Population pharmacokinetic modeling of simeprevir-odalasvir interaction in healthy volunteers

E. Valade (1), E. Hoeben (1), T.N. Kakuda (2), M. McClure (2), C. Westland (2), J. Perez Ruixo (1) and O. Ackaert (1)

(1) Janssen Research and Development, Global Clinical Pharmacology, Turnhoutseweg 30, B-2340 Beerse, Belgium; (2) Alios BioPharma, Inc., part of the Janssen Pharmaceutical Companies, South San Francisco, CA, USA.

INTRODUCTION

Hepatitis C virus (HCV) is a worldwide public health problem since the number of total global viraemic HCV infections is estimated at 71 million. The combination of a new nucleotide analog inhibitor AL-335 with Odalasvir (ACH-3102 or ODV), a NS5A inhibitor and Simeprevir (SMV), a NS3/4A protease inhibitor is being evaluated as a potential safe, convenient and efficacious oral fixed dose combination for the treatment of chronic HCV infection.

Results from *in vitro* experiments demonstrate SMV metabolism by the hepatic CYP3A4 and reported SMV as a substrate for Pgp/MDR1, MRP2, OATP1B1/3 and OATP2B1, as well as an inhibitor of OATP1B1/3, Pgp/MDR1 and MRP2. Biliary excretion is also the predominant route for the elimination of ODV. In vitro data suggest that ODV is an OATB1B1 substrate and an inhibitor of Pgp/MDR1.

In the phase I AL335-602 study, the pharmacokinetics of the combination ODV + SMV + AL-335 has been studied in healthy volunteers (HV) [1]. No influence of AL-335 on ODV and SMV PK was observed whereas significant effects of SMV and ODV on AL-335 PK were described. A significant dual interaction between ODV and SMV was observed.

OBJECTIVE

To develop a joint population pharmacokinetic (PK) model describing the PK drug-drug interaction (DDI) between SMV and ODV.

To understand the pharmacokinetic behavior of these 2 compounds given in combination in order to support the development of the combination of AL-335 + ODV + SMV.

METHODS

Clinical Data

The data used in the analysis were obtained from a phase 1, open-label, two group, fixed-sequence study in healthy volunteers (Figure 1). Dosing regimen was 800 mg QD for AL-335, 150 mg QD for SMV and 150 mg loading dose + 50 mg QD for ODV. A total of 997 SMV (344 in monotherapy or with AL-335, 653 in combination with ODV +/- AL-335) and 1215 ODV (403 in monotherapy or with AL-335, 812 in combination with SMV +/- AL-335) plasma concentrations were used.

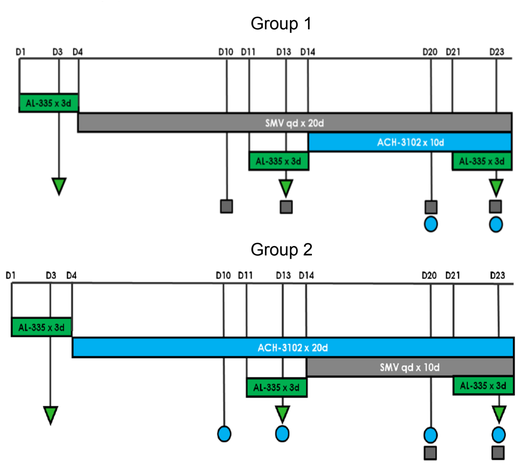
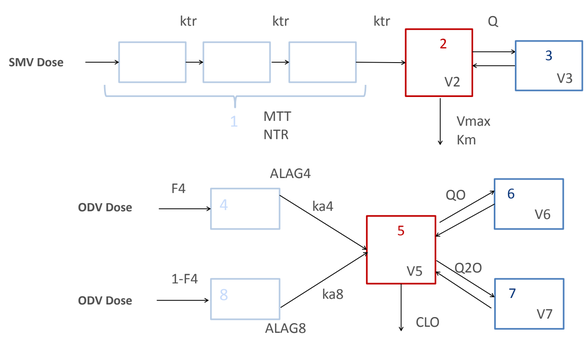


Figure 1. Clinical study design: study treatments and sampling schedule

Modeling

The data were analyzed by a non-linear mixed effects modeling approach, using NONMEM software [2].

- To quantify the PK of SMV and ODV in the absence of interaction, previous models describing the PK of SMV [3] and ODV (data on file) in monotherapy were used (Figure 2).



With ktr for transit rate constant, MTT for mean transit time, NTR for number of transit compartments, V2 for central volume of distribution, Q for inter-compartmental clearance, V3 for peripheral volume of distribution, Vmax for maximum elimination capacity and Km for Michaelis constant, corresponding to the SMV concentration that produces 50 % of the maximum elimination capacity.

With Ftot for relative bioavailability, F4 for relative fraction that passes through first absorption compartment, ALAG4 and ALAG8 for lag-times in each absorption compartment, ka4 and ka8 for absorption rate constants in each absorption compartment, V5 for central volume of distribution, CLO for elimination clearance, QO for first inter-compartmental clearance, Q2O for second inter-compartmental clearance, V6 and V7 for first and second peripheral volumes of distribution.

Figure 2. Schematic overview of the population PK models for SMV and ODV in monotherapy

- To investigate the dual interaction, parameters were fixed to previous estimates and the effect of a compound on the other one was tested as a categorical covariate or as being dependent on the other compound's predicted concentration at each time point. The effect of SMV on ODV apparent clearance (*CLO/F*tot) and relative bioavailability (Ftot) was evaluated. Similarly, the effect of ODV on SMV mean transit time, relative bioavailability (F_1), and the parameters quantifying the SMV Michaelis-Menten elimination (V_{max} and K_m) was investigated. Interaction model parameters were first evaluated with FO method and selected models were estimated with FOCE interaction method.
- The resulting joint population PK model was used to simulate different dosing regimens of ODV and SMV in combination.

RESULTS

The effect of ODV on SMV was best described by a combination of a categorical effect on SMV F_1 and a competitive inhibition on SMV elimination depending on ODV predicted concentrations.

$$F_1 = 1 \cdot \theta_{odv\_F1}{}^{COMB}$$

$$CLS/F_1 = \frac{Vmax/F_1 \cdot [SMV]}{Km \cdot \left(1 + \frac{[ODV]}{Ki}\right) + [SMV]}$$

With θ_{ODV_F1} the effect of ODV on SMV F_1, COMB a categorical covariate equal to 1 if ODV is co-administered with SMV, [SMV] the predicted SMV concentration (A(2)/V2), [ODV] the predicted ODV concentration (A(5)/V5) and Ki the inhibitory constant of ODV on SMV.

The effect of SMV on ODV was best described by an inhibition of CLO/Ftot with an I_{max} model depending on SMV predicted concentrations.

$$\frac{CLO}{Ftot} = TCLO \cdot \left(1 - \frac{Imax \cdot [SMV]}{IC_{50} + [SMV]}\right)$$

With TCLO the typical value of ODV apparent elimination clearance, Imax the maximum inhibition on TCLO, [SMV] the predicted SMV concentration (A(2)/V2), and IC_{50} the SMV concentration at which 50% of maximum inhibition of TCLO is reached.

Table 1. Population PK parameters for the joint ODV-SMV model

ODV Parameters *		SMV Parameters *		DDI		
ka4 (h^{-1})	0.0207	**MTT (h)**	2.48	Parameter	Estimate	RSE (%)
F4	1.33	**NTR**	2.98		**ODV**	
ALAG4 (h)	1.42	**F1**	1	**Imax**	0.467	4.3 %
ka8 (h^{-1})	0.2	**Vmax/F1 (µg/h)**	58825	**IC_{50} (µg/L)**	257	27.4 %
ALAG8 (h)	4.56	**Km (µg/L)**	8960	**σ^2 add**	871	17.7 %
Ftot	2.3	**V2/F1 (L)**	60	**σ^2 prop**	0.0162	9.7 %
V5/Ftot (L)	7.39	**Q/F1 (L/h)**	2.14		**SMV**	
CLO/Ftot (L/h)	7.66	**V3/F1 (L)**	139	**θ_{ODV_F1}**	1.26	16.3 %
QO/Ftot (L/h)	15.6	**ω^2 MTT**	0.0727	**Ki (µg/L)**	1610	35.1 %
V6/Ftot (L)	1360	**ω^2 F1**	0.208	**σ^2 prop**	0.23	10.7 %
Q2O/Ftot (L/h)	4.67	**ω^2 Vmax/F1**	0.158			
V7/Ftot (L)	3610	**ω^2 V3/F1**	3.75			
ω^2 F4-Ftot	0.479	**ω^2 IOV F1**	0.0221			

*fixed parameters

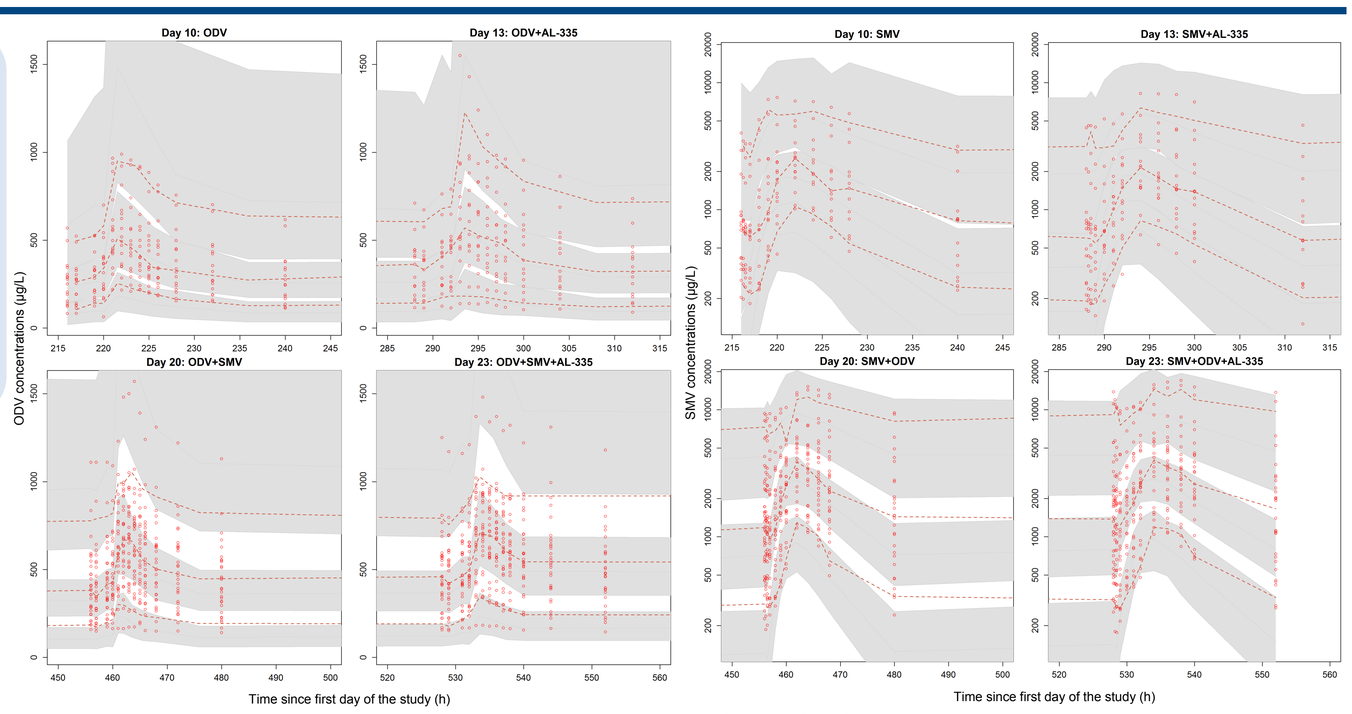


Figure 3. Visual predictive check of the joint ODV-SMV model

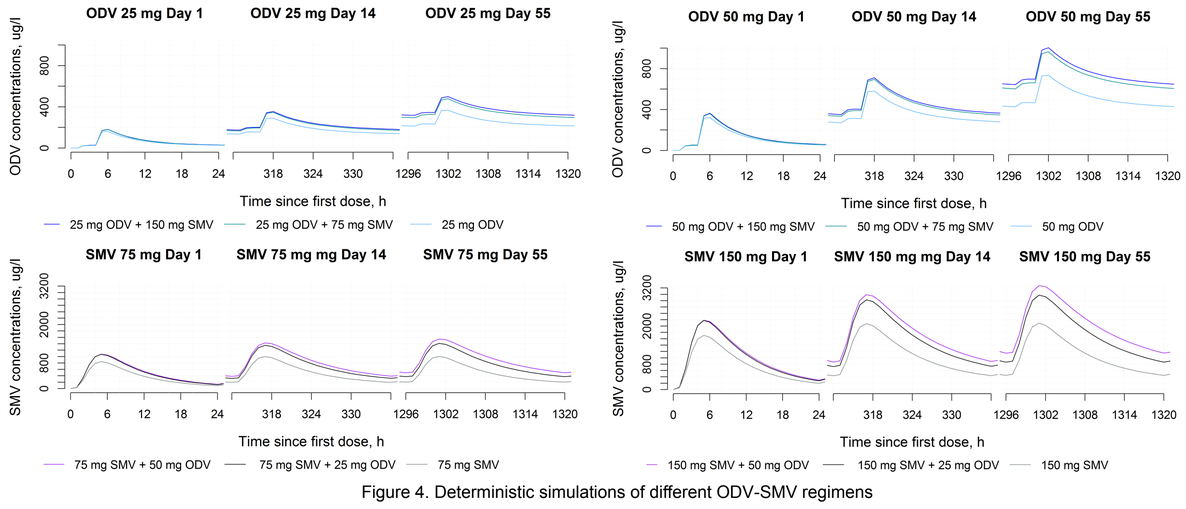


Figure 4. Deterministic simulations of different ODV-SMV regimens

CONCLUSION

- A population PK model describing the dual ODV-SMV PK interaction has been developed in HV and was able to capture the increase of SMV and ODV exposures when administered together.
- The increase of SMV exposure may be explained by Pgp inhibition and/or OATP1B1 competitive inhibition by ODV. The increase in ODV exposure may result from competitive inhibition of OATP1B1 by SMV.
- This model can be used to investigate the impact of these PK interactions in patients with HCV infection and to support the design of future clinical studies with ODV – SMV combination.

REFERENCES

[1] Kakuda TN, *et al.* Pharmacokinetics (PK), safety and tolerability of the 2- and 3-direct acting antiviral (DAA) combination of AL-335, odalasvir (ODV) and simeprevir (SMV) administered once-daily (QD) in healthy volunteers (HVs). AASLD 2016; abstract 1456.

[2] NONMEM Users Guides (1989–2009). Beal SL, Sheiner LB, Boeckmann AJ, and Bauer RJ (eds). Icon Development Solutions, Ellicott City, MD.

[3] Viberg A, Petersson K, Hoeben E, Brochot A. A population PK model for simeprevir in healthy volunteers and patients. PAGE meeting; 2016; Lisboa, Portugal. Available from: http://www.page-meeting.org/?abstract=3368.

Janssen Infectious Diseases & Vaccines

PHARMACEUTICAL COMPANIES OF Johnson & Johnson