Evaluation of drug-drug interaction potential of ensitrelvir for CYP3A by clinical studies and physiologically-based pharmacokinetic model

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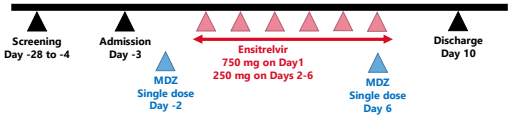
Introduction and Purpose

- Ensitrelvir is a new drug candidate to treat COVID-19.
- According to the in vitro drug-drug interaction (DDI) study, time-dependent inhibition by ensitrelvir was observed on cytochrome P450 3A (CYP3A).
- The purpose of this study was to evaluate the effect of ensitrelvir on the pharmacokinetics (PK) of CYP3A substrates including midazolam (MDZ), dexamethasone (DEX), and prednisolone (PLS) by clinical DDI studies and physiologically-based pharmacokinetic (PBPK) analyses.

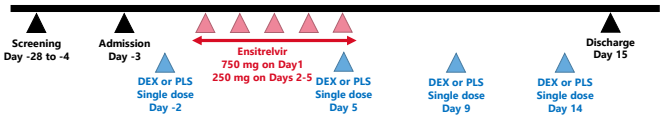
Methods

1) Clinical studies:

- The effect of once daily multiple-dose of ensitrelvir with the loading dose on Day 1/ maintenance dose (750/250mg, suspension) for 6 days on the PK of MDZ was assessed, as follow.



- The effects of once daily multiple-doses of ensitrelvir with 750/250mg (tablet) for 5 days on the PK of DEX and PLS were also assessed. DEX or PLS were administered on Days -2, 5 (coadministration with ensitrelvir), 9 and 14 to evaluate the effects after the last dose of ensitrelvir, as follow.

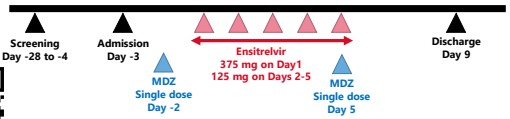


2) PBPK analyses:

- The effects of once daily multiple-dose of ensitrelvir with expected therapeutic dose (the loading dose on Day 1/maintenance dose [375/125mg] for 5 days as tablet) on the PK of CYP3A substrates were predicted using Simcyp PBPK Simulator (Version 20, Certara UK Limited, UK).

3) Clinical study with expected therapeutic dose:

- To clarify the actual effect of ensitrelvir (375/125mg, tablet) on the PK of MDZ, the effect of once daily multiple-dose of ensitrelvir with 375/125mg for 5 days on the PK of MDZ was assessed.



PK parameters were estimated by WinNonlin and analysis of variance (ANOVA) as statistical analysis was performed by SAS.

Results: 1) Clinical studies

Fig.1 PK profile of midazolam

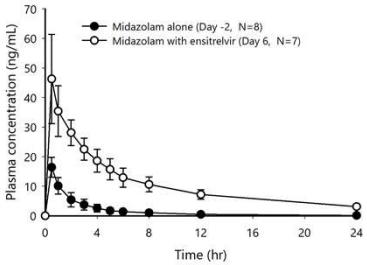


Table.1 Result of statistical analysis for DDI with midazolam

Parameters	Midazolam with ensitrelvir / Midazolam alone		
	GLS Mean Ratio	90% CIs of Ratio	
		Lower	Upper
C_{max}	2.78	2.33	3.30
$AUC_{0\text{-last}}$	7.23	5.58	9.36
$AUC_{0\text{-inf}}$*	8.80	6.71	11.55

CI = confidence interval; GLS Mean = geometric least squares mean
* N=5 (Midazolam with ensitrelvir)

Ensitrelvir with 750/250mg strongly inhibited CYP3A

Fig.2 PK profile of dexamethasone (Left) and prednisolone (Right)

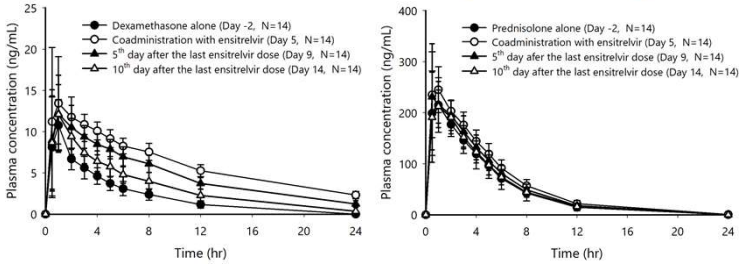


Table.2 Result of statistical analysis for DDI with dexamethasone

Parameters	Coadministration with ensitrelvir (Day 5) / Dexamethasone alone (Day -2)			5th Day after the last ensitrelvir dose (Day 9) / Dexamethasone alone (Day -2)			10th Day after the last ensitrelvir dose (Day 14) / Dexamethasone alone (Day -2)		
	GLS Mean Ratio	90% CIs of Ratio		GLS Mean Ratio	90% CIs of Ratio		GLS Mean Ratio	90% CIs of Ratio	
		Lower	Upper		Lower	Upper		Lower	Upper
C_{max}	1.47	1.30	1.67	1.24	1.09	1.40	1.17	1.04	1.33
$AUC_{0\text{-last}}$	3.18	2.96	3.42	2.45	2.28	2.63	1.56	1.45	1.68
$AUC_{0\text{-inf}}$	3.47	3.23	3.72	2.38	2.23	2.54	1.58	1.47	1.70

Table.3 Result of statistical analysis for DDI with Prednisolone

Parameters	Coadministration with ensitrelvir (Day 5) / Prednisolone alone (Day -2)			5th Day after the last ensitrelvir dose (Day 9) / Prednisolone alone (Day -2)			10th Day after the last ensitrelvir dose (Day 14) / Prednisolone alone (Day -2)		
	GLS Mean Ratio	90% CIs of Ratio		GLS Mean Ratio	90% CIs of Ratio		GLS Mean Ratio	90% CIs of Ratio	
		Lower	Upper		Lower	Upper		Lower	Upper
C_{max}	1.11	1.00	1.24	1.10	0.99	1.22	0.99	0.89	1.10
$AUC_{0\text{-last}}$	1.24	1.21	1.28	1.11	1.08	1.15	1.03	1.00	1.06
$AUC_{0\text{-inf}}$	1.25	1.22	1.28	1.12	1.10	1.15	1.04	1.01	1.07

- **Ensitrelvir increased the exposures of DEX when co-administered with ensitrelvir on Day 5 and the effect was diminished over time**
- **No meaningful effect of ensitrelvir on the PK of PLS was confirmed**

Results: 2) PBPK analyses

Table.4 PBPK parameters of ensitrelvir

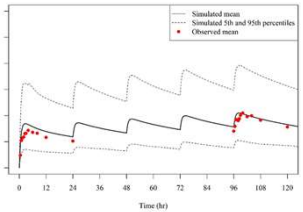
	Parameters and Models	Parameter Unit	Values
Physicochemical Properties	MW	g/mol	531.88
	log P	-	2.8
	Compound type	Monoprotic base	
	B/P ratio	-	0.572
	$f_{u,plasma}$	-	0.023
Absorption	Absorption model	First-order model	
	f_a (CV%)	-	1 (30) for suspension, 0.7 (30) for tablet
	k_a (CV%)	1/hr	1.66 (30)
	$f_{u,gut}$	-	Predicted
Distribution	Distribution model	Minimal PBPK model	
	V_{ss} (CV%)	L/kg	0.287 (30)
	V_{ss}	L/kg	0.061
	K_{in} and k_{out}	1/hr	0.0328, 0.151
Elimination	Elimination model	Enzyme kinetics	
	CYP3A CL_{int} (Recombinant)	µL/min/pmol	0.00708
	Additional clearance CL_{int} (HLM)	µL/min/mg	1.36
	CLr	L/hr	0.0498
Interaction	Enzyme	CYP3A4/ CYP3A5	
	k_{inact}	µM	84
	K_I	hr^{-1}	2.76
	$f_{u,mic}$	-	0.5

Table.5 Simulated AUC ratio from PBPK model with ensitrelvir (750/250 mg)

	Simulated AUC ratio (N =10×10)[a]	
	Midazolam	Dexamethasone
C_{max}	2.69 (2.28, 3.40)	1.46 (1.41, 1.53)
$AUC_{0\text{-inf}}$	8.85 (6.69, 11.21)	3.23 (2.91, 3.76)

[a]Geometric mean value for all participants (range of geometric mean values for virtual 10 trials).

Fig.3 Simulated PK profile of ensitrelvir at 750/250 mg



- Our PBPK model could well describe the PK profiles of ensitrelvir following multiple dose administration of ensitrelvir (750/250 mg) and the AUC ratio on DDI studies with MDZ and DEX (Table 1, 2, 5).
- As results of DDI simulation with MDZ, ensitrelvir would increase the AUC of MDZ by 3.83-fold following ensitrelvir 375/125mg for 5 days.

PBPK model suggested the ensitrelvir is moderate CYP3A inhibitor

Results: 3) Clinical study with expected therapeutic dose

Fig.4 PK profile of midazolam

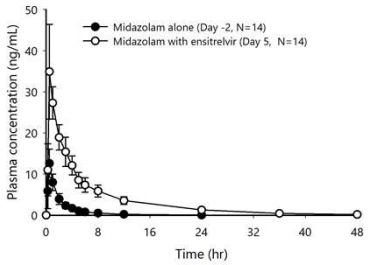


Table.6 Result of statistical analysis for DDI with midazolam

Parameters	Midazolam with ensitrelvir / Midazolam alone		
	GLS Mean Ratio	90% CIs of Ratio	
		Lower	Upper
C_{max}	2.80	2.38	3.30
$AUC_{0\text{-last}}$	6.90	6.27	7.59
$AUC_{0\text{-inf}}$	6.77	6.16	7.44

CI = confidence interval; GLS Mean = geometric least squares mean

Ensitrelvir with 375/125mg also strongly inhibited CYP3A

- Ensitrelvir increased the AUCR of MDZ by 6.77-fold, although the PBPK predicted the AUCR of MDZ by 3.83-fold.
- The reason why the PBPK model underpredicted is under investigation.

Conclusion

The effects of ensitrelvir on the PK of CYP3A substrates were evaluated. This study found that ensitrelvir with 375/125mg is strong CYP3A inhibitor, although PBPK model simulated as moderate CYP3A inhibitor. In addition, ensitrelvir increased the exposures of DEX when co-administered with ensitrelvir on Day 5 and the effect was diminished over time, and no meaningful effect of ensitrelvir on the PK of PLS was confirmed.

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