Voriconazole, but not Posaconazole, Exposures Are Significantly Decreased by Letemovir (MK-8228) Coadministration in Healthy Subjects

Abstract

Introduction: Letemovir (MK-8228) is a potent inhibitor of the cytomegalovirus (CMV) terminase complex that is being developed for the prophylaxis of cytomegalovirus (CMV) infection in transplant patients, who often receive antifungal prophylaxis. The pharmacokinetics (PK) of the single antifungal posaconazole were studied in healthy volunteers with their tolerability when coadministered with letermovir.

Methods

Subjects: Healthy, non-smoking, female volunteers from 18 to 55 years of age with a body mass index (BMI) of 18.5 to 30 kg/m² were included in the studies. Subjects received treatment with letermovir and posaconazole (28-day, 14-day, or 7-day periods) as described in Figure 1. Letermovir and posaconazole study design: This was a randomized, open-label, randomized, dose-response, 2-period, 2-sequence, balanced, crossover trial. Subjects received either letermovir or placebo for 14 days, followed by PK sampling for posaconazole. Safety was monitored during the voriconazole coadministration. Letermovir was well tolerated at the doses administered.

Results:

- •  Letermovir was found to be an inhibitor and inducer of CYP3A4 in vitro and a clear inhibitor of CYP3A4 in vivo. Although inhibition of CYP3A4 was observed, it was not detectable in the area under the concentration-time curve (AUC) of voriconazole P-gp inhibitors. Therefore, the therapeutic index of voriconazole was not affected.

- •  Posaconazole is a substrate of CYP2C9. The interaction of voriconazole with CYP2C9 will likely affect the pharmacokinetics of posaconazole by inhibiting P-gp expression, resulting in an increase in posaconazole exposure when coadministered with voriconazole and letermovir.

- •  Posaconazole was also a substrate of CYP3A4. During the interaction of letermovir with CYP3A4, letermovir reduces the expression of CYP3A4, leading to lower metabolism of P-gp substrates, including posaconazole.

- •  Furthermore, this study indicated that P-gp inhibition by letermovir results in reduced expression of P-gp and decreased CYP3A4 expression, leading to a decrease in P-gp-mediated drug metabolism.

- •  The interaction of letermovir with CYP3A4 also affects the expression of P-gp, further reducing the expression of P-gp and decreasing the metabolism of P-gp substrates.

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- •  The data suggest that letermovir and posaconazole coadministration is well tolerated in healthy female subjects.

Safety:

- •  No serious adverse events were reported, and all adverse events were mild or moderate in severity.

- •  There were no changes in ECGs, electrocardiograms, urinalysis, or hepatic laboratory tests that suggested a relationship to letermovir in either study.

Conclusions:

- •  Letermovir and posaconazole concentrations following coadministration and alone were not different. When coadministered with letermovir, there is a decrease in posaconazole exposure, which may be clinically significant.

- •  The results suggest that letermovir and posaconazole coadministration is well tolerated in healthy female subjects.

References


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Disclosure

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Table 1: Safety and tolerability data following administration with or without coadministration of letermovir in healthy female subjects.

Table 2: PK analysis of voriconazole and posaconazole concentrations following administration with or without letermovir.

Table 3: PK analysis of voriconazole and posaconazole concentrations following administration with or without letermovir.