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Population Pharmacokinetic Analysis of Ensitrelvir, an Inhibitor of 3C-like (3CL) Protease of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) for patients with SARS-CoV-2 Infection

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Introduction and Purpose

- Ensitrelvir is a novel oral inhibitor of 3CL protease of SARS-CoV-2, which is essential for viral replication.
- Ensitrelvir was approved in Japan for the treatment SARS-CoV-2 infection under the Emergency Regulatory Approval System in November 2022.
- Ensitrelvir is administered once daily for 5 days with 375 mg on Day 1 followed by 125 mg.
- The aim of this study is to build a population pharmacokinetic (PK) model to assess covariates on ensitrelvir PK.

Methods

1) Population PK Analysis

Population PK analysis was performed by using NONMEM ver. 7.4 (ICON Development Solutions, US) with stepwise covariate model (SCM) building tool in Perl-speaks NONMEM ver. 4.9 (developed by Rikard Nordgren).

Data: A total of 8034 plasma ensitrelvir concentrations from 2060 healthy participants in Phase 1 studies and patients in Phase 2/3 study were obtained and used for the analysis.

Table.1 Background Characteristics of Participants

Study	Background characteristics	Mean (SD)	Median (range)
Overall (N = 2060, 8034 points) [Phase 1 study (n=175, 4341 points) Phase 2/3 study (n=1885, 3693 points)]	Body weight (kg)	63.8 (13.6)	62.6 (35.0 - 156.0)
	BMI (kg/m^2)	23.0 (3.8)	22.5 (7.0 - 49.8)
	Age (years)	36.5 (12.8)	35 (12 - 76)
	ALT (U/L)	26.3 (23.4)	19 (0 - 349)
	AST (U/L)	25.4 (13.7)	22 (10 - 272)
	BIL (mg/dL)	0.5 (0.3)	0.5 (0.1 - 2.1)
	ALB (g/dL)	4.4 (0.3)	4.4 (0.5 - 5.8)
	CrCL (mL/min)	115.3 (30.7)	111.9 (46.0 - 354.6)
	Scr (mg/dL)	0.76 (0.17)	0.76 (0.37 - 1.43)
	eGFR (mL/min/1.73 m^2)	88.1 (19.8)	85.9 (36.4 - 242.9)
	eGFRabs (mL/min)	84.3 (20.3)	82.5 (31.5 - 278.8)
	Formulation (Suspension : Tablet) *	62 (3.0%) : 1998 (97.0%)	
	Sex (Male : Female) *	1183 (57.4%) : 877 (42.6%)	
	Adolescent (12 to < 18 years : >= 18 years) *	34 (1.7%) : 2026 (98.4%)	
	Race (Asian : White : Others) *	2030 (98.5%) : 25 (1.2%) : 5 (0.2%)	
	Country (Japan : Korea : Vietnam) *	1484 (72.0%) : 130 (6.3%) : 446 (21.7%)	
	Health status (Healthy : Infected by SARS-CoV-2) *	175 (8.5%) : 1885 (91.5%)	

ALB = albumin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BIL = total bilirubin; BMI = body mass index; CrCL = creatinine clearance; eGFR = estimated glomerular filtration rate; eGFRabs = absolute estimated glomerular filtration rate; Scr = serum creatinine
*: Number of participants (percentage of all participants).

Base model:

- Structural PK model: Two-compartment model with first-order elimination and first-order absorption.
- Inter-individual variability: exponential error model
- Intra-individual variability: proportional and additive error model

Covariate model: Constructed full model by SCM with a forward selection ($p<0.01$) and inferential assessment. Then assessed the selected covariates with a backward selection ($p<0.005$). Finally tested omega block and inferential assessment.

Candidates of covariate

- CL/F: body weight, age, adolescent or not, sex, race, country, ALT, ALB, total bilirubin, creatinine clearance, serum clearance, patient or not
- Vc/F: body weight, age, adolescent or not, sex, race, country, ALB, patient or not
- Absorption rate constant (ka): fasted or fed, formulation
- Bioavailability (F1): fasted or fed, formulation, patient or not

Model evaluation: The final model was evaluated by Diagnostic plots, visual predictive check (VPC) and bootstrapping.

2) Post-hoc Exposure Parameters in Patients

Exposure parameters (C_{max}, plasma concentration 24 hours post-dose [C_{24}] and AUC) on Days 1 and 5 were estimated by Bayesian approach with the final population PK model when ensitrelvir was administered at once daily for 5 days with 375 mg on Day 1 followed by 125 mg (125 mg group) or at once daily for 5 days with 750 mg on Day 1 followed by 250 mg (250 mg group) in Phase 2/3 Study.

3) PK/Pharmacodynamic (PD) Relationship

PK/PD relationship between change from baseline of SARS-CoV-2 viral RNA load on Day 4 and C_{24} on Day 1 were assessed in Phase 3 part of Phase 2/3 study. The C_{24} was categorized by 0 to <10, 10 to < 20, 20 to < 30, 30 to < 40 and ≥ 40 μg/mL.

Results: 1) Population PK Analysis

- The final model included the effect of body weight on CL/F, the effect of body weight on Vc/F, the effects of food and formulation on Ka. The final population PK parameters and the results of bootstrapping (rate: 90.2%) are shown in Table 2.
- Diagnostic plots (goodness-of-fit) are shown in Fig.1.
- Prediction-corrected VPC by race (Asian/White) for data following multiple doses in Phase 1 and 2/3 studies are shown in Fig.2, indicating good predictive performance of the final model.

Fig. 1. Goodness-of-fit Plots for Final Model

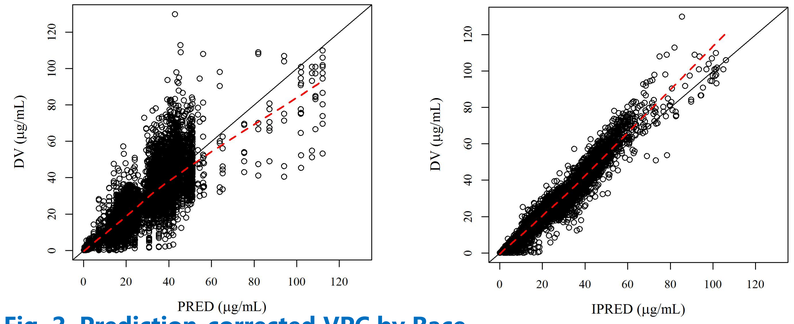


Fig. 2. Prediction-corrected VPC by Race

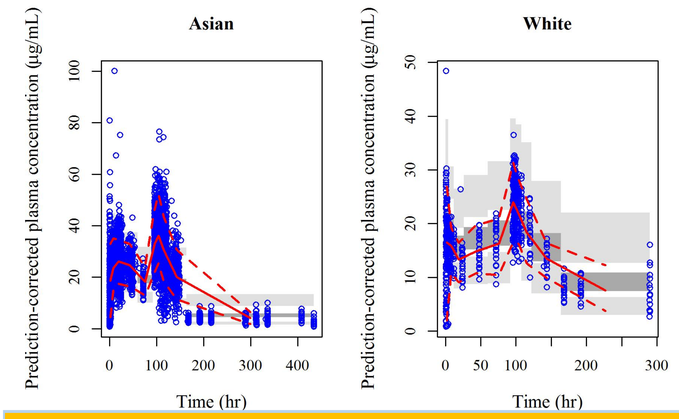


Table.2 Population PK Parameters of Ensitrelvir and Results of Bootstrap

Pharmacokinetic parameters	Units	Final Model Estimates	Final Model 95% CIs (lower - upper)	Final Model %RSE	Bootstrap estimates Median	Bootstrap estimates 95% CIs (lower - upper)
Ka	(1/hr)	1.50	1.25 - 1.75	8.6	1.50	1.23 - 1.80
CL/F	(L/hr)	0.211	0.208 - 0.214	0.8	0.211	0.207 - 0.214
Vc/F	(L)	14.7	13.9 - 15.5	2.7	14.8	13.9 - 15.5
Q/F	(L/hr)	0.539	0.321 - 0.757	20.6	0.534	0.331 - 0.823
Vp/F	(L)	2.50	1.80 - 3.20	14.3	2.49	1.74 - 3.26
Effect of food on Ka		0.594	0.398 - 0.790	16.8	0.599	0.447 - 1.00
Effect of formulation on Ka		0.362	0.262 - 0.462	14.1	0.367	0.280 - 0.469
Effect of body weight on CL/F		0.521	0.456 - 0.586	6.4	0.527	0.459 - 0.585
Effect of body weight on Vc/F		1.04	0.960 - 1.12	3.9	1.04	0.959 - 1.11
Inter-individual variability						
Ka	%	72.9	64.3 - 80.6	11.3	72.1	64.4 - 80.4
CL/F	%	21.3	19.7 - 22.8	7.4	21.3	20.0 - 23.0
Covariance between CL/F and Vc/F		0.0216 (R = 0.691)	0.0173 - 0.0259	10.0	0.0217	0.0179 - 0.0263
Vc/F	%	14.7	12.8 - 16.3	12.3	14.6	12.7 - 16.5
Intra-individual variability						
Proportional residual error	%	19.9	18.5 - 21.3	3.6	19.8	18.6 - 21.2
Additive residual error	(μg/mL)	0.0317	0.0224 - 0.0410	14.9	0.0331	0.00945 - 0.0570

CI = confidence interval; R = coefficient of correlation; %RSE = relative standard error in percent

Ka = 1.50 × (0.594 for food) × (0.362 for formulation)
CL/F = 0.211 × (body weight/62.6) $^{0.521}$
Vc/F = 14.7 × (body weight/62.6) $^{1.04}$
Q/F = 0.539
Vp/F = 2.50 [food: 1 = administration within 2 hours after a meal, 0 = other; formulation: 1 = tablet, 0 = suspension]

- Body weigh on CL/F and Vc/F
- Food and formulation on Ka

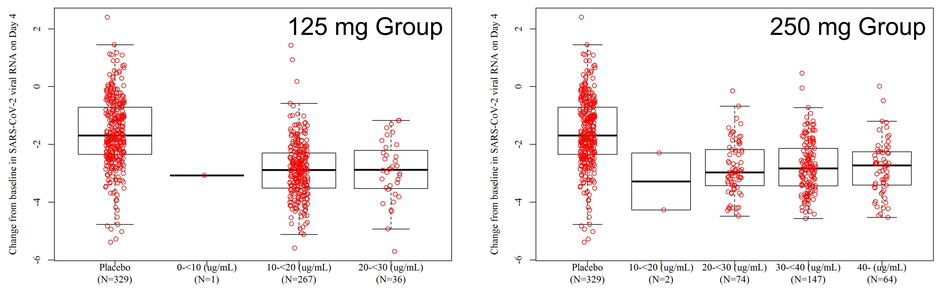
Results: 2) Post-hoc Exposure Parameters in Patients

Table.3 Post-hoc Exposure Parameters in Patients of Phase 2/3 Study

Dose	Day Parameters	Day 1 C_{max} (μg/mL)	Day 1 C_{24} (μg/mL)	Day 1 AUC (μg.hr/mL)	Day 5 C_{max} (μg/mL)	Day 5 C_{24} (μg/mL)	Day 5 AUC (μg.hr/mL)
125 mg Group	n	943	943	943	925	925	925
	Mean	23.4	16.6	437.5	26.6	19.5	578.5
	SD	5.00	3.04	96.53	4.87	3.48	116.7
	CV (%)	21.3	18.3	22.1	18.3	17.8	20.2
250 mg Group	n	942	942	942	920	920	920
	Mean	48.9	34.8	909.5	56.4	41.8	1233
	SD	10.7	6.70	205.1	11.00	8.05	269.5
	CV (%)	21.9	19.2	22.6	19.6	19.3	21.9

Results: 3) PK/PD Relationship

Fig. 3. Relationship between Change from Baseline of SARS-Cov-2 Virus RNA on Day 4 and C_{24} on Day 1



No difference of exposure/dose for anti-virus effect

Conclusion

The population PK model was developed based on the plasma ensitrelvir concentration data from participants including patients infected with SARS-CoV-2, and body weight was the most important covariate on ensitrelvir PK. There was no difference of exposure and dose for anti-viral effect, supporting the selection of the clinical dose (Loading dose 375 mg on Day 1/maintenance dose 125 mg on Days 2-5) regardless body weight.