Application of Complementary Statistical and Modeling Analyses to Identify Predictors of Sustained Virologic Response in Patients with Chronic Hepatitis C

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Objective: Identify predictors of sustained virologic response 12 weeks post-treatment (SVR12) in a phase II study in chronic HCV patients receiving grazoprevir/elbasvir (100mg/50mg) with sofosbuvir (400mg) QD for various treatment durations, (i.e., 4, 6, 8, or 12 weeks), and quantify their impact on SVR12.

Methods: Two independent but complementary analyses, Random Forrest Classification Analysis (RFCA) using the package randomForest in Rv3.1.0 and Logistic Regression (LR) implemented in NONMEMv7.1.2, were used. A total of 27 factors, including patient specific covariates related to disease (e.g. baseline viral load (BVL)), general demographics (e.g. weight), plasma concentrations of each drug, and treatment duration were explored. Explored predictors for the LR model were selected based on initial data exploration and results from the RFCA. A preliminary population pharmacokinetic model was used to simulate elbasvir concentrations and compare the predicted probability of SVR12 between a 50mg and 100mg QD dose (in combination with 100mg grazoprevir and 400mg sofosbuvir).

Results: Duration of treatment followed by elbasvir concentrations were the most important predictors of SVR12 from RFCA and the only significant predictors during LR. While RFCA revealed BVL as an important predictor (although not as important as treatment duration), this was not confirmed with LR due to a coincidental study imbalance such that subjects with the least duration of treatment also had higher BVL. Simulations demonstrated 50mg QD for 12 weeks achieves near maximal response and increasing the dose to 100mg does not increase the predicted probability of SVR12, with 90%CI of 98-100% for both doses.

Conclusions: The combined approaches gave novel insights into the data and robustly identified predictors of SVR12, i.e. treatment duration and elbasvir concentrations. Through the unique advantages of each approach the synergistic benefit was highlighted as RFCA had a low computational time to evaluate a large number of potential predictors, including confounded variables, while LR had predictive ability.