Real-world safety and effectiveness of ensitrelvir in COVID-19 patients with risk factor: a post-marketing surveillance in Japan

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Background and Purpose

- Ensitrelvir fumaric acid (hereafter, ensitrelvir) is a novel inhibitor of the SARS-CoV-2 3CL protease, which processes essential SARS-CoV-2 polyproteins for viral replication.[1,2] Emergency approval for the indication of "SARS-CoV-2 infection" was granted in November 2022 by the Ministry of Health, Labour and Welfare (MHLW) in Japan, and standard approval was granted in March 2024.[3,4]
- A post marketing surveillance (PMS) evaluated the safety and effectiveness of ensitrelvir in real-world clinical practice in Japan.[5] This final analysis includes data from 3760 patients from November 2022 to August 2023.

Conclusions

- Results of the analysis suggest that ensitrelvir is well tolerated and effective in patients with risk factors as well as patients without risk factors. No new safety signals were identified.

Methods

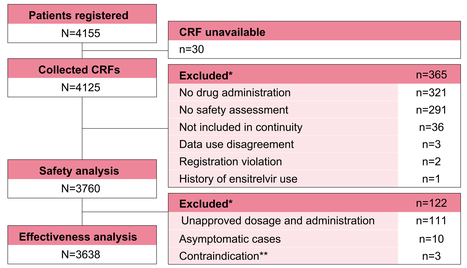
Table 1: Objectives and Survey Outline

Study design	Multicenter, single-arm, observational study
Objective	To evaluate safety and effectiveness in clinical practice
Study population	SARS-CoV-2-infected subjects
Enrollment	3000 (planned), 4155 (actual registration; from Nov 22, 2022, to Aug 10, 2023)
Survey method	Continuous survey method with enrollment
Dosage and administration	Oral administration of ensitrelvir tablet QD for 5 days: loading dose on Day 1 (375 mg), followed by maintenance doses on Days 2-5 (125 mg)
Observation period	28 days

Results

- Of 4155 patients, 3760 were included in the safety analysis set and 3638 in the effectiveness analysis set.

Figure 1: Patient Disposition



*Duplicate reasons.
**Includes one positive pregnancy test and two cases where contraindicated medications were used.

Table 2: Baseline and Demographic Characteristics (Efficacy Analysis Set)

Item	Patients, n (%)		
	Overall	SR*	HR*
Efficacy analysis population	**3638 (100)**	**2735 (75.2)**	**903 (24.8)**
Age, years			
Mean ± (SD)	43.5 ± 17.6	37.6 ± 13.8	61.2 ± 16.0
<15	95 (2.6)	91 (3.3)	4 (0.4)
15–<65	3111 (85.5)	2644 (96.7)	467 (51.7)
≥65	432 (11.9)	0 (0.0)	432 (47.8)
Sex			
Male	1774 (48.8)	1315 (48.1)	459 (50.8)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Breastfeeding	1 (0.1)	1 (0.1)	0 (0.0)
Comorbidities			
Yes	797 (21.9)	157 (5.7)	640 (70.9)
Concomitant medications			
Yes	3199 (87.9)	2396 (87.6)	803 (88.9)
COVID-19 infection history			
Yes	324 (8.9)	251 (9.2)	73 (8.1)
Vaccination history			
Yes	2671 (73.4)	1957 (71.6)	714 (79.1)
Severity before administration**			
Mild	3557 (97.8)	2681 (98.0)	876 (97.0)
Moderate I	78 (2.1)	54 (2.0)	24 (2.7)
Moderate II	3 (0.1)	0 (0.0)	3 (0.3)
Time from onset to initiation of ensitrelvir treatment			
<72 hours	3351 (92.1)	2540 (92.9)	811 (89.8)
72-120 hours	249 (6.8)	162 (5.9)	87 (9.6)
>120 hours	16 (0.4)	13 (0.5)	3 (0.3)

*Ministry of health, labour and welfare. Covid-19 treatment guidance, version 8, 9
**Ministry of health, labour and welfare. Covid-19 treatment guidance, version 8.1

Safety

Safety Analysis Set, N=3760

- Overall, 379 ADRs (SR, 7.1%; HR, 7.6%) occurred (serious, n=5), most commonly, diarrhoea (n=91), nausea (n=43), headaches (n=42), vomiting (n=24), and rash (n=20). Approximately 90% of ADRs occurred within 5 days after administration. Approximately 70% of ADRs recovered (including remission) within 4-5 days from the onset.

Figure 2: Frequency of ADRs by Baseline Characteristics

		Number of patients for analysis	Number of patients with ADRs	%	P value
All patients		3760	271	7.21	
Age (years)	<15	97	4	4.12	0.2528
	15–<65	3211	240	7.47	
	≥65	452	27	5.97	
Sex	Male	1823	91	4.99	<0.0001
	Female	1937	180	9.29	
History of COVID-19 infection	No	3255	245	7.53	0.2106
	Yes	336	19	5.65	
	Unknown	169	7	4.14	
History of vaccination	No	324	27	8.33	0.6115
	Yes	2758	208	7.54	
	Unknown	678	36	5.31	
Presence of high-risk factors for COVID-19	No	2821	200	7.09	0.6284
	Yes	939	71	7.56	
High-risk factors for COVID-19 (duplicate)	Age >65 years	452	27	5.97	
	Malignant tumors	31	3	9.68	
	Chronic respiratory diseases	77	6	7.79	
	Chronic kidney disease	15	2	13.33	
	Diabetes mellitus	98	3	3.06	
	Hypertension	352	27	7.67	
	Dyslipidemia	253	28	11.07	
	Cardiovascular disease	68	7	10.29	
	Cerebrovascular disease	30	4	13.33	
	Obesity (BMI ≥30 kg/m²)	50	6	12.00	
	Smoking habit	149	9	6.04	
	Use of immunosuppressants/modulators	18	4	22.22	
	Other	17	3	17.65	
Concomitant medications	No	474	32	6.75	0.6811
	Yes	3286	239	7.27	
Severity of pre administration	Asymptomatic	10	1	10.00	0.9229
	Mild	3666	265	7.23	
	Moderate I	81	5	6.17	
	Moderate II	3	0	0.00	
Comorbidities	No	2926	186	6.36	0.0002
	Yes	834	85	10.19	

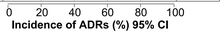


Table 3: ADRs Reported by ≥3 Patients

SOC	Preferred term	Events	Seriousness	
			Serious	Non serious
Metabolism and nutrition disorders	Decreased appetite	5	-	5
Psychiatric disorders	Insomnia	3	-	3
Nervous system disorders	Dizziness	9	-	9
	Headache	42	1	41
	Hypoaesthesia	3	-	3
	Parosmia	3	-	3
Respiratory, thoracic and mediastinal disorders	Cough	3	-	3
	Oropharyngeal pain	3	-	3
Gastrointestinal disorders	Abdominal discomfort	4	-	4
	Abdominal distension	3	-	3
	Abdominal pain	10	-	10
	Abdominal pain upper	7	-	7
	Diarrhoea	91	-	91
	Nausea	43	1	42
	Vomiting	24	1	23
	Faeces soft	12	-	12
Skin and subcutaneous tissue disorders	Erythema	3	-	3
	Pruritus	9	-	9
	Rash	20	-	20
	Urticaria	7	-	7
Reproductive system and breast disorders	Intermenstrual bleeding	3	-	3
General disorders and administration site conditions	Chest pain	3	-	3

Effectiveness

Effectiveness Analysis Set, N=3638

- The overall median time to resolution was 36.0 hours for fever and 156.0 hours for all symptoms.
- Compared to the SR group, the median time to resolution of respiratory symptoms, gastrointestinal symptoms and all symptoms was shorter in the HR group (Table 4).
- The influence on the median time to improvement of fever and all symptoms was suggested to be age, gender, vaccine administration, and high-risk factors (Figure 3).
- The median time to resolution of fever was shorter in the group received administration <72 hours than the other groups (Figure 3).
- Hospitalization was required for 14 patients (0.4%; SR, n=4; HR, n=10). Two patients (0.1%) died (SR, n=1; HR, n=1) of acute heart failure and subarachnoid hemorrhage, respectively; both unrelated to COVID-19 and ensitrelvir administration.

Table 4: Time to Resolution of Symptoms

	Fever*		Systemic symptoms**		Respiratory symptoms***		Gastrointestinal symptoms#		All symptoms†	
n	SR	HR	SR	HR	SR	HR	SR	HR	SR	HR
	1645	547	2244	757	2183	762	222	62	2424	854
Median (hours) (95% CI)	36.0 (36.0, 48.0)	36.0 (24.0, 36.0)	60.0 (60.0, 72.0)	60.0 (48.0, 60.0)	144.0 (132.0, 144.0)	120.0 (120.0, 132.0)	48.0 (36.0, 48.0)	36.0 (24.0, 48.0)	168.0 (156.0, 180.0)	144.0 (132.0, 156.0)

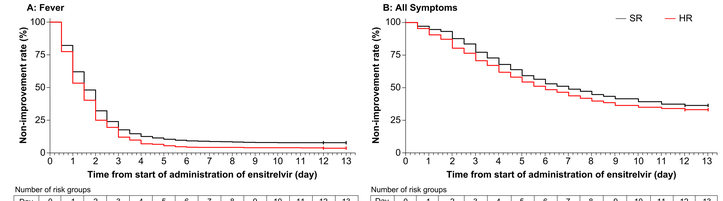
*Resolution of fever was defined as the first time when <37°C was maintained for 24 hours or longer. **Systemic symptoms include lethargy or fatigue, muscle or body pain, headache, chills or shivering, hotness or fever, taste dysfunctions, and smell dysfunctions. ***Respiratory symptoms include stuffy or runny nose, sore throat, cough, and shortness of breath (dyspnoea). #Gastro intestinal symptoms include nausea, vomiting, and diarrhoea.
†Resolution of all symptoms was defined as the first time when none of the fever, systemic, respiratory, and gastrointestinal symptoms persisted for 24 hours or longer.

Figure 3: Time to Resolution of Fever and All Symptoms By Patient Characteristics

		Fever			All symptoms		
		n	Median (hours) 95% CI	P-value*	n	Median (hours) 95% CI	P-value*
Age (years)	<15	68	36.0	<0.0001	85	96.0	<0.0001
	15–<65	1871	36.0		2781	168.0	
	≥65	253	24.0		412	108.0	
Gender	Male	1079	36.0	0.0076	1563	144.0	<0.0001
	Female	1113	36.0		1715	192.0	
History of COVID-19 infection	No	1877	36.0	0.0716	2841	168.0	<0.0001
	Yes	230	48.0		304	96.0	
	Unknown	85	24.0		133	144.0	
History of vaccination	No	199	48.0	0.0010	271	144.0	<0.0001
	Yes	1599	36.0		2458	156.0	
	Unknown	394	36.0		549	180.0	
Presence of high-risk factors for COVID-19	No (SR)	1645	36.0	<0.0001	2424	168.0	0.0003
	Yes (HR)	547	36.0		854	144.0	
High-risk factors for COVID-19	Age >65 years	253	24.0		412	108.0	
	Malignant tumors	19	36.0		28	240.0	
	Chronic respiratory diseases	49	36.0		71	-	
	Chronic kidney disease	10	36.0		13	72.0	
	Diabetes mellitus	56	30.0		91	132.0	
	Hypertension	204	36.0		322	144.0	
	Dyslipidemia	146	24.0		230	144.0	
	Cardiovascular disease	38	30.0		60	168.0	
	Cerebrovascular disease	15	24.0		24	180.0	
	Obesity (BMI >30)	34	48.0		44	276.0	
	Smoking habit	83	36.0		137	132.0	
	Immunodeficiency**	10	30.0		15	216.0	
	Other	11	12.0		16	120.0	
Concomitant medications	No	279	36.0	0.1993	415	132.0	0.0210
	Yes	1913	36.0		2863	168.0	
Time from onset to start of administration (hours)	<72	2080	36.0	0.0099	3013	156.0	0.2778
	72-120	98	24.0		234	180.0	
	>120	5	60.0		14	-	
Severity of pre administration	Mild	2145	36.0	0.8652	3204	156.0	0.2067
	Moderate I	44	48.0		71	216.0	
	Moderate II	3	60.0		3	60.0	

*Generalized Wilcoxon Test. **Immunodeficiency after organ transplantation.

Figure 4: Time to Resolution in HR and SR Patients



Number of risk groups

Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13
SR	1645	1351	792	394	241	188	159	148	141	132	131	129	128	102
HR	547	424	220	107	54	36	26	23	23	22	22	22	21	15

Number of risk groups

Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13
SR	2424	2354	2257	2025	1764	1549	1370	1240	1146	1050	1005	953	907	613
HR	854	815	744	653	573	496	437	397	358	329	311	299	291	200

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Abbreviations: 3CL, 3C-like protease; ADR, adverse drug reaction; BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; CRF, case report form; HR, high risk; MHLW, Ministry of Health, Labour and Welfare; PMS, post marketing surveillance; QD, once daily; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SOC, system organ class; SR, standard risk.