed at the bioanalytical lab. However, the lab was audited in 2008 (near the time of this study) and the lab practices were found to be acceptable (NDA 209939 SDN 27). Due to the methods being overall acceptable in our assessment, we consider the bioanalytical methods to be acceptable despite the missing chromatograms.	
Labeling Recommendations	
This study is applicable to labeling only for the effect of tacrolimus on letermovir. We agree with the proposed labeling recommendation that there is no significant effect of tacrolimus on letermovir.	
Relevant links within the submission	
CSR \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p013\p013.pdf	
Bioanalytical report \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p013\inter-laboratory-standardization-methods-quality-assurance.pdf	

P016 – DDI midazolam

Study #	P016	Study Period	4/21/10-5/21/10
Title	An open-label, single centre trial to investigate influence of 240 mg AIC090027 once daily dosing on the pharmacokinetics of a single dose of oral and intravenous midazolam		

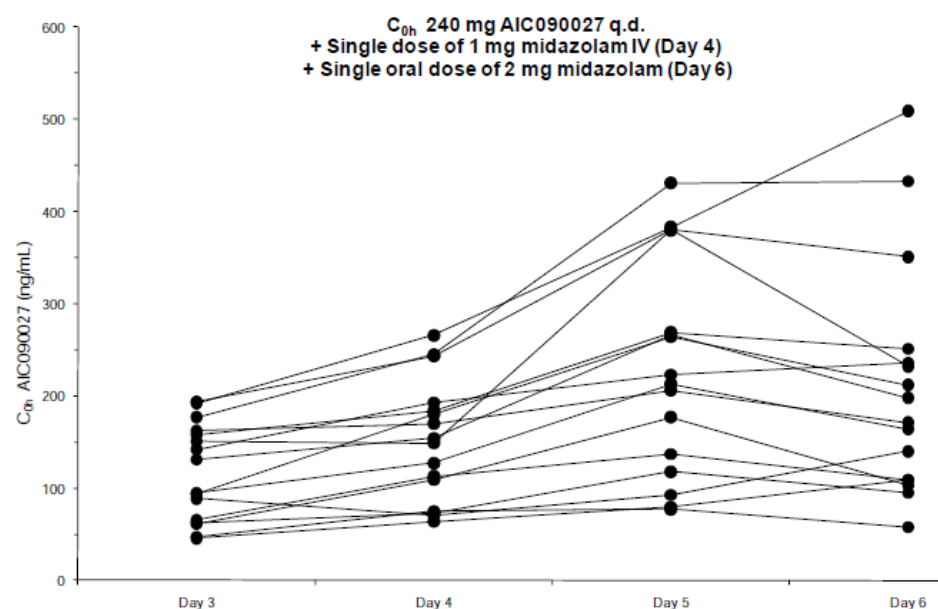
STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i>	Determine the effect of letermovir on the PK of IV and oral midazolam and 1-hydroxy-midazolam
<i>Rationale:</i>	Letermovir is an in vitro time-dependent inhibitor and an inducer of CYP3A and midazolam is a probe substrate for CYP3A
<i>Study design:</i>	This was an open-label, single center study. All subjects received the following: 1. Single 1 mg IV dose of midazolam on Day -4 and Day 4 2. Single 2 mg oral dose of midazolam on Day -2 and Day 6 3. Letermovir 240 mg QD PO was administered once daily from Day 1 to Day 6.
<i>Population:</i>	Healthy adult females
<i>Dose Selection:</i>	Letermovir 240 mg QD was chosen because the applicant thought this dose would produce maximum CYP3A inhibition and because acceptable safety of letermovir 240 mg had been previously shown. Midazolam doses were selected based on safety considerations to be well below the recommended dose range for treatment.
<i>Administration:</i>	☒ Fasted ☐ Fed
<i>Formulation:</i>	Letermovir 240 mg tablet (PMF1 formulation), midazolam 1 mg/mL solution for IV injection, and midazolam 2 mg/mL oral solution
<i>Excluded concomitant medications:</i>	No medications were allowed except for hormonal contraceptives and acetaminophen
<i>PK sampling:</i>	Intensive plasma samples were collected through 24 hours postdose on days -4, -2, 4, and 6 for measurement of midazolam and 1-hydroxy-midazolam concentrations. Pre-dose plasma samples were collected on days 3-6 for measurement of letermovir concentrations.
<i>Bioanalytical methods:</i>	Midazolam and 1-hydroxy-midazolam method 011/10-05.MM, letermovir method 08-061
RESULTS	
Demographics	Sixteen subjects were enrolled and all completed the study. Mean age was 32 years, mean weight was 63 kg, and all subjects were white.
Protocol Deviations	No major deviations were reported.
Concomitant medications	Concomitant medications included oral contraceptives (n=13 subjects) and paracetamol (n=1).
Pharmacokinetics (CSR page 76)	In the presence vs. absence of letermovir, the oral and IV midazolam AUC ratio was 2.3 and 1.5, respectively (Table 48, Table 49, Table 50). Geometric mean letermovir pre-dose concentrations were 137 ng/mL on day 4, 201 ng/mL on day 5, and 180 ng/mL on day 6 (Figure 25).

Table 48. Midazolam and 1-hydroxy-midazolam exposure changes in the presence vs. absence of letermovir.

PK parameter	Midazolam route	Midazolam PK parameter ratio (90% CI)	1-hydroxy-midazolam PK parameter ratio (90% CI)
C _{max}	PO	1.72 (1.55, 1.92)	1.18 (0.98, 1.43)
AUC	PO	2.25 (2.04, 2.49)	1.44 (1.22, 1.70)
C _{max}	IV	1.05 (0.94, 1.17)	0.79 (0.67, 0.93)
AUC	IV	1.47 (1.37, 1.58)	0.99 (0.90, 1.08)

Source: CSR section 11.

Figure 25. Letermovir pre-dose concentrations.



Source: CSR page 530.

Table 49. IV midazolam PK parameters.

Pharmacokinetics of midazolam (arithmetic mean $\pm$ SD, t _{max} : median [range])	Day -4: Single dose of 1 mg midazolam i.v.	Day 4: 240 mg AIC090027 once daily + single dose of 1 mg midazolam i.v
n	16	16
C _{max} , μ g/L	21.63 $\pm$ 5.114	22.56 $\pm$ 4.192
t _{max} , h	0.25 (0.25-0.80)	0.25 (0.25-0.75)
AUC _{0-last} , μ g.h/L	34.29 $\pm$ 8.638	49.73 $\pm$ 10.77
AUC _{0-∞} , μ g.h/L	35.13 $\pm$ 8.621	51.14 $\pm$ 11.39
λ_z , 1/h	0.1742 $\pm$ 0.04794	0.1461 $\pm$ 0.02720
t _{1/2z} , h	4.226 $\pm$ 0.9956	4.882 $\pm$ 0.8126
CL, L/h	30.52 $\pm$ 9.377	20.55 $\pm$ 4.880
V _d , L	180.2 $\pm$ 54.23	141.2 $\pm$ 24.80

Source: CSR, page 79.

Table 50. Oral midazolam PK parameters.

Pharmacokinetics of midazolam (arithmetic mean $\pm$ SD, $t_{\max}$: median [range])	Day -2: Single oral dose of 2 mg midazolam			Day 6: 240 mg AIC090027 once daily + single oral dose of 2 mg midazolam		
n	16 ^a			16		
$C_{\max}$, $\mu\text{g/L}$	8.701	$\pm$	1.804	15.09	$\pm$	3.688
$t_{\max}$, h	0.75 (0.50-1.00)			0.75 (0.50-1.00)		
$\text{AUC}_{0-\text{last}}$, $\mu\text{g}\cdot\text{h/L}$	18.83	$\pm$	5.425	42.42	$\pm$	12.19
$\text{AUC}_{0-\infty}$, $\mu\text{g}\cdot\text{h/L}$	20.59*	$\pm$	4.817*	44.25	$\pm$	13.05
λ_z , 1/h	0.1740*	$\pm$	0.05220*	0.1575	$\pm$	0.03251
$t_{1/2z}$, h	4.330*	$\pm$	1.336*	4.553	$\pm$	0.8141
CL/F, L/h	102.6*	$\pm$	26.44*	50.03	$\pm$	18.77
V_d/F , L	624.6*	$\pm$	217.6*	317.1	$\pm$	84.77

* Accurate determination not possible

^a n=15 for $\text{AUC}_{0-\infty}$, λ_z , $t_{1/2z}$, CL/F, V_d/F

Source: CSR, page 79.

Safety

There were no discontinuations due to AEs, SAEs, or deaths during the study.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion	
Letermovir pre-dose concentrations increased ~50% between day 4 and 5 and were comparable between day 5 and 6, indicating steady-state may not have been reached by day 4 when the effect on IV midazolam was assessed. However, even at steady-state letermovir exposure, it is unlikely that the effect on IV midazolam would exceed the effect on PO midazolam. Therefore, labeling recommendations for midazolam would apply to both oral and IV midazolam. The clinical dose of letermovir is 480 mg PO and a lower dose of 240 mg was evaluated in this study. We requested the applicant to conduct PBPK simulations of the effect of 480 mg letermovir on the PK of midazolam. The predicted effect of 480 mg letermovir on midazolam was comparable to the observed effect of 240 mg letermovir on midazolam, with letermovir being considered a moderate CYP3A inhibitor at both doses (See QBR section 2.2.2).	
Labeling Recommendations	
(b) (4)	
CSR \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p016\p016.pdf Bioanalytical report -letermovir \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\04jhjhw\04jhjhw.pdf -midazolam and 1-hydroxymidazolam \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\04jhjb\04jhjb.pdf	

P018 part C – DDI digoxin

Study #	P018 Part C	Study Period	10/28/11-1/21/12
Title	A SINGLE CENTRE TRIAL TO INVESTIGATE THE EFFECT OF LETERMOVIR UNDER STEADY STATE CONDITIONS ON THE PHARMACOKINETICS OF A SINGLE ORAL DOSE OF DIGOXIN, A SENSITIVE P-GLYCOPROTEIN SUBSTRATE		

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

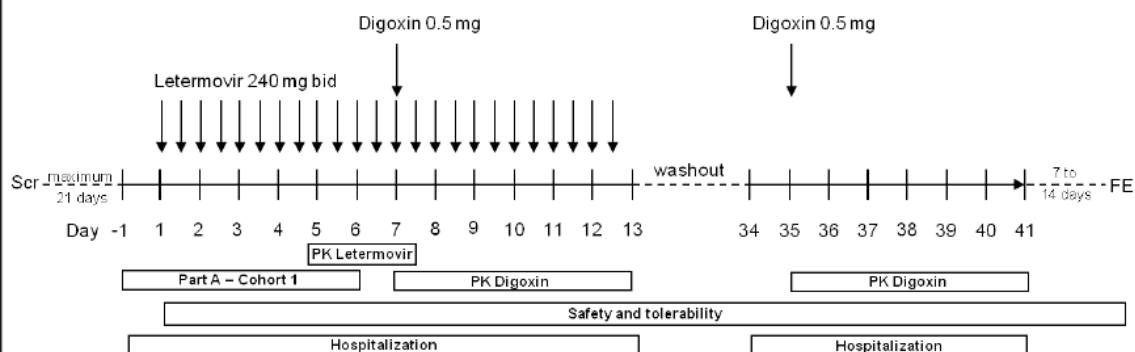
Objectives: Determine the effect of letermovir on the PK of digoxin

Rationale: Letermovir could modulate Pgp and digoxin is a probe substrate of Pgp

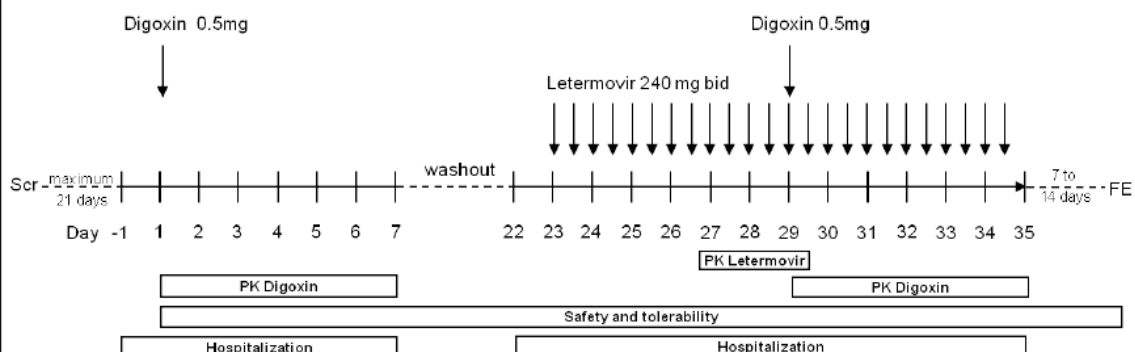
Study design:

Open-label, 2-period, 2-sequence, cross-over study.

Part C - sequence 1: 12 subjects



Part C - sequence 2: 12 subjects



The time between the two digoxin doses was 28 days in order to allow approximate synchronization of individual subject menstrual cycles because female sex hormones may alter Pgp expression levels.

Population: Healthy adult females

Dose Selection: The letermovir dose of 240 mg BID was considered to be within the anticipated therapeutic range

Administration: ☒ Fasted ☐ Fed

Formulation: Letermovir 240 mg tablets (PMF1 formulation), digoxin (Lanoxin) 0.25 mg tablets

Excluded concomitant medications: None were allowed with the exception of acetaminophen

PK sampling: Intensive PK sampling through 14 hours postdose for digoxin on days 7 and 35 of sequence

1 and days 1 and 29 of sequence 2. Intensive PK sampling through 24 hours postdose for letermovir on day 6 of sequence 1 and day 28 of sequence 2.

Bioanalytical methods: Letermovir method 08-061 and digoxin method 11-040

RESULTS

Demographics

Twenty-four subjects were enrolled and 22 completed the study. One subject discontinued after testing positive for cannabinoids and another due to a positive pregnancy test. Mean age was 28 years, mean weight was 68 kg, and 19/24 subjects were Caucasian.

Protocol Deviations

Two major protocol deviations were reported. These include the testing positive for cannabinoids (n=1) and testing positive for pregnancy (n=1). Both subjects were discontinued from the study.

Concomitant medications

There was no reported use of prohibited concomitant medications.

Pharmacokinetics (CSR page 52)

Digoxin exposures were decreased in the presence of letermovir; C_{max} and AUC ratios (90% CI) were 0.75 (0.63, 0.89) and 0.88 (0.80, 0.96), respectively. PK parameters are shown below (Table 51, Table 52).

Table 51. Digoxin PK parameters.

Pharmacokinetics of digoxin (mean ± SD, t _{max} : median [range])	Single dose of 0.5 mg digoxin (reference)	Single dose of 0.5 mg digoxin + 240 mg letermovir bid (test, all data)	Single dose of 0.5 mg digoxin + 240 mg letermovir bid (test, paired data)
n	22	24	22
*C _{max} , ng/mL	2.992±0.9325	2.453±1.018	2.327±0.912
t _{max} , h	1.00 (0.50-2.00)	0.75 (0.50-3.00)	0.75 (0.50-3.00)
*AUC _{0-last} , ng.h/mL	37.44±9.461	33.60±9.931	33.14±9.649
*AUC _{0-∞} , ng.h/mL	40.45±10.51	36.62±10.17	36.25±9.958
*λ _z , 1/h	0.01927±0.002289	0.01845±0.002238	0.01822±0.002146
*t _{1/2z} , h	36.51±4.787	38.09±4.498	38.53±4.374

* Arithmetic means

Source: CSR, page 56.

Table 52. Letermovir PK parameters.

Pharmacokinetics of letermovir (mean ± SD, t _{max} : median [range])	240 mg letermovir bid (all data)	240 mg letermovir bid (paired data)
n	24	22
*C _{0h} , ng/mL	1941±1039	1948±1049
*C _{min} , ng/mL	1656±1013	1683±1033
*C _{ss,max} , ng/mL	9841±2703	9844±2716
t _{max} , h	2.00 (1.50-3.00)	2.00 (1.50-3.00)
*C _{ss,av} , ng/mL	4254±1358	4269±1336
*AUC _{t,ss} , ng.h/mL	50870±16306	51051±16068
*CL/F, L/h	5.148±1.530	5.095±1.442

* Arithmetic means

Source: CSR, page 61.

Safety

There were no discontinuations due to AEs, SAEs, or deaths during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☒ Yes ☐ No

Study Conduct

- Protocol deviations do not affect the integrity of the study ☒ Yes ☐ No ☐ N/A
- Use of prohibited concomitant medications did not affect the integrity of the study ☒ Yes ☐ No ☐ N/A
- Bioanalytical method performance in acceptable ☒ Yes ☐ No

Study Results

The study results are acceptable as reported by the sponsor ☒ Yes ☐ No

Discussion

The letermovir dose evaluated in this study (240 mg BID) differed from the recommended dose in proposed labeling (480 mg QD). However, the total daily letermovir dose is the same and the effect of letermovir on digoxin AUC would be likely similar.

Labeling Recommendations

Mean digoxin AUC was 12% lower in the presence of letermovir. Proposed labeling states that there were no clinically relevant changes in digoxin plasma concentrations following coadministration with letermovir. We agree with this recommendation.

Relevant links within the submission

CSR part C

<\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\p018v03\p018v03.pdf>

Bioanalytical part C

<\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\p018v03\inter-laboratory-standardization-methods-quality-assurance.pdf>

P022 – DDI mycophenolate

Study #	PN022	Study Period	12/9/13-2/6/14
Title	An open-label, fixed sequence study to characterize the pharmacokinetic interaction between MK-8228 (letermovir) and mycophenolic acid, the active metabolite of mycophenolate mofetil, in healthy female subjects		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i> Determine the effect of letermovir on the PK of MPA (active metabolite of MMF) and the effect of MMF on the PK of letermovir	
<i>Rationale:</i> Letermovir and MMF are likely to be coadministered in HSCT recipients	
<i>Study design:</i> Open-label, fixed sequence, single and multiple dose study. Treatments: MMF 1 g PO on days 1 and 12 Letermovir 480 mg PO on days 5 and 8-16	
<i>Population:</i> Healthy adult females	
<i>Dose Selection:</i> Letermovir: 480 mg is the proposed dose in labeling MMF: 1 g is an approved dose	
<i>Administration:</i> ☒ Fasted ☐ Fed	
<i>Formulation:</i> letermovir PMF2 240 mg tablet and MMF 500 mg (oral dosage form unspecified)	
<i>Excluded concomitant medications:</i> No medications were allowed with the exception of acetaminophen and hormonal contraceptives	
<i>PK sampling:</i> MPA: Intensive PK through 96 hours postdose on days 1 and 12 Letermovir: Intensive PK through 24 hours postdose on days 5 and 16 and through 72 hours postdose on day 12	
<i>Bioanalytical methods:</i> letermovir method BP-0032 and MPA method ANI 10415.03	
RESULTS	
Demographics Fourteen subjects were enrolled. Mean age was 32 years and mean weight was 67 kg. Ten subjects were black and four were white.	
Protocol Deviations Three deviations were reported. One subject was enrolled despite failed inclusion criteria. The subject participated in a non-interventional study with a blood draw within 4 weeks of screening. The subject was enrolled because the previous study was non-interventional. Another deviation consisted of an enrolled subject with an induced abortion 39 days prior to enrollment. A third deviation consisted of a subject who took topical metronidazole without reporting it to the research staff.	
Concomitant medications Use of prohibited systemic medications included cold medication (acetaminophen plus dextromethorphan plus doxylamine plus phenylephrine, n=1 subject), flu vaccine (n=1), and camphor plus eucalyptus oil plus menthol (n=1).	

Pharmacokinetics (CSR page 52)

When coadministered with letermovir, MPA Cmax and AUC ratios (90% CI) were 0.96 (0.82, 1.12) and 1.08 (0.97, 1.20), respectively (Table 53). When coadministered with MMF, letermovir Cmax and AUC ratios (90% CI) were 1.11 (0.93, 1.34) and 1.18 (1.04, 1.32), respectively (Table 54).

Table 53. MPA PK parameters.

MPA PK Parameter	MMF+MK			MMF Alone			MMF+MK / MMF Alone		Pseudo Within Subject %CV ^b
	N	GM ^a	95% CI	N	GM ^a	95% CI	GMR (%)	90% CI	
AUCinf (hr•ng/mL)	14	68131	(58187, 79775)	14	63108	(53152, 74928)	108.0	(96.8, 120.4)	4.36
Cmax (ng/mL)	14	22881	(18520, 28268)	14	23858	(19489, 29207)	95.9	(81.9, 112.3)	6.29
Tmax (hr) ^c	14	0.52	(0.5, 2.0)	14	0.52	(0.5, 2.0)			
T1/2 (hr) ^d	14	13.1	42.6	14	13.3	27.2			

^aBack-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.

^bPseudo within-subject %CV = $100 \cdot \text{Sqrt}[(\sigma_A^2 + \sigma_B^2 - 2 \cdot \sigma_{AB})/2]$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments (expressed as a percent)

Source: CSR, page 52.

Table 54. Letermovir PK parameters.

MK-8228 PK Parameter	MMF+MK			MK Alone			MMF+MK / MK Alone		Pseudo Within Subject %CV ^b
	N	GM ^a	95% CI	N	GM ^a	95% CI	GMR (%)	90% CI	
AUC0-24 (hr•ng/mL)	14	84011	(61722, 114351)	14	71482	(55593, 91911)	117.5	(104.4, 132.3)	4.74
Cmax (ng/mL)	14	14497	(10748, 19553)	14	13018	(10721, 15807)	111.4	(92.5, 134.1)	7.42
Tmax (hr) ^c	14	2.0	(1.0 – 3.0)	14	2.2	(1.0 – 3.0)			
T1/2 (hr) ^d	14	NC	NC	13	13.8 ^e	44.3			

^aBack-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.

^bPseudo within-subject %CV = $100 \cdot \text{Sqrt}[(\sigma_A^2 + \sigma_B^2 - 2 \cdot \sigma_{AB})/2]$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments (expressed as a percent); NC=Not calculated

Source: CSR, page 55.

Safety

There were no discontinuations due to AEs, SAEs, or deaths during the study.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion and Labeling Recommendations	
Letermovir disposition is primarily mediated by OATP-mediated hepatic uptake. There are no known OATP inducers. For this reason a single dose of MMF is acceptable for determining the effect of MMF on letermovir PK. Section 7.3 of proposed labeling states there is no clinically significant interaction between letermovir and MMF. We agree with this statement.	
Relevant links within the submission	
CSR \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p022\p022.pdf Bioanalytical -letermovir: \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\03wgfk\03wgfk.pdf -MPA: \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\03vnh6\03vnh6.pdf	

P023 – DDI atorvastatin

Study #	P023	Study Period	10/19/15-11/29/15
Title	A Drug-Drug Interaction Study with Letemovir and Atorvastatin in Healthy Female Subjects		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i> Determine the effect of letemovir on the PK of atorvastatin and its metabolites	
<i>Rationale:</i> Letemovir is an inhibitor of multiple pathways (OATP1B1, CYP3A) affecting the disposition of atorvastatin and its metabolites	
<i>Study design:</i> Open-label, fixed-sequence, 2-period study. Period 1: Atorvastatin 20 mg PO on day 1 Three day washout period Period 2: Atorvastatin 20 mg PO on day 8 Letemovir 480 mg PO QD on days 1-10	
<i>Population:</i> Healthy adult females	
<i>Dose Selection:</i> Letemovir: 480 mg QD is the proposed clinical dose Atorvastatin: 20 mg is an approved dose	
<i>Administration:</i> ☒ Fasted ☐ Fed	
<i>Formulation:</i> Letemovir PMF3 480 mg tablet and atorvastatin (Lipitor®) 20 mg tablet	
<i>Excluded concomitant medications:</i> No medications were allowed with the exception of hormonal contraceptives and acetaminophen.	
<i>PK sampling:</i> Intensive sampling through 72 hours postdose on day 1 of period 1 and day 8 of period 2	
<i>Bioanalytical methods:</i> Atorvastatin, orthohydroxyatorvastatin, and parahydroxyatorvastatin concentrations were determined using method (b) (4) 1560-14	
RESULTS	
Demographics Fourteen subjects were enrolled and 13 completed the study. Mean age was 47 years and mean weight was 69 kg. Thirteen subjects (93%) were Caucasian.	
Protocol Deviations No major deviations were reported.	
Concomitant medications Use of concomitant medications included acetaminophen (n=1 subject) and diphenhydramine (n=1).	
Pharmacokinetics (CSR page 57) When coadministered with letemovir, atorvastatin exposures were increased ~3-fold while atorvastatin metabolite exposures were generally not significantly changed (Table 55, Table 56, Table 57, Table 58).	

Table 55. Statistical comparison of atorvastatin and metabolite PK parameters.

	Geometric mean ratio (90% CI)		
	Cmax	AUC	Cmin
Atorvastatin	2.17 (1.76, 2.67)	3.29 (2.84, 3.82)	3.62 (2.87, 4.55)
Orthohydroxyatorvastatin	0.40 (0.33, 0.50)	0.91 (0.77, 1.06)	1.41 (1.21, 1.63)
Parahydroxyatorvastatin	1.16 (0.94, 1.45)	1.04 (0.81, 1.34)	0.95 (0.80, 1.13)

Source: CSR section 11.

Table 56. Atorvastatin PK parameters.

Atorvastatin Pharmacokinetic Parameter	Atorvastatin Alone			Atorvastatin + Letermovir			Atorvastatin + Letermovir/ Atorvastatin Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (ng•hr/mL)	14	40.2	(29.0, 55.7)	13	132	(98.0, 178)	3.29	(2.84, 3.82)	21.3
AUC _{0-last} [‡] (ng•hr/mL)	14	39.7	(28.6, 55.0)	13	130	(96.0, 176)	3.27	(2.81, 3.81)	21.7
C _{max} [‡] (ng/mL)	14	7.12	(5.14, 9.87)	13	15.4	(11.3, 21.0)	2.17	(1.76, 2.67)	29.9
C ₂₄ [‡] (ng/mL)	14	0.263	(0.171, 0.404)	13	0.950	(0.654, 1.38)	3.62	(2.87, 4.55)	33.2
T _{max} [§] (hr)	14	1.00	(0.50, 4.00)	13	3.00	(0.50, 4.02)			
Apparent terminal t _{1/2} (hr)	14	11.03	23.6	13	12.66	16.5			
CL/F (L/hr)	14	497.51	61.2	13	145.23	53.5			
VZ/F (L)	14	7913.80	60.0	13	2652.27	62.7			

Atorvastatin Alone: A single oral dose of 20 mg atorvastatin administered on Day 1 in Period 1

Atorvastatin + Letermovir: Multiple oral QD doses of 480 mg letermovir administered on Days 1 - 10 with a single oral dose of 20 mg atorvastatin co-administered on Day 8 in Period 2

[†]Pseudo within-subject %CV = $100 \times \sqrt{(\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.[‡]Back-transformed least-squares means and confidence intervals from the linear mixed-effects model performed on natural log-transformed values.[§]Median (Minimum, Maximum) reported for T_{max}.^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}, CL/F, and VZ/F.[‡]One (1) subject was discontinued on Day 1 of Period 2.

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio

Source: CSR page 58.

Table 57. Orthohydroxyatorvastatin PK parameters.

Orthohydroxyatorvastatin Pharmacokinetic Parameter	Atorvastatin Alone			Atorvastatin + Letermovir			Atorvastatin + Letermovir/ Atorvastatin Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (ng•hr/mL)	14	51.6	(38.8, 68.8)	13	46.9	(33.6, 65.4)	0.91	(0.77, 1.06)	22.7
AUC _{0-last} [‡] (ng•hr/mL)	14	50.7	(38.1, 67.5)	13	44.3	(32.0, 61.5)	0.87	(0.75, 1.02)	22.1
C _{max} [‡] (ng/mL)	14	5.16	(3.87, 6.89)	13	2.09	(1.50, 2.92)	0.40	(0.33, 0.50)	29.9
C ₂₄ [‡] (ng/mL)	14	0.421	(0.302, 0.588)	13	0.592	(0.407, 0.859)	1.41	(1.21, 1.63)	21.5
RAUC _{0-∞} [‡]	14	1.25	(1.01, 1.55)	13	0.347	(0.271, 0.446)			18.5
T _{max} [§] (hr)	14	1.26	(0.50, 4.00)	13	4.00	(2.99, 8.00)			
Apparent terminal t _{1/2} (hr)	14	12.79	20.3	13	15.11	31.0			

Atorvastatin Alone: A single oral dose of 20 mg atorvastatin administered on Day 1 in Period 1

Atorvastatin + Letermovir: Multiple oral QD doses of 480 mg letermovir administered on Days 1 - 10 with a single oral dose of 20 mg atorvastatin co-administered on Day 8 in Period 2

RAUC_{0-∞} (Metabolite/Parent) = (AUC_{0-∞}Metabolite/AUC_{0-∞}Parent) x (MW Parent/MW Metabolite)

[†]Pseudo within-subject %CV = 100 x Sqrt[($\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB}$)/2], where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares means and confidence intervals from the linear mixed-effects model performed on natural log-transformed values.

[§]Median (Minimum, Maximum) reported for T_{max}.

^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.

^{*}One (1) subject was discontinued on Day 1 of Period 2.

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio

Source: CSR page 60.

Table 58. Parahydroxyatorvastatin PK parameters.

Parahydroxyatorvastatin Pharmacokinetic Parameter	Atorvastatin Alone			Atorvastatin + Letermovir			Atorvastatin + Letermovir/ Atorvastatin Alone		Pseudo Within Subject %CV [†]
	N [‡]	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (ng•hr/mL)	13	6.88	(5.22, 9.07)	6	7.16	(4.99, 10.3)	1.04	(0.81, 1.34)	21.3
AUC _{0-last} [‡] (ng•hr/mL)	14	5.38	(3.70, 7.81)	13	5.98	(4.20, 8.52)	1.11	(0.96, 1.29)	20.9
C _{max} [‡] (ng/mL)	14	0.159	(0.104, 0.243)	13	0.185	(0.130, 0.264)	1.16	(0.94, 1.45)	31.5
C ₂₄ [‡] (ng/mL)	14	0.0894	(0.0631, 0.127)	13	0.0848	(0.0564, 0.128)	0.95	(0.80, 1.13)	25.0
RAUC _{0-∞} [‡]	13	0.179	(0.146, 0.219)	6	0.0587	(0.0442, 0.0779)			14.6
T _{max} [§] (hr)	14	6.01	(0.50, 36.00)	13	35.99	(2.99, 36.00)			
Apparent terminal t _{1/2} (hr)	13	30.37	40.5	6	33.49	47.0			

Atorvastatin Alone: A single oral dose of 20 mg atorvastatin administered on Day 1 in Period 1
Atorvastatin + Letermovir: Multiple oral QD doses of 480 mg letermovir administered on Days 1 - 10 with a single oral dose of 20 mg atorvastatin co-administered on Day 8 in Period 2
RAUC_{0-∞} (Metabolite/Parent) = (AUC_{0-∞}Metabolite/AUC_{0-∞}Parent) x (MW Parent/MW Metabolite)
[†]Pseudo within-subject %CV = 100 x Sqrt[(σ_A² + σ_B² - 2*σ_{AB})/2], where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares means and confidence intervals from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
[¶]One (1) subject was discontinued on Day 1 of Period 2.
[#]The terminal phase could not be captured for 7 subjects, and as a result AUC_{0-∞}, RAUC_{0-∞}, and apparent terminal t_{1/2} could not be determined.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio

Source: CSR page 61.

Safety

One subject discontinued due to an AE of allergic dermatitis in period 1 following dosing of atorvastatin alone. There were no SAEs or deaths during the study.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion	
Several in vitro studies show atorvastatin to be an inhibitor of OATP1B1, which is the primary pathway affecting letermovir disposition (PMID 21861202, 15616150, 10601278, 22541068). The PK of letermovir was not assessed in this study so the potential effect of atorvastatin on letermovir was not evaluated in this study. However, proposed labeling addresses the potential effect of atorvastatin on letermovir in that section 7.1 states that OATP inhibitors may increase letermovir concentrations.	
Labeling Recommendations	
(b) (4) (b) (4). Examples of other drugs with the same recommendation not to exceed an atorvastatin dose of 20 mg (per atorvastatin labeling) are saquinavir/ritonavir, darunavir/ritonavir, fosamprenavir, and fosamprenavir/ritonavir. These drugs increase atorvastatin AUC by 2.5-3.9-fold. We agree with the proposed recommendation for use of atorvastatin with letermovir because it is consistent with atorvastatin labeling for similar interactions. For other statins, where the magnitude of statin exposure increase when coadministered with letermovir is unknown, we agree with the proposed language (b) (4) (b) (4). In addition, we recommend adding that the lowest necessary dose should be used.	
Relevant links within the submission	
CSR \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p023\p023.pdf Bioanalytical \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p023\publications-based-on-trial.pdf	

P025 – DDI voriconazole

Study #	P025	Study Period	1/29/14-3/22/14
Title	An Open-label, Fixed Sequence Study to Assess the Effect of MK-8228 (letermovir) on the Pharmacokinetics of Voriconazole in Healthy Female Subjects		

STUDY SUMMARY (As Reported by the Applicant)								
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS								
<i>Objectives:</i> Determine the effect of letermovir on the PK of voriconazole								
<i>Rationale:</i> Letermovir and antifungals are likely to be coadministered in the transplant population								
<i>Study design:</i>								
		Day(s)						
N	Drug	1	2 to 3	4	5 to 8	9	10 to 11	12
14	Voriconazole	400 mg Q12h	200 mg Q12h	200 mg single dose	-	400 mg Q12h	200 mg Q12h	200 mg single dose
	MK-8228	-	-	-	480 mg QD	480 mg QD	480 mg QD	480 mg QD
N = number of subjects; Q12h: every 12 hours; QD: once daily.								
<i>Population:</i> Healthy female adults								
<i>Dose Selection:</i> Letermovir 480 mg QD is the clinical dose. Recommended voriconazole dosing is 200 mg BID. 400 mg BID was used on day 1 to accelerate the time to steady-state.								
<i>Administration:</i> ☒ Fasted ☐ Fed								
<i>Formulation:</i> Letermovir 240 mg tablet (PMF2 formulation) and voriconazole (manufacturer not specified) 200 mg tablet								
<i>Excluded concomitant medications:</i> None were allowed								
<i>PK sampling (Voriconazole):</i> Predose samples on day 1, 4, and 12, and intensive sampling through 12 hours postdose on days 4 and 12								
<i>Bioanalytical methods:</i> Voriconazole method 85030RQU								
RESULTS								
Demographics								
Fourteen subjects were enrolled and 12 completed the study. One subject discontinued due to a protocol violation and another withdrew consent due to family emergency. Mean age was 35 years, mean weight was 74 kg, and 10/14 subjects were black.								
Protocol Deviations								
No major deviations were reported. One subject discontinued the study due to a protocol violation of failure to comply with clinic rules.								
Concomitant medications								
No use of concomitant medications was reported.								
Pharmacokinetics (CSR page 48)								
In the presence vs. absence of letermovir, voriconazole C _{max} and AUC ratios (90% CI) were 0.61 (0.53, 0.71) and 0.56 (0.51, 0.62), respectively (Table 59). When administered alone, geometric mean voriconazole AUC _{0-12h} in this study (17.6 µg*h/mL) was ~40% higher than reported in voriconazole labeling for a dose of 200 mg PO BID (12.4 µg*h/mL).								

Table 59. Voriconazole PK parameters.

Parameter	Voriconazole alone (Day 4)			Voriconazole + MK-8228 (Day 12)			Voriconazole + MK-8228 (Day 12)/Voriconazole alone (Day 4)		Pseudo Within Subject CV (%) [2]
	N [1]	GM	95% CI	N [1]	GM	95% CI	GMR	90% CI	
AUC ₀₋₁₂ (µg·h/mL)	14	17.6	(12.9, 24.0)	12	9.82	(7.30, 13.2)	0.56	(0.51, 0.62)	13.2
C _{max} (µg/mL)	14	2.80	(2.30, 3.40)	12	1.71	(1.33, 2.20)	0.61	(0.53, 0.71)	19.8
C _{12h} (µg/mL)	14	0.767	74.9	12	0.352	90.1			
T _{max} (hr)	14	1.75	(1.00; 4.00)	12	2.00	(1.47; 4.02)			

Treatment = Voriconazole 400 mg Q12h (Day 1 and 9); Voriconazole 200 mg Q12h (Day 2 to 3 and Day 10 to 11); Voriconazole 200 mg single dose (Day 4 and 12); MK-8228 480 mg QD (Day 5 to 12).

AUC₀₋₁₂ = area under the concentration-time curve from time zero to 12 hours; CI = confidence interval;

C_{max} = maximum plasma concentration; CV% = coefficient of variation %; GM = geometric mean; GMR = geometric mean ratio; PK = pharmacokinetic.

A repeated measures mixed model analysis of variance with fixed effect for treatment. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the treatment measurements within each subject via the REPEATED statement in SAS® PROC MIXED.

Geometric means, GMR, and their CI are shown on the original scale of measurement.

[1] 'N' represents the number of subjects exposed to each treatment used in the mixed model.

[2] Pseudo Within-Subject CV = $100 \times \sqrt{(\text{Var}(x_1) + \text{Var}(x_2) - 2 \times \text{Cov}(x_1, x_2)) / 2}$, where Var(x₁) is the estimated variance of 'voriconazole (Day 4)' and var(x₂) is the estimated variance of 'voriconazole + MK-8228 (Day 12)', and Cov(x₁, x₂) is the estimated covariance of the two treatments.

The difference in 'N' on Day 4 (N=14) and Day 12 (N=12) is due to two subject withdrawals: Subject AN0006 withdrew consent; Subject AN0005 was withdrawn due to a protocol deviation.

Geometric mean and CV% are reported for C_{12h} and are not model based.

Median (min, max) are reported for T_{max}.

Source: CSR, page 51.

Safety

No discontinuations due to AEs, SAEs, or deaths were reported during the study.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion and labeling recommendations	
Voriconazole is a substrate of CYP2C9, CYP2C19, and CYP3A. In vitro, letermovir was found to induce CYP3A and to not induce CYP2C19; CYP2C9 was not evaluated. In vivo, letermovir is a net inhibitor of CYP3A. The lower voriconazole AUC when coadministered with letermovir could be explained by induction of CYP2C9 by letermovir, hence our request for a PMC study to evaluate this in vitro. There is a clinical need for the use of voriconazole in the immunosuppressed population and it was commonly used in the phase 3 study. Labeling recommendations for use of voriconazole with letermovir have not been finalized and will be discussed in an addendum to this review.	
Relevant links within the submission	
CSR \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p025\p025.pdf	
Bioanalytical report \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p025\publications-based-on-trial.pdf	

P032 – DDI cyclosporine

Study #	P032	Study Period	8/11/14-10/31/14
Title	A Multiple Dose Study of MK-8228 and a Drug-Drug Interaction Study with MK-8228 and Cyclosporin A in Healthy Female Subjects of Japanese Ethnicity		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i> Compare the PK of letermovir in Japanese vs. non-Japanese subjects, determine the effect of cyclosporine on the PK of letermovir	
<i>Rationale:</i> To satisfy US requirements for study of letermovir PK in subjects of different ethnicities	
<i>Study design:</i> Cross-over, double-blind, multiple dose, fixed sequence trial. Period 1: 480 mg letermovir or placebo QD PO for 7 days Washout: at least 3 days Period 2: 240 mg letermovir or placebo QD for 8 days plus a single dose of cyclosporine 200 mg PO on day 8	
<i>Population:</i> Healthy Japanese-American (the study was conducted in California) women aged 20-65 years. Subjects must have four grandparents of Japanese descent.	
<i>Dose Selection:</i> -Letermovir: 480 mg PO without CsA and 240 mg PO with CsA was evaluated in the phase 3 study -Cyclosporine: 200 mg is consistent with dosing used in clinical trials	
<i>Administration:</i> ☒ Fasted ☐ Fed	
<i>Formulation:</i> letermovir 240 mg PMF3 tablet and cyclosporine 100 mg capsule	
<i>Excluded concomitant medications:</i> Use of any concomitant medications required sponsor and investigator approval with the exception of acetaminophen and hormonal contraceptives.	
<i>PK sampling:</i> Predose samples daily in both periods. Intensive PK sampling through 72 hours postdose in period 1 on days 1 and 7 and through 24 hours postdose in period 2 on days 1, 7, and 8.	
<i>Bioanalytical methods:</i> Letermovir method BP-0032 (cyclosporine was not measured)	
RESULTS	
Demographics Three placebo subjects enrolled and all completed the study. Fourteen subjects were enrolled in the letermovir arm and 12 completed the study. Two subjects withdrew consent and were withdrawn from the trial. Mean age and weight in the letermovir arm was 44 years and 59 kg, respectively.	
Protocol Deviations No major deviations were reported.	
Concomitant medications Use of prior medications included vitamins (n=1 subject) and use of concomitant systemic medications included acetaminophen (n=1) and ibuprofen (n=1).	
Pharmacokinetics (CSR page 59) In a cross-study comparison of letermovir exposures from multiple doses of 480 mg QD PO between Japanese vs. non-Japanese healthy women, C _{max} and AUC ratios (90% CI) were 1.60 (1.22, 2.09) and 1.92 (1.40, 2.64), respectively (Table 60). Letermovir exposures were increased in the presence of cyclosporine, with C _{max} and AUC ratios (90% CI) of 1.48 (1.33, 1.65) and 2.11 (1.97, 2.26), respectively (Table 61).	

Table 60. Letermovir PK parameters in Japanese and non-Japanese subjects.

Parameter	Japanese			Non-Japanese			Japanese/ Non-Japanese		rMSE (%)
	N [1]	GM	95% CI	N [1]	GM	95% CI	GMR	90% CI	
AUC0-24hr (ng.h/mL)	12	137000	(103000, 182000)	14	71500	(55100, 92800)	1.92	(1.40, 2.64)	47.3
Css max (ng/mL)	12	20800	(16400, 26400)	14	13000	(10400, 16200)	1.60	(1.22, 2.09)	39.9
Css av (ng/mL)	12	5720	(4310, 7580)	14	2980	(2290, 3870)	1.92	(1.40, 2.64)	47.3

ANOVA = analysis of variance; AUC0-24hr = area under the concentration-time curve from time zero to 24 hours; C24hr = plasma concentration at 24 hours post-dose; CI = confidence interval; Css av = average concentration of drug during a dosing interval; Css max = maximum plasma concentration; GM = geometric means; GMR = ratio of geometric means; rMSE = square root of the residual error from the model; ss = steady state.

Data for historical controls obtained from non-Japanese female subjects who received 480 mg letermovir orally once daily from Day 8 to Day 16 in MK-8228 Protocol Number (PN) 022.

ANOVA model with a factor of ethnic group (Japanese, Non-Japanese) was utilized.

Geometric means, GMR, and their CIs are shown on the original scale of measurement.

[1] Shows the number of subjects exposed to 480 mg dose in each ethnic group that were used in the linear model.

Source: CSR, page 65.

Table 61. Letermovir PK parameters with and without coadministration of cyclosporine.

Parameter	Letermovir + Cyclosporin (Day 8)			Letermovir (Day 7)			Letermovir + Cyclosporin A/ Letermovir		Pseudo Within Subject %CV (%) [2]
	N [1]	GM	95% CI	N [1]	GM	95% CI	GMR	90% CI	
AUC0-24hr (ng.h/mL)	12	105000	(89000, 124000)	12	49900	(40700, 61100)	2.11	(1.97, 2.26)	9.5
Css max (ng/mL)	12	14300	(12600, 16300)	12	9680	(8010, 11700)	1.48	(1.33, 1.65)	14.7
Css av (ng/mL)	12	4380	(3710, 5180)	12	2080	(1700, 2550)	2.11	(1.97, 2.26)	9.5

AUC0-24hr = area under the concentration-time curve from time zero to 24 hours; CI – confidence interval; Css av = average concentration of drug during a dosing interval; Css max = maximum plasma concentration; GM = geometric means; GMR = ratio of geometric means; rMSE = square root of the residual error from the model; ss = steady state.

A linear mixed-effect model with fixed effect for treatment. An unstructured covariance matrix will be used to allow for unequal treatment variances and to model the correlation between the treatment measurements within each subject.

Geometric means, GMR and their CIs are shown on the original scale of measurement.

[1] Shows the number of subjects exposed to 240 mg dose at each day that were used in the mixed model.

[2] Pseudo within-subject %CV = $100 \times \sqrt{(\sigma^2_{A2} + \sigma^2_{B2} - 2 \times \text{covAB})/2}$, where σ^2_{A2} and σ^2_{B2} are the estimated variances on the log scale for the 2 treatment groups, and covAB is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

Period 2: 240 mg letermovir or placebo once daily on Days 1 to 8 and single dose 200 mg cyclosporin A concomitantly on Day 8.

Source: CSR, page 75.

Safety

There were no discontinuations due to AEs, SAEs, or deaths during the study.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion and labeling recommendations Regarding the effect of race/ethnicity on letermovir PK, letermovir exposures in Asian subjects were evaluated in several studies. These findings are discussed in section 2 of the QBR. The results from this study for the effect of cyclosporine on the PK of letermovir are in section 12.3 of proposed labeling. In proposed labeling, recommended letermovir dosing when coadministered with cyclosporine is 240 mg QD PO or IV. This is the dosing regimen that was used in phase 3 study P001. In study P001, approximately half of subjects used concomitant cyclosporine, and PO and IV letermovir exposures differed depending on the presence of cyclosporine. However, based on the observation of flat exposure-response relationships for efficacy, we agree with the proposed dosing recommendations in labeling.	
Relevant links within the submission CSR \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\p032\p032.pdf Bioanalytical \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\p032\publications-based-on-trial.pdf	

P033 – DDI posaconazole

Study #	P033	Study Period	10/22/14-11/18/14
Title	A Pharmacokinetic Drug Interaction Study of MK-8228 (Letermovir) and Posaconazole in Healthy Female Subjects		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i> Determine the effect of letermovir on the PK of posaconazole	
<i>Rationale:</i> Letermovir and posaconazole are likely to be coadministered in HSCT recipients	
<i>Study design:</i> Open-label, two-period, two-treatment, fixed-sequence, crossover study. Period 1: Posaconazole 300 mg PO on day 1 The length of the washout period was not reported Period 2: Letermovir 480 mg PO QD on days 1-14 Posaconazole 300 mg PO on day 14	
<i>Population:</i> Healthy adult females	
<i>Dose Selection:</i> Letermovir 480 mg QD is the proposed clinical dose. Posaconazole 300 mg QD is the approved dose for delayed-release tablets.	
<i>Administration:</i> ☒ Fasted ☐ Fed	
<i>Formulation:</i> letermovir 480 mg PMF3 tablet and posaconazole (Noxafil) 100 mg delayed-release tablets	
<i>Excluded concomitant medications:</i> All medications with the exception of hormonal contraceptives, non-systemic products, and occasional use of common analgesics.	
<i>PK sampling:</i> Intensive sampling through 168 hours postdose on day 1 of period 1 and day 14 of period 2	
<i>Bioanalytical methods:</i> posaconazole method LCMSC 549	
RESULTS	
Demographics Sixteen subjects were enrolled and 13 completed the study. Three subjects were discontinued, one for testing positive for cannabinoids, and two for abnormal period 2 check-in labs.	
Protocol Deviations No major deviations were reported.	
Concomitant medications There was no reported use of prohibited concomitant medications.	
Pharmacokinetics (CSR page 42) In the presence vs. absence of letermovir, posaconazole Cmax and AUC ratios (90% CI) were 1.11 (0.95, 1.29) and 0.98 (0.82, 1.17), respectively (Table 62).	

Table 62. Posaconazole PK parameters.

<i>PK Parameter[†]</i>	<i>Posaconazole 3 x 100 mg DR tablets (Day 1/Period 1)</i>			<i>Posaconazole 3 x 100 mg DR tablets + Letemovir 1 x 480 mg tablets (Day 14/Period 2)</i>			<i>Posaconazole 3 x 100 mg DR tablets + Letemovir 1 x 480 mg tablets (Day 14/Period 2)/ Posaconazole 3 x 100 mg DR tablets (Day 1/Period 1)</i>		
	<i>N</i>	<i>GM</i>	<i>95% CI</i>	<i>N</i>	<i>GM</i>	<i>95% CI</i>	<i>GMR (%)</i>	<i>90% CI for GMR</i>	<i>Intra-Sbj % CV[‡]</i>
<i>AUC_{0-inf} (hr·ng/mL)</i>	16	31600	25300 - 39400	13	30900	25000 - 38300	98.00	82.32 - 116.68	25.6
<i>AUC_{0-last} (hr·ng/mL)</i>	16	29700	23800 - 37000	13	29600	23700 - 37000	99.66	83.50 - 118.94	25.8
<i>C_{max} (ng/mL)</i>	16	834	683 - 1020	13	927	756 - 1140	111.04	95.26 - 129.45	22.3
<i>C₂₄ (ng/mL)</i>	16	386	320 - 465	13	426	352 - 517	110.42	93.55 - 130.33	24.4

[†] Estimated based on the elements of the variance-covariance matrix as: $CV(\%) = 100 \cdot \sqrt{(\sigma_T^2 + \sigma_R^2 - 2 \cdot \sigma_{TR})/2}$

[‡] Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values

GM = Geometric least-squares mean; *CI* = Confidence interval; *GMR* = Geometric least-squares mean ratio between treatments

Source: CSR, page 48.

Safety

There were no discontinuations due to AEs, SAEs, or deaths during the study.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion	
The length of the washout period was not reported. However, all pre-dose concentrations were undetectable, indicating that the washout period was acceptable. The effect of posaconazole on the PK of letermovir was not evaluated in this study. OATP appears to be the primary enzyme or transporter mediating its hepatic elimination. Posaconazole was used in 35 of 412 (8.5%) subjects in phase 3 study P001. Use of posaconazole was not identified as a covariate for letermovir clearance or bioavailability in the popPK analysis. However, this is not a definitive analysis to rule out an effect of posaconazole on the PK of letermovir. There are no in vitro (Pharmapendium) or in vivo (posaconazole labeling and University of Washington Drug Interaction Database) data ruling out an effect of posaconazole on OATP. Overall, it is unclear whether posaconazole affects the PK of letermovir.	
Labeling Recommendations	
Section 7.3 of proposed labeling states that there is no clinically significant interaction between posaconazole and letermovir. We agree that letermovir does not affect the PK of posaconazole. It has not been shown that posaconazole does not affect the PK of letermovir, therefore the language for section 7.3 should be clarified to state that no dose adjustment of posaconazole is needed when coadministered with letermovir.	
Relevant links within the submission	
CSR \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p033\p033.pdf Bioanalytical \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p033\publications-based-on-trial.pdf	

P034 – DDI acyclovir

Study #	P034	Study Period	12/5/14-1/23/15
Title	A Drug-Drug Interaction Study with Letermovir and Acyclovir in Healthy Female Subjects		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i> Determine the effect of letermovir on the PK of acyclovir	
<i>Rationale:</i> Acyclovir is commonly used in the HSCT population. Acyclovir is an OAT3 substrate and letermovir is an in vitro OAT3 inhibitor.	
<i>Study design:</i> Open-label, fixed-sequence, single-group study.	
Treatments -acyclovir 400 mg single dose PO on day 1 and day 7 -letermovir 480 mg QD PO on days 2-7	
<i>Population:</i> Healthy females aged 19-55 years	
<i>Dose Selection:</i> -Acyclovir 400 mg is in the range of approved doses -Letermovir 480 mg is the recommended dose	
<i>Administration:</i> ☒ Fasted ☐ Fed	
<i>Formulation:</i> PMF3 tablet	
<i>Excluded concomitant medications:</i> Medications were not allowed before (within 14 days) or during the study with the exception of hormonal contraceptives and acetaminophen	
<i>PK sampling:</i> Intensive PK through 24 hours postdose on days 1 and 7	
<i>Bioanalytical methods:</i> Acyclovir method 65018ALQL	
RESULTS	
Demographics Sixteen subjects were enrolled and 13 completed the study. One subject was discontinued due to an AE and two subjects withdrew consent. Mean age was 33 years, 15/16 subjects were Caucasian, and mean weight was 71 kg.	
Protocol Deviations No major protocol deviations were reported.	
Concomitant medications Concomitant therapy consisted of hormonal contraceptives used by six subjects.	
Pharmacokinetics (CSR page 47) The PK analysis was limited to the thirteen subjects who received both treatments. Acyclovir C _{max} and AUC ratios (90% CI) (acyclovir + letermovir / acyclovir alone) were 0.82 (0.71, 0.93) and 1.02 (0.87, 1.20), respectively (Table 63).	

Table 63. Acyclovir PK parameters.

Pharmacokinetic Parameter	Acyclovir Alone			Acyclovir + Letermovir			Acyclovir + Letermovir/ Acyclovir Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (µg·hr/mL)	16	3.39	(3.08, 3.75)	13	3.48	(2.88, 4.20)	1.02	(0.87, 1.20)	22.741
C _{max} [‡] (µg/mL)	16	0.639	(0.568, 0.719)	13	0.521	(0.438, 0.620)	0.82	(0.71, 0.93)	18.695
T _{max} [§] (hr)	16	1.51	(1.00, 5.00)	13	2.02	(1.04, 4.00)			
Apparent terminal t _{1/2} [§] (hr)	16	5.59	47.60	13	5.08	26.43			

Acyclovir Alone: A single oral dose of 400 mg acyclovir administered on Day 1.
Acyclovir + Letermovir: Multiple oral doses of 480 mg letermovir QD on Days 2 – 7 with 400 mg acyclovir co-administered on Day 7.

[†]Pseudo within-subject %CV = $100 \times \sqrt{[(\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB})/2]}$, where σ_A^2 and σ_B^2 are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.

[§]Median (Min, Max) reported for T_{max}.

^{||}Geometric mean and Geometric CV reported for apparent terminal t_{1/2}.

[‡]Three (3) subjects were dropped following Acyclovir Alone, no available data for Acyclovir + Letermovir.

[§]The acyclovir apparent terminal t_{1/2} value was greater than ½ the time of the pharmacokinetic sampling duration (24 hours) for 1 subject following the Acyclovir Alone treatment (note: there was at least 3 points selected for the calculation of the elimination phase).

GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval

Source: CSR page 48.

Safety

One subject discontinued due to an AE of vomiting on day 7 that was considered related to both acyclovir and letermovir therapy. There were no SAEs or deaths during the study.

REVIEWER ASSESSMENTThe study design is acceptable ☒ Yes ☐ No**Study Conduct**

- Protocol deviations do not affect the integrity of the study ☒ Yes ☐ No ☐ N/A
- Use of prohibited concomitant medications did not affect the integrity of the study ☒ Yes ☐ No ☐ N/A
- Bioanalytical method performance in acceptable ☒ Yes ☐ No

Study ResultsThe study results are acceptable as reported by the sponsor ☒ Yes ☐ No**Discussion**

There were no issues with this study.

Labeling Recommendations

We agree with the statement in proposed labeling that there were no clinically relevant changes in acyclovir plasma concentrations upon coadministration with letermovir.

Relevant links within the submission

CSR

<\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p034\p034.pdf>

Bioanalytical report

<\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p034\publications-based-on-trial.pdf>

P035 – DDI ethinyl estradiol and levonorgestrel

Study #	P035	Study Period	10/7/15
Title	A Study to Assess the Effects of Multiple Oral Doses of Letemovir on the Single-Dose Pharmacokinetics of an Oral Contraceptive (Ethinyl Estradiol and Levonorgestrel) in Healthy Adult Non-Childbearing Female Subjects		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i>	Determine the effect letemovir on the PK of ethinyl estradiol (EE) and levonorgestrel (LNG)
<i>Rationale:</i>	Patients who may require the use of letemovir may include women of childbearing potential who may be using oral hormonal contraception
<i>Study design:</i>	Open-label, fixed-sequence, 2-period study.
Period 1	0.03 mg EE/0.15 mg LNG PO on day 1
7 day washout	
Period 2	Letemovir 480 mg QD on days 1-12 0.03 mg EE/0.15 mg LNG PO on day 8
<i>Population:</i>	Healthy adult females who have undergone bilateral oophorectomy and/or hysterectomy or are postmenopausal with amenorrhea
<i>Dose Selection:</i>	Letemovir 480 mg QD is the proposed clinical dose. 0.03 mg EE/0.15 mg LNG PO is a standard dose.
<i>Administration:</i>	☒ Fasted ☐ Fed
<i>Formulation:</i>	Letemovir 480 mg PMF3 tablet, and 0.03 mg EE/0.15 mg LNG tablet
<i>Excluded concomitant medications:</i>	No concomitant medications were allowed with the exception of ibuprofen
<i>PK sampling:</i>	Intensive plasma sampling through 120 hours postdose on day 1 of period 1 and day 8 of period 2
<i>Bioanalytical methods:</i>	EE method 75066AEKE and LNG method 145017AJPB
RESULTS	
Demographics	Twenty-two subjects were enrolled and all completed the study. Mean age was 57 years, mean weight was 71 kg, and 21/22 subjects were white.
Protocol Deviations	No major deviations were reported.
Concomitant medications	Use of concomitant medications included ibuprofen by subject 0012, and subject 0022 used morphine, ranitidine, and polyethylene glycol.

Pharmacokinetics (CSR page 54)

In the presence vs. absence of letermovir, EE Cmax and AUC ratios (90% CI) were 0.89 (0.83, 0.96) and 1.42 (1.32, 1.52), respectively (Table 64). LNG ratios were 0.95 (0.86, 1.04) and 1.36 (1.30, 1.43) (Table 65). Letermovir PK was not assessed.

Table 64. Ethinyl estradiol PK parameters.

Ethinyl Estradiol Pharmacokinetic Parameter	N	OC Alone		OC + Letermovir		OC + Letermovir/ OC Alone		Pseudo Within Subject %CV [†]
		GM	95% CI	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (pg•hr/mL)	22	909	(789, 1050)	1290	(1130, 1470)	1.42	(1.32, 1.52)	13.8
AUC _{0-last} [‡] (pg•hr/mL)	22	860	(740, 999)	1230	(1080, 1410)	1.43	(1.33, 1.54)	14.2
Cmax [‡] (pg/mL)	22	80.5	(71.9, 90.1)	71.8	(64.7, 79.7)	0.89	(0.83, 0.96)	14.1
Tmax [§] (hr)	22	1.50	(1.00, 2.00)	1.75	(1.00, 5.99)			
Apparent terminal t _{1/2} (hr)	22	20.53	23.7	23.09	20.3			

OC Alone: A single oral dose of 0.03 mg EE/0.15 mg LNG administered on Day 1 in Period 1
 OC + Letermovir: Multiple oral QD doses of 480 mg letermovir administered on Days 1 - 12 with a single oral dose of 0.03 mg EE/0.15 mg LNG co-administered on Day 8 in Period 2
[†]Pseudo within-subject %CV = $100 \times \sqrt{(\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares means and confidence intervals from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for Tmax.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio

Source: CSR, page 55.

Table 65. Levonorgestrel PK parameters.

Levonorgestrel Pharmacokinetic Parameter	N	OC Alone		OC + Letermovir		OC + Letermovir/ OC Alone		Pseudo Within Subject %CV [†]
		GM	95% CI	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (ng•hr/mL)	22	41.9	(35.9, 48.9)	57.1	(48.3, 67.7)	1.36	(1.30, 1.43)	9.2
AUC _{0-last} [‡] (ng•hr/mL)	22	37.3	(31.7, 43.8)	50.4	(42.3, 60.1)	1.35	(1.29, 1.42)	8.9
Cmax [‡] (ng/mL)	22	3.17	(2.67, 3.76)	3.01	(2.53, 3.57)	0.95	(0.86, 1.04)	18.2
Tmax [§] (hr)	22	1.01	(0.51, 2.00)	1.00	(0.50, 4.00)			
Apparent terminal t _{1/2} (hr)	22	38.77	22.4	37.99	21.6			

OC Alone: A single oral dose of 0.03 mg EE/0.15 mg LNG administered on Day 1 in Period 1
 OC + Letermovir: Multiple oral QD doses of 480 mg letermovir administered on Days 1 - 12 with a single oral dose of 0.03 mg EE/0.15 mg LNG co-administered on Day 8 in Period 2
[†]Pseudo within-subject %CV = $100 \times \sqrt{(\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares means and confidence intervals from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for Tmax.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio

Source: CSR, page 56.

Safety

There were no discontinuations due to AEs, SAEs, or deaths during the study.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion and labeling recommendations	
Despite a 42% increase in EE AUC when given with letermovir, proposed letermovir labeling states (b) (4). Other drugs that increase by ~40-60% include etoricoxib, ketoconazole, teriflunomide, and voriconazole. The recommendation for use of EE with etoricoxib or voriconazole is to use caution and monitor for EE toxicity. There is no recommendation for use of EE with ketoconazole or teriflunomide. Because letermovir therapy is of a relatively limited duration and because it is not possible to monitor for blood clots, we agree with the applicant's recommendation (b) (4). In the phase 3 study, there was no reported use of "contraceptives", "ethinyl estradiol", "hormonal contraceptives", or "oral contraceptives", and one reported use of "other estrogens". We think letermovir labeling should mention EE by name (b) (4) in order to be specific. Despite a 36% increase in LNG AUC when given with letermovir, proposed letermovir labeling states (b) (4). In labeling of other drugs that similarly increase LNG AUC by ~30-60% (primaquine, teriflunomide, netupitant and palonosetron, and chloroquine), there are no clinical recommendations for use with LNG. We agree with proposed labeling (b) (4). We think letermovir labeling should mention LNG by name (b) (4) because the effect of letermovir on LNG cannot be extrapolated to other progestins.	
Relevant links within the submission	
CSR \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p035\p035.pdf	
Bioanalytical \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p035\publications-based-on-trial.pdf	

P036 – DDI sirolimus

Study #	P036	Study Period	5/10/16-7/7/16
Title	A One-Way Drug-Drug Interaction Study to Determine the Effects of Multiple Oral Doses of Letemovir on the Single-Dose Pharmacokinetics of Sirolimus in Healthy Adult Female Subjects		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i> Determine the effect of letemovir on the PK of sirolimus	
<i>Rationale:</i> Letemovir is likely to be coadministered with sirolimus in transplant recipients	
<i>Study design:</i> Period 1 -sirolimus 2 mg PO on day 1 15 day washout Period 2 -sirolimus 2 mg PO on day 8 -letemovir 480 mg PO QD on days 1-16	
<i>Population:</i> Healthy adult females	
<i>Dose Selection:</i> Letemovir 480 mg QD is the proposed clinical dose. Sirolimus 2 mg is within its therapeutic dosing range.	
<i>Administration:</i> ☒ Fasted ☐ Fed	
<i>Formulation:</i> Letemovir 480 mg tablet (FMI formulation) and sirolimus 2 mg tablets	
<i>Excluded concomitant medications:</i> No medications were allowed except acetaminophen	
<i>PK sampling:</i> Intensive plasma sampling through 216 hours postdose on day 1 of period 1 and day 8 of period 2 for measurement of sirolimus concentrations. Period 2 plasma sampling for letemovir concentrations were collected predose on days 1-7, and intensive samples through 24 hours postdose on day 7.	
<i>Bioanalytical methods:</i> Letemovir method (b) (4) 1514-14 and sirolimus method 125035AFOT	
RESULTS	
Demographics Fourteen subjects were enrolled and 13 completed the study. Mean age was 37 years, mean weight was 68 kg, and 12/14 subjects were white.	
Protocol Deviations No major deviations were reported.	
Concomitant medications Two subjects used acetaminophen.	
Pharmacokinetics (CSR page 50) In the presence vs. absence of letemovir, sirolimus C _{max} and AUC ratios (90% CI) were 2.76 (2.48, 3.06) and 3.40 (3.01, 3.85), respectively (Table 66).	

Table 66. Sirolimus PK parameters.

Sirolimus Pharmacokinetic Parameters	Sirolimus Alone			Sirolimus + Letermovir			Sirolimus + Letermovir/ Sirolimus Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (ng•hr/mL)	14	149	(128, 173)	13	506	(442, 578)	3.40	(3.01, 3.85)	17.3
AUC ₀₋₁₂ [‡] (ng•hr/mL)	14	37.9	(33.5, 42.9)	13	109	(97.1, 123)	2.88	(2.63, 3.15)	13.0
AUC ₀₋₂₄ [‡] (ng•hr/mL)	14	56.3	(49.8, 63.7)	13	169	(151, 188)	2.99	(2.71, 3.30)	14.1
AUC _{0-last} [‡] (ng•hr/mL)	14	134	(115, 155)	13	438	(386, 497)	3.28	(2.92, 3.68)	16.2
C _{max} [‡] (ng/mL)	14	5.39	(4.60, 6.33)	13	14.9	(13.0, 17.0)	2.76	(2.48, 3.06)	15.1
C ₁₂ [‡] (ng/mL)	14	1.87	(1.56, 2.24)	13	6.34	(5.48, 7.35)	3.39	(2.84, 4.06)	26.0
C ₂₄ [‡] (ng/mL)	14	1.19	(1.00, 1.41)	13	3.75	(3.33, 4.22)	3.15	(2.80, 3.55)	17.0
T _{max} [§] (hr)	14	2.00	(1.50, 6.00)	13	3.49	(2.00, 7.99)			
Apparent terminal t _{1/2} (hr)	14	75.04	17.3	13	88.64	16.7			
CL/F (L/hr)	14	13.5	26.6	13	3.88	20.7			
V _z /F (L)	14	1460	24.5	13	496	22.6			

Sirolimus Alone: A single oral dose of 2 mg sirolimus administered on Day 1 in Period 1

Sirolimus + Letermovir: Multiple oral QD doses of 480 mg letermovir administered on Days 1 – 16 with a single oral dose of 2 mg sirolimus coadministered on Day 8 in Period 2

[†]Pseudo within-subject %CV = $100 \times \sqrt{(\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effect model performed on natural log-transformed values.

[§]Median (Minimum, Maximum) reported for T_{max}.

^{||}Geometric mean and geometric percent coefficient of variation reported for apparent terminal t_{1/2}, CL/F and V_z/F.

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio

[†]One (1) subject was discontinued on Day 3 of Period 2.

Source: CSR, page 51.

Safety

One subject discontinued due to an AE of vomiting. There were no SAEs or deaths during the study.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion and labeling recommendations Proposed letermovir labeling says to monitor sirolimus concentrations during coadministration and upon discontinuation of letermovir and to dose adjust sirolimus accordingly. This recommendation is consistent with sirolimus labeling, which states to exercise caution when administering with CYP3A/Pgp inhibitors. Letermovir is likely to be used with cyclosporine and sirolimus in the transplant population. Both cyclosporine and letermovir are CYP3A inhibitors and the combination of letermovir and cyclosporine could potentially increase sirolimus concentrations more than letermovir alone or cyclosporine alone. Based on a finding that cyclosporine does not affect sirolimus concentrations when sirolimus was given 4 hours later, sirolimus labeling states that sirolimus should be taken 4 hours after administration of cyclosporine. While cyclosporine has a shorter half-life than letermovir (8.4 hours vs. ~12 hours), we think that by giving letermovir at the same time as cyclosporine it is likely that there would be a limited effect of letermovir in combination with cyclosporine on sirolimus concentrations. For this reason, we propose to revise labeling to state that letermovir and cyclosporine should be given at the same time when used with sirolimus.	
Relevant links within the submission CSR \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p036\p036.pdf Bioanalytical report -letermovir \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p036\publications-based-on-trial.pdf -sirolimus \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\p036\publications-based-on-trial.pdf	

Human PK studies in healthy volunteers

P005 – single and multiple ascending IV doses

Study #	P005	Study Period	7/17/12-4/17/13
Title	A single-center, 2-part trial to investigate the safety, tolerability, and pharmacokinetics of (A) single ascending intravenous doses and (B) multiple intravenous doses of letermovir		

STUDY SUMMARY (As Reported by the Applicant)						
OBJECTIVES, TRIAL DESIGN AND PK ASSESSMENTS						
<i>Objectives:</i> Safety, PK, effect on the QT interval						
<i>Study design:</i>						
Randomized, double-blind, placebo-controlled study.						
Treatments						
-Cohorts 1-4 and 6: single ascending dose (120->240->480->720->960 mg IV)						
-Cohort 5: 240 mg IV QD on days 1 and days 8-14						
<i>Population:</i> Healthy females aged 18-45 years						
<i>Dose Selection:</i> The first three dose steps were covered by previous human trials. This is the first study to evaluate the cyclodextrin IV formulation.						
<i>Administration:</i> ☒ Fasted ☐ Fed						
<i>Formulation:</i> Cyclodextrin IV formulation						
<i>Excluded concomitant medications:</i> No medications were allowed within 10 days of study drug administration or during the study with the exception of acetaminophen and hormonal contraceptives						
<i>PK sampling:</i> Day 1 and day 14 intensive PK through 96 h postdose						
<i>Bioanalytical methods:</i> Letermovir method 08-061						
RESULTS						
Demographics (subjects who received placebo are not included)						
Study #	N enrolled	N completed	Race	Age (years)	Weight (kg)	BMI (kg/m ²)
Part A	30	30	100% Caucasian	32	65	23
Part B	8	5. Three subjects discontinued prematurely for unstated reasons.	100% Caucasian	32	71	25
Protocol Deviations						
No major protocol deviations were reported.						
Concomitant medications						
Concomitant medications were used by 36/38 (95%) of subjects. The most common medications were hormonal contraceptives and analgesics.						
Pharmacokinetics (CSR page 81)						
With increasing IV doses, AUC increased more than proportionally ($p < 0.0001$) while C _{max} increased proportionally ($p = 0.49$). Mean half-life was higher after multiple doses. PK parameters are shown below (Table 67, Table 68).						

Table 67. Letemovir PK parameters in cohorts 1-4 and 6.

Variables*	Letemovir				
	120 mg	240 mg	480 mg	720 mg	960 mg
N	6	6	6	6	6
C _{max} [ng/mL]	7,439 (1,353)	15,751 (3,512)	27,333 (4,423)	39,064 (3,060)	57,209 (7,617)
t _{max} [h]	0.50 (0.50–0.50)	0.50 (0.50–0.50)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (0.75–1.00)
AUC _{0-last} [h.ng/mL]	13,574 (3,803)	32,475 (9,278)	105,415 (21,329)	167,401 (23,271)	249,713 (59,371)
AUC _{0-∞} [h.ng/mL]	13,640 (3,824)	32,510 (9,274)	105,662 (21,551)	167,580 (23,152)	250,079 (59,152)
V _d [L]	158.5 (44.59)	124.3 (44.61)	86.91 (25.28)	74.08 (32.00)	79.02 (42.40)
CL [L/h]	9.417 (2.706)	7.965 (2.482)	4.707 (0.9807)	4.361 (0.5644)	4.042 (1.043)
MRT [h]	6.144 (1.842)	5.613 (1.222)	7.205 (1.709)	6.717 (1.072)	6.741 (1.212)
λ _z [1/h]	0.0246 (0.01936)	0.06578 (0.009723)	0.05708 (0.01530)	0.06612 (0.0213)	0.05870 (0.01837)
t _{1/2z} [h]	12.19 (4.324)	10.77 (1.906)	13.05 (4.096)	11.56 (4.108)	12.94 (4.503)
C _{max} /D [ng/mL/mg]	61.99 (11.27)	65.63 (14.63)	56.94 (9.215)	54.26 (4.251)	59.59 (7.934)
AUC _{0-last} /D [h.ng/mL]	113.1 (31.69)	135.3 (38.66)	219.6 (44.44)	232.5 (32.32)	260.1 (61.84)
AUC _{0-∞} /D [h.ng/mL]	113.7 (31.86)	135.5 (38.64)	220.1 (44.90)	232.8 (32.16)	260.5 (61.62)

* Data are arithmetic mean (standard deviation), for t_{max} median (range, ie minimum to maximum) are given
See Table 11.1-2 for values of Cohort 5, 240mg.

Source: CSR, page 84.

Table 68. Letemovir PK parameters in cohort 5.

Variables	Letemovir 240 mg	
	After single dose, Day 1	After multiple doses, Day 14
n	8	5
C _{0h} [ng/mL]	—	193.2 (86.23)
C _{min} [ng/mL]	—	171.8 (59.59)
C _{max} [ng/mL]	14,730 (1,207)	15,877 (1,949)
t _{max} [h]	0.50 (0.50–0.50)	0.50 (0.50–0.50)
AUC _{0-last} [h.ng/mL]	29,980 (5,409)	—
AUC _{0-∞} [h.ng/mL]	30,138 (5,477)	—
AUC _t [h.ng/mL]	27,475 (4,441)	33,609 (6,725)
C _{ss av} [ng/mL]	—	1,400 (280.4)
FI [%]	—	1,143 (189.9)
V _d [L]	192.7 (64.16)	—
V _{ss} [L]	—	60.32 (26.69)
CL [L/h]	8.233 (1.722)	7.350 (1.314)
MRT [h]	7.312 (3.315)	8.364 (3.866)
λ _z [1/h]	0.04691 (0.01765)	0.03728 (0.02199)
t _{1/2z} [h]	16.72 (6.270)	28.31 (23.78)
C _{max} /D [ng/mL/mg]	61.38 (5.028)	—
AUC _{0-last} /D [h.ng/mL]	124.9 (22.54)	—
AUC _{0-∞} /D [h.ng/mL]	125.6 (22.82)	—
R _{A(AUC)}	—	1.215 (0.3299)
R _{A(Cmax)}	—	1.033 (0.09772)
R _{Tdep}	—	0.9255 (0.2053)

Data are arithmetic mean (standard deviation), for t_{max} median (range, ie minimum to maximum) are given

* For a single subject (Subject 507) the criteria for accurate determination of λ_z were not met. Excluding this subject resulted in mean ± SD values for λ_z, t_{1/2z}, V_{ss} and MRT of 0.04410±0.01831 1/h, 18.11±7.706 h, 52.16±22.48 L, and 6.889±2.330 h, respectively.

Source: CSR, page 89.

Safety

One subject in the SD 960 mg IV cohort had an SAE of nausea and vomiting. There were no discontinuations due to AEs or deaths.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion	
The CSR states that no QTcF values >450 ms and no increases in QTcF from baseline >30 ms were observed. We did not review the QT findings in this study because a dedicated study with a positive control arm (P004) evaluated the effect of letermovir on the QT interval.	
Labeling Recommendations	
We agree with the following statements in proposed labeling derived from the results of this study:	
(b) (4)	(b) (4)
(b) (4) accumulation ratio of 1.22 for AUC and 1.03 for Cmax.	
The accumulation ratio was derived from letermovir dosing of 240 mg IV QD.	
Relevant links within the submission	
CSR	
\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\p005v01\p005v01.pdf	
Bioanalytical	
\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\p005v01\inter-laboratory-standardization-methods-quality-assurance.pdf	

P009 – multiple escalating doses

Study #	P009	Study Period	8/21/06-1/15/07
Title	Multiple dose escalating study in healthy male subjects to investigate safety, tolerability and pharmacokinetics of BAY 73-6327		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i> Safety, PK, effect of letermovir on midazolam PK	
<i>Rationale:</i> Not stated	
<i>Study design:</i> Randomized, placebo-controlled, multiple dose escalating study. MAD cohorts: 40 mg PO QD, 40 mg PO BID, or 80 mg PO BID -all treatments for 7 days -the 40 mg QD and 80 mg BID cohorts were conducted with and without midazolam	
<i>Population:</i> Healthy white males aged 18-45 years	
<i>Dose Selection:</i> Single doses up to 80 mg had been previously evaluated. The estimated effective dose at the time was 80 mg BID.	
<i>Administration:</i> ☒ Fasted ☐ Fed	
<i>Formulation:</i> FFP2 tablet	
<i>Excluded concomitant medications:</i> Use of concomitant medications before or during the trial was not permitted.	
<i>PK sampling:</i> Day 1 and day 6 intensive PK through 24 h (day 1) or 72 h (day 7) postdose	
<i>Bioanalytical methods:</i> Letermovir methods M1210 (plasma) and M1295 (urine)	
RESULTS	
Demographics Thirty-four subjects were enrolled, 32 received study drug, and 29 subjects completed the study. Mean age was 33 years and median weight was 81 kg.	
Protocol Deviations No major protocol deviations were reported.	
Concomitant medications One subject in each of the 80 mg BID and 40 mg BID plus midazolam groups used acetaminophen.	
Pharmacokinetics (CSR page 72) Letermovir AUC appeared to increase greater than proportionally with dose after single and multiple doses while Cmax was approximately proportional after single and multiple doses (statistical analysis for proportionality was not conducted) PK parameters are shown below.	

Table 69. Day 1 letermovir plasma PK parameters.

Parameter	Unit	BAY 73-6327 40 mg od (n=6)	BAY 73-6327 40 mg bid (n=6)	BAY 73-6327 80 mg bid (n=5)
AUC	µg*h/L	3053/42.1 (1709-5227)	2261/29.2 (1291-2794)	6195/5.9 (5777-6550)
AUC _{norm}	kg*h/L	6.262/38.4 (3.375-10.32)	4.368/28.6 (2.646-5.587)	6.006/19.0 (4.909-7.400)
AUC/D	h/L	0.07631/42.1 (0.04272-0.1307)	0.05652/29.2 (0.03227-0.06984)	0.07743/5.9 (0.07221-0.08188)
AUC(0-t _n) ^a	µg*h/L	2964/42.7 (1654-5131)	2052/26.9 (1244-2600)	5674/6.2 (5236-6028)
C _{max}	µg/L	897.6/31.2 (580.4-1420)	724.3/31.1 (400.4-884.0)	1820/23.1 (1338-2404)
C _{max, norm}	kg/L	1.841/29.0 (1.146-2.804)	1.399/28.1 (0.8208-1.757)	1.765/23.9 (1.323-2.251)
C _{max} /D	1/L	0.02244/31.2 (0.01451-0.03549)	0.01811/31.1 (0.01001-0.02210)	0.02276/23.1 (0.01672-0.03005)
C _{trough}	µg/L	11.74/38.9 (6.219-17.16)	34.01/48.07 (14.46-46.22)	102.4/7.5 (93.59-112.0)
t _{1/2}	h	5.785/20.9 (4.453-7.221)	4.030/38.3 (2.359-6.050)	3.783/5.8 (3.466-4.044)
t _{max} ^b	h	1.250 (1.000-1.500)	1.250 (0.5000-1.500)	1.000 (1.000-1.500)
MRT	h	5.393/5.6 (5.076-5.720)	4.656/20.8 (3.422-5.722)	4.621/7.3 (4.249-5.114)
CL/f	L/h	13.10/42.1 (7.653-23.41)	17.69/29.2 (14.32-30.99)	12.91/5.9 (12.21-13.85)

a AUC(0-t_n) = AUC(0-24) for the BAY 73-6327 40 mg od dose group and AUC(0-12) for the BAY 73-6327 bid dose groups

b Median (range)

Source: CSR, page 93.

Table 70. Letermovir day 7 plasma PK parameters.

Parameter	Unit	BAY 73-6327 40 mg od (n=6)	BAY 73-6327 40 mg bid (n=6)	BAY 73-6327 80 mg bid (n=5)
AUC(144-t _n) ^a	µg*h/L	3130/42.3 (1535-4613)	3113/41.9 (1896-5258)	9638/19.1 (7928-13090)
AUC(144-216)	µg*h/L	3433/40.1 (1709-4957)	4063/51.2 (2094-7546)	13070/30.9 (8989-20130)
AUC _{norm} (144-t _n) ^a	kg*h/L	6.420/40.1 (3.031-9.110)	6.015/38.5 (3.887-10.52)	9.345/14.2 (7.593-10.96)
AUC _{norm} (144-216)	kg*h/L	7.043/38.8 (3.375-9.790)	7.849/47.4 (4.293-15.09)	12.68/18.4 (10.22-16.86)
AUC(144-156)/D	h/L	0.07824/42.3 (0.03837-0.1153)	0.07783/41.9 (0.04740-0.1314)	0.1205/19.1 (0.09910-0.1636)
C _{max}	µg/L	812.9/41.3 (388.9-1153)	934.6/33.5 (516.3-1347)	2394/6.7 (2184-2619)
C _{max, norm}	kg/L	1.668/40.1 (0.7680-2.119)	1.806/29.6 (1.058-2.357)	2.321/12.6 (1.914-2.624)
C _{max} /D	1/L	0.02032/41.3 (0.009721-0.02883)	0.02337/33.5 (0.01291-0.03367)	0.02992/6.7 (0.02730-0.03273)
C _{trough}	µg/L	22.05/41.9 (11.55-32.43)	74.40/68.3 (28.13-157.9)	273.4/43.0 (155.2-464.8)
t _{1/2}	h	13.56/41.3 (9.397-23.97)	9.442/56.8 (4.157-16.24)	9.536/32.9 (6.248-12.52)
t _{max} ^b	h	1.250 (1.000-2.000)	1.000 (1.000-1.000)	1.000 (1.000-2.000)
MRT	h	8.195/20.7 (6.098-10.89)	7.382/25.3 (4.999-10.03)	8.304/30.6 (5.427-11.12)
CL _{ss} /f	L/h	12.78/42.3 (8.672-26.06)	12.85/41.9 (7.608-21.10)	8.301/19.1 (6.112-10.09)
PTF	%	607.5/6.9 (541.5-662.4)	328.9/26.5 (219.1-487.3)	262.2/17.1 (197.5-307.0)
R _A C _{max} (R _{A1})		0.9056/20.3 (0.6700-1.108)	1.290/15.9 (1.118-1.600)	1.315/26.7 (1.011-1.824)
R _{A4}		1.025/13.4 (0.8825-1.205)	1.377/25.5 (0.9242-1.882)	1.556/23.8 (1.219-2.233)

a AUC(144-t_n) = AUC(144-168) for the BAY 73-6327 40 mg od dose group and AUC(144-156) for the BAY 73-6327 bid dose groups

b Median (range)

Source: CSR, page 95.

Across dose groups, the mean percent of dose excreted in urine on day 1 and day 7 was ~0.3-0.6%.

Safety

There were two discontinuations. One subject experienced QT prolongation prior to administration of study drug and was withdrawn from the study. The other discontinuation was due to withdrawal of consent. There were no SAEs or deaths during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☒ Yes ☐ No

Study Conduct

- Protocol deviations do not affect the integrity of the study ☒ Yes ☐ No ☐ N/A
- Use of prohibited concomitant medications did not affect the integrity of the study ☒ Yes ☐ No ☐ N/A
- Bioanalytical method performance in acceptable ☒ Yes ☐ No

Study Results

The study results are acceptable as reported by the sponsor ☒ Yes ☐ No

Discussion

Although this study did not directly impact labeling, it was reviewed because it is in the phase 1 letermovir popPK dataset and predictions from the model are in proposed labeling.

Urine PK data and bioanalytical methods were not reviewed because they are not cited in labeling. However, the urine data are consistent with the mass balance study where negligible renal excretion of letermovir was observed.

Midazolam PK data and bioanalytical methods were not reviewed because they are not cited in labeling. Also, the midazolam data are not informative because the proposed letermovir dose (480 mg) is much higher than the highest dose evaluated in this study (80 mg BID).

Labeling Recommendations

This study did not directly impact labeling.

Relevant links within the submission

CSR

<\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\p009\p009.pdf>

Bioanalytical

<\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\p009\inter-laboratory-standardization-methods-quality-assurance.pdf>

P014 – relative bioavailability or tablet formulations FFP2 and PMF1

Study #	P014	Study Period	4/21/09-6/1/09
Title	A RANDOMIZED, SINGLE CENTER TRIAL TO DETERMINE THE RELATIVE BIOAVAILABILITY OF SOLID ORAL FORMULATIONS OF AIC090027		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i> Determine the relative bioavailability of the FFP versus PMF1 tablet formulations	
<i>Rationale:</i> To develop a new tablet formulation with different dose strengths	
<i>Study design:</i> open label, single-center, single-dose, randomized, five-period, five-treatment crossover trial	
Treatments: A: 20 mg x 12 (reference) B: 30 mg x 8 C: 60 mg x 4 D: 120 mg x 2 E: 240 mg x 1	
<i>Population:</i> Healthy adult females	
Dose Selection: The purpose of the study is to evaluate the exposure of new tablet strengths 30, 60, 120, and 240 mg	
<i>Administration:</i> ☒ Fasted ☐ Fed	
<i>Formulation:</i> FFP2 and PMF1 tablets	
<i>Excluded concomitant medications:</i> No concomitant medications were allowed with the exception of acetaminophen and hormonal contraceptives	
<i>PK sampling:</i> -Intensive PK sampling through 72 hours post-dose in each cohort -7 day washout between doses	
<i>Bioanalytical methods:</i> Ietermovir method 09-010	
RESULTS	
Demographics Fifteen subjects enrolled and 100% completed the study. Mean age was 36 years and mean weight was 61 kg. All subjects were Caucasian.	
Protocol Deviations No major protocol deviations were reported.	
Concomitant medications Nine (60%) subjects reported use of hormonal contraceptives.	
Pharmacokinetics (CSR page 57) The 90% confidence interval of C_{max} and AUC ratios were within 80-125% for all comparisons with the exception of comparison C vs. A, where the C_{max} ratio (90% CI) was 0.91 (0.78, 1.05).	
Safety There were no discontinuations due to AEs, SAEs, or deaths during the study.	

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion	
In this study, each of the new tablet strengths was shown to have similar exposure compared to the reference 20 mg tablet. Although this study did not directly impact labeling, it was reviewed because it is in the phase 1 letermovir popPK dataset and predictions from the model are in proposed labeling.	
Labeling Recommendations	
This study did not directly impact labeling.	
Relevant links within the submission	
CSR \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\p014\p014.pdf	
Bioanalytical -see Appendix 16.5 of CSR	

P017 – Absolute BA (30 mg), single ascending IV doses

Study #	P017	Study Period	9/16/11-6/6/12
Title	A single center trial to investigate the relative exposure and bioavailability of 30 mg letermovir (AIC090027) given intravenously compared to oral dosing (30 mg) and the safety, tolerability and pharmacokinetics of single ascending intravenous doses of letermovir		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i> Absolute BA (30 mg) and PK of letermovir after single ascending IV doses	
<i>Rationale:</i> Due to the patient population, an IV formulation was of interest. This is the first study of the IV formulation.	
<i>Study design:</i> Cohort 1: -Design: open-label, cross-over study -Sample size: 12 subjects -Treatment: single dose of 30 mg PO and 30 mg IV with a washout period of one week between doses Cohorts 2-5: -Design: single dose, randomized, parallel, double-blind, and placebo-controlled study -Sample size: in each cohort, six subjects were to receive letermovir and two subjects were to receive placebo -Treatments: Cohort 2: 60 mg IV x 1 Cohort 3: 120 mg IV x 1 Cohort 4: 240 mg IV x 1 Cohort 5: 480 mg IV x 1	
<i>Population:</i> Healthy adult females 18-45 years of age	
<i>Dose Selection:</i> The starting IV dose of 30 mg was thought to result in lower exposures compared to the highest oral doses that were previously administered.	
<i>Administration:</i> ☒ Fasted ☐ Fed	
<i>Formulation:</i> PMF1 tablet and IV (b) (4) formulations	
<i>Excluded concomitant medications:</i> No concomitant medications were allowed with the exception of acetaminophen and hormonal contraceptives	
<i>PK sampling:</i> Intensive sampling through 72 hours postdose	
<i>Bioanalytical methods:</i> letermovir method 08-061	
RESULTS	
Demographics Cohort 1: -12 subjects were enrolled and all completed the study -Mean age was 32 years, mean weight was 67 kg, and all subjects were Caucasian Cohort 2: -32 subjects were enrolled and 30 completed the study. Two subjects in cohort 5 did not receive study drug.	

-Mean age was 32 years, mean weight was 68 kg, and 28/30 subjects were Caucasian

Protocol Deviations

No major protocol deviations were reported.

Concomitant medications

Cohort 1: use of prohibited medications included one subject who used lactulose for constipation.
Cohorts 2-5: use of systemic prohibited medications included antithrombotic agents (n=3 subjects), vasoprotectives (n=2), antibiotics (n=1), and anti-inflammation products (n=2)

Pharmacokinetics (CSR page 81)

In cohort 1, absolute BA (AUC ratio [90% CI] of oral to IV letermovir) was 0.76 (0.68, 0.84).

In cohorts 2-5, exposures increased more than proportionally with dose across the dose range of 30-480 mg IV (Table 71).

Table 71. Dose proportionality.

Dose (mg)	Mean AUC (ng*h/mL)	AUC fold change compared to next lowest dose
30	2245	NA
60	5436	2.42
120	12244	2.25
240	31242	2.55
480	88569	2.83

PK parameters are shown below (Table 72, Table 73).

Table 72. Cohort 1 PK parameters.

Pharmacokinetics of letermovir (mean $\pm$ SD, t_{max} : median [range])	Cohort 1: 30 mg letermovir 30 min iv infusion	Cohort 1: 30 mg letermovir oral
n	12 ^a	12 ^b
C_{max}, ng/mL	1209 $\pm$ 235.3	363.5 $\pm$ 118.4
t_{max}, h	0.50 (0.50-0.50)	1.50 (1.00-3.00)
AUC_{0-last}, ng*h/mL	1980 $\pm$ 473.5	1544 $\pm$ 478.9
AUC_{0-∞}, ng*h/mL	2245 ^c $\pm$ 353.4 ^c	1802 ^d $\pm$ 298.8 ^d
λ_z, 1/h	0.05837 ^c $\pm$ 0.01335 ^c	0.04983 ^d $\pm$ 0.01593 ^d
t_{1/2z}, h	12.66 ^c $\pm$ 4.082 ^c	15.49 ^d $\pm$ 5.869 ^d
CL(/F), L/h	13.66 ^c $\pm$ 2.215 ^c	17.07 ^d $\pm$ 2.857 ^d
V_D (/F), L	251.5 ^c $\pm$ 92.34 ^c	382.2 ^d $\pm$ 175.2 ^d
MRT, h	5.543 ^c $\pm$ 0.6608 ^c	8.509 ^d $\pm$ 1.919 ^d

^a n=8 for AUC_{0- ∞} , λ_z , t_{1/2term}, CL, V_D and MRT

^b n=9 for AUC_{0- ∞} , ng*h/mL, λ_z , t_{1/2term}, CL/F, V_D /F and MRT

^c Accurate determination not possible in 4 subjects

^d Accurate determination not possible in 6 subjects

Source: CSR page 85.

Table 73. Cohort 2-5 PK parameters.

Pharmacokinetic parameter (mean $\pm$ SD, t _{max} : median [range])	Ietermovir iv infusion				
	Cohort 1: 30 mg 30 min iv infusion	Cohort 2: 60 mg 30 min iv infusion	Cohort 3: 120 mg 30 min iv infusion	Cohort 4: 240 mg 30 min iv infusion	Cohort 5: 480 mg 60 min iv infusion
n	12 ^a	6 ^b	6	6	4
C _{max} , ng/mL	1209 $\pm$ 235.3	2953 $\pm$ 353.1	6166 $\pm$ 360.8	14207 $\pm$ 3082	27328 $\pm$ 3401
t _{max} , h	0.50 (0.50-0.50)	0.50 (0.50-0.50)	0.50 (0.50-0.50)	0.50 (0.50-0.50)	1.00 (1.00-1.00)
AUC _{0-last} , ng $\cdot$ h/mL	1980 $\pm$ 473.5	5049 $\pm$ 1170	12025 $\pm$ 1745	31140 $\pm$ 8810	87389 $\pm$ 22188
AUC _{0-∞} , ng $\cdot$ h/mL	2245 $\pm$ 353.4 ^c	5436 $\pm$ 974.7 ^d	12244 $\pm$ 2061 ^e	31242 $\pm$ 8804	88569 $\pm$ 23460 ^f
λ_z , 1/h	0.05837 ^c $\pm$ 0.01335 ^c	0.05243 ^c $\pm$ 0.01839 ^d	0.05409 ^e $\pm$ 0.02816 ^e	0.07152 $\pm$ 0.02978	0.07149 ^f $\pm$ 0.04333 ^f
t _{1/2z} , h	12.66 $\pm$ 4.082 ^c	14.68 ^d $\pm$ 5.340 ^d	18.31 ^e $\pm$ 14.92 ^e	11.21 $\pm$ 4.667	15.43 ^f $\pm$ 13.80 ^f
CL, L/h	13.66 ^c $\pm$ 2.215 ^c	11.31 ^d $\pm$ 1.883 ^d	10.02 ^e $\pm$ 1.613 ^e	8.126 $\pm$ 1.951	5.721 ^f $\pm$ 1.521 ^f
V _D , L	251.5 ^c $\pm$ 92.34 ^c	238.1 ^d $\pm$ 83.86 ^d	240.7 ^e $\pm$ 145.0 ^e	132.1 $\pm$ 59.47	115.7 ^f $\pm$ 79.84 ^f
MRT, h	5.543 ^c $\pm$ 0.6608 ^c	6.740 ^d $\pm$ 1.578 ^d	7.121 ^e $\pm$ 4.118 ^e	5.196 $\pm$ 0.8774	6.591 ^f $\pm$ 3.593 ^f
C _{max} /D, ng/mL/mg	40.30 ^c $\pm$ 7.844 ^c	49.21 ^d $\pm$ 5.885 ^d	51.39 ^e $\pm$ 3.006 ^e	59.20 $\pm$ 12.84	56.93 ^f $\pm$ 7.086 ^f
AUC _{0-last} /D, ng $\cdot$ h/mL/mg	65.99 ^c $\pm$ 15.78 ^c	84.15 ^d $\pm$ 19.50 ^d	100.2 ^e $\pm$ 14.54 ^e	129.8 $\pm$ 36.71	182.1 ^f $\pm$ 46.22 ^f
AUC _{0-∞} /D, ng $\cdot$ h/mL/mg	74.85 ^c $\pm$ 11.78 ^c	90.61 ^d $\pm$ 16.25 ^d	102.0 ^e $\pm$ 17.17 ^e	130.2 $\pm$ 36.68	184.5 ^f $\pm$ 48.88 ^f

^a n=8 for AUC_{0- ∞} , AUC_{0- ∞} /D, λ_z , t_{1/2term}, CL, V_D and MRT^b n=5 for AUC_{0- ∞} , AUC_{0- ∞} /D, λ_z , t_{1/2term}, CL, V_D and MRT^c Accurate determination not possible in 4 subjects^d Accurate determination not possible in 2 subjects^e Accurate determination not possible in 1 subjects^f Accurate determination not possible in 1 subjects

Source: CSR page 89.

Safety

In cohort 1, there were no discontinuations due to AEs, SAEs, or deaths.

In cohorts 2-5, there were two SAEs of infusion site thrombosis in the 480 mg cohort. Non-serious infusion site thrombosis was reported in one subject in the 60 mg and 240 mg cohorts. Due to AEs observed in cohort 5, the trial was stopped after four subjects were treated with Ietermovir in cohort 5. There were no discontinuations due to AEs or deaths in cohorts 2-5.

REVIEWER ASSESSMENT
The study design is acceptable ☒ Yes ☐ No
Study Conduct - Protocol deviations do not affect the integrity of the study ☒ Yes ☐ No - Use of prohibited concomitant medications did not affect the integrity of the study ☒ Yes ☐ No - Bioanalytical method performance in acceptable ☒ Yes ☐ No
Study Results The study results are acceptable as reported by the sponsor ☒ Yes ☐ No
Discussion Although this study did not directly impact labeling, it was reviewed because it is in the phase 1 letermovir popPK dataset and predictions from the model are in proposed labeling. Absolute BA at a dose of 30 mg was found to be 76% in this study. Absolute BA was also assessed in the phase 1 popPK model. The phase 1 popPK dataset contained 12 studies across various doses, formulations, and both PO and IV administration. Absolute BA was estimated to be 94%. Infusion site reactions were observed in three of four subjects in the 480 mg cohort, classified as SAEs in two subjects. Cmax and AUC values in this cohort appeared to be comparable between subjects with infusion site reactions (n=3) and without (n=1) (CSR page 90). Due to the infusion site AEs observed with the IV (b) (4) formulation, a cyclodextran IV formulation was developed and was administered in the phase 3 study.
Labeling Recommendations This study did not directly impact labeling.
Relevant links within the submission CSR \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\p017\p017.pdf Bioanalytical \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\04jhjq\04jhjq.pdf

P018 Part A – PO single and multiple ascending doses

Study #	P018 Part A	Study Period	10/28/11-3/2/12
Title	A SINGLE CENTRE TRIAL TO INVESTIGATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SINGLE AND MULTIPLE ASCENDING ORAL DOSES OF LETERMОВIR		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i> Safety, determine MTD, PK, effect of high dose letermovir on the QTc interval	
<i>Rationale:</i> Not stated	
<i>Study design:</i> Seven cohorts were planned but three cohorts (1, 2, and 7) were conducted. Cohort 1 was open-label and cohorts 2 and 7 were randomized, double-blind, and placebo-controlled. <i>Treatments:</i> -Cohort 1: 240 mg PO BID on days 1 and 4-10 -Cohort 2: 360 mg PO BID on days 1 and 4-10 -Cohort 7: 360 mg PO QD on days 1 and 4-10	
<i>Population:</i> Healthy adult females	
<i>Dose Selection:</i> 240 mg BID and 360 mg QD had been previously studied	
<i>Administration:</i> ☒ Fasted ☐ Fed	
<i>Formulation:</i> PMF1 tablet	
<i>Excluded concomitant medications:</i> Concomitant medications were not allowed with the exception of acetaminophen	
<i>PK sampling:</i> intensive sampling through 72 hours in cohorts 1-2 and through 120 hours in cohort 7 on days 1 and 10	
<i>Bioanalytical methods:</i> letermovir method 08-061	
RESULTS	
Demographics Thirty-two subjects enrolled and all completed the study. Mean age was 28 years and mean weight was 67 kg. 26/32 subjects were white.	
Protocol Deviations No major protocol deviations were reported.	
Concomitant medications Use of prohibited medication consisted of one subject who used ibuprofen.	
Pharmacokinetics (CSR page 56) Exposure increased more than proportionally with daily dose. One subject in cohort 2 had high exposures relative to other subjects in the cohort. PK parameters are shown below (Table 74).	

Table 74. Letemovir PK parameters.

<i>Pharmacokinetics of letemovir</i> (mean ± SD, t _{max} : median [range])	Cohort 1: 240 mg letemovir b.i.d.	Cohort 7: 360 mg letemovir q.d.	Cohort 2: 360 mg letemovir b.i.d.
n	12	8	8 ^a
Day 1			
C _{max} , ng/mL	-	9140 ± 1913	10750 ± 2142
t _{max} , h	-	2.54 (1.00-3.00)	2.00 (2.00-3.02)
AUC _{0-12h} , ng·h/mL	-	40854 ± 8391	52829 ± 14672
AUC _{0-24h} , ng·h/mL	-	48005 ± 11879	-
AUC _{0-last} , ng·h/mL	-	52846 ± 14466	70414 ± 27395
AUC _{0-∞} , ng·h/mL	-	53404 ± 14697	71220 ± 27733
λ _z , 1/h	-	0.04881 ± 0.007908	0.04833 ± 0.01284
t _{1/2z} , h	-	14.57 ± 2.630	15.37 ± 4.731
CL/F, L/h	-	7.206 ± 1.978	5.547 ± 1.520
V _d /F, L	-	151.6 ± 49.46	125.0 ± 59.98
MRT, h	-	9.765 ± 1.823	10.31 ± 1.720
Day 5			
C _{0h} , ng/mL	-	339.8 ± 198.3	4200 ± 3470
Day 6			
C _{0h} , ng/mL	-	526.0 ± 244.6	5859 ± 4832
Day 7			
C _{0h} , ng/mL	-	513.3 ± 286.6	5788 ± 5246
Day 8			
C _{0h} , ng/mL	-	618.8 ± 382.1	6076 ± 5507
Day 5/Day 9			
C _{0h} , ng/mL	1834 ± 1213	619.3 ± 321.4	6588 ± 5408
Day 6/Day 10			
C _{0h} , ng/mL	2056 ± 1291	670.9 ± 347.7	5837 ± 4382
C _{min} , ng/mL	1766 ± 1288	527.5 ± 256.3	3849 ± 2780
C _{ss,avg} , ng/mL	9721 ± 3493	7971 ± 3038	15441 ± 4417
t _{max} , h	2.00 (1.50-2.50)	2.00 (1.00-5.02)	2.00 (1.00-4.00)
AUC _{0-12h,ss} , ng·h/mL	51973 ± 19873	-	103308 ± 45464
AUC _{0-24h,ss} , ng·h/mL	-	55952 ± 21034	-
C _{ss,30'} , ng/mL	4343 ± 1652	2329 ± 873.8	8601 ± 3775
FI, %	195.4 ± 74.13	332.9 ± 119.9	144.7 ± 30.51
λ _z , 1/h	-	0.04044 ± 0.01870	0.03052* ± 0.01111*
t _{1/2z} , h	-	21.53 ± 11.79	24.87* ± 7.452*
CL/F, L/h	5.177 ± 1.764	7.437 ± 3.240	3.884 ± 1.083
V _{ss} /F, L	-	241.8 ± 208.9	145.4* ± 71.40*
MRT, h	-	14.09 ± 3.636	14.77* ± 2.187*
RA(C _{max})	-	0.8568 ± 0.2396	1.473 ± 0.4245
RA(AUC)	-	1.136 ± 0.2002	1.918 ± 0.3391

^a n=6 for Day 10 λ_z, t_{1/2z}, V_{ss}/F and MRT

* Accurate determination not possible

Source: CSR, page 60.

Safety

There were no discontinuations due to AEs, SAEs, or deaths during the study.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion	
Although Part A of this study did not directly impact labeling, it was reviewed because it is in the phase 1 letermovir popPK dataset and predictions from the model are in proposed labeling.	
Labeling Recommendations	
Part A of this study did not directly impact labeling.	
Relevant links within the submission	
CSR part A \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\p018v01\p018v01.pdf	
Bioanalytical part A \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\p018v01\inter-laboratory-standardization-methods-quality-assurance.pdf	

P018 Part B – single and multiple IV doses

Study #	P018 Part B	Study Period	4/30/12-9/7/12
Title	A SINGLE CENTRE TRIAL TO INVESTIGATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SINGLE AND ONCE DAILY INTRAVENOUS INFUSIONS OF LETERMОВIR GIVEN AS (b) (4)		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i> PK and safety of single and once daily IV infusions	
<i>Rationale:</i> Not reported	
<i>Study design:</i> Cohort 1: -Period 1: Single 120 mg IV infusion on day 1 -Seven day washout between day 1 of period 1 and day 1 of period 2 -Period 2: 120 mg IV infusion on days 1-7 Cohort 2 -Period 1: Single 240 mg IV infusion on day 1 -Seven day washout between day 1 of period 1 and day 1 of period 2 -Period 2: 240 mg IV infusion on days 1-7 Each cohort consisted of eight subjects who received letermovir and four subjects who received placebo.	
<i>Population:</i> Healthy adult females	
<i>Dose Selection:</i> At the time of the study, the starting dose of 120 mg was in the anticipated therapeutic range.	
<i>Administration:</i> ☒ Fasted ☐ Fed	
<i>Formulation:</i> IV (b) (4)	
<i>Excluded concomitant medications:</i> No medications were allowed with the exception of acetaminophen.	
<i>PK sampling:</i> Intensive PK sampling through 96 hours postdose on day 1 of period one and day 7 of period 2	
<i>Bioanalytical methods:</i> Letermovir method 08-061	
RESULTS	
Demographics Twenty four subjects were randomized and 21 completed the study. Mean age was 23 years and mean weight was 67 kg.	
Protocol Deviations No major deviations were reported.	
Concomitant medications Use of systemic prohibited medications included ibuprofen (n=3) and tinzaparin (n=1).	
Pharmacokinetics (CSR page 62) Comparing the 120 mg versus 240 mg groups on days 1 and 7, dose-normalized Cmax and AUC were similar (CSR page 70).	

Table 75. Single dose letermovir PK parameters.

PK of letermovir (mean±SD, t_{max} : median [range])	Single infusion of 120 mg letermovir infused over 60 minutes	Single infusion of 240 mg letermovir infused over 60 minutes
N	8	8
Day 1		
C_{max} , ng/mL	5,984±1,010	13,180±1,946
t_{max} , h	1.00 (0.75-1.00)	1.00 (1.00-1.02)
AUC_{0-24h} , ng.h/mL	16,333±4,258	36,217±10,193
AUC_{0-last} , ng.h/mL	17,847±4,979	38,882±11,516
$AUC_{0-\infty}$, ng.h/mL	18,018±5,042	39,158±11,588
λ_z , 1/h	0.04138±0.01509	0.05170±0.03006
$t_{1/2z}$, h	18.97±7.219	17.84±9.463
CL, L/h	7.074±1.772	6.618±1.929
V_d , L	193.3±84.29	169.9±106.3
MRT, h	8.077±1.864	7.112±2.222

Source: CSR, page 67.

Table 76. Multiple dose letermovir PK parameters.

PK of letermovir (mean±SD, t_{max} : median [range])	Once daily infusion from Day 1 to Day 7 of 120 mg letermovir infused over 60 minutes	Once daily infusion from Day 1 to Day 7 of 240 mg letermovir infused over 60 minutes
N	7	6 ^a
Day 7		
C_{0h} , ng/mL	139.4±27.70	272.4±149.8
C_{min} , ng/mL	132.4±26.55	241.8±118.7
$C_{ss,max}$, ng/mL	6,014±1,018	13,972±2,135
t_{max} , h	1.00 (0.75-1.05)	1.00 (1.00-1.02)
$AUC_{\tau,ss}$, ng.h/mL	19,869±2,696	43,914±11,392
$C_{ss,av}$, ng/mL	827.9±112.4	1,830±474.9
FI, %	715.1±114.3	800.4±107.3
λ_z , 1/h	0.03375±0.01417	0.04077±0.01671
$t_{1/2z}$, h	23.31±7.845	20.70±11.01
CL, L/h	6.138±0.8572	5.821±1.677
V_{ss} , L	65.41±19.05	50.12±14.87
MRT, h	10.65±2.769	8.824±2.525
$R_A(C_{max})$	1.046±0.1930	1.084±0.07641
$R_A(AUC)$	1.328±0.1097	1.233±0.1410

^aN=5 for C_{0h} , C_{min} and FI

Source: CSR, page 67.

Safety

Three subjects discontinued the study due to an SAE or AE (Table 77). There was one SAE of potential DVT of the brachial vein on the non-infusion arm. There were no deaths in the study.

Table 77. Discontinuations due to AEs.

Subject	Dose group (mg)	AE or SAE	AE type	Onset	PK parameters	Notes
B0102	120	SAE	potential DVT of the brachial vein on the non-infusion arm	Period 1, day 3	28490 ng*h/mL	This subject had the highest AUC value in cohort 1 (mean was 18018 ng*h/mL)
B0203	240	AE	infusion site thrombosis	Period 2, day 4	C ₀ on day 4 was 167 ng/mL	AUC was not available for this subject. Median C ₀ on day 4 was 189 ng/mL.
B0211	240	AE	infusion site thrombosis	Period 2, day 2	C ₀ on day 3 was 466 ng/mL	AUC was not available for this subject. Median C ₀ on day 3 was 201 ng/mL.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion	
Although this study did not directly impact labeling, it was reviewed because it is in the phase 1 letermovir popPK dataset and predictions from the model are in proposed labeling. In this study, letermovir exposures were dose proportional after single and multiple IV doses of 120-240 mg. This result differs from study P017, where after single ascending doses of 60-480 mg IV, exposures increased more than proportionally with dose. In general, oral and IV letermovir exposures have been found to increase more than proportionally with dose. Two subjects in the 240 mg group discontinued the study due to infusion site thrombosis. Ultimately, the IV (b) (4) formulation used in this study was discontinued. An IV cyclodextran formulation was developed and was administered in the phase 3 study.	
Labeling Recommendations	
This study did not directly impact labeling.	
Relevant links within the submission	
CSR part B \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\p018v02\p018v02.pdf Bioanalytical part B \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\p018v02\inter-laboratory-standardization-methods-quality-assurance.pdf	

P026 – multiple PO and IV doses

Study #	P026	Study Period	12/16/13-3/18/14
Title	A Single-center, 2-Part, Randomized, Double-blind, Placebo-controlled Study to Assess Safety, Tolerability and Pharmacokinetics Following Multiple High Oral Doses of MK-8228 and Multiple Intravenous Doses of the MK-8228 Cyclodextrin Formulation in Healthy Female Subjects		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i> Safety and PK	
<i>Rationale:</i> Not stated	
<i>Study design:</i> Randomized, double-blind, placebo-controlled trial. Part 1: 720 mg letermovir or placebo PO BID for 14 days Part 2: 480 mg IV QD for 7 days	
<i>Population:</i> Healthy adult females	
<i>Dose Selection:</i> The PO and IV dose planned for the phase 3 study was 480 mg QD. 720 mg BID was evaluated in this study in order to cover anticipated higher exposures in patients with renal or hepatic impairment. The IV dose evaluated in this study is the planned phase 3 dose of 480 mg QD.	
<i>Administration:</i> ☒ Fasted ☐ Fed In Part 1, breakfast was given within an hour of dosing on non-PK days, but was not given on PK days (days 1 and 14).	
<i>Formulation:</i> PMF2 tablet and IV cyclodextrin	
<i>Excluded concomitant medications:</i> No medications were allowed with the exception of acetaminophen, hormonal contraceptives, and vitamins and minerals.	
<i>PK sampling:</i> Intensive PK sampling through 72 hours postdose on days 1 and 14 (Part 1) or days 1 and 7 (Part 2).	
<i>Bioanalytical methods:</i> Letermovir method BP-0032	
RESULTS	
Demographics Thirty-six subjects were enrolled and 33 completed the study. Twenty-three subjects were black and twelve were white. Mean age was 33 years. Mean weight across treatment groups was 70-80 kg.	
Protocol Deviations No major deviations were reported.	
Concomitant medications Use of prohibited systemic medications included metronidazole (n=1 subject), loperamide (n=1), acetaminophen + dextromethorphan hydrobromide + doxylamine succinate + pseudoephedrine (n=1), and valacyclovir (n=1).	
Pharmacokinetics (CSR page 71) In Part 1, vomiting was reported for six subjects. Vomiting occurred on PK sampling days for four subjects. C _{max} values for subjects who vomited were reported to be similar to subjects who did not vomit. PK parameters are shown below for Part 1 (Table 78, Table 79) and Part 2.	

Table 78. Part 1, day 1 letermovir PK parameters.

Subject	AUC0-12hr (ng.h/mL)	Cmax (ng/mL)	C12hr (ng/mL)	Tmax (h)
AN0001	76800	15700	1790	3.00
AN0002	152000	23700	9240	5.03
AN0003	100000	19800	2280	2.50
AN0006	111000	16000	3430	3.00
AN0007	101000	23000	2140	3.00
AN0008	135000	20500	4750	2.50
AN0009	149000	21600	9030	5.00
AN0010	103000	18200	3450	3.00
AN0011	104000	13200	3680	3.00
AN0013	54100	12400	931	2.02
AN0015	138000	24200	5280	3.00
AN0016	66000	10100	2080	3.00
AN0017	178000	23600	8230	3.00
AN0018	96000	15600	1420	2.02
AN0020	71600	16500	1770	2.50
AN0021	214000	32600	11000	3.00
AN0022	145000	26000	3830	3.00
AN0024	117000	15800	6650	5.02
n	18	18	18	18
Mean	117000	19400	4500	3.14
SD	41000	5600	3080	0.924
CV%	34.9	28.9	68.4	29.4
Minimum	54100	10100	931	2.02
Median	107000	19000	3570	3.00
Maximum	214000	32600	11000	5.03
Geometric Mean	111000	18600	3570	3.03
GCV%	36.8	30.1	82.0	27.1

SD = Standard deviation.

CV = Arithmetic coefficient of variation is calculated in the original scale with the equation: $100 \times (SD/Mean)$.GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: $100 \times \sqrt{\exp(s^2) - 1}$,where s^2 is the observed variance on the natural log-scale.

Source: CSR, page 75.

Table 79. Part 1, day 14 letermovir PK parameters.

Subject	AUC0-12hr (ng.h/mL)	Cmax (ng/mL)	C12hr (ng/mL)	Tmax (h)	CL/F (L/h)	t1/2 (h)	Vz/F (L)	Ra Cmax	Ra C12hr	Ra AUC0-12hr
AN0001	170000	25100	4550	2.50	4.23	9.58	58.5	1.60	2.54	2.22
AN0002	192000	29500	5200	2.00	3.76	13.21	71.6	1.24	0.560	1.26
AN0003	129000	24000	2530	2.00	5.57	22.55	181	1.21	1.11	1.29
AN0006	159000	22700	5040	3.00	4.53	36.46	238	1.42	1.47	1.43
AN0007	76000	16800	1100	2.50	9.48	15.20	208	0.730	0.510	0.760
AN0008*										
AN0009	205000	29800	10200	5.00	3.51	12.76	64.6	1.38	1.13	1.38
AN0010	124000	21600	2810	3.00	5.83	10.59	89.1	1.19	0.810	1.19
AN0011	175000	29400	4440	2.48	4.12	8.93	53.2	2.23	1.21	1.69
AN0013	109000	21700	1090	2.50	6.59	11.25	107	1.75	1.17	2.02
AN0015	190000	34300	4290	3.00	3.80	47.77	262	1.42	0.810	1.38
AN0016	100000	20500	739	3.02	7.19	9.66	100	2.03	0.360	1.52
AN0017	317000	46600	6750	3.00	2.27	11.93	39.1	1.97	0.820	1.78
AN0018	136000	21600	2800	5.02	5.29	16.51	126	1.38	1.97	1.42
AN0020	191000	30600	5740	2.50	3.77	14.89	80.9	1.85	3.24	2.67
AN0021	300000	40500	10400	3.00	2.40	15.02	51.9	1.24	0.950	1.40
AN0022	370000	44800	17600	5.00	1.95	9.35	26.3	1.72	4.60	2.55
AN0024	109000	16300	2530	2.50	6.64	23.24	222	1.03	0.380	0.930
n	17	17	17	17	17	17	17	17	17	17
Mean	179000	28000	5170	3.06	4.76	16.99	116	1.49	1.39	1.58
SD	81300	9120	4250	0.985	1.97	10.5	76.0	0.391	1.13	0.523
CV%	45.3	32.6	82.4	32.2	41.4	61.9	65.3	26.2	81.1	33.1
Minimum	76000	16300	739	2.00	1.95	8.93	26.3	0.730	0.360	0.760
Median	170000	25100	4440	3.00	4.23	13.21	89.1	1.42	1.11	1.42
Maximum	370000	46600	17600	5.02	9.48	47.77	262	2.23	4.60	2.67
Geometric Mean	164000	26700	3800	2.94	4.38	14.97	94.6	1.44	1.08	1.50
GCV%	44.8	32.1	101.8	29.2	44.8	50.9	76.4	28.4	81.0	33.7

SD = Standard deviation.

CV = Arithmetic coefficient of variation is calculated in the original scale with the equation: $100 \times (SD/Mean)$.GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: $100 \times \sqrt{\exp(s^2) - 1}$, where s^2 is the observed variance on the natural log-scale.

* Subject AN0008 discontinued after the morning dose on Day 7; therefore, no pharmacokinetic parameters were available for Day 14.

Source: CSR, page 76.

Table 80. Part 2, day 1 letermovir PK parameters.

Subject	AUC0-24hr (ng.h/mL)	AUC0-12hr (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	Ceoi (ng/mL)	C24hr (ng/mL)
AN0025	102000	89500	28000	0.98	28000	460
AN0026	85100	75300	25400	1.00	25400	402
AN0027	149000	127000	33800	1.02	33800	676
AN0029	116000	97500	26600	1.02	26600	622
AN0030	67900	63800	24100	1.00	24100	117
AN0031	102000	87100	24700	1.00	24700	625
AN0034	144000	120000	29000	1.00	29000	964
AN0035	68200	61100	22200	1.02	22200	354
AN0036	104000	94200	29100	1.00	29100	302
n	9	9	9	9	9	9
Mean	104000	90600	27000	1.00	27000	502
SD	28900	22600	3450	0.011	3450	249
CV%	27.7	25.0	12.8	1.1	12.8	49.5
Minimum	67900	61100	22200	0.98	22200	117
Median	102000	89500	26600	1.00	26600	460
Maximum	149000	127000	33800	1.02	33800	964
Geometric Mean	101000	88100	26800	1.00	26800	437
GCV%	28.8	25.6	12.6	1.1	12.6	67.4

SD = Standard deviation; Ceoi = Concentration at the end of infusion

CV = Arithmetic coefficient of variation is calculated in the original scale with the equation: $100 \times (SD/Mean)$.

GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: $100 \times \sqrt{\exp(s^2) - 1}$,

where s^2 is the observed variance on the natural log-scale.

Source: CSR, page 82.

Table 81. Part 2, day 7 PK parameters.

Subject	AUC0-24hr (ng.h/mL)	AUC0-12hr (ng.h/mL)	Ceoi (ng/mL)	Cmax (ng/mL)	Tmax (h)	C24hr (ng/mL)	t1/2 (h)	CL (L/h)	Vz (L)	Vss (L)	MRT (h)	Ra Cmax	Ra C24hr	Ra AUC0-24hr
AN0025	117000	94100	25700	25700	1.03	1470	15.99	5.10	118	52.4	10.3	0.920	3.20	1.14
AN0026	119000	98800	28600	28600	0.98	1200	14.91	4.86	104	44.3	9.11	1.13	2.99	1.40
AN0027	171000	144000	35200	35200	0.98	1120	6.85	3.32	32.8	23.0	6.93	1.04	1.66	1.15
AN0029	115000	97900	26000	26000	0.97	933	16.00	4.90	113	40.4	8.23	0.980	1.50	0.990
AN0030	86400	77400	26800	26800	0.95	396	5.47	6.20	48.9	29.8	4.80	1.11	3.38	1.27
AN0031	123000	97100	27200	27200	1.00	1660	9.62	4.94	68.6	50.3	10.2	1.10	2.66	1.20
AN0034	223000	168000	33500	33500	0.95	2490	14.08	2.86	58.1	37.7	13.2	1.16	2.58	1.55
AN0035	85500	75300	22600	22600	1.02	859	13.68	6.38	126	45.8	7.19	1.02	2.43	1.25
AN0036	117000	104000	32200	32200	1.00	756	18.19	4.64	122	29.9	6.44	1.11	2.50	1.12
n	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Mean	129000	106000	28600	28600	0.99	1210	12.75	4.80	87.9	39.3	8.48	1.06	2.54	1.23
SD	43200	30400	4140	4140	0.029	611	4.41	1.15	35.7	10.1	2.51	0.079	0.635	0.165
CV%	33.6	28.6	14.4	14.4	2.9	50.5	34.6	23.9	40.6	25.6	29.6	7.4	25.0	13.4
Minimum	85500	75300	22600	22600	0.95	396	5.47	2.86	32.8	23.0	4.80	0.920	1.50	0.990
Median	117000	97900	27200	27200	0.98	1120	14.08	4.90	104	40.4	8.23	1.10	2.58	1.20
Maximum	223000	168000	35200	35200	1.03	2490	18.19	6.38	126	52.4	13.2	1.16	3.38	1.55
Geometric Mean	123000	103000	28400	28400	0.99	1080	11.91	4.66	80.1	38.0	8.16	1.06	2.46	1.22
GCV%	30.9	26.6	14.4	14.4	2.9	56.2	43.9	26.6	51.5	28.2	30.8	7.6	28.3	13.2

SD = Standard deviation; Ceoi = Concentration at the end of infusion

CV = Arithmetic coefficient of variation is calculated in the original scale with the equation: $100 \times (SD/Mean)$.

GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: $100 \times \sqrt{\exp(s^2) - 1}$, where s^2 is the observed variance on the natural log-scale.

Source: CSR, page 83.

Safety

There were no discontinuations due to AEs, SAEs, or deaths in the study.

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion	
Although this study did not directly impact labeling, it was reviewed because it is in the phase 1 letermovir popPK dataset and predictions from the model are in proposed labeling.	
Labeling Recommendations	
This study did not directly impact labeling.	
Relevant links within the submission	
CSR \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\p026\p026.pdf	
Bioanalytical \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\p026\publications-based-on-trial.pdf	

P028 – relative bioavailability study of 240 mg and 480 mg tablets

Study #	P028	Study Period	6/23/14-8/5/14
Title	A study to evaluate the comparative bioavailability of one tablet of 480 mg MK-8228 and two tablets of 240 mg MK-8228 under fasted conditions in healthy subjects		

STUDY SUMMARY (As Reported by the Applicant)	
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS	
<i>Objectives:</i> Relative bioavailability of 240 mg and 480 mg tablets	
<i>Rationale:</i> Both the 240 mg and 480 mg tablets will be used in the phase 3 study	
<i>Study design:</i> Randomized, two-way cross-over, single site, open-label study. Subjects were randomized to a treatment sequence of A->B or B->A Treatment A: Single oral dose of one letermovir 480 mg tablet Washout: at least 7 days between dosing Treatment B: Single oral dose of two letermovir 240 mg tablets	
<i>Population:</i> Healthy adult females	
<i>Dose Selection:</i> The 240 mg and 480 mg tablets were used in the phase 3 study	
<i>Administration:</i> ☒ Fasted ☐ Fed	
<i>Formulation:</i> PMF3 tablets	
<i>Excluded concomitant medications:</i> No medications were allowed with the exception of acetaminophen and hormonal contraceptives unless the investigator and sponsor agreed that the medication could be used.	
<i>PK sampling:</i> Day 1 intensive PK sampling through 72 hours postdose in periods 1 and 2	
<i>Bioanalytical methods:</i> (b) (4) 1514-14	
RESULTS	
Demographics Fourteen subjects were enrolled and all completed the study. Mean age was 22 years and mean weight was 64 kg. All subjects were Caucasian.	
Protocol Deviations No major protocol deviations were reported.	
Concomitant medications There was no reported use of prohibited medications.	
Pharmacokinetics (CSR page 39) C _{max} and AUC ratios and 90% CIs for treatments A/B were within 80-125%.	
Safety There were no discontinuations due to AEs, SAEs, or deaths during the study.	

REVIEWER ASSESSMENT	
The study design is acceptable ☒ Yes ☐ No	
Study Conduct	
Protocol deviations do not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Use of prohibited concomitant medications did not affect the integrity of the study	☒ Yes ☐ No ☐ N/A
Bioanalytical method performance in acceptable	☒ Yes ☐ No
Study Results	
The study results are acceptable as reported by the sponsor ☒ Yes ☐ No	
Discussion	
In the phase 3 study, both the 240 mg and 480 mg tablets were used. This study showed that the two tablet strengths result in similar exposures at a dose of 480 mg.	
Labeling Recommendations	
The results of this study are consistent with proposed letermovir dosing of 480 mg QD or 240 mg QD when coadministered with cyclosporine.	
Relevant links within the submission	
CSR \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\p028\p028.pdf	
Bioanalytical \\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\p028\inter-laboratory-standardization-methods-quality-assurance.pdf	

Human PK studies in healthy Japanese volunteers

P027 – single ascending oral and IV doses in healthy Japanese subjects

Study #	P027	Study Period	1/16/14 – 4/22/14
Title	A Single Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of MK-8228 in Japanese Healthy Female Subjects		
Location of study site(s)	Tokyo, Japan		

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: Determine the safety and PK of oral and IV letermovir in Japanese subjects

Rationale: The reason for conducting a trial in Japanese subjects was not stated

Study design:

Randomized, placebo-controlled, double-blind, single dose escalation study.

Each subject received three escalating single oral or IV doses of letermovir or placebo with a 7 day wash-out between periods.

Part 1 (oral dosing)

Panel	SD [†]		
	Period 1	Period 2 [‡]	Period 3 [‡]
A (N = 8)	MK-8228 240 mg po	MK-8228 480 mg po	MK-8228 720 mg po
[†] Within each treatment period, 6 subjects were randomized to receive MK-8228 and 2 subjects to receive matching placebo according to a computer-generated allocation schedule. [‡] The suggested doses were to be adjusted downward based on evaluation of safety, tolerability, data observed in previous treatment periods. SD: single dose PO: oral dose			

Part 2 (IV dosing)

Panel	SD [†]		
	Period 1	Period 2 [‡]	Period 3 [‡]
B ^{§,} (N = 8)	MK-8228 240 mg IV	MK-8228 480 mg IV	MK-8228 960 mg IV
[†] Within each treatment period, 6 subjects were randomized to receive MK-8228 and 2 subjects to receive matching placebo according to a computer-generated allocation schedule. [‡] The suggested doses were to be adjusted downward based on evaluation of safety, tolerability, data observed in previous treatment periods. [§] Sixty (60) minutes infusion for 240, 480 and 960 mg dosing. MK-8228 and matching placebo were diluted in 0.9% saline. IV matching placebo contained the same excipients as MK-8228 active. SD: single dose IV: intravenous			

Population: Healthy Japanese females aged 20-55 years with a history of clinically significant disease

Dose Selection: Doses of 240-960 mg were chosen to bracket anticipated exposures in the phase 3 study

Administration: ☒ Fasted ☐ Fed

Formulation: PMF2 tablet and cyclodextrin IV formulation

Excluded concomitant medications: Subjects requiring medications within 2 weeks before administration

of study drug or during the study were not eligible. However, certain unspecified medications were permitted.

PK sampling: Intensive PK samples were collected after oral and IV dosing through 72 hours postdose.

Bioanalytical methods: Method BP-0032 was used to measure letermovir plasma concentrations.

RESULTS

Demographics

Sixteen subjects were enrolled and all completed the study. Mean age was 36 years and mean weight was 53 kg.

Protocol Deviations

Major deviations were defined as those that may significant impact the trial results or adversely impact the subjects. No major deviations were reported.

Concomitant medications

One subject used acetaminophen on day 20.

Pharmacokinetics (CSR page 56)

With increasing oral and IV doses, AUC increased more than proportionally (Table 82) and C_{max} increased slightly less than proportionally (data not shown). In a cross-study comparison at a dose of 480 mg, mean exposures were 1.5- to 2.5-fold higher in Japanese vs. non-Japanese subjects (Table 82).

Table 82. Statistical comparisons for dose proportionality and for PK in Japanese vs. non-Japanese.

Route	Comparison	Dose	PK parameter	Exposure ratio (90% CI)
PO	Dose proportionality	480 mg vs. 240 mg	AUC _{0-inf}	2.62 (2.15, 3.21)
		720 mg vs. 480 mg	AUC _{0-inf}	1.78 (1.46, 2.18)
	Japanese/non-Japanese	480 mg	AUC _{0-inf}	2.53 (1.88, 3.39)
			C _{max}	1.52 (1.16, 1.98)
IV	Dose proportionality	480 mg vs. 240 mg	AUC _{0-inf}	2.97 (2.69, 3.28)
		960 mg vs. 480 mg	AUC _{0-inf}	2.85 (2.58, 3.15)
	Japanese/non-Japanese	480 mg	AUC _{0-inf}	1.69 (1.28, 2.23)
			C _{max}	1.51 (1.25, 1.84)

PK parameters are shown below (Table 83, Table 84, Table 85).

Table 83. Part 1 letermovir PK parameters.

Part 1 (PO)				
Parameter	240 mg [†] (N=6)	480 mg [†] (N=6)	720 mg [†] (N=6)	rMSE [‡]
AUC _{0-∞} (ng/mL•hr) [†]	62404.9 (44943.1,86651.2)	163806.1 (117970.7,227450.1)	292124.4 (210383.6,405624.0)	0.172
AUC _{0-12hr} (ng/mL•hr) [†]	50105.8 (38015.0,66042.2)	118481.4 (89891.1,156164.9)	199905.0 (151666.7,263485.6)	0.144
AUC _{0-24hr} (ng/mL•hr) [†]	58175.7 (42161.6,80272.4)	147981.7 (107246.5,204189.2)	261833.9 (189758.4,361285.6)	0.161
C _{max} (ng/mL) [†]	11022.7 (8842.9,13739.7)	18653.2 (14964.6,23251.1)	29439.5 (23617.9,36696.1)	0.133
T _{max} (hr)	2.25 (1.00,3.00)	3.00 (3.00,5.00)	4.00 (2.50,8.00)	--
t _{1/2} (hr) [§]	9.96 (23)	9.66 (37)	13.34 (50)	--

[†] Back-transformed least squares mean and 95% confidence interval from mixed effects model performed on natural log-transformed values.
[‡] rMSE: Square root of conditional mean squared error (residual error) from linear mixed effects model. rMSE*100% approximates the within-subject %CV on the raw scale.
[†] Subjects in Panel A were given PO of 240mg, 480mg, 720mg or placebo.
^{||} Median (range)
[§] Geometric mean (%CV)

Source: CSR, page 57.

Table 84. Comparison of letermovir PK parameters between Japanese and non-Japanese subjects.

		Japanese			non-Japanese			Ratio (Japanese/non-Japanese)		rMSE [‡]
PK Parameter	Dose (mg)	N	GM [†]	95% CI [†]	N	GM [†]	95% CI [†]	GMR [†]	90% CI [†]	
AUC _{0-∞} (ng/mL •hr)	240	6	61790.8	(45811.0,83344.7)	27	41348.2	(35908.4,47612.1)	1.49	(1.14,1.97)	0.359
	480	6	179573.7	(133200.4,242091.6)	14	71105.2	(58474.8,86463.8)	2.53	(1.88,3.39)	0.348
	720	6	302583.9	(179595.4,509795.8)	-	--	--	--	--	0.497
AUC _{0-12hr} (ng/mL •hr)	240	6	49197.1	(37744.5,64124.5)	12	23512.2	(19494.7,28357.7)	2.09	(1.60,2.73)	0.306
	480	6	128214.0	(93493.7,175828.0)	-	--	--	--	--	0.301
	720	6	207413.4	(152140.8,282766.4)	18	110640.2	(92513.8,132318.0)	1.87	(1.39,2.52)	0.366
C _{max} (ng/mL)	240	6	10830.6	(8716.8,13457.0)	39	7725.3	(7094.6,8412.0)	1.40	(1.15,1.70)	0.264
	480	6	19613.0	(14975.0,25687.5)	14	12918.3	(10826.7,15414.1)	1.52	(1.16,1.98)	0.315
	720	6	30593.8	(23815.5,39301.4)	18	18601.7	(16097.2,21495.8)	1.64	(1.29,2.09)	0.296

[†] Back-transformed least squares mean and confidence interval estimated at each dose from an analysis of variance model performed on the log-transformed values.
[‡] rMSE: Square root of conditional mean squared error (residual error) from an analysis of variance model. rMSE*100% approximates the %CV on the raw scale.
⁻⁻⁻ historical data is not available

Source: CSR, page 63.

Table 85. Part 2 letermovir PK parameters.

Part 2 (IV)				
Parameter	240 mg ^{¶¶} (N=6)	480 mg ^{¶¶} (N=6)	960 mg ^{¶¶} (N=6)	rMSE [‡]
AUC _{0-∞} (ng/mL•hr) [†]	58851.3 (47035.9,73634.7)	174891.1 (139778.8,218823.5)	498939.2 (398768.9,624272.1)	0.085
AUC _{0-24hr} (ng/mL•hr) [†]	55321.8 (44145.7,69327.2)	163764.4 (130680.8,205223.5)	462943.1 (369419.6,580143.2)	0.092
C _{eoI} (ng/mL) [†]	18637.9 (16109.2,21563.5)	40565.7 (35062.0,46933.3)	81406.4 (70361.7,94184.8)	0.079
t _{1/2} (hr) [§]	11.79 (64)	10.79 (34)	12.37 (49)	--
V _z (L) [†]	71.1 (43.2,116.9)	48.3 (29.3,79.4)	33.1 (20.1,54.5)	0.330
CL (L/hr) [†]	4.1 (3.3,5.1)	2.7 (2.2,3.4)	1.9 (1.5,2.4)	0.085

[†] Back-transformed least squares mean and 95% confidence interval from mixed effects model performed on natural log-transformed values.
[‡] rMSE: Square root of conditional mean squared error (residual error) from linear mixed effects model. rMSE*100% approximates the within-subject %CV on the raw scale.
^{¶¶} Subjects in Panel B were given IV of 240mg, 480, 960mg or placebo.
[§] Geometric mean (%CV)

Source: CSR, page 68.

Safety

There were no discontinuations due to AEs, SAEs, or deaths.

REVIEWER ASSESSMENTThe study design is acceptable ☒ Yes ☐ No**Study Conduct**

- Protocol deviations do not affect the integrity of the study ☒ Yes ☐ No ☐ N/A
- Use of prohibited concomitant medications did not affect the integrity of the study ☒ Yes ☐ No ☐ N/A
- Bioanalytical method performance was acceptable ☒ Yes ☐ No

Study ResultsThe study results are acceptable as reported by the sponsor ☒ Yes ☐ No**Discussion and labeling recommendations**

Letermovir exposures in Asian subjects were evaluated in several studies. These findings are discussed in section 2 of the QBR.

Relevant links within the submission

CSR

<\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\p027\p027.pdf>

Bioanalytical

<\\cdsesub1\evsprod\nda209939\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\p027\publications-based-on-trial.pdf>

In vitro studies

Metabolism characterization

Enzymes Involved in Biotransformation of BAY 73-6327 in Man In Vitro																					
Study #	PK021																				
Link	\\cdsesub1\evsprod\nda209939\0000\m4\42-stud-rep\422-pk\4226-pk-drug-interact\pk021mk8228.pdf																				
Objectives	Determine which enzymes are involved in the metabolism of letermovir																				
METHODS																					
System	Human liver microsomes and recombinant CYP isoforms																				
Was an appropriate system used?	☒ Yes ☐ No																				
Controls concentrations	<table border="1"> <thead> <tr> <th>Enzyme</th> <th>Inhibitor (concentration)</th> </tr> </thead> <tbody> <tr> <td>CYP1A2</td> <td>Furafylline (20 µM)</td> </tr> <tr> <td>CYP2C8</td> <td>Quercetin (10 and 50 µM)</td> </tr> <tr> <td>CYP2C9</td> <td>Sulfaphenazole 10 µM</td> </tr> <tr> <td>CYP2C19</td> <td>Benzyphenobarbital µM</td> </tr> <tr> <td>CYP2D6</td> <td>Quinidine 5 µM</td> </tr> <tr> <td>CYP2E1</td> <td>Methylpyrazole 200 µM</td> </tr> <tr> <td>CYP3A4</td> <td>Azamulin 1 and 10 µM</td> </tr> <tr> <td>CYP3A4</td> <td>Ketoconazole 1 and 10 µM</td> </tr> <tr> <td>Nonspecific</td> <td>1-Amino-1H-benzotriazole 1000 µM</td> </tr> </tbody> </table>	Enzyme	Inhibitor (concentration)	CYP1A2	Furafylline (20 µM)	CYP2C8	Quercetin (10 and 50 µM)	CYP2C9	Sulfaphenazole 10 µM	CYP2C19	Benzyphenobarbital µM	CYP2D6	Quinidine 5 µM	CYP2E1	Methylpyrazole 200 µM	CYP3A4	Azamulin 1 and 10 µM	CYP3A4	Ketoconazole 1 and 10 µM	Nonspecific	1-Amino-1H-benzotriazole 1000 µM
Enzyme	Inhibitor (concentration)																				
CYP1A2	Furafylline (20 µM)																				
CYP2C8	Quercetin (10 and 50 µM)																				
CYP2C9	Sulfaphenazole 10 µM																				
CYP2C19	Benzyphenobarbital µM																				
CYP2D6	Quinidine 5 µM																				
CYP2E1	Methylpyrazole 200 µM																				
CYP3A4	Azamulin 1 and 10 µM																				
CYP3A4	Ketoconazole 1 and 10 µM																				
Nonspecific	1-Amino-1H-benzotriazole 1000 µM																				
Are controls and control concentrations appropriate?	☒ Yes ☐ No All of the control inhibitors were listed on the FDA Drug Interaction website with the exception of benzyphenobarbital, which has been identified as a selective CYP2C19 inhibitor in publications (for example, PMID 15155548).																				
Test (substrate or inhibitor) drug concentrations	Letermovir (substrate) 9.9 µM																				
Were test drug concentrations appropriate?	☒ Yes ☐ No																				

RESULTS AND LABEL RECOMMENDATIONS

Enzyme	Is letermovir a substrate based on HLM experiments with CYP inhibitors?	Is letermovir a substrate based on incubations with recombinant enzymes?	Proposed label recommendation	Do we agree with the proposed label recommendation?
CYP1A2	No	No	Section 12.3: "In vitro results indicate that letermovir is a substrate of ... UGT1A1, and UGT1A3". (b) (4) oxidative metabolism is considered to be a minor elimination pathway based on in vivo human data."	☒ Yes ☐ No
CYP2A6		No		
CYP2B6		No		
CYP2C8	No	No		
CYP2C9	No	No		
CYP2C18		No		
CYP2C19	No	No		
CYP2D6	No	Yes		
CYP2E1	No	No		
CYP2J2		Yes		
CYP3A4	Yes	Yes		
CYP3A5	Yes	Yes		
CYP4A11		No		
UGT1A1		Yes		
UGT1A3		Yes		
UGT1A6		No		
UGT1A7		No		
UGT1A8		No		
UGT1A9		No		
UGT1A10		No		
UGT2B4		No		
UGT2B7		No		
UGT2B15		No		
UGT2B17		No		

Protein binding

Investigation of the Stability in Plasma, Binding to Plasma Proteins, Reversibility of Binding, and Erythrocyte/Plasma Partitioning of [14C]BAY 73-6327 in Vitro	
Study #	PK011
Link	\\cdsesub1\evsprod\nda209939\0000\m4\42-stud-rep\422-pk\4223-distrib\pk011mk8228.pdf
Objectives	Determine letermovir stability in plasma, protein binding, and blood cell partitioning
METHODS	
- Stability in plasma was determined after incubation of human plasma for 3 hours at 37°C - Binding to human plasma proteins was determined using ultrafiltration. The letermovir concentration range was 0.2-97 mg/L. Protein binding was also assessed as a function of pH 7.2-7.8. - Reversibility of binding was assessed by incubating letermovir with plasma, then determining radioactivity recovery after precipitating plasma proteins with acetonitrile. - Blood cell partitioning was assessed by incubating letermovir 0.1-10 mg/L with whole blood, separating blood cells by centrifugation, then measuring letermovir concentrations in blood and plasma.	
RESULTS (as reported by the applicant)	
- Letermovir was stable at 3 hours at 37°C - Fraction unbound in human plasma was 1.33% at 50 mg/L and 2.14% at 100 mg/L. The main binding protein was serum albumin; α_1-acid glycoprotein contributed moderately. - Fraction unbound was unchanged across a pH of 7.2-7.8. - Protein binding was fully reversible - The human blood to plasma ratio is 0.56	
LABEL RECOMMENDATIONS	
We agree with the relevant proposed labeling statements in section 12.3:	
(b) (4)	

CYP induction

Study #	Title																																								
PK002	EVALUATION OF INDUCTION POTENTIAL OF CYTOCHROME P450 ISOFORMS BY L-005225800 IN CRYOPRESERVED HUMAN HEPATOCYTES																																								
PK026	Evaluation of the CYP Induction Potential of BAY 73-6327 in Cultured Human Hepatocytes																																								
PK031	Evaluation of MK-8228 as an Inducer of CYP3A4 in Cryopreserved Human Hepatocytes and Predicting the Magnitude of Drug Interaction Using the Relative Induction Score (RIS) Model (PK031)																																								
Link	PK002 \\cdsesub1\evsprod\nda209939\0000\m4\42-stud-rep\422-pk\4226-pk-drug-interact\pk002mk8228.pdf PK026 \\cdsesub1\evsprod\nda209939\0000\m4\42-stud-rep\422-pk\4226-pk-drug-interact\pk026mk8228.pdf PK031 \\cdsesub1\evsprod\nda209939\0000\m4\42-stud-rep\422-pk\4226-pk-drug-interact\pk031mk8228.pdf																																								
Objectives	Determine if letermovir is an inducer of CYP enzymes																																								
METHODS																																									
System and controls	<table><tr><th>Study</th><th>System</th><th># donors</th><th>Incubation time</th></tr><tr><td>PK002</td><td>Cryopreserved human hepatocytes</td><td>3</td><td>48 hours</td></tr><tr><td>PK026</td><td>Cultured human hepatocytes</td><td>3</td><td>5 days</td></tr><tr><td>PK031</td><td>Cryopreserved human hepatocytes</td><td>1</td><td>48 hours</td></tr></table> <table><tr><th></th><th>PK002</th><th>PK026</th><th>PK031</th></tr><tr><th>CYP</th><th colspan="3">Positive control inducer (concentration)</th></tr><tr><td>CYP1A2</td><td>Omeprazole 50 µM</td><td>Omeprazole</td><td rowspan="3">NA</td></tr><tr><td>CYP2B6</td><td>Phenobarbital 1000 µM</td><td>Rifampicin</td></tr><tr><td>CYP2C19</td><td>NA</td><td rowspan="2">Rifampicin</td></tr><tr><td>CYP3A4/5</td><td>Rifampicin 10 µM</td><td>None</td></tr></table>				Study	System	# donors	Incubation time	PK002	Cryopreserved human hepatocytes	3	48 hours	PK026	Cultured human hepatocytes	3	5 days	PK031	Cryopreserved human hepatocytes	1	48 hours		PK002	PK026	PK031	CYP	Positive control inducer (concentration)			CYP1A2	Omeprazole 50 µM	Omeprazole	NA	CYP2B6	Phenobarbital 1000 µM	Rifampicin	CYP2C19	NA	Rifampicin	CYP3A4/5	Rifampicin 10 µM	None
Study	System	# donors	Incubation time																																						
PK002	Cryopreserved human hepatocytes	3	48 hours																																						
PK026	Cultured human hepatocytes	3	5 days																																						
PK031	Cryopreserved human hepatocytes	1	48 hours																																						
	PK002	PK026	PK031																																						
CYP	Positive control inducer (concentration)																																								
CYP1A2	Omeprazole 50 µM	Omeprazole	NA																																						
CYP2B6	Phenobarbital 1000 µM	Rifampicin																																							
CYP2C19	NA	Rifampicin																																							
CYP3A4/5	Rifampicin 10 µM		None																																						
Was the study design appropriate?	<table><tr><th>Study</th><th>Was the study design appropriate?</th></tr><tr><td>PK002</td><td>☒ Yes ☐ No</td></tr><tr><td>PK026</td><td>☒ Yes ☐ No</td></tr><tr><td>PK031</td><td>☐ Yes ☒ No One hepatocyte donor was used and there was no positive control. FDA guidance recommends three donors and use of positive controls.</td></tr></table>				Study	Was the study design appropriate?	PK002	☒ Yes ☐ No	PK026	☒ Yes ☐ No	PK031	☐ Yes ☒ No One hepatocyte donor was used and there was no positive control. FDA guidance recommends three donors and use of positive controls.																													
Study	Was the study design appropriate?																																								
PK002	☒ Yes ☐ No																																								
PK026	☒ Yes ☐ No																																								
PK031	☐ Yes ☒ No One hepatocyte donor was used and there was no positive control. FDA guidance recommends three donors and use of positive controls.																																								
Were test drug concentrations appropriate?	In the phase 3 study, median Cmax was 6.6 µM and median Cmin was 1.4 µM. <table><tr><th>Study</th><th>Letermovir concentration</th><th>Were test drug concentrations appropriate?</th></tr></table>				Study	Letermovir concentration	Were test drug concentrations appropriate?																																		
Study	Letermovir concentration	Were test drug concentrations appropriate?																																							

	PK002	0.1 – 20 µM		☒ Yes ☐ No				
	PK026	5-1000 ng/mL (0.009 – 1.75 µM)		☐ Yes ☒ No The maximum concentrations evaluated were approximately three times lower than Cmax.				
	PK031	0.1 – 100 µM		☒ Yes ☐ No				
RESULTS AND LABEL RECOMMENDATIONS								
	PK002	PK026	PK031	PK002	PK026	PK031		
CYP	Fold change mRNA			Fold change enzyme activity			Proposed label recommendation	Do we agree with the proposed label recommendation?
CYP1A2	No change	No change	NA	No change	No change	NA	None	☐ Yes ☒ No Labeling should state that letermovir is not a CYP1A2 inducer.
CYP2B6	Max 1.0-2.4 fold (1-8% of positive control)	No change		2.4-4.7 fold (29-65% of positive control)	No change		Section 12.3: “Letermovir is an inducer of CYP2B6 in vitro; the clinical relevance is unknown”	☒ Yes ☐ No
CYP2C19	NA	No change		NA	No change		Section 12.3: “Co-administration of TRADEMARK reduced the exposure of voriconazole, most likely due to the induction of voriconazole elimination pathways, CYP2C9 and CYP2C19.”	☐ Yes ☒ No Given that CYP2C19 induction was not observed, it is unclear why the applicant proposes to state that induction of CYP2C19 is likely. We will ask the applicant for their rationale.
CYP3A4/5	Max of 5.4-19.6 fold (42-69% of positive control)	No change	Max 4.8 fold (49% of positive control)	No change	No change	Not evaluated	Section 12.3: “Letermovir is a time-dependent inhibitor and inducer of CYP3A in vitro.”	☒ Yes ☐ No Although the study design for PK031 was not sufficient for labeling, CYP3A induction was also demonstrated in study PK002.

CYP inhibition

Study #	Title																																																							
PK018	In Vitro Evaluation of AIC090027 as an Inhibitor of Human Cytochrome P450 Enzymes																																																							
PK019	Determination of the Inhibitory Potency of BAY 73-6327 Towards Human CYP Isoforms																																																							
Link	PK018 \\cdsesub1\evsprod\nda209939\0000\m4\42-stud-rep\422-pk\4226-pk-drug-interact\pk018mk8228.pdf PK019 \\cdsesub1\evsprod\nda209939\0000\m4\42-stud-rep\422-pk\4226-pk-drug-interact\pk019mk8228.pdf																																																							
Objectives	Determine if letermovir is an inhibitor of CYP enzymes																																																							
METHODS																																																								
System	<table border="1"> <thead> <tr> <th>Study</th><th>System</th></tr> </thead> <tbody> <tr> <td>PK018</td><td>Human liver microsomes</td></tr> <tr> <td>PK019</td><td>Human liver microsomes or recombinant enzymes</td></tr> </tbody> </table>	Study	System	PK018	Human liver microsomes	PK019	Human liver microsomes or recombinant enzymes																																																	
Study	System																																																							
PK018	Human liver microsomes																																																							
PK019	Human liver microsomes or recombinant enzymes																																																							
Was an appropriate system used?	☒ Yes ☐ No																																																							
Controls	<table border="1"> <thead> <tr> <th></th><th>PK018</th><th>PK019</th><th>PK018</th><th>PK019</th></tr> </thead> <tbody> <tr> <td>Enzyme</td><td colspan="2">Probe substrate</td><td colspan="2">Probe inhibitor</td></tr> <tr> <td>CYP1A2</td><td colspan="2">Phenacetin</td><td>A-Naphthoflavone</td><td>Fluvoxamine</td></tr> <tr> <td>CYP2A6</td><td colspan="2">Coumarin</td><td>Nicotine</td><td>None</td></tr> <tr> <td>CYP2B6</td><td>Efavirenz</td><td>NA</td><td>Orphenadrine</td><td>NA</td></tr> <tr> <td>CYP2C8</td><td colspan="2">Amodiaquine</td><td>Montelukast</td><td>Quercetin</td></tr> <tr> <td>CYP2C9</td><td colspan="2">Diclofenac</td><td colspan="2">Sulphaphenazole</td></tr> <tr> <td>CYP2C19</td><td colspan="2">Mephenytoin</td><td>Modafinil</td><td>None</td></tr> <tr> <td>CYP2D6</td><td colspan="2">Dextromethorphan</td><td>Quinidine</td><td>Fluoxetine</td></tr> <tr> <td>CYP2E1</td><td colspan="2">Chlorzoxazone</td><td>4-methylpyrazole</td><td>None</td></tr> <tr> <td>CYP3A4/5</td><td colspan="2">Midazolam</td><td colspan="2">Ketoconazole</td></tr> </tbody> </table>		PK018	PK019	PK018	PK019	Enzyme	Probe substrate		Probe inhibitor		CYP1A2	Phenacetin		A-Naphthoflavone	Fluvoxamine	CYP2A6	Coumarin		Nicotine	None	CYP2B6	Efavirenz	NA	Orphenadrine	NA	CYP2C8	Amodiaquine		Montelukast	Quercetin	CYP2C9	Diclofenac		Sulphaphenazole		CYP2C19	Mephenytoin		Modafinil	None	CYP2D6	Dextromethorphan		Quinidine	Fluoxetine	CYP2E1	Chlorzoxazone		4-methylpyrazole	None	CYP3A4/5	Midazolam		Ketoconazole	
	PK018	PK019	PK018	PK019																																																				
Enzyme	Probe substrate		Probe inhibitor																																																					
CYP1A2	Phenacetin		A-Naphthoflavone	Fluvoxamine																																																				
CYP2A6	Coumarin		Nicotine	None																																																				
CYP2B6	Efavirenz	NA	Orphenadrine	NA																																																				
CYP2C8	Amodiaquine		Montelukast	Quercetin																																																				
CYP2C9	Diclofenac		Sulphaphenazole																																																					
CYP2C19	Mephenytoin		Modafinil	None																																																				
CYP2D6	Dextromethorphan		Quinidine	Fluoxetine																																																				
CYP2E1	Chlorzoxazone		4-methylpyrazole	None																																																				
CYP3A4/5	Midazolam		Ketoconazole																																																					
Were controls appropriate?	☒ Yes ☐ No																																																							
Test drug concentrations	PK018: letermovir 0.1-100 μ M PK019: letermovir 1.5-50 μ M																																																							
Were test drug concentrations appropriate?	☒ Yes ☐ No																																																							

RESULTS AND LABEL RECOMMENDATIONS

	PK108	PK019		
CYP	IC ₅₀ (μM)		Proposed label recommendation regarding CYP inhibition	Do we agree with the proposed label recommendation?
CYP1A2	>100	>50	None	☒ Yes ☐ No The R value for CYP2B6 is less than the threshold to require a human interaction study
CYP2A6				
CYP2B6	54 ¹	NA		
CYP2C8	0.34 ^{1,2}	0.15	Section 12.3: "Letermovir is a reversible inhibitor of CYP2C8 in vitro"	☒ Yes ☐ No
CYP2C9	>100	>50	None	☐ Yes ☒ No The absence of an effect should be stated in labeling
CYP2C19				
CYP2D6				
CYP2E1				
CYP3A4/5	Rev: >100 TDI: 6.7 ²	Rev: >50 TDI: 9.9 ²	Section 12.3: "Letermovir is a time-dependent inhibitor and inducer of CYP3A in vitro"	☒ Yes ☐ No

¹Mixed competitive-noncompetitive inhibition model. ²R values were not calculated because a mechanistic prediction (CYP2C8) or a human interaction study (CYP3A4) was conducted. ND = not determined as IC₅₀ was >100 μM; rev = reversible.

Transporter studies

PK033 - Pgp

Evaluation of MK-8228 as a Substrate of Human P-gp (PK033)											
Study #	PK033										
Link	\\cdsesub1\evsprod\nda209939\0000\m4\42-stud-rep\422-pk\4226-pk-drug-interact\pk033mk8228.pdf										
Objectives	Determine if letermovir is a substrate of Pgp										
METHODS											
System	Transfected LLC-PK1 cells										
Was an appropriate system used?	☒ Yes ☐ No										
Control concentrations	<table border="1"> <thead> <tr> <th>Transporter</th> <th>Substrate (concentration)</th> <th>Inhibitor (concentration)</th> </tr> </thead> <tbody> <tr> <td>Pgp</td> <td>Verapamil 1 μM</td> <td></td> </tr> </tbody> </table>					Transporter	Substrate (concentration)	Inhibitor (concentration)	Pgp	Verapamil 1 μ M	
Transporter	Substrate (concentration)	Inhibitor (concentration)									
Pgp	Verapamil 1 μ M										
Are controls and control concentrations appropriate?	☒ Yes ☐ No										
Test (substrate or inhibitor) drug concentrations	Letermovir (substrate) 0.1 and 1 μ M										
Were test drug concentrations appropriate?	☒ Yes ☐ No										
RESULTS AND LABEL RECOMMENDATIONS											
Transporter	Substrate	Inhibitor	IC ₅₀ (μ M)	Proposed label recommendation	Do we agree with the proposed label recommendation?						
Pgp	Yes			Section 12.3: "In vitro results indicate that letermovir is a substrate of ... P-gp"	☒ Yes ☐ No						

PK001 – OATP1B1, OATP1B3, OAT3, OCT2, BCRP

Interactions of MK-8228 with the Human Liver Uptake Transporters, OATP1B1 and OATP1B3, the Human Renal Uptake Transporters, OAT3 and OCT2, and the Human Efflux Transporter, BCRP (PK001)																																																								
Study #	PK001																																																							
Link	\\cdsesub1\evsprod\nda209939\0000\m4\42-stud-rep\422-pk\4226-pk-drug-interact\pk001mk8228.pdf																																																							
Objectives	- Determine if letermovir is an inhibitor of OATP1B1, OATP1B3, OAT3, or OCT2 - Determine if letermovir is a substrate of BCRP																																																							
METHODS																																																								
System	BCRP, OATP1B1, OATP1B3, OAT3: MDCKII cells OCT2: CHO-K1 cells																																																							
Were appropriate systems used?	☒ Yes ☐ No																																																							
Control concentrations	<table border="1"> <thead> <tr> <th>Transporter</th> <th>Compound</th> <th>Substrate</th> <th>Inhibitor</th> <th>Concentrations (μM)</th> </tr> </thead> <tbody> <tr> <td>BCRP</td> <td>Ko143</td> <td></td> <td>X</td> <td>2</td> </tr> <tr> <td></td> <td>Prazosin</td> <td>X</td> <td></td> <td>5</td> </tr> <tr> <td>OATP1B1</td> <td>Pitavastatin</td> <td>X</td> <td></td> <td>0.1</td> </tr> <tr> <td></td> <td>Cyclosporine</td> <td></td> <td>X</td> <td>5</td> </tr> <tr> <td>OATP1B3</td> <td>Sulfobromophthalein</td> <td>X</td> <td></td> <td>0.1</td> </tr> <tr> <td></td> <td>Cyclosporine</td> <td></td> <td>X</td> <td>5</td> </tr> <tr> <td>OAT3</td> <td>Estrone sulfate</td> <td>X</td> <td></td> <td>1</td> </tr> <tr> <td></td> <td>Probenecid</td> <td></td> <td>X</td> <td>1000</td> </tr> <tr> <td>OCT2</td> <td>Metformin</td> <td>X</td> <td></td> <td>10</td> </tr> <tr> <td></td> <td>Quinidine</td> <td></td> <td>X</td> <td>100</td> </tr> </tbody> </table>	Transporter	Compound	Substrate	Inhibitor	Concentrations (μM)	BCRP	Ko143		X	2		Prazosin	X		5	OATP1B1	Pitavastatin	X		0.1		Cyclosporine		X	5	OATP1B3	Sulfobromophthalein	X		0.1		Cyclosporine		X	5	OAT3	Estrone sulfate	X		1		Probenecid		X	1000	OCT2	Metformin	X		10		Quinidine		X	100
Transporter	Compound	Substrate	Inhibitor	Concentrations (μM)																																																				
BCRP	Ko143		X	2																																																				
	Prazosin	X		5																																																				
OATP1B1	Pitavastatin	X		0.1																																																				
	Cyclosporine		X	5																																																				
OATP1B3	Sulfobromophthalein	X		0.1																																																				
	Cyclosporine		X	5																																																				
OAT3	Estrone sulfate	X		1																																																				
	Probenecid		X	1000																																																				
OCT2	Metformin	X		10																																																				
	Quinidine		X	100																																																				
Are controls and control concentrations appropriate?	☒ Yes ☐ No All controls were listed on the FDA Drug Interaction website with the exception of sulfobromophthalein and quinidine. Sulfobromophthalein has been evaluated as a substrate of OATP1B3 in several publications. Several studies report quinidine as an OCT2 inhibitor in PharmaPendium.																																																							
Test (substrate or inhibitor) drug concentrations	<table border="1"> <thead> <tr> <th>Transporter</th> <th>Substrate</th> <th>Inhibitor</th> <th>Letermovir concentrations (μM)</th> </tr> </thead> <tbody> <tr> <td>BCRP</td> <td>X</td> <td></td> <td>1</td> </tr> <tr> <td>OATP1B1, OATP1B3, OAT3</td> <td></td> <td>X</td> <td>Multiple, ≤25</td> </tr> <tr> <td>OCT2</td> <td></td> <td>X</td> <td>Multiple, ≤100</td> </tr> </tbody> </table>	Transporter	Substrate	Inhibitor	Letermovir concentrations (μM)	BCRP	X		1	OATP1B1, OATP1B3, OAT3		X	Multiple, ≤25	OCT2		X	Multiple, ≤100																																							
Transporter	Substrate	Inhibitor	Letermovir concentrations (μM)																																																					
BCRP	X		1																																																					
OATP1B1, OATP1B3, OAT3		X	Multiple, ≤25																																																					
OCT2		X	Multiple, ≤100																																																					
Were test drug concentrations appropriate?	☒ Yes ☐ No In the phase 3 study, letermovir median Cmax was 3786 ng/mL (6.6 μM) and median Cmin was 776 ng/mL (1.4 μM).																																																							

RESULTS AND LABEL RECOMMENDATIONS

Transporter	Substrate	Inhibitor	IC ₅₀ (μM)	R value ¹	Proposed label recommendation	Do we agree with the proposed label recommendation?
BCRP	Unclear			NA	None	☒ Yes ☐ No Studies showing clinically significant effects or an absence of an effect should be included in labeling. However, the result of this study is an unclear effect.
OATP1B1		Yes	2.9 ± 0.4		Section 7.1: “Letermovir is an inhibitor of OATP1B1/3 transporters”	☒ Yes ☐ No
OATP1B3		Yes	1.1 ± 0.1		Section 12.3: “Letermovir inhibited ... OAT3 ... in vitro.”	
OAT3		Yes	2.5 ± 0.3			
OCT2		No	~100	0.0009	None	☐ Yes ☒ No The absence of an effect of letermovir on OCT2 should be stated in labeling.

¹R values were not calculated for OATP1B1/3 or OAT3 because clinical interaction studies were done with atorvastatin and acyclovir, respectively. Atorvastatin is a recommended OATP substrate per the FDA Drug Interaction website. Acyclovir was reported to be an OAT3 substrate (PMID 22190696) and would likely be coadministered with letermovir in the HSCT population.

PK027 - Pgp, MRP2, BCRP, BSEP

In vitro interaction studies of AIC090027 with human ABCB1/P-gp (MDR1), ABCC2 (MRP2), ABCG2 (BCRP) and BSEP ABC efflux transporters																	
Study #	PK027																
Link	\\cdsesub1\evsprod\nda209939\0000\m4\42-stud-rep\422-pk\4226-pk-drug-interact\pk027mk8228.pdf																
Objectives	- Determine if letermovir is an inhibitor of Pgp, MRP2, BCRP, and BSEP (part 1) - Determine if letermovir is a substrate of Pgp, MRP2, BCRP, and BSEP (part 2)																
METHODS																	
System	Transfected Sf9 vesicles																
Was an appropriate system used?	☒ Yes ☐ No																
Control concentrations	<table border="1"> <thead> <tr> <th>Transporter</th> <th>Substrate (concentration)</th> <th>Inhibitor (concentration)</th> </tr> </thead> <tbody> <tr> <td>Pgp</td> <td>NMQ 2 μM</td> <td>Verapamil 100 μM</td> </tr> <tr> <td>MRP2</td> <td>E₂17βG 50 μM</td> <td>Benzbromarone 100 μM</td> </tr> <tr> <td>BCRP</td> <td>MTX 100 μM</td> <td>Ko134 1 μM</td> </tr> <tr> <td>BSEP</td> <td>Taurocholate 2 μM</td> <td>Cyclosporin A 20 μM</td> </tr> </tbody> </table> E₂17βG = estradiol-17-β-D-glucuronide; MTX = methotrexate; NMQ = N-methyl-quinidine.		Transporter	Substrate (concentration)	Inhibitor (concentration)	Pgp	NMQ 2 μ M	Verapamil 100 μ M	MRP2	E ₂ 17 β G 50 μ M	Benzbromarone 100 μ M	BCRP	MTX 100 μ M	Ko134 1 μ M	BSEP	Taurocholate 2 μ M	Cyclosporin A 20 μ M
Transporter	Substrate (concentration)	Inhibitor (concentration)															
Pgp	NMQ 2 μ M	Verapamil 100 μ M															
MRP2	E ₂ 17 β G 50 μ M	Benzbromarone 100 μ M															
BCRP	MTX 100 μ M	Ko134 1 μ M															
BSEP	Taurocholate 2 μ M	Cyclosporin A 20 μ M															
Are controls and control concentrations appropriate?	☒ Yes ☐ No Quinidine, verapamil, and Ko134 were listed as recommended substrates/inhibitors on the FDA DDI webpage. Data supporting the use of benzbromarone, MTX, and cyclosporine as probe substrates or inhibitors were found in Pharmapendium. E217 β G and taurocholate were found to have been used as probe substrates in published transport studies.																
Test (substrate or inhibitor) drug concentrations	Letermovir as inhibitor: 0.14, 0.41, 1.2, 3.7, 11, 33 and 100 μ M Letermovir as substrate: 1, 10, and 100 μ M																
Were test drug concentrations appropriate?	☒ Yes ☐ No Plasma concentrations in patients are ~1-6 μ M.																

RESULTS AND LABEL RECOMMENDATIONS

Transporter	Substrate	Inhibitor	IC ₅₀ (μM) ¹	Proposed label recommendation	Do we agree with the proposed label recommendation?
Pgp	No			Section 12.3: “In vitro results indicate that letermovir is a substrate of ... P-gp”	☒ Yes ☐ No Letermovir was found to be a Pgp substrate in several other studies
MRP2	No				☐ Yes ☒ No Results demonstrating the absence of an effect should be described in labeling
BCRP	No				
BSEP	Yes				☒ Yes ☐ No BSEP is not mentioned in current guidance
Pgp		Yes	13.7	Section 12.3: “Letermovir inhibited efflux transporters P-gp, breast cancer resistance protein (BCRP), bile salt export pump (BSEP), multidrug resistance-associated protein 2 (MRP2... in vitro”	☒ Yes ☐ No
MRP2		Yes	47.2		
BCRP		Yes	29.1		
BSEP		Yes	30.4		

¹R values were not calculated for inhibition of Pgp or BCRP because clinical interaction studies were done with digoxin and cyclosporine, respectively. Equations for calculation of R values for MRP2 or BSEP are not listed in FDA guidance.

PK028 – OATP1B1, OATP1B3, OATP2B1, OCT1, OAT1

In vitro Interaction Studies of AIC090027 with human OATP1B1 (OATP2, OATP-C), OATP1B3 (OATPS), OATP2B1 (OATP-B), OCT1 and OAT1 Uptake Transporters																				
Study #	PK028																			
Link	\\cdsesub1\evsprod\nda209939\0000\m4\42-stud-rep\422-pk\4226-pk-drug-interact\pk028mk8228.pdf																			
Objectives	Determine if letermovir is an inhibitor (part 1) or substrate (part 2) of OATP1B1, OATP1B3, OATP2B1, OCT1, and OAT1																			
METHODS																				
System	Transfected CHO cells																			
Was an appropriate system used?	☒ Yes ☐ No																			
Control concentrations	<table border="1"> <thead> <tr> <th>Transporter</th> <th>Substrate</th> <th>Inhibitor</th> </tr> </thead> <tbody> <tr> <td>OATP1B1</td> <td>E3S 0.1 µM</td> <td>Cerivastatin 100 µM</td> </tr> <tr> <td>OATP1B3</td> <td>Fluo-3 10 µM</td> <td>Fluvastatin 30 µM</td> </tr> <tr> <td>OATP2B1</td> <td>E3S 1 µM</td> <td>Fluvastatin 10 µM</td> </tr> <tr> <td>OAT1</td> <td>PAH 0.5 µM</td> <td>Benzbromarone 200 µM</td> </tr> <tr> <td>OCT1</td> <td>TEA 3.6 µM</td> <td>Verapamil 100 µM</td> </tr> </tbody> </table> E3S = estrone-3-sulfate; Fluo-3 = 4-(2, 7-Dichloro-6-hydroxy-3-oxo-9-xanthenyl)-4'-methyl-2,2'-(ethylenedioxy)dianiline-N,N,N',N'-tetraacetic acid; PAH = p-aminohippuric acid; TEA = tetraethylammonium chloride.		Transporter	Substrate	Inhibitor	OATP1B1	E3S 0.1 µM	Cerivastatin 100 µM	OATP1B3	Fluo-3 10 µM	Fluvastatin 30 µM	OATP2B1	E3S 1 µM	Fluvastatin 10 µM	OAT1	PAH 0.5 µM	Benzbromarone 200 µM	OCT1	TEA 3.6 µM	Verapamil 100 µM
Transporter	Substrate	Inhibitor																		
OATP1B1	E3S 0.1 µM	Cerivastatin 100 µM																		
OATP1B3	Fluo-3 10 µM	Fluvastatin 30 µM																		
OATP2B1	E3S 1 µM	Fluvastatin 10 µM																		
OAT1	PAH 0.5 µM	Benzbromarone 200 µM																		
OCT1	TEA 3.6 µM	Verapamil 100 µM																		
Are controls and control concentrations appropriate?	☒ Yes ☐ No E3S and PAH were listed as probe substrates on the FDA DDI website. Other probe substrates and inhibitors besides Fluo-3 and PAH were found to have studies supporting their being a substrate/inhibitor of the respective transporters in PharmaPendium. Fluo-3 and PAH were found to have been used as probe substrates in published studies.																			
Test (substrate or inhibitor) drug concentrations	Inhibitor: letermovir 0.14, 0.41, 1.2, 3.7, 11,33 and 100 µM Substrate: letermovir 0.5 and 5 µM																			
Were test drug concentrations appropriate?	☒ Yes ☐ No																			

RESULTS AND LABEL RECOMMENDATIONS

Transporter	Substrate	Inhibitor	IC ₅₀ (μM)	Proposed label recommendation	Do we agree with the proposed label recommendation?
OATP1B1		Yes	13	Section 7.1: "Letermovir is an inhibitor of OATP1B1/3 transporters."	☒ Yes ☐ No
OATP1B3		Yes	2.2		
OATP2B1		Yes	30	None	☒ Yes ☐ No There is no mention of OATP2B1 if FDA guidance
OAT1		No		None	☐ Yes ☒ No Per FDA guidance, inhibition of OAT1 by the investigational drug should be evaluated. Lack of effect on OAT1 should be stated in labeling.
OCT1		Yes	65	None	☒ Yes ☐ No There is no mention of OATP2B1 if FDA guidance
OATP1B1	Yes			Section 7.1: "Letermovir is a substrate of organic anion-transporting polypeptide 1B1/3 (OATP1B1/3) transporters"	☒ Yes ☐ No
OATP1B3	Yes				
OATP2B1	No			No mention in labeling	☒ Yes ☐ No There is no mention of OATP2B1 in the FDA DDI guidance
OAT1	No				☐ Yes ☒ No OAT1 is mentioned in current FDA guidance. Studies showing an absence of an effect should be stated in labeling.
OCT1	No				☒ Yes ☐ No There is no mention of OCT1 in the FDA DDI guidance

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARIO SAMPSON
08/08/2017

JEFFRY FLORIAN
08/08/2017

ISLAM R YOUNIS
08/08/2017

JOHN A LAZOR
08/08/2017