A mechanistic model describing the effect of respiratory syncytial virus (RSV) kinetics on clinical symptom score, and disease attenuation by presatovir (GS-5806)

Justin D. Lutz1, Kashyap Patel2, Patrick Smith2, Jason W. Chien3, Robert Jordan4, Yan Xin1, Srin Ramanathan1 and Anita Mathias1

Departments of 1Clinical Pharmacology, 3Clinical Research and 4Biology, Gilead Sciences, Foster City, CA; 2d3-Medicine, Parsippany, NJ

Objectives: RSV infection causes potentially fatal disease in infants and immunocompromised adults. Unfortunately, options for management of RSV infection are limited. The objective of this work was to characterize the dynamics between RSV load, clinical symptom score (CSS) and the exposure of presatovir, a potent viral fusion inhibitor.

Methods: Data from healthy adult volunteers challenged with RSV (Memphis 37b) and then administered either presatovir or placebo were previously reported1. RSV kinetics was described using a mechanistic target-cell limited model2, which includes an eclipse phase (k) between epithelial cell infection (β) and viral production (p) rates. An indirect response model described the relationship between viral load and CSS, a sum of 10 symptoms each assessed on a 4-point scale. Viral transition and cell mortality rates were fixed based on reported estimates3. Based on mechanism of action, it was assumed that presatovir would decrease viral load by inhibiting β. Model evaluation was based on biological plausibility of parameters and Visual Predictive Checks (VPCs).

Results: Diagnostic plots and VPCs indicate that the model accurately described viral load and CSS. Between-subject variability (160–600%) was well estimated (% relative standard error of 5–32%). After placebo the model estimated reproductive number (R0) was in a biologically realistic range (5–36) providing additional confidence in model performance. A simple Emax model best described presatovir inhibition of β, with an EC50 of 20ng/mL, in agreement with in vitro data (11ng/mL).

Conclusions: The developed model provides a quantitative link between RSV viral load and CSS and further mechanistic insight into the impact of fusion inhibitors on RSV infection.

References:

The results in this abstract are planned to be presented in part at the RSV Symposium in Patagonia, Argentina, September 28th to October 1st, 2016, and published in the conference proceedings (abstract number T.B.D.)