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No Evidence of a Drug-Drug Interaction Between Letermovir (MK-8228) and Mycophenolate Mofetil

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Poster #330

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Abstract

Introduction: Letermovir (MK-8228) is a potent, once-daily inhibitor of the cytomegalovirus (CMV) terminase complex that is being developed for the prophylaxis of CMV infection in transplant patients. This study evaluated the pharmacokinetic interactions, safety, and tolerability of letermovir when coadministered in healthy subjects with mycophenolate mofetil (MMF), which is the morpholinoethyl ester prodrug of mycophenolic acid (MPA).

Methods: This was an open-label trial in 14 healthy female subjects that explored the pharmacokinetic parameters of a single 1 g oral dose of MMF administered alone on Day 1 and coadministered on Day 12 with 480 mg oral once-daily letermovir given on Day 5 and from Day 8 continued through Day 16. Letermovir PK was assessed at single dose (Day 5) and at steady state on Day 12 (with MMF) and Day 16 (alone following MMF washout).

Results: Coadministration of 480 mg qd letermovir at steady state with a single dose of 1 g of MMF had no effect on the pharmacokinetics of MPA. The MPA $AUC_{0\text{-}inf}$ and C_{max} geometric mean ratios (GMRs) [90% confidence interval] for the comparison (MMF with letermovir/MMF alone) were 1.08 [0.96, 1.21] and 0.96 [0.81, 1.13], respectively. Coadministration of a single dose of 1 g MMF with 480 mg qd letermovir at steady state had no clinically meaningful effect on the pharmacokinetics of letermovir, with $AUC_{0\text{-}24}$ and C_{max} GMR of 1.18 [1.04, 1.32] and 1.11 [0.93, 1.34], respectively. The letermovir geometric mean accumulation ratio (Day 16/Day 5) and 95% CI were 1.13 [0.90, 1.42] for $AUC_{0\text{-}24}$ and 1.01 [0.79, 1.28] for C_{max}, indicating that accumulation of letermovir when administered as daily doses is minimal. All related AEs were reported as mild in severity and resolved.

Conclusions: Multiple-dose administration of 480 mg letermovir daily with a single dose of 1 g MMF was generally well tolerated by the healthy subjects in this study. Coadministration of letermovir and MMF had no clinically meaningful effect on the PK of letermovir or MPA. Letermovir and MMF may be coadministered without dose adjustment.

Background

- Letermovir (MK-8228) belongs to a new class (terminase inhibitors) of anticytomegalovirus (CMV) agents and is a once-daily inhibitor in development to prevent CMV infection and disease in transplant patients
- Mycophenolate mofetil (MMF) is indicated for prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac, or hepatic transplants and is likely to be used as comedication in transplant patients
- Mycophenolic acid (MPA), the active metabolite of MMF, is metabolized by several glucuronyl transferases (UGT1A7/8/9/10 and UGT2B7), CYP3A4/5, and CYP2C8 and is a substrate of the transporters OATP1B1 and 1B3 and the P-glycoprotein (P-gp). Letermovir is an inhibitor of CYP3A4 and CYP2C8 as well as OATP1B1, OATP1B3, and possibly P-gp. Thus, concentrations of MPA may potentially increase with letermovir coadministration
- This trial investigated the potential effect of letermovir on MPA pharmacokinetics and also explored potential effects of MMF/MPA on letermovir pharmacokinetics

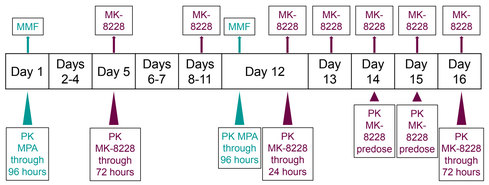
Aims

- To determine the effect of letermovir at steady state on the pharmacokinetic parameters of MPA following coadministration of a single dose of MMF to healthy female subjects. PK parameters included $AUC_{0\text{-}inf}$, C_{max}, T_{max}, and apparent terminal $t_{1/2}$
- To determine the effect of a single dose of MMF on the steady-state pharmacokinetic parameters of letermovir in healthy female subjects. Parameters included $AUC_{0\text{-}24}$, C_{max}, T_{max}, and apparent terminal $t_{1/2}$

Subjects and Methods

- This was an open-label, fixed-sequence, single- and multiple-dose trial to characterize the pharmacokinetic interaction between letermovir and MPA in 14 healthy adult females
- Eligible subjects received 1 g oral MMF on Days 1 and 12 and 480 mg oral once-daily letermovir on Day 5 and Days 8-16. Blood samples for pharmacokinetic evaluation (after an 8-hour fast) were collected on Days 1, 5, 12, and 16
- Pharmacokinetic sampling of plasma for MPA and for letermovir was obtained at prespecified time points
- Safety assessments and monitoring were performed throughout the duration of the study

Figure 1. Study Design



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Results

Subject Demographics

- All 14 subjects enrolled in this trial were female subjects between the ages of 20 and 49 years at screening with a body mass index (BMI) of 20.1 to 31.9 kg/m^2. The mean age of subjects was 32.3 years. In total, 10 subjects (71.4%) were black or African American and 4 (28.6%) were white. (*) One of the subjects who reported her race as black or African American also reported being of American Indian or Alaska Native descent (**Table 1**).

Table 1. Subject Characteristics

	Number of Subjects N=14 n (%)
Female	14 (100.0)
Age (yr)	32.3
Range	20 to 49
BMI (kg/m^2), range	20.1 to 31.9
Race	
Black or African American	10* (71.4)
White	4 (28.6)

Safety and Tolerability

- Oral administration of 480 mg letermovir once daily was ~~reasonably~~ well tolerated by the healthy female subjects
- Drug-related AEs all belonged to the Gastrointestinal Disorders System Organ Class (8 subjects, 57.1%), except for one event of fatigue. All drug-related AEs were mild in intensity and were transient
- The events of diarrhea (3 subjects; 21.4%) were all single events. Two subjects (14.3%) reported single events of abdominal pain starting 45 minutes to ~2 hours after dosing on Days 13 (concomitant with nausea) and 16 (concomitant with diarrhea), respectively, with a duration of less than 3 hours. Vomiting occurred in one subject (7.1%) on a single occasion (Day 11, ~30 minutes after dosing, duration <1 min). Nausea was reported by 6 subjects (42.9%) on one or more occasions between Day 5 and Day 15
- Most gastrointestinal AEs occurred relatively shortly after dosing and were transient

Letermovir (MK-8228) Pharmacokinetics

- A mean concentration profile of 480 mg letermovir (MK-8228) alone was compared to the mean concentration profile of 480 mg letermovir (MK-8228) when MMF was coadministered **(Figure 2)**
- The mean letermovir plasma concentration-time profile reached its peak at 2 hours postdose on Days 5, 12, and 16. All subjects had quantifiable plasma letermovir concentrations at the last time point drawn: 24 hours postdose on Day 12 and 72 hours postdose on Days 5 and 16. Mean trough concentrations ranged from 583 to 803 ng/mL, with %CV ranging from 43.1 to 67.2
- Summary statistical comparison of PK parameters from subjects administered 480 mg letermovir (MK-8228) alone compared to 480 mg letermovir (MK-8228) when MMF is coadministered in **Table 2**

Figure 2 (A) Mean letermovir concentration (linear scale) vs time by treatment group (letermovir single dose on Day 5, letermovir multiple dose + MMF single dose on Day 12, and letermovir multiple dose on Day 16); Figure 2B (semi-log scale)

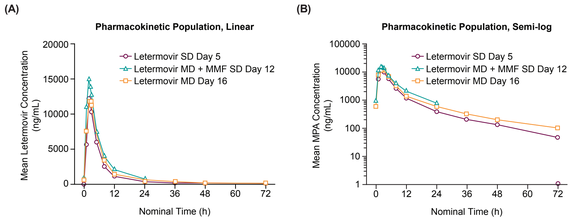

Table 2. Letermovir pharmacokinetics post-480 mg multiple dosing alone (Day 16) or coadministered with a single dose of 1 g MMF (Day 12)

	MMF + Letermovir N=14		Letermovir Alone N=14		MMF + Letermovir vs Letermovir Alone		
~~MPA~~ PK Parameter	Geometric Mean	95% CI	Geometric Mean	95% CI	GMR	90% CI	Pseudo Within Subject %CV
$AUC_{0\text{-}24}$ (hr*ng/mL)	84,011	(61,722, 114,351)	71,482	(55,593, 91,911)	1.18	(1.04, 1.32)	4.74
C_{max} (ng/mL)	14,497	(10,748, 19,553)	13,018	(10,721, 15,807)	1.11	(0.93, 1.34)	7.42
T_{max} (hr)	2.0	(1.0, 3.0)	2.2	(1.0, 3.0)	--	--	--
$T_{1/2}$ (hr)	--	--	13.8	44.3	--	--	--

CI=confidence interval, PK=pharmacokinetics, CV=coefficient of variance, GMR=geometric least-squares mean ratio between treatments, MPA=mycophenolic acid, MMF=mycophenolate mofetil.

Back-transformed least-squares mean and CI was from linear mixed-effects model performed on natural log-transformed values.

Pseudo within-subject %CV = 100*sqrt[(σ_A^2 + σ_B^2 – 2*σ_{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.

MPA Pharmacokinetics

- **Figure 3A** presents the mean MPA concentration (linear scale) vs time plots with data separated by treatment (MMF single dose on Day 1 and MMF single dose + letermovir multiple dose on Day 12) in the pharmacokinetic population. Figure 3B presents these data on a semi-log scale for MPA
- All subjects had no quantifiable predose concentrations of MPA on Day 1. The mean MPA plasma concentration-time profile reached its peak at 0.5 hours postdose on Days 1 and 12. All subjects had quantifiable plasma MPA concentrations up to 36 hours postdose on both Day 1 and Day 12

Table 3. Summary of pharmacokinetic parameters of mycophenolic acid (MPA) following single-dose administration of 1 g mycophenolate mofetil (MMF) (Day 1) alone or with 480 mg letermovir dosed to steady state (Day 12)

	MMF + Letermovir N=14		MMF Alone N=14		MMF + Letermovir/ MMF Alone		
MPA PK Paramete	Geometric Mean	95% CI	Geometric Mean	95% CI	GMR	90% CI	Pseudo Within Subject %CV
$AUC_{0\text{-}\infty}$ (hr*ng/mL)	68,131	(58,187, 79,775)	63,108	(53,152, 74,928)	1.08	(96.8, 120.4)	4.36
C_{max} (ng/mL)	22,881	(18,520, 28,268)	23,858	(19,489, 29,207)	0.95	(81.9, 112.3)	6.29
T_{max} (hr)	0.52	(0.5, 2.0)	0.52	(0.5, 2.0)	--	--	--
$T_{1/2}$ (hr)	13.1	42.6	13.3	27.2	--	--	--

CI=confidence interval, PK=pharmacokinetics, CV=coefficient of variance, GMR=geometric least-squares mean ratio between treatments, MPA=mycophenolic acid, MMF=mycophenolate mofetil.

Back-transformed least-squares mean and CI was from linear mixed-effects model performed on natural log-transformed values.

Pseudo within-subject %CV = 100*sqrt[(σ_A^2 + σ_B^2 – 2*σ_{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.

Figure 3 (A) Mean MPA concentration (linear scale) vs time plots with data separated by treatment (MMF single dose on Day 1 and MMF single dose + letermovir multiple dose on Day 12) (B) Semi-log scale

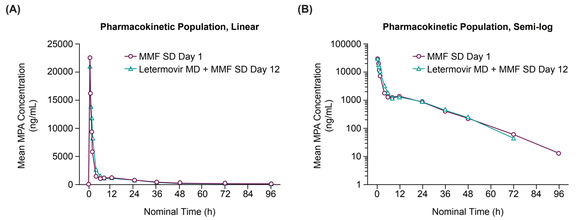

Table 4. Accumulation (GMR%) and time linearity (GMR%) based on letermovir pharmacokinetic parameters in the pharmacokinetic population

	Day 5 N=14		Day 16 N=14	Accumulation Ratio (Day 16/Day 5)		Time Linearity (Day 16 $AUC_{0\text{-}24}$/Day 5 AUC_{inf})	
PK Parameter	$AUC_{0\text{-}24}$	AUC_{inf}	$AUC_{0\text{-}24}$	GMR (90% CI)	Pseudo Within Subject %CV	GMR (90% CI)	Pseudo Within Subject %CV
AUC (hr*ng/mL)	63,056 (51,600, 77,057)	71,128 (58,059, 87,140)	71,482 (55,593, 91,911)	113.4 (90.8, 141.5)	7.26	100.5 (83.8, 120.5)	7.25
C_{max} (ng/mL)	12,918 (10,725, 15,561)		13,018 (10,721, 15,807)	100.8 (79.6, 127.5)	7.71	NA	NA

CI=confidence interval, CV=coefficient of variance, GMR=geometric least-squares mean ratio between treatments (expressed as a percent), SD=single dose, MD=multiple dose.

For Day 5 and Day 16, $AUC_{0\text{-}24}$ and $AUC_{0\text{-}\infty}$ absolute values were back-transformed least-squares mean and 95% CI were from mixed-effects model performed on natural log-transformed values.

Geometric mean ratio (%) and 90% CI were from mixed-effects model performed on natural log-transformed values. Day 16 $AUC_{0\text{-}24}$/Day 5 $AUC_{0\text{-}24}$ was used for ratio of AUCs.

Pseudo within-subject %CV=100*sqrt[(σ_A^2 + σ_B^2 – 2*σ_{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.

Discussion

Letermovir Pharmacokinetics

- The estimated GMR and 90% confidence interval for the comparison (letermovir with MMF/letermovir alone) were 1.18 (1.04, 1.32) for letermovir $AUC_{0\text{-}24}$ and 1.11 (0.93, 1.34) for letermovir C_{max}. The CI for AUC, but not C_{max}, lay completely above 1, suggesting a small increase in letermovir exposure when dosed with MMF
- Letermovir T_{max} was about 2 hours whether administered alone or administered with MMF
- The geometric mean linearity ratio (MD $AUC_{0\text{-}24}$/SD $AUC_{0\text{-}\infty}$) and 90% CI for letermovir were 1.01 (0.84, 1.21), indicating consistency with linear kinetics **(Table 4)**
- The geometric mean accumulation ratio and 90% CI for letermovir were 1.13 (0.91, 1.42) for $AUC_{0\text{-}24}$ and 1.01 (0.80, 1.28) for C_{max} **(Table 4)**

MPA Pharmacokinetics

- The estimated GMR and 90% confidence interval for the comparison (MMF with letermovir/MMF alone) were 1.08 (0.96, 1.21) for MPA $AUC_{0\text{-}\infty}$ and 0.96 (0.81, 1.13) for MPA C_{max}. The GMRs were close to 1 and the confidence intervals included 1, suggesting that coadministration with letermovir had no effect on the single-dose PK of MPA
- Median T_{max} was the same whether MMF was administered with letermovir or administered alone (0.52 hr), as was terminal half-life (geometric mean ~13 hr)

Conclusions

- Multiple-dose administration of 480 mg letermovir daily with a single dose of 1 g MMF was generally well tolerated by the healthy subjects in this study
- Coadministration of letermovir and MMF had no clinically meaningful effect on the PK of letermovir or MPA
- Letermovir and MMF may be coadministered without dose adjustment

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