ORIGINAL ARTICLE

Ensitrelvir for Covid-19 Postexposure Prophylaxis in Household Contacts

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ABSTRACT

BACKGROUND

Ensitrelvir, an oral inhibitor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 3C-like protease, is approved in Japan for the treatment of mild-to-moderate coronavirus disease 2019 (Covid-19). Previously, no antiviral agents were approved for postexposure prophylaxis in household contacts of patients with Covid-19.

METHODS

In this double-blind, randomized, placebo-controlled trial, we randomly assigned persons who were SARS-CoV-2–negative on local diagnostic testing but were household contacts of a patient with Covid-19 (the index patient) to receive either ensitrelvir (375 mg on day 1 and 125 mg daily on days 2 through 5) or placebo within 72 hours after symptom onset in the index patient. The primary end point was Covid-19 (defined by a central laboratory–confirmed positive reverse-transcriptase–polymerase-chain-reaction assay and the presence of ≥1 of 14 prespecified Covid-19 symptoms lasting ≥48 hours) by day 10 in a household contact in the modified intention-to-treat population (all the participants who underwent randomization, had a central laboratory–confirmed negative RT-PCR test for SARS-CoV-2 at baseline, and received at least one dose of the trial drug or placebo).

RESULTS

The modified intention-to-treat population included 1030 participants in the ensitrelvir group and 1011 in the placebo group. The mean age of the participants was 42.4 years; 71.1% had undergone randomization within 48 hours after symptom onset in the index patient, and 37.0% had at least one risk factor for severe Covid-19. The incidence of Covid-19 was lower in the ensitrelvir group than in the placebo group (2.9% vs. 9.0%; risk ratio, 0.33; 95% confidence interval [CI], 0.22 to 0.49; P<0.001). The incidence of adverse events during the trial was similar in the two groups (15.1% in the ensitrelvir group and 15.5% in the placebo group), as was the incidence of serious adverse events (0.2% in each group). No Covid-19–related hospitalizations or deaths were reported.

CONCLUSIONS

Ensitrelvir administered to household contacts of a patient with Covid-19 within 72 hours after symptom onset in the index patient was effective in preventing Covid-19 in the contacts. (Funded by Shionogi; SCORPIO-PEP Japan Registry for Clinical Trials number, jRCT2031230124; ClinicalTrials.gov number, NCT05897541.)

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Despite improved outcomes that have resulted from vaccination and acquired immunity, coronavirus disease 2019 (Covid-19) continues to impose substantial global burdens, especially in high-risk populations,[1-3] because of rapidly waning immunity[4] and emergence of new variants. Households are key sites for transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with secondary attack rates of up to 32 to 48% among household contacts during the omicron era.[5-8] Nonpharmaceutical interventions (e.g., masking, isolation, and ventilation) may lower the risk of household transmission, but such interventions are not fully protective and their use in households varies widely.[9] Effective strategies to prevent transmission to exposed household contacts are needed, particularly with regard to those at increased risk for complications.

For influenza, timely postexposure prophylaxis with antiviral agents such as oral oseltamivir or baloxavir is effective in protecting household contacts against illness.[10-12] In contrast, previous trials of postexposure prophylaxis with nirmatrelvir–ritonavir[13] and molnupiravir[14] did not show significant protection against Covid-19 in exposed household contacts, leaving an unmet need for an oral antiviral postexposure prophylactic with an acceptable side-effect profile.

Ensitrelvir, an oral inhibitor of SARS-CoV-2 3C-like protease, has potent in vitro activity against SARS-CoV-2 variants, including omicron.[15-17] Ensitrelvir is currently approved in Japan for treating mild-to-moderate Covid-19 in patients 12 years of age or older, and on the basis of the findings in the current trial, is approved in that country for postexposure prophylaxis in contacts 12 years of age or older.[18] In patients at standard risk who had mild-to-moderate Covid-19 or asymptomatic infection, ensitrelvir was associated with significant antiviral efficacy and numerical reduction in the incidence of acute and respiratory symptoms.[19,20] The phase 3 SCORPIO-SR trial (Stopping Covid-19 Progression with Early Protease Inhibitor Treatment in Standard-Risk Patients), which also enrolled patients at high risk, showed an approximate 1-day reduction in five Covid-19 symptoms when treatment was initiated within 3 days after symptom onset.[21] Adverse effects included mild-to-moderate, reversible, dose-related decreases in high-density lipoprotein (HDL) levels and increases in triglyceride levels.[21] In the phase 3 SCORPIO-HR (Stopping Covid-19 Progression with Early Protease Inhibitor Treatment in High-Risk Patients) trial, which enrolled nonhospitalized adults with mild-to-moderate Covid-19 who were at standard or high risk for severe Covid-19, ensitrelvir showed antiviral efficacy but did not notably reduce the time to symptom resolution.[22] In light of the antiviral efficacy shown with ensitrelvir, we conducted a randomized, controlled trial, the phase 3 SCORPIO-PEP (Stopping Covid-19 Progression with Early Protease Inhibitor Treatment for Post-Exposure Prophylaxis) trial, to determine whether ensitrelvir would be efficacious as postexposure prophylaxis in persons exposed to SARS-CoV-2 in a household setting.

METHODS

TRIAL DESIGN AND OVERSIGHT

This phase 3, double-blind, randomized, placebo-controlled trial evaluated the efficacy and safety of ensitrelvir when used as postexposure prophylaxis in household contacts who were exposed to SARS-CoV-2. The trial was conducted from June 2023 through mid-September 2024 in the United States, Argentina, Japan, South Africa, and Vietnam. Details regarding the ethical trial conduct and responsibilities related to the trial drugs are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The authors who were employees of the sponsor (Shionogi) were involved in the trial design, data collection, and data analysis. Initial versions of the manuscript were written by the first author. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available at NEJM.org).

TRIAL POPULATION

An index patient was defined as the first person with documented Covid-19 in a household. To be eligible, adult and pediatric index patients were required to have had at least 1 of 14 prespecified Covid-19 symptoms (see the Supplementary Appendix) and a positive SARS-CoV-2 test (antigen test or reverse-transcriptase–polymerase-chain-reaction [RT-PCR] assay) within 72 hours before the participating household contact underwent randomization. The index patient received antiviral treatment at the discretion of each investigator.

The intention-to-treat population included enrolled household contacts who were at least 12

years of age, had a negative local SARS-CoV-2 test as described above, and were enrolled within 72 hours after symptom onset in the index patient. The modified intention-to-treat population included all the participants who had undergone randomization, had a central laboratory–confirmed, negative RT-PCR test for SARS-CoV-2 at baseline, and received at least one dose of ensitrelvir or placebo. The intention-to-treat baseline RT-PCR–positive population included the participants who had undergone randomization and had a central laboratory–confirmed, positive RT-PCR test for SARS-CoV-2 at baseline. Multiple contacts from the same household could be enrolled in the trial; randomization was conducted at the individual participant level. Key exclusion criteria for household contacts included fever or Covid-19 symptoms, documented SARS-CoV-2 infection or receipt of SARS-CoV-2 vaccine within the previous 6 months, and pregnancy. Additional details regarding the inclusion and exclusion criteria, prohibited previous or concomitant therapies, and trial assessments are provided in the Supplementary Appendix and the protocol.

RANDOMIZATION

Eligible household contacts were randomly assigned in a 1:1 ratio to receive ensitrelvir at a dose of 375 mg (3 tablets) daily on day 1 and 125 mg (1 tablet) on days 2 through 5 or matching placebo tablets (Fig. S1). Ingestion of the first dose was observed directly by the trial staff. Randomization was stratified according to the interval between symptom onset in the index patient and the time of enrollment of the household contact (<48 hours or ≥48 hours) and geographic region. If Covid-19 developed in a participating household contact, approved Covid-19 antiviral treatments were permitted, but investigational treatments were prohibited.

EFFICACY END POINTS

Nasopharyngeal swabs were obtained from participants on days 1, 3, 6, 10, 15, 21, and 28 for RT-PCR detection of SARS-CoV-2. The primary efficacy end point was laboratory-confirmed Covid-19 within 10 days after administration of the trial drug or placebo in a household contact who was RT-PCR negative at baseline. Laboratory-confirmed Covid-19 was defined as RT-PCR positivity for SARS-CoV-2 and the presence of at least 1 of the 14 prespecified Covid-19 symptoms lasting for at least 48 hours (or a worsening symptom score from baseline in the case of preexisting symptoms). The primary efficacy end-point analysis was conducted in the modified intention-to-treat population, and a key secondary analysis of the primary efficacy end point was conducted in the intention-to-treat population, which included all the participants who had undergone randomization. A key secondary end point was laboratory-confirmed SARS-CoV-2 infection, regardless of the presence of symptoms, in a household contact within 10 days after administration of the trial drug or placebo. Other secondary end points, including the prespecified subgroup analyses, are described in the Supplementary Appendix. Safety end points included the frequency and severity of adverse clinical and laboratory events.

STATISTICAL ANALYSIS

Assuming an incidence of symptomatic infection in 7% of the participants in the placebo group, we determined that 2200 household contacts would be sufficient to yield 92 events and would provide the trial with 90% power at a two-sided significance level of 0.05 to detect a risk ratio of 0.5 for the primary end point. The primary end point was analyzed with a generalized estimating equation approach based on a Poisson regression model to estimate the risk ratio and 95% confidence interval (unadjusted for multiplicity testing). A fixed-sequence testing procedure was applied for multiplicity adjustments of the primary and key secondary analysis of the primary end point. No multiplicity adjustments were made for other secondary end points, including prespecified subgroup analyses. All analyses were performed with SAS System software, version 9.4 (SAS Institute) (see the Supplementary Appendix).

RESULTS

INDEX PATIENTS

A total of 1496 index patients with Covid-19 underwent screening; 1319 were enrolled, of whom 83.8% were adults and 56.0% were female, with the majority residing in the United States (55.0%) or Japan (39.3%) (Table S1 in the Supplementary Appendix). Antiviral therapy was initiated in 18.7% of the index patients, most often with ensitrelvir (13.6%). Approximately 83% of the index patients had multiple household contacts.

HOUSEHOLD CONTACTS

Overall, 2524 household contacts of an index patient were screened for eligibility. A total of 2387 household contacts (the intention-to-treat population) were randomly assigned to a trial group: 1194 to receive ensitrelvir and 1193 to receive placebo (Fig. 1). Among the participants in the intention-to-treat population, 85.5% (1030 in the ensitrelvir group and 1011 in the placebo group) had tested negative for SARS-CoV-2 at baseline, as confirmed by RT-PCR testing at a central laboratory, and received at least one dose of the trial drug or placebo (the modified intention-to-treat population) (Fig. 1). No notable between-group differences in baseline characteristics were found among the household contacts (Table 1 and Tables S2 and S3); 59.3% of the participants were female, the mean age was 42.4 years, and 9.3% were 65 years of age or older (Table 1). The characteristics of the trial participants at baseline were largely representative of the expected population of household contacts of persons with Covid-19 (Table S4).

Most household contacts (71.1%) were enrolled less than 48 hours after symptom onset in the index patient. Approximately 37% had risk factors

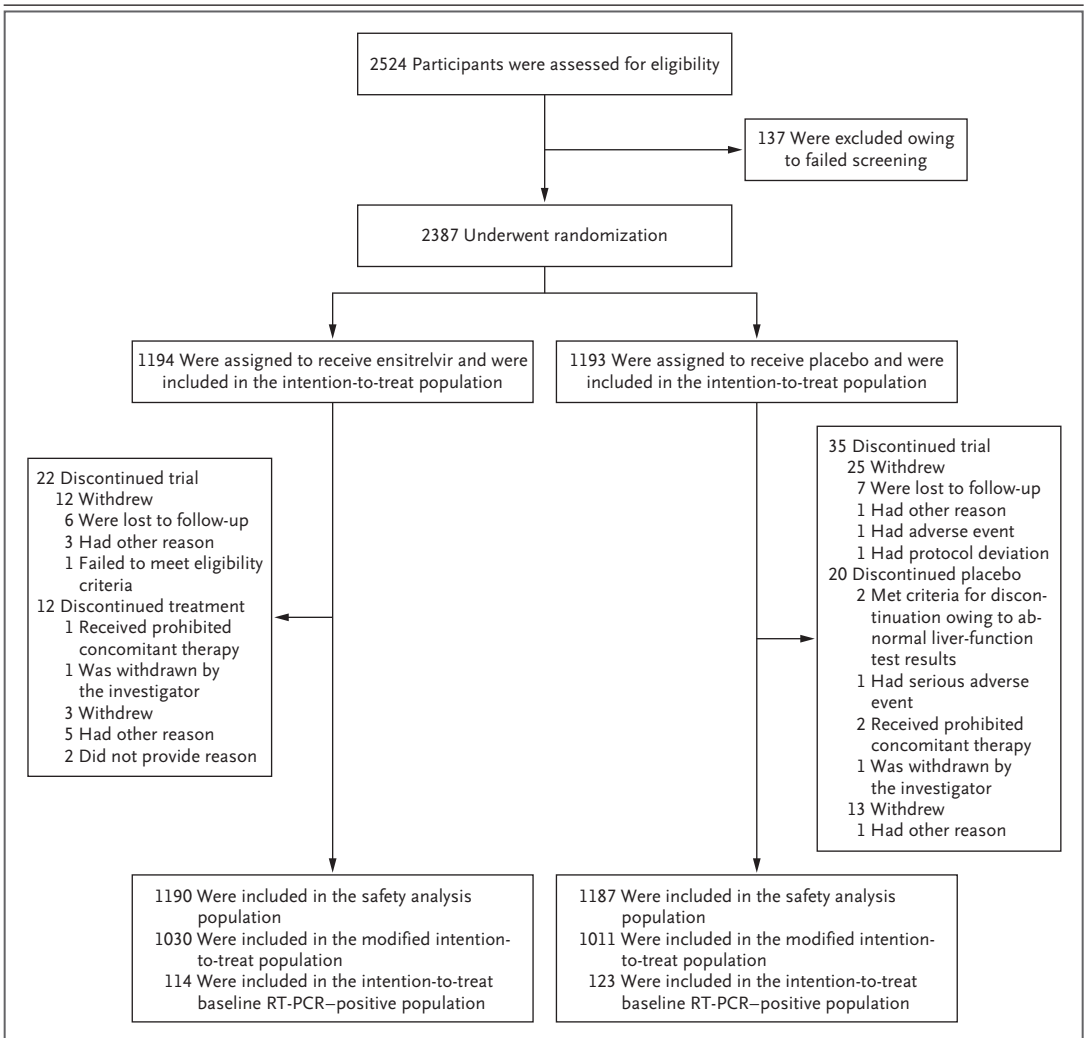


Figure 1. Screening, Randomization, and Follow-up.

The intention-to-treat analysis population included all eligible patients who underwent randomization. The safety analysis population included all household contacts who received at least 1 dose of ensitrelvir or placebo. The modified intention-to-treat population included all the participants who had undergone randomization, had a central laboratory–confirmed, negative reverse-transcriptase–polymerase chain reaction assay (RT-PCR) test for severe acute respiratory syndrome coronavirus 2 infection at baseline, and received at least one dose of ensitrelvir or placebo.

for severe illness, most commonly obesity, smoking, and age over 65 years. At the time of screening, 2.9% of the household contacts in the intention-to-treat population had preexisting symptoms due to underlying conditions. More than 98% of the household contacts were positive for antinucleocapsid or antispike antibodies or both. Among the participants in the modified intention-to-treat and safety analysis populations, 86.3% and 99.7%, respectively, of those in the ensitrelvir group and 84.7% and 99.5%, respectively, of those in the placebo group completed their prespecified regimen.

POSTEXPOSURE PROPHYLAXIS EFFICACY

The incidence of RT-PCR–confirmed Covid-19 by day 10 (the primary end point) in the modified intention-to-treat population was significantly lower in the ensitrelvir group than in the placebo group (2.9% vs. 9.0%; risk ratio, 0.33; 95% confidence interval [CI], 0.22 to 0.49; P<0.001) (Fig. 2A and Table S5). In contrast to the rapid increase in illnesses by day 2 among those in the placebo group, fewer events occurred among participants in the ensitrelvir group by days 10 to 12; after that point, new events occurred in a similar percentage of participants in the two trial groups, so the finding of a lower incidence of Covid-19 in the ensitrelvir group was maintained (Figs. S2, S3, and S4). In the intention-to-treat population, the incidence of RT-PCR–confirmed Covid-19 was significantly lower in the ensitrelvir group than in the placebo group (4.4% vs. 10.2%; risk ratio, 0.43; 95% CI, 0.32 to 0.59; P<0.001) (Fig. 2B) through day 10.

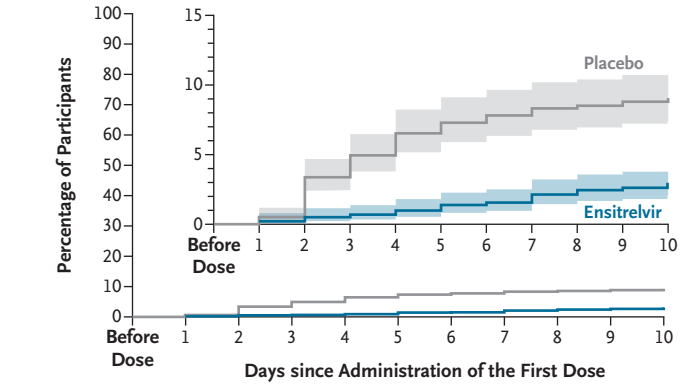
OTHER SECONDARY END POINTS

Results of prespecified subgroup analyses are shown in Figure 3. The benefits of ensitrelvir prophylaxis generally appeared to be consistent across most subgroups, including older adults and persons who had risk factors for severe disease. The incidence of Covid-19 among household contacts who received placebo appeared to be lower in the United States than in Japan. In one of the secondary end-point analyses in the modified intention-to-treat population, the percentage of household contacts in whom RT-PCR–confirmed infection developed, regardless of the presence of symptoms, through day 10 appeared to be lower with ensitrelvir than with placebo (14.0% vs. 21.5%; risk ratio, 0.66; 95% CI, 0.55 to 0.79) (Table S6). The results of the pharmacokinetic analyses are provided in Figure S5.

Table 1. Characteristics of the Participants at Baseline (Modified Intention-to-Treat Population).*

Characteristics	Ensitrelvir (N=1030)	Placebo (N=1011)
Age — yr	41.8±16.9	43.0±16.1
Age range — no. (%)		
<18 yr	64 (6.2)	54 (5.3)
18–64 yr	867 (84.2)	867 (85.8)
≥65 yr	99 (9.6)	90 (8.9)
Female sex — no. (%)	584 (56.7)	627 (62.0)
Body-mass index†	26.4 (5.7)	26.6 (5.3)
Race or ethnic group — no. (%)‡		
White	632 (61.4)	615 (60.8)
Black or African American	51 (5.0)	56 (5.5)
Asian	325 (31.6)	321 (31.8)
American Indian or Alaska Native	2 (0.2)	4 (0.4)
Other	20 (1.9)	15 (1.5)
Hispanic or Latino ethnic group — no. (%)‡	620 (60.2)	623 (61.6)
Duration from symptom onset in index patient to enrollment of participant — no. of participants (%)		
<48 hr	732 (71.1)	720 (71.2)
≥48 hr	298 (28.9)	291 (28.8)
Geographic region — no. (%)		
United States	692 (67.2)	683 (67.6)
South America	7 (0.7)	4 (0.4)
Africa	6 (0.6)	5 (0.5)
Asia (except Japan)	59 (5.7)	49 (4.8)
Japan	266 (25.8)	270 (26.7)
High risk for severe illness — no. (%)§	382 (37.1)	374 (37.0)
Index patient antiviral treatment — no. (%)	140 (13.6)	134 (13.3)
Ensitrelvir¶	101 (9.8)	90 (8.9)
Nirmatrelvir or ritonavir	25 (2.4)	33 (3.3)
Molnupiravir	12 (1.2)	11 (1.1)
Trial regimen of ensitrelvir or placebo¶	2 (0.2)	0

* Plus–minus values are means ±SD. The modified intention-to-treat population consisted of household contacts who tested negative for severe acute respiratory syndrome coronavirus 2 on local diagnostic testing at baseline.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race and ethnic group were reported by the participant.
§ Some high-risk factors for severe illness are obesity, cardiovascular disease, chronic lung disease, chronic kidney disease, chronic liver disease, Down syndrome, sickle-cell disease, immunocompromise conditions or treatment for immunocompromise conditions, dementia, diabetes mellitus, smoking, and history of stroke or cerebrovascular disease.
¶ Data are specific to Japan only; ensitrelvir is currently approved only in Japan for treatment of mild-to-moderate coronavirus disease 2019 in patients 12 years of age or older. Two index patients were enrolled in another randomized, double-blind trial of ensitrelvir and might have received ensitrelvir.



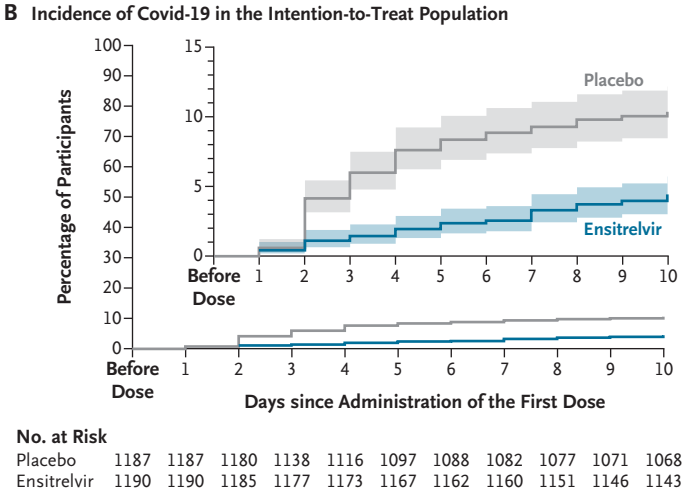


Figure 2. Incidence of Covid-19 through Day 10.

Shown is the incidence of coronavirus disease 2019 (Covid-19) in the modified intention-to-treat population (Panel A) and the intention-to-treat population (Panel B). Participants who underwent randomization but did not receive ensitrelvir or placebo were excluded from the analyses. The shaded regions represent 95% confidence intervals for the cumulative incidence curves. Confidence intervals were not adjusted for multiplicity and should not be used to infer definitive treatment effects. The insets show the same data on an expanded y axis.

POST HOC ANALYSES

Viral loads appeared to be lower among the ensitrelvir recipients than among the placebo recipients with regard to those who already had infection at baseline (the intention-to-treat baseline RT-PCR–positive population) (Table S7) and in those in whom infection and illness developed while they were receiving postexposure prophylaxis (Fig. S6). Ensitrelvir recipients in both these subgroups appeared to have lower symptom scores early in their illness than placebo recipients (Fig. S7).

3C-LIKE PROTEASE SUBSTITUTIONS

Among household contacts who received ensitrelvir, genome sequencing identified variants with amino acid substitutions that occurred during treatment in 20 participants (1.9%) in the modified intention-to-treat population and 17 (14.9%) in the intention-to-treat baseline RT-PCR–positive population (Table S8). Of the associated index patients, 20 did not receive any antiviral treatment, whereas 10 received ensitrelvir, 2 received molnupiravir, and 3 received nirmatrelvir–ritonavir. This distribution was proportionally similar to that among index patients who had household contacts who did not have amino acid substitutions that occurred with ensitrelvir treatment. No amino acid substitutions related to ensitrelvir treatment were detected in placebo recipients, including in 101 who were exposed to ensitrelvir-treated index patients. Among household contacts who had amino acid substitutions that occurred during ensitrelvir treatment, 25 had Covid-19 symptoms.

SAFETY AND ADVERSE EVENTS

Adverse events that occurred during the trial were reported in 15.1% and 15.5% of household contacts receiving ensitrelvir and placebo, respectively (Table 2). The most common adverse events (occurring in ≥1% of all participants) were headache, diarrhea, nasopharyngitis, cough, fatigue, and influenza.

Serious adverse events that occurred during the trial that were assessed by the investigator to be unrelated to the trial drug or placebo were reported in four household contacts. With ensitrelvir, one household contact had an umbilical hernia on day 5, and another had a urinary tract infection that was diagnosed on day 9 and pneumonia on day 25. With placebo, one household contact reported colitis on day 29, and another had elevated hepatic enzyme levels on day 6. All serious adverse events that occurred during the trial resolved or the participant fully recovered. No Covid-19–related hospitalizations or deaths were reported.

No differences between the groups were shown in laboratory studies except for a decline in blood HDL concentration in household con-

tacts receiving ensitrelvir. On day 6, the relative reductions from baseline in median HDL concentration were 27% (baseline, 1.32 mmol per liter [51.04 mg per deciliter]; day 6, 0.96 mmol per liter [37.12 mg per deciliter]) with ensitrelvir and 4% (baseline, 1.32 mmol per liter; day 6, 1.27 mmol per liter [49.11 mg per deciliter]) with placebo. The concentrations approached baseline levels by day 15 in both groups. No notable changes in median triglyceride concentrations were observed.

DISCUSSION

In this randomized, placebo-controlled trial, a 5-day regimen of ensitrelvir postexposure prophylaxis, as compared with placebo, was effective in preventing Covid-19 among household contacts and showed significant reductions in the relative risk of Covid-19 through day 10 of 67% in the modified intention-to-treat population and of 57% in the intention-to-treat population. In addition, in the subgroup analysis involving the household contacts with risk factors, the percentage of those in whom Covid-19 developed was 2.4% in the ensitrelvir group and 9.9% in the placebo group. Ensitrelvir postexposure prophylaxis was also associated with a 34% relative risk reduction in SARS-CoV-2 transmission within households.

The point estimate of protective efficacy for ensitrelvir postexposure prophylaxis (67.0%) was numerically higher than those reported in trials of nirmatrelvir–ritonavir (29.8 to 35.5%)[13] and molnupiravir (23.6%)[14] that involved populations with symptomatic SARS-CoV-2 infection. Several

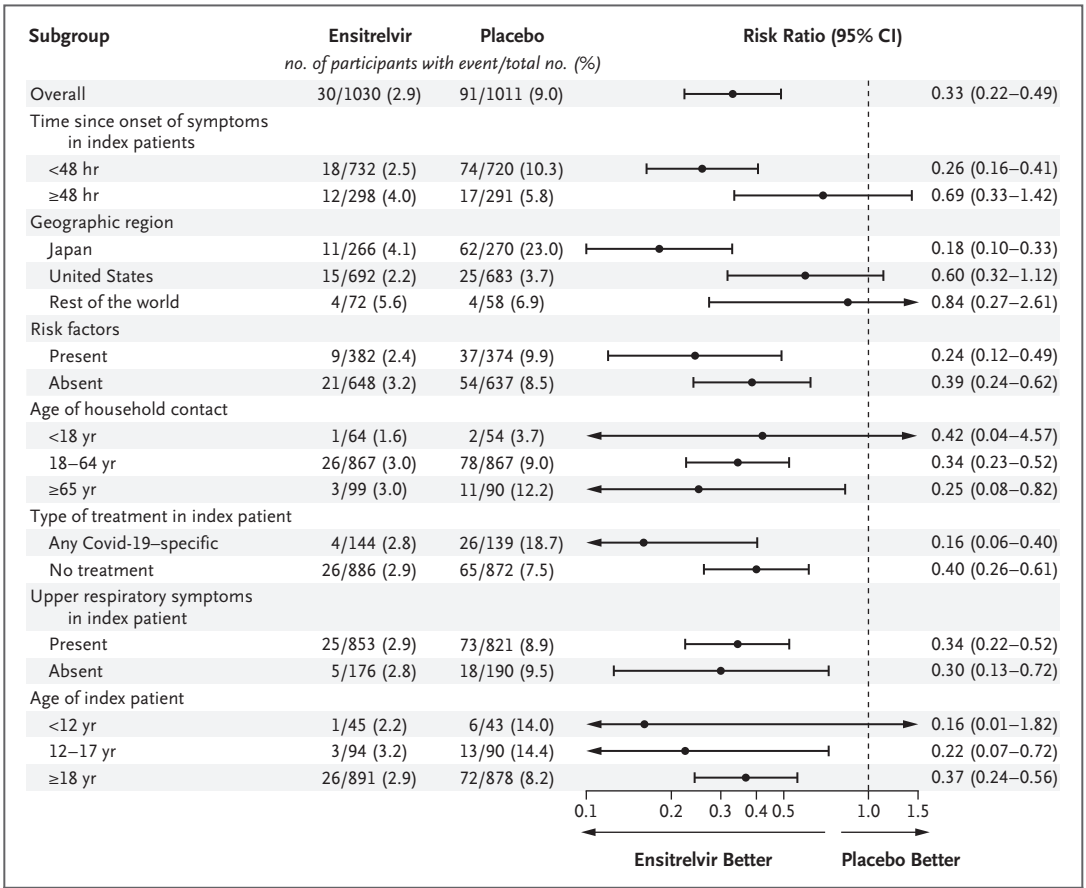


Figure 3. Subgroup Analysis of the Incidence of Covid-19 in the Modified Intention-to-Treat Population.

Geographic region and index-patient age were not prespecified variables for subgroup analyses but were included in post hoc analyses. Confidence intervals for subgroups were not adjusted for multiplicity and should not be used to infer definitive treatment effects.

Table 2. Adverse Events (Safety Analysis Population).*

Adverse Event	Ensitrelvir (N=1190)			Placebo (N=1187)		
	no. of events	*no. of patients with event*	*% of patients (95% CI)*	*no. of events*	*no. of patients with event*	*% of patients (95% CI)*
Any	303	180	15.1 (13.1–17.3)	307	184	15.5 (13.5–17.7)
Type of event†						
Infection or infestation	63	51	4.3	63	57	4.8
Nasopharyngitis	16	16	1.3	15	15	1.3
Influenza	19	13	1.1	23	19	1.6
Gastrointestinal disorder	48	42	3.5	38	31	2.6
Diarrhea	23	21	1.8	17	15	1.3
Nervous-system disorder	46	39	3.3	43	39	3.3
Headache	40	35	2.9	32	30	2.5
Respiratory, thoracic, or mediastinal disorder	40	32	2.7	40	27	2.3
Cough	14	14	1.2	9	7	0.6
Oropharyngeal pain	11	11	0.9	19	17	1.4
General disorder	26	20	1.7	31	24	2.0
Fatigue	16	13	1.1	14	12	1.0
Any serious adverse event	3	2	0.2 (0.0–0.6)	2	2	0.2 (0.0–0.6)
Any adverse event related to trial drug or placebo	23	19	1.6 (1.0–2.5)	30	21	1.8 (1.1–2.7)
Any serious adverse event related to trial drug or placebo	0	0	0.0 (0.0–0.3)	0	0	0.0 (0.0–0.3)
Any adverse event leading to drug or placebo discontinuation	1	1	<0.1 (0.0–0.5)	1	1	<0.1 (0.0–0.5)
Any adverse event leading to trial discontinuation	0	0	0.0 (0.0–0.3)	1	1	<0.1 (0.0–0.5)
Any adverse event leading to death	0	0	0.0 (0.0–0.3)	0	0	0.0 (0.0–0.3)

* A participant could have more than one type of adverse event. Percentages are based on the number of participants in the safety analysis population (all participants randomly assigned to a trial group who received ≥1 dose of ensitrelvir or placebo). Adverse events are shown in the descending order of frequency of system organ class and preferred term based on the ensitrelvir group, and were coded according to the *Medical Dictionary for Regulatory Activities*, version 26.0. The two-sided 95% confidence intervals were calculated with the Clopper–Pearson method.

† Shown are adverse events that occurred during the trial in 1% or more of the participants.

factors may explain the efficacy of ensitrelvir postexposure prophylaxis observed in our trial as compared with the results from previous trials,[13,14] including differences in trial designs, particularly the time to initiation of postexposure prophylaxis (≤72 hours vs. 96–120 hours after illness onset in index patients), a more precise definition of illness (minimum symptom duration of 48 hours vs. 24 hours), and a shorter time frame for assessment of the primary end point (through day 10 vs. day 14). Additional contributing factors may include differences in household composition, use of nonpharmaceutical interventions, circulating variant types, and background immunity from previous infections or vaccinations. Even with a less-stringent Covid-19 definition (occurrence of ≥1 symptom for ≥24 hours up to day 15) in the current trial, the frequency of illness appeared to remain lower with ensitrelvir (58% relative risk reduction).

We found that among household contacts who received placebo, the incidence of Covid-19

was considerably lower in the United States than in Japan. In the nirmatrelvir–ritonavir postexposure prophylaxis trial, in which nearly 70% of the participants were from the United States, the percentage of the placebo recipients in whom Covid-19 developed was also low (3.9%), similar to findings in the current trial, in which Covid-19 developed in 3.7% of placebo recipients in the United States.[13] Multiple factors may have contributed to differences in transmission rates, including the use of nonpharmaceutical interventions, individual behavior of index patients and household contacts, household size, circulating variants,[23] immunity, and other factors. In addition, nasopharyngeal viral loads among index patients in Japan were on average 1.68 $\log_{10}$ copies per milliliter higher than those among patients in the United States, a factor that might contribute to a higher risk of transmission. Nonetheless, the direction of the point estimate for efficacy supports a clinical benefit with ensitrelvir postexposure prophylaxis in both Japan and the United States.

The protective efficacy of ensitrelvir in our trial is consistent with results from previous trials that showed that most SARS-CoV-2 transmissions to household contacts occur within 10 days after illness onset in index patients.[9,24-26] Although some cases occurring after day 10 may represent occurrences of household transmission, most cases are probably due to exposure in other settings. Of note, in our trial, the mean plasma concentration of ensitrelvir on day 10 was above the target concentration (2.99 to 3.70 μg per milliliter) estimated in nonclinical studies.[16,17] These results suggest that the prolonged plasma elimination half-life of ensitrelvir provides effective prophylactic activity well beyond the 5-day administration period.

No new safety signals were identified with regard to the incidence of patient-reported adverse events as compared with the incidence reported with placebo. Alterations in plasma HDL levels were reversible and not associated with clinical events.

Because ensitrelvir was administered to a minority of index patients in Japan, and given that there had been previous reports of an association between amino acid substitutions that occurred during treatment and reduced susceptibility to ensitrelvir,[27] we assessed the theoretical risk of rapid emergence and transmission to household contacts by sequencing breakthrough infections. Ensitrelvir treatment in the index patients was not associated with reduced postexposure prophylaxis efficacy in the corresponding household contacts, which suggests that prophylaxis failures were not the result of the transmission of variants with amino acid substitutions that occurred during treatment. No incidents of transmission from ensitrelvir-treated index patients to household contacts who received placebo were documented, a finding that is consistent with the low incidence of variants with amino acid substitutions occurring during treatment (<0.5%) that were reported in the GISAID (Global Initiative on Sharing All Influenza Data) database,[28] and the Japan Institute for Health Security[29] has not reported such amino acid substitutions in clinical specimens even with the widespread use of the drug in Japan since November 2022. However, further studies are needed to monitor this potential risk.

The strengths of this trial include the inclusion of household contacts from diverse age groups and geographic locations, well-matched baseline characteristics, a trial design that included detailed virologic assessments and compliance drug monitoring with blood laboratory evaluations, and well-defined end points. The inclusion of a highly immune population and persons at high risk strengthens the generalizability of the findings and is representative of the current immunologic status of SARS-CoV-2 globally.

Multiple aspects can influence the likelihood of household transmission, including physical household size, masking practices, social distancing, and the use of other public health and social measures; however, a limitation of this trial was the failure to collect these data. The use of antiviral agents in index patients may have further reduced the risk of transmission, potentially affecting the efficacy of postexposure prophylaxis, particularly in Japan, where antiviral treatment was administered to 38% of the index patients as compared with approximately 6% in the United States. The index patients did not have sequence data from follow-up samples with which to detect possible amino acid substitutions occurring during treatment that might confer reduced susceptibility. In addition, because ensitrelvir is a moderately strong cytochrome P450 3A inhibitor,

its use warrants careful consideration of potential drug–drug interactions. Accordingly, persons who were receiving contraindicated medications were excluded from participation.

In this trial, the prompt initiation of oral ensitrelvir postexposure prophylaxis was effective in preventing Covid-19 in household contacts, including those with risk factors for severe disease, without apparent safety concerns. These findings suggest the potential effectiveness of ensitrelvir in reducing the risk of illness in other unprotected contexts, such as during outbreaks in acute and long-term care facilities.

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