Nonlinear Pharmacokinetics of Letermovir in Phase 1 Suggest a Role of Induction

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**Objectives:** Letermovir is in Phase 3 development for the prophylaxis of cytomegalovirus (CMV) infection in transplant patients. Letermovir pharmacokinetics (PK) are complex with greater than dose proportional increases in exposure, changes in PK characteristics but limited accumulation upon multiple dosing and large variability in absorption profiles upon oral administration. Previous models were sufficient for informing dose selection for the Phase 3 study, but did not support critical questions such as predicting the impact of drug-drug interactions or sub-populations. The development of an updated population PK model describing all healthy volunteer data will enable support of such critical questions concerning the first 8-15 days of dosing prior to reaching steady state.

**Methods:** The full dataset included 6730 observations obtained in 8 Phase I studies (219 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 4.2.0).

**Results:** The final Phase I model was a 4-compartment model with concentration dependent nonlinear clearance and inter-compartmental clearance, a Savic transit absorption model, and inter-individual variability on key parameters. The model included induction of clearance. After 8-15 days the induction effect reached its steady-state, resulting in an increase of clearance by approximately 12%, 12% or 71% upon multiple PO dosing of 240 or 480 mg (QD) or 720 mg (BID), respectively. No clinically relevant covariates were identified.

**Conclusions:** The final model describes the complex letermovir PK in healthy volunteers during the first days of dosing prior to steady state. The model enables support of critical questions that may arise concerning the short-term effect of intrinsic and extrinsic factors which may impact PK.