Safety 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 the exposure of DCV, ASV, and BCV and liver-related laboratory abnormalities (Grade3/4 ALT, AST and total bilirubin), and to evaluate the impact of selected covariates on the exposure-response (E-R) relationships.

Methods: The E-R analysis was performed with data from one Phase2 and three Phase3 studies in HCV infected-subjects. The probability of Grade3/4 liver-related laboratory abnormalities were modeled using linear logistic regression. Selected covariates (eg, demographic, baseline laboratory, disease related and treatment) were tested using a forward-addition (p<0.05) and backward-elimination (p<0.01) approach. Model evaluations were conducted by comparing the observed incidence rates with the final model simulations stratified by covariates and visual predictive checks.

Results: The final model for ALT elevations included the effect of Asian race and ASV exposure, and the effect of body weight in non-Asian subjects. Similar to ALT, Asian race was the most important factor contributing to Grade3/4 AST elevation; no other covariate or exposure effect tested was significant. The final model for total bilirubin elevation included the effect of Asian race, fibrosis-category and ASV exposure.

Conclusions: Higher ASV exposure was associated with increases in Grade3/4 ALT and total bilirubin elevations rates, but the impact on the ALT elevation was not clinically relevant and the effect on the total bilirubin elevation in the range of observed ASV exposure was smaller than the other significant covariates. The impact of ASV exposure on Grade3/4 AST elevation rate was not significant. Asian subjects had greater Grade3/4 ALT, AST and total bilirubin elevation rates than non-Asians. In addition, Grade3/4 ALT rates increased with decreasing body weight in non-Asian subjects and subjects with fibrosis-category4 had a higher rate of total bilirubin elevations compared to subjects with fibrosis category0-3.