Letermovir Exposure is Similar in HSCT Patients and Healthy Volunteers

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Objectives: Letermovir is a potent, well-tolerated, inhibitor of the cytomegalovirus (CMV) terminase complex that is being developed for the prophylaxis of CMV infection in hematopoietic stem cell transplant (HSCT) patients. In a Phase 2b trial (AIC246-01-II-02) Letermovir was administered orally for 84 days at 60, 120 or 240 mg QD. Although letermovir pharmacokinetics (PK) following multiple doses in patients was similar to that in healthy volunteers (HV), PK following single dose administration was not previously reconciled with multiple dosing. This analysis aims to evaluate PK differences between patients and HV, leveraging the updated Phase 1 population PK model that describes PK non-linearities and putative induction.

Methods: The analysis included 1041 PK samples from 83 patients collected at predose, 0.5-1h, 1-3h, 3-5h and 8-10h postdose on day 8 or 15 plus weekly trough samples. Modeling was performed using NONMEM 7.3 with stepwise-covariate modeling (PsN 4.2.0). Simulations were performed to confirm the previously selected Phase 3 dosing regimen.

Results: The final PK model was a 2-compartment model with nonlinear clearance, first-order absorption with lag-time, inter-individual variability on several parameters and inter-occasion variability on the relative bioavailability. Induction and nonlinear distribution could not be estimated in Phase 2 due to sparse PK sampling. Nonetheless, the model offered novel insight: differences in single dose PK in HV could be attributed to putative induction (increase) of clearance. Simulations also confirmed that 92% of patients reach the target exposure after administration of the Phase 3 dose, 480 mg letermovir QD.

Conclusions: The model bridges single and multiple dose letermovir administration which has not been previously described. This model provides insight which may be required to address critical questions such as the impact of intrinsic and extrinsic factors on letermovir exposure in patients, and will serve as the basis for the analysis of Phase 3 data.