PREDICTION OF DRUG-DRUG INTERACTION OF ENSITRELVIR AS CYP3A SUBSTRATE USING PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL

○Kana Horiuchi[1], Hiroki Koshimichi[2], Takanobu Matsuzaki[1], Ryosuke Shimizu[2], Ryuji Kubota[2], Shingo Sakamoto[1]

1 Laboratory for Drug Discovery and Development, Shionogi & Co., Ltd., Osaka, Japan
2 Clinical Pharmacology & Pharmacokinetics, Project Management Department, Shionogi & Co., Ltd. Osaka, Japan

SHIONOGI

COI : The authors have no financial conflicts of interest to disclose concerning the poster

Abstract

- Ensitrelvir is approved in Japan for patients with COVID-19 and is an investigation product in the US that is currently undergoing a comprehensive development program across a range of patient populations.
- Complex drug-drug interaction (DDI) simulations for ensitrelvir, which is an inhibitor, an inducer and a substrate on CYP3A, is challenging because it is necessary to set many relevant parameters.
- The physiologically-based pharmacokinetic (PBPK) model for ensitrelvir was developed and DDI simulations with CYP3A inducers were performed using developed PBPK model.

Objectives

We aim to develop a PBPK model for ensitrelvir to evaluate an effect of a CYP3A inducer on the PK of ensitrelvir with PBPK modeling and simulation.

Methods

Simcyp version 22 was used to develop PBPK model and simulate the DDIs.

PBPK model building and verification

The PBPK model for ensitrelvir was developed by setting relevant parameters via stepwise optimization.

1. The PBPK model for ensitrelvir was developed based on the physicochemical parameters, in vitro CYP inhibition/induction parameters, and estimated PK parameters from population pharmacokinetic analysis of plasma concentration-time profile after single oral administration in healthy adult subjects.
2. Contribution ratio of CYP3A in ensitrelvir clearance was estimated from mass balance study.
3. Parameter optimization was performed from sensitivity analysis to describe ensitrelvir clinical PK results, which were ensitrelvir PK profile after 375/125 mg for 5 days or 750/250 mg for 6 days and DDI studies with a CYP3A substrate (midazolam).
4. PBPK model verification was performed using clinical DDI study with a CYP3A substrate (dexamethasone).

PBPK model application

DDI simulations between ensitrelvir and CYP3A inducers (rifampicin and carbamazepine) were performed using the developed PBPK model. The PBPK model of CYP3A inducers in Simcyp Simulator compound library was used.

Simulation settings

- Population: Sim-Healthy volunteer, proportion of females=0.5, age=20-50, N=140 (14 subjects ×10 trials)

Conclusions

- **The PBPK model for ensitrelvir as an inhibitor, and inducer, and a substrate of CYP3A was developed.**
- **The PBPK analyses suggest that CYP3A inducers would not have a clinically meaningful effect on the PK of ensitrelvir.**
- **PBPK model building for drugs which have various features such as ensitrelvir is challenging but using the clinical study information (mass balance, several DDI) and conducting the optimization about in vitro DDI parameter are useful approach for PBPK model building.**

Results : PBPK model building and verification

PBPK model building of ensitrelvir

Table 1. PBPK model Parameters of ensitrelvir

	Parameters	Unit	Values	Source
Physicochemical Properties	MW	g/mol	531.88	-
	Compound type	Monoprotic base		-
	log P and pKa	-	2.8, 4.4	In silico data
	B/P ratio	-	0.572	In vitro data
	$f_{u,plasma}$	-	0.023	
Absorption First-order model	f_a	-	0.765	Clinical data
	k_a	1/hr	1.5	
	$f_{u,gut}$	-	1	Assumed
Distribution Minimal PBPK model	V_{ss}	L/kg	0.211	Clinical data
	V_{sac}	L/kg	0.0306	
	k_{in} and k_{out}	hr^{-1}	0.0367, 0.216	
Elimination Enzyme kinetics model	CYP3A CL_{int}	µL/min/pmol	0.00246	Simcyp retrograde model
	Additional clearance CL_{int}	µL/min/mg	1.01	
	CL_r	L/hr	0.0498	Clinical data
Interaction Inhibition CYP3A4/5	k_{inact}	hr^{-1}	2.76	In vitro data
	K_I	µM	84	
	$f_{u,mic}$	-	0.35	Sensitivity analysis
Interaction Induction CYP3A4	E_{max}	-	11.3	In vitro data
	EC_{50}	µM	21.0	
	$f_{u,inc}$	-	1	Assumed

PK simulation of ensitrelvir using developed PBPK model

Dose regimen ➢ Ensitrelvir : 375 mg on Day 1, 125 mg on Days 2-5 (A) or 750 mg on Day 1, 250 mg on Days 2-5 (B)

Ensitrelvir parameters on Day 5	(A)		(B)	
	Simulated	Observed	Simulated	Observed
$AUC_{0\text{-}24\ hr}$ (µg·hr/mL)	531	425-597	1070	853-1340
C_{max} (µg/mL)	24.9	21.9-30.4	50.3	43.9-66.3

Simulated: geometric mean value, Observed: range of geometric mean values for 4 cohorts

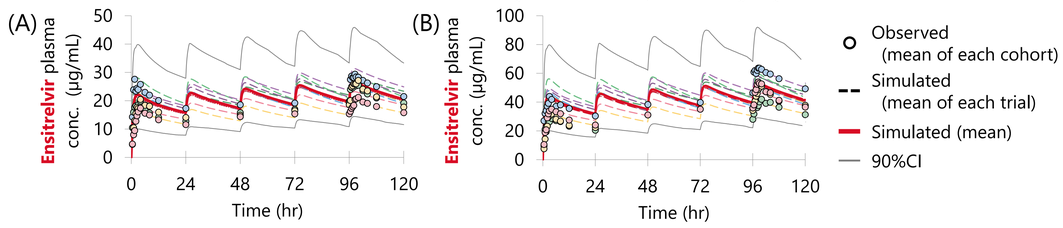


Figure 1. Comparison Results between Simulated and Observed PK of Ensitrelvir

The developed PBPK model of ensitrelvir was able to adequately describe the PK of ensitrelvir and the results from clinical DDI studies with CYP3A substrates.

DDI simulation of midazolam with ensitrelvir

Dose regimen ➢ Ensitrelvir : 375 mg on Day 1, 125 mg on Days 2-5 (A) or 750 mg on Day 1, 250 mg on Days 2-6 (B)
➢ Midazolam : 2 mg on Day 5 (A) or 2 mg on Day 6 (B)

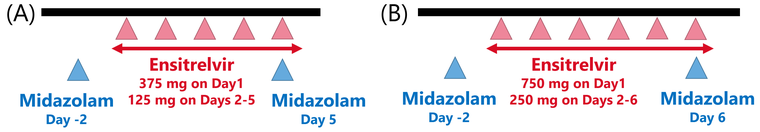


Table 2. Comparison between Simulated and Observed Midazolam DDI Parameters

Midazolam parameters		Simulated	Observed
A	AUC_{inf} ratio	6.71 (5.23-8.00)	6.77 (6.16-7.44)
	C_{max} ratio	2.85 (2.38-3.28)	2.80 (2.38-3.30)
B	AUC_{inf} ratio	9.39 (7.22-11.3)	8.80 (6.71-11.5)
	C_{max} ratio	3.13 (2.60-3.65)	2.78 (2.33-3.30)

Simulated: geometric mean (trial min-max), Observed: geometric mean (90%CI)

DDI simulation of dexamethasone with ensitrelvir

Dose regimen ➢ Ensitrelvir : 750 mg on Day 1, 250 mg on Days 2-5
➢ Dexamethasone : 1 mg on Day 5, Day 9 and Day 14

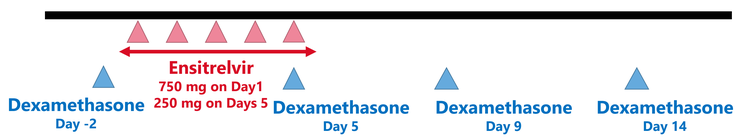


Table 3. Comparison between Simulated and Observed Dexamethasone DDI Parameters

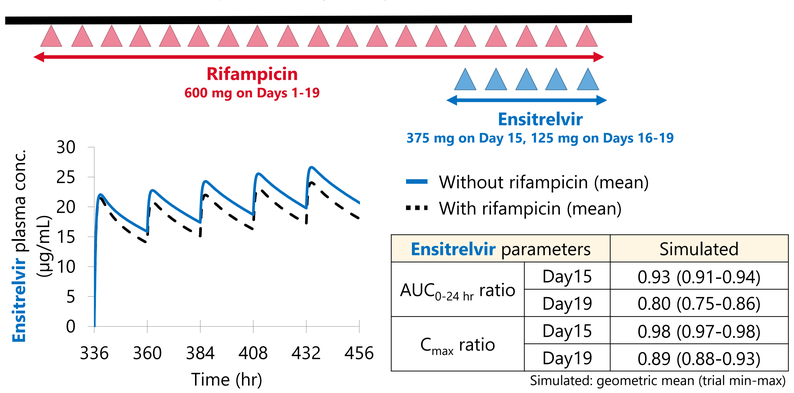
Dexamethasone parameters		Simulated	Observed
AUC_{inf} ratio (*$AUC_{0\text{-}24\ hr}$ ratio)	Day5	3.74 (3.22-4.15)	3.47 (3.23-3.72)
	Day9*	2.47 (2.13-2.84)	2.45 (2.28-2.63)
	Day14*	1.86 (1.61-2.21)	1.56 (1.45-1.68)
C_{max} ratio	Day5	1.51 (1.37-1.63)	1.47 (1.30-1.67)
	Day9	1.45 (1.32-1.55)	1.24 (1.09-1.40)
	Day14	1.30 (1.20-1.40)	1.17 (1.04-1.33)

Simulated: geometric mean (trial min-max), Observed: geometric mean (90%CI)

Results : PBPK model application

DDI simulation of ensitrelvir with rifampicin

Dose regimen ➢ Ensitrelvir : 375 mg on Day 15 and 125 mg on Days 16-19
➢ Rifampicin : 600 mg on Days 1-19



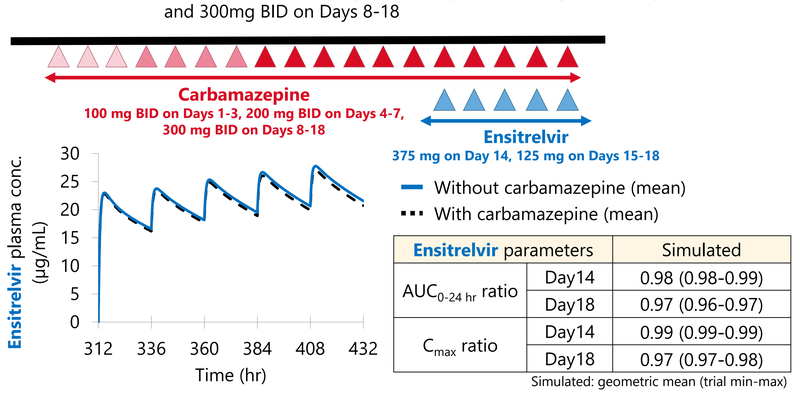
Ensitrelvir parameters		Simulated
$AUC_{0\text{-}24\ hr}$ ratio	Day15	0.93 (0.91-0.94)
	Day19	0.80 (0.75-0.86)
C_{max} ratio	Day15	0.98 (0.97-0.98)
	Day19	0.89 (0.88-0.93)

Simulated: geometric mean (trial min-max)

Figure 2. Simulated Ensitrelvir DDI Parameters with Rifampicin

DDI simulation of ensitrelvir with carbamazepine

Dose regimen ➢ Ensitrelvir : 375 mg on Day 14 and 125 mg on Days 15-18
➢ Carbamazepine : 100 mg BID on Days 1-3, 200 mg BID on Days 4-7 and 300mg BID on Days 8-18



Ensitrelvir parameters		Simulated
$AUC_{0\text{-}24\ hr}$ ratio	Day14	0.98 (0.98-0.99)
	Day18	0.97 (0.96-0.97)
C_{max} ratio	Day14	0.99 (0.99-0.99)
	Day18	0.97 (0.97-0.98)

Simulated: geometric mean (trial min-max)

Figure 3. Simulated Ensitrelvir DDI Parameters with Carbamazepine

The DDI simulation results indicated that CYP3A inducers would not decrease the AUC of ensitrelvir.