Safety and Effectiveness of Ensitrelvir for the Treatment of COVID-19 in Japanese Clinical Practice: a Post-marketing Surveillance (Interim Analysis)

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Background and purpose

- Ensitrelvir fumaric acid (hereafter, ensitrelvir, Xocova®) is a novel anti-SARS-CoV-2 drug and an inhibitor of the SARS-CoV-2 3CL protease which processes SARS-CoV-2 polyproteins essential for viral replication . Emergency approval was granted by the Ministry of Health, Labor, and Welfare (MHLW) in Japan in November 2022 for the indication of "SARS-CoV-2 infection".
- A post-marketing surveillance (hereafter "PMS") is currently on-going to evaluate the safety and effectiveness of ensitrelvir in real world clinical practice in Japan. As of 20th July 2023, a total of 1682 patients were enrolled and the interim analysis was conducted.

Method

Table 1. Study Outline

Study design	Multicenter, single-arm, observational study
Objective	To evaluate safety and effectiveness
Study population	SARS-CoV-2-infected subjects with mild/moderate symptoms
Enrollment	3000 (planned), 1682 (from 22 Nov 2022 to 20 Jul 2023)
Outcome measures	Patient demographics, concomitant medications, other therapy and procedures for COVID-19, adverse events*, adverse drug reactions**, and clinical symptoms (body temperature, presence or absence of systematic symptoms, respiratory symptoms, and gastrointestinal symptoms) using the patient questionnaire
Major eligibility criteria	Age ≧12 and first exposure to ensitrelvir
Dosage and administration	Oral administration of ensitrelvir tablet q.d. for 5 days, loading dose at Day 1(375 mg) followed by 4 days maintenance doses (125 mg)
Observation period	28 days

Before administration | **Observation period**

▲Day1 ▲2 ▲3 ▲4 ▲5 Administration of ensitrelvir ▲Day28

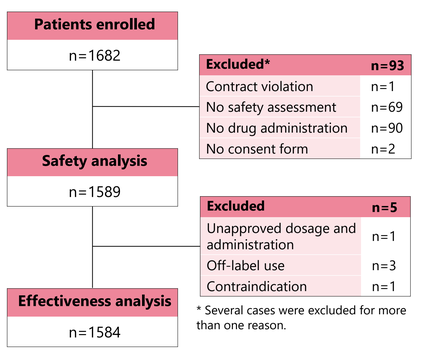
Outcome measures	Before administration	1-9 days	10-14 days	15-28 days
Medical examination				
Patient demographics	✓			
COVID-19 symptoms	✓			
Concomitant medications	✓	✓	✓	✓
Other therapy and procedures for COVID-19	✓	✓	✓	✓
Hospitalization/death		✓	✓	✓
Adverse events		✓	✓	✓
Patient questionnaire				
Administration of ensitrelvir		1-5 days		
Body temperature		AM・PM	PM	
Symptoms		AM・PM	PM	
Adverse events		✓	✓	

According to the International Conference of Harmonisation Tripartite Guideline E2D version4[1)] :
*Adverse Events were defined as any untoward medical occurrences in patients administered a medicinal product and which did not necessarily have a causal relationship with treatment
**Adverse drug reactions (ADRs), which could be an AE or SAE, were defined as reactions for which a causal relationship with the drug was suspected by either the reporting physician or the sponsor.

Results

Out of 1682 patients, 1589 were evaluated for safety and 1584 for effectiveness (**Figure 1**).

Figure 1. Patient Population



* Several cases were excluded for more than one reason.

** Risk factors for aggravation of the new coronavirus infectious disease (COVID-19) include 65 and over, malignancy, chronic respiratory illness (COPD etc.), chronic kidney disease, diabetes mellitus, hypertension, hyperlipemia, cardiovascular disease, cerebrovascular disease, obesity (BMI 30 or more), smoking habit, immunodeficiency after solid organ transplantation, and use of immunosuppressant/immunomodulatory drugs[2)]
*** Based on the severity classification of Clinical Manegement of Patients with COVID-19 Version 8.1[2)]

Table 2. Baseline Demographic Characteristics

Characteristics, n (%)		Safety analysis set (N=1589)	Effectiveness analysis set (N=1584)
Age, years	< 15	48 (3.0)	48 (3.0)
	15 -< 65	1358 (85.5)	1355 (85.5)
	≥ 65	183 (11.5)	181 (11.4)
Sex	Male	764 (48.1)	762 (48.1)
	Female	825 (51.9)	822 (51.9)
History of COVID-19 infection	No	1380 (86.8)	1376 (86.9)
	Yes	174 (11.0)	174 (11.0)
Vaccinated	No	153 (9.6)	153 (9.7)
	Yes	1239 (78.0)	1234 (77.9)
High-risk factors** for COVID-19	No	1192 (75.0)	1190 (75.1)
	Yes	397 (25.0)	394 (24.9)
Concomitant drugs	Without	194 (12.2)	193 (12.2)
	With	1395 (87.8)	1391 (87.8)
Time from onset to administration of ensitrelvir, hrs	< 72	1445 (90.9)	1443 (91.1)
	72 - < 120	32 (83)	132 (8.3)
	≥ 120	5 (0.3)	5 (0.3)
Severity of COVID-19 symptoms***	Asymptomatic	3 (0.2)	0
	Mild	1556 (97.9)	1554 (98.1)
	Moderate I	28 (1.8)	28 (1.8)
	Moderate II	2 (0.1)	2 (0.1)
	Severe	0	0

Safety

Safety Analysis Set, N=1589

The most common ADRs were "diarrhea" in 38 cases (2.4%), "nausea" in 20 cases (1.3%), and "headache" in 18 cases (1.1%). No serious ADRs were observed. One case of pregnancy was reported and no ADRs have been observed. ADRs occurred most frequently 1 to 2 days after the start of administration, and 90.7% occurred within 5 days after the start of administration of ensitrelvir (**Table 4**).

Table 3. Frequency of ADRs by Demographic Characteristics

Characteristics		N	ADR, %
All subjects		1589	8.1
Age, years	< 15	48	2.1
	15 -< 65	1358	8.8
	≥ 65	183	4.4
Sex	Male	764	5.0
	Female	825	10.9
History of COVID-19 infection	No	1380	8.3
	Yes	174	4.6
	Unknown	35	14.3
Vaccinated	No	153	8.5
	Yes	1239	8.3
	Unknown	197	6.1
High-risk factors for COVID-19	No	1192	8.8
	Yes	397	5.8
Concomitant medications	No	194	6.7
	Yes	1395	8.2
Severity of pre-administration	Asymptomatic	3	33.3
	Mild	1556	8.1
	Moderate I	28	3.6
	Moderate II	2	0

Table 4. Timing of Onset and Outcome of ADRs ≧3 events

*MedDRA version 26.0

ADRs	Preferred term*	event	Onset (days)							Time to recovery or recovering (days)							
			1	2	3	4-5	6-9	10-14	15-28	1	2	3	4-5	6-9	10-14	15-28	29≦
Metabolism and nutrition disorders	Decreased appetite	3	1	1			1					1	2				
Nervous system disorders	Dizziness	3	1	1			1				1		1	1			
	Headache	19	11	5	1	1	1			1	3	2	11	1			
	Taste disorder	3	1	1	1								1		1		
Respiratory, thoracic and mediastinal disorders	Cough	3	1				1		1		1		1		1		
Gastrointestinal disorders	Abdominal discomfort	3		1		1	1					1	1				
	Abdominal pain	6	2	1		3					1	4	1				
	Abdominal pain upper	5	2	2	1						2	1	1		1		
	Diarrhoea	38	7	11	12	7	1			2	10	13	10	2			
	Nausea	20	3	6	5	6				4	7	2	5	1			
	Vomiting	7	1	3		1	2				3	1	2	1			
	Faeces soft	6		2	2	1	1			2	1			3			
Skin and subcutaneous tissue disorders	Pruritus	5	3		2					1			3	1			
	Rash	10	2	4	2	2				2	2	1	1	2		1	1
	Urticaria	3	1	2						1		1		1			
General disorders and administration site conditions	Pyrexia	5	2	2					1		3			1	1		

Effectiveness

Effectiveness Analysis Set, N=1584

The median time to resolution of fever was about 1.5 days and 6.5 days for all symptoms. Respiratory symptoms persisted more than twice as longer as other symptoms(**Table 5**).

Table 5. Time to Resolution of Fever and Symptoms

	Fever[1)]	Systemic symptoms[2)]	Respiratory symptoms[3)]	Gastrointestinal symptoms[4)]	All symptoms[5)]
Cases	1002	1431	1421	122	1583
Median, hours (95% confidence interval)	36.0 (−*)	60.0 (−*)	144.0 (132.0, 156.0)	48.0 (36.0, 48.0)	156.0 (144.0, 168.0)

1) Resolution of fever was defined as the first time when <37℃ was maintained for 24 hours or longer. 2) Systemic symptoms include lethargy or fatigue, muscle or body pain, headache, chills or shivering, hotness or fever, taste dysfunctions, and smell dysfunctions. 3) Respiratory symptoms include stuffy or runny nose, sore throat, cough, and shortness of breath (dyspnoea). 4) Gastro-intestinal symptoms include nausea, vomiting, and diarrhoea. 5) Resolution of all symptoms was defined as the first time when none of fever, systemic, respiratory, and gastrointestinal symptoms persisted for 24 hours or longer. * The lower bound of the 95% confidence interval (CI) for the Kaplan-Meier estimate was above 50% just before the median, and the upper bound of the 95% CI was below 50% just after the median, therefore the 95% CI was not estimated.

Table 6. Hospitalization Incidence and Mortality due to COVID-19

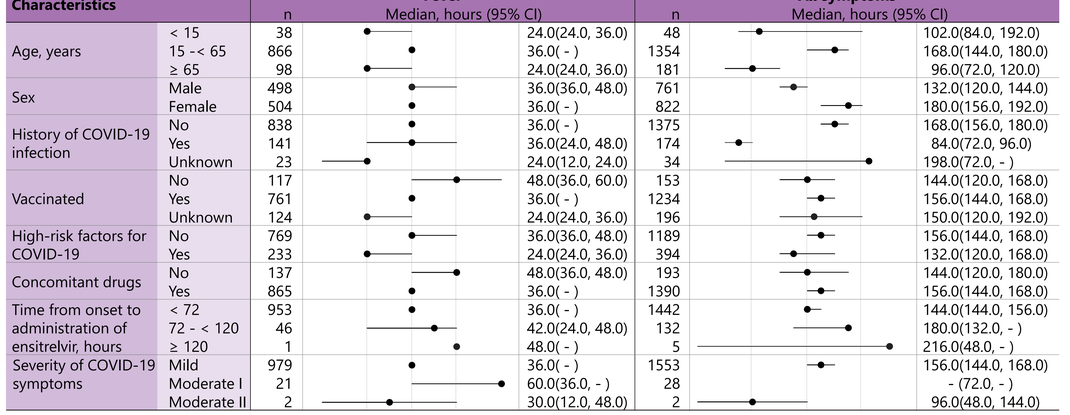
Outcomes	n	%
Hospitalized	4	0.3
Death	0	0.0

Four (0.3%) patients were hospitalized due to aggravated COVID-19, and 3 of 4 hospitalizations had high-risk factors (**Table 6**). One of 4 hospitalizations also had respiratory failure due to exacerbation of chronic obstructive pulmonary disease. One patient died due to a subarachnoid hemorrhage to be not related to ensitrelvir, but there were no deaths due to COVID-19.

Age of ≥ 65 and high-risk factors did not prolong the time to fever or all symptom resolution (**Figure 2**).

Figure 2. Time to Resolution of Fever and All Symptoms by Demographic Characteristics

Characteristics		Fever n	Fever Median, hours (95% CI)	All symptoms n	All symptoms Median, hours (95% CI)
Age, years	< 15	38	24.0(24.0, 36.0)	48	102.0(84.0, 192.0)
	15 -< 65	866	36.0(-)	1354	168.0(144.0, 180.0)
	≥ 65	98	24.0(24.0, 36.0)	181	96.0(72.0, 120.0)
Sex	Male	498	36.0(36.0, 48.0)	761	132.0(120.0, 144.0)
	Female	504	36.0(-)	822	180.0(156.0, 192.0)
History of COVID-19 infection	No	838	36.0(-)	1375	168.0(156.0, 180.0)
	Yes	141	36.0(24.0, 48.0)	174	84.0(72.0, 96.0)
	Unknown	23	24.0(12.0, 24.0)	34	198.0(72.0, -)
Vaccinated	No	117	48.0(36.0, 60.0)	153	144.0(120.0, 168.0)
	Yes	761	36.0(-)	1234	156.0(144.0, 168.0)
	Unknown	124	24.0(24.0, 36.0)	196	150.0(120.0, 192.0)
High-risk factors for COVID-19	No	769	36.0(36.0, 48.0)	1189	156.0(144.0, 168.0)
	Yes	233	24.0(24.0, 36.0)	394	132.0(120.0, 168.0)
Concomitant drugs	No	137	48.0(36.0, 48.0)	193	144.0(120.0, 180.0)
	Yes	865	36.0(-)	1390	156.0(144.0, 168.0)
Time from onset to administration of ensitrelvir, hours	< 72	953	36.0(-)	1442	144.0(144.0, 156.0)
	72 - < 120	46	42.0(24.0, 48.0)	132	180.0(132.0, -)
	≥ 120	1	48.0(-)	5	216.0(48.0, -)
Severity of COVID-19 symptoms	Mild	979	36.0(-)	1553	156.0(144.0, 168.0)
	Moderate I	21	60.0(36.0, -)	28	- (72.0, -)
	Moderate II	2	30.0(12.0, 48.0)	2	96.0(48.0, 144.0)



(-) : The lower bound of the 95% CI for the Kaplan-Meier estimate was above 50% just before the median, and the upper bound of the 95% CI was below 50% just after the median, therefore the 95% CI was not estimated.

Summary and limitation

- As a result of the interim analysis of a post-marketing surveillance, no new concerns about the tolerability and effectiveness of ensitrelvir were identified and it was suggested that ensitrelvir was well tolerated and effective in patients with or without risk factors.
- The resolution in symptoms is based on self-reports from patients, the possibility of recall bias cannot be ruled out, and the analysis data contains a certain number of missing values.
- This survey was conducted in real world clinical practice, it would not be possible to directly compare the results with those obtained up to the time of approval.
- This study did not include a placebo or active comparator control group, the interpretation of the results may be limited.

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References
1) ICH HARMONISED TRIPARTITE GUIDELINE; CLINICAL SAFETY DATA MANAGEMENT:DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING E2A [https://database.ich.org/sites/default/files/E2A_Guideline.pdf]
2) A guide for front-line healthcare workers; Clinical Management of Patients with COVID-19 Version 8.1