Report on the Deliberation Results

March 4, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Xocova Tablets 125 mg
Non-proprietary Name	Ensitrelvir Fumaric Acid (JAN*)
Applicant	Shionogi & Co., Ltd.
Date of Application	June 8, 2023

Results of Deliberation

In its meeting held on March 4, 2024, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 8 years.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

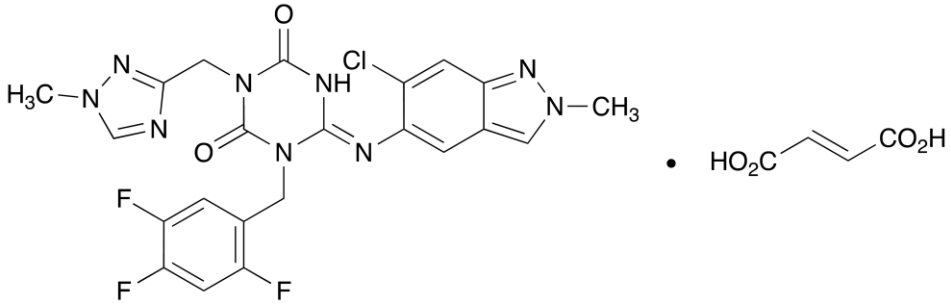
Review Report

February 19, 2024
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Xocova Tablets 125 mg
Non-proprietary Name	Ensitrelvir Fumaric Acid
Applicant	Shionogi & Co., Ltd.
Date of Application	June 8, 2023
Dosage Form/Strength	Each tablet contains 152.3 mg of ensitrelvir fumaric acid (125 mg of ensitrelvir).
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{22}H_{17}ClF_3N_9O_2 \bullet C_4H_4O_4$

Molecular weight: 647.95

Chemical name: (6*E*)-6-[(6-Chloro-2-methyl-2*H*-indazol-5-yl)imino]-3-[(1-methyl-1*H*-1,2,4-triazol-3-yl)methyl]-1-[(2,4,5-trifluorophenyl)methyl]-1,3,5-triazinane-2,4-dione monofumaric acid

Items Warranting Special Mention

None

Reviewing Office Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19), and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition.

Indication

Disease caused by SARS-CoV-2 infection (COVID-19)

Dosage and Administration

The usual dose in ≥12-year-old pediatric patients and adults is ensitrelvir 375 mg on Day 1 and ensitrelvir 125 mg from Days 2 to 5, administered orally once daily.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

January 19, 2024

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Xocova Tablets 125 mg
Non-proprietary Name	Ensitrelvir Fumaric Acid
Applicant	Shionogi & Co., Ltd.
Date of Application	June 8, 2023
Dosage Form/Strength	Each tablet contains 152.3 mg of ensitrelvir fumaric acid (125 mg of ensitrelvir).

Proposed Indication

Disease caused by SARS-CoV-2 infection (COVID-19)

Proposed Dosage and Administration

The usual dose in ≥12-year-old pediatric patients and adults is ensitrelvir 375 mg on Day 1 and ensitrelvir 125 mg from Days 2 to 5, administered orally once daily.

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

COVID-19 is a disease caused by SARS-CoV-2 infection. The main symptoms are upper respiratory tract symptoms such as pharyngodynia, nasal discharge, and nasal obstruction, as well as systemic symptoms such as malaise, fever, and myalgia. Patients with mild disease often have symptomatic relief within a week of onset. Patients at high risk of severe disease may experience lower respiratory tract infections, leading to acute respiratory distress syndrome and multiple organ failure, albeit only at a low frequency in patients infected with the Omicron variant, the prevalent variant after the end of 2021 (Guidelines for Diagnosis and Treatment of COVID-19, ver. 10.0, dated August 21, 2023).

In Japan, the following drugs are approved for marketing for the treatment of COVID-19: remdesivir (brand name: Veklury for Intravenous Injection 100 mg), casirivimab (genetical recombination)/imdevimab (genetical recombination) (brand name: Ronapreve for Intravenous Infusion Set 300, etc.), sotrovimab (genetical recombination) (brand name: Xevudy for Intravenous Infusion 500 mg), tixagevimab (genetical recombination)/cilgavimab (genetical recombination) (brand name: Evusheld Intramuscular Injection Set),[1)] molnupiravir (brand name: Lagevrio Capsules 200 mg), and nirmatrelvir/ritonavir (brand name: Paxlovid PACK).

Ensitrelvir is an inhibitor of 3C-like (3CL) protease of SARS-CoV-2, a compound discovered by the joint study of Hokkaido University and Shionogi & Co., Ltd. Ensitrelvir suppresses viral replication by inhibiting the cleavage of the polyprotein.

Ensitrelvir was granted Emergency Approval on November 22, 2022 for the indication of COVID-19, according to the provisions of Article 14-2-2, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145, 1960) with an effective period of 1 year. Subsequently, the applicant submitted an application for full marketing approval of ensitrelvir within the effective period of the Emergency Approval, according to the provisions of Article 14 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, with the claim that the safety and efficacy of ensitrelvir against COVID-19 were demonstrated by the results of phase III part of the global phase II/III study (Study 2108T1221 [Study T1221]) and other data. PMDA has reviewed the application data submitted or renewed after the Emergency Approval. As of December 2023, ensitrelvir is not approved in any country or region outside Japan.

2. Quality and Outline of the Review Conducted by PMDA

In addition to the data submitted for the Emergency Approval, the following results of stability studies were submitted based on the stability study plan presented for the Emergency Approval.

2.1 Drug substance

2.1.1 Stability of drug substance

Table 1 shows the results of stability studies on the drug substance. Results demonstrated the stability of the drug substance.

1) Approved for treatment and prevention of disease cause by SARS-CoV-2 infection (COVID-19).

Table 1. Stability studies of drug substance

Study	Primary batch	Temperature	Humidity	Storage condition	Storage period
Long-term	3 pilot-scale batches	25°C	60% RH	Low-density polyethylene bag (double-layered) + fiber drum	12 months
Accelerated	3 pilot-scale batches	40°C	75% RH		6 months

Based on the above, a retest period of 24 months was proposed for the drug substance stored in a double-layered polyethylene bag placed in a fiber drum at room temperature, based on Guideline on Evaluation of Stability Data (ICH Q1E Guidelines). The long-term stability study will be continued for [redacted] months.

2.2 Drug product

2.2.1 Stability of drug product

Table 2 shows the results of the stability studies on the drug product. Results demonstrated the stability of the drug product.

Table 2. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	1 pilot scale batch 2 small scale batches	25°C	60% RH	Blister pack ([redacted])	24 months
Accelerated	1 pilot scale batch 2 small scale batches	40°C	75% RH		6 months

Based on the above, a shelf life of 36 months has been proposed for the drug product stored in a blister pack ([redacted]) at room temperature, based on the ICH Q1E Guideline. Long-term stability study will be continued for [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the newly submitted data, PMDA has concluded that the proposed shelf lives of the drug substance and the drug product were appropriate.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

In addition to the data submitted for the Emergency Approval, the applicant submitted results of newly conducted primary pharmacodynamic studies. In this section, data are expressed in means unless specified otherwise.

3.1 Primary pharmacodynamics

3.1.1 Inhibition of SARS-CoV-2 3CL protease (CTD 4.2.1.1-1, 4.2.1.1-3, and 4.2.1.1-4)

The inhibitory activity of ensitrelvir against SARS-CoV-2 3CL proteases was evaluated based on the reaction between SARS-CoV-2 3CL proteases containing various amino acid substitutions and their substrates. As shown in Table 3, ensitrelvir inhibited the proteases to a similar extent regardless of amino acid substitution.

Table 3. Inhibitory activity of ensitrelvir against SARS-CoV-2 3CL protease

Amino acid substitution in SARS-CoV-2 3CL protease	Main strains with the substitution	IC_{50} (nmol/L)
No amino acid substitution	A (original strain)	13.2
T24I	C.1.2	14.0
K88R	C.37 (Lambda variant)	12.1
A193V	B.1.351 (Beta variant)	10.2
H246Y	P.1 (Gamma variant)	12.5
A255V	B.1.1.318	10.1

3.1.2 *In vitro* antiviral activity

3.1.2.1 *In vitro* antiviral activity (CTD 4.2.1.1-5, 4.2.1.1-13 to 4.2.1.1-15, 4.2.1.1-18 to 4.2.1.1-20, and 4.2.1.1-38)

VeroE6/transmembrane protease, serine 2 (TMPRSS2) cells or the 3D organ culture model of human tracheal epithelium prepared from primary human nasal or bronchial epithelial cells, were infected with clinical isolates of SARS-CoV-2, to evaluate the antiviral activity of ensitrelvir based on cell degeneration. As shown in Table 4, antiviral activity of ensitrelvir against various variants (all of which were Omicron sublineages or recombinants) was similar to that against the original strain.

Table 4. *In vitro* antiviral activity of ensitrelvir against SARS-CoV-2

Cells	Viral isolate	Viral strain	EC_{50} (μmol/L)	
			Ensitrelvir	Remdesivir
VeroE6/TMPRSS2	hCoV-19/Japan/TY/WK-521/2020	A (original strain)	0.37	1.9
	hCoV-19/Japan/TY41-721/2022	BA.2.12.1	0.24	0.49
	hCoV-19/Japan/TY41-763/2022	BA.4.6	0.30	0.87
	hCoV-19/Japan/TY41-704/2022	BA.5.2.1	0.37	1.7
	hCoV-19/Japan/TY41-820/2022	BF.7	0.51	1.2
	hCoV-19/Japan/TY41-828/2022	BF.7.4.1	0.55	1.6
	hCoV-19/Japan/TY41-796/2022	BQ.1.1	0.48	2.2
	hCoV-19/Japan/TY41-832/2022	CH.1.1.11	0.38	1.2
	hCoV-19/Japan/TY41-795/2022	XBB.1	0.33	0.95
	hCoV-19/Japan/23-018/2022	XBB.1.5	0.57	1.0
	hCoV-19/Japan/TY41-951/2023	XBB.1.9.1	0.99	3.0
	hCoV-19/Japan/TY41-984/2023	XBB.1.16	0.33	1.1
	hCoV-19/Japan/TY41-831/2022	XBF	0.29	1.0
3D organ culture model of human tracheal epithelium prepared from primary human nasal epithelial cells	hCoV-19/Japan/TY38-873/2021	BA.1.18	0.0236,[a] 0.0827[b]	-
	hCoV-19/Japan/TY41-702/2022	BE.1	0.0420[b]	-
3D organ culture model of human tracheal epithelium prepared from primary human bronchial epithelium cells	hCoV-19/Japan/TY38-873/2021	BA.1.18	0.0114,[c] 0.127[d]	-

-, Not measured
a) Cultured for 1 day
b) Cultured for 2 days
c) Cultured for 3 days
d) Cultured for 4 days

3.1.3 Resistance profile

3.1.3.1 Studies on competitive proliferative capacity of SARS-CoV-2 strains with resistant mutation (CTD 4.2.1.1-28)

The amino acid substitutions in SARS-CoV-2 3CL protease (D48G, M49L, P52S, S144A, and M49L/S144A) observed in the *in vitro* resistance acquisition study (see Section 3.1.3.1 in Review Report on Xocova Tablets 125 mg dated June 17, 2022) were introduced into SARS-CoV-2 (rgSARS-CoV-2/Hu/DP/Kng/19-020 strain, lineage A) to generate recombinant viruses. Then, competitive proliferative

capacity between the parent strain and the recombinant viruses was investigated. When the 3D organ culture model of primary human nasal epithelial cells was coinfected with the parent strain and a recombinant virus in a 1:1 or 1:9 ratio, the strains with P52S or M49L/S144A substitution exhibited a lower competitive proliferative capacity than the parent strain, whereas strains with other amino acid substitutions showed similar proliferative capacity as the parent strain.

3.1.4 Effect of coadministration of ensitrelvir with other anti-SARS-CoV-2 drugs (CTD 4.2.1.1-32)

The effect of ensitrelvir in combination with other anti-SARS-CoV-2 drugs (antibody products) was investigated. Table 5 shows the results, which demonstrated an additive effect but not a synergistic or competitive effect.

Table 5. Effect of coadministration of ensitrelvir with other anti-COVID-19 drugs

Viral isolate (strain)	Concomitant drug	Combination index[a)]	Assessment[b)]
hCoV-19/Japan/TY11-927-P1/2021 (B.1.617.2, Delta variant)	Sotrovimab	0.874	Additive
		0.971	Additive
		0.828	Additive
	Bebtelovimab[c)]	1.04	Additive
		0.938	Additive
		0.992	Additive
	Tixagevimab/cilgavimab	1.18	Additive
		1.19	Additive
		1.04	Additive

VeroE6/TMPRSS2 cells were used.

a) Drugs for coadministration were mixed at a ratio approximate to 50% effective concentration (EC_{50}) of each drug according to Chou-Talalay method (*Adv Enzyme Regul.* 1984;22:27-55), in order to calculate the combination index under the condition where the 2 drugs contribute almost equally to the inhibitory effect.

b) CI ≤0.8 was considered as a synergistic effect, 0.8<CI<1.2 as an additive effect, and 1.2≤CI as a competitive effect.

c) Not approved in Japan.

3.R Outline of the review conducted by PMDA

3.R.1 Antiviral activity of ensitrelvir against SARS-CoV-2

The applicant's explanation about the antiviral activity of ensitrelvir against SARS-CoV-2:

The antiviral activity (EC_{50}) of ensitrelvir against Omicron sub-lineages investigated after the Emergency Approval was similar to that against the strains investigated before the Emergency Approval (i.e., original strain; Alpha, Beta, Gamma, Delta, Theta, and Mu variants; and Omicron sub-lineages BA.2.75, BA.4, BA.5, and XE) [see Section 3.1.2.1 of this Review Report and Section 3.1.2.1 of Review Report on Xocova Tablets 125 mg dated June 17, 2022].

PMDA's view:

The applicant's explanation about the antiviral activity of ensitrelvir against SARS-CoV-2 is acceptable. Since antiviral activity of ensitrelvir against novel variants is critical information regarding the efficacy, relevant information should be collected continuously, and new findings should be provided promptly to healthcare professionals, etc. when they become available.

3.R.2 Resistance profile of SARS-CoV-2 against ensitrelvir

The applicant's explanation:

The amino acid substitutions shown in Table 6 have been reported to cause a ≥3-fold reduction in inhibitory activity of ensitrelvir against SARS-CoV-2 3CL protease or in antiviral activity *in vitro*. However, the effect of each amino acid substitution on the clinical efficacy of ensitrelvir is unclear.

Table 6. Amino acid substitutions that caused a ≥3-fold reduction in the inhibitory activity of ensitrelvir against SARS-CoV-2 3CL protease or in its antiviral activity

Method for assessment	Amino acid substitutions that caused a ≥3-fold reduction in SARS-CoV-2 3CL protease inhibitory activity or in antiviral activity (inhibitory or antiviral activity ratio versus wild-type SARS-CoV-2 3CL protease or wild-type strain)	Reference source
Evaluation of protease inhibitory activity using recombinant SARS-CoV-2 3CL proteases with an amino acid substitution	M49I (6.09), M49T (3.55), N142S (4.54), G143S (15.9), R188S (5.76), A191T (3.89), A191V (3.45)	a, b
Cellular assay system using cells expressing SARS-CoV-2 3CL protease	T45I (3.7-4.1), D48Y (2.1-5.0), M49I (9.4-12.4), M49T (4.0), Y54C (3.1), E166A (35.2), E166V (77.9), L167F (5.2-20.3), P168del (3.5-6.8), Q192R (3.2), T45I/M49L (54.5), T45I/P168del (>10), T45I/A173V (4.2/2.2), D48Y/P168del (>10-39.9), M49I/P168del (>10-52.5), M49L/P168del (127), L50F/E166A (28.8), L50F/E166V (20.9), P168del/A173V (3.4), P168del/A173V (2.8/3.1)	c, d, e
Cellular assay system using SARS-CoV-2 replicon	P168del (3.6), A173V (7.8), P168del/A173V (3.3)	d
Antiviral activity evaluation using recombinant SARS-CoV-2	E166A (9.1), E166V (23), T21I/E166V (3.4), M49L/E166A (197), L50F/E166V (3.7), E166A/L167V (38), L50F/E166A/L167V (44)	a, f, g

"del" means deletion.

Reference sources are as follows:

a) *mBio.* 2023;14: e0281522, b) *J Biol Chem.* 2023;29: 103004, c) *Sci Transl Med.* 2023;15: eabq7360, d) *Sci Adv.* 2023;9: eade8778, e) *npj Antimicrob Resist.* 2023;1: 9, f) *Nature.* 2023;613: 558-64, g) *Nat Commun.* 2023;14: 3952

PMDA's view:

After the Emergency Approval, multiple SARS-CoV-2 strains have emerged with amino acid substitutions that reduce antiviral activity of ensitrelvir. The effect of the amino acid substitutions on the clinical efficacy of ensitrelvir is unclear at present. The efficacy of ensitrelvir may be weakened in the future if a strain with such an amino acid substitution becomes prevalent. The applicant should continue to collect information on the emergence of strains that may exhibit resistance to ensitrelvir, and should promptly provide healthcare professionals, etc. with new information regarding resistance mutations if it becomes available.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

In addition to the data submitted for the Emergency Approval, the applicant submitted results of newly conducted non-clinical pharmacokinetic studies that evaluated pharmacokinetic interactions of ensitrelvir.

4.1 Pharmacokinetic interactions

4.1.1 Inhibition of drug transporter (CTD 5.3.2.2-07)

Using membrane vesicles engineered to express human bile-salt export pump (BSEP), the inhibitory effect of ensitrelvir (0-150 μmol/L) against the transport of a BSEP substrate (^{3}H-labeled taurocholic acid sodium salt hydrate, 2 μmol/L) was investigated. Ensitrelvir did not show any clear inhibitory effect against the transport (50% inhibitory concentration [IC_{50}], >150 μmol/L).

4.R Outline of the review conducted by PMDA

On the basis of the additional study data submitted, PMDA concluded that there were no new concerns in terms of nonclinical pharmacokinetics.

5. Toxicity and Outline of the Review Conducted by PMDA

In addition to the data submitted for the Emergency Approval, the applicant submitted results of a reverse mutation assay of an impurity and of a study on the mechanism of decreased high density lipoprotein (HDL) cholesterol.

5.1 Safety evaluation of an impurity (CTD 4.2.3.7-17)

Impurity Z, a raw material of the starting material of the drug substance, is a potential impurity of the drug substance. An Ames test of Impurity Z was conducted according to ICH M7 Guideline: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. Results showed that Impurity Z was mutagenic. This mutagenic impurity was already identified as an impurity with a warning structure before the Emergency Approval. The residual amount of Impurity Z in the drug substance has therefore been controlled at a certain level to ensure that human exposure to Impurity Z remains below the acceptable threshold recommended by the Threshold of Toxicological Concern (TTC) (see Section 2.1.2 in Review Report on Xocova Tablets 125 mg dated June 17, 2022).

5.2 Mechanism of decrease in HDL cholesterol

In the Japanese phase I study (Study 2102T1211 [Study T1211]), a decrease in blood HDL cholesterol was observed in subjects receiving ensitrelvir. The following study was conducted to elucidate the mechanism of decreased HDL cholesterol (Table 7). Thus, in order to investigate whether ensitrelvir promotes cholesterol excretion outside the body, the effect of ensitrelvir on cholesterol excretion in feces and bile was investigated using cynomolgus monkeys. Results showed that ensitrelvir did not affect fecal or biliary excretion of cholesterol.

Table 7. Summary of study on the mechanism of decrease in HDL cholesterol

Test system	Testing method	Results	Attached document CTD
Male cynomolgus monkey	Oral ensitrelvir 10 mg/kg/day was administered to monkeys for 10 days. Before and after the administration, the amounts of total cholesterol and total cholic acid (metabolite of cholesterol) in feces and bile were measured over time.	Ensitrelvir had no effect on the amounts of total cholesterol and total cholic acid in feces and bile.	4.2.3.7-18, 4.2.3.7-19

5.R Outline of the review conducted by PMDA

PMDA concluded that no new safety concerns were suggested by the additionally submitted toxicity data.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Plasma ensitrelvir concentration was measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS; lower limit of quantitation, 10.0 or 200 ng/mL). The commercial formulation was used in phase III part of the global phase II/III study (Study T1221).

6.2 Clinical pharmacology

In addition to the data submitted for the Emergency Approval, the applicant submitted results of the following studies: Mass balance study, pharmacokinetics (PK) study in subjects with hepatic or renal impairment, population pharmacokinetics (PPK) analysis based on PK data in phase III part of the global phase II/III study (Study T1221), etc. Unless otherwise specified, numerical values are presented as means.

6.2.1 Mass balance study (CTD 5.3.3.1-03 and 5.3.3.1-04, Study 2135T1216 [Study T1216] [[redacted] 202[redacted] to [redacted] 202[redacted]])

A single dose of ^{14}C-labeled ensitrelvir 375 mg (92.2 μCi) was administered orally to 6 non-Japanese healthy subjects under fasted conditions to investigate the mass balance. The urinary and fecal excretion rate up to 456 hours post-dose was 25.8% and 64.8%, respectively, of the radioactivity administered. In the urine (up to 168 hours post-dose) and feces (up to 240 hours post-dose[2)]), mainly unchanged ensitrelvir was detected (19.0% [urine] and 50.7% [feces] of the radioactivity administered). In plasma, mainly unchanged ensitrelvir (95.6% of total plasma radioactivity) was detected up to 192 hours post-dose. No metabolites exceeding 10% of total plasma radioactivity were observed.

6.2.2 Intrinsic factor PK studies

6.2.2.1 Foreign phase I study in subjects with hepatic impairment (CTD 5.3.3.3-01, Study 2127T1213 [Study T1213] [August 2022 to April 2023])

Table 8 shows PK parameters following a single oral administration of ensitrelvir 375 mg in non-Japanese subjects with mild to moderate hepatic impairment (Child-Pugh class A or B) or with normal hepatic function. Given the plasma protein-unbound rate, etc., described below, the results suggested that the presence or extent of hepatic impairment does not affect ensitrelvir exposure. The plasma protein-unbound rate (geometrical mean) at 3 hours after ensitrelvir administration was 1.47% in subjects with normal hepatic functions, 1.38% in subjects with mild hepatic impairment, and 1.59% in subjects with moderate hepatic impairment, showing no significant differences.

2) In 1 of the 6 subjects, radioactivity in feces was measured from 24 to 360 hours after administration.

Table 8. PK parameters following a single oral administration of ensitrelvir in subjects with normal hepatic function or with hepatic impairment

Extent of hepatic impairment	N	C_{max} (μg/mL)	AUC_{last} (μg•h/mL)	The least squares geometric mean ratio [90% CI] (hepatic impairment/normal hepatic function)	
				C_{max}	AUC_{last}
Normal	8	20.5 (15.1)	1,130 (24.7)	-	-
Mild	9	18.2 (17.0)	1,137 (31.6)	0.89 [0.77, 1.02]	1.01 [0.79, 1.28]
Moderate	8	15.3 (30.4)	979.4 (25.2)	0.74 [0.60, 0.91]	0.87 [0.70, 1.08]

Geometric mean (CV%)

6.2.2.2 Foreign phase I study in subjects with renal impairment (CTD 5.3.3.3-02, Study 2128T1214 [Study T1214] [July 2022 to May 2023])

Table 9 shows PK parameters by renal function level (estimated glomerular filtration rate (eGFR) [mL/min]; normal [≥90], mild impairment [≥60 to <90], moderate impairment [≥30 to <60], severe impairment [<30]) following a single administration of ensitrelvir 375 mg in non-Japanese adult subjects. Although ensitrelvir exposure tended to increase in subjects with renal impairment, the extent of exposure did not differ between subjects with different severity of renal impairment. The plasma protein-unbound rate (geometric mean) at 3 hours after ensitrelvir administration was 1.30% in subjects with normal renal function, 1.43% in subjects with mild renal impairment, 1.25% in subjects with moderate renal impairment, and 1.72% in subjects with severe renal impairment, showing no significant difference.

Table 9. PK parameters following a single oral administration of ensitrelvir in subjects with normal renal function or with renal impairment.

Extent of renal impairment	N	C_{max} (μg/mL)	AUC_{last} (μg•h/mL)	The least squares geometric mean ratio [90% CI] (renal impairment/normal renal function)	
				C_{max}	AUC_{last}
Normal	8	15.5 (34.7)	977.3 (25.9)	-	-
Mild	8	20.5 (18.9)	1,398 (20.7)	1.32 [1.04, 1.68]	1.43 [1.17, 1.75]
Moderate	8	20.5 (12.6)	1,445 (24.5)	1.33 [1.06, 1.66]	1.48 [1.19, 1.84]
Severe	8	17.2 (19.8)	1,512 (23.4)	1.11 [0.87, 1.42]	1.55 [1.25, 1.92]

Geometric mean (CV%)

6.2.3 PPK analysis (CTD 5.3.3.5-02)

PPK analysis was conducted[3)] (software, NONMEM version 7.4 and up) using plasma ensitrelvir concentration data obtained at 8,034 time points from a total of 2,060 subjects in Cohorts Q to T of a Japanese phase I study (Study T1211), a Japanese phase I study (Study 2130T1215 [Study T1215]), and phase IIb/III part and phase III part of the global phase II/III study (Study T1221), together with the data used for the PPK model submitted for the Emergency Approval (Review Report on Xocova Tablets 125 mg dated June 17, 2022). The results showed that the revised final model was described by a 2-compartment model with the first order absorption process as with the original model; the following parameters were selected as covariates in the same manner as in the original model: Body weight for apparent total clearance (CL/F) and apparent volume of distribution in central compartment (Vc/F), and

3) Characteristics (median [range]) of subjects included in PPK analysis were as follows: Body weight, 62.6 [35.0, 156.0] kg; body mass index (BMI), 22.5 [7.0, 49.8] kg/m^2; age, 35 [12, 76] years; aspartate aminotransferase (AST), 22 [10, 272] U/L; alanine aminotransferase (ALT), 19 [0, 349] U/L; albumin, 4.4 [0.5, 5.8] g/dL; total bilirubin, 0.5 [0.1, 2.1] mg/dL; CrCL, 111.9 [46.0, 354.6] mL/min; serum creatinine concentration (Scr), 0.76 [0.37, 1.43] mg/dL; eGFR, 85.9 [36.4, 242.9] mL/min/1.73 m^2; eGFR unadjusted for body surface area, 82.5 [31.5, 278.8] mL/min.

effect of food (fasted or fed) and effect of formulation (suspension or tablets) for first order absorption rate constant (Ka).[4)5)]

Table 10 shows PK parameters of ensitrelvir in all subjects of the global phase II/III study (Study T1221), estimated from the final model.

Table 10. PK parameters of ensitrelvir in global phase II/III study (Study T1221) (estimated values)

Dose (mg)	N	Day of measurement	C_{max} (μg/mL)	AUC_{tau} (μg·h/mL)	$C_{24\,h}$ (μg/mL)
375/125[a)]	943	Day 1	23.4 ± 5.00	437.5 ± 96.53	16.6 ± 3.04
	925	Day 5	26.6 ± 4.87	578.5 ± 116.7	19.5 ± 3.48
750/250[b)]	942	Day 1	48.9 ± 10.7	909.5 ± 205.1	34.8 ± 6.70
	920	Day 5	56.4 ± 11.0	1,233 ± 269.5	41.8 ± 8.05

Mean ± standard deviation (SD)
a) Once-daily oral administration of ensitrelvir at 375 mg on Day 1 and at 125 mg from Days 2 to 5
b) Once-daily oral administration of ensitrelvir at 750 mg on Day 1 and at 250 mg from Days 2 to 5

6.R Outline of the review conducted by PMDA

6.R.1 Pharmacokinetics in subjects with hepatic or renal impairment

The applicant explained the pharmacokinetics of ensitrelvir in patients with hepatic or renal impairment and the necessity of change to the cautions provided in the package insert, based on the results of the clinical pharmacology studies in subjects with hepatic or renal impairment [see Sections 6.2.2.1 and 6.2.2.2], which were obtained after the Emergency Approval of ensitrelvir.

The applicant's explanation:

Patients with hepatic impairment

At the Emergency Approval, the following cautions were issued because the main elimination pathway of ensitrelvir is metabolism in the liver and therefore patients with severely reduced hepatic function may have an increase in plasma ensitrelvir exposure: (1) Ensitrelvir exposure may increase in patients with moderate hepatic impairment, and (2) ensitrelvir is not recommended for patients with severe hepatic impairment because ensitrelvir exposure may markedly increase in those patients (see Section 6.R.4 of Review Report on Xocova Tablets 125 mg dated June 17, 2022).

However, no significant difference was observed in plasma ensitrelvir exposure (C_{max}, AUC_{last}) in subjects with mild to moderate hepatic impairment in the clinical pharmacological study of ensitrelvir involving subjects with mild to moderate hepatic impairment (Study T1213) [see Section 6.2.2.1]. Since the global phase II/III study (Study T1221) demonstrated the safety of ensitrelvir of up to twice the proposed dose (ensitrelvir 750/250 mg) [see Section 7.1], the plasma ensitrelvir exposure is unlikely to increase to a clinically problematic level even in patients with severe hepatic impairment. Accordingly,

4) The following factors were investigated as possible covariates:
CL/F: Body weight, BMI, age (continuous variables), age (≥12 to <18 years, ≥18 years), sex, race (Asian, White, or other), region (Japan, South Korea, or Vietnam), AST, ALT, albumin, total bilirubin, CrCL, Scr, eGFR, eGFR unadjusted for body surface area, and health condition (healthy subjects or subjects infected with SARS-CoV-2)
Vc/F: Body weight, BMI, age (continuous variables), age (≥12 to <18 years, ≥18 years), sex, race (Asian, White, or other), region (Japan, South Korea or Vietnam), albumin, and health condition (healthy subjects or subjects infected with SARS-CoV-2)
Ka: Effect of food (fasted or fed) and effect of formulation (suspension or tablets)
Relative BA (F_1): Effect of food (fasted or fed), effect of formulation (suspension or tablets), and health condition (healthy subjects or subjects infected with SARS-CoV-2)

5) Health condition (healthy subjects or subjects infected with SARS-CoV-2) was selected as a covariate for CL/F in the original PPK model (Review Report on Xocova Tablets 125 mg dated June 17, 2022), but not in the revised PPK model.

it is acceptable to delete the above-mentioned cautions in the package insert prepared at the time of Emergency Approval.

Patients with renal impairment
In the clinical pharmacology study in subjects with mild, moderate, or severe renal impairment (Study T1214), ensitrelvir exposure (AUC_{last}) tended to increase by approximately 50% in subjects with renal impairment compared with the level in subjects with normal renal function [see Section 6.2.2.2]. However, it is unnecessary to issue a new safety-related caution for the use of ensitrelvir in patients with renal impairment because the global phase II/III study (Study T1221) demonstrated the safety of ensitrelvir of up to twice the proposed dose (ensitrelvir 750/250 mg) [see Section 7.1].

PMDA's view:
Given the submitted study results and the applicant's discussion, the applicant's following proposal is acceptable: (a) Cautions related to hepatic impairment should be deleted, and (b) additional cautions related to renal impairment are not required. However, since no clinical study data are available on ensitrelvir administered to patients with severe hepatic impairment, the applicant should continue to collect data after the market launch and communicate new findings to healthcare professionals, etc. appropriately as soon as available. In patients with hepatic or renal impairment under treatment with colchicine, blood colchicine level may increase by the potent CYP3A-inhibitory effect of ensitrelvir; the caution in the current package insert (i.e., ensitrelvir is contraindicated in patients with hepatic or renal impairment under treatment with colchicine.) should remain unchanged.

6.R.2 Coadministration with CYP3A inhibitor or inducer

The applicant explained the appropriateness of providing cautions related to drug-drug interactions between ensitrelvir and a potent CYP3A inhibitor or inducer, taking account of the results of PK analysis (preliminary data) in the ongoing clinical drug interaction study (Study 2305T1218 [Study T1218]).

The applicant's explanation:
Table 11 shows PK parameters of ensitrelvir in combination with a potent CYP3A inducer (carbamazepine) or a potent CYP3A inhibitor (itraconazole). Coadministration with the potent CYP3A inducer (carbamazepine) caused a decrease in plasma ensitrelvir exposure (AUC_{tau} and $C_{24\ h}$) by approximately 50% on Day 5, which may result in decreased effect of ensitrelvir. Taking into account the magnitude of the effect, the cautions provided in the current package insert (i.e., strong CYP inducers are listed in the "Contraindications for coadministration" section and moderate CYP3A inducers in the "Precautions for concomitant use" section) should remain unchanged.

Coadministration with the potent CYP3A inhibitor (itraconazole) caused a 5% to 31% increase in plasma ensitrelvir exposure (C_{max}, AUC_{tau}), whereas the global phase II/III study (Study T1221) demonstrated the safety of ensitrelvir of up to twice the proposed dose (ensitrelvir 750/250 mg) [see Section 7.1]. It is therefore unnecessary to provide a new caution on concomitant use with CYP3A inhibitors. A summary report of the clinical drug interaction study (Study T1218) will be prepared in the future.

Table 11. Effect of concomitant drugs on PK parameters of ensitrelvir

Dosage regimen of ensitrelvir	Concomitant drug		Day of ensitrelvir administration	No. of subjects[a]	The least squares geometric mean ratio [90% CI] (ensitrelvir + a concomitant drug/ ensitrelvir alone)		
	Drug	Dosage regimen			C_{max}	AUC_{tau}	$C_{24\,h}$
375/125 mg once daily[b]	Carbamazepine	300 mg twice daily[c]	Day 1	3[d]/14	0.92 [0.66, 1.28]	0.79 [0.63, 0.99]	0.65 [0.53, 0.81]
			Day 5	3[d]/14	0.62 [0.55, 0.69]	0.54 [0.50, 0.59]	0.48 [0.42, 0.55]
375/125 mg once daily[b]	Itraconazole	200 mg once daily[e]	Day 1	13/14	1.05 [0.98, 1.14]	1.10 [1.03, 1.18]	1.27 [1.15, 1.39]
			Day 5	13/14	1.24 [1.18, 1.30]	1.31 [1.26, 1.38]	1.40 [1.33, 1.48]

a) Number of subjects receiving ensitrelvir with a concomitant drug/number of subjects receiving ensitrelvir alone
b) Once-daily oral ensitrelvir at 375 mg on Day 1 and at 125 mg from Days 2 to 5
c) Twice-daily oral carbamazepine at 100 mg on Days 1 to 3, at 200 mg from Days 4 to 7, and at 300 mg from Day 8 onward.
d) In total, 13 subjects received carbamazepine. In 5 of the 13 subjects, the study was discontinued due to an adverse event (erythema) that occurred during carbamazepine monotherapy. In another 5 subjects, the carbamazepine dose was increased but then decreased due to an adverse event (e.g., monocytosis, thrombocytopenia, auditory disorder) or at the discretion of the investigator. As a result, 3 of the 13 subjects completed coadministration of carbamazepine without dose reduction.
e) Only on Day 1, itraconazole was administered at 200 mg twice daily orally.

PMDA's view:

The applicant's explanation is acceptable. After the preparation of the summary report of the clinical drug interaction study (Study T1218), the study results should be communicated to healthcare professionals, etc. in an appropriate manner.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

In addition to the data submitted for the Emergency Approval, the applicant submitted results of phase III part of the global phase II/III study (Study T1221) as the main efficacy and safety data (Table 12[6]). Results of the phase IIa and IIb parts are presented in the review report for Emergency Approval (Review Report on Xocova Tablets 125 mg dated June 17, 2022).

Table 12. Summary of main clinical study

Category	Region	Study code	Phase	Population	No. of subjects enrolled	Outline of dosage regimen	Main endpoints
Evaluation	Global	T1221	II/III	Phase IIa part: Asymptomatic SARS-CoV-2 carriers and patients with COVID-19 Phase IIb part: Patients with COVID-19 Phase III part: Patients with COVID-19	Phase IIa part: (a) 22 (b) 23 (c) 24 Phase IIb part: (a) 142 (b) 143 (c) 143 Phase III part: (a) 607 (b) 606 (c) 608	All parts: (a) Once-daily oral ensitrelvir at 375 mg on Day 1 and at 125 mg from Days 2 to 5. (b) Once-daily oral ensitrelvir at 750 mg on Day 1 and at 250 mg from Days 2 to 5. (c) Once-daily oral placebo for 5 days.	Efficacy Safety

6) For the present application, the applicant submitted the clinical study report that summarized results of not only the primary endpoint and main secondary endpoints (whose preliminary results were submitted before the Emergency Approval) but also other secondary endpoints.

7.1 Global phase II/III study (CTD 5.3.5.1-01, Study T1221; jRCT2031210350 [September 2021 to August 2022])

7.1.1 Phase III part [February to August 2022]

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 3 countries (Japan, Vietnam, and South Korea) to investigate the efficacy and safety of ensitrelvir in patients with COVID-19 (target sample size, 780 subjects [260 per group]). Table 13 shows the main inclusion/exclusion criteria for this study. The main amendments made to the study protocol during the conduct of phase III part are described in Section 10.

Table 13. Main inclusion/exclusion criteria

Inclusion criteria	1. Subjects ≥12 to <18 years old weighing ≥40 kg, and those ≥18 to <70 years old[a)] 2. SARS-CoV-2 positive (confirmed by PCR, etc. of a sample collected within 120 hours before randomization) 3. Onset of at least 1 of 14 symptoms[b)] of COVID-19 within 120 hours before randomization 4. At least 1 moderate (score 2)[c)] or severe symptom among 12 symptoms[d)] of COVID-19 at the time of randomization. Subjects with such a symptom(s) that have been present since before the onset of COVID-19 are eligible only if they consider that the symptom(s) have worsened after SARS-CoV-2 infection. 5. Subjects who can take contraceptive measures from the start of study treatment through 10 days after the end of study treatment. 6. Women who are not pregnant or not possibly pregnant
Exclusion criteria	1. SpO_2 ≤93% (room air) 2. Subjects who need oxygen therapy 3. Subjects who need mechanical ventilation 4. Current or chronic history of moderate or severe liver disease (Grade ≥2 in CTCAE, ver. 5.0) 5. Current or chronic history of moderate or severe kidney disease (Grade ≥2 in CTCAE, ver. 5.0)

a) Age limitation for subjects weighing ≥40 kg was changed from "≥12 to <20 years" to "≥12 to <18 years" in the protocol ver. 9 (dated July 8, 2022).
b) (1) Malaise or tiredness, (2) muscle or body aches, (3) headache, (4) chills or sweating, (5) feverish or pyrexia, (6) stuffy or runny nose, (7) sore throat, (8) cough, (9) shortness of breath (dyspnea), (10) nausea, (11) vomiting, (12) diarrhea, (13) taste abnormality, and (14) dysosmia
c) Symptoms were scored by the subject on a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe).
d) (1) Malaise or tiredness, (2) muscle or body aches, (3) headache, (4) chills or sweating, (5) feverish or pyrexia, (6) stuffy or runny nose, (7) sore throat, (8) cough, (9) shortness of breath (dyspnea), (10) nausea, (11) vomiting, and (12) diarrhea

The study drug was administered orally at the following dosage: (a) once-daily oral ensitrelvir at 375 mg on Day 1 and at 125 mg from Days 2 to 5 (ensitrelvir 375/125 mg group), (b) once-daily oral ensitrelvir at 750 mg on Day 1 and at 250 mg from Days 2 to 5 (ensitrelvir 750/250 mg group), or (c) placebo once daily for 5 days.

After the completion of enrollment of subjects in phase IIb part, the phase III part started on February 10, 2022. The observation period (follow-up period, Day 1 [the first day of study treatment] through Day 28) in all subjects was completed on August 8, 2022. The protocol was amended to ver. 10 on September 20, 2022 (last amendment before unblinding on September 23, 2022), in order to change the dose for efficacy evaluation, primary endpoint, main efficacy analysis population, sample size required, method for the primary analysis, etc. After the amendment, data from phase III part were analyzed [see Section 7.R.1.3 for the effect of protocol amendment].

Of 1,821 randomized subjects (607 in the ensitrelvir 375/125 mg group, 606 in the ensitrelvir 750/250 group, 608 in the placebo group),[7)] 1,808 subjects who received at least 1 dose of the study drug (604 in

[7)] A site management organization (SMO) involved in this study at a study site was found to have violated GCP in a clinical study of another product. The reliability of data from subjects enrolled at the study site was evaluated, and it was determined that there was no need to exclude the subjects.

the ensitrelvir 375/125 mg group, 599 in the ensitrelvir 750/250 group, 605 in the placebo group) were included in the safety analysis population. Of the 1,821 randomized subjects, 1,798 subjects were included in the intention to treat (ITT) population (603 in the ensitrelvir 375/125 mg group, 595 in the ensitrelvir 750/250 group, 600 in the placebo group) because they tested positive for SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR) on baseline nasopharyngeal swab.[8)] Of the subjects in the ITT population, 1,030 subjects were included in the primary efficacy analysis population (347 in the ensitrelvir 375/125 mg group, 340 in the ensitrelvir 750/250 mg group, 343 in the placebo group) because they experienced the onset of COVID-19 symptoms within <72 hours before randomization.

In total, 52 subjects discontinued the study (11 in the ensitrelvir 375/125 mg group, 21 in the ensitrelvir 750/250 mg group, 20 in the placebo group). The reasons for the discontinuation were the subject's request in 24 subjects (3 in the ensitrelvir 375/125 mg group, 11 in the ensitrelvir 750/250 mg group, 10 in the placebo group), protocol violation in 5 subjects (3 in the ensitrelvir 375/125 mg group, 1 in the ensitrelvir 750/250 mg group, 1 in the placebo group), adverse events in 4 subjects (2 in the ensitrelvir 750/250 mg group, 2 in the placebo group), disease progression in 1 subject (placebo group), and other in 18 subjects (5 in the ensitrelvir 375/125 mg group, 7 in the ensitrelvir 750/250 mg group, 6 in the placebo group).

The primary efficacy endpoint was defined as "the time from the start of study treatment to resolution of 5 symptoms of COVID-19," and "Resolution" was defined as the condition in which all 5 symptoms met the following criteria:

- Symptoms that had been present before the onset of COVID-19 and were considered by the subject to have worsened at baseline (at test before administration): Improved severity[9)] from baseline or the same severity as baseline (i.e., from severe to moderate or better, from moderate to mild or better, or from mild to mild or better) is maintained for at least 24 hours.
- Symptoms that had been present before the onset of COVID-19 and were NOT considered by the subject to have worsened at baseline (at test before administration): The same severity as baseline or improved severity[9)] from baseline (i.e., from severe to severe or better, from moderate to moderate or better, or from mild to mild or better) is maintained for at least 24 hours.
- Other symptoms (i.e., symptoms that were not present before the onset of COVID-19 and developed after baseline [test before administration]): An asymptomatic condition is maintained for at least 24 hours.

The results of the primary endpoint (Table 14 and Figure 1) demonstrate a statistically significant difference between the ensitrelvir 375/125 mg and placebo groups. No death or hospitalization occurred as of Day 28 in either group in the ITT population.

SARS-CoV-2 variants detected in the participating countries during the enrollment period were mainly BA.1, BA.2, and BA.5.[10)]

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8) Samples were collected the day before or on the day of starting the study treatment.
9) The severity of symptoms were scored by the subjects themselves on a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe).
10) CoVariants. Overview of Variants in Countries: https://covariants.org/

Table 14. Time to resolution of 5 symptoms of COVID-19 (primary endpoint) (only in subjects who experienced the onset of COVID-19 symptoms within <72 hours before randomization in the ITT population of phase III part)

		Ensitrelvir 375/125 mg	Ensitrelvir 750/250 mg	Placebo
Entire population	Number of subjects[a)]	336	329	321
	Number of subjects who achieved resolution	254	262	233
	Median time (h) to resolution of 5 symptoms of COVID-19	167.9	171.2	192.2
	P value[b)]	0.0407	-	
	Hazard ratio [95% CI][c)]	1.14 [0.95, 1.36]	1.22 [1.03, 1.46]	
Japanese subpopulation	Number of subjects[a)]	179	154	163
	Number of subjects who achieved resolution	134	123	120
	Median time (h) to resolution of 5 symptoms of COVID-19	165.8	151.6	172.1
	Hazard ratio [95% CI][c)]	1.04 [0.81, 1.33]	1.27 [0.98, 1.63]	

a) Subjects were excluded from the analysis if the baseline scores of 5 symptoms were all zero or if a baseline symptom score(s) were missing.
b) Stratified Peto-Prentice generalized Wilcoxon test stratified by vaccination against COVID-19 (yes, no), at a two-sided significance level of 5%
c) Cox proportional hazard model stratified by vaccination against COVID-19 (yes, no)

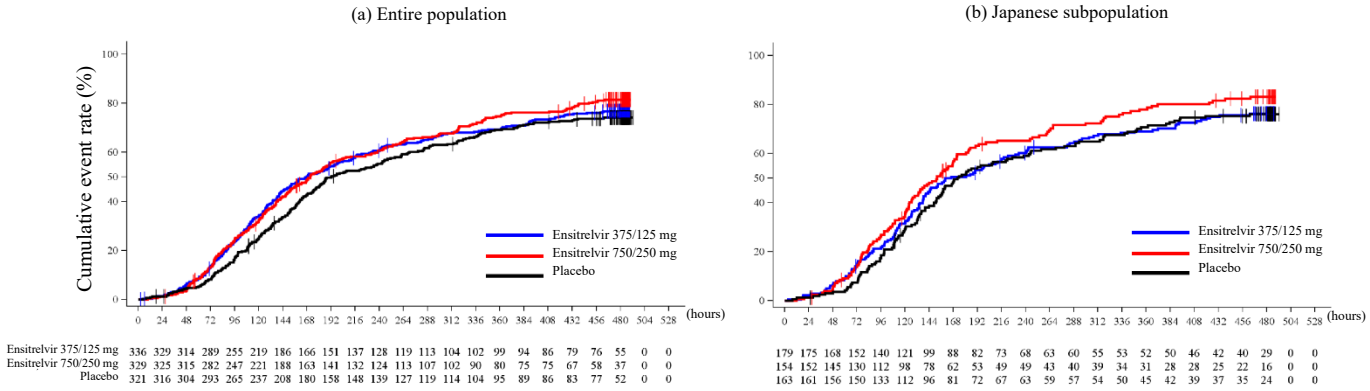

Figure 1. Cumulative rate of resolution expressed by "time to resolution of 5 symptoms of COVID-19" (primary endpoint) (only in subjects who experienced the onset of COVID-19 symptoms within <72 hours before randomization in ITT population of phase III part)

As for safety,[11)] the following are the incidences of adverse events and adverse drug reactions,[12)] respectively: 44.2% (267 of 604 subjects) and 24.5% (148 of 604 subjects) in the ensitrelvir 375/125 mg group; 53.6% (321 of 599 subjects) and 36.2% (217 of 599 subjects) in the ensitrelvir 750/250 mg group; and 24.8% (150 of 605 subjects) and 9.9% (60 of 605 subjects) in the placebo group. Table 15 shows the incidence of adverse events and adverse drug reactions occurring in ≥2 subjects in any group.

11) Adverse events and adverse drug reactions observed on or before Day 28
12) Adverse events considered to be related to the study drug by the investigator, etc.

Table 15. Adverse events and adverse drug reactions occurring in ≥2 subjects in any group (phase III part: safety analysis population)

Event	Adverse events			Adverse drug reactions		
	Ensitrelvir 375/125 mg (N = 604)	Ensitrelvir 750/250 mg (N = 599)	Placebo (N = 605)	Ensitrelvir 375/125 mg (N = 604)	Ensitrelvir 750/250 mg (N = 599)	Placebo (N = 605)
All events	267 (44.2)	321 (53.6)	150 (24.8)	148 (24.5)	217 (36.2)	60 (9.9)
High density lipoprotein decreased	188 (31.1)	231 (38.6)	23 (3.8)	111 (18.4)	157 (26.2)	9 (1.5)
Blood triglycerides increased	49 (8.1)	74 (12.4)	32 (5.3)	16 (2.6)	37 (6.2)	17 (2.8)
Blood bilirubin increased	36 (6.0)	56 (9.3)	6 (1.0)	17 (2.8)	35 (5.8)	3 (0.5)
Blood cholesterol decreased	20 (3.3)	28 (4.7)	3 (0.5)	8 (1.3)	12 (2.0)	1 (0.2)
Bilirubin conjugated increased	15 (2.5)	20 (3.3)	3 (0.5)	1 (0.2)	2 (0.3)	1 (0.2)
Blood creatine phosphokinase increased	14 (2.3)	8 (1.3)	11 (1.8)	4 (0.7)	1 (0.2)	1 (0.2)
Headache	13 (2.2)	20 (3.3)	14 (2.3)	4 (0.7)	13 (2.2)	2 (0.3)
Blood lactate dehydrogenase increased	6 (1.0)	15 (2.5)	6 (1.0)	4 (0.7)	8 (1.3)	4 (0.7)
ALT increased	6 (1.0)	11 (1.8)	11 (1.8)	3 (0.5)	6 (1.0)	7 (1.2)
Diarrhoea	6 (1.0)	9 (1.5)	12 (2.0)	5 (0.8)	8 (1.3)	7 (1.2)
Dizziness	6 (1.0)	1 (0.2)	4 (0.7)	4 (0.7)	1 (0.2)	2 (0.3)
Blood potassium decreased	6 (1.0)	0	1 (0.2)	1 (0.2)	0	1 (0.2)
Low density lipoprotein increased	5 (0.8)	3 (0.5)	4 (0.7)	2 (0.3)	1 (0.2)	3 (0.5)
Nausea	4 (0.7)	11 (1.8)	1 (0.2)	2 (0.3)	5 (0.8)	0
AST increased	4 (0.7)	9 (1.5)	12 (2.0)	1 (0.2)	5 (0.8)	7 (1.2)
Vomiting	4 (0.7)	8 (1.3)	0	2 (0.3)	4 (0.7)	0
Blood uric acid increased	4 (0.7)	6 (1.0)	4 (0.7)	2 (0.3)	3 (0.5)	1 (0.2)
Blood phosphorus increased	3 (0.5)	2 (0.3)	3 (0.5)	1 (0.2)	2 (0.3)	2 (0.3)
Somnolence	3 (0.5)	2 (0.3)	0	3 (0.5)	1 (0.2)	0
Seasonal allergy	3 (0.5)	1 (0.2)	1 (0.2)	0	0	0
Paraesthesia	3 (0.5)	0	1 (0.2)	2 (0.3)	0	0
Rash	2 (0.3)	7 (1.2)	5 (0.8)	0	5 (0.8)	1 (0.2)
Urticaria	2 (0.3)	3 (0.5)	1 (0.2)	0	2 (0.3)	0
Blood cholesterol increased	2 (0.3)	2 (0.3)	3 (0.5)	0	1 (0.2)	0
Back pain	2 (0.3)	2 (0.3)	3 (0.5)	0	0	0
Nasopharyngitis	2 (0.3)	2 (0.3)	2 (0.3)	0	0	0
Hypertriglyceridaemia	2 (0.3)	2 (0.3)	1 (0.2)	1 (0.2)	2 (0.3)	1 (0.2)
Dyspepsia	2 (0.3)	2 (0.3)	0	1 (0.2)	1 (0.2)	0
Blood iron increased	2 (0.3)	2 (0.3)	0	0	0	0
Constipation	2 (0.3)	1 (0.2)	3 (0.5)	0	0	0
Blood alkaline phosphatase increased	2 (0.3)	1 (0.2)	0	0	1 (0.2)	0
Hypertension	2 (0.3)	1 (0.2)	0	0	0	0
Chest pain	2 (0.3)	1 (0.2)	0	0	0	0
Dyslipidaemia	2 (0.3)	0	1 (0.2)	2 (0.3)	0	0
Blood bilirubin unconjugated increased	2 (0.3)	0	0	2 (0.3)	0	0
Eosinophil count increased	2 (0.3)	0	0	0	0	0
White blood cell count decreased	2 (0.3)	0	0	0	0	0
Tonsillitis	2 (0.3)	0	0	0	0	0
Anaemia	2 (0.3)	0	0	0	0	0
Insomnia	1 (0.2)	3 (0.5)	2 (0.3)	0	2 (0.3)	1 (0.2)
Abdominal discomfort	1 (0.2)	3 (0.5)	0	0	1 (0.2)	0
Eczema	1 (0.2)	2 (0.3)	1 (0.2)	1 (0.2)	0	1 (0.2)
Blood pressure increased	1 (0.2)	1 (0.2)	4 (0.7)	0	0	0
γ-GTP increased	1 (0.2)	1 (0.2)	3 (0.5)	1 (0.2)	0	2 (0.3)
C-reactive protein increased	1 (0.2)	1 (0.2)	2 (0.3)	0	0	2 (0.3)
Heavy menstrual bleeding	1 (0.2)	1 (0.2)	2 (0.3)	0	0	0
White blood cell count increased	1 (0.2)	0	2 (0.3)	0	0	0
Tension headache	1 (0.2)	0	2 (0.3)	0	0	0
Pruritus	1 (0.2)	0	2 (0.3)	0	0	0
Pyrexia	1 (0.2)	0	2 (0.3)	0	0	0
Transaminases increased	0	3 (0.5)	0	0	1 (0.2)	0
Blood cholinesterase increased	0	2 (0.3)	0	0	0	0
Blood urea increased	0	2 (0.3)	0	0	0	0
Toothache	0	2 (0.3)	0	0	0	0
Low density lipoprotein decreased	0	1 (0.2)	2 (0.3)	0	1 (0.2)	2 (0.3)
Neutrophil count decreased	0	0	2 (0.3)	0	0	1 (0.2)
Pain in extremity	0	0	2 (0.3)	0	0	0

n (%), Medical dictionary for regulatory activities (MedDRA) ver.24.0

There was no adverse event resulting in death.

Serious adverse events occurred in 1 subject (heavy menstrual bleeding) in the ensitrelvir 375/125 mg group and in 1 subject (cholecystitis acute) in the placebo group. Both events were causally unrelated to the study drug, with the outcome of "resolved."

Adverse events leading to treatment discontinuation occurred in 4 subjects (eczema, vomiting, rash, and hypertension in 1 subject each) in the ensitrelvir 375/125 mg group, in 6 subjects (rash in 2 subjects, nausea, headache, abdominal pain, presyncope, and vomiting in 1 subject each [1 of the 6 subjects had 2 events]) in the ensitrelvir 750/250 mg group, and in 2 subjects (hypoaesthesia, muscular weakness, and headache in 1 subject each [1 of the 2 subjects had 2 events]) in the placebo group. Of these, the events in the following subjects were causally related to the study drug: 2 subjects (eczema and vomiting in 1 subject each) in the ensitrelvir 375/125 mg group; 2 subjects (rash in both) in the ensitrelvir 750/250 mg group; and in 1 subject (hypoaesthesia and muscular weakness in the same subject) in the placebo group. The outcome of all events was "resolved" or "resolving."

The following are the incidences of adverse events and adverse drug reactions, respectively, in the Japanese subpopulation: 52.8% (179 of 339 subjects) and 23.9% (81 of 339 subjects) in the ensitrelvir 375/125 mg group; 64.6% (201 of 311 subjects) and 38.6% (120 of 311 subjects) in the ensitrelvir 750/250 mg group; and 25.3% (81 of 320 subjects) and 5.0% (16 of 320 subjects) in the placebo group. Table 16 shows adverse events and adverse drug reactions occurring in ≥2 subjects in any group.

Table 16. Adverse events and adverse drug reactions occurring in ≥2 subjects in any group of Japanese subpopulation (phase III part: safety analysis population)

Event	Adverse events			Adverse drug reactions		
	Ensitrelvir 375/125 mg (N = 339)	Ensitrelvir 750/250 mg (N = 311)	Placebo (N =320)	Ensitrelvir 375/125 mg (N = 339)	Ensitrelvir 750/250 mg (N = 311)	Placebo (N =320)
All events	179 (52.8)	201 (64.6)	81 (25.3)	81 (23.9)	120 (38.6)	16 (5.0)
High density lipoprotein decreased	142 (41.9)	171 (55.0)	17 (5.3)	68 (20.1)	104 (33.4)	4 (1.3)
Blood triglycerides increased	29 (8.6)	36 (11.6)	15 (4.7)	1 (0.3)	7 (2.3)	4 (1.3)
Blood bilirubin increased	18 (5.3)	25 (8.0)	2 (0.6)	0	6 (1.9)	1 (0.3)
Bilirubin conjugated increased	14 (4.1)	16 (5.1)	1 (0.3)	0	0	0
Blood cholesterol decreased	13 (3.8)	16 (5.1)	3 (0.9)	1 (0.3)	1 (0.3)	1 (0.3)
Headache	10 (2.9)	10 (3.2)	12 (3.8)	1 (0.3)	3 (1.0)	0
Blood creatine phosphokinase increased	7 (2.1)	5 (1.6)	7 (2.2)	0	0	1 (0.3)
Nausea	4 (1.2)	10 (3.2)	1 (0.3)	2 (0.6)	4 (1.3)	0
Diarrhoea	4 (1.2)	5 (1.6)	7 (2.2)	3 (0.9)	4 (1.3)	3 (0.9)
Vomiting	4 (1.2)	4 (1.3)	0	2 (0.6)	1 (0.3)	0
ALT increased	3 (0.9)	5 (1.6)	4 (1.3)	1 (0.3)	0	2 (0.6)
AST increased	3 (0.9)	3 (1.0)	3 (0.9)	1 (0.3)	0	2 (0.6)
Seasonal allergy	3 (0.9)	1 (0.3)	1 (0.3)	0	0	0
Rash	2 (0.6)	4 (1.3)	3 (0.9)	0	2 (0.6)	1 (0.3)
Urticaria	2 (0.6)	3 (1.0)	1 (0.3)	0	2 (0.6)	0
Back pain	2 (0.6)	2 (0.6)	3 (0.9)	0	0	0
Nasopharyngitis	2 (0.6)	2 (0.6)	2 (0.6)	0	0	0
Blood iron increased	2 (0.6)	2 (0.6)	0	0	0	0
Constipation	2 (0.6)	1 (0.3)	3 (0.9)	0	0	0
Chest pain	2 (0.6)	1 (0.3)	0	0	0	0
Dyslipidaemia	2 (0.6)	0	0	2 (0.6)	0	0
White blood cell count decreased	2 (0.6)	0	0	0	0	0
Tonsillitis	2 (0.6)	0	0	0	0	0
Eczema	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)	0	1 (0.3)
γ-GTP increased	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)	0	1 (0.3)
Tension headache	1 (0.3)	0	2 (0.6)	0	0	0
Transaminases increased	0	3 (1.0)	0	0	1 (0.3)	0
Dyspepsia	0	2 (0.6)	0	0	1 (0.3)	0
Blood lactate dehydrogenase increased	0	2 (0.6)	0	0	0	0
Toothache	0	2 (0.6)	0	0	0	0
Low density lipoprotein decreased	0	0	2 (0.6)	0	0	2 (0.6)
Pyrexia	0	0	2 (0.6)	0	0	0

n (%), MedDRA ver.24.0

There was no adverse event resulting in death.

A serious adverse event occurred in 1 subject (heavy menstrual bleeding) in the ensitrelvir 375/125 mg group. The event was causally unrelated to the study drug, with the outcome of "resolved."

Adverse events leading to treatment discontinuation occurred in 3 subjects (eczema, vomiting, and rash in 1 subject each) in the ensitrelvir 375/125 mg group, in 5 subjects (rash, nausea, headache, abdominal pain, presyncope, and vomiting in 1 subject each [1 of the 5 subjects had 2 events]) in the ensitrelvir 750/250 mg group, and in 1 subject (headache) in the placebo group. Of these, the events in the following subjects were causally related to the study drug: 2 subjects (eczema and vomiting in 1 subject each) in the ensitrelvir 375/125 mg group and in 1 subject (rash) in the ensitrelvir 750/250 mg group. The outcome of all events was "resolved."

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Results of phase III part of the global phase II/III study (Study T1221)

The applicant's explanation about the results of phase III part of the global phase II/III study (Study T1221) on ensitrelvir:

The result of the primary endpoint in phase III part of the global phase II/III study (Study T1221) was not different from the preliminary data submitted for the Emergency Approval. Thus, a statistically significant difference was observed between the ensitrelvir 375/125 mg and placebo groups in the primary endpoint "time from the start of study treatment to resolution of 5 symptoms[13)] of COVID-19" (only in subjects who experienced the onset of COVID-19 symptoms within <72 hours before randomization in ITT population) [see Table 14 in Section 7.1.1].

This result demonstrates the efficacy of ensitrelvir 375/125 mg against COVID-19.

PMDA's view:

In phase III part of the global phase II/III study (Study T1221), the primary endpoint "time from the start of study treatment to resolution of 5 symptoms of COVID-19" (only in subjects who experienced the onset of COVID-19 symptoms within <72 hours before randomization in ITT population) significantly differed between the ensitrelvir 375/125 mg and placebo groups [see Table 14 in Section 7.1.1]. The difference between the ensitrelvir 375/125 mg and placebo groups tended to be smaller in the Japanese subpopulation than in the entire population [see Table 14 in Section 7.1.1] although exact reason is unknown [see Section 7.R.1.2]. However, this does not deny the efficacy of ensitrelvir in the Japanese population because, in the Japanese subpopulation also, the ensitrelvir 375/125 mg group showed an improving tendency compared with the placebo group.

Timing of the protocol amendment (i.e., immediately before the unblinding) was not appropriate, but the amendment was made under blinded conditions and the content of amendment was not clinically inappropriate; therefore the appropriateness of the protocol amendment should not be denied [see Section 7.R.1.3]. Incidentally, the result of the original primary endpoint did not show a statistically significant difference between the ensitrelvir 375/125 mg and placebo groups [see Section 7.R.1.3].

Based on the above, PMDA concluded that efficacy of ensitrelvir against COVID-19 was demonstrated.

This conclusion of PMDA will be discussed at the Expert Discussion.

7.R.1.2 Efficacy in Japanese patients

The applicant's explanation about the results in the Japanese subpopulation in phase III part of the global phase II/III study (Study T1221):

Table 17 and Figure 2 show the results of the primary endpoint in phase III part of the global phase II/III study (Study T1221) in the Japanese and non-Japanese subpopulations. The difference between the

13) The applicant explained that the efficacy in phase III part was evaluated based on the following 5 symptoms of COVID-19:
(1) Malaise or tiredness, (2) feverish or pyrexia, (3) stuffy or runny nose, (4) sore throat, and (5) cough.

ensitrelvir 375/125 mg and placebo groups was smaller in the Japanese subpopulation than in the non-Japanese subpopulation.

Table 17. Time to resolution of 5 symptoms of COVID-19 (primary endpoint) in Japanese and non-Japanese subpopulations
(only in subjects who experienced the onset of COVID-19 symptoms within <72 hours before randomization in ITT population of phase III part)

	Japanese		Non-Japanese	
	Ensitrelvir 375/125 mg	Placebo	Ensitrelvir 375/125 mg	Placebo
Number of subjects[a)]	179	163	157	158
Number of subjects who recovered	134	120	120	113
Median time (h) to resolution of 5 symptoms of COVID-19	165.8	172.1	168.5	234.4
Difference from placebo [95% CI]	−6.3 [−61.8, 48.6]	-	−65.9 [−115.7, 2.3]	-
Hazard ratio [95% CI][b)]	1.04 [0.81, 1.33]		1.24 [0.96, 1.61]	

a) Subjects were excluded from the analysis if the baseline scores of 5 symptoms were all zero or if a baseline symptom score(s) were missing.
b) Cox proportional hazard model stratified by vaccination against COVID-19 (yes, no)

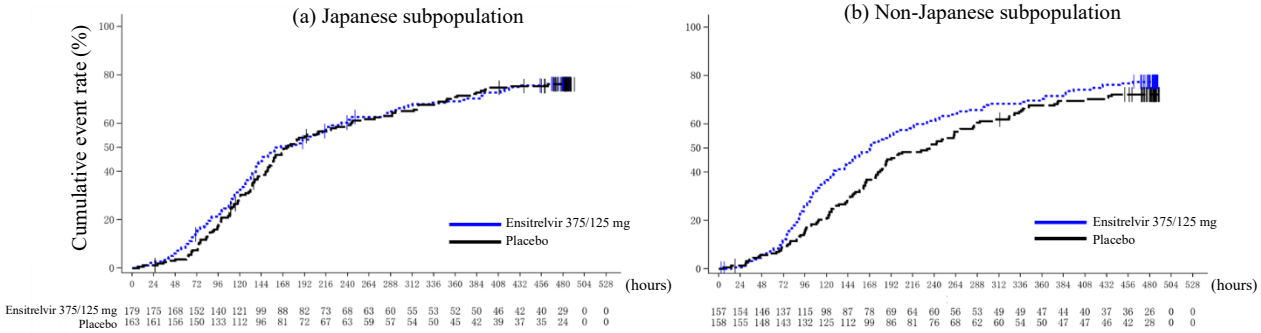

Figure 2. Cumulative rate of resolution expressed by "time from the start of study treatment to resolution of symptoms of COVID-19" in the Japanese and non-Japanese subpopulations
(only in subjects who experienced the onset of COVID-19 symptoms within <72 hours before randomization in ITT population of phase III part)

The difference in the results of primary endpoint between the ensitrelvir 375/125 mg and placebo groups was smaller in the Japanese subpopulation than in the non-Japanese subpopulation. In order to investigate causes of the smaller difference in the Japanese subpopulation, subject characteristics of the subpopulations collected in advance were compared; the following characteristics differed between the subpopulations: Sex, concomitant acetaminophen (yes, no), baseline SARS-CoV-2-neutralizing antibody titer, messenger ribonucleic acid (mRNA) vaccination (yes, no), drinking habit (yes, no), smoking habit (yes, no), treatment environment, time from symptom onset to randomization, and complication(s) (yes, no), and previous treatment (yes, no). In addition, the following subject characteristics were listed as those that may affect the difference between the ensitrelvir 375/125 mg and placebo groups in the entire population (i.e., subject characteristics where there were clearly different magnitude or direction of between-group differences among categories under the subject characteristics): Concomitant acetaminophen, baseline SARS-CoV-2-neutralizing antibody titer, anti-SARS-CoV-2 mRNA vaccination, treatment environment, and time from symptom onset to randomization. Table 18 shows the results of the primary endpoint, classified by the subject characteristics.

Some categories under subject characteristics had only a very small number of subjects in the Japanese and/or non-Japanese subpopulations, and between-group differences were not consistent across both subpopulations. Therefore the applicant does not consider that the differences in between-group difference (375/125 mg ensitrelvir vs. placebo) between both subpopulations was caused by the difference in subject distribution among categories under subjects characteristics between the Japanese and non-Japanese subpopulations.

Table 18. Time to resolution of 5 symptoms of COVID-19 (primary endpoint) by subject characteristics (only in subjects who experienced the onset of COVID-19 symptoms within <72 hours before randomization in ITT population of phase III part)

		Entire population		Japanese subpopulation		Non-Japanese subpopulation	
		Ensitrelvir 375/125 mg	Placebo	Ensitrelvir 375/125 mg	Placebo	Ensitrelvir 375/125 mg	Placebo
Concomitant acetaminophen (yes, no)	Yes	194.5 (131) 10.1 [−107.1, 80.7]	184.4 (101)	189.8 (104) 17.8 [−62.7, 112.5]	172.1 (87)	194.5 (27) −237.6 [−309.7, 48.2]	432.1 (14)
	No	159.1 (205) −38.6 [−96.1, 3.5]	197.8 (220)	138.4 (75) −35.4 [−121.9, 58.8]	173.8 (76)	168.2 (130) −36.1 [−107.7, 5.6]	204.4 (144)
Baseline SARS-CoV-2-neutralizing antibody titer	≤10	180.6 (149) −5.6 [−93.5, 48.7]	186.3 (156)	165.8 (107) −14.8 [−111.3, 52.8]	180.6 (100)	220.0 (42) −0.7 [−118.5, 144.7]	220.7 (56)
	>10 and ≤20	217.0 (59) 19.3 [−149.0, 94.3]	197.8 (52)	242.4 (25) 36.2 [−198.6, 216.4]	206.3 (20)	198.4 (34) 12.0 [−179.6, 83.5]	186.4 (32)
	>20	145.0 (127) −47.1 [−120.1, −6.0]	192.1 (113)	152.5 (47) 1.1 [−69.0, 81.4]	151.4 (43)	141.1 (80) −101.9 [−192.8, −17.4]	242.9 (70)
Administration of mRNA vaccine against SARS-CoV-2	Yes	167.9 (258) −13.8 [−81.7, 25.7]	181.7 (230)	159.9 (154) −6.6 [−54.9, 54.3]	166.5 (135)	169.6 (104) −72.6 [−146.8, 20.4]	242.3 (95)
	Once	168.8 (66) −93.6 [−204.9, 16.4]	262.4 (65)	- (2) -	- (2)	168.8 (64) −93.6 [−204.0, 13.4]	262.4 (63)
	Twice	158.8 (124) −21.8 [−92.1, 50.4]	180.6 (114)	158.8 (101) −21.8 [−133.3, 54.1]	180.6 (91)	179.2 (23) −0.4 [−129.7, 109.7]	179.7 (23) -
	≥3 times	184.6 (68) 33.2 [−64.7, 146.0]	151.4 (51)	180.6 (51) 36.7 [−24.0, 148.0]	143.9 (42)	265.2 (17) −19.0 [−310.4, 215.9]	284.1 (9)
	No	160.1 (78) −59.9 [−131.6, 42.4]	219.9 (91)	197.6 (25) −22.3 [−196.2, 195.0]	219.9 (28)	151.6 (53) −80.3 [−138.5, 49.6]	231.8 (63)
Treatment environment on Day 1	Outpatient	158.8 (94) −62.7 [−131.7, 13.4]	221.5 (75)	158.8 (84) −67.9 [−161.3, 11.4]	226.7 (63)	161.8 (10) −15.1 [−147.2, 209.8]	176.9 (12)
	Home	166.3 (136) −38.1 [−116.8, 0.2]	204.4 (137)	(0) -	(0)	166.3 (136) −38.1 [−116.8, 0.2]	204.4 (137)
	Accommodation	180.6 (75) 25.3 [−28.5, 169.1]	155.3 (73)	165.8 (73) 29.9 [−25.9, 120.9]	135.9 (72)	- (2) -	- (1)
	Hospitalization	233.1 (31) −12.3 [−299.4, 212.9]	245.3 (36)	218.1 (22) 37.2 [−161.9, 253.3]	180.8 (28)	302.1 (9) -	- (8)
Treatment environment on Day 2	Outpatient	187.8 (58) −52.9 [−137.9, 21.1]	240.7 (60)	189.7 (55) −36.9 [−151.5, 38.4]	226.7 (53)	111.7 (3) −139.3 [−194.0, −10.3]	251.0 (7)
	Home	158.4 (170) −39.4 [−109.0, −1.0]	197.8 (150)	133.6 (27) −73.7 [−167.5, 146.6]	207.3 (9)	167.1 (143) −30.7 [−106.4, 6.5]	197.8 (141)
	Accommodation	180.6 (75) 23.5 [−29.3, 168.1]	157.1 (75)	165.8 (73) 10.5 [−29.8, 116.5]	155.3 (74)	- (2) -	- (1)
	Hospitalization	233.1 (32) −28.6 [−309.2, 171.0]	261.7 (34)	218.1 (23) 35.1 [−241.9, 260.1]	183.0 (26)	302.1 (9) -	- (8)
Time from symptom onset to randomization	<24 h	158.6 (50) −38.9 [−145.7, 54.4]	197.5 (45)	158.8 (15) −9.8 [−147.2, 89.8]	168.6 (10)	158.4 (35) −46.0 [−209.4, 62.1]	204.4 (35)
	≥24 h and <48 h	159.1 (123) −47.1 [−110.8, 5.0]	206.3 (124)	158.4 (62) −22.5 [−134.6, 89.2]	180.8 (55)	159.1 (61) −80.8 [−141.0, −0.9]	239.9 (69)
	≥48 h and <72 h	189.7 (163) 9.1 [−83.1, 59.5]	180.6 (152)	184.6 (102) 17.2 [−85.7, 75.1]	167.4 (98)	212.5 (61) −3.6 [−161.0, 165.3]	216.1 (54)

Upper row: Median time (h) to resolution of 5 symptoms of COVID-19 (number of subjects); -, Unable to calculate
Lower row: Difference from placebo [95% confidence interval (CI)]; -, Unable to calculate
Subjects were excluded from the analysis if the baseline scores of 5 symptoms were all zero or if a baseline symptom score(s) were missing.

PMDA's view:

The applicant explained that it was difficult to identify the reasons the Japanese subpopulation had a smaller difference in the results of primary endpoint between the ensitrelvir 375/125 mg and placebo groups than the non-Japanese subpopulation; this is understandable. In the Japanese subpopulation also, the ensitrelvir 375/125 mg group showed an improving tendency in the primary endpoint compared with the placebo group, and the efficacy of ensitrelvir has been demonstrated in the entire population. Therefore, the above-presented results do not deny the efficacy of ensitrelvir in Japanese patients.

7.R.1.3 Effect of protocol amendment in phase III part of the global phase II/III study (Study T1221)

The applicant's explanation about the timing of protocol amendment and the results before and after the amendment in phase III part of the global phase II/III study (Study T1221):

In phase III part of the global phase II/III study (study T1221), the clinical study protocol was amended to ver. 10 on September 20, 2022 (last amendment before unblinding on September 23, 2022), in order to change the dose for efficacy evaluation, primary endpoint, main efficacy analysis population, sample size required, and method for the primary analysis, etc. (Table 19). After the amendment, data from phase III part were analyzed [see Section 7.1.1].

Table 19. Main amendments to the study protocol
(Underlined part: difference between the versions. See Section 10 for main amendments made to the study protocol during the conduct of the study.)

	Before amendment Protocol Ver. 9 (amended on July 8, 2022)	After amendment Protocol Ver. 10 (amended on September 20, 2022)
Dose for efficacy evaluation	• Ensitrelvir 375/125 mg • Ensitrelvir 750/250 mg	• Ensitrelvir 375/125 mg
Primary endpoint	The time from the start of study treatment to resolution of 12 symptoms of COVID-19 12 symptoms: (1) Malaise or tiredness, (2) muscle or body aches, (3) headache, (4) chills or sweating, (5) feverish or pyrexia, (6) stuffy or runny nose, (7) sore throat, (8) cough, (9) shortness of breath (dyspnea), (10) nausea, (11) vomiting, (12) diarrhea	The time from the start of study treatment to resolution of 5 symptoms of COVID-19 5 symptoms: (1) Malaise or tiredness, (2) feverish or pyrexia, (3) stuffy or runny nose, (4) sore throat, and (5) cough.
Main efficacy analysis population	ITT population	Subjects who experienced the onset of COVID-19 symptoms within <72 hours before randomization in ITT population
Sample size required	1,590 subjects (530 per group)	780 subjects (260 per group)
Method for the primary analysis	Stratified log-rank test	Stratified Peto-Prentice generalized Wilcoxon test

Analysis after the protocol amendment showed a statistically significant difference in the primary endpoint between the 375/125 mg and placebo groups (Table 14). Table 20 and Figure 3 show the analysis results under the conditions before the protocol amendment (see Table 19); these results showed no statistically significant difference between the placebo and ensitrelvir 375/125 mg groups in the original primary endpoint "time from the start of study treatment to resolution of 12 symptoms of COVID-19" in the ITT population. As shown in Table 20 and Figure 3, no clear difference was observed between the placebo and ensitrelvir 375/125 mg groups in the time to resolution of symptoms, even when 5 symptoms were used as the endpoint in the ITT population.

Table 20. Time from the start of study treatment to resolution of symptoms of COVID-19 (phase III part: ITT population)

		Ensitrelvir 375/125 mg	Ensitrelvir 750/250 mg	Placebo
12 symptoms	Number of subjects[a)]	582	577	572
	Number of subjects who achieved resolution	401	423	403
	Median time (h) to resolution of symptoms of COVID-19	200.0	192.1	221.5
	P value[b)c)]	0.7830	0.2903	
	Hazard ratio [95% CI][d)]	0.98 [0.85, 1.12]	1.08 [0.94, 1.23]	
5 symptoms	Number of subjects[a)]	582	575	572
	Number of subjects who achieved resolution	425	433	412
	Median time (h) to resolution of symptoms of COVID-19	189.7	177.3	200.3
	Hazard ratio [95% CI][d)]	1.03 [0.90, 1.18]	1.11 [0.97, 1.27]	

a) Subjects were excluded from the analysis if the baseline scores of symptoms were all zero or if a baseline symptom score(s) were missing.
b) Log-rank test stratified by time from the onset of COVID-19 symptoms to randomization (<72 hours, ≥72 hours) and vaccination against COVID-19 (yes, no)
c) The two-sided significance level of the entire study was 5%. Multiplicity of the hypothesis testing was adjusted by Bonferroni's method. Comparison between ensitrelvir 375/125 mg and placebo and between ensitrelvir 750/250 mg and placebo was made at a two-sided significance level of 2.5%.
d) Cox proportional hazard model stratified by time from the onset of COVID-19 symptoms to randomization (<72 hours, ≥72 hours) and vaccination against COVID-19 (yes, no)

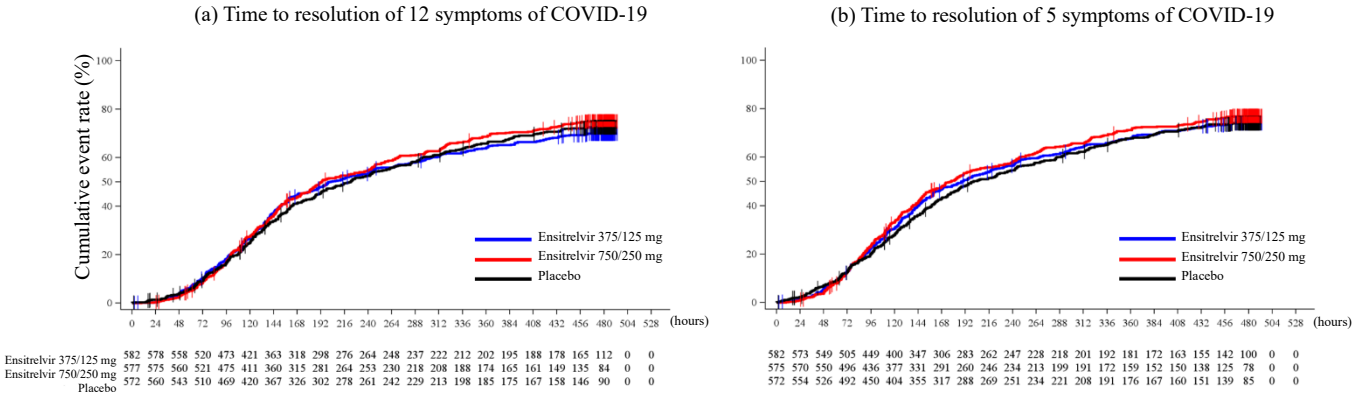

Figure 3. Cumulative rate of resolution expressed by "time from the start of study treatment to resolution of symptoms of COVID-19" (phase III part: ITT population)

In order to assess the effect of the amendments to the primary endpoint, main efficacy analysis population, and method for the primary analysis, results of the primary endpoint before and after these amendments in the protocol were compared. Table 21 shows the results.

Table 21. Time to resolution of COVID-19 symptoms (phase III part)

Mian efficacy analysis population	ITT population (before amendment)				Subjects who experienced the onset of COVID-19 symptoms within <72 hours before randomization in ITT population (after amendment)			
Number of symptoms in the primary endpoint	12 symptoms (before amendment)		5 symptoms (after amendment)		12 symptoms (before amendment)		5 symptoms (after amendment)	
Treatment	Ensitrelvir 375/125 mg	Placebo	Ensitrelvir 375/125 mg	Placebo	Ensitrelvir 375/125 mg	Placebo	Ensitrelvir 375/125 mg	Placebo
Number of subjects[a)]	582	572	582	572	336	321	336	321
Number of subjects who achieved resolution	401	403	425	412	244	227	254	233
Median time (h) to resolution of symptoms of COVID-19	200.0	221.5	189.7	200.3	179.2	213.2	167.9	192.2
Difference from placebo [95% CI]	−21.5 [−55.1, 29.3]	-	−10.6 [−56.9, 21.3]	-	−34.0 [−85.9, 8.3]	-	−24.3 [−78.7, 11.7]	-
P value by stratified log-rank test[b)] (before amendment)	0.7830		0.6368		0.2367		0.1471	
P value by Stratified Peto-Prentice generalized Wilcoxon test[b)] (after amendment)	0.7626		0.4352		0.0651		0.0407	
Hazard ratio [95% CI][b)c)]	0.98 [0.85, 1.12]		1.03 [0.90, 1.18]		1.11 [0.93, 1.33]		1.14 [0.95, 1.36]	

a) Subjects were excluded from the analysis if the baseline scores of symptoms were all zero or if a baseline symptom score(s) were missing.
b) Subjects of ITT population were stratified by vaccination against COVID-19 (yes, no). Only in subjects of ITT population who experienced the onset of COVID-19 symptoms within <72 hours before randomization were stratified by time from the onset of COVID-19 symptoms to randomization (<72 hours, ≥72 hours) and by vaccination against COVID-19 (yes, no).
c) Cox proportional hazard model

PMDA's view:

The amendments to all of the above parameters (i.e., the primary endpoint, the main efficacy analysis population, and the method for the primary analysis) appear to have affected the results of the primary endpoint of phase III part; particularly the amendment to the main efficacy analysis population may have had the greatest impact. Since phase III part of the global phase II/III study (Study T1221) was conducted as a confirmatory study on the efficacy of ensitrelvir, the impact of these parameters should have been fully examined before the start of phase III part, and thereafter the study should have been planned and conducted. However, the frequent changes in the prevalent SARS-CoV-2 strains, particularly the prevalence of the Omicron variant, have changed the clinical symptoms of COVID-19. For this reason, it is understandable to some extent that appropriately selecting the primary endpoint, the efficacy analysis population, etc. before the start of phase III part was very difficult. The timing of protocol amendment (i.e., immediately before the unblinding) was not appropriate, but the amendment was made under blinded conditions and the content of amendment was not clinically inappropriate; therefore the appropriateness of evaluating the efficacy of ensitrelvir based on the amended protocol should not be denied (see Section 4.R.1 of Third Review Report on Xocova Tablets 125 mg dated November 15, 2022).

7.R.2 Safety

7.R.2.1 Safety in global phase II/III study (Study T1221)

The applicant's explanation about the safety profile of ensitrelvir in the global phase II/III study (Study T1221):

Table 22 shows the summary of safety data from the pooled analysis[14)] of 3 parts (phase IIa part, phase IIb part, and phase III part) of the global phase II/III study (Study T1221).

Table 22. Summary of safety in global phase II/III study (Study T1221) (pooled 3 parts, safety analysis population)

	Entire population		Japanese subpopulation	
	Ensitrelvir 375/125 mg (N = 763)	Placebo (N = 766)	Ensitrelvir 375/125 mg (N = 496)	Placebo (N = 478)
Adverse events	325 (42.6)	205 (26.8)	237 (47.8)	135 (28.2)
Adverse drug reactions	172 (22.5)	67 (8.7)	105 (21.2)	23 (4.8)
Serious adverse events	1 (0.1)	3 (0.4)	1 (0.2)	2 (0.4)
Adverse events resulting in death	0	0	0	0
Adverse events leading to treatment discontinuation	6 (0.8)	2 (0.3)	5 (1.0)	1 (0.2)

n (%)

In the entire population, the incidences of adverse events and adverse drug reactions were higher in the ensitrelvir 375/125 mg group than in the placebo group. No death occurred in either group. Serious adverse events occurred in 1 subject (heavy menstrual bleeding) in the ensitrelvir 375/125 mg group and in 3 subjects (thoracic vertebral fracture, facial paralysis, and cholecystitis acute in 1 subject each) in the placebo group; all of them were causally unrelated to the study drug, with the outcome of "resolving" or "resolved." Adverse events leading to discontinuation of the study drug occurred in 6 subjects (eczema in 2 subjects, nausea, headache, vomiting, rash, and hypertension in 1 subject each [1 of the 6 subjects had 2 events]) in the ensitrelvir 375/125 mg group and in 2 subjects [headache, muscular weakness, and hypoaesthesia in 1 subject each [1 of the 2 subjects had 2 events]) in the placebo group. Of these, the events in the following subjects were causally related to the study drug: 4 subjects (eczema in 2 subjects, nausea, headache, and vomiting in 1 subject each [1 of the 4 subjects had 2 events]) in the ensitrelvir 375/125 mg group and 1 subject (muscular weakness and hypoaesthesia in the same subject) in the placebo group. The outcome of all events was "resolving" or "resolved."

In the Japanese subpopulation, the incidences of adverse events and adverse drug reactions were higher in the ensitrelvir 375/125 mg group than in the placebo group. No death occurred in either group. Serious adverse events occurred in 1 subject (heavy menstrual bleeding) in the ensitrelvir 375/125 mg group and in 2 subjects (thoracic vertebral fracture and facial paralysis in 1 subject each) in the placebo group; all of these events were causally unrelated to the study drug, with the outcome of "resolving" or "resolved." Adverse events leading to discontinuation of the study drug occurred in 5 subjects (eczema in 2 subjects, nausea, headache, vomiting, and rash in 1 subject each [1 of the 5 subjects had 2 events]) in the ensitrelvir 375/125 mg group and in 1 subject (headache) in the placebo group. Of these, the events in the following subjects were causally related to the study drug: 4 subjects (eczema 2 subjects, nausea, headache, and vomiting in 1 subject each [1 of the 4 subjects had 2 events]) in the ensitrelvir 375/125 mg group. The outcome of all events was "resolved."

14) This pooled analysis used data of subjects with mild to moderate COVID-19 and excluded data of subjects with asymptomatic SARS-CoV-2 infection randomized in the phase IIa part.

Table 23 shows the adverse events and adverse drug reactions reported by ≥2% of subjects in either group in the 3-part pooled analysis of the global phase II/III study (Study T1221).

Table 23. Adverse events and adverse drug reactions reported by ≥2% of subjects in either group in the global phase II/III study (Study T1221) (pooled 3 parts, safety analysis population)

Event	Entire population				Japanese subpopulation			
	Adverse events		Adverse drug reactions		Adverse events		Adverse drug reactions	
	Ensitrelvir 375/125 mg (N = 763)	Placebo (N = 766)	Ensitrelvir 375/125 mg (N = 763)	Placebo (N = 766)	Ensitrelvir 375/125 mg (N = 496)	Placebo (N = 478)	Ensitrelvir 375/125 mg (N = 496)	Placebo (N = 478)
All events	325 (42.6)	205 (26.8)	172 (22.5)	67 (8.7)	237 (47.8)	135 (28.2)	105 (21.2)	23 (4.8)
High density lipoprotein decreased	222 (29.1)	30 (3.9)	127 (16.6)	9 (1.2)	176 (35.5)	24 (5.0)	84 (16.9)	4 (0.8)
Blood triglycerides increased	50 (6.6)	33 (4.3)	17 (2.2)	17 (2.2)	30 (6.0)	16 (3.3)	2 (0.4)	4 (0.8)
Blood bilirubin increased	37 (4.8)	7 (0.9)	18 (2.4)	4 (0.5)	19 (3.8)	3 (0.6)	1 (0.2)	2 (0.4)
Blood cholesterol decreased	20 (2.6)	3 (0.4)	8 (1.0)	1 (0.1)	13 (2.6)	3 (0.6)	1 (0.2)	1 (0.2)
Headache	17 (2.2)	14 (1.8)	5 (0.7)	2 (0.3)	14 (2.8)	12 (2.5)	2 (0.4)	0
Bilirubin conjugated increased	15 (2.0)	3 (0.4)	1 (0.1)	1 (0.1)	14 (2.8)	1 (0.2)	0	0
Blood creatine phosphokinase increased	14 (1.8)	16 (2.1)	4 (0.5)	1 (0.1)	7 (1.4)	12 (2.5)	0	1 (0.2)

n (%), MedDRA ver.24.0

Adverse events reported by ≥2% of subjects in either group were all laboratory-related events, except for headache. All of these events were nonserious and mild or moderate in severity, and most of them resolved.

Thus, there were no particular concerns regarding the safety of ensitrelvir in patients with COVID-19.

7.R.2.2 Post-marketing safety

The applicant's explanation about the post-marketing safety data of ensitrelvir:

The general use-results survey is ongoing since November 2022, when ensitrelvir was granted the Emergency Approval. In the survey (data locked on July 20, 2023), adverse drug reactions occurred in 8.1% (128 of 1,589) of patients subjected to safety analysis. The main adverse reactions were diarrhoea in 2.4% (38 of 1,589) of patients, nausea in 1.3% (20 of 1,589 patients), headache in 1.1% (18 of 1,589 patients), and rash in 0.6% (10 of 1,589 patients). There were no serious adverse drug reactions. The outcome was "resolved" or "resolving" except for "not resolved" in 5 events (taste disorder, diplopia, diarrhoea, nausea, and eczema [1 event each]) and "unknown" in 6 events (intermenstrual bleeding [2 events], headache, abdominal discomfort, drug eruption, and chest pain [1 event each]).

After the market launch, as of June 14, 2023, serious anaphylactic events (Standardized MedDRA Query [SMQ] "Anaphylactic reaction" [narrow]) occurred in 3 patients (anaphylactic reaction in 2 patients, anaphylactic shock in 1 patient). A causal relationship to ensitrelvir could not be ruled out for anaphylactic reaction and anaphylactic shock in 1 patient each. There was a temporal correlation between administration of ensitrelvir and occurrence of anaphylaxis in these patients, and anaphylaxis may result in serious outcome; this necessitated additional safety measures. Therefore in July 2023

anaphylaxis was classified as an important identified risk of ensitrelvir and listed under the “Clinically significant adverse reactions” section of the package insert to call for attention.

Thus, the post-marketing data have revealed no new safety concerns different from the safety profile in the global Phase II/III study (T1221 study), except for anaphylaxis, and a caution for anaphylaxis has already been issued. The applicant therefore considers that there is no need to change the current safety measures.

The applicant’s explanation about ensuring proper use of ensitrelvir in pregnant or possibly pregnant women, in view of the potential teratogenic risk associated with ensitrelvir:
Since the time of Emergency Approval, the following actions have been taken to address teratogenicity, a potential risk associated with ensitrelvir: As a usual risk minimization activity, cautions have been included in the “2. Contraindications,” “9.4 Patients with Reproductive Potential,” and “9.5 Pregnant Women” sections of the package insert as well as in “Drug Guide for Patients.” As additional risk minimization activities, information materials for healthcare professionals (“Request regarding pregnant or possibly pregnant women or women of childbearing potential”) and for patients (“For female patients prescribed Xocova Tablets 125 mg and their family members”) have been prepared and distributed.

According to the post-marketing data as of November 12, 2023,[15] 26 patients were found to be pregnant and 6 patients reported their possible pregnancy to their attending physician (32 patients in total) after receiving ensitrelvir. Of these patients, 27 continued their pregnancy, and the outcomes of those who provided consent are being followed-up. Of the 5 patients who discontinued pregnancy, 2 had spontaneous abortion [redacted]; the causal relationship between these events and ensitrelvir was “unknown” or “unrelated.”

The applicant considers that appropriate safety measures have been implemented to address teratogenicity, a potential risk associated with ensitrelvir. For example, each time a case of pregnancy is found after administration of ensitrelvir, the applicant examined the problems and then revised information materials and issued cautions (see Table 24) to ensure that safety measures are properly implemented. The applicant plans to keep working to prevent recurrence of similar cases.

[15] Estimated number of patients treated with ensitrelvir is 849,658 (calculated from the number of patients registered at the registration center and from the quantity of ensitrelvir delivered).

Table 24. Revision of "Pregnancy-related RMP Materials" and issuance of "Dear Healthcare Professional" letter for ensitrelvir

Date	Material revised	Revision/cautions
November 2022 (at Emergency Approval)		• First edition prepared
January 2023	Information materials for patients and healthcare professionals	• Description in the section of the precaution for "pregnant or possibly pregnant women" was modified in each information material. • "Report of early post-marketing phase vigilance on Xocova Tablets" [the third interim report (supplementary issue) was issued to raise alertness.
March 2023	Information materials for patients and healthcare professionals	• Information material for patients was newly prepared and other information materials were revised, to strongly caution women of childbearing potential about pregnancy and to ensure that unused ensitrelvir is not passed on to (and taken by) others, especially women of childbearing potential. • "Report of early post-marketing phase vigilance on Xocova Tablets" [the seventh interim report (supplementary issue) was issued to raise alertness.
June 2023	Information materials for patients and healthcare professionals	• Each information material was revised to emphasize "importance of checking the status of sexual intercourse" and "the possibility of becoming pregnant even if contraception is used" in order to enhance alertness regarding pregnant or possibly pregnant women • "Report on post-marketing safety information on Xocova Tablets (first report)" was issued to raise alertness.
August 2023	None	• No information materials were revised. "Reports on post-marketing safety information on Xocova Tablets (second to fifth reports)" were issued to raise alertness.
October 2023	None	

PMDA's view:

Similar to the assessment during the review process for the Emergency Approval (see Section 4.R.3 of "Third Review Report on Xocova Tablets 125 mg dated November 15, 2022"), the global phase II/III study (Study T1221) have shown no major concerns for the safety profile of ensitrelvir in patients with COVID-19. With the accumulation of anaphylaxis cases from the post-marketing data, anaphylaxis was classified as an important identified risk and was listed under the "Clinically significant adverse reactions" section of the package insert. The applicant explained that the current cautions should remain unchanged other than addition of anaphylaxis; this is acceptable. However, if new findings are obtained from the ongoing general use-results survey, they should be promptly provided to healthcare professionals, etc.

Some pregnant or possibly pregnant women were found to have received ensitrelvir after marketing. The applicant explained that no additional safety measures are required at the moment because the applicant has taken further precautionary actions (e.g., revision of information materials for patients and healthcare professionals) to prevent ensitrelvir from being used in pregnant or possibly pregnant women. This explanation is acceptable but the applicant should continue promoting proper use of ensitrelvir.

This conclusion of PMDA will be discussed at the Expert Discussion.

7.R.3 Clinical positioning and indication

PMDA's view on the clinical positioning and indication of ensitrelvir:

Patients who have mild to moderate I[16] symptoms of COVID-19 were eligible for enrollment in phase III part of the global phase II/III study (Study T1221). Accordingly, ensitrelvir offers a treatment option for these patients, and thus COVID-19 is acceptable as the indication of ensitrelvir. Ensitrelvir can be administered regardless of vaccination status[17] or risk factors for severe COVID-19.[18] The package insert should state that ensitrelvir has been studied for its effect on symptoms of COVID-19.

This conclusion of PMDA will be discussed at the Expert Discussion.

The following points require attention: Efficacy of ensitrelvir 375/125 mg against COVID-19 has been demonstrated in patients who experienced the onset of symptoms within <72 hours before starting the treatment, while no data are available to support efficacy in patients starting treatment 72 hours after onset of symptoms. The package insert issued at the time of Emergency Approval cautioned that ensitrelvir 375/125 mg was presumed to have efficacy against COVID-19 in patients who start to receive ensitrelvir <72 hours after the symptom onset. Based on the discussions in Section 7.R.1, etc., PMDA will decide whether further cautions are necessary, taking account of comments raised in the Expert Discussion.

7.R.4 Dosage and administration

In view of the review for the Emergency Approval (see Sections 6.R.2 and 6.R.3 of Review Report on Xocova Tablets 125 mg dated June 17, 2022) and the discussion on the efficacy and safety based on the results from phase III part of the global phase II/III study (Study T1221), PMDA has concluded that the following dosage regimen is acceptable: Ensitrelvir 375 mg on Day 1 and ensitrelvir 125 mg from Days 2 to 5, administered orally once daily, in ≥12 year-old pediatric patients and adult patients.

7.R.5 Post-marketing investigations

After the Emergency Approval, the applicant has been conducting a general use-results survey to confirm the safety of ensitrelvir in clinical practice (target sample size, 3,000 subjects).

Based on the review in Section 7.R.2, PMDA has concluded that no additional review is necessary at present because no new safety issues have arisen since the time of Emergency Approval, except for anaphylaxis, and because cautionary actions have already been taken to raise alertness about anaphylaxis. However, if new findings are obtained from the ongoing general use-results survey, etc., they should be

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16) Guidelines for Diagnosis and Treatment of COVID-19, ver. 8.1, by the Ministry of Health, Labour and Welfare

17) In the ITT population, approximately 90% of subjects who experienced the onset of COVID-19 symptoms within <72 hours before randomization had received vaccine against COVID-19.

18) The following are main risk factors for severe COVID-19 identified in subjects (i.e., subjects who experienced the onset of COVID-19 symptoms within <72 hours before randomization in the ITT population)
- Smoking (15.9% [55 of 347 subjects] in the ensitrelvir 375/125 mg group, 16.5% [56 of 340 subjects] in the ensitrelvir 750/250 mg group, and 14.0% [48 of 343 subjects] in the placebo group)
- Dyslipidaemia (8.4% [29 of 347 subjects] in the ensitrelvir 375/125 mg group, 5.0% [17 of 340 subjects] in the ensitrelvir 750/250 mg group, and 7.6% [26 of 343 subjects] in the placebo group)
- BMI ≥30 kg/m^2 (6.6% [23 of 347 subjects] in the ensitrelvir 375/125 mg group, 4.4% [15 of 340 subjects] in the ensitrelvir 750/250 mg group, and 3.5% [12 of 343 subjects] in the placebo group)
- Hypertension (6.3% [22 of 347 subjects] in the ensitrelvir 375/125 mg group, 2.9% [10 of 340 subjects] in the ensitrelvir 750/250 mg group, and 4.1% [14 of 343 subjects] in the placebo group)

promptly provided to healthcare professionals, etc. and the need for additional investigation should be discussed.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection is currently ongoing. Results and the conclusion of PMDA are reported in the Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GPSP inspection

The inspection is currently ongoing. Results and the conclusion of PMDA are reported in the Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that ensitrelvir has efficacy in the treatment of COVID-19, and that ensitrelvir has acceptable safety in view of its benefits. Patients who have mild to moderate I[16)] symptoms of COVID-19 were eligible for enrollment in phase III part of the global phase II/III study (Study T1221). Accordingly, ensitrelvir offers a treatment option for such patients. PMDA has concluded that ensitrelvir may be approved if ensitrelvir is not considered to have any particular problems based on comments from the Expert Discussion.

10. Other

The following are main amendments made to the clinical study protocol during the conduct of phase III part of the global phase II/III study (Study T1221):

Protocol Ver. 7 (amended on February 7, 2022)	
Doses for efficacy evaluation	Ensitrelvir 375/125 mg and ensitrelvir 750/250 mg
Primary endpoint	Time from the start of study treatment to recovery[a)] from 12 symptoms[b)] of COVID-19
Primary efficacy analysis population	Subjects with ≥3 moderate symptoms in the ITT2 population (ITT2 population consisted of randomized subjects who tested positive by RT-PCR on nasopharyngeal swab either at Visit 1 [before the start of treatment] or at Visit 2)
Sample size required	1,260 subjects (420 per group)
Justification for sample size	The median time to recovery from symptoms was assumed to be 7 days in the placebo group and 5.5 days in both ensitrelvir groups (hazard ratio to the placebo group assumed to be 1.27). The drop-out rate due to a negative RT-PCR test performed immediately before enrollment was assumed to be approximately 10%. With these assumptions, the sample size required to ensure 80% statistical power by log-rank test with a two-sided significance level of 2.5% was calculated to be 1,128 patients with COVID-19 who have ≥3 moderate symptoms in the 3 groups combined (376 patients per group).
Analysis method for the primary endpoint	Stratified log-rank test
Method for adjusting multiplicity of hypothesis testing	Bonferroni method was used. The two-sided significance level was 2.5% for the comparison between each ensitrelvir and placebo groups in the analysis of the primary endpoint.
Interim analysis	An interim analysis is conducted for early termination for efficacy when follow-up is completed in 50% of the target number of subjects. Multiplicity of hypothesis testing in the interim analysis is adjusted by O'Brien-Fleming type α-spending function.
Protocol Ver. 8 (amended on April 5, 2022)	
Doses for efficacy evaluation	Ensitrelvir 375/125 mg and ensitrelvir 750/250 mg
Primary endpoint	Time from the start of study treatment to resolution[c)] of 12 symptoms[b)] of COVID-19
Primary efficacy analysis population	ITT1 population (randomized subjects with a positive SARS-CoV-2 virus titer in baseline nasopharyngeal swab)
Sample size required	1,785 subjects (595 per group)

Justification for sample size	The median time to resolution of symptoms was assumed to be 10 days in the placebo group and 8 days in both ensitrelvir groups (hazard ratio to the placebo group assumed to be 1.25). The drop-out rate due to a negative SARS-CoV-2 viral titer at Visit 1 (before administration) was assumed to be 20%. With these assumptions, the sample size required to ensure 80% statistical power by log-rank test at a two-sided significance level of 2.5% was calculated to be 1,785 patients with COVID-19 in the 3 groups combined (595 patients per group).
Analysis method for the primary endpoint	Stratified log-rank test
Method for adjusting multiplicity of hypothesis testing	Bonferroni method was used. The two-sided significance level was 2.5% for the comparison between each ensitrelvir and placebo groups in the analysis of the primary endpoint.
Interim analysis	Description on the interim analysis was deleted because, based on the progress of enrollment, the target sample size (1,785) was expected to be reached before the interim analysis.
Protocol Ver. 9 (amended on July 8, 2022)	
Doses for efficacy evaluation	Ensitrelvir 375/125 mg and ensitrelvir 750/250 mg
Primary endpoint	Time from the start of study treatment to resolution[c)] of 12 symptoms[b)] of COVID-19
Primary efficacy analysis population	ITT population
Sample size required	1,590 subjects (530 per group)
Justification for sample size	The median time to resolution of symptoms was assumed to be 10 days in the placebo group and 8 days in both ensitrelvir groups (hazard ratio to the placebo group assumed to be 1.25). The drop-out rate due to a negative RT-PCR test performed immediately before enrollment was assumed to be 10%. With these assumptions, the sample size required to ensure 80% statistical power by log-rank test at a two-sided significance level of 2.5% was calculated to be 1,590 patients with COVID-19 in the 3 groups combined (530 patients per group).
Analysis method for the primary endpoint	Stratified log-rank test
Method for adjusting multiplicity of hypothesis testing	Bonferroni method was used. The two-sided significance level was 2.5% for the comparison between each ensitrelvir and placebo groups in the analysis of the primary endpoint.
Protocol Ver. 10 (amended on September 20, 2022)	
Dose for efficacy evaluation	Ensitrelvir 375/125 mg
Primary endpoint	Time from the start of study treatment to resolution[c)] of 5 symptoms[d)] of COVID-19
Primary efficacy analysis population	Only in subjects who experienced the onset of COVID-19 symptoms within <72 hours before randomization in the ITT population
Sample size required	780 subjects (260 per group)
Justification for sample size	Weibull distribution was assumed (median Weibull distribution assumed to be 8.3 days in the ensitrelvir 375/125 mg group and 11.1 days in the placebo group), based on the Kaplan-Meier curve of the time to resolution of symptoms in subjects who experienced the onset of COVID-19 symptoms within <72 hours before randomization in phase IIb part. The drop-out rate due to a negative RT-PCR test performed immediately before enrollment was assumed to be 10%. With these assumptions, the number of subjects required to ensure 80% statistical power by Peto-Prentice generalized Wilcoxon test at a two-sided significance level of 5%, was calculated to be 780 patients with COVID-19 who experienced the onset of symptoms within <72 hours before randomization in the 3 groups combined (230 patients per group).
Analysis method for the primary endpoint	Stratified Peto-Prentice generalized Wilcoxon test
Method for adjusting multiplicity of hypothesis testing	Since only the 375/125 mg dose is used, adjustment for the multiplicity of hypothesis testing is not required.

a) "Recovery" was defined as the condition in which all 12 symptoms met the following criteria:
   - Symptoms that had been present before the onset of COVID-19 and were considered by the subject to have worsened at baseline (at test before administration): Improved severity from baseline (i.e., from severe to moderate or better, or from moderate to mild or better) is maintained for at least 24 hours
   - Symptoms that had been present before the onset of COVID-19 and were NOT considered by the subject to have worsened at baseline (at test before administration): Improved severity from baseline or the same severity as baseline (i.e., from severe to severe or better, or from moderate to moderate or better) is maintained for at least 24 hours.
   - Other symptoms (i.e., symptoms that were not present before the onset of COVID-19 and developed after baseline [test before administration]): A mild or an asymptomatic condition is maintained for at least 24 hours.

b) The 12 symptoms caused by COVID-19: (1) Malaise or tiredness, (2) muscle or body aches, (3) headache, (4) chills or sweating, (5) feverish or pyrexia, (6) stuffy or runny nose, (7) sore throat, (8) cough, (9) shortness of breath (dyspnea), (10) nausea, (11) vomiting, (12) diarrhea

c) See Section 7.1.1 for the definition of "resolution"

d) The 5 symptoms caused by COVID-19: (1) Malaise or tiredness, (2) feverish or pyrexia, (3) stuffy or runny nose, (4) sore throat, and (5) cough.

Review Report (2)

February 19, 2024

Product Submitted for Approval

Brand Name	Xocova Tablets 125 mg
Non-proprietary Name	Ensitrelvir Fumaric Acid
Applicant	Shionogi & Co., Ltd.
Date of Application	June 8, 2023

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc., concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc., by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

The following comments were raised from the expert advisors at the Expert Discussion on issues described in the Review Report (1) of Sections "7.R.1 Efficacy," "7.R.2 Safety," "7.R.3 Clinical positioning and indication," and "7.R.5 Post-marketing investigations," but the PMDA's conclusion was finally supported.

- In phase III part of the global phase II/III study (Study T1221), the efficacy of ensitrelvir was not demonstrated by the analysis before protocol amendment, and even the hazard ratio calculated by the analysis after protocol amendment was not large (1.14 [95% CI; 0.95, 1.36]). Given these findings, the observed efficacy is not a robust result. However, this does not necessitate a change to the regulatory decision made at the time of Emergency Approval.
- Anaphylaxis is a serious event that can lead to serious outcomes, requiring careful attention.

1.1 Precautionary statement on administration to patients eligible for treatment with ensitrelvir

PMDA's view:
The following points require careful consideration:
The efficacy of ensitrelvir 375/125 mg against COVID-19 has been demonstrated in patients who experienced symptom onset within <72 hours before starting treatment, whereas no data are available to support efficacy in patients starting treatment ≥72 hours after symptom onset [see Section 7.R.3 of the Review Report (1)]. In order to make it clear that ensitrelvir is intended for the patient population in

whom ensitrelvir showed efficacy, a precautionary statement regarding the time from symptom onset should be provided in the package insert.

At the Expert Discussion, the above conclusion of PMDA was supported by the expert advisors.

PMDA instructed the applicant to modify the "Precautions Concerning Dosage and Administration" section of the package insert as shown below. The applicant responded appropriately.

Precautions Concerning Dosage and Administration
Ensitrelvir should be administered ~~promptly~~ within 72 hours after the onset of COVID-19 symptoms. ~~Ensitrelvir is presumed to have efficacy when administered within 3 days after the onset of symptoms.~~ No clinical study data are available that support the efficacy of ensitrelvir in patients who started treatment ≥72 hours after the onset of symptoms.
(The underlined words are added to, and the strikethrough words are deleted from, the text for the Emergency Approval.)

1.2 Risk management plan (draft)

In view of the discussion in Section "7.R.5 Post-marketing investigations" in the Review Report (1) and the comments from the expert advisors at the Expert Discussion, PMDA has concluded that, in addition to collecting information through usual pharmacovigilance activities, the risk management plan for ensitrelvir should include the safety and efficacy specifications presented in Table 25, and that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities presented in Tables 26 and 27.

Table 25. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risk	Important potential risk	Important missing information
Anaphylaxis	Teratogenicity	None
Efficacy specification		
None		

Table 26. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
General use-results survey[a)]	None	• Preparation and distribution of information material for healthcare professionals ("Xocova Tablets 125 mg: Request regarding pregnant or possibly pregnant women or women of childbearing potential") • Preparation and distribution of information material for patients ("For female patients prescribed Xocova Tablets 125 mg and their family members")

a) General use-results survey has been ongoing since the Emergency Approval

Table 27. Outline of general use-results survey

Objective	To evaluate the safety of ensitrelvir in clinical practice
Survey method	Consecutive patients
Population	Patients treated with ensitrelvir
Observation period	28 days from the start of treatment
Planned sample size	3,000
Main survey items	Patient characteristics, ensitrelvir exposure, concomitant drugs, symptoms before and after treatment, adverse events, and hospitalization or death after the start of treatment

(No change from the time of Emergency Approval)

1.3 Resistance profile of SARS-CoV-2 against ensitrelvir

The applicant's explanation:

Amino acid sequence of SARS-CoV-2 3CL protease was analyzed using samples obtained before and after ensitrelvir administration from 204 of the 345 subjects receiving ensitrelvir 375/125 mg in phase III part of the global phase II/III study (Study T1221). Results showed that the amino acid substitutions listed in Table 28 were detected in 19 subjects at some points after ensitrelvir administration.

Table 28. Amino acid substitutions in SARS-CoV-2 3CL protease detected at some points after ensitrelvir administration in phase III part of global phase II/III study (Study T1221)

Amino acid substitution	Number of subjects with amino acid substitution	Change in *in vitro* antiviral activity of ensitrelvir (ratio to EC_{50} of the parent strain)
T25A	1[a)]	-
T25I	1[b)]	-
D48Y	1	-
M49I	3[a)]	-
M49L	12[a)]	17[c)]
S123Y	1	-
S144A	2[b)]	9.2[c)]
D216H	1	-

-, Not investigated.
a) Includes 1 subject showing T25A and M49L substitutions on Day 6 and M49I substitution on Day 9.
b) Includes 1 subject showing T25I and S144A substitutions on Day 14.
c) See Section 3.1.3.2 of Review Report on Xocova Tablets 125 mg dated June 17, 2022.

PMDA's view:

Some of the SARS-CoV-2 3CL protease amino acid substitutions detected in the clinical study are associated with reduced sensitivity to ensitrelvir *in vitro*. Although the relationship between amino acid substitutions and the clinical efficacy of ensitrelvir is unknown, there is a possibility that resistant strains may emerge in patients using ensitrelvir in clinical practice and compromise the efficacy of the drug. The emergence of resistant mutations is critical information regarding the efficacy of ensitrelvir. Therefore relevant information should be collected continuously from published reports and other sources, and appropriate actions should be taken based on new findings.

1.4 Coadministration with CYP3A inhibitors or inducers

After the finalization of the Review Report (1), the applicant submitted the clinical study report of the clinical drug interaction study (Study T1218). PMDA reviewed the report and found no changes from the preliminary results, and therefore decided that there was no need to change the PMDA's conclusion described in Section 6.R.2 of the Review Report (1).

1.5 The latest safety data after the market launch

The applicant's explanation about the latest safety data of ensitrelvir after the market launch:

The general use-results survey is ongoing since November 2022, when ensitrelvir was granted the Emergency Approval. Among 2,440 patients subjected to safety analysis in the survey (data locked on November 21, 2023), adverse drug reactions occurred in 7.6% (186 of 2,440 patients). The main adverse drug reactions were diarrhoea in 2.2% (53 of 2,440 patients), nausea in 1.2% (30 of 2,440 patients), headache in 1.2% (29 of 2,440 patients), vomiting in 0.7% (17 of 2,440 patients), and rash in 0.6% (15 of 2,440 patients). The outcome was "resolved" or "resolving," except for 6 "unresolved" events (taste disorder, diplopia, diarrhoea, nausea, eczema, and urticaria [1 event each]) and 13 "unknown" events (intermenstrual bleeding [2 events] and depressed level of consciousness, headache, visual impairment, abdominal discomfort, diarrhoea, nausea, vomiting, drug eruption, chest pain, feeling abnormal, and feeling hot [1 event each]). A serious adverse drug reaction (generalised oedema) occurred in 1 patient, and its outcome was "resolved."

In the post-marketing safety information as of January 14, 2024,[19] 14 events of anaphylaxis-related serious adverse drug reactions (anaphylactic reaction [10 events] and anaphylactic shock [4 events]) occurred but did not result in serious outcomes.

After receiving ensitrelvir, 31 patients were found to be pregnant and 3 patients reported their possible pregnancy to their attending physician (34 patients in total). [redacted] In total, 27 continued their pregnancy, and the outcomes of those who provided consent are being followed-up. Of 6 patients who discontinued pregnancy, 3 had spontaneous abortion [redacted]; the causal relationship between these events and ensitrelvir was "unknown" or "unrelated."

Thus the post-marketing data have revealed no new safety concerns. The applicant therefore considers that there is no need to change the current safety measures.

PMDA concluded that there was no need to change its conclusion described in Section 7.R.2 of the Review Report (1).

1.6 Development of ensitrelvir in children

The applicant is conducting a clinical study for development of ensitrelvir in children with COVID-19 aged ≥6 and <12 years.

PMDA's view:

Since COVID-19 occurs in children aged <12 years as well and their current treatment options are limited, it is meaningful to develop ensitrelvir for children aged ≥6 and <12 years.

[19] Estimated number of patients treated with ensitrelvir is 925,237 (calculated from the number of patients registered at the registration center and from the quantity of ensitrelvir delivered).

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GPSP inspection

The new drug application data (CTD 5.3.6-02 General use results survey report [interim report]) were subjected to an on-site GPSP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.3 Other

The applicant submitted the results of phase III part of the global phase II/III study (Study T1221) (submission of the study results was an approval condition of Emergency Approval). In response to this, PMDA conducted a document-based inspection and a data integrity assessment as well as an on-site GCP inspection in accordance with the provisions of Article 14-2-2, Paragraph 2 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. As a result, PMDA concluded that there were no obstacles to conducting its review based on the study results.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that ensitrelvir may be approved for the following indication and dosage and administration, with the following approval condition. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. Both the drug product and its drug substance are classified as powerful drugs.

Indication

Disease caused by SARS-CoV-2 infection (COVID-19)

Dosage and Administration

The usual dose in ≥12-year-old pediatric patients and adults is ensitrelvir 375 mg on Day 1 and ensitrelvir 125 mg from Days 2 to 5, administered orally once daily.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

3CL	3C-like
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
AUC_{last}	Area under the concentration-time curve from time 0 to the last observed concentration
AUC_{tau}	Area under the concentration-time curve over the dosing interval
BMI	Body mass index
BSEP	Bile-salt export pump
Casirivimab	Casirivimab (genetical recombination)
Cilgavimab	Cilgavimab (genetical recombination)
CL/F	Apparent total clearance
C_{max}	Maximum concentration
CrCL	Creatinine clearance
EC_{50}	50% effective concentration
eGFR	Estimated glomerular filtration rate
HDL	High density lipoprotein
IC_{50}	50% inhibitory concentration
ICH M7 Guideline	Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (PSEHB/PED Notification No. 1110-3 dated November 10, 2015)
ICH Q1E Guideline	Evaluation for Stability Data (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
Imdevimab	Imdevimab (genetical recombination)
ITT	Intention to Treat
Ka	First order absorption rate constant
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
PCR	Polymerase chain reaction
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
RH	Relative humidity
RNA	Ribonucleic acid
RT-PCR	Reverse transcription PCR
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
Scr	Serum creatinine concentration
SMQ	Standardized MedDRA Query
Sotrovimab	Sotrovimab (genetical recombination)
Study T1211	Study 2102T1211
Study T1213	Study 2127T1213
Study T1214	Study 2128T1214
Study T1215	Study 2130T1215
Study T1216	Study 2135T1216
Study T1218	Study 2305T1218
Study T1221	Study 2108T1221
Tixagevimab	Tixagevimab (genetical recombination)
TMPRSS2	Transmembrane protease, serine 2
Vc/F	Apparent volume of distribution in central compartment
Xocova	Xocova Tablets 125 mg

γ-GTP	Gamma-glutamyltransferase