No Change of Pharmacokinetics of Metformin by Concomitant Use of Ensitrelvir

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Introduction & Purpose

- Ensitrelvir is a new drug candidate to treat COVID-19.
- Ensitrelvir exhibited an inhibition potency for organic cation transporter 1 (OCT1) and multi drug and toxin extrusion protein 1 (MATE1) in in vitro study. According to DDI guidance, a clinical drug-drug interaction (DDI) study was recommended.
- Metformin is widely used for treatment of diabetes and is a sensitive substrate for OCT1 and MATE1. DDI simulations of metformin with or without ensitrelvir were performed using physiologically-based pharmacokinetic (PBPK) modeling and simulation as a prospective study. Based on the results of DDI simulations, we applied for new drug application (NDA) of ensitrelvir in Japan before conducting a clinical DDI study.
- After NDA, a clinical DDI study of metformin with ensitrelvir was preformed and the results were compared to DDI simulation results.

Methods

Simcyp version 20 was used to develop PBPK model and simulate the DDIs.

PBPK model building and verification

- The PBPK model of ensitrelvir was developed based on the physicochemical parameters, in vitro transporter inhibition parameters, and estimated PK parameters from plasma concentration-time profile after single oral administration in Japanese adult subjects.

PBPK model application

- DDI simulations were performed using the developed PBPK model.
- The in vitro 50% inhibitory concentration (IC_{50}) values of each transporter were used as inhibition constant (K_i) for DDI simulations.

Simulation settings

- Population: Sim-Healthy volunteer, proportion of females=0.5, age=20-50, N=10 subjects×10 trials
- Dose: ensitrelvir 1000 mg and 500 mg, metformin 390 mg (as free)
- Sensitivity analysis: K_i and 1/10 K_i, added 1/30 K_i (requested by PMDA)

Table.1 Summary of in vitro DDI Parameters for DDI Simulations

Transporters	In vitro IC_{50} (μmol/L)	K_i in PBPK model (μmol/L)			f_{uinc}
		Base model	1/10 K_i model	1/30 K_i model	
OCT1	7.24	7.24	0.724	0.241	1
OCT2	202	202	20.2	6.73	
MATE1	82.3	82.3	8.23	2.74	
MATE2K	> 250				

Results

PK simulation of ensitrelvir

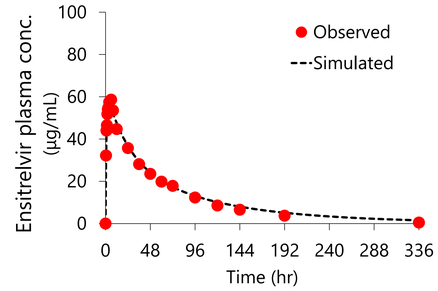
- The developed PBPK model was able to well describe the plasma concentration-time profile of ensitrelvir at 1000 mg (Fig. 1).

DDI simulation of metformin with or without ensitrelvir

- Judging from DDI simulation results, ensitrelvir has no in vivo DDI potential via OCT1 and MATE1 inhibition at 1000 and 500* mg (Fig.2, 3).

*Ensitrelvil Cmax value at Day 5 (clinical dose regimen: 375/125mg for 5 days) was similar to after 500 mg single oral administration.

Ensitrelvir at 1000 mg

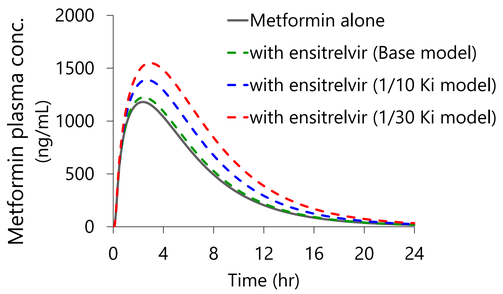


Parameters		Geometric Mean (90% CI)
C_{max} (μg/mL)	observed	63.8
	simulated	53.0 (27.7-100)
AUC_{0-inf} (μg·hr/mL)	observed	3370
	simulated	3946 (2592-6087)

CI = confidence interval

Fig. 1 Comparison Results between Simulated and Observed PK of Ensitrelvir after **1000 mg** Single Oral Administration

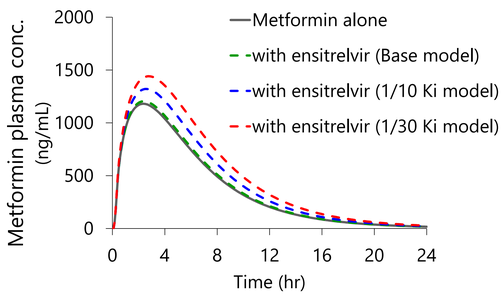
Ensitrelvir at 1000 mg



Parameters		Geometric Mean (90% CI)
C_{max} ratio	Base model	1.04 (1.01-1.08)
	1/10 K_i model	1.18 (1.09-1.38)
	1/30 K_i model	1.32 (1.17-1.57)
AUC_{0-24} ratio	Base model	1.05 (1.02-1.11)
	1/10 K_i model	1.26 (1.12-1.52)
	1/30 K_i model	1.50 (1.25-1.98)

Fig. 2 Simulated Metformin PK Profile with or without Ensitrelvir after **1000 mg** Single Oral Administration

Ensitrelvir at 500 mg



Parameters		Geometric Mean (90% CI)
C_{max} ratio	Base model	1.02 (1.01-1.05)
	1/10 K_i model	1.12 (1.05-1.25)
	1/30 K_i model	1.23 (1.12-1.45)
AUC_{0-24} ratio	Base model	1.03 (1.01-1.06)
	1/10 K_i model	1.17 (1.07-1.35)
	1/30 K_i model	1.34 (1.16-1.65)

Fig. 3 Simulated Metformin PK Profile with or without Ensitrelvir after **500 mg** Single Oral Administration

Answers – results of clinical DDI study

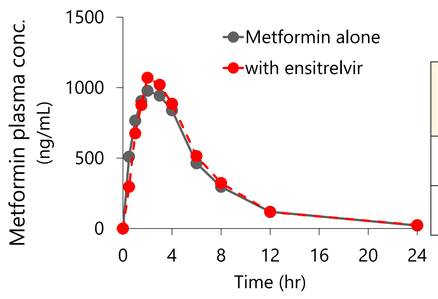
- A clinical DDI study was performed under the following conditions.

Clinical settings

- Population: Japanese healthy participant, proportion of females=0, age=20-51, 14 subjects
- Dose: ensitrelvir 500 mg
  metformin 390 mg (as free)

- Metformin C_{max} and AUC_{0-inf} ratio were 1.03 and 1.02, respectively (Fig. 4).

Ensitrelvir at 500 mg



Parameters	Geometric Mean (90% CI)
C_{max} ratio	1.03 (0.91-1.16)
AUC_{0-inf} ratio	1.02 (0.94-1.11)

Fig. 4 Metformin PK profiles of Clinical DDI Study with or without Ensitrelvir after **500 mg** Single Oral Administration

Conclusion

- Ensitrelvir does not have a clinically meaningful effect on the pharmacokinetic profile of OCT1 and/or MATE1 substrates including metformin as indicated PBPK simulation results.
- Although the "Base model" predicted clinical DDI results well in this study, DDI simulation results under conservative conditions such as using 1/10 K_i model or 1/30 K_i model are also important to explain safety to regulatory agencies without conducting a clinical DDI study.