Xocova - Use in Renal Impairment

This medical response contains information in addition to that provided in the XOCOVA® (ensitrelvir) tablets, for oral use Full Prescribing Information approved by the U.S. Food and Drug Administration (FDA). Shionogi does not recommend the use of XOCOVA in any manner other than as described in the Full Prescribing Information. **Please read the attached XOCOVA Full Prescribing Information.**

1. SUMMARY

- No dosage adjustment for XOCOVA is recommended in patients with mild, moderate, or severe renal impairment.[1] The pharmacokinetics and safety of ensitrelvir have not been studied in Phase 1, 2, or 3 studies for patients with kidney failure receiving dialysis[2-12]
- A Phase 1 study to assess safety, tolerability, and PK of ensitrelvir in participants with renal impairment was conducted in the United States (US). Ensitrelvir was well tolerated by participants with renal impairment, and no dose adjustment for ensitrelvir use was deemed required due to renal function. Patients with severe renal impairment were excluded from this study if they required hemodialysis[2,8]
- Renal impairment considerations from the XOCOVA clinical trial program can be found in the **Appendix**.
- **Kitamura et al** conducted a prospective, single-arm study evaluated plasma concentrations of ensitrelvir in 8 adults with mild COVID-19 undergoing hemodialysis. Geometric mean plasma concentrations remained stable during treatment and were similar before and after dialysis sessions (18.0 µg/mL and 16.4 µg/mL, respectively).[13]
- **Yamato et al** conducted a single-center, retrospective chart review assessed the outcomes of patients treated with ensitrelvir for SARS-CoV-2, including 13 patients with renal impairment 7 of which were receiving hemodialysis. At final measurement, 53.8% (7/13) of patients with renal impairment had achieved viral clearance after 5 days of treatment, and three experienced viral rebound without disease progression[14]

2. PHASE 1 RENAL STUDY: ASSESSMENT OF ENSITRELVIR IN PATIENTS WITH RENAL IMPAIRMENT

Study Design

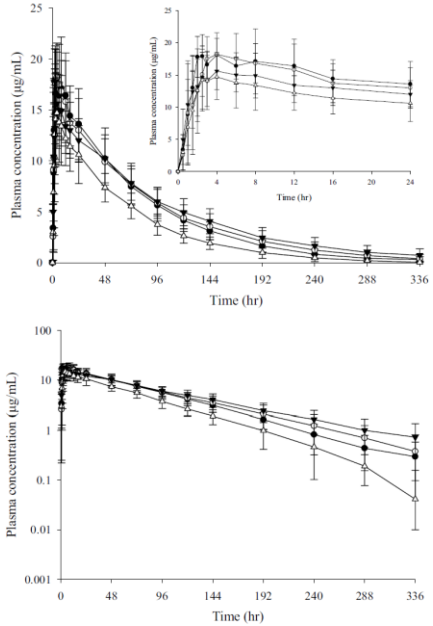
A Phase 1, open-label, nonrandomized, parallel-group study (NCT05363215) investigated the effect of renal function on the PK, safety, and tolerability of ensitrelvir. Ensitrelvir was administered as a single 375 mg dose to 24 patients: eight with mild (estimated glomerular filtration rate [eGFR] 60-89 mL/min), eight with moderate (eGFR 30-59 mL/min), or eight with severe (eGFR <30 mL/min) renal impairment and eight matched controls with normal renal function (eGFR ≥90 mL/min). Patients with severe renal impairment were excluded if they required hemodialysis.[2]

Results

- Plasma concentrations of ensitrelvir were higher for patients with renal impairment vs those with normal renal function (**Figure 1**)[2]
- Geometric mean renal clearance (CL_R) values were 0.0561, 0.0327, 0.0406, and 0.0325 L/h for patients with normal, mild, moderate, and severe renal function, respectively[2]

- Unbound fraction was similar across study groups (regardless of renal function); geometric means at 3 and 24 hours ranged from 0.0125 to 0.0127 for patients with normal renal function, and 0.0118 to 0.0165 for patients with mild, moderate, and severe renal impairment[2]
- Analyses of variance (ANOVA) of PK values determined that:
  - Geometric mean ratios of maximum serum concentration (C_{max}) (90% confidence interval [CI]) were 1.3239 (1.0409-1.6837), 1.3274 (1.0608-1.6611), and 1.1141 (0.8737-1.4206) for participants with mild, moderate, and severe renal impairment, respectively, compared to controls (**Table 1**)[2]
  - $AUC_{0\text{-inf}}$ (90% CI) was 1.4374 (1.1716-1.7636), 1.4885 (1.1883-1.8646), and 1.6021 (1.2782-2.0080), for participants with mild, moderate, and severe renal impairment, respectively, compared to controls (**Table 1**)[2]
- Ensitrelvir was well tolerated by participants with renal impairment. Treatment-emergent adverse events (TEAEs) were reported for 37.5% (3/8) of participants with mild renal impairment and 25.0% (2/8) of participants with moderate renal impairment. No TEAEs were reported for participants with severe renal impairment or normal renal function. No deaths or serious TEAEs were reported[8]
- No dose adjustment for ensitrelvir use was deemed required due to renal function[2]

Figure 1. Pharmacokinetic Profiles of Participants With Normal Renal Function and Renal Impairment Following Single-Dose Administration of Ensitrelvir 375 mg[2]



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Participants with normal renal impairment, filled circles; with mild renal impairment, open circles; with moderate renal impairment filled triangles; with severe renal impairment, open triangles. The upper figure is in linear scale and the lower figure is in semilogarithmic scale.
Abbreviation: hr, hours.

Table 1. Pharmacokinetic Parameters of Ensitrelvir 375 mg for Each Renal Function Group[2]

Parameter	Mild Impairment/Normal Function			Moderate Impairment/Normal Function			Severe Impairment/Normal Function		
	GLS Mean Ratio	90% CIs of Ratio		GLS Mean Ratio	90% CIs of Ratio		GLS Mean Ratio	90% CIs of Ratio	
		Lower	Upper		Lower	Upper		Lower	Upper
C_{max} (μg/mL)	1.3239	1.0409	1.6837	1.3274	1.0608	1.6611	1.1141	0.8737	1.4206
AUC_{0-last} (μg·h/mL)	1.4303	1.1668	1.7532	1.4780	1.1882	1.8385	1.5475	1.2494	1.9167
AUC_{0-inf} (μg·h/mL)	1.4374	1.1716	1.7636	1.4885	1.1883	1.8646	1.6021	1.2782	2.0080
$t_{1/2,z}$ (h)	1.1855	0.9252	1.5190	1.2434	0.9874	1.5658	1.6072	1.2627	2.0457

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Abbreviations: AUC_{0-inf}, area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-last}, area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration after dosing; CI, confidence interval; C_{max}, maximum serum concentration; GLS, geometric least squares; h, hours; $t_{1/2,z}$, terminal elimination half-life.

3. PROSPECTIVE STUDY

Study Design

An open-label, prospective, single-arm (jRCTs071240069) study, conducted from December 2024 through April 2025 across 6 hemodialysis (HD) centers in Japan, evaluated the efficacy and safety of ensitrelvir for the treatment of COVID-19 in adult participants (≥18 years of age) with mild COVID-19 undergoing hemodialysis.[13] In Japan, XOCOVA is approved for both treatment of COVID-19 and post-exposure prophylaxis.[1] Participants in this study were eligible if they had mild SARS-CoV-2 infection confirmed within 72 hours of symptom onset and had been receiving maintenance hemodialysis for at least 12 weeks..[13] Participants were given 375 mg of ensitrelvir on Day 1 followed by 125 mg of ensitrelvir on Days 2-5.[13] Study visits were conducted on Days 1, 3, 5, and 8 to collect blood samples.[13]

Endpoints

Primary Endpoint: plasma concentration of ensitrelvir at predefined time points relative to dialysis[13]

Baseline Characteristics

- 8 participants were enrolled and included in the pharmacokinetic, effectiveness and safety analyses[13]
  - Mean±SD time from symptom onset to ensitrelvir administration was 30.7±20.2 hours
  - 6/8 participants were vaccinated for SARS-CoV-2 (3 participants with ≥8 doses, 1 with 5 doses, 1 with 4 doses, and 1 with 3 doses)
- All participants underwent hemodialysis ≥3 times a week during the study period[13]
  - Serum creatinine levels on at the start of dialysis (Day 3) ranged from 5.79 to 15.25 mg/dL

Results

- Plasma ensitrelvir concentrations (geometric mean) remained stable throughout treatment and were comparable before (18.0 μg/mL) and after (16.4 μg/mL) dialysis (**Table 2**)[13]

- The trend of plasma ensitrelvir concentrations before, during, and after hemodialysis is shown in **Figure 2**

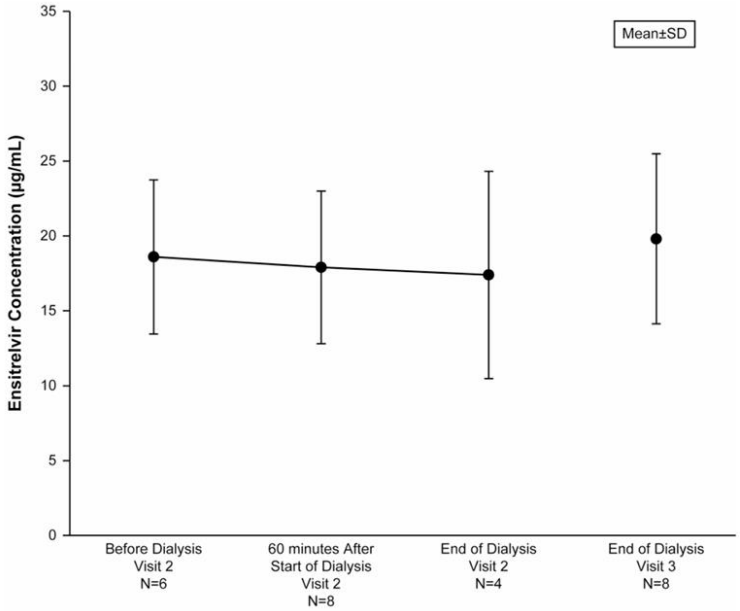
- By Visit 4 (Day 8), all participants (8/8) were assessed by investigators as having a clinically effective response to treatment with ensitrelvir[13]
  - Of the 8 participants, 5 were febrile at baseline (axillary temperature >37.0 °C). Following ensitrelvir initiation, fever resolved (<37.0 °C) within 16.6–48.0 hours in 4 participants, while the remaining participant achieved temperature normalization after 59.2 hours.
- Viral load of all participants decreased by Visit 4 (Day 8)[13]
  - 7/8 participants achieved titers below the lower level of quantification (<1.1 $\log_{10}$ $TCID_{50}$/mL)
  - Viral titer of the remaining participant decreased from 3.5 to 1.1 $\log_{10}$ $TCID_{50}$/mL
- No cases of disease progression (including deaths, hospitalizations, or ICU admissions), TEAEs, or lab abnormalities were reported[13]

Table 2. Plasma Concentration of Ensitrelvir throughout Treatment Period[13]

Timepoint	Visit 2 Before Dialysis (n=6)	Visit 2 60 Minutes after Dialysis (n=8)	Visit 2 End of Dialysis (n=4)	Visit 3 End of Dialysis (n=8)
Plasma Concentration (mean±SD [µg/mL])	18.6±5.14	17.9±5.09	17.4±6.91	19.8±5.68
Geometric Mean Plasma Concentration (µg/mL), Geometric CV (%)	18.0, 28.5	17.3, 28.6	16.4, 40.1	19.2, 28.2

Visit 2 occurred on Day 3 and Visit 3 occurred on Day 5
Abbreviations: CV, coefficient of variation; µg, micrograms; mL, milliliters; SD, standard deviation.

Figure 2. Ensitrelvir Plasma Concentrations throughout Hemodialysis[13]



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Kitamura M et al. *Infect Dis Ther*. 2026;15(5):1451-1466. doi: 10.1007/s40121-026-01327-2.
Abbreviation: µg, micrograms; mL, milliliters; SD, standard deviation.

4. RETROSPECTIVE CHART REVIEW

Study Design

A single-center, retrospective chart review assessed the outcomes of patients treated with ensitrelvir for SARS-CoV-2 in the Rinku General Medical Center between November 2022 and April 2023. 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.[14]

Results

- A total of 32 patients were included in the analysis, of which 13 patients had renal impairment, including eight with chronic kidney disease (CKD), one with acute kidney failure, two with chronic kidney failure, one with kidney failure of unspecified severity, and one with kidney stone disease and kidney injury. Seven patients were receiving hemodialysis[14,15]
- All patients received 5 days of ensitrelvir treatment. By Day 6, 30.8% (4/13) of patients with renal impairment had viral clearance (defined as an antigen level of <89.73 pg/mL)[14,15]
    - Of these patients, Patient 9 had achieved viral clearance on Day 5 but had viral rebound (defined as an increase of antigen level of >89.73 pg/mL after viral clearance) on Day 6
    - At final measurement, 53.8% (7/13) of patients with renal impairment had achieved viral clearance
- Viral rebound occurred in 23.1% (3/13) of patients with renal impairment[14,15]
    - Two out of the three patients had CKD (Patients 9 and 25) and did not experience a rebound of clinical symptoms; Patient 9 did not require additional antiviral treatment and Patient 25 received remdesivir from Day 9 to Day 14
    - Patient 28 (acute renal failure) experienced both viral and symptomatic rebound with a transient increase of body temperature ≥37.5 ˚C at the time of viral rebound and received remdesivir treatment from Day 12 to Day 16, with viral clearance documented on Day 15 and Day 16
    - None of the three patients with rebound had disease progression
- Virology outcome data for patients with renal impairment are presented in **Table 3**
- All patients, regardless of renal impairment status, experienced clinical improvement as assessed by the investigator at the end of ensitrelvir treatment (Day 5). No patients, including those with renal impairment, discontinued treatment, there were no treatment-related adverse events, no patients progressed to severe disease, none were admitted to the intensive care unit, and no treatment-related deaths occurred[14,15]

Table 3. Virology Outcomes for Patients with Renal Impairment in a Single-Center Chart Review[14,15]

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)																	
5	Unstable angina pectoris, organizing pneumonia, CHF, CKD, hypothyroidism, DM	Remdesivir[b] Casirivimab/ imdevimab	5000	5000		5000	5000	5000				1233.07	494.52		254.76	8.67	44.64		Viral Clearance	
9[c]	AAV, CKD, DM, HTN	Remdesivir[b] Molnupiravir Tixagevimab/ cilgavimab	5000	5000		2587.88		4.77	1210.73		5000	5000	5000							Viral Rebound (at Day 6)
10[d]	Recurrent follicular lymphoma, post-HSCT, CKD, HTN, hemodialysis	Molnupiravir		1227.48		182.59	200.71													
15	CKD, abdominal aortic aneurysm, HTN			5000			5000		665.36		352.02			8.56	1.30	4.21	0.01		Viral Clearance	
19	CKD, DM, HTN, hemodialysis	Remdesivir	5000			344.33														
20	Kidney stone disease, acute myelogenous leukemia, post hematopoietic stem cell transplantation, kidney injury, HTN			5000[a]			5000	97.79		344.12	5000				4664.69					
22	Asthma, bronchitis, liver failure, cerebral infarction, renal failure	Remdesivir[b]	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, CHF, CKD, HTN, hemodialysis	Remdesivir Molnupiravir		88.50	2.89	0.09												Viral Clearance	Viral Clearance	
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)
27	Atrial fibrillation, chronic hepatitis B, CHF, chronic renal failure, pyelonephritis, HTN	Remdesivir[b] 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			168.5			86.65	1.39	14.97	6.59	496.04					Viral Rebound[f] (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, HTN, hemodialysis	Remdesivir Casirivimab/ imdevimab	5000		1125.20															

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Shading indicates days patients were hospitalized.

Abbreviations: AAV, anti-neutrophil cytoplasmic antibody–associated vasculitis; CABG, coronary artery bypass graft; CHF, chronic heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; EOT, end of treatment; HSCT, hematopoietic stem cell transplant; HTN, hypertension; IgAN, immunoglobulin A nephropathy; PCR Ct, polymerase chain reaction cycle threshold; T2D, Type 2 diabetes.

[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 received ≥3 days of remdesivir. [c]Patient received rituximab at Day -48. [d]Patient received rituximab at Day -15. [e]PCR positive at Day 1. [f]Viral clearance documented on Day 15 and Day 16.

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.[1]

Contraindications

XOCOVA is contraindicated in patients with a history of clinically significant hypersensitivity reactions to ensitrelvir or any other components of the product.[1]

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.[1]

As stated in the XOCOVA Full Prescribing Information:

Section 7.3 Table 1 from the XOCOVA FPI provides example(s) of drugs that are contraindicated with XOCOVA.[1]

- *The table is provided as a guide and is not a comprehensive list of all possible drugs that may interact with XOCOVA.*
- *The healthcare provider should consult other appropriate resources, such as the prescribing information for the interacting drug, for comprehensive information on dosing and monitoring with concomitant use of a strong CYP3A inhibitor, like XOCOVA.*

Excerpted below is information from Table 1 listing examples of medicines contraindicated with Xocova due to potential renal complications. **See Table 1** in the XOCOVA FPI for the complete examples of drugs contraindicated with XOCOVA.

Excerpted Section of Table 1, XOCOVA FPI:

Relevant Examples of Drugs Contraindicated with XOCOVA Due to Risk of Potentially Serious or Fatal Interaction[1]

Drug Class	Examples of Drug within Class	Effect on Drug Concentration	Clinical Comment
Antigout agents	colchicine	↑ colchicine	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Immunosuppressants	voclosporin	↑ voclosporin	Co-administration is contraindicated due to potential for acute and/or chronic nephrotoxicity.

Section 8.6 – Renal Impairment

No dosage adjustment for XOCOVA is recommended in patients with mild, moderate, or severe renal impairment.

Section 12.3 - Pharmacokinetics

No clinically significant differences in the pharmacokinetics of ensitrelvir was observed in mild (estimated glomerular filtration rate [eGFR] 60 to <90 mL/min as determined by MDRD equation), moderate (eGFR 30-<60 mL/min), or severe (eGFR 15-<30 mL/min) renal impairment, or mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. The pharmacokinetics and

safety of ensitrelvir have not been studied in patients with severe hepatic impairment (Child-Pugh Class C) or patients with kidney failure receiving dialysis.[1]

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, ABBREVIATIONS, & REFERENCES

Literature Search

As of July 2026, a computerized search of the published medical literature using internal and external databases (ie, Medline® and Embase®) identified an additional relevant reference regarding information on ensitrelvir use in patients with renal impairment.

Yoshida R, Sasaki T, Ohsaki Y. Real-world efficacy of ensitrelvir in hospitalized patients with COVID-19 in Japan: a retrospective observational study. *Cureus*. 2024;16(5):e61048. doi: 10.7759/cureus.61048

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. doi:10.1186/s40780-024-00361-x.

Miyagawa N, Yamanouchi S, Fujimoto H, et al. Successful Management of Severe COVID-19 in a Kidney Transplant Recipient Safe Co-Administered Tacrolimus and Ensitrelvir: A Case Report. *Reports (MDPI)*. 2026;9(2)doi:10.3390/reports9020159

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	HD	hemodialysis
AAV	anti-neutrophil cytoplasmic antibody–associated vasculitis	HSCT	hematopoietic stem cell transplant
ANOVA	analysis of variance	HTN	hypertension
$AUC_{0\text{-inf}}$	area under the plasma concentration-time curve from time 0 to infinity	ICU	Intensive Care Unit
$AUC_{0\text{-last}}$	area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration after dosing	IgAN	immunoglobulin A nephropathy
C	Celsius	h	hours
CABG	coronary artery bypass graft	MHLW	Ministry of Health, Labour and Welfare
CHF	chronic heart failure	mg	milligrams
CI	confidence interval	ng	nanograms
CKD	chronic kidney disease	PCR	Polymerase chain reaction
CLR	renal clearance	PCR Ct	polymerase chain reaction cycle threshold
C_{max}	maximum serum concentration	PK	pharmacokinetics
COVID-19	coronavirus disease 19	SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
CrCl	creatinine clearance	SCORPIO-HR	Stopping COVID-19 pRogression with early Protease InhibitOr-High Risk
CV	coefficient of variance	SCORPIO-PEP	Stopping COVID-19 pRogression with early Protease InhibitOr-Post-Exposure Prevention
CYP3A	cytochrome P450 3A	SoC	standard of care
DDI	drug-drug interactions	$t_{1/2,z}$	terminal elimination half-life
DM	diabetes mellitus	T2D	Type 2 diabetes
eGFR	estimated glomerular filtration rate	TEAE	treatment-emergent adverse event
EOT	end of treatment	US	United States
GLS	geometric least square		

References

1. XOCOVA® (ensitrelvir) tablets, for oral use [Prescribing Information]. Shionogi Inc.
2. Katsube T, Kezbor S, Shimizu R, Kubota R. Effect of renal impairment on pharmacokinetics and safety of ensitrelvir, a SARS-CoV-2 3CL protease inhibitor. *Infectious diseases and therapy*. 2024;doi:10.1007/s40121-024-00946-x
3. A phase 1 study of S-217622. Accessed April 8, 2024. https://rctportal.niph.go.jp/en/detail?trial_id=jRCT2031210202.
4. Shimizu R, Sonoyama T, Fukuhara T, Kuwata A, Matsuo Y, Kubota R. Safety, tolerability, and pharmacokinetics of the novel antiviral agent ensitrelvir fumaric acid, a SARS-CoV-2 3CL protease inhibitor, in healthy adults. *Antimicrob Agents Chemother*. 2022;66(10):e0063222. doi:10.1128/aac.00632-22

5. Shimizu R, Sonoyama T, Fukuhara T, et al. Evaluation of the drug-drug interaction potential of ensitrelvir fumaric acid with Cytochrome P450 3A substrates in healthy Japanese adults. *Clin Drug Investig*. 2023;43(5):335-346. doi:10.1007/s40261-023-01265-8.
6. Shimizu R, Sonoyama T, Fukuhara T, Kuwata A, Matsuo Y, Kubota R. A phase 1 study of ensitrelvir fumaric acid tablets evaluating the safety, pharmacokinetics and food effect in healthy adult populations. *Clin Drug Investig*. 2023;43(10):785-797. doi:10.1007/s40261-023-01309-z
7. Ohmagari N, Yotsuyanagi H, Doi Y, et al. Ensitrelvir for asymptomatic and mild symptoms only COVID-19 patients in phase 2b/3 part. Poster presented at: ECCMID 2023; April 15 - 18, 2023; Copenhagen, Denmark.
8. A study to assess S-217622 in participants with renal impairment and healthy participants. Accessed March 11, 2024. https://clinicaltrials.gov/study/NCT05363215.
9. A phase 2/3 study of S-217622 in participants with SARS-CoV-2 infection. Accessed February 19, 2024. https://jrct.niph.go.jp/en-latest-detail/jRCT2031210350
10. Ensitrelvir Data on File 1. Shionogi Inc.
11. A study to compare S-217622 with placebo in non-hospitalized high-risk participants with COVID-19 (SCORPIO-HR). Clinicaltrials.gov.NCT05305547. Accessed August 29, 2022. https://clinicaltrials.gov/ct2/show/NCT05305547
12. Phase 3 study of S-217622 in prevention of symptomatic SARS-CoV-2 infection (SCORPIO-PEP). NLM Identifier: NCT05897541. Last accessed June 18, 2025. https://clinicaltrials.gov/study/NCT05897541?term=scorpio-pep&rank=1.
13. Kitamura M, Takazono T, Hosogaya N, et al. Prospective study of treatment with ensitrelvir for COVID-19 in patients undergoing hemodialysis (PROTECT-HD). *Infectious diseases and therapy*. 2026;doi:10.1007/s40121-026-01327-2
14. 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
15. 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;(Suppl)doi:10.1016/j.jiac.2024.02.015
16. Mukae H, Yotsuyanagi H, Ohmagari N, et al. A randomized phase 2/3 study of ensitrelvir, a novel oral SARS-CoV-2 3C-Like protease inhibitor, in Japanese patients with mild-to-moderate COVID-19 or asymptomatic SARS-CoV-2 infection: results of the phase 2a part. [Published online ahead of print 13 September 2022]. *Antimicrob Agents Chemother*. 2022:e0069722. doi:10.1128/aac.00697-22.
17. Mukae H, Yotsuyanagi H, Ohmagari N, et al. Efficacy and Safety of Ensitrelvir in Patients With Mild-to-Moderate Coronavirus Disease 2019: The Phase 2b Part of a Randomized, Placebo-Controlled, Phase 2/3 Study. *Clin Infect Dis*. 2023;76(8):1403-1411. doi:10.1093/cid/ciac933.
18. Yotsuyanagi H, Ohmagari N, Doi Y, et al. Efficacy and safety of 5-day oral ensitrelvir for patients with mild to moderate COVID-19 the SCORPIO-SR randomized clinical trial. *JAMA Netw Open*. 2024;7(2):e2354991. doi:10.1001/jamanetworkopen.2023.54991.
19. Shionogi provides updates from SCORPIO-HR, a global phase 3 study of ensitrelvir for non-hospitalized participants with COVID-19. May 13, 2024. Accessed May 13, 2024. https://www.shionogi.com/global/en/news/2024/05/E_20240513_1.html
20. A Phase 3 study of S-217622 in pediatric participants. Accessed September 20, 2023. https://rctportal.niph.go.jp/en/detail?trial_id=jRCT2031230140.

ENCLOSURE

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

APPENDIX

RENAL IMPAIRMENT REPRESENTATION IN ENSITRELVIR CLINICAL TRIAL PROGRAM

Multiple clinical trials have been conducted to evaluate the efficacy and safety of ensitrelvir in patients with COVID-19; some of these trials excluded patients with renal impairment. **Table 5** lists ensitrelvir clinical trials and renal impairment considerations.

Table 5. Descriptions of Ensitrelvir Clinical Trials and Renal Impairment Considerations

Study Name	Trial Status	Study Design	Description	Renal Impairment Allowances
A Study to Assess S-217622 in Participants With Renal Impairment and Healthy Participants[2,8] (NCT05363215)	Completed	Phase 1, open-label, parallel-group	Assessing the PK, safety, and tolerability of ensitrelvir in participants with mild, moderate, and severe renal impairment, and control participants with normal renal function	Enrolled patients with mild (eGFR 60-89 mL/min), moderate (eGFR 30-59 mL/min), or severe (eGFR <30 mL/min) renal impairment and matched controls with normal renal function (eGFR ≥90 mL/min). Patients with severe renal impairment were excluded if they required hemodialysis. Study Details
A Phase 1 Study of S-217622 in Healthy Adult Participants[3-6] (jRCT2031210202)	Completed	Phase 1	A seven-part study to assess the safety, tolerability, and PK of single and multiple doses of ensitrelvir in healthy participants, as well as the effect of food, the comparison of PK of ensitrelvir in healthy Japanese and White participants, and DDI potential of ensitrelvir with CYP3A substrates	Excluded patients with history of renal conditions
Phase 2/3 Study[7,9,10,16-18] (jRCT2031210350)	Completed	Phase 2/3, multicenter, randomized, double-blind, placebo-controlled	Evaluated the efficacy and safety of oral, once daily 125 mg or 250 mg ensitrelvir vs placebo given for 5 days in patients with mild-to-moderate COVID-19 or asymptomatic SARS-CoV-2 infection regardless of risk factors for progressing to severe disease	Excluded patients with current or chronic history of moderate or severe kidney disease

SCORPIO-HR[11,19] (NCT05305547)	Completed	Phase 3, randomized, double-blind, placebo-controlled, multicenter	A 24-week clinical study assessed the safety, clinical and antiviral effects of ensitrelvir (oral once daily for 5 days) vs placebo in nonhospitalized patients with confirmed symptomatic COVID-19 with or without high risk factors for severe COVID-19	Excluded patients with renal impairment (defined as CrCl <30 mL/min by Cockcroft-Gault or requiring dialysis)
SCORPIO-PEP[12,19] (NCT05897541)	Completed	Phase 3, randomized, double-blind, placebo-controlled, multicenter	Evaluating the safety and efficacy of ensitrelvir (oral once daily for 5 days) in the prevention of symptomatic COVID-19 from household contacts of people who tested positive for COVID-19, when compared to placebo	Excludes patients with renal impairment (defined as CrCl <30 mL/min by Cockcroft-Gault or requiring dialysis)
Pediatric trial[19,20] (jRCT2031230140)	Completed	Phase 3, randomized, double-blind, placebo-controlled	Evaluated the safety and efficacy of ensitrelvir (oral once daily for 5 days) in children with at least one moderate or severe COVID-19 symptom at screening	Excluded patients with renal impairment (defined as CrCl of <30 mL/min by the Schwartz formula or requiring dialysis)
PROTECT-HD[13] (jRCTs071240069)	Completed	Prospective, single-arm, open-label	Evaluated efficacy and safety of ensitrelvir for the treatment of COVID-19 (oral once daily for 5 days) in participants with mild COVID-19 undergoing hemodialysis	• 8 participants were included, and treatment was deemed clinically effective by Day 8 • Plasma ensitrelvir concentrations (geometric mean) remained stable before (18.0 µg/mL) and after (16.4 µg/mL) dialysis • No TEAEs, hospitalizations, or severe COVID-19 related complications occurred

Abbreviations: COVID-19, coronavirus disease 19; CrCl, creatinine clearance; CYP3A, cytochrome P450 3A; DDI, drug-drug interactions; eGFR, estimated glomerular filtration rate; PK, pharmacokinetics; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SoC, standard of care.