A Population PK Model for Simeprevir in Healthy Volunteers and Patients

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Introduction:

- Simeprevir (SMV) is a once-daily capsule, second-generation hepatitis C virus (HCV) NS3/4A protease inhibitor with pangenotypic activity, with the exception of HCV genotype (GT) 3.
- SMV is approved in combination with peginterferon/ribavirin (PR) for HCV GT 1 infection, and as part of an interferon-free combination with sofosbuvir (SOF) for HCV GT1 infection in the US, and GT1 , GT4 and for HCV/HIV infection in the EU. Sustained virologic response 12 weeks after the planned end of treatment (SVR12) rates of ~80% have been reported in Phase III trials of SMV + PR in HCV GT1- and GT4-infected treatment-naïve and prior-relapser patients[1-4].

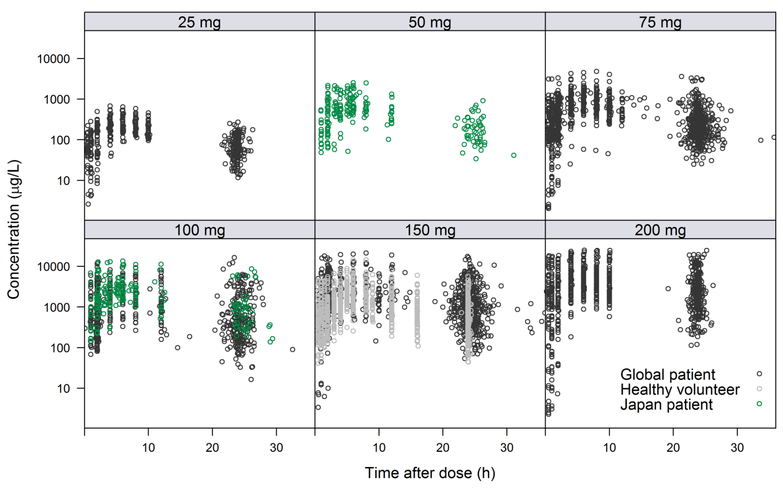
Objectives:

- Construct a population pharmacokinetic (PopPK) model characterizing the time course of simeprevir including terms for variability within and between individuals (IIV), as well as inter-occasion variability (IOV).
- Quantify potential non-linearity as a function of dose and/or simeprevir concentration.
- Test if any covariate, including HCV genotype (GT 1 vs. GT 4), health status (healthy volunteers vs. HCV patients) and patient ethnicity, is associated with changes in the pharmacokinetic (PK) parameter estimates of simeprevir.

Methods:

PK data from 15 different trials were included in the analysis, covering Phase I to Phase III (Figure 1). The dose levels ranged from 25-200 mg daily dose and 4 of the studies were performed in patients in Japan. In total 21024 PK observations from 2183 healthy volunteers and patients were included in the analysis. Rich data (defined as >2 samples within one dosing interval) was used for structural model development while the remaining data was used for covariate search with the exception of the study with data from HCV GT 4 patients which was not included in the model development.

Figure 1. Observed Concentration vs. Time After Dose by Dose



Results:

The final base popPK model describes the temporal course of simeprevir in patients using a two compartment model with a Michaelis Menten elimination from the central compartment. Absorption was described with 3 transit compartments with a mean transit time of 2.5 h. Random effects parameters describing IIV were estimated for maximum elimination capacity (Vmax), peripheral volume of distribution (Vp), relative bioavailability (F) and mean absorption transit time. IOV was quantified on relative bioavailability. The maximum elimination capacity was estimated to be higher in healthy volunteers compared to patients. Further, Asian patients were estimated to have a higher relative bioavailability as compared to global patients. Parameter estimates for the base model without covariates are shown in Table 1. The impact of patient covariates on PK was evaluated using the linearized stepwise forward inclusion method with backwards elimination[5]. The covariates investigated were body weight, ethnicity, gender, age, bilirubin, ALT, AST, albumin and METAVIR score (baseline values). The model chosen as the final covariate model included METAVIR score on relative bioavailability and peripheral volume of distribution, gender on relative bioavailability, age on maximum elimination capacity and mean transit time for absorption and ALT on bioavailability. Predictions of AUC0-24h at steady state for each dose level based on the final covariate model can be found in Figure 3. The impact of the covariates on exposure were all minor, especially in relation to the large unexplained variability in exposure (Figure 4).

Table 1. Estimated Parameters Base Model

Parameter	Estimate	95% CI
Vmax (mg/(L*h))	44700	(41700 - 47700)
Higher Vmax in healthy volunteer (%)	31.6	(12.5 - 50.8)
Central volume of distribution (L)	31.6	(57.1 - 62.8)
Inter comparment clearance (L/h)	2.14	(2.00 - 2.28)
Peripheral volume of distribution (L)	139	(129 - 149)
Difference Asian relative bioavailability (F)	0.867	(0.746 - 0.988)
Km (mg/L)	8960	(8180 - 9740)
Number transit compartments	2.98	(2.90 - 3.05)
Mean transit time (h)	2.48	(2.43 - 2.53)
Proportional error (%)	31.3	(0.311 - 0.315)
IIV Vmax	0.158	(0.139 - 0.177)
IIV Vp	3.75	(3.18 - 4.33)
IIV F	0.208	(0.181 - 0.236)
IIV mean transit time absorption	0.0727	(0.0662 - 0.0791)
IOV F	0.22	(0.211 - 0.229)

Figure 2. Visual Predictive Check of the Base Model

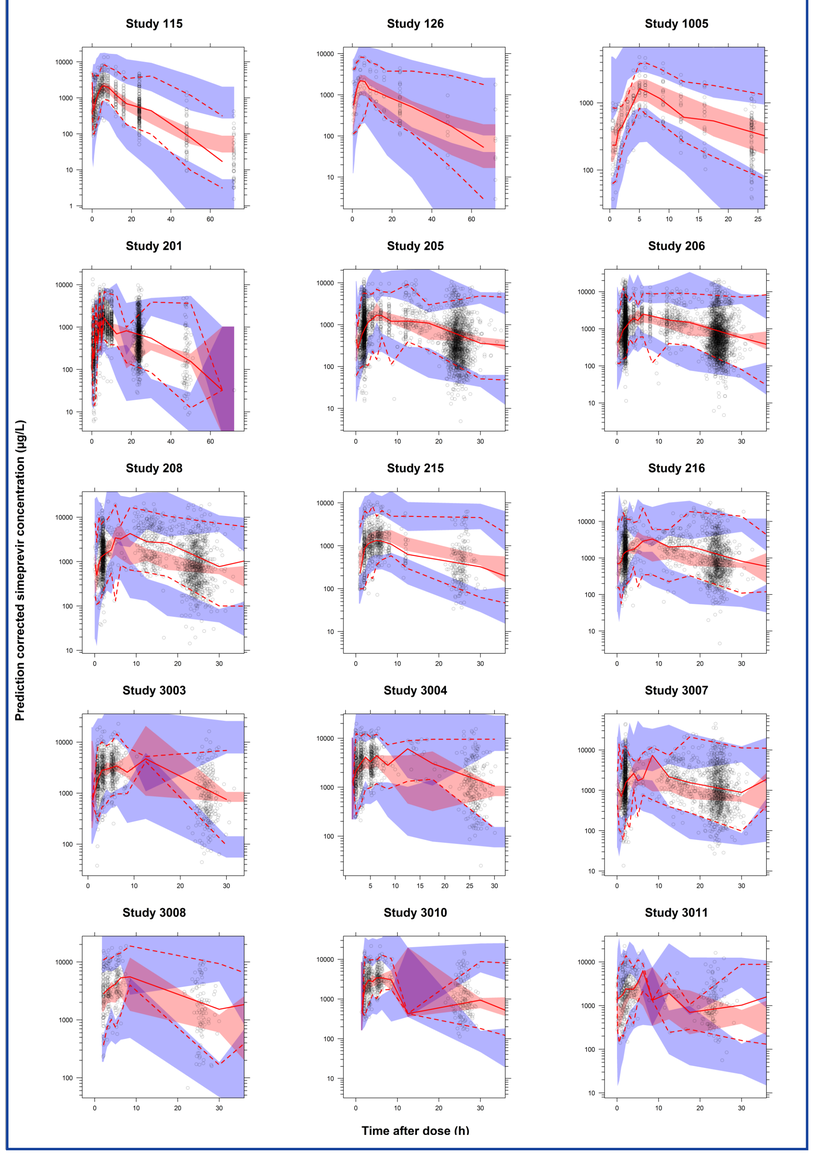
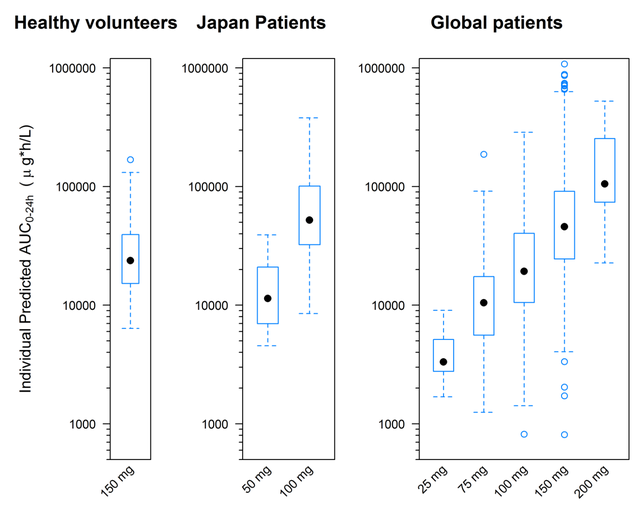


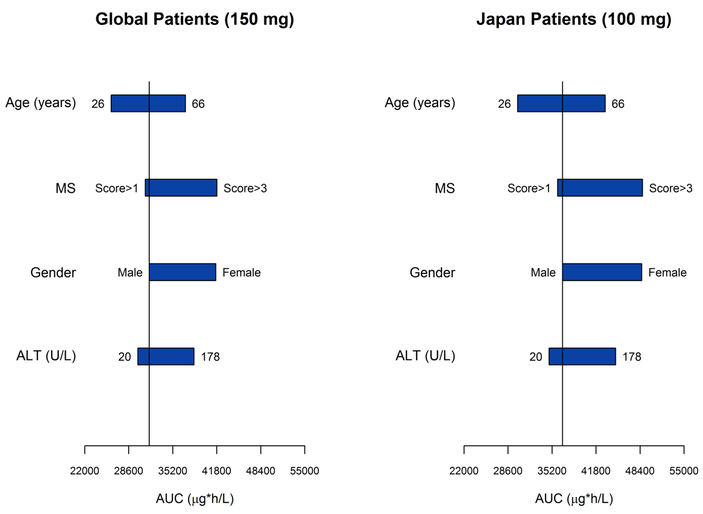
Figure 3. Individual Predicted $AUC_{0\text{-}24h}$ vs Dose by Healthy Volunteers, Japan Patients or Global Patients, Based on Final Covariate Model



The filled dot shows the median of the data, values between the first and the third quartile (25% and 75%) are within the box. The end of the whiskers extend to the highest and lowest prediction up to a maximum of 1.5 time the box height. The open dots are outliers.

$AUC_{0\text{-}24h}$ (median and 5th to 95th percentile) at steady state following 150 mg daily dosing of simeprevir in global patients was estimated to 46900 µg·h/L (10900-285000), while C_{0h} was estimated to 1030 µg/L (149-9500). The visual predictive checks indicate good model predictive performance for all studies including the study with genotype 4 patients (study 3011) not included in the model development (Figure 2).

Figure 4. The Impact of Covariates on $AUC_{0\text{-}24h}$



The vertical line shows the exposure in an typical patient (50 years old male with ALT of 53 (IU=L) and METAVIR Score (MS) of 1). The left and right end of the bar illustrates the $AUC_{0\text{-}24h}$ in a patient with the 5th or 95th percentile covariate value. E.g. for age, the 5th and 95th percentiles of age are 26 and 66 years. For METAVIR Score (MS) the left end of the bar represents a patient with MS score > 1 but < 4 and the right end of the bar a patient with MS score = 4.

Conclusions

The time course of simeprevir PK was described by a two compartment model with a Michaelis Menten elimination and transit compartments for absorption. The variability in simeprevir exposure was large and the model suggests that the majority of this variability is associated with the peripheral volume of distribution where IIV was estimated to 188%. The largest covariate effect was found for Asian patients with a relative bioavailability predicted to be 70.4% higher as compared to global patients. However, the covariate effects on exposures were very small compared with the observed random variability, indicating that the clinical relevance of the effect of METAVIR score, gender, age and ALT on simeprevir exposure is limited.

References:

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