Immuno-Viral Dynamics Modeling of Letermovir for Treatment of Human Cytomegalovirus (HCMV) Infection in Post-Transplant Settings

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Objectives: Letermovir is a novel inhibitor of human cytomegalovirus (HCMV) being developed for HCMV prophylaxis in hematopoietic stem cell transplants (HSCT). A viral dynamics model that integrates viral replication, the immune response, and letermovir’s hypothesized mechanism of action targeting the viral terminase complex has been developed from literature models and clinical and non-clinical letermovir data.

Methods: A published HCMV immuno-viral dynamics model [1] was modified to account for letermovir’s hypothesized mechanism of action (see Figure). Clinical drug effect was translated from an Emax model of in vitro data from over 50 HCMV viral strains isolated from clinical samples. Data from literature and the development program informed virus and immune function parameter estimates and initial conditions. Letermovir population pharmacokinetics (PK) models generated PK profiles for dosing regimens of interest. Model qualification consisted of comparing viral load reduction and failure rate projections against outcomes from a Phase 2a preemptive treatment study [2] and a Phase 2b prophylaxis study [3].

Results: A broad diversity of initial subject conditions coupled with limited subject-level observations, especially for the preemptive treatment study, limited quantitative qualification capabilities. Instead, subjects were stratified into scenarios (initial conditions and dosing regimens) representative of Phase 2a and 2b subjects. Simulations based on these representative scenarios using the final letermovir-specific integrated population PK and immuno-viral dynamics model were found to qualitatively reproduce observed clinical outcomes.

Conclusions: A letermovir-specific immuno-viral dynamics model was developed that qualitatively reproduces clinical outcomes. The model enables support of critical questions which may arise concerning HCMV infection in HSCT.

References:
Figure 1. Letermovir MOA-Specific Immuno-Viral Dynamics Model Schematic Diagram for treatment of HCMV Infection in Post-Transplant Settings: Compartments are indicated by circles, while arrows indicate processes. Infected cells arise from either reactivation of latently infected cells or through infection of susceptible cells by viable virions. The fraction, $f_v$, of viable virions to non-infectious virus produced by infected cells is determined by letermovir exposure-response characteristics and dose regimen. Immune response enhances the clearance of infected cells from the system. The level of immune effector cells is suppressed by immunosuppressants but stimulated by both non-infectious virus and viable virions. Processes that are increasing or decreasing the values of the compartments are indicated with directional arrows while arrows that loop back towards a compartment indicate maintenance of cell/virion populations. Arrows directed toward null compartments, $\emptyset$, indicate clearance from the system.