

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

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## BACKGROUND

- All oral combination regimen of daclatasvir (DCV) and asunaprevir (ASV) was approved for the treatment of HCV genotype 1 infected patients in Japan July 2014
- Daclatasvir (DCV)
  - Pangenotypic<sup>a</sup> NS5A inhibitor, low potential for drug-drug interactions
  - Safe and well tolerated
  - Studied in >13,000 patients worldwide
  - Approved in Europe and Japan; under regulatory review in the US
- Asunaprevir (ASV)
  - NS3 protease inhibitor
  - Clinical data in GT 1 and 4
  - Approved in Japan
- Based on Phase 2 studies and initial exposure-response analyses<sup>1</sup>, 60 mg QD of DCV and 100 mg BID of ASV softgel capsule (equivalent to 200 mg BID tablet in Phase 2) were selected as the Phase 3 doses
- High rate of efficacy (in IFN ineligible-naïve/intolerant and prior non-responders) treated with DUAL in Japan Phase 3 study<sup>2</sup>

<sup>a</sup> Pangenotypic: GT 1-6 *in vitro* and GT 1-4 in clinical trials

## OBJECTIVES

- The objectives of the current analysis were:
  - To characterize the relationship between the exposures of DCV and ASV and sustained virological response (SVR) in Japanese subjects who are HCV genotype (GT) 1b non-responders to pegIFNα/RBV or IFNβ/RBV, and IFN based therapy ineligible/naïve/intolerant receiving DUAL (DCV + ASV)
  - To provide insight into patient covariates that are most closely associated with efficacy

## METHODS

- Data sources**
  - Data from 265 subjects from 2 clinical studies (Phase 2 and Phase 3 studies) in Japanese HCV GT-1 subjects
  - The analysis included non-responders to pegIFNα/RBV or IFNβ/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 were performed using NONMEM (version 7.2)
  - Diagnostic graphics, exploratory analysis and post processing of NONMEM output were performed using SAS and S-plus (version 9.2 for SAS, version 8.2 for S-plus)
- Analysis endpoint and covariates of interest**
  - Efficacy Response: Sustained Virological Response (SVR12) (yes/no) using modified intent to treat data (mITT)
  - Defined as HCV RNA below limit of detection at 12 weeks after treatment completion
  - ASV and DCV exposure: Cavgss, calculated as the geometric mean of average plasma concentration (Cavg) after Day 14, predicted from final PPK models for ASV and DCV (Poster # IV-19)<sup>3</sup>

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

Covariate	Unit	Value
Baseline Age	years	Numeric
Baseline Body Weight	kg	Numeric
Gender	-	Male, Female
Baseline ALT Level	U/L	Numeric
Baseline creatinine clearance	mL/min	Numeric
IL28B Genotype (rs12979860)	-	CC, Non-CC
Y93H baseline resistance	-	No, Yes
Baseline Viral Load	Log <sub>10</sub> IU/mL	Numeric
Patient Type	-	Null/Partial-responder Interferon Based Therapy Ineligible/Naïve/Intolerant
Cirrhosis	-	No, Yes
Study	-	Phase 2 (AI447017), Phase 3 (AI447026)
OATP1B1 haplotype	-	*1B/*1B, *1B/*1A, *1A/*1A, *1A/*1A, *1A/*14, *1A/*15, *1B/*17, *1A/*17, OTHER, MISSING

## E-R model development

- The E-R relationship described using a logistic regression model. The probability that a subject achieves SVR12 (P(SVR12)) was characterized using a binary logistic regression such as

$$P(SVR12) = \frac{e^{\mu}}{1 + e^{\mu}}$$

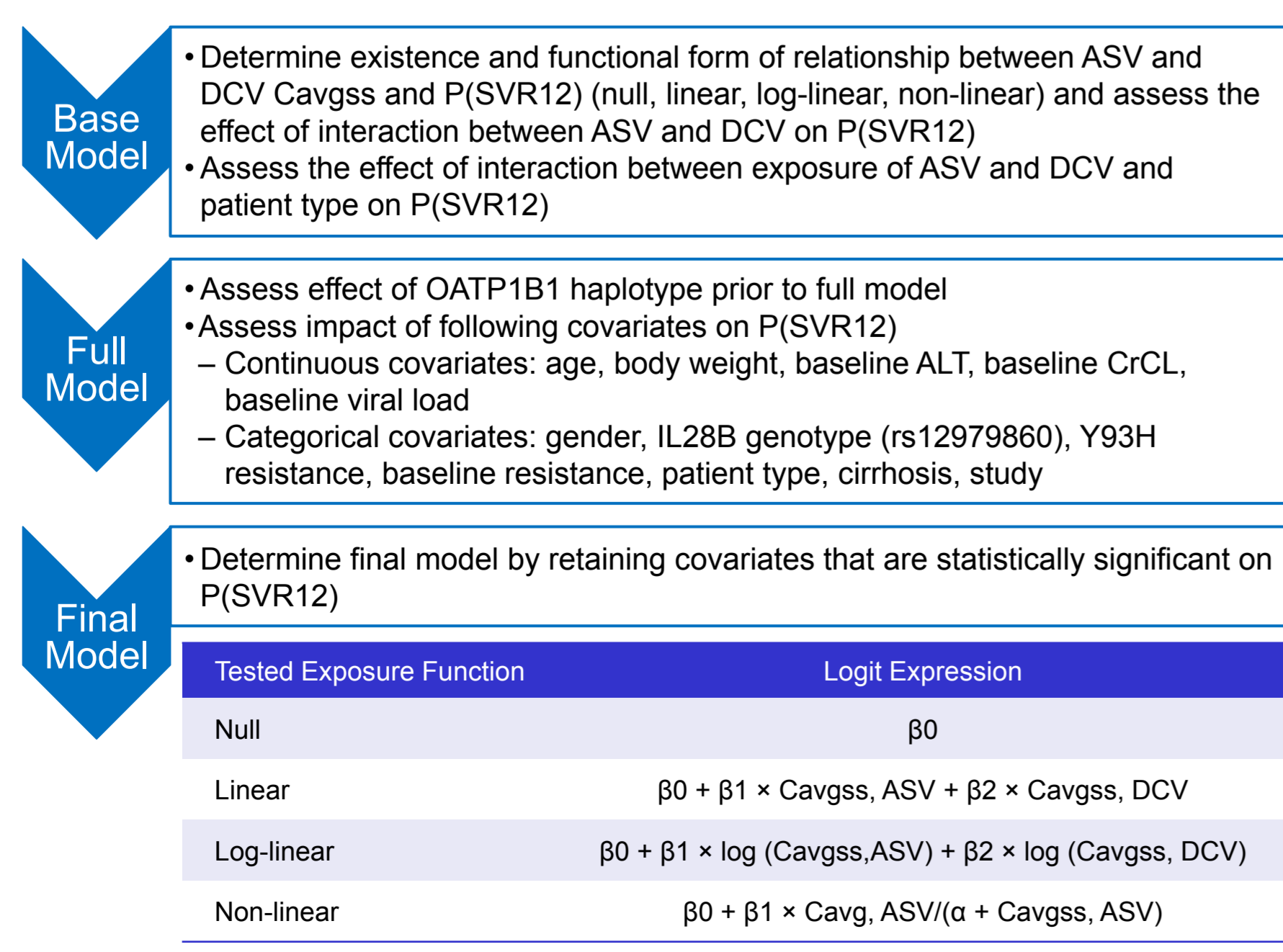
Where  $\mu$  is the logit transform of P(SVR12). The logit (log-odds) is given by

$$\mu = \log \frac{P}{1-P} = \beta_0 + \beta_1 X_i$$

Where  $\beta$  is a parameter vector representing the effect of the predictor variable vector  $X_i$  on the logit of achieving SVR12, where  $X_i$  consists of the covariate (predictor) values for each subject. The functional form relating predictor variable ( $X_i$ ) and logit of the binary response ( $\mu$ ) were tested as linear, log-linear or non-linear relationships

- Base model was developed to establish the existence and functional form of a relationship between ASV and DCV exposure and P(SVR12)
- OATP1B1 haplotype was tested in a univariate fashion on the base model before testing the full model and full model was developed by incorporating all the other covariates.
- The final model was obtained by retaining all statistically significant covariates ( $p < 0.01$ ) following a backward elimination method
  - Cavgss for ASV and DCV and the term describing their interactions were re-specified to be included in the base model regardless of their statistical significance to allow for identification of potential covariate exposure interactions
- The model parameters were estimated by maximum likelihood. Models were assessed by the likelihood ratio test (LRT) for nested models, and by the Bayesian Information Criteria (BIC) for non-nested models

Figure 1. Schematic Overview of E-R Model Development

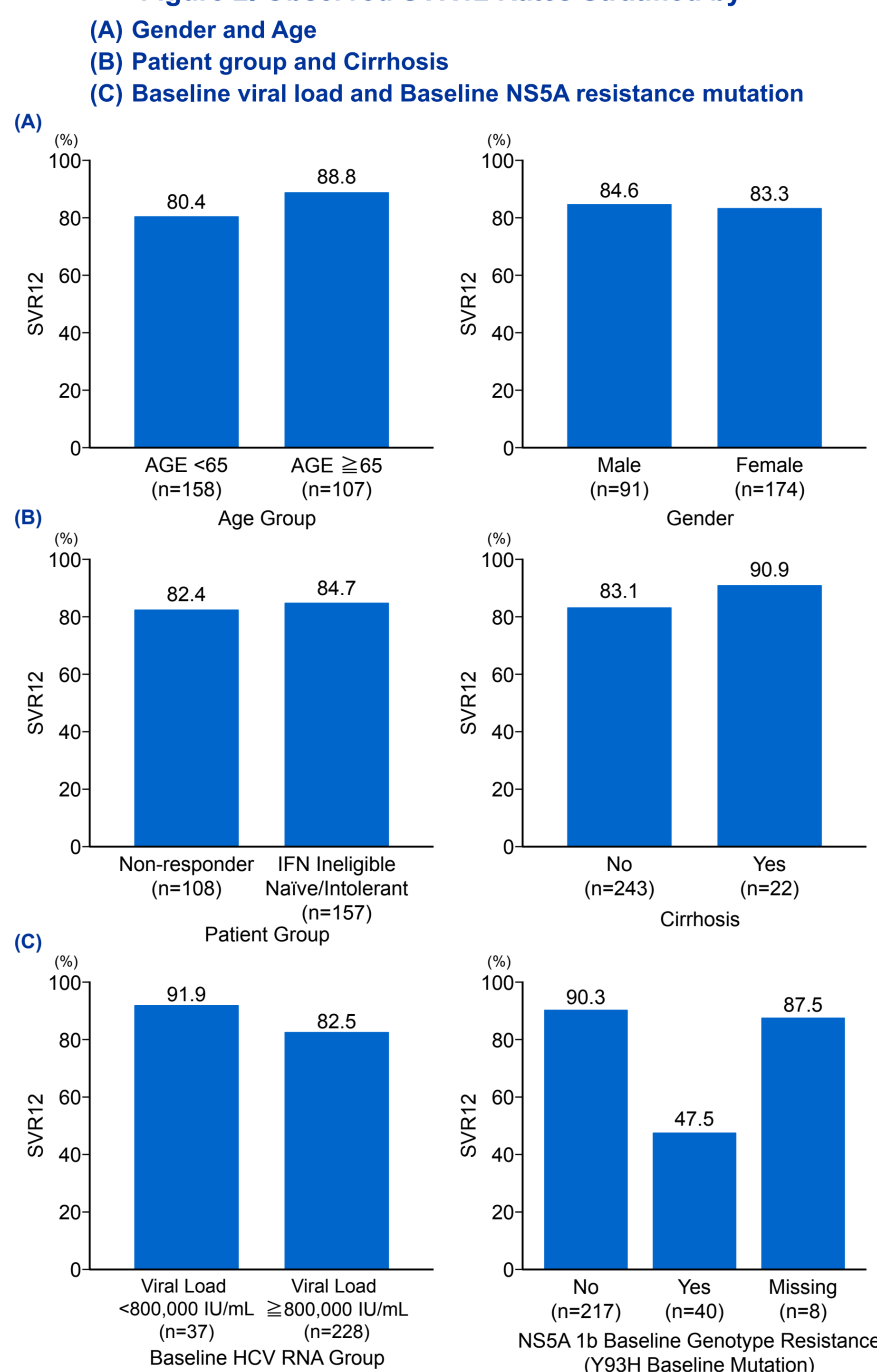


## RESULTS

Table 2. Summary of Covariates of Interest

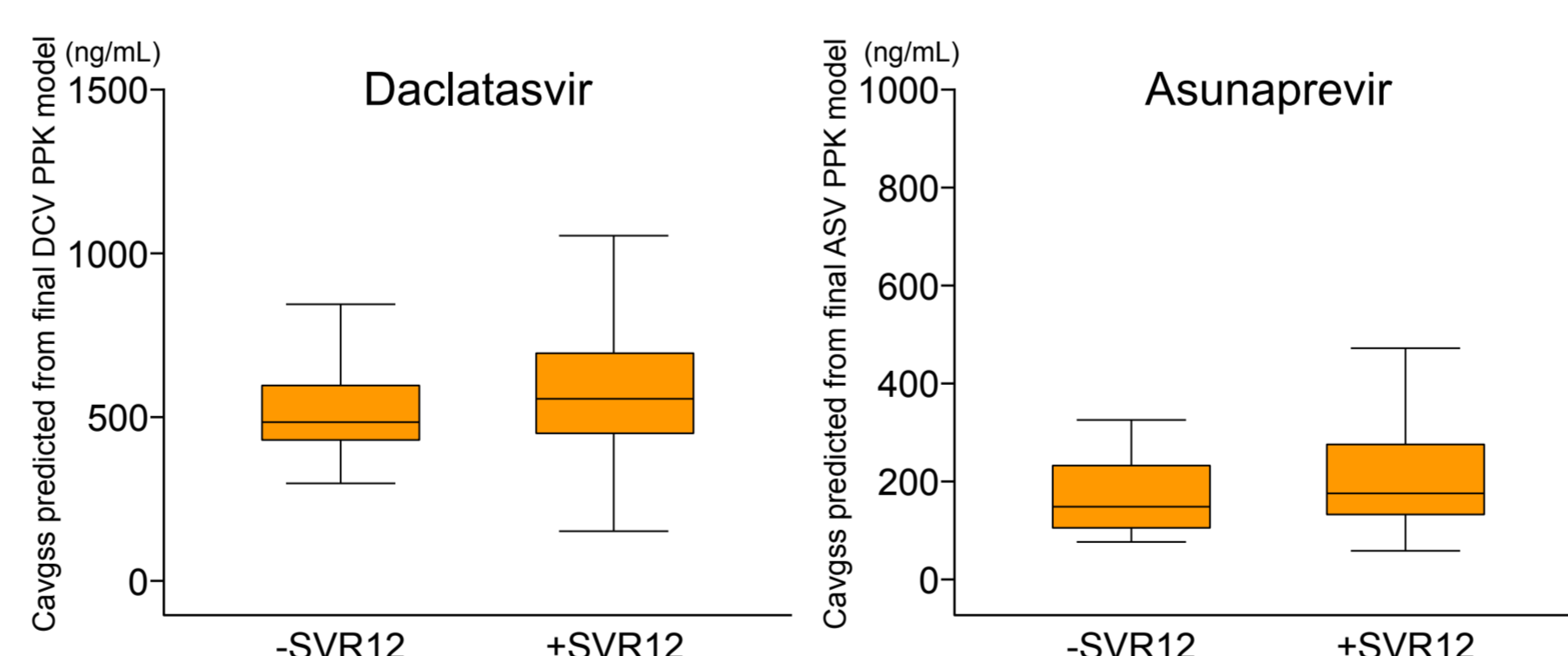
Covariate	N = 265
Age, median years (range)	62 (24-75)
Weight, median kg (range)	55.0 (36.0-93.4)
Male, n (%)	91 (34.3)
Female, n (%)	174 (65.7)
Patient group	
Non-Responder, n (%)	108 (40.8)
IFN ineligible naïve/intolerant, n (%)	157 (59.3)
Cirrhosis, n (%)	
no/yes	243 (91.7) / 22 (8.3)
Baseline viral load log <sub>10</sub> , median IU/mL (range)	6.8 (4.9-7.7)
DCV + ASV Cavgss, median ng/mL (range)	
DCV (60mg QD)	557.41 (148.8-1486.0)
ASV (tablet 600mg BID)	590.16 (379.4-2111.2)
ASV (tablet 200mg BID)	268.4 (91.0-440.3)
ASV (softgel 100mg BID)	163.7 (59.3-947.1)
NS5A resistance mutation	
Y93H no/yes/missing, n (%)	217 (81.9) / 40 (15.1) / 8 (3.0)

Figure 2. Observed SVR12 Rates Stratified by



- Presence of NS5A baseline mutation Y93H was the most significant predictor of lower SVR12.
- Although Y93H covariate had missing variable, the missing data was used for model development without imputation.

Figure 3. DCV and ASV Average Concentrations in Subjects with and without SVR12



The lower and upper ends of the boxes represent the 25th and 75th percentiles of the distribution, the line in the box represents the median, and the whiskers are drawn from the upper edge of the box to the largest value within 1.5 times of interquartile range above 75th percentile, and from the lower edge of the box to the smallest value within 1.5 times of interquartile range below 25th percentile.

- DCV + ASV Cavgss in subjects with and without SVR12 were comparable with considerable overlap

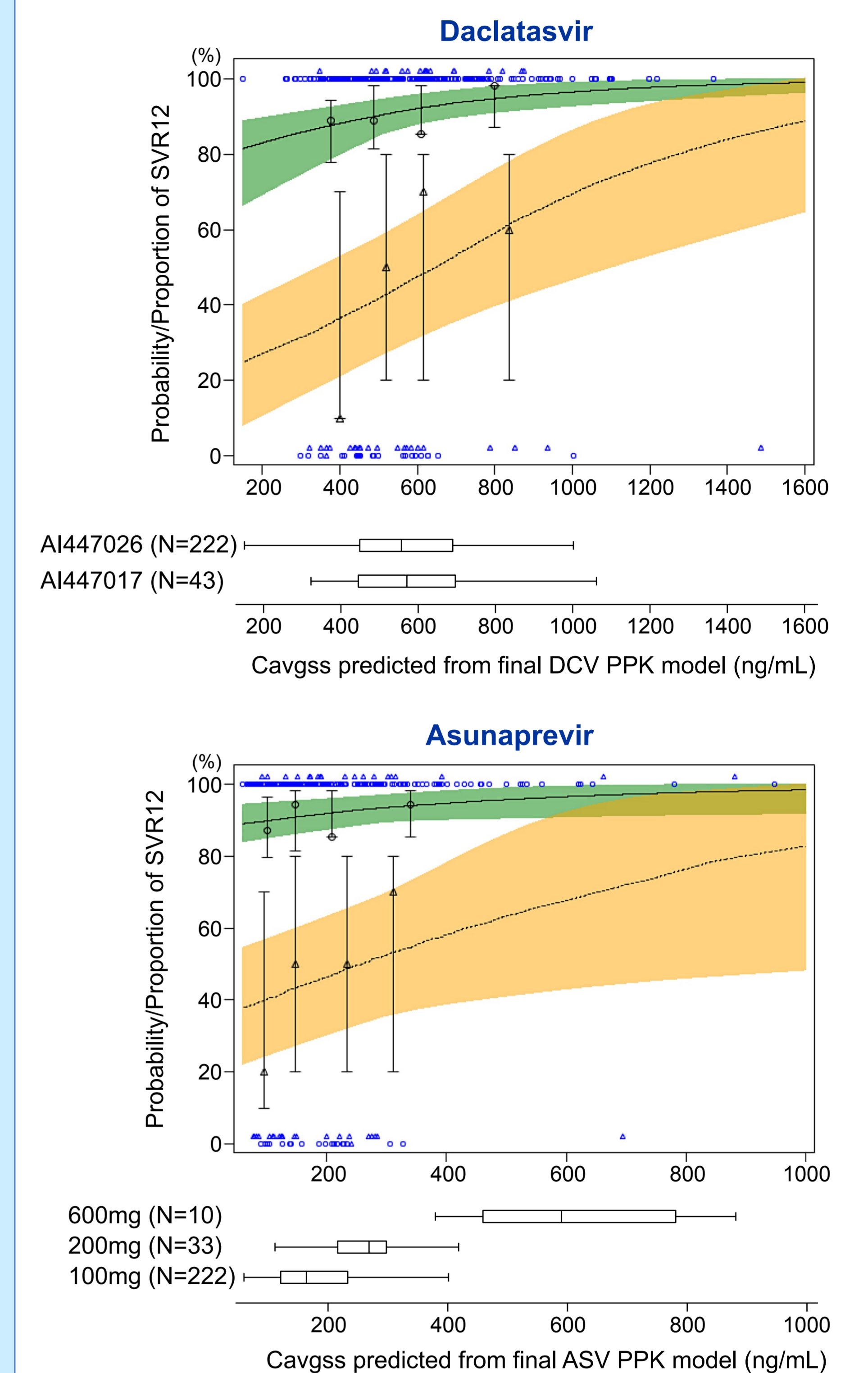
Table 3. Summary of Parameter Estimates in the Final Model for SVR12

Parameter	Estimate	Standard Error (RSE%)*	95% Confidence Interval*
ASV slope	0.0069	0.00236 (34.2)	-0.00109 - 0.0103
DCV slope	0.00368	0.000587 (16.0)	0.00192 - 0.00501
Interactions between ASV and DCV ( $\times 10^{-3}$ )	-0.00912	0.00253 (27.7)	-0.0122 - 0.0154
Presence of Y93H	-2.53	0.415 (16.4)	-3.48 - -1.83
Y93H missing	-0.508	1.10 (217)	-2.12 - 705

- A linear logistic regression model with Cavgss for both DCV and ASV and interaction between exposure of both compounds as the predictor variable was selected as the final base model, as this model provided an adequate and best parsimonious fit to the data for SVR12.
- The OATP1B1 haplotype was not statistically significant at 1% level of LRT relative to the base model and therefore they were not retained in the model.
- Covariate relationships were considered to be statistically significant provided that the relationship was significant at a 1% level of LRT relative to the full model. Based on this criterion, only the Y93H baseline mutation was retained in the final model (Table 3).
- In the final model, the slope for DCV Cavgss was statistically significant, but slope for ASV Cavgss and interaction between DCV and ASV were not (Table 3).

## RESULTS (cont.)

Figure 3. Observed Proportion and Model Predicted Probability of SVR12 versus Cavgss and the Effect of NS5A Resistance Mutations



The symbols represent the proportion of responders, grouped by quartiles of Cavgss and plotted at the median for the groups (circle; subjects without Y93H mutation, triangle; subjects with Y93H mutation); the centered curves and shaded areas represent median values and 95% confidence intervals of the model-predicted response probability, respectively (solid line; subjects without Y93H mutation, dotted line; subjects with Y93H mutation); the vertical bars represent the 95% model prediction intervals of the SVR12 rate, grouped by quartiles of Cavgss and plotted at the median for the groups; the boxplot shows the distribution of Cavgss by dose or study

## DISCUSSION

- High SVR12 rate was observed in the subjects without Y93H baseline mutation throughout observed exposure for DCV and ASV (Figure 3).
  - median: 91%, 95%CI: 88% - 96%, 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 NS5A resistance polymorphism was the most significant covariates for SVR12.
  - Presence of Y93H polymorphism was expected to result in a median predicted SVR12 of 45% (95% CI: 29% - 61%) at median Cavgss for DCV and ASV.
  - Simulations based on the final E-R model suggested that the probability of virologic failure in the presence of the Y93H mutation appears to be higher at low DCV and ASV concentrations (Figure 3).
- There was a shallow relationship between DCV exposure and SVR12, and a flatter and none or no significant relationship between ASV exposure and SVR12 (Figure 3).

## CONCLUSIONS

- The presence of the signature NS5A Y93H mutation at baseline was the only significant parameter of 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), Baseline 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-1b HCV infected Japanese subjects and no dose adjustment is needed based on any of the covariates tested.

## REFERENCES

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