Nonlinear Pharmacokinetics of Letermovir (LET) Following Oral and IV Administration in Healthy Volunteers
M. Prohn1, D. Zhang2, C. Davis3, P. Sabato3, S. Macha3, A. Viberg1, K. Dykstra1, C. R. Cho3

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Objectives: LET is a novel drug inhibiting the human cytomegalovirus virus (CMV) terminase complex. In a pivotal double-blind, randomized, placebo-controlled phase 3 trial for the prophylaxis of clinically significant CMV infection (CS-CMV) in HCT recipients with serological evidence of prior CMV infection, LET treatment for up to 14 weeks post-HCT significantly reduced CS-CMV through 24 weeks post-HCT. Phase 1 studies showed LET pharmacokinetics (PK) are complex with greater than dose-proportional increases in exposure and large variability in absorption profiles. To understand PK in HCT recipients, a staged approach was taken. First, a model of rich phase 1 data was developed. Then a simplified model was then developed to characterize LET PK in HCT recipients[1]. Both models were used to identify clinically relevant covariates that may be predictive of LET exposure.

Methods: Data from multiple Phase 1 studies were integrated in this analysis. The full dataset included 9008 observations obtained in 12 Phase 1 studies (280 healthy volunteers) obtained after either single or multiple dose PO or IV administrations of 30-960 mg Letermovir. Modeling was performed using NONMEM 7.3 with stepwise-covariate modeling (SCM, PsN 4.2.6).

Results: The final Phase I model was a 4-compartment model with concentration-dependent nonlinear clearance, Q1, and induction of clearance. A TCAM model[2] was used to describe LET absorption after oral administration. Covariate effects of Asian race (on Vd) and weight (on Vd and CLmax) were identified to impact LET exposure. Other intrinsic factors including the effect of genetic variants of OATP1B1 (RS4149056 and RS2306283) and UGT1A1 (RS4148323) did not have a significant effect.

Conclusions: The final model adequately described the complex LET PK in healthy volunteers after both single and multiple dose IV and PO dose administration ranging from 30 mg to 960 mg. The model adequately described intra-subject variability allowing the evaluation of covariate effects on LET PK.

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