Exposure-Response Analysis for Daclatasvir and Asunaprevir in Japanese Subjects with Hepatitis C Virus Infection

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BACKGROUND

- All six combination-regimens of daclatasvir (DCV) and asunaprevir (ASV) were approved for the treatment of HCV genotype 1 infected patients in Japan in July 2014
- Daclatasvir (DCV): – Pangenotypic-NS5A inhibitor, low potential for drug-drug interactions – Safe and well tolerated – Studied in >13,000 patients worldwide – Approved in Europe and Japan after regulatory review in the US
- Asunaprevir (ASV): – NS3 protease inhibitor – Clinical results: GT 1, 4, 6, 7 – Approved in Japan
- Based on 2 trials and initial exposure-response analyses, 80 μg of DCV and 100 μg BID of ASV softgel capsule (equivalent to 200 μg BID tablet in Phase 2) were selected as the Phase 3 doses
- High rate of efficacy (in HCV ineligible naïve/intolerant and prior non-responders) tested with DCV in Japan Phase 3 study

OBJECTIVES

- The objectives of the current analysis were:
  - To characterize the relationship between the exposure of DCV and ASV and sustained virological response (SVR) in Japanese subjects who are HCV genotype (GT) 1 non-responders to peg-IFN/RBV or PEG-IFN/RBV, and IFN based therapy ineligible naïve/intolerant

METHODS

Data sources

- Data from 295 subjects from 2 clinical studies (Phase 2 and Phase 3 studies) in Japanese HCV GT-1 subjects
- The analysis included non-responders to peg-IFN/RBV or PEG-IFN/RBV, and IFN based therapy ineligible naïve/intolerant subjects

Analysis platforms

- Data assembly and modifications were performed using SAS (version 9.2)
- Final datasets were generated as a SAS transport file
- Model development was performed using NONMEM (version 7.2)
- Diagnostic graphics, exploratory analysis and post-processing of NONMEM output were also performed using SAS and S-Plus (version 8.2 for Unix)

Analysis endpoints and covariates of interest

- SVR12: Sustained Virological Response (yes/no), using analysis endpoint and covariates of interest

Model development

- Defined as HCV RNA below limit of detection at 12 weeks after treatment

RESULTS

Table 1. Description of Covariates Tested for E-R Relationship

- Covariate | Description | N | N (%)
- Baseline Body Weight (kg) | Numerics | 288 | 100
- Gender | Male | 174 (65.7)
- Female | 107 (40.3)
- Baseline ALT Level (U/L) | Numerics | 288 | 100
- Alanine Transaminase | 45-60 | 157 (59.3)
- >60 | 133 (46.8)
- Cirrhosis (yes or no) | Binary | 174 (65.7)
- No | 157 (59.3)
- Yes | 22 (8.4)
- Study | Phase 2 (AI447017), Phase 3 (AI447026) | Binary | 174 (65.7)
- Phase 2 | 43 (15.1)
- Phase 3 | 131 (46.0)

Figure 3. DCV and ASV Average Concentrations in Subjects with and without SVR

Figure 2. Observed SVR12 Rates Stratified by
(A) Gender and Age
(B) Patient group and Cirrhosis

DISCUSSION

- High SVR12 rates were observed in the subjects without Y93H baseline mutation throughout observed exposure for DCV and ASV (Figure 3)
- Median: 95% CI: 85% – 98% at median Cavgss for DCV and ASV
- Model evaluation plots demonstrated that the final model is able to predict the observed SVR rates (SVR rates for each quartile of exposure, Figure 3)
- Baseline Y93H polymorphism was the most significant covariate for SVR12

CONCLUSIONS

- The presence of the signature NNS Y93H mutation at baseline was the only significant parameter for SVR12 in the final E-R model
- There is no evidence of a clinically meaningful effect of the following covariates on SVR rate: Baseline Age, Baseline Body weight, Gender, Baseline Creatinine Clearance, Baseline ALT level, IL28B Genotype (rs12979860), Basal viral load, patient type (non-responder or IFN Based Therapy ineligible naïve/intolerant subject), cirrhosis (yes or no), Study, OATP1B1 haplotype
- Overall the ER model supported the high SVR12 rates for the DUAL combination in GT-1 HCV infected Japanese subjects and no dose adjustment is needed based on any of the covariates tested.

REFERENCES


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