Efficacy Exposure-Response Analysis for Daclatasvir /Asunaprevir/Beclabuvir Regimen in Hepatitis C Virus Infected Subjects

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**Objectives:** The combination regimen of daclatasvir, asunaprevir and beclabuvir (DCV/ASV/BCV regimen) is being developed as fixed-dose-combination for the treatment of HCV infection in Japan. The objectives of this analysis were to characterize the relationship between DCV, ASV, and BCV exposure and sustained virologic response at post-treatment week 12 (SVR12) in HCV infected-subjects, and to evaluate the impact of demographic covariates and clinical factors on the exposure-response (E-R) relationship.

**Methods:** The efficacy E-R analysis was performed with data from one Phase2 and three Phase3 studies in HCV infected-subjects treated with DCV/ASV/BCV regimen. The relationship between the probability of achieving SVR12 and exposure for DCV, ASV and BCV was described using a logistic regression model, and included assessments of the potential covariate effects. The impacts of the covariates related to demographic, laboratory, disease and treatment on the rate of SVR12 and interactions of covariates with the individual drug effects were tested using a univariate-covariate-screening process (p<0.05), followed by a stepwise-forward-addition (p<0.05) and backward-elimination (p<0.01) approach. Model evaluation was conducted using visual predictive checks of the final model and presented stratified by covariates of interest.

**Results:** The final model for SVR12 included: effects of non-genotype-1a status, resistance-associated NS5A Q30 variant in genotype-1a subjects, and baseline RNA level on the intercept, and effect of prior peg-interferon failure on the BCV slope. The 95% confidence intervals for the slope of the relationships between DCV, ASV, and BCV and SVR12 included zero. Subject gender, race, age, weight, fibrosis score, ALT, and cirrhosis status had no statistically significant impact on the rate of SVR12.

**Conclusions:** The individual E-R relationships with DCV, ASV, and BCV, administered as the DCV/ASV/BCV regimen, were relatively flat and the effects of exposure were not significant. With the exception of the Q30 variant in genotype-1a subjects, statistically significant covariate effects had little impact on SVR12 rates. Overall the E-R model supported the high SVR12 rates for DCV/ASV/BCV regimen in HCV infected-subjects.