Viral Dynamics Modeling and Simulation to Support Development of Grazoprevir (GZR) and Elbasvir (EBR) for Treatment of Hepatitis C (HCV) Infection
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Objectives: To characterize the dose-response relationships for EBR/GZR in the treatment of genotype (GT) 1 and 4 Hepatitis C (HCV) infection and to simulate expected outcomes of regimens with reduced EBR/GZR doses.

Methods: A 2-species viral dynamics model was developed and qualified using viral load and sustained virologic response (SVR12) data from studies in which GZR and EBR were administered as monotherapy at a range of doses; a study in which GZR (25, 50, or 100 mg) was administered for 12 weeks in combination with Pegylated Interferon/Ribavirin (PR); and studies in which 100 mg GZR + 20 or 50 mg EBR ±RBV were administered for 8 or 12 weeks. The effect of EBR/GZR in inhibiting production of HCV from infected cells was related to GZR and EBR doses using a sigmoid Emax relationship. The death rate of infected cells was assumed to increase for doses or regimens that lead to greater antiviral activity. Efficacy and resistance parameters were scaled based on in vitro relative potency data to predict efficacy in genotypes other than GT1.

Results: The final model accurately describes both the time-course of decline in HCV viral load for short-term monotherapy treatments and SVR12 for longer-term treatment across the range of doses, treatment durations, and regimens studied. Simulations were conducted to explore the effect of reducing the exposure of one or both compounds. Reducing the dose of either EBR or GZR by half compared to the recommended doses of 50 mg EBR/100 mg GZR still results in high projected SVR12 rates.

Conclusions: Dose response relationships for GZR and EBR were characterized using monotherapy data and data from clinical studies that evaluated varying EBR and GZR doses and varying regimens. The model allowed simulation of the likely outcome of reduced doses/exposures of EBR/GZR in a combination regimen, and supported assessment of acceptable reductions in exposure for both compounds.