PBPK modeling to characterize the interplay between metabolism and transport in the disposition of simeprevir in healthy volunteers and HCV infected patients

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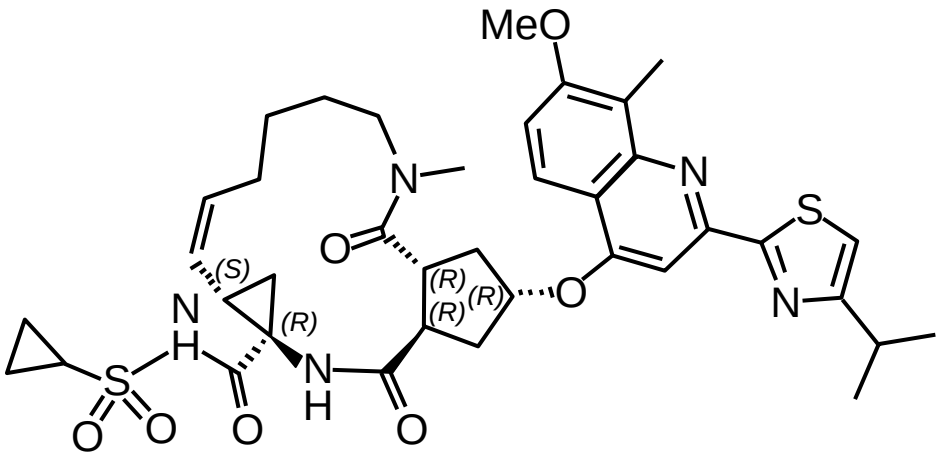
Simeprevir (SMV/TMC435)



- Once-daily capsule, HCV NS3/4A protease inhibitor
- Approved in Japan, Canada, the USA, Russia and Europe
- Antiviral activity in patients infected with HCV GT 1, 2, 4, 5, and 6

- Phase III trials of SMV+PR in HCV GT 1- and GT 4-infected treatment-naïves and relapsers showed SVR12 rates ~80%[1–4]
- In a Phase II trial (COSMOS) of SMV + sofosbuvir ± ribavirin in HCV GT 1-infected treatment-naïves and prior null responders, the overall SVR12 rate was 92.2%[5,6]
- Safe and well tolerated (~3800 patients treated in clinical trials to date)
- In development as part of IFN-free combinations

GT, genotype; IFN, interferon; PR, peginterferon-α-2a/-2b + ribavirin; SVR12, sustained virologic response 12 weeks after end of treatment

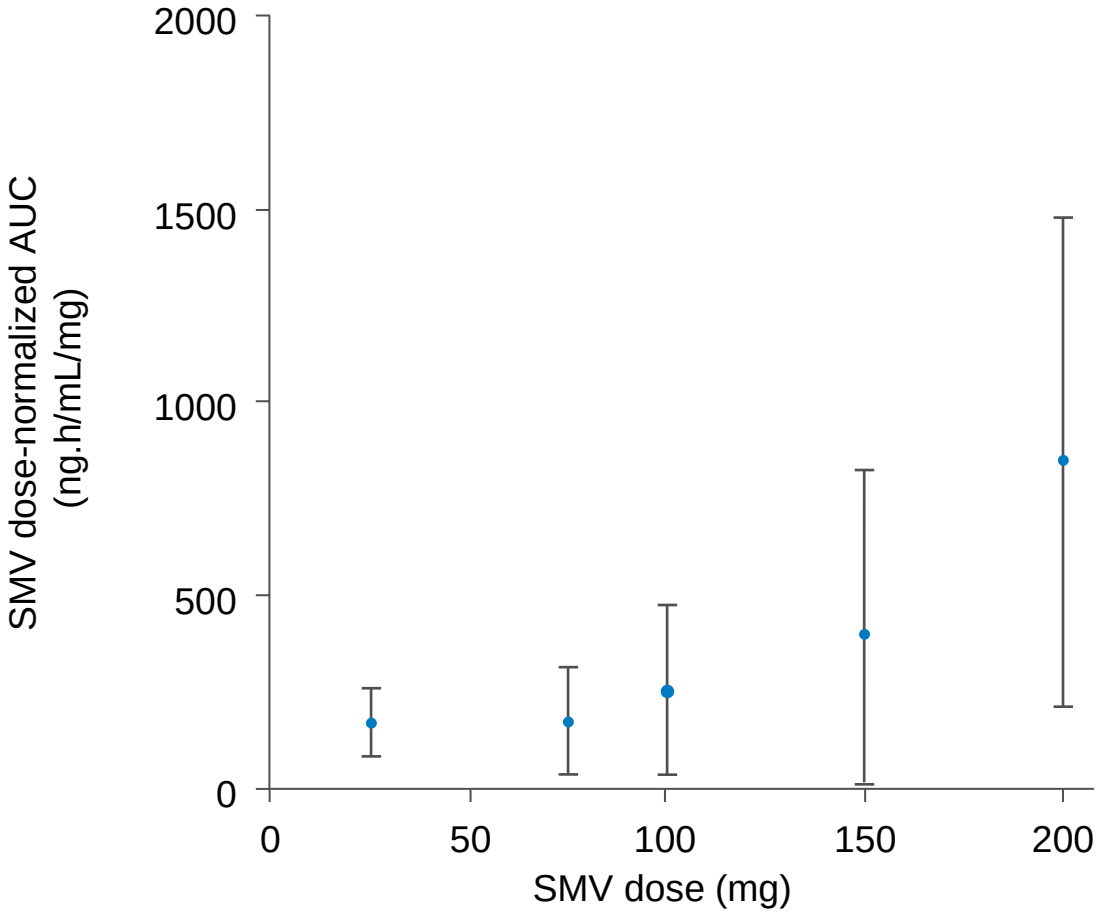
1. Jacobson I *et al*. Lancet In press; 2. Manns M *et al*. Lancet In press; 3. Forns X *et al*. Gastroenterology Mar 3 [Epub ahead of print]; 4. Moreno C *et al*. HepDART 2013; 5. Lawitz E *et al*. EASL 2014; 6. Sukowski MS *et al.* EASL 2014.

Pharmacokinetic challenges of simeprevir

- Substantial interpatient variability in plasma concentrations
  - No correlation with sustained virologic response (SVR) at therapeutic dose
- More than dose-proportional increase in exposure
- Increase in exposure on repeated dosing
  - Steady-state achieved in approximately 7 days
- Difference in pharmacokinetics between healthy volunteers and patients: 2–3-fold higher exposure in patients
- Ethnic differences: higher exposure in Japanese patients
- Substrate of several uptake and efflux transporters

Dose-normalized AUC vs dose in HCV patients

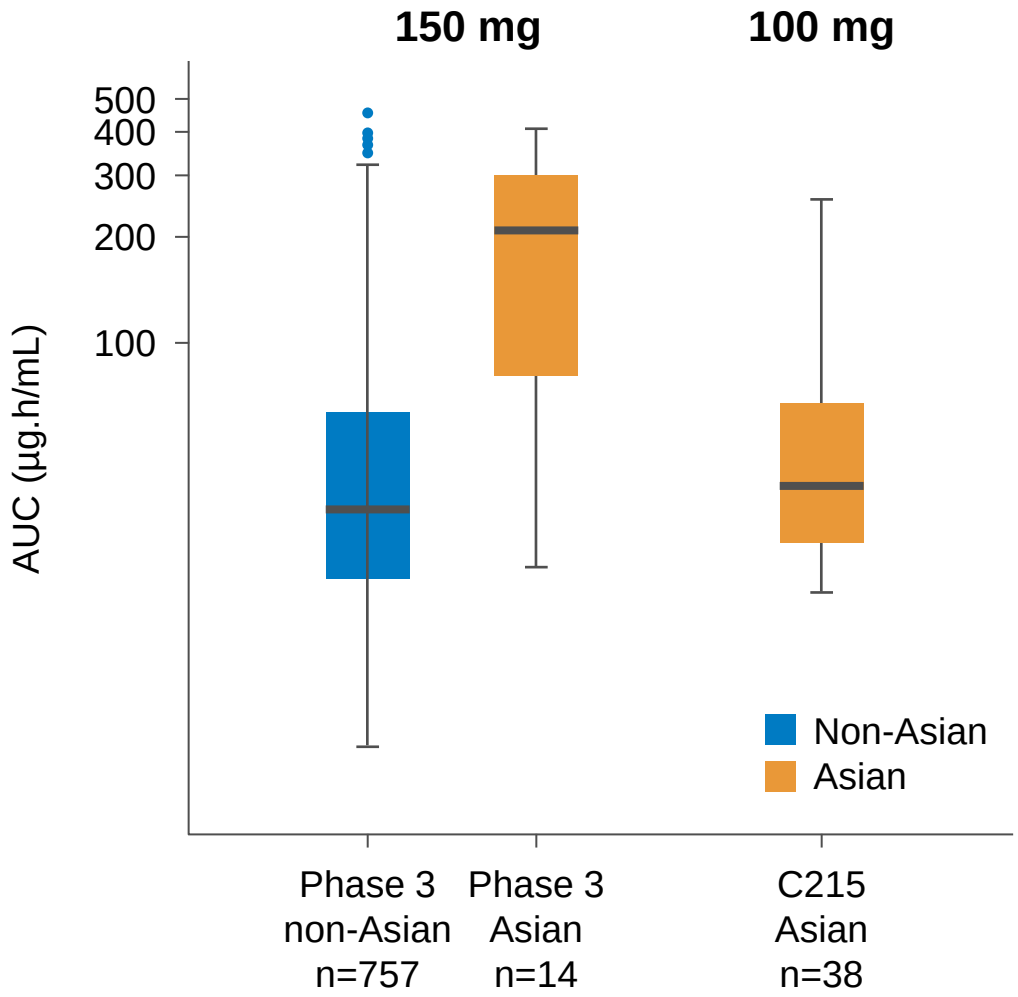
Phase 2/3 studies C201, C205, C206, C208, C216, HPC3007



Dose (mg)	% CV	N
25	52	18
75	79	177
100	87	196
150	111	1133
200	75	30

CV, coefficient of variation

AUC in non-Asian global phase 3 studies and in a Japanese phase 2 study

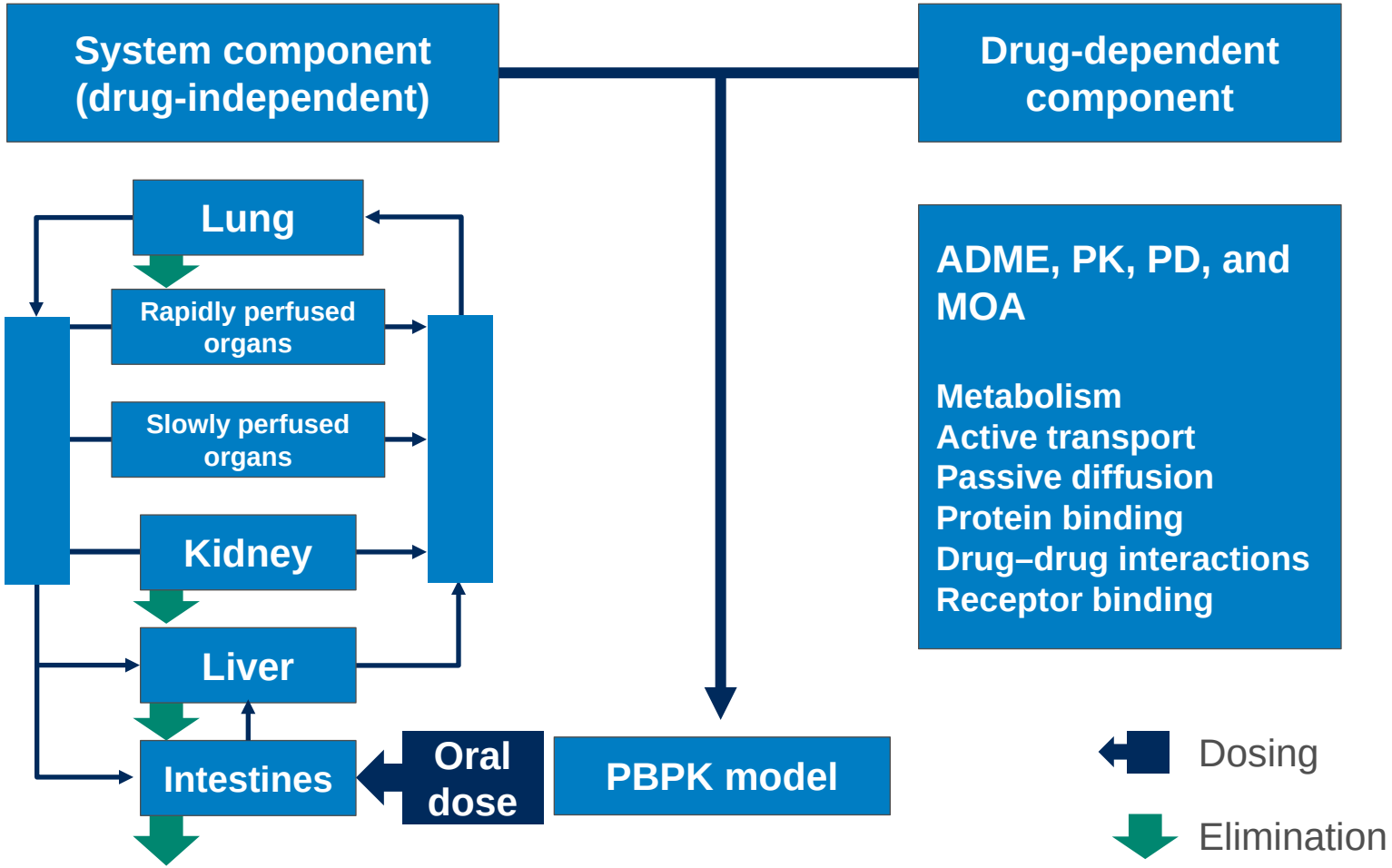


Use of PBPK modeling to understand:

- Reason for non-linear PK
- Reason for large interpatient variability
- Mechanism for difference between healthy volunteers and HCV-infected patients
- Ethnic differences
- Drug–drug interactions in HCV-infected patients

PBPK, physiologically based pharmacokinetic

PBPK model components

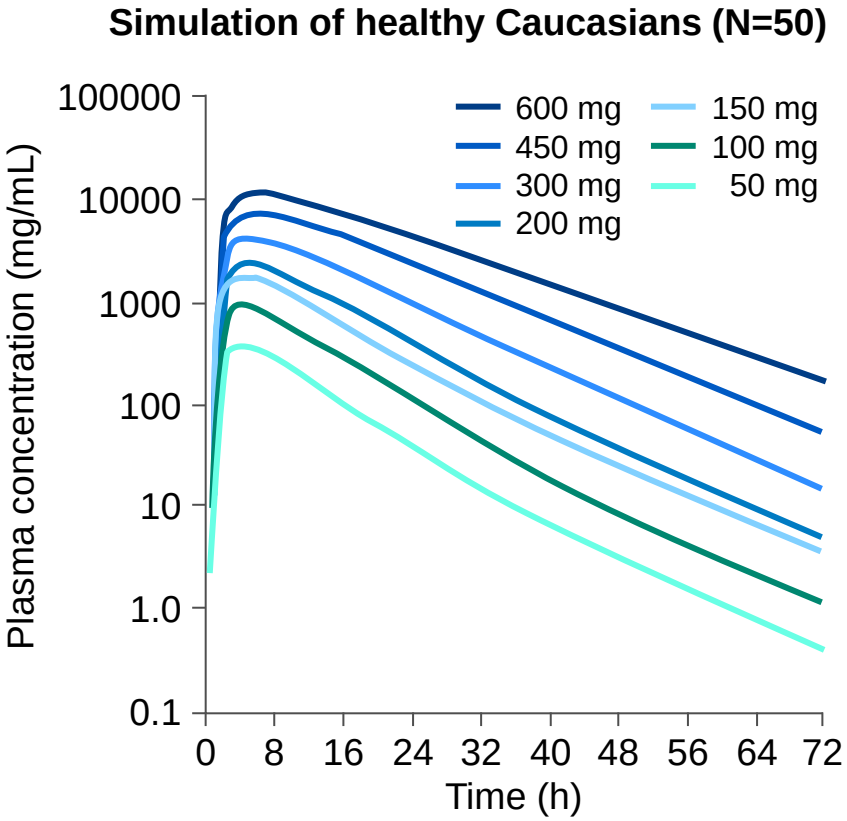


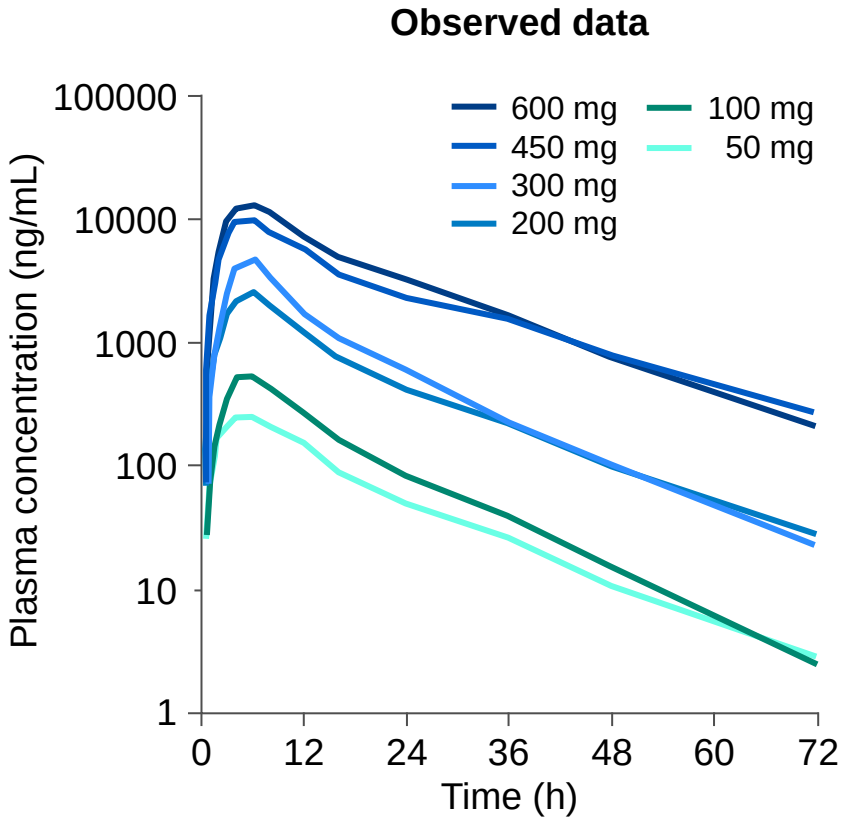
MOA, mode of action

Simeprevir parameters used for simulations

- Physicochemical properties
- Low solubilities at all pH
- Saturation of hepatic uptake (non-linear distribution)
- Saturation of liver and gut CYP3A4 (non-linear clearance)
- Clinical pharmacokinetics in healthy volunteers
- Not included:
  - Active efflux in gastro-intestinal tract via, for example, P-gp; not considered to play a major role, confirmed by data from drug-drug interaction with cyclosporine and data from single dose ritonavir

Model verification:
Simulating the known – single dose studies

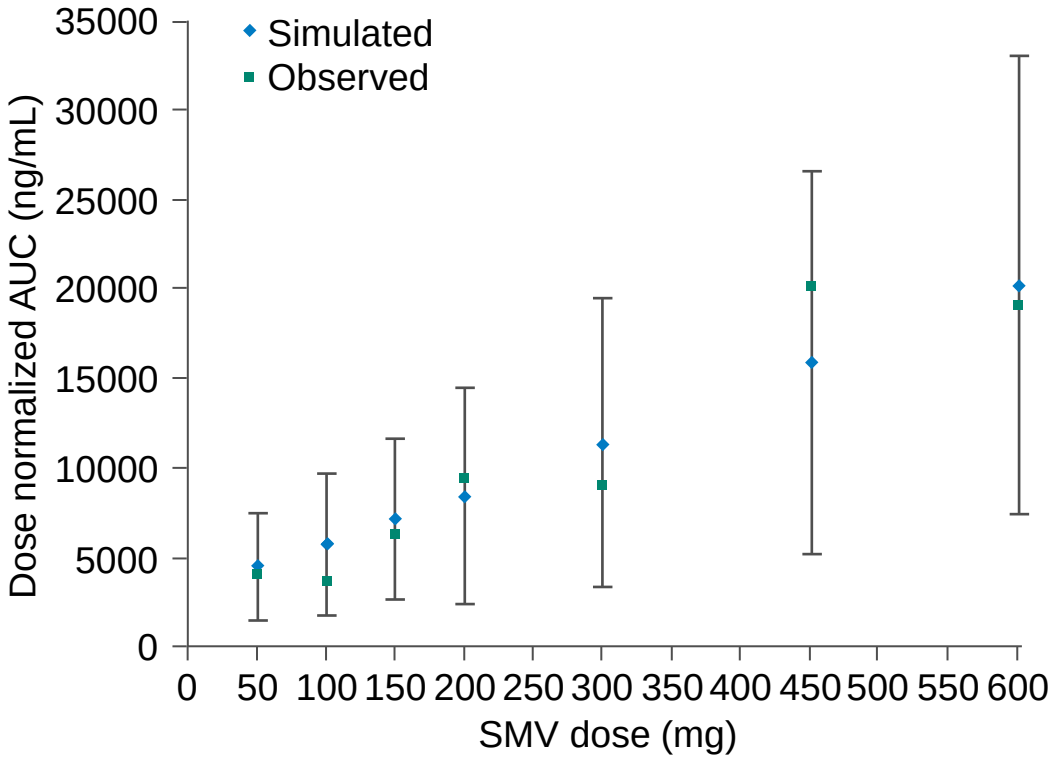




- Minimal change in half-life despite pronounced non-linear increase in exposure with dose
  - Saturable gut and liver CYP3A4 metabolism, and saturation of active uptake
- Simultaneous decrease in both V_d and Cl, therefore $t_{1/2}$ remains constant

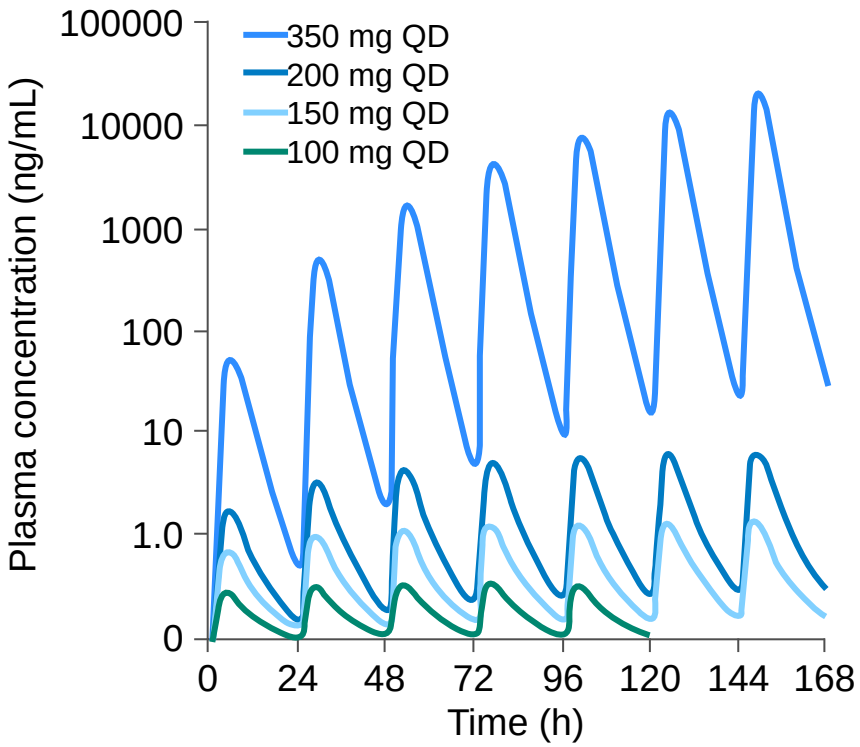
Model verification:
Simulating the known – single dose studies

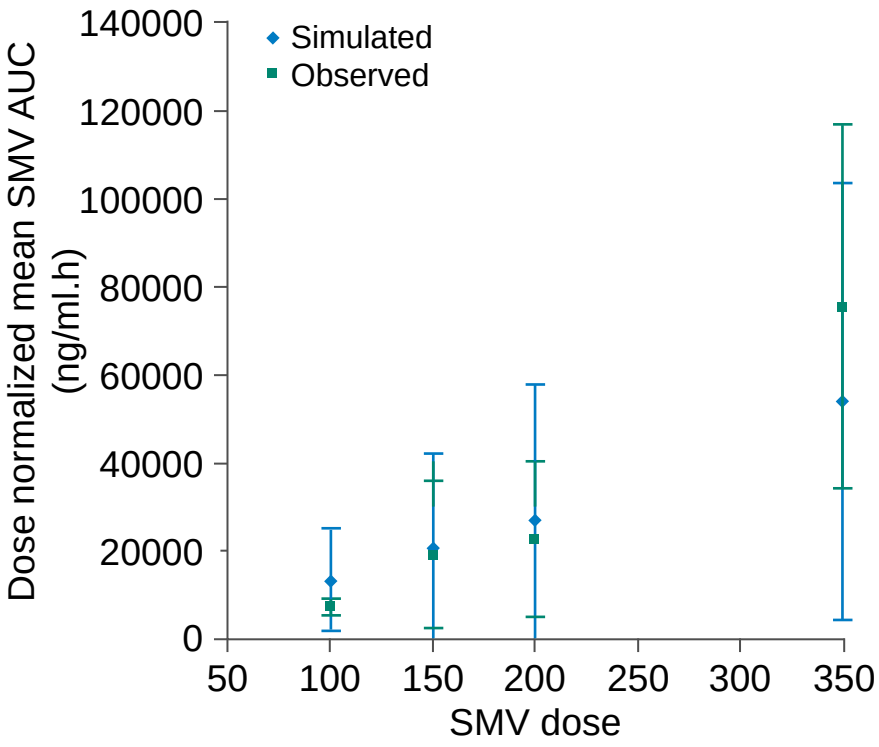
Simulated average (±SD) and observed average SMV plasma AUC_{0-72h} after single dose administration



- AUC dose normalized versus the 50 mg SMV dose. Simulations performed in 54 healthy Caucasian male volunteers. Observed data in 6 patients except for 150 mg SMV dose in 24 patients

Model verification:
Simulating the known – multiple dose studies





- Dose and time-dependant PK is explained by saturable clearance and saturable distribution
  - Lack of time-dependent inhibition was also confirmed from midazolam DDI studies

Model verification:
DDI studies

- Simulation of the following interactions, and comparison with clinical DDI studies in healthy volunteers:
  - CYP3A4 interaction without impact on hepatic uptake
    - Ritonavir (100 mg QD/BID) and erythromycin (500 mg TID) inhibit intestinal and hepatic CYP3A4 and intestinal P-gp but not hepatic OATPs
  - OATP interaction without impact on metabolic clearance
    - Cyclosporine (100 mg) inhibits intestinal P-gp and hepatic OATPs
  - Combined OATP and CYP3A4 interactions
    - Rifampicin (600 mg QD) inhibits OATP and induces liver and intestinal CYP3A. Also inhibits hepatic MRP2 and induces intestinal P-gp

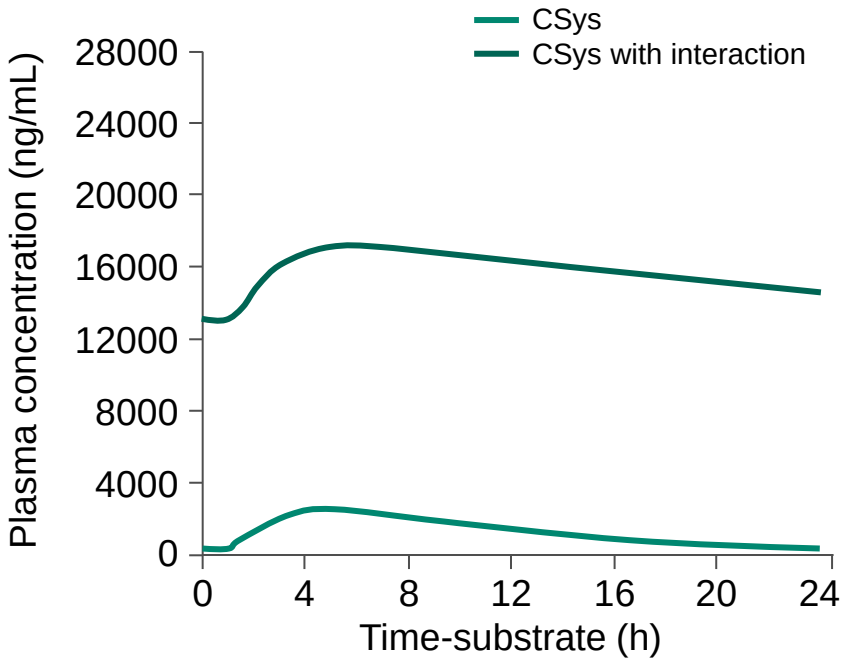
MRP, multidrug resistance-associated protein; P-gp, P-glycoprotein

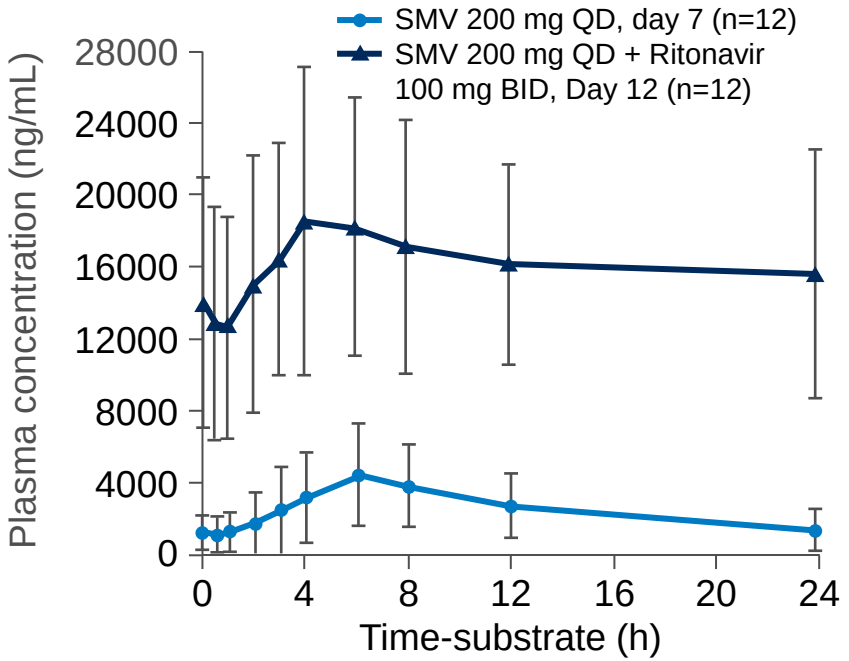
Model verification:
Compound file modification to match clinical data

- Efavirenz 600 mg QD
  - modification of published model by Rekic *et al*. fu_{gut} was reduced to remove intestinal CYP3A4 induction
- Ritonavir 100 mg QD and BID
  - modified to include CYP3A4 inactivation kinetic parameters so that complete inhibition of gut and liver CYP3A4 is achieved (Ernest *et al*., Mathias *et al*.)
- Rifampicin 600 mg QD
  - Model by Xu *et al.* was used. Induction of CYP3A4 on Day 1 was removed. OATP1B1/3 K_i modified based on published statin interactions (Maeda *et al*.)
- Erythromycin 500 mg TID
  - Simcyp Sim-file was used unmodified
- Cyclosporine 100 mg
  - Model by Varma *et al.* was modified. CYP3A4 Cl_{int} added. Lag time, F_a, K_a included in first-order absorption model, muscle K_p reduced to match observed $V_{d,ss}$. OATP inhibition, $F_{u,\ inc}$ and CYP3A4 K_i were modified to match published DDI data

Model verification:
Ritonavir DDI

Plasma concentration time profile for 200 mg QD. SMV administration for 7 days with and without 100 mg BID ritonavir in healthy Caucasian volunteers (study C104), and simulated data in 36 patients





	Simulated GMR		Observed GMR	
	C_{max}	AUC	C_{max}	AUC
Ritonavir	5.8	10	4.7 (3.8–5.8)	7.2 (5.6–9.2)

PBPK DDI summary

Source: FDA clinical pharmacology review (modified)

PBPK model simulated and observed exposure changes of SMV by different enzyme and/or transport inhibitors and inducers

Inhibitor / inducer (mechanisms)	SMV dose	AUC (C_{max}) ratio		Explanation of observed DDI findings
		Sim	Obs	
Ritonavir (Strong CYP3A inhibitor)	Single	2.1 (13)	1.8 (1.3)	CYP3A inhibition augmented OATP saturation over time
	Multiple	10 (5.8)	7.2 (4.7)	
Erythromycin (moderate CYP3A inhibitor)	Single	1.4 (1.1)	-	Erythromycin DDI study was done using lower SMV dose (150mg) than the ritonavir study (200mg). At lower doses, stronger interaction is seen
	Multiple	6.2 (3.7)	7.5 (4.5)	
Cyclosporine (OATP inhibitor)	Multiple	1.3 (C_{min} ratio)	1.2 (C_{min} ratio)	OATP saturation after multiple dosing diminished inhibitor effect
Rifampin (strong CYP3A inducer, OATP inhibitor)	Single	2.1 (1.8)	-	OATP inhibition + CYP3A4 induction: ↑C_{max} and ↓AUC of SMV
	Multiple	0.6 (1.1)	0.5 (1.3)	
Efavirenz (moderate CYP3A inducer)	Multiple	0.3 (0.6)	0.5 (0.3)	CYP3A induction only, no effect on OATP

Summary

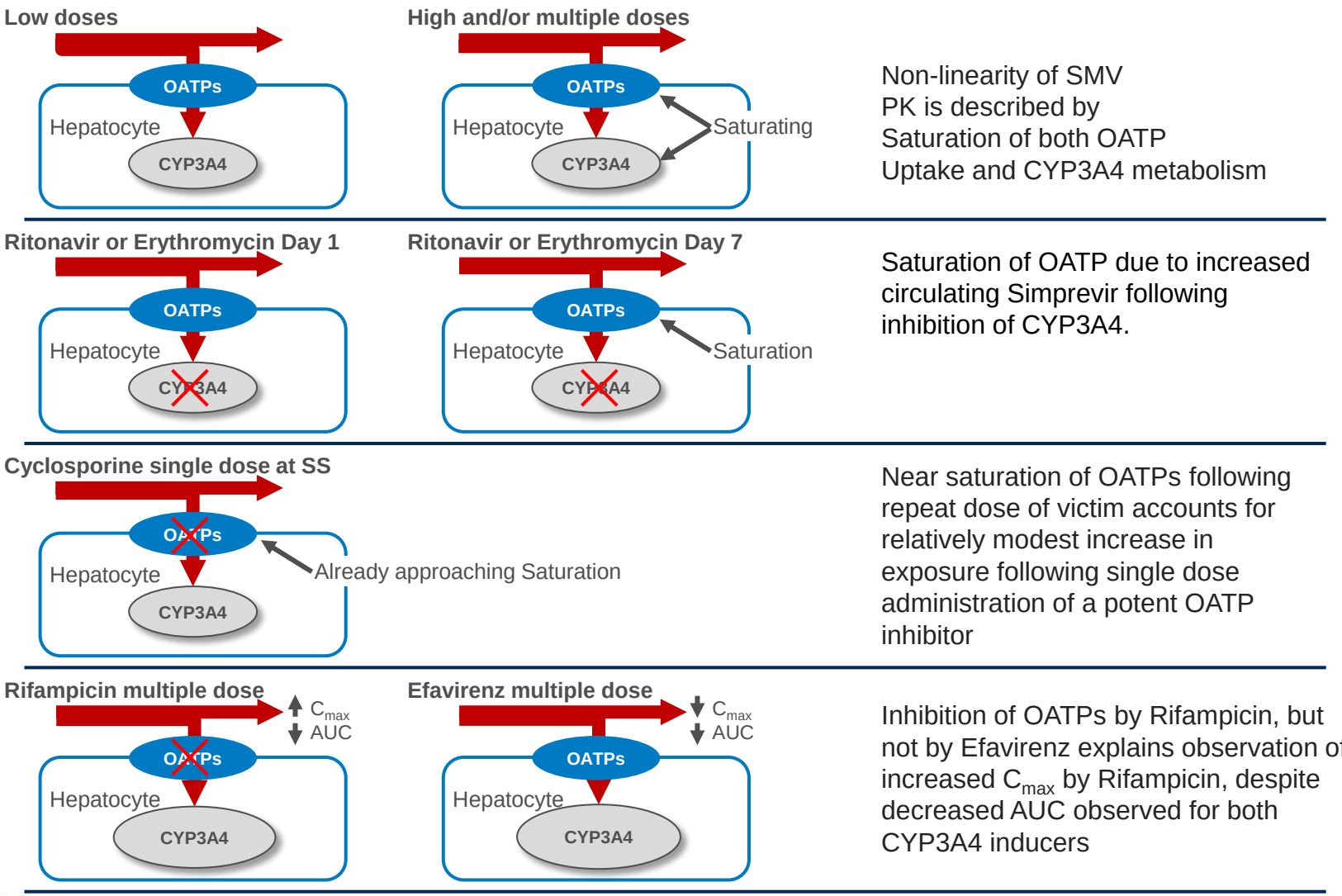
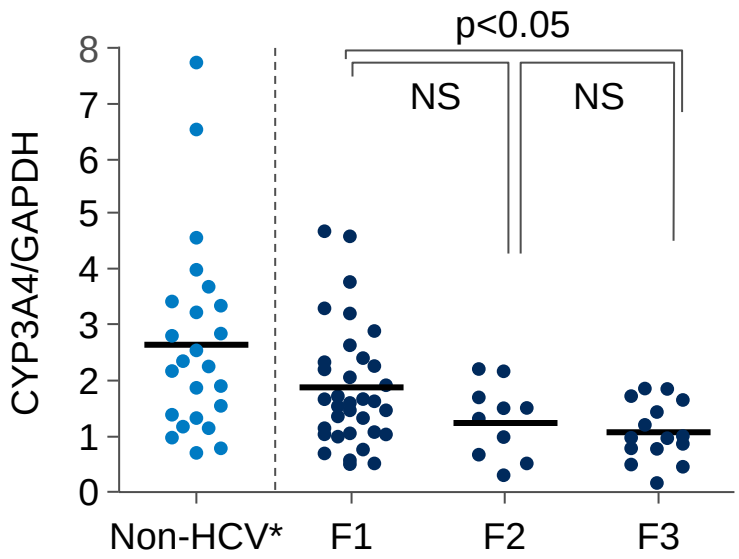
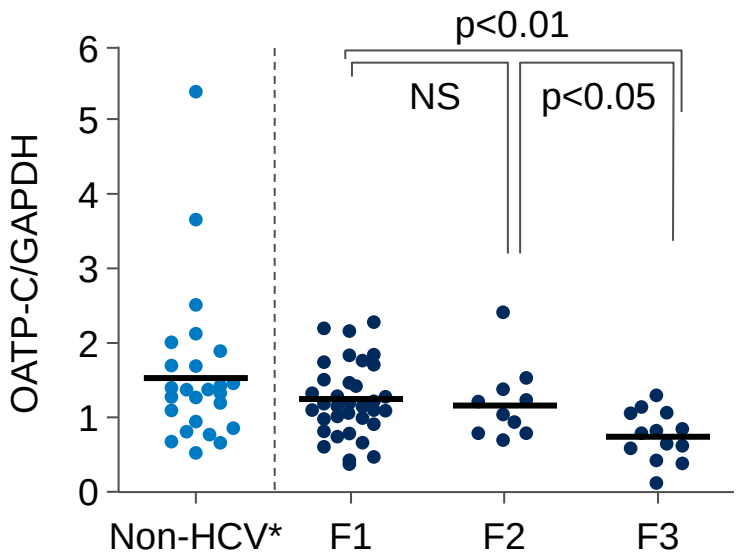


Figure reproduced with permission of John Keogh, JPK Consulting and modified

A population of HCV patients was created

- Changes were incorporated into the model for mild hepatic impairment
- Liver volume in HCV patients was 10% lower[1,2]
- CYP3A4 abundance was decreased from 137 pmol/mg protein to 108.1 pmol/mg protein[3]
- This resulted in 30% lower liver CYP3A4 Cl_{int}

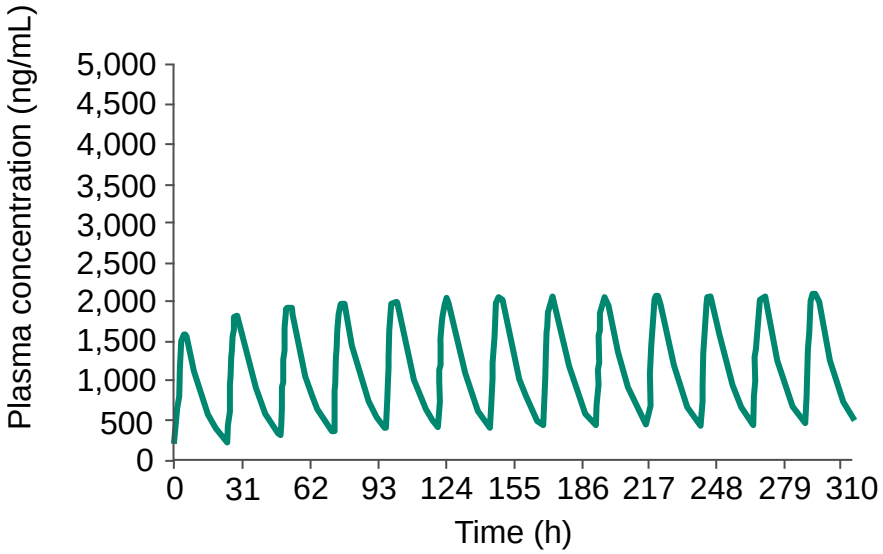




1. Lin et al Hepatogastroenterology 1998; 2. Johnson et al Clin Pharmacokinet 2010; 3. Nakai et al. DMD 2008

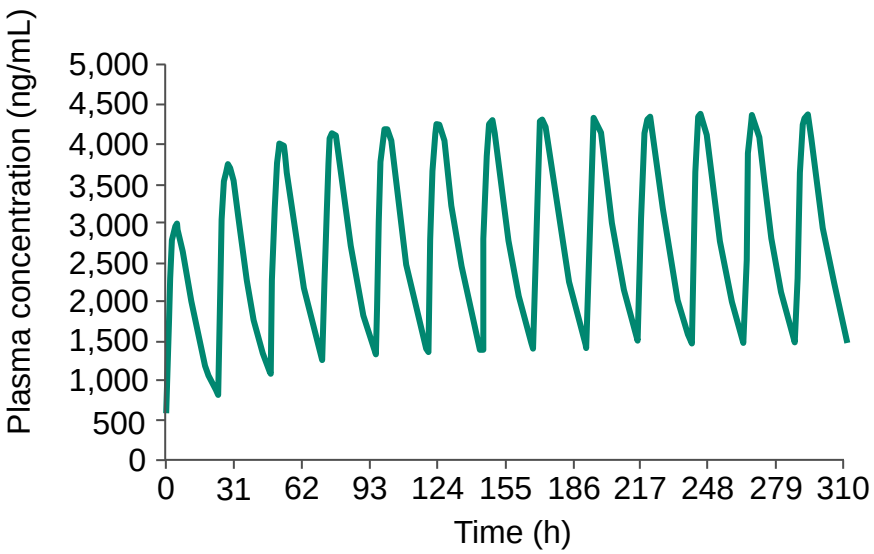
Simulating the known:
Healthy volunteers and patients dosed SMV 150mg QD

Healthy volunteers



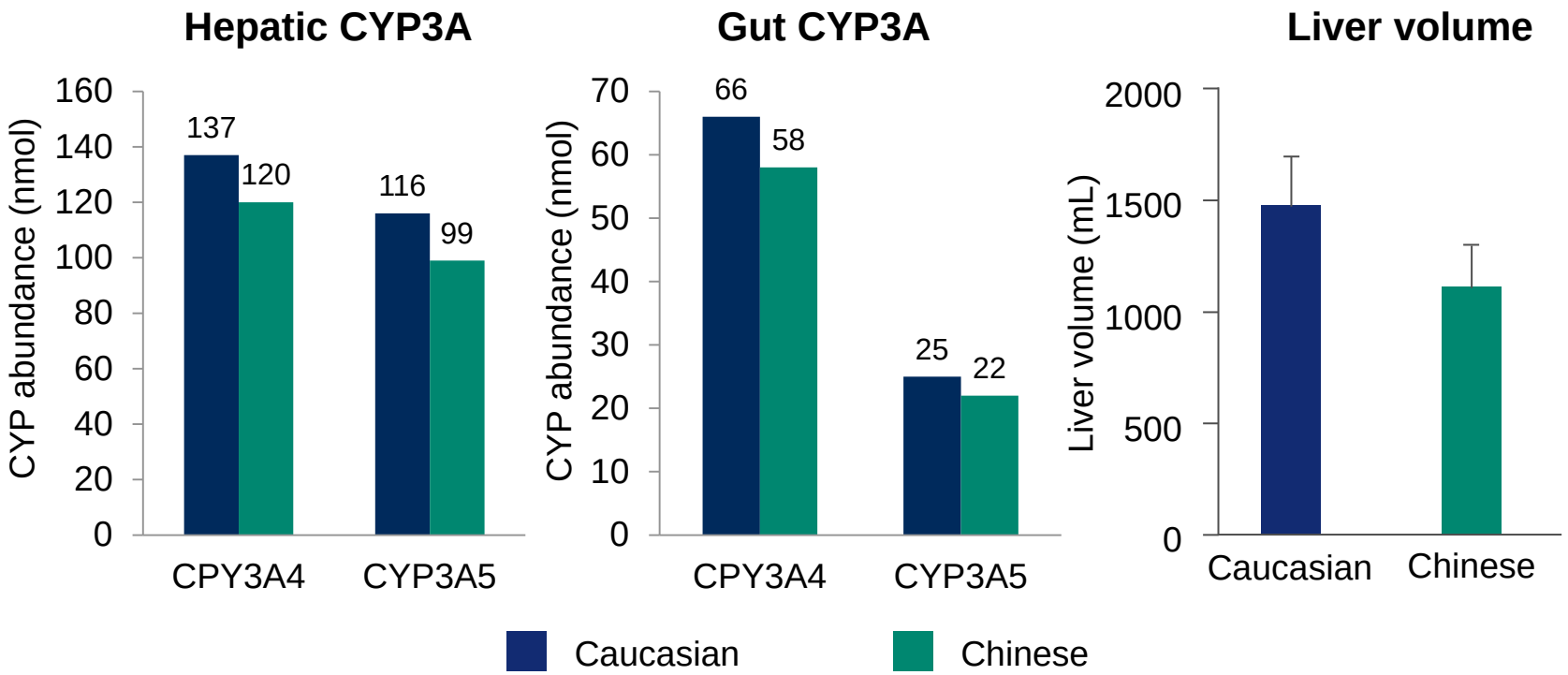
t_{max} (h)	C_{max} (ng/mL)	AUC (ng/mL.h)
3.90	2129	26951

Patients



t_{max} (h)	C_{max} (ng/mL)	AUC (ng/mL.h)
4.52	4385	71316

CYP3A abundance in Caucasian vs Chinese patients



- Liver volume in Chinese patients is >30% smaller than in Caucasian patients
- Hepatic CYP3A4 abundance per mg protein is slightly lower in Chinese patients vs Caucasian patients
- Lower OATP1B1 hepatic uptake transporter expression levels in Japanese patient

Barter et al. Clin Pharmacokinet 2013; Tomita et al. Clin Pharmacol Ther 2013

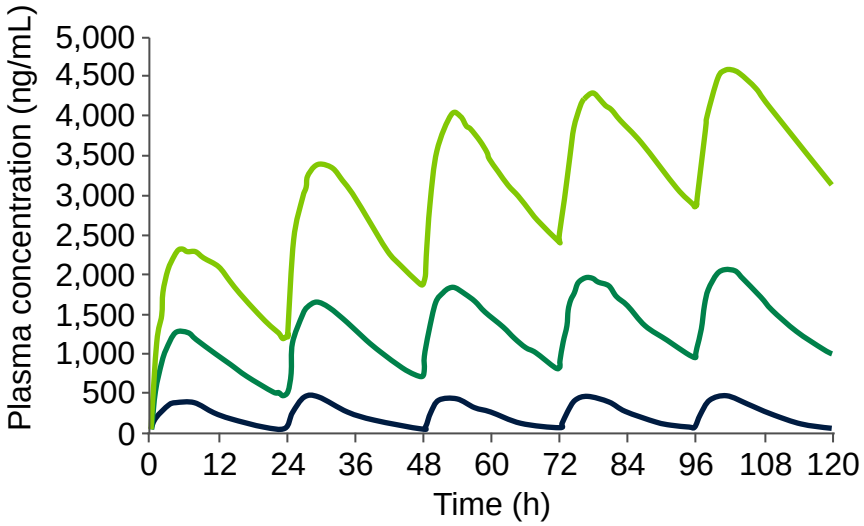
Simulations:
Chinese vs Caucasian healthy volunteers

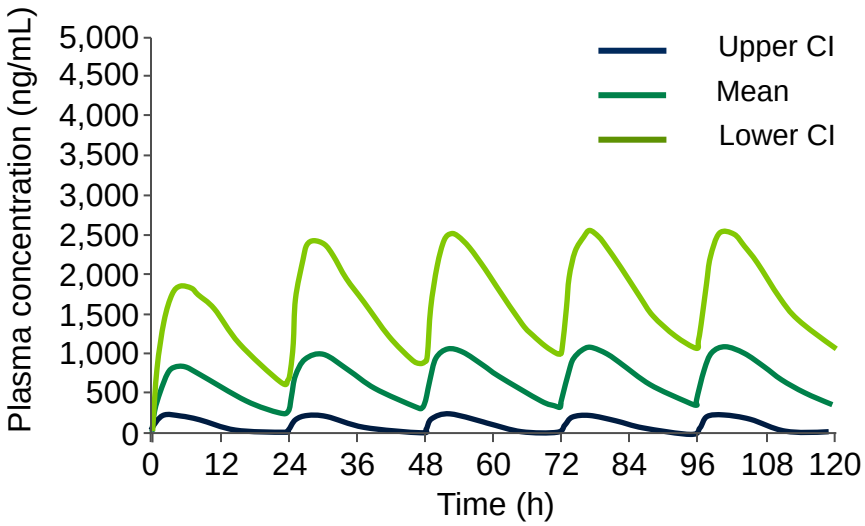
Chinese patients (N=40)

C_{max} (ng/mL)	AUC (ng/mL.h)
2071	38292

Caucasian patients (N=40)

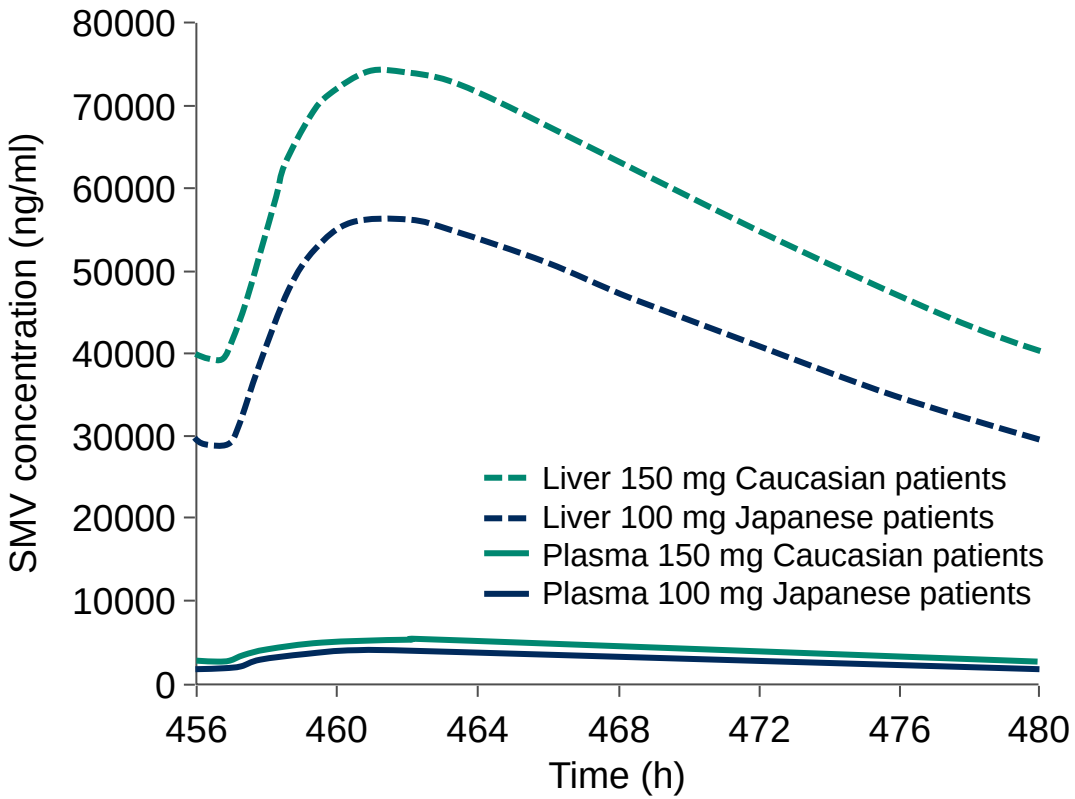
C_{max} (ng/mL)	AUC (ng/mL.h)
1098	17895





- Incorporating differences in liver volume and CYP3A4 expression into the model gives plasma exposures in Chinese patients 2-fold higher than in Caucasian patients at 100 mg

Simulating the unknown:
Liver concentrations of SMV in Japanese and Caucasian patients



- Physiological factors incorporated into the model: Japanese patients have 15% lower liver volume, lower CYP3A4 abundance, and intrinsically lower OATP1B1 baseline activity

Simulating the unknown:
DDI in patients

	AUC ratio healthy volunteers	AUC ratio HCV patients
CYP 3A inhibitors		
Ritonavir 100 mg BID	10	5.1
Erythromycin	6.2	4.9
CYP 3A inducers		
Efavirenz	0.3	0.23
Rifampicin	0.54	0.32
OATP substrate		
Rosuvastatin	2.9	2.8

Regulatory feedback
FDA PBPK modeling review memo online

- Questions addressed by the submitted PBPK modeling report and additional information requested by the Office of Clinical Pharmacology include:
  - What are the major mechanisms contributing to non-linear PK of SMV?
  - Can DDI with SMV be predicted?
- In addition, sponsor simulated PK of SMV in various specific populations and projected liver concentrations of SMV in Caucasian and Asian HCV patients

Regulatory feedback
FDA PBPK modeling review memo online

Conclusion

- Sponsor's PBPK modeling and simulation reasonably captured non-linear PK of SMV
- Saturation of OATP transporter mediated drug distribution into the liver and saturation of CYP3A4 metabolism together appear to be the plausible mechanisms contributing to the non-linear PK and differential effects of CYP3A4 and/or OATP modulators observed in the DDI studies
- The model can be used to predict other untested DDI situations and to evaluate the effect of various intrinsic factors (eg. ethnicity, liver disease) on SMV exposure

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