Translational PK-PD-Viral Dynamics (VD) Modeling: An Application in Respiratory Syncytial Virus (RSV) Program

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Objectives: RSV, common cause of lower respiratory tract infections, usually results in self-limiting flu-like signs and symptoms, but can cause serious complications in children, elderly and immune-compromised populations. This work illustrates the application of a translational PK-PD-VD modelling approach in an early phase RSV program, focusing on characterizing the anti-viral activity of benchmark compound RSV604.

Methods: RSV kinetics in human appears to be similar to influenza, with slightly prolonged viral production. A target cell-limited acute VD model with delayed virus production, originally developed for Influenza A infection [1], was fitted to the viral load data in RSV-challenged study [2]. RSV604 anti-viral activity was simulated by linking its PK and in-vitro EC50 to the VD model. Emax model was used to describe the inhibitory effect of the compound on viral production rate. It was assumed that RSV production could be completely inhibited by RSV604. The EC50 parameter in this model was fixed to the average of in-vitro RSV604 EC50 values against common clinical isolates of RSV [3].

Results: The VD model was able to capture the observed RSV viral load in challenged subjects without pharmacological intervention. Simulations demonstrated a larger beneficial effect if treatment is initiated earlier, however, treatment initiated as late as 6 days post infection (dpi) can still offer some benefit. Following 3 days QD dosing of 450 mg RSV604 initiated at 6 dpi, the viral load is predicted to be approximately 1 log (PFU/mL) less than the placebo group.

Conclusion: The integrated PK-PD-VD model can be applied in the early phase RSV program to provide a more integrated comparison of various compounds against the benchmark compound, to guide the selection of the lead compound, and to inform clinical study design e.g. dosing strategy and treatment window.

References: