Xocova - Real-World Evidence

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1. SUMMARY

Surveillance Study

Japanese Postmarketing Surveillance Study

- A multicenter, observational postmarketing surveillance study in Japan conducted by **Hayashi et al (2025)** evaluated the safety and efficacy of ensitrelvir (375 mg on Day 1 and 125 mg on Days 2 to 5) in clinical practice. In the final analysis, which enrolled 4155 patients from November 2022 to December 2023[1]
    - In the effectiveness analysis set (n=3638), median time to resolution of fever was 1.5 days and median time to resolution of all symptoms was 6.5 days
    - The most common adverse drug reactions (ADRs) in the safety analysis set (N=3760) were diarrhea (n=91), nausea (n=43), headache (n=42), vomiting (n=24), and rash (n=20)
    - A total of 14 (0.4%) patients were hospitalized, ten of whom had high-risk factors. There were two deaths, which were unrelated to ensitrelvir use or COVID-19 infection

Retrospective Studies

Retrospective Cohort Study in Nonhospitalized High-Risk Patients

- A retrospective database cohort study in Japan conducted by **Takazono et al (2024)** compared the outcomes of nonhospitalized patients with high risk of severe COVID-19 disease who received ensitrelvir to patients who received no antiviral treatment. High-risk patients treated with ensitrelvir had lower incidence of:[2]
    - All-cause hospitalization (0.494% vs 0.785%; risk ratio [RR], 0.629 [95% confidence interval (CI), 0.420-0.943]; risk difference [RD], −0.291 [95% CI, −0.494 to −0.088])
    - Respiratory and heart rate monitoring (0.143% vs 0.269%; RR, 0.531 [95% CI, 0.261-1.081]; RD, −0.126 [95% CI, −0.230 to −0.022])
    - Oxygen therapy (0.095% vs 0.149%; RR, 0.635 [95% CI, 0.258-1.563]; RD, −0.055 [95% CI, −0.141 to 0.032])

Retrospective Chart Review in Hospitalized Patients

- A single-center, retrospective chart review by **Yamato et al (2024)** assessed the outcomes of hospitalized, predominantly elderly patients with a range of comorbidities who were treated with ensitrelvir (375 mg on Day 1 and 125 mg on Days 2 to 5) at Rinku General Medical Center in Japan[3]
    - At final measurement, 78.1% (25/32) of patients had achieved viral clearance after 5 days of treatment, and 12.5% (4/32) experienced viral rebound without disease progression. All patients had clinical improvement at the end of ensitrelvir treatment. There was one death unrelated to COVID-19 or ensitrelvir use
    - In a subgroup analysis of patients (n=21) with persistent COVID-19 after ≥3 days of remdesivir treatment, 66.7% of patients had viral clearance after 5 days of ensitrelvir treatment and 9.5% experienced viral rebound without symptom rebound. All patients had clinical improvement at the end of ensitrelvir treatment

Retrospective Observational Comparative Study in Hospitalized Patients

- A single-center, retrospective observational study by **Yoshida et al (2024)** compared the outcomes of treatment with remdesivir (n=85), molnupiravir (n=44), or ensitrelvir (n=25) in hospitalized, predominantly elderly patients at Yoshida Hospital in Japan[4]
    - Ensitrelvir treatment resulted in lower viral antigen levels on Day 10 compared to remdesivir or molnupiravir and a higher antigen-negative conversion rate (40% vs 20% and 4.54%, respectively)
    - Duration of hospitalization was significantly shorter in patients treated with ensitrelvir compared to molnupiravir (11.04±0.212 vs 12.7±0.354 days; *P*=0.0013). Differences in hospitalization duration between ensitrelvir and remdesivir did not reach statistical significance (11.04±0.212 vs 12.11±0.369 days; *P*=0.1264)
    - Mean ± standard error of the mean [SEM] time for fever resolution was similar in patients treated with remdesivir (3.493±0.1784 days), molnupiravir (3.432±0.1958 days), and ensitrelvir (2.882±0.3417 days)

Retrospective Case Series of Ensitrelvir in Nonhospitalized Patients

- **Abe et al (2024)** conducted a retrospective case series in Japan evaluating real-world outcomes in symptomatic, vaccinated, nonhospitalized patients with mild-to-moderate COVID-19 treated with ensitrelvir between December 2022 and January 2023, with follow-up of up to 60 days; all patients were infected with the SARS-CoV-2 Omicron BA.5 variant, and symptom outcomes were descriptively compared with historical control data.[5]
    - Symptoms improved within 2 days in 33% of patients and within 3-6 days in an additional 33%; one patient had mild cough, and 5 patients had mild sore throat persisting beyond 6 days, with no symptom recurrence reported during follow-up.
    - Mean SARS-CoV-2 Ct values increased from 21.82 at symptom onset to 37.65 by Day 6, with Ct values >35 reported within 6 days in 10 patients and undetectable viral RNA by Day 9 in most patients; greater increases in Ct values between Day 0 and Day 3 were observed among patients who initiated treatment within 48 hours of symptom onset.
    - No increases in viral load based on Ct values, no newly emergent adverse events, no symptom recurrence, and no post-acute sequelae of COVID-19 were reported during the follow-up period.

Prospective Studies

Prospective Observational Cohort Study in Healthcare Workers

- A prospective observational cohort study in Japan by **Miyashita et al (2024)** evaluated the efficacy of ensitrelvir (n=206) or symptomatic treatment (n=427) for the treatment of cough due to COVID-19 in healthcare workers[6]
    - Various cough measures were evaluated using the Japanese Leicester Cough Questionnaire (J-LCQ), resulting in a significant difference in the J-LCQ scores between groups at all time points (3.17 on day 4, 3.24 on day 7, and 2.46 on day 14)

Prospective Cohort Study in Outpatients and Inpatients with COVID-19

- **Hibino et al. (2025)** conducted a large, prospective, nationwide Japanese cohort study evaluating oral antivirals' effect on post-COVID-19 condition (PCC) in outpatients.[7]
    - Outpatients aged ≥12 with symptomatic COVID-19 were followed, comparing those who received oral antivirals (ensitrelvir, nirmatrelvir/ritonavir, or molnupiravir) to those who did not.
    - The primary endpoint was PCC incidence (persistent fatigue, cough, dyspnea, smell disorder, or taste disorder at both Days 28 and 84). Unadjusted PCC incidence was 24.3% (530/2181) of the antiviral group vs 26.2% (1443/5518) of the no-antiviral group; when adjusted for baseline

characteristics, PCC incidence was 21.5% antiviral vs 25.1% no-antiviral and risk ratio for antivirals was 0.86 (95% CI: 0.78–0.93; *P*<0.001).

2. SURVEILLANCE STUDY

Japanese Post-Marketing Surveillance Study

Study Design

A multicenter, observational postmarketing surveillance study conducted by **Hayashi et al (2025)** evaluated the safety and effectiveness of ensitrelvir in real-world clinical practice in Japan from November 2022 to December 2023. The study included patients in both standard-risk (SR) and high-risk (HR) populations that had mild to moderate symptoms. Patients received once-daily oral treatment with ensitrelvir over 5 days with a 375 mg loading dose on Day 1 and 125 mg maintenance dose on Days 2 to 5.[1]

Patients were observed for 28 days after administration of ensitrelvir. Outcome measures included incidence of hospitalization/mortality, adverse events, and clinical symptoms (including body temperature) from the patient questionnaire. ADRs were defined as either adverse events or serious adverse events for which a causal relationship with the drug is suspected by either the reporting physician or the sponsor.[1]

Results

- There were 4155 patients enrolled in the final analysis, of which 3760 patients were in the safety analysis set and 3638 patients were in the effectiveness analysis set[1]
    - High-risk factors for COVID-19 disease (defined as age 65 and over, malignancy, chronic respiratory illness, chronic kidney disease, diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, cerebrovascular disease, obesity [BMI 30 kg/m^2 or more], smoking habit, and use of immunosuppressant/immunomodulatory drugs) were present in 25% (939/3760) and 24.8% (903/3638) of patients in the safety analysis set and effectiveness analysis set, respectively
- In the effectiveness analysis set, median time to resolution of fever (defined as the first time when body temperature of <37°C was maintained for ≥24 hours) was 1.5 days and median time to resolution of all symptoms was 6.5 days (defined as the first time when none of fever, systemic, respiratory, and gastrointestinal symptoms persisted for ≥24 hours) (**Table 1**)[1]
    - Median time to resolution of systemic, respiratory, and gastrointestinal symptoms was 60.0, 132.0, and 48.0 hours, respectively
    - Median time to resolution of fever was similar between SR (n=1645) and HR (n=547) subgroups (36.0 hours). Median time to resolution of all symptoms was 168.0 hours in SR patients (n=2424) and 144.0 hours in HR patients (n=854)
- In the safety analysis set, the incidence of ADRs was 7.2%. A total of 379 ADRs were reported, including 5 serious ADRs and 374 non-serious ADRs[1]
    - The 5 serious ADRs reported in 3 patients (generalized edema, headache, nausea, cold sweat, and vomiting) resolved within 3-5 days.
    - Most ADRs (n=348) occurred within 5 days of initiating ensitrelvir, with the highest number occurring on Day 2 (n=138).
    - The most frequently reported ADRs were diarrhea (n=91), nausea (n=43), headache (n=42), vomiting (n=24), and rash (n=20).

- The incidence of ADRs was 7.1% in SR subgroup and 7.6% in HR subgroup (P=0.6284).
- Outcomes of ADRs were recovered (including remission; n=344), not recovered (n=10), andunknown (n=25); no ADRs resulted in sequelae or death.
- During the observation period, hospitalization occurred in 14 patients (0.4%), including hospitalizations due to COVID-19 exacerbation (n=10) and other causes.
- Two patients (0.1%) died during the observation period; neither death was attributed to COVID-19 nor to ensitrelvir treatment.

Table 1. Time to Resolution of Fever and Symptoms (Effectiveness Analysis Set)[1]

	Fever[a] (n=2192)	All Symptoms[b] (n=3278)	Systemic Symptoms[c] (n=3001)	Respiratory Symptoms[d] (n=2945)	Gastrointestinal Symptoms[e] (n=284)
Median, hours (95% CI)	36.0 -*	156.0 (156.0, 168.0)	60.0 -*	132.0 (132.0, 144.0)	48.0 (36.0, 48.0)

Table adapted from Hayashi et al. *Japan Society of Chemotherapy.* 2025.
Abbreviations: CI, confidence interval.
[a]Resolution of fever was defined as the first time when body temperature of <37 ˚C was maintained for ≥24 h.
[b]Resolution of all symptoms was defined as the first time when none of fever, systemic, respiratory, and gastrointestinal symptoms persisted for ≥24 h.
[c]Resolution of systemic symptoms was defined as the first time when low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, taste disorder, and smell disorder was not observed for ≥24 h.
[d]Resolution of respiratory symptoms was defined as the first time when stuffy or runny nose, sore throat, cough, and shortness of breath was not observed for ≥24 h.
[e]Resolution of gastrointestinal symptoms was defined as the first time when nausea, vomiting, and diarrhoea was not observed for ≥24 h.
*The lower bound of the 95 % CI for the Kaplan-Meier estimate was above 50 % immediately before the median, and the upper bound of the 95 % CI was below 50 % immediately after the median; therefore, the 95 % CI was not estimated.

3. RETROSPECTIVE STUDIES

Retrospective Cohort Study in Nonhospitalized High-Risk Patients

Study Design

Takazono et al. (2024) conducted a retrospective cohort study which analyzed a large database of health insurance claims to assess real-world effectiveness of ensitrelvir in nonhospitalized patients in Japan. The outcomes of patients who received ensitrelvir between November 2022 and July 2023 (B.1.1.529 [Omicron] dominant period) were compared with patients who received no antiviral treatment. The primary analysis target population consisted of patients who were aged ≥18 years and had at least one risk factor for severe COVID-19 disease according to MHLW guidelines who could be tracked for 6 months before diagnosis with COVID-19 up to 1 month following that date. Risk factors for severe disease included age ≥65 years, malignancy, chronic pulmonary disease, chronic renal disease, diabetes, hypertensive disease, dyslipidemia, cardiovascular disease, cerebrovascular disease, morbid obesity, immunosuppressive disorders, and HIV/AIDS.[2]

The primary endpoint was all-cause hospitalization (starting on Days 2-28). Secondary endpoints included:[2]

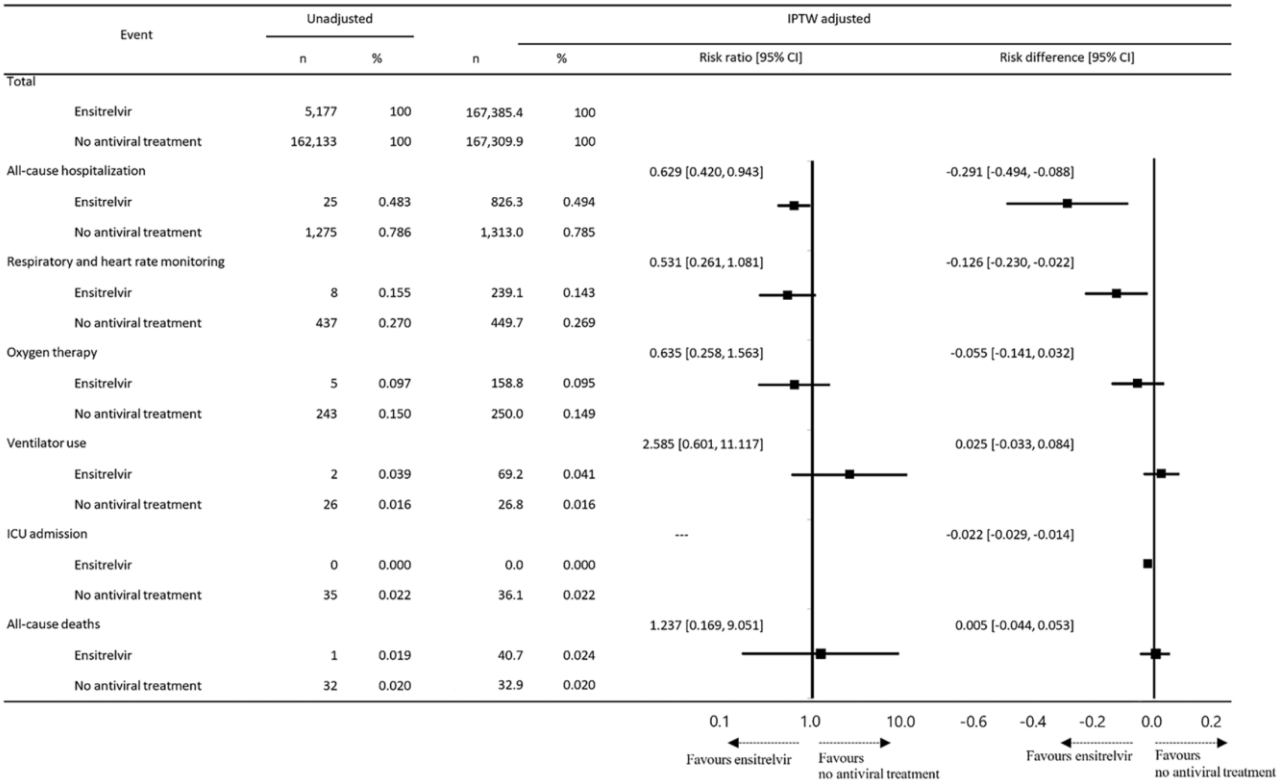
- Respiratory and heart rate monitoring (starting on Days 2-28)
- Oxygen therapy (starting on Days 2-28)
- Ventilator use (starting on Days 2-28)
- Intensive care unit (ICU) admission (starting on Days 2-28)
- All-cause death (within the following month)

Baseline demographic and clinical characteristics between the treatment groups were standardized by employing a propensity score, calculated through a logistic regression analysis in which covariates were selected based on their relevance to COVID-19 disease severity, and applying the inverse probability of treatment weighting (IPTW) method.[2]

Results

- A total of 167,310 eligible high-risk patients were included in the analysis, of which 5177 (3.1%) were treated with ensitrelvir and 162,133 (96.9%) did not receive antiviral treatment[2]
- Incidence of all-cause hospitalization (primary endpoint) was significantly lower in high-risk patients who received ensitrelvir compared with no antiviral treatment (0.494% vs 0.785%; RR, 0.629 [95% CI, 0.420-0.943]; RD, −0.291 [95% CI, −0.494 to −0.088]) (**Figure 1**)[2]
    - In the overall (N=666,865 [ensitrelvir n=20,735; no antiviral treatment n=646,130]) population, which included patients not at risk of severe COVID-19 disease, incidence of all-cause hospitalization was significantly lower in patients who received ensitrelvir compared with no antiviral treatment (0.287% vs 0.413%; RR, 0.696 [95% CI, 0.537-0.903]; RD, −0.125 [95% CI, −0.201 to −0.050])
    - In a post-hoc analysis in high-risk patients aged ≥65 years, incidence of all-cause hospitalization was lower in patients who received ensitrelvir compared with no antiviral treatment (0% [0/380] vs 1.298% [199/15,336]; *P*=0.0166 using Fisher's exact test)
- Incidence of respiratory and heart rate monitoring (secondary endpoint) was lower in high-risk patients who received ensitrelvir compared with no antiviral treatment (0.143% vs 0.269%; RR, 0.531 [95% CI, 0.261-1.081]; RD, −0.126 [95% CI, −0.230 to −0.022]) (**Figure 1**)[2]
- Incidence of oxygen therapy (secondary endpoint) was lower in high-risk patients who received ensitrelvir compared with no antiviral treatment (0.095% vs 0.149%; RR, 0.635 [95% CI, 0.258-1.563]; RD, −0.055 [95% CI, −0.141 to 0.032]) (**Figure 1**)[2]
- Other secondary endpoint events (ie, ventilator use, ICU admission, and all-cause death) were difficult to assess due to the limited number of unadjusted incidences (0-2 cases) (**Figure 1**)[2]
- Cumulative incidence of all-cause hospitalization was suppressed up to Day 28 in high-risk patients who received ensitrelvir compared with no antiviral treatment; the 95% CIs of each group did not overlap from Day 2 to Day 12 (**Figure 2**)[2]

Figure 1. Incidence and Risk of Events[a] in High-Risk Patients Who Received Ensitrelvir Compared With No Antiviral Treatment[2]

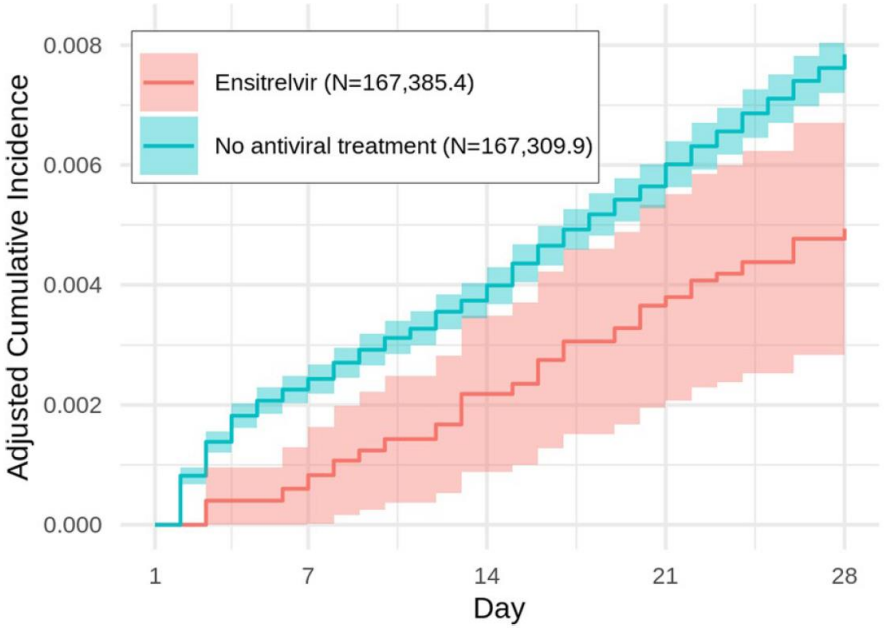


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Takazono T et al. *Infect Dis Ther*. 2024;13(8):1821-1833. doi: 10.1007/s40121-024-01010-4

Abbreviations: CI, confidence interval; ICU, intensive care unit; IPTW, inverse probability of treatment weighting.

[a]Incidence, risk ratio, and risk difference were adjusted by inverse probability of treatment weighting.

Figure 2. Cumulative Incidence[a] of All-Cause Hospitalization in High-Risk Patients Who Received Ensitrelvir Compared With No Antiviral Treatment[2]



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Takazono T et al. *Infect Dis Ther*. 2024;13(8):1821-1833. doi: 10.1007/s40121-024-01010-4
[a]Incidence was adjusted by inverse probability of treatment weighting.

Retrospective Chart Review in Hospitalized Patients

Study Design

Yamato et al. (2024) conducted a single-center, retrospective chart review assessed the outcomes of hospitalized patients treated with ensitrelvir in a real-world setting in the Rinku General Medical Center in Izumisano, Japan between November 2022 and April 2023. Severity of COVID-19 disease prior to ensitrelvir treatment was classified according to MHLW guidelines in Japan.[3]

Patients received daily oral treatment with ensitrelvir over 5 days with a 375 mg loading dose on Day 1 and 125 mg maintenance dose on Days 2 to 5. Antiviral activity as indicated by polymerase chain reaction or antigen testing and investigator assessments of clinical improvement were used to assess effectiveness.[3]

Results

- A total of 32 patients were included in the analysis, all of whom received 5 days of ensitrelvir treatment[3]
    - Average age of the study population was 73.5 years and most patients (78.1%; 25/32) were aged ≥65 years
    - Comorbidities included hypertension in 78.1% (25/32), chronic kidney disease in 25% (8/32), hemodialysis in 22.6% (7/32), and malignant tumors in 28.1% (9/32) of patients
    - Severity of COVID-19 disease at the start of treatment was mild in 65.6% (21/32), moderate I in 12.5% (4/32), and moderate II in 21.9% (7/32) of patients
- Antiviral treatment had previously been administered to 93.8% (30/32) of patients, the most common of which was remdesivir in 87.5% (28/32) of patients[3]

    - Remdesivir monotherapy was given to 21.9% (7/32) of patients, and remdesivir with casirivimab/imdevimab was given to 56.3% (18/32) of patients
    - Remdesivir therapy was administered for ≥3 days in 75% (21/28) of patients (mean, 6.6 days; range, 3-22 days)
- By Day 6, 56.3% (18/32) of patients had viral clearance (defined as an antigen level of <89.73 pg/mL) and 15.6% (5/32) of patients had antigen level below the lower limit of quantification (LLoQ, <1.34 pg/mL). At final measurement, 78.1% (25/32) of patients had achieved viral clearance[3]
- Viral rebound occurred in 12.5% (4/32) of patients; none of these patients had disease progression[3]
- Virology outcome data are presented in **Table 2**[3]
- All patients experienced clinical improvement as assessed by the investigator at the end of ensitrelvir treatment (Day 5). No patients discontinued treatment, there were no treatment-related adverse events (TRAEs), no patients progressed to severe disease, none were admitted to the ICU, and no treatment-related deaths occurred. A total of 16 patients were discharged from hospital by Day 14, and 15 patients were discharged from Day 15 (range, Day 15-78)[3]
    - One patient death (Day 55) occurred due to anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis and was determined to be unrelated to COVID-19

Subgroup Analysis of Patients With Persistent COVID-19 After Remdesivir Treatment

- A subgroup analysis was performed in 21 patients who were administered remdesivir for ≥3 days before switching to ensitrelvir[3,8]
    - Comorbidities included malignant tumors in 33.3% (7/21), diabetes mellitus in 28.6% (6/21), and renal failure in 19% (4/21) of patients[8]
    - Severity of COVID-19 disease in this subgroup of patients was mild in 81% (17/21), moderate I in 9.5% (2/21), and moderate II in 9.5% (2/21) of patients (COVID-19 disease severity criteria is according to Japanese guidelines and takes into account blood oxygen saturation and clinical condition)[8]
- By Day 5, 66.7% of patients had viral clearance[8]
- Viral rebound occurred in 9.5% (2/21) of patients; neither of these patients had rebound of symptoms or received additional antiviral therapy[8]
- Virology outcome data for all study patients, including those in the subgroup analysis, are presented in **Table 2**. All patients experienced clinical improvement as assessed by the investigator at the end of ensitrelvir treatment (Day 5). There were no TRAEs, no patients progressed to severe disease or were admitted to the ICU through Day 28, and no treatment-related deaths occurred. A total of 20 patients were discharged from hospital by Day 77[3,8]

Table 2. Virology Outcomes in a Single-Center Chart Review in Hospitalized Patients[3]

Patient	Underlying Diseases	Prior SARS-CoV-2 Treatment	Days From Start of Ensitrelvir Administration															Treatment Outcome by Day 6[a]	Treatment Outcome at Final Measurement[a]	Viral Rebound
			Day -1 and Day 0	Day 1	Day 2	Day 3	Day 4	Day 5 (EOT)	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14			
			Quantitative Viral Antigen (pg/mL)																	
1[b]	Esophageal cancer, HTN	Remdesivir[c]	5000	5000		571.44			21.75	18.67	9.43	2.81	0.06	4.79	0.01	0.10		Viral Clearance	Viral Clearance	
2[b]	T2D, chronic atrial fibrillation, chronic subdural hematoma, hydrocephalus, HTN	Remdesivir[c] Molnupiravir	3429.86	235.08	10.35	1.06	0.95											Viral Clearance	Viral Clearance	
3	DM, HTN	Remdesivir	5000		5000			113.88		0.01									Viral Clearance	
4[b]	Exertional angina pectoris, lung cancer, cerebral infarction, dyslipidema, HTN	Remdesivir[c]	255.09	5000			36.55		25.72	1.61	0.30	0.01						Viral Clearance	Viral Clearance	
5[b]	Unstable angina pectoris, organizing pneumonia, CHF, CKD, hypothyroidism, DM	Remdesivir[c] Casirivimab/ imdevimab	5000	5000		5000	5000	5000				1233.07	494.52		254.76	8.67	44.64		Viral Clearance	
6[b]	Traumatic subarachnoid hemorrhage, heart failure, asymptomatic myocardial ischemia, cerebral contusion, HTN	Remdesivir[c]	5000	5000		1394.43		39.12	43.49	46.30		28.65	0.83	0.89				Viral Clearance	Viral Clearance	
7[b]	Liver metastasis from cancer of the sigmoid colon, breast cancer	Remdesivir[c] Casirivimab/ imdevimab		5000		1676.19					27.73								Viral Clearance	
8[b]	Osteoarthritis	Remdesivir[c] Casirivimab/ imdevimab	5000	2728.74	3736.13	142.46		13.50	0.30									Viral Clearance	Viral Clearance	
9[b,d]	AAV, CKD, DM, HTN	Remdesivir[c] Molnupiravir Tixagevimab/ cilgavimab	5000	5000		2587.88		4.77	1210.73		5000	5000	5000							Viral Rebound (at Day 6)
10[e]	Recurrent FL, post-HSCT, CKD, HTN, hemodialysis	Molnupiravir		1227.48		182.59	200.71													
11[b]	Asthma, cerebral infarction, HTN	Remdesivir[c] Casirivimab/ imdevimab	5000	5000	5000		1086.83	4091.46			16.27	11.83	3.76	1.73	0.01				Viral Clearance	
12[b]	atrial fibrillation, malignant melanoma, HTN	Remdesivir[c] Casirivimab/ imdevimab	5000			1.04	0.11											Viral Clearance	Viral Clearance	
13	Bronchiectasis, previous history of TB, HTN	Remdesivir	5000		5000			0.75										Viral Clearance	Viral Clearance	
14[b]	Pulmonary metastasis from cancer of the sigmoid colon, suspected catheter-related BSI, chronic gastritis, angina pectoris, dyslipidemia, T2D	Remdesivir[c] Casirivimab/ imdevimab	5000	5000			87.07	25.39	8.50	6.81	7.94	94.59	0.14	2.29	0.05	1.73	0.57	Viral Clearance	Viral Clearance	Viral Rebound (at Day 9)
15	CKD, abdominal aortic aneurysm, HTN	None		5000			5000		665.36		352.02			8.56	1.30	4.21	0.01		Viral Clearance	
16[b]	Valve disorders, gastric ulceration, dyslipidemia, HTN	Remdesivir[c] Casirivimab/ imdevimab	5000	5000		53.22			2.10	0.62								Viral Clearance	Viral Clearance	
17[b]	CHF, DM, cerebral infarction, pyelonephritis, ischemic heart disease	Remdesivir[c] Casirivimab/ imdevimab	5000	5000			537.86		84.40	7.89	43.06	3.56	2.08	0.01	0.06			Viral Clearance	Viral Clearance	
18[b]	Depression, upper gastrointestinal bleeding, HTN	Remdesivir[c] Casirivimab/ imdevimab	4328.71	5000		5000			2468.05		5000		3637.23			114.93	12.95		Viral Clearance	
19	CKD, DM, HTN, hemodialysis	Remdesivir	5000			344.33														
20	Kidney stone disease, acute myelogenous leukemia, post-HSCT, kidney injury, HTN	None		5000[f]			5000	97.79		344.12	5000				4664.69					
21[b]	Candidemia, asthma, colorectal cancer, peritoneal metastases, dyslipidemia, HTN	Remdesivir[c] Casirivimab/ imdevimab	1727.71	2393.09		1354.45			2.51	1.61	1.05	2.59	1.03	0.01				Viral Clearance	Viral Clearance	
22[b]	Asthma, bronchitis, liver failure, cerebral infarction, renal failure	Remdesivir[c]	5000		5000			7.42	8.09	1.97	4.39	0.71	2.78	0.67	1.72	0.08	0.24	Viral Clearance	Viral Clearance	
23	IgAN, congestive heart failure, CKD, HTN, hemodialysis	Remdesivir Molnupiravir		88.50	2.89	0.09												Viral Clearance	Viral Clearance	
24[b]	AAV, UTI, dyslipidemia, HTN	Remdesivir[c] Casirivimab/ imdevimab	5000	5000			223.72		2.37	8.01	5.99	41.02		1.23	0.01					
25	T2D, chronic renal failure, angina pectoris, hypothyroidism, post-cerebral infarction status, hemodialysis	Remdesivir Casirivimab/ imdevimab	5000		267.69		38.25				84.65	301			38.23	2.40	8.13	Viral Clearance	Viral Clearance	Viral Rebound (at Day 9)
26[b]	Benign prostatic hyperplasia, gastric cancer, cholelithiasis, cerebral infarction, RA	Remdesivir[c] Casirivimab/ imdevimab	1305.00	5000			1021.42				19.95	1.89	0.57	0.24					Viral Clearance	
27[b]	atrial fibrillation, chronic hepatitis B, CHF, chronic renal failure, pyelonephritis, HTN	Remdesivir[c] Casirivimab/ imdevimab	5000			1767.49	274.52	245.85	147.76	111.48			3.44	6.81	1.92	1.15	0.56		Viral Clearance	
28	Acute renal failure, empyema, HTN, hemodialysis	Casirivimab/ imdevimab		PCR Ct 16.6	5000			168.50			86.65	1.39	14.97	6.59	496.04					Viral Rebound[g] (at Day 12)
29	Post-CABG, CKD, DM, dyslipidemia, HTN, hemodialysis	Remdesivir Casirivimab/ imdevimab	1635.16		115.32		1463.78		41.1									Viral Clearance	Viral Clearance	
30	Lacunar infarction, CKD, DM, HTM, hemodialysis	Remdesivir Casirivimab/ imdevimab	5000		1125.20															
31[b]	Organizing pneumonia, chronic obstructive, pulmonary disease, cerebral infarction, HTN, T2D	Remdesivir[c] Casirivimab/ imdevimab	5000	5000		5000		1330.12												
32[b]	Dyslipidemia, cerebral infarction, HTN	Remdesivir[c] Casirivimab/ imdevimab	5000	5000		1292.38			63.29		9.86	11.31	1.56	0.01				Viral Clearance	Viral Clearance	

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Shading indicates days the patient was hospitalized.

Abbreviations: AAV, ANCA-associated vasculitis; BSI, bloodstream infection; ANCA, anti-neutrophil cytoplasmic antibody; CABG, coronary artery bypass graft; CHF, chronic heart failure; CKD, chronic kidney disease; Ct, cycle threshold; DM, diabetes mellitus; EOT, end of treatment; FL, follicular lymphoma; HSCT, hematopoietic stem cell transplant; HTN, hypertension; IgAN, immunoglobulin A nephropathy; PCR, polymerase chain reaction; RA, rheumatoid arthritis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T2D, Type 2 diabetes; TB, tuberculosis; UTI, urinary tract infection.
[a]Viral clearance defined as an antigen level of <89.73 pg/mL; viral rebound defined as an increase of antigen level of >89.73 pg/mL after viral clearance. [b]Patient was included in the subgroup analysis. [c]Patient received ≥3 days of remdesivir. [d]Patient received rituximab at Day -48. [e]Patient received rituximab at Day -15. [f]PCR positive at Day 1. [g]Viral clearance documented on Day 15 and Day 16.

Retrospective Observational Comparative Study in Hospitalized Patients

Study Design

Yoshida et al. (2024) conducted a retrospective observational study which used real-world data from electronic health records and patient follow-ups to compare the effectiveness of three different antiviral drugs in patients who were diagnosed with COVID-19 and required hospitalization. Remdesivir, molnupiravir, or ensitrelvir were selected by the attending physician and administered to patients postadmission to Yoshida Hospital in Asahikawa City, Japan between July 1, 2022 to September 15, 2023.[4]

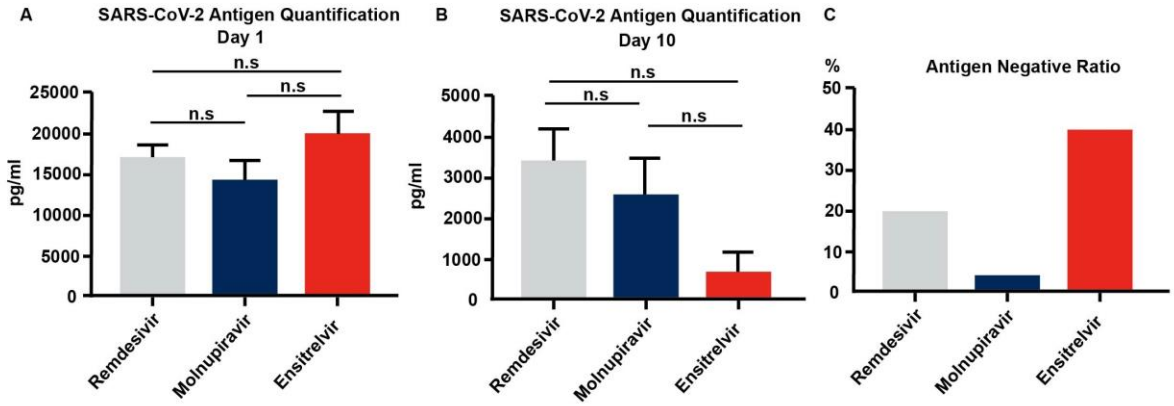
Outcomes were assessed by measuring SARS-CoV-2 antigen levels, duration of hospitalization, and time for fever resolution.[4]

Results

- The study included 154 patients, of whom 85 received remdesivir, 44 received molnupiravir, and 25 received ensitrelvir[4]
    - Due to many of the patients being referred from chronic care facilities and nursing homes, average age of the study population was high at 83.7 (range, 53-104) years
- On Day 10 of antiviral treatment, viral antigen levels were lower in patients treated with ensitrelvir (antigen level not reported) compared with remdesivir (3383±770.7 pg/mL; *P*=0.0662) or molnupiravir (2587±884.4 pg/mL; *P*=0.1275), although the differences did not reach statistical significance (**Figures 3A and 3B**)[4]
- Antigen-negative conversion rate after 10 days of antiviral treatment was highest for patients treated with ensitrelvir (40%; 10/25) compared to remdesivir (20%; 17/85) and molnupiravir (4.54%; 2/44), indicating a more rapid viral clearance with ensitrelvir (**Figure 3C**)[4]
- Viral antigen levels surged from admission to Day 10 of treatment in all treatment groups; resurgence rates were lowest for patients treated with ensitrelvir (8%; 2/25) compared to remdesivir (22.3%; 19/85) and molnupiravir (20.4%; 9/44) (**Figure 4**)[4]
- Duration of hospitalization was significantly shorter in patients treated with ensitrelvir compared to molnupiravir (11.04±0.212 vs 12.7±0.354 days; *P*=0.0013). No significant differences in hospitalization duration were observed between ensitrelvir and remdesivir (11.04±0.212 vs 12.11±0.369; *P*=0.1264) or remdesivir and molnupiravir (*P*=0.2982) (**Figure 5A**)[4]
- Patients were classified into two categories based on whether viral antigen levels decreased from admission to Day 10 after treatment (Down group; n=124) or increased (Up group; n=30). Average duration of hospitalization was significantly shorter in the Down group compared to the Up group (11.57 days vs 14.3 days, respectively; *P*<0.0001) (**Figure 5B**)[4]
- Fever exceeding 37 °C was present at admission in 78.8% (67/85), 80.4% (37/46), and 68% (17/25), of patients treated with remdesivir, molnupiravir, and ensitrelvir, respectively. Mean ± SEM time for fever at admission to decrease to below 37 °C was not statistically different between patients treated

with remdesivir (3.493±0.1784 days), molnupiravir (3.432±0.1958 days), and ensitrelvir (2.882±0.3417 days)[4]

Figure 3. SARS-CoV-2 Antigen Quantification (A; B) and Antigen-Negative Conversion (C) in Patients Treated with Remdesivir, Molnupiravir, or Ensitrelvir[4]

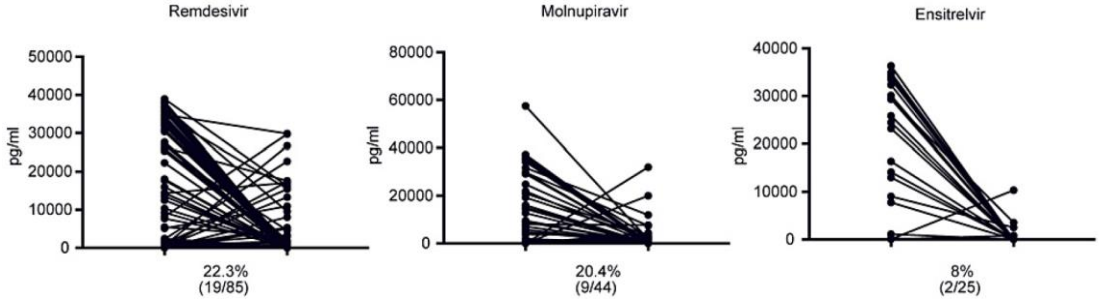


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Statistical significance was assessed using an unpaired two-tailed Student's t-test and one-way analysis of variance, followed by the Tukey post-hoc test. A *P*-value of ≥0.05 was n.s. Error bars represent mean ± SEM.

Abbreviations: n.s., not significant; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SEM, standard error of the mean.

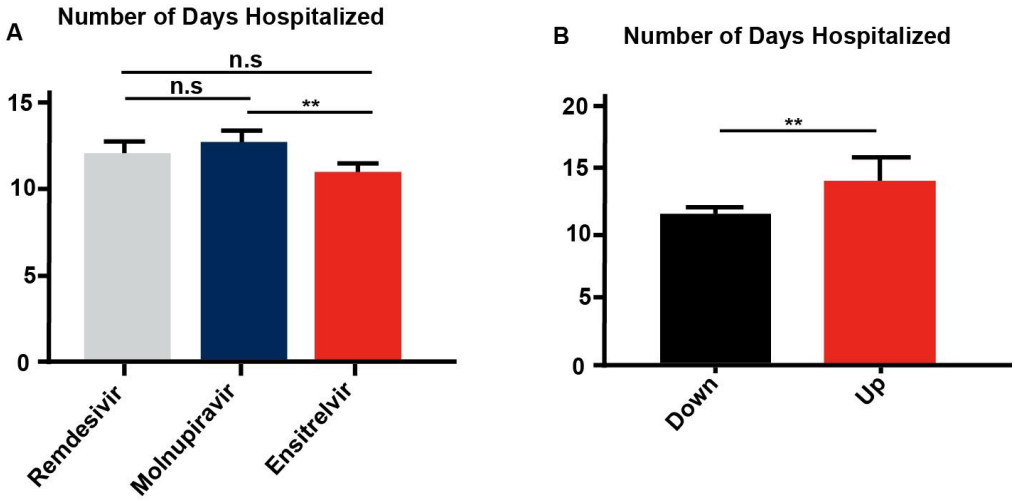
Figure 4. SARS-CoV-2 Antigen Resurgence Rates From Admission to Day 10 of Treatment with Remdesivir, Molnupiravir, or Ensitrelvir[4]



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Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Figure 5. Duration of Hospitalization (A) in Patients Treated with Remdesivir, Molnupiravir, or Ensitrelvir and (B) in the SARS-CoV-2 Antigen Down and Up Groups[4]



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Statistical significance was assessed using an unpaired two-tailed Student's t-test and one-way analysis of variance, followed by the Tukey post-hoc test. A *P*-value of <0.05 was considered statistically significant and a *P*-value of ≥0.05 was n.s. Asterisks indicate significance, with ** representing *P*<0.005. Error bars represent mean ± SEM.
Abbreviations: n.s., not significant; SEM, standard error of the mean.

Retrospective Case Series of Ensitrelvir in Nonhospitalized Patients

Study Design

Abe et al. (2024) conducted a retrospective case series in Japan evaluating real-world outcomes in symptomatic, vaccinated, outpatients with mild-to-moderate COVID-19 treated with ensitrelvir between December 1, 2022, and January 31, 2023. The study population comprised 18 patients with a median age of 39.5 years (range: 26-56 years) who were treated with a 5-day oral regimen of ensitrelvir consisting of 3 tablets (each tablet 125 mg) every 8 hours on Day 1, followed by 1 tablet daily from Day 2-5.[5]

Sore throat was the most commonly reported presenting symptom, and mild fever was reported by most patients. Underlying conditions were reported in a small number of patients, including chronic sinusitis, allergic rhinitis, and bronchial asthma. All patients were infected with the SARS-CoV-2 Omicron BA.5 variant, as confirmed through Sanger sequencing. Patients were followed for up to 60 days after treatment initiation to assess symptom course, virologic outcomes, adverse events, and post-acute sequelae of COVID-19 (PASC); symptom outcomes were descriptively compared with historical control data.[5]

Results

Efficacy

- Clinical Outcomes
    - Symptoms such as sore throat and mild fever improved after initiation of ensitrelvir treatment. Symptoms improved within 2 days in 33% of patients, and between 3 and 6 days in an additional 33% of patients.[5]

    - One patient had mild cough, and 5 patients had mild sore throat persisting beyond 6 days.[5]
- Virologic Outcomes
    - Mean cycle threshold (Ct) values increased from 21.82 at symptom onset to 37.65 by Day 6.[5]
    - Ten patients had Ct values >35 within 6 days of treatment initiation.[5]
    - SARS-CoV-2 RNA became undetectable by Day 9 in most patients.[5]
    - Greater increases in Ct values between Day 0 and Day 3 were observed in patients who initiated treatment within 48 hours of symptom onset.[5]
- Symptom outcomes were descriptively compared with historical control data. In untreated outpatients with mild symptomatic Omicron variant infection, the median time to symptom resolution was reported as 8.5 days (95% CI: 6-11 days; data not shown). In the ensitrelvir-treated cohort, the majority of patients (>66%) had symptom resolution reported within a median of 1.4 days (95% CI: 1-6 days).[5]

Safety

- No increases in viral load, as assessed by Ct values, were observed during follow-up.[5]
- No patients experienced symptom recurrence or newly emergent adverse events.[5]
- No signs or symptoms of post-acute sequelae of COVID-19 were reported during the follow-up period.[5]

4. PROSPECTIVE STUDIES

Prospective Observational Cohort Study in Healthcare Workers

Study Design

Miyashita et al. (2024) conducted a prospective observational cohort study in Japan to evaluate the efficacy of ensitrelvir (n=206) or symptomatic treatment (n=427) for the treatment of cough due to COVID-19 in healthcare workers. Participants included employees of five hospital-associated facilities with PCR-confirmed COVID-19 Omicron variant and cough symptoms between November 2022 and September 2023. Patients in the ensitrelvir arm took 375 mg on day 1 followed by 125 mg on days 2-5, and those in the symptomatic treatment arm took treatments including acetaminophen 600 mg, dextromethorphan hydrobromide hydrate 45 mg, and ambroxol hydrochloride 45 mg for 5 days.[6]

Cough severity, frequency, and cough-specific quality of life (QOL) were measured by the Japanese Leicester Cough Questionnaire (J-LCQ), which consisted of 19 questions with a 7-point Likert scale and a total score ranging from 3 to 21 where higher scores indicate better QOL.[6]

Results

Baseline characteristics were similar between groups, including comorbidities, time from onset to administration, and COVID-19 vaccination.[6]

- The population was 73.8% female (ensitrelvir group n=161; symptomatic treatment group n=306); the mean age was 35 years in the ensitrelvir group and 39.5 years in the symptomatic treatment group
- The baseline J-LCQ score was 10.55 (±2.85) and 11.01 (±2.55) for the ensitrelvir and symptomatic treatment groups, respectively

- Most patients started treatment between 24-48 hours after onset (49.5% [n=102] in ensitrelvir group and 45.2% [n=193] in symptomatic group)
- Most of the ensitrelvir and symptomatic arm populations received at least one vaccination (92.2% [n=190] and 95.1% [n=406], respectively)

A significant difference in the Leicester Cough Questionnaire scores between groups was demonstrated at all time points (3.17 on day 4, 3.24 on day 7, and 2.46 on day 14), see **Table 3**.[6]

Table 3. Change from Baseline to Each Administration Time in J-LCQ score[6]

Administration Time		Ensitrelvir (N=206)	Symptomatic Treatment (N=427)
Day 4	Score Change [95% CI]	5.31 [4.95, 5.68]	2.14 [1.82, 2.47]
	Difference from symptomatic treatment [95% CI]	Not applicable	3.17 [2.90, 3.44]
Day 7	Score Change [95% CI]	8.38 [8.00, 8.76]	5.14 [4.81, 5.47]
	Difference from symptomatic treatment [95% CI]	Not applicable	3.24 [2.94, 3.54]
Day 14	Score Change [95% CI]	10.04 [9.67, 10.40]	7.58 [7.25, 7.90]
	Difference from symptomatic treatment [95% CI]	Not applicable	2.46 [2.19, 2.73]

Adapted from Miyashita et al. 2024.
Abbreviations: CI, confidence interval; J-LCQ, Japanese Leicester Cough Questionnaire.

Statistical analyses were conducted by age, gender, cough intensity, presence of comorbidities, timing of drug initiation, and number of vaccinations. In all subgroups, the ensitrelvir group had a significantly improved J-LCQ score compared to the symptomatic treatment group.[6]

Prospective Cohort Study in Outpatients and Inpatients with COVID-19

The ANCHOR-01 study was a prospective, multi-institutional, nationwide registry-based cohort study conducted in Japan to evaluate the impact of oral antivirals on PCC in outpatients, conducted by **Hibino et al (2025)**.[7]

Methods

- Outpatients aged 12 years and older with confirmed symptomatic SARS-CoV-2 infection were enrolled between February and October 2024 and followed until January 2025. Patients were divided into two groups: those who received oral antivirals (ensitrelvir, nirmatrelvir/ritonavir, or molnupiravir) and those who did not receive oral antivirals, with treatment decisions aligned to national COVID-19 guidelines. Patient-reported outcomes related to PCC were collected via electronic questionnaires on Days 28 and 84.[7]
- The primary endpoint was the incidence of PCC, defined as the persistence of any of five symptoms (fatigue, cough, dyspnea or respiratory distress, smell disorder, taste disorder) on both Days 28 and 84, excluding symptoms not attributed to COVID-19. Statistical analyses included risk ratios (RRs)

and risk differences (estimated using modified Poisson and least squares regression models), adjusted for baseline characteristics.[7]

Results

Generally, baseline characteristics were balanced between groups, but the study population had more underlying comorbidities antiviral group had a higher median age (58.0 years vs 45.0 years) compared to the no-antiviral group.[7]

Efficacy

- In the unadjusted analysis, 1443/5518 patients (26.2%) in the no-antiviral group developed PCC, compared with 530/2181 patients (24.3%) in the antiviral group[7]
- After adjusting for covariates, PCC risk was found to be significantly lower among those who received antivirals (21.5% with antivirals vs. 25.1% with no-antivirals, with a risk ratio of 0.86 (95% confidence interval: 0.78–0.93; *P* <0.001) and a risk difference of -4.14 percentage points (95% CI: -6.34 to -1.94; *P* <0.001)[7]
- When analyzed by specific antiviral and adjusting for covariates, ensitrelvir (21.7%; RR 0.86; 95% CI 0.79–0.95) and molnupiravir (20.4%: RR 0.81; 95% CI 0.67-0.98) notably reduced the incidence of PCC compared to the no-antiviral group (25.1%) (**Table 4**)[7]
- The prevalence of individual symptoms showed that the risks of smell and taste disorders were significantly reduced in the antiviral group (**Table 5**), while cough and fatigue exhibited a trend toward reduction.[7]
- Risk reduction of PCC seen in subgroups across all ages, regardless of risk factors for severe disease. Although no adjustment for multiplicity was performed, therefore the 95% Cls are descriptive only and should not be interpreted as formal hypothesis tests (**Figure 6**).[7]

Table 4. Unadjusted and Adjusted Incidence of PCC According to Antiviral Treatments[7]

Treatment Group	PCC Incidence			Adjusted RR (95% CI)
	Adjusted n/N	Unadjusted (%)	Adjusted (%)	
No-antiviral	**1443/5518**	**26.2**	**25.1**	**Reference**
Antiviral overall	**530/2181**	**24.3**	**21.5**	**0.86 (0.78–0.93)***
Ensitrelvir	**412/1698**	**24.3**	**21.7**	**0.86 (0.79–0.95)***
Nirmatrelvir	**25/98**	**25.5**	**22.2**	**0.88 (0.63–1.24)**
Molnupiravir	**93/385**	**24.2**	**20.4**	**0.81 (0.67–0.98)***

Adapted from Hibino et al. 2025. Poster presented at AVG and IMRP. 2025.
Abbreviations: PCC, post-COVID-19 condition; RR, risk ratio; CI, confidence interval.
***P<0.05.**

Table 5. Incidence of Five Prespecified PCC Symptoms Persisting from Day 28 to 84 in Patients without Antivirals, and their RR in the Antiviral versus No-Antiviral Groups[7]

Symptom	Frequency of PCC Unadjusted %(n/N)	Adjusted RR (95% CI)
Cough	15.3 (843/5518)	0.89 (0.78-1.00)
Dyspnea	3.7 (206/5518)	0.99 (0.77-1.28)
Fatigue	13.0 (715/5518)	0.92 (0.80 – 1.05)
Smell Disorder	5.3 (292/5518)	0.43 (0.32-0.58)*
Taste Disorder	4.6 (251/5518)	0.59 (0.45-0.78)*

Adapted from Hibino et al. 2025. Poster presented at AVG and IMRP. 2025.
Abbreviations: PCC, post-COVID-19 condition; RR, risk ratio; CI, confidence interval.
***P<0.05.**

Figure 6. Incidence of PCC According to Prespecified Subgroups[7]

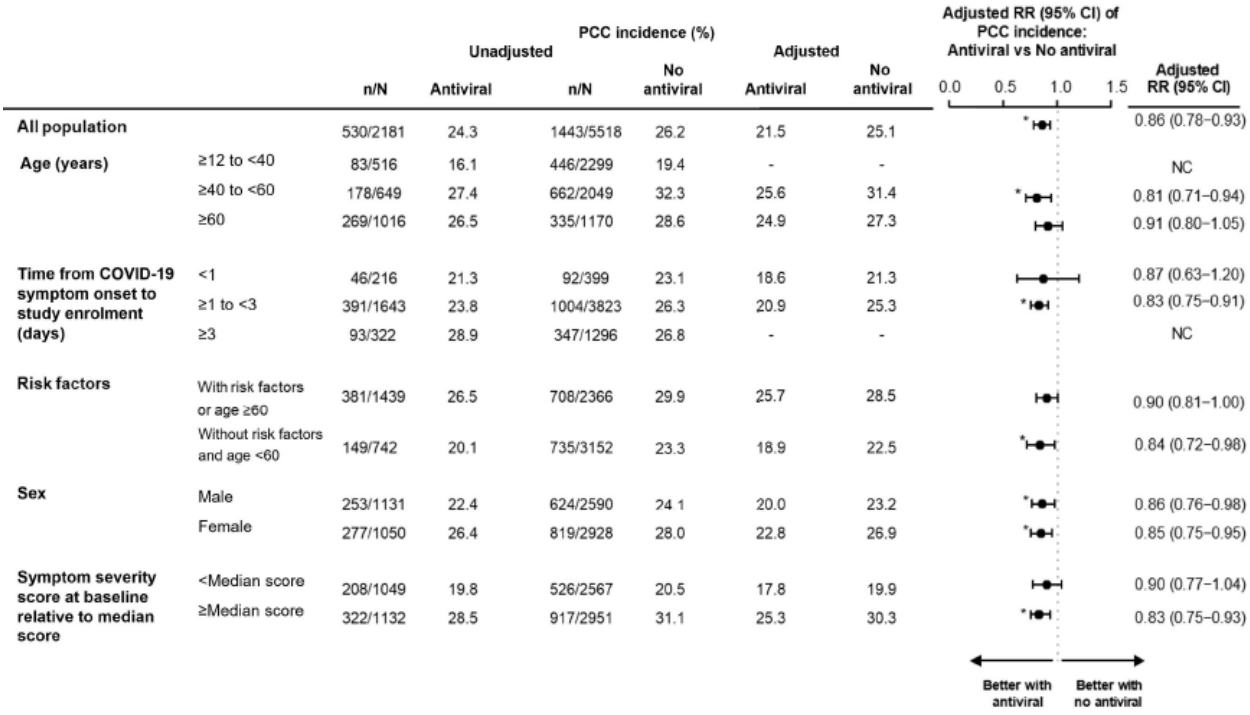


Figure adopted from Hibino et al. Poster presented at AVG and IMRP. 2025.
No adjustment for multiplicity was performed; hence, the 95% Cls are descriptive only and should not be interpreted as formal hypothesis tests.
Abbreviations: PCC, post-COVID-19 condition; RR, risk ratio; CI, confidence interval.
*P<0.05.

5. RELEVANT PRESCRIBING INFORMATION

INDICATIONS AND USAGE

XOCOVA is indicated for post-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and adolescents 12 years of age and older following contact with an individual who has COVID-19.[9]

CONTRAINDICATIONS

XOCOVA is contraindicated in patients with a history of clinically significant hypersensitivity reactions to ensitrelvir or any other components of the product.[9]

XOCOVA is contraindicated in patients taking drugs that are:

- Primarily metabolized by CYP3A for which elevated concentrations may be associated with serious and/or life-threatening reactions and
- Strong CYP3A inducers because they may significantly reduce ensitrelvir plasma concentrations, leading to the potential loss of virologic response.[9]

Please read the attached Xocova **Full Prescribing Information**. The use of Xocova in any manner other than as described in the Full Prescribing Information approved by the U.S. Food and Drug Administration (FDA) is not recommended.

6. LITERATURE SEARCH

As of April 2026, a computerized search of the published medical literature using internal and external databases (ie, Medline® and Embase®) has identified additional relevant references regarding ensitrelvir and real-world evidence. For your review, these references are listed in the bibliography that follows:

Alshukairi AN, Al-Qahtani AA, Obeid DA, et al. Molecular epidemiology of SARS-CoV-2 and clinical manifestations among organ transplant recipients with COVID-19. Viruses. 2023;16(1):25.

Jung S, Yagi Y, Fukushima K, et al. Successful dual antiviral therapy with remdesivir and ensitrelvir in a case of prolonged COVID-19 following B-cell depleting immunotherapy for malignant lymphoma. IDCases. 2023;34:e01890.

Sayan M, Arikan A, Sanlidag E. Molecular epidemiology of SARS-CoV-2 omicron sub-lineages isolated from Turkish patients infected with COVID-19. Viruses. 2023;15(5):1066. [Web Link]

Seki M, Mitsutake K, Shimizu A, et al. Ensitrelvir improved SARS-CoV-2 viral titers of COVID-19 patients refractory to remdesivir: viral titers decreased by ensitrelvir rather than remdesivir in COVID-19 patients. World J Clin Med Res. 2023;3(1):27-31.

Doi A, Ota M, Saito M, et al. Sporadic occurrence of ensitrelvir-resistant SARS-CoV-2, Japan. Emerg Infect Dis. 2024;30(6):1289-1291.

Furuya C, Yasuda H, Hiki M, et al. Case report: ensitrelvir for treatment of persistent COVID-19 in lymphoma patients: a report of two cases. Front Immunol. 2024;15:1287300.

Naganawa H, Katada Y, Nakagawa S, et al. Influence of ensitrelvir or nirmatrelvir/ritonavir on tacrolimus clearance in kidney transplant recipients: a single-center case series. J Pharm Health Care Sci. 2024;10(1):37.

Sakamaki I, Negoro E, Iwasaki H, et al. Ensitrelvir eradicates persistent SARS-CoV-2 infection in a follicular lymphoma patient treated with anti-CD20 antibodies. J Infect Chemother. 2024;30(2):147-149.

Kitamura M, Takazono T, Hosogaya N, et al. Prospective Study of Treatment with Ensitrelvir for COVID-19 in Patients Undergoing Hemodialysis (PROTECT-HD). Infect Dis Ther. 2026. Published online April 1, 2026.

Kawai N, Bando T, Goto T, et al. Durations of fever and other symptoms among COVID-19 outpatients administered ensitrelvir during the 2023 Japanese XBB epidemic period. J Infect Chemother. 2025;31(12):102852.

Ikeuchi K, Saito M, Okushin K, et al. Comparative effectiveness of antiviral treatment on household transmission of SARS- CoV-2: a retrospective cohort study using administrative data. BMC Infect. Dis. 2025;25(1).

Takikawa K, Sota M, Imai Y, et al. Efficacy of oral antivirals and combination therapy with remdesivir in hematological patients with COVID-19. J. Infect. Chemother. 2025;31(10).

Omori K, Kitagawa H, Takamori A, et al. Antiviral combination therapy in severely immunocompromised patients with persistent or recurrent COVID-19. J. Infect. Chemother. 2025;31(10).

Maruyama S, Wada D, Inoue A, et al. Efficacy of initial combination therapy with anti-SARS-CoV-2 antivirals targeting viral clearance in COVID-19 patients with B-cell lymphoma treated with anti-CD20 antibodies: A retrospective single-centre study in Japan. J. Infect. Chemother. 2025;31(7).

Hirai J, Hanai Y. Comparative study of ensitrelvir and symptomatic therapy in healthcare workers with mild COVID-19: A single center retrospective analysis in Chiba, Japan. J Infect Chemother. 2025;31(4):102668.

Takano T, Aiba H, Takemura H, et al. Combination Therapy With Ensitrelvir and Remdesivir Versus Antiviral Monotherapy in Patients Receiving Anti-CD20 Monoclonal Antibody Therapy: A Retrospective Cohort Study. Cureus. 2025;17(12):e99402.

Miyashita N, Horita N, Nakamori Y, et al. Effectiveness of ensitrelvir for cough caused by COVID-19 Omicron variant in patients with asthma. Microbiol Spectr: 13:e03407-24.

Mukae H, Yotsuyanagi H, Ohmagari N, et al. Ensitrelvir as a novel treatment option for mild-to-moderate COVID-19: a narrative literature review. Therapeutic Advances in Infectious Disease. 2025;12.

Khorramnia S, Pakzad Moghadam SH, Sarkoohi A, et al. Ensitrelvir for the treatment of COVID-19: A systematic review of evidence. Jpn J Infect Dis. Published online July 31, 2025.

Hirsch C, Kreuzberger N, Skoetz N, et al. Efficacy and safety of antiviral therapies for the treatment of persistent COVID- 19 in immunocompromised patients since the Omicron surge: a systematic review. J Antimicrob Chemother. 2025;80(3):633-644.

Tomita T, Miyazawa S, Sonoyama T. Treatment with ensitrelvir for COVID-19 in hospitalized patients of very advanced age: Case series. Medicine (Baltimore). 2024;103(30):e39080.

Katsuta M, Kitazono M, Nagai N, et al. The time to return-to-work in healthcare workers with COVID-19 treated with ensitrelvir, a novel oral inhibitor of 3C-like protease of SARS-CoV-2: An observational study utilizing pre-existing data from a single hospital. J Infect Chemother. 2025;31(4):102669.

Seki M, Kubosawa C, Ono M, et al. Clinical features of patients with COVID-19 recurrence during hospitalization in the Omicron variant surge. Infect Drug Resist. 2024;17:5011-5015. Published 2024 Nov 11.

Hibino M, Shintani A, Murayama H, et al. Impact of oral antiviral therapy on subsequent hospital visits and antibacterial use in COVID-19 outpatients within 28 days. Oral presentation presented at: APCCMI; November 2-4, 2025; Bangkok, Thailand.

Please keep in mind that medical literature databases, while considered a major source of biomedical information, are selective in their sources, and the information derived from it should not be considered all-inclusive.

ABBREVIATIONS

3CL, 3-chymotrypsin-like
AAV, ANCA-associated vasculitis
ADR, adverse drug reaction
ANCA, antineutrophil cytoplasmic antibody
BMI, body mass index
BSI, bloodstream infection
CABG, coronary artery bypass graft
CHF, chronic heart failure
CI, confidence interval
CKD, chronic kidney disease
COVID-19, coronavirus disease 19
DM, diabetes mellitus
EOT, end of treatment
ESV, ensitrelvir
F, female
FL, follicular lymphoma
HIV/AIDS; human immunodeficiency virus/acquired immunodeficiency syndrome
HSCT, hematopoietic stem cell transplant
HTN, hypertension
HR, high-risk
ICU, intensive care unit
IgAN, immunoglobulin A nephropathy

IPTW, inverse probability of treatment weighting
J-LCQ, Japanese Leicester Cough Questionnaire
LLoQ, lower limit of quantification
MHLW, Ministry of Health, Labour and Welfare
n.s., not significant
PCR, polymerase chain reaction
QOL, quality of life
PK, pharmacokinetics
RA, rheumatoid arthritis
RD, risk difference
RDV, remdesivir
RR, risk ratio
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2
SEM, standard error of the mean
SR, standard-risk
T2D, Type 2 diabetes
TB, tuberculosis
TRAE, treatment-related adverse event
US, United States
UTI, urinary tract infection

REFERENCES

1. Hayashi N, Tsukimura E, Ogura E. Ensitrelvir for the treatment of COVID-19: Final analysis of a post-marketing surveillance from Japan. *Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy*. Mar 2025;31(3):102574. doi:10.1016/j.jiac.2024.12.003
2. Takazono T, Fujita S, Komeda T, et al. Real-World effectiveness of ensitrelvir in reducing severe outcomes in outpatients at high risk for COVID-19. [Published online ahead of print: June 14,2024]. *Infectious diseases and therapy*. 2024;(Suppl)doi:10.1007/s40121-024-01010-4.
3. Yamato M, Kinoshita M, Miyazawa S, Seki M, Mizuno T, Sonoyama T. Ensitrelvir in patients with SARS-CoV-2: A retrospective chart review. *Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy*. 2024;doi:10.1016/j.jiac.2024.02.015
4. Yoshida R, Sasaki T, Ohsaki Y. Real-World efficacy of ensitrelvir in hospitalized patients ithw COVID-19 in Japan: a retrospective observational study. *Cureus*. 2024;16(5):e61048. doi:10.7759/cureus.61048.
5. Abe S, Wannigama DL, Suzuki Y, et al. Real world effectiveness of early ensitrelvir treatment in patients with SARS-CoV-2, a retrospective case series. *New Microbes New Infect*. Dec 2024;62:101522. doi:10.1016/j.nmni.2024.101522
6. Miyashita N, Nakamori Y, Ogata M, Fukuda N, Yamura A, Ito T. Efficacy of ensitrelvir for cough due to COVID-19 Omicron variant in medical healthcare workers. *Antimicrob Agents Chemother*. 2024;68(10):e0106424. doi:10.1128/aac.01064-24
7. Hibino M, Shintani A, Murayama H, et al. Real-world impact of early outpatient COVID-19 antiviral treatment on post-COVID-19 condition: the ANCHOR-01 study. Poster presented at: AVG and IMRP; September 17 - 20, 2025; Singapore.
8. Yamato M, Kinoshita K, Miyazawa S, Seki M, Mizuno T, Sonoyama T. Ensitrelvir as a treatment option for persistent SARS-CoV-2 infection after remdesivir in hospitalized patients with comorbidities: A single-center series from Japan. Poster presented at: EWSI 2023; September 17-20, 2023; Valencia, Spain.

9. Xocova® (ensitrelvir) tablets, for oral use [Prescribing Information]. Shionogi Inc.

ENCLOSURE

Xocova® (ensitrelvir) tablets, for oral use [Prescribing Information]. Shionogi Inc.