Interpretation of Dose-Dependent Pharmacokinetics of Ruzasvir Using Both Physiologically Based Pharmacokinetic and Population Pharmacokinetic Modeling Approaches

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Abstract

Objectives: Ruzasvir (MK-8408) is a potent HCV NS5A complex inhibitor that was clinically studied from 4 to 600 mg as single and multiple doses. Non-compartmental analysis showed that MK-8408 exhibits approximately dose-proportional pharmacokinetics (PK) over the range of 60 to 140 mg and behaves supraproportional from 4 to 60 mg and subproportional from 140 to 600 mg. Dose-dependent PK of MK-8408 was characterized and interpreted usingphysiologically based pharmacokinetic (PBPK) and population pharmacokinetic (PopPK) approaches.

Methods: MK-8408 is a P-gp substrate and demonstrates a steep pH-dependent aqueous solubility within the range in the gastrointestinal (GI) environment. We hypothesized that the unique dose-exposure relationship of MK-8408 was caused by the interplay of P-gp saturation and solubility-limited absorption. PBPK (Gastroplus) and PopPK (NONMEM) models were developed; the two aforementioned factors impacting absorption were estimated.

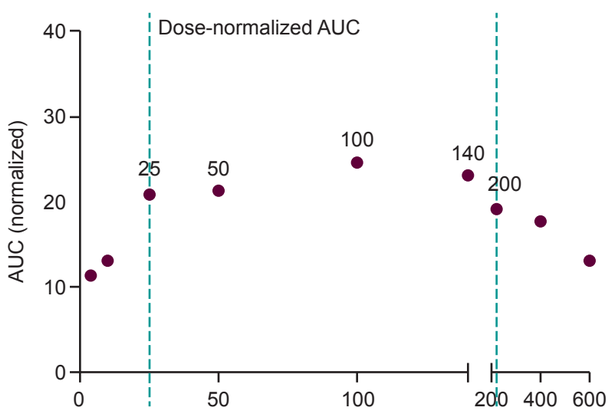
Results: MK-8408 concentration profiles and dose-exposure relationship were reasonably described by both PBPK and PopPK models. The average prediction errors of AUC and C_{max} (vs observed values) by the PBPK model were less than 30% and 25%, respectively. In the PopPK model, dose-dependent PK was handled by varying bioavailability: a rational function to characterize the increasing bioavailability over 10-140 mg and a Weibull model to characterize the decreasing bioavailability over 140-600 mg. Relevant covariates were also included in the PopPK model.

Conclusions: The modeling exploration suggested that the dose-dependent PK of MK-8408 could potentially be explained by our hypothesis: greater than dose proportionality at lower doses could be related to the effect of efflux transporter in the GI tract, the dose-proportional PK at the middle range could be caused by saturation of efflux transporter, and less than dose proportionality at high doses could possibly be attributed to the combined effect of saturated efflux process and solubility-limited absorption.

BACKGROUND AND INTRODUCTION

- MK-8408 is an NS5A inhibitor, in development for the treatment of HCV infection
- MK-8408 is a weakly basic compound with steep pH-dependent solubility within the physiological pH. The compound has solubility of 9.34 mg/mL in SGF and 0.00325 mg/mL in FaSSIF. Although MK-8408 is expected to be fully dissolved in the stomach in the range of clinical dose, the dissolved drug can precipitate in the small intestine when pH in the small intestine is elevated, resulting in decreased drug absorption
- In LLC-PK1 cells, MK-8408 had low permeability. MK-8408 was also a substrate of human and rat P-gp in vitro. It is possible that P-gp may play a role in limiting the absorption of MK-8408 as well as contributing to its overall elimination
- The pharmacokinetics (PK) of MK-8408 was evaluated from 4 to 600 mg as single and multiple doses (**Table 1**)
- Non-compartmental analysis showed that MK-8408 exhibits approximate PK over the range of 60 to 140 mg, greater than dose proportional from 4 to 60 mg, and less than dose proportional from 140 to 600 mg (**Figure 1**)

Figure 1. Dose-Normalized AUC of MK-8408 in Healthy Subjects Over 4 to 600 mg



METHODS AND RESULTS

Population PK (PopPK) Model (NONMEM)

Table 1. Data Availability for PopPK Model Development

Study	N	Form (N/period)			Food (N/period)				Dose (N/period)											
		1 (Suspen-sion)	2 (Cap-sules)	4 (FDC1M)	0 (Fasted)	1 (Low fat)	2 (Mod. fat)	3 (High fat)	4	10	25	30	50	60	100	120	140	200	400	600
MK-8408P001	16[a]	16			16				6	6	6		6		6		6			
MK-8408P002[b]	30		30		24	6	6	6				6		18	6					
MK-8408P004	16		16		16									16						
MK-8408P007	43		43		43													6	6	41
MK-3682P008	18		18		18									18						
MK-3682P016	11[a]		11		11									11						
MK-3682P020	24[a]		23	24	24			12						24						

[a]Trials partly included in analysis (P001: fasted only, P016/020: capsule FDC1M only)
[b]In P002 only, the 60 mg dose was given with meals (low to high fat)

Figure 2. MK-8408 PopPK Model Structure

Final Structural Model

- IIV on:
  - V2
  - CL
- KA:
  - Formulation effect
  - Food effect (formulation dependent)
- F1:
  - Food effect
  - Formulation effect

Less Than Dose Proportional Region:

Rational function: $FF1 = Dose \times \theta13/(1+ Dose \times \theta13)$

Greater Than Dose Proportional Region:

Weibull equation: $\mathrm{FF1} = \theta14 \times e^{\theta15 \times LOG(DOSE-140)}$

Where $\theta14 = 1$

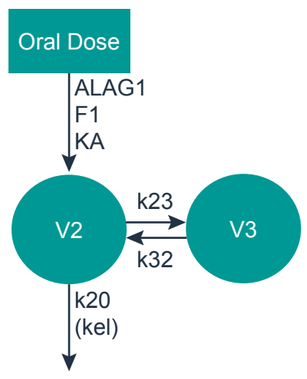


Figure 3. Goodness-of-Fit Plots of PopPK Model

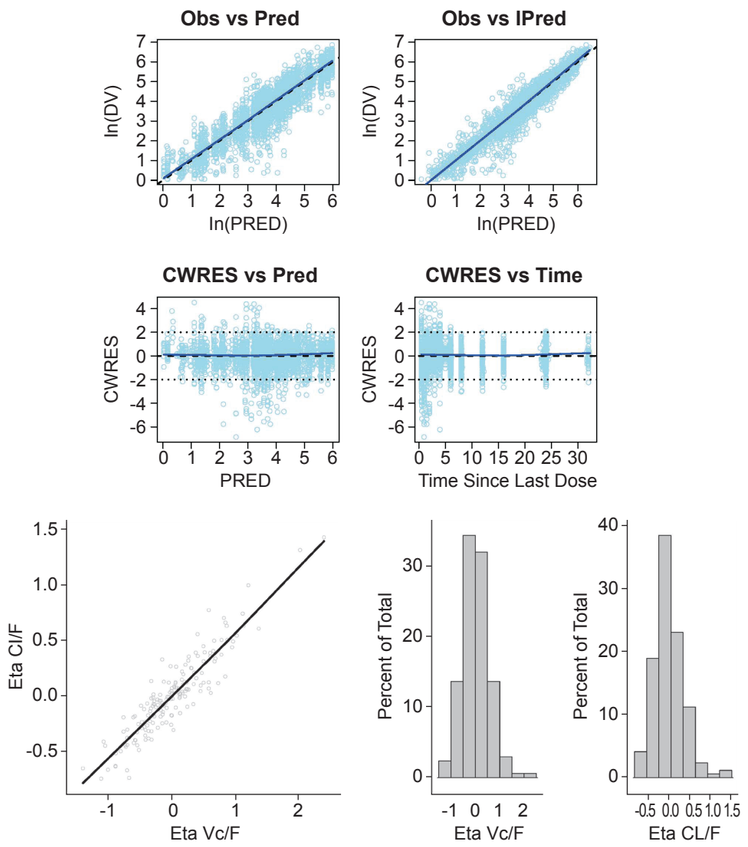


Table 2. Parameter Estimates of the PopPK Model

Par	Description	Value	[95% CI] or SE (%)
θ1	Central compartment volume (L), Vc/F	340	[270 – 430]
θ2	Oral clearance (L/hr), Cl/F	37.6	[31.4 – 45.1]
θ3	Peripheral compartment volume (L), Vp/F	616	[551 – 690]
θ4	Intercompartmental clearance (L/hr), Q/F	40.6	[35.3 – 46.7]
θ5	Absorption rate solids: Capsule/FDC1M (hr^{-1}), Ka	0.436	[0.377 – 0.503]
θ6	Lag time (hr), ALAG1	0.448	[0.440 – 0.457]
θ7	Relative bioavailability, tablet, F1	0.776	[0.652 – 0.900]
θ8	Absorption rate suspension (hr^{-1}), Ka	1.22	[0.858 – 1.73]
θ9	Food eff. on Ka-unformulated	0.528	[0.327 – 0.730]
θ10	Food eff. on Ka-tablet	0.471	[0.184 – 0.758]
θ11	Food eff. F1 for capsule	0.429	[0.351 – 0.506]
θ12	Food eff. F1 for tablet	0.961	[0.731 – 1.19]
θ13	Slope – dose effect on F1 for 4-140 mg dose	0.321	[0.0845 – 0.558]
θ15	Slope – dose effect on F1 for >140 mg dose	-0.139	[-0.176 – -0.102]
θ16	Proportional residual error	0.383	[0.355 – 0.412]
ωVc	Interindividual variability in central volume	0.347	16.5
ωCl	Interindividual variability in clearance	0.136	17.5
Covη1, η2	Covariance V2/CL	0.871	18.1

Physiologically Based Absorption Model (Gastroplus)

Table 3. Parameters Used in Gastroplus Absorption Model

Physicochemical Properties

SGF solubility: 9.34 mg/mL

FaSSIF solubility: 0.0072 mg/mL

Effective permeability: 0.69 X 10^{-4} cm/sec

Precipitation time (sec): Dose dependent

Bile salt solubilization ratio: 25,900

Log P: 2.94; **pKa:** 5.84

Dosage form: Suspension/capsule

Particle size: 1 µm (diameter)

pH	Solubility (mg/mL)
1.0	36.1
2.7	4.18
2.9	0.43
3.3	0.036
3.7	0.012
4.5	0.003
6.5	0.003

PK Parameters:

CL: 0.0672 L/hr/kg

f_{up} (%): 0.1

Vc: 0.368 L/kg

B/P: 0.72

Vt: 1.17 L/kg

First-pass extraction ratio (%): 7.3

GI Physiology Profiles: Opt LogD Model SA/V 6.1; human fasted

Compartment Data									Enzyme and Transporter Regional Distributions	
Compartment	Peff	ASF	pH	Transit Time (h)	Volume (mL)	Length (cm)	Radius (cm)	SEF	Bile Salt (mM)	P-gp Apical Expr	P-gp Apical Turn
Stomach	0	0.0	1.30	0.50	46.56	28.29	9.67	1.000	0.0	0.0	5.0E-4
Duodenum	0	2.786	6.00	0.26	41.56	14.13	1.53	4.235	2.800	0.485	5.0E-4
Jejunum 1	0	2.747	6.20	0.93	154.2	58.40	1.45	3.949	2.330	0.587	5.0E-4
Jejunum 2	0	2.728	6.40	0.74	122.3	58.40	1.29	3.489	2.030	0.656	5.0E-4
Ileum 1	0	2.699	6.60	0.58	94.29	58.40	1.13	3.029	1.410	0.697	5.0E-4
Ileum 2	0	2.649	6.90	0.42	70.53	58.40	0.98	2.569	1.160	0.766	5.0E-4
Ileum 3	0	2.588	7.40	0.29	49.83	58.40	0.82	2.109	0.140	0.829	5.0E-4
Caecum	0	0.100	6.40	4.19	47.49	13.19	3.39	1.790	0.0	0.928	5.0E-4
Asc Colon	0	0.100	6.80	12.57	50.33	27.65	2.41	2.480	0.0	0.917	5.0E-4

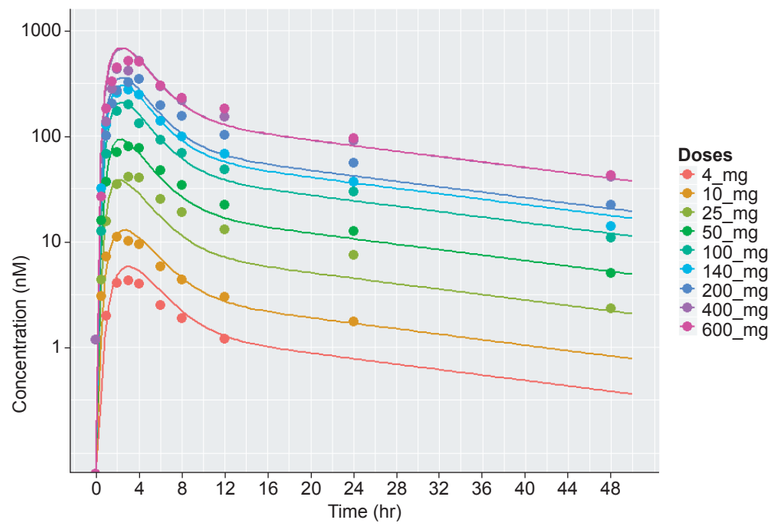
Optimized P-gp efflux kinetics:
Vmax: 0.469 µg/sec
Km = 0.144 µg/mL

Table 4. Predicted and Observed MK-8408 PK Parameters

Dose	AUC_{inf} (nM*hr)			C_{max} (nM)			T_{max} (hr)		Precipitation Time (sec)
	OBS	PRE	Fold Error[a]	OBS	PRE	Fold Error	OBS	PRE	
4 mg	46	74	1.61	4.15	5.79	1.39	3	3	1200
10 mg	132	161	1.22	11.6	12.7	1.09	2	2.7	
25 mg	529	433	1.22	38.8	38.0	1.02	3.5	2.2	
50 mg	1070	1025	1.04	84.6	93	1.10	3.5	2.3	
100 mg	2470	2346	1.05	200	209	1.05	3	2.4	
140 mg	3270	3457	1.06	262	304	1.16	2	2.5	
200 mg	3840	4035	1.05	278	356	1.28	3.5	2.4	900
400 mg	7110	7772	1.09	466	674	1.45	4	2.5	800
600 mg	7910	7806	1.01	511	682	1.33	3.5	2.4	500

OBS, Observed data; PRE, Predicted data
[a]Fold Error = $10^{|Log(PRE/OBS)|}$

Figure 4. PBPK Model Fitting of MK-8408



CONCLUSION

- Both PopPK and PBPK models reasonably described the dose-dependent PK of MK-8408
- The PopPK model characterized the dose effect on the relative bioavailability of MK-8408, while the PBPK model characterized the nonlinear absorption from the physiological perspective (interaction between efflux transporter and pH-dependent solubility)
- The dose-dependent PK of MK-8408 could potentially be explained by our hypothesis: greater than dose proportionality at lower doses could be related to the effect of efflux transporter in the GI tract, the dose-proportional PK at the middle range could be caused by saturation of efflux transporter, and less than dose proportionality at high doses could possibly be attributed to the combined effect of saturated efflux process and solubility-limited absorption

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