ORIGINAL ARTICLE

Oral Simnotrelvir for Adult Patients with Mild-to-Moderate Covid-19

Bin Cao, M.D., Yeming Wang, M.D., Hongzhou Lu, M.D., Chaolin Huang, M.D., Yumei Yang, M.D., Ph.D., Lianhan Shang, M.D., Zhu Chen, M.D., Rongmeng Jiang, M.D., Yihe Liu, M.D., Ling Lin, M.D., Ping Peng, M.D., Fuxiang Wang, M.D., Fengyun Gong, M.D., Honglin Hu, M.S., Cong Cheng, M.D., Xiangyang Yao, M.D., Xianwei Ye, M.D., Hourong Zhou, M.D., Yinzhong Shen, M.D., Chenfan Liu, M.D., Chunying Wang, M.D., Zhennan Yi, M.D., Bijie Hu, M.D., Jiuyang Xu, M.D., Xiaoying Gu, Ph.D., Jingshan Shen, Ph.D., Yechun Xu, Ph.D., Leike Zhang, Ph.D., Jia Fan, M.D., Renhong Tang, Ph.D., and Chen Wang, M.D.

ABSTRACT

BACKGROUND

Simnotrelvir is an oral 3-chymotrypsin–like protease inhibitor that has been found to have in vitro activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and potential efficacy in a phase 1B trial.

METHODS

In this phase 2–3, double-blind, randomized, placebo-controlled trial, we assigned patients who had mild-to-moderate coronavirus disease 2019 (Covid-19) and onset of symptoms within the past 3 days in a 1:1 ratio to receive 750 mg of simnotrelvir plus 100 mg of ritonavir or placebo twice daily for 5 days. The primary efficacy end point was the time to sustained resolution of symptoms, defined as the absence of 11 Covid-19–related symptoms for 2 consecutive days. Safety and changes in viral load were also assessed.

RESULTS

A total of 1208 patients were enrolled at 35 sites in China; 603 were assigned to receive simnotrelvir and 605 to receive placebo. Among patients in the modified intention-to-treat population who received the first dose of trial drug or placebo within 72 hours after symptom onset, the time to sustained resolution of Covid-19 symptoms was significantly shorter in the simnotrelvir group than in the placebo group (180.1 hours [95% confidence interval {CI}, 162.1 to 201.6] vs. 216.0 hours [95% CI, 203.4 to 228.1]; median difference, −35.8 hours [95% CI, −60.1 to −12.4]; P=0.006 by Peto–Prentice test). On day 5, the decrease in viral load from baseline was greater in the simnotrelvir group than in the placebo group (mean difference [±SE], −1.51±0.14 $\log_{10}$ copies per milliliter; 95% CI, −1.79 to −1.24). The incidence of adverse events during treatment was higher in the simnotrelvir group than in the placebo group (29.0% vs. 21.6%). Most adverse events were mild or moderate.

CONCLUSIONS

Early administration of simnotrelvir plus ritonavir shortened the time to the resolution of symptoms among adult patients with Covid-19, without evident safety concerns. (Funded by Jiangsu Simcere Pharmaceutical; ClinicalTrials.gov number, NCT05506176.)

The authors' affiliations are listed in the Appendix. Dr. Cao can be contacted at caobin_ben@163.com or at the China–Japan Friendship Hospital, No. 2, E. Yinghua Rd., Chaoyang District, Beijing, China 100029. Dr. Tang can be contacted at renhong.tang@simceregroup.com or at Building 23, No. 699-18, Xuanwu Ave., Nanjing, China. Dr. Chen Wang can be contacted at cyh-birm@263.net or at the China–Japan Friendship Hospital, No. 2, E. Yinghua Rd., Chaoyang District, Beijing, China 100029.

Drs. Cao, Y. Wang, Lu, Huang, and Yang contributed equally to this article.

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The ongoing coronavirus disease 2019 (Covid-19) pandemic continues to inflict an important burden on global health and health care systems worldwide.[1] Vaccination can lessen the effect of the disease in high-risk groups but is less effective in preventing infections caused by emerging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants with strong immune evasion.[2,3] Effective antiviral agents are needed for the treatment of SARS-CoV-2 infections. Several small-molecule drugs (e.g., nirmatrelvir[4] and ensitrelvir[5]) targeting the SARS-CoV-2 3-chymotrypsin–like cysteine protease enzyme (3CLpro, also known as main protease [Mpro]) are available. However, because of the high costs of the drugs and inequity in their distribution, more drug options are needed to accelerate the resolution of symptoms among patients with mild-to-moderate Covid-19.

Simnotrelvir (SIM0417) is an oral small-molecule antiviral agent that also targets the SARS-CoV-2 3CLpro. On January 29, 2023, it was approved for use under an emergency conditional authorization for the treatment of mild-to-moderate Covid-19 in China.[6] In vitro simnotrelvir showed antiviral activity with a half maximal effective concentration of 43 nmol per liter against the SARS-CoV-2 omicron variant B.1.1.529.1, which was evaluated in Vero E6 cells in combination with CP-100356 (a P-glycoprotein inhibitor).[7] The results of the first-in-human study of simnotrelvir in healthy participants showed that exposure to the highest single dose of 1200 mg of simnotrelvir plus 100 mg of ritonavir and the highest multiple doses of 750 mg of simnotrelvir plus 100 mg of ritonavir twice daily had a clinically acceptable side-effect profile.[8] In a phase 1B trial, 750 mg of simnotrelvir plus 100 mg of ritonavir was found to have an acceptable safety profile and a faster associated decrease in viral load than a regimen of 300 mg of simnotrelvir plus 100 mg of ritonavir.[9]

We conducted a phase 2–3, double-blind, randomized, placebo-controlled trial to investigate the efficacy and safety of simnotrelvir plus ritonavir in the treatment of adult patients with mild-to-moderate Covid-19.

Methods

Trial Design, Patients, and Oversight

We initiated this trial on August 19, 2022, in China. To be eligible for participation, patients needed to be at least 18 years of age, to have onset of signs or symptoms of Covid-19 within 3 days before the first dose of trial drug or placebo, to have at least one sign or symptom of Covid-19 before the first dose of trial drug or placebo, and to have mild or moderate illness. Definitions of disease severity used in the trial were from the Food and Drug Administration and are provided in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.[10] Key exclusion criteria were an anticipated need for a high-flow nasal cannula, noninvasive ventilation, invasive ventilation, or extracorporeal membranous oxygenation within 48 hours; serious kidney, liver, or acute cardiovascular disease; and current or expected use of any medications or substances that have substantial drug interactions with cytochrome P-450 3A4 (Table S2). Detailed eligibility criteria are provided in the protocol, available at NEJM.org.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. The trial was approved by the ethics committee at each site. Written informed consent was obtained from all patients. Safety oversight was performed by the sponsor (Jiangsu Simcere Pharmaceutical) and an independent data and safety monitoring committee. The trial was designed in conjunction with representatives of the sponsor, and statisticians employed by the sponsor analyzed the data. The authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol. Two academic authors and two authors who are employees of the sponsor wrote the first draft. There was no agreement concerning confidentiality between the sponsor and the authors or the research institutions.

Procedures

Eligible patients were randomly assigned, in a 1:1 ratio through a centralized, interactive-response technology system, to receive either 750 mg of simnotrelvir (two tablets, 375 mg per tablet) plus 100 mg of ritonavir or matching placebo twice daily for 5 days. Randomization was stratified in blocks of six according to geographic region, age group (<65 years or ≥65 years), and Covid-19 vaccination status (not fully vaccinated, received primary vaccination, or received booster vaccination). Patients and investigators were unaware of the randomization assignments. The placebo tablets were composed of the same nonpharmaco-

logic fillers and were visually identical to the active drugs. Patients were allowed to take relief medication (ibuprofen or acetaminophen). All the patients were quarantined and closely observed in designated hospitals in accordance with local policy during the trial. Adherence to the trial drug or placebo was assessed by nurses who were unaware of the randomization assignments.

ASSESSMENTS

Patients assessed the severity of 11 Covid-19–associated signs and symptoms (listed in the protocol). The severity was scored on a 4-point scale (with 0 indicating no symptoms, 1 mild symptoms, 2 moderate symptoms, and 3 severe symptoms) twice daily from the time of the first dose (day 1) to day 14 and once daily on days 15 through 29 and was recorded in diaries (Table S3). For vomiting and diarrhea, the point scale was based on the symptom frequency. For other items, the point scale was based on the patient's reply to the question, "What was the severity of your symptom during the previous 12 hours?" (days 1 through 14) or "What was the severity of your symptom during the previous 24 hours?" (days 15 through 29). On days 0, 1, 5, 14, and 29, safety laboratory tests (hematologic tests, blood chemical tests, and electrocardiography) were performed.

Nasopharyngeal or oropharyngeal swab specimens were obtained on days 1, 3, 5 (end-of-treatment visit), 7, 9, and 14 for quantitation of SARS-CoV-2 RNA through reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay at a central laboratory. The type of sample collected (nasopharyngeal or oropharyngeal) was planned to be consistent across all sample points for each individual patient. Adverse events were assessed during the treatment period and for 29 days after the first dose.

END POINTS

The modified intention-to-treat population was defined as all patients who received at least one dose of trial drug or placebo and had a diagnosis of SARS-CoV-2 infection confirmed by RT-PCR, no influenza virus infection, at least one Covid-19–related symptom at baseline, and at least one postbaseline visit (Table S4). Because it was determined that a number of the patients had received the first dose of trial drug or placebo between 72 and 96 hours after the onset of Covid-19 symptoms, patients in the modified intention-to-treat population who had received the first dose of trial drug or placebo within 72 hours were included in a separate analysis population (the modified intention-to-treat–1 population), which served as the main analysis population.

The primary efficacy end point was the time to sustained resolution of symptoms, defined as the time from the first dose to the time when all 11 Covid-19–related symptoms were rated by the patients as absent (i.e., a score of 0) for 2 consecutive days. The primary efficacy end-point analysis was performed in the modified intention-to-treat–1 population as prespecified in the protocol. The validation of the primary end point is shown in Table S5. Secondary efficacy end points included the time to sustained alleviation of all 11 targeted Covid-19 symptoms (defined as a score of ≤1), the occurrence of severe Covid-19, and death. The time to patient-reported return to usual (pre–Covid-19) health status was also explored with the use of the Global Impression Questions (GIQ) scale.[11] Post hoc efficacy analyses included the time to resolution of respiratory symptoms and the time to resolution of systemic symptoms.

Virologic end points included the changes from baseline in the SARS-CoV-2 RNA viral load (see Supplementary Methods). The analyses involved patients with available virologic data in the modified intention-to-treat–1 population. The safety end points included the frequency and severity of adverse events that occurred during the treatment period or the follow-up period (i.e., events that started on or before day 29), which were assessed in all patients who received at least one dose of trial drug or placebo. The safety events were coded according to the *Medical Dictionary for Regulatory Activities*, version 25.0. Exploratory analyses of viral rebound and symptom rebound in the full analysis population were conducted, as well as assessments of drug resistance (see Supplementary Methods).

STATISTICAL ANALYSIS

Assuming that only 80% of 1200 patients enrolled in the trial would be included in the primary analysis, we calculated that a sample of 960 patients, with 949 of these patients having sustained resolution of symptoms, would provide at least 90% power to detect a 24-hour difference in the median time to sustained resolution of symptoms between the simnotrelvir group and the placebo

group at a two-sided significance level of 0.05. Two efficacy interim analysis were planned for when 45% and 70% of the total predicted instances of resolution had occurred in this population.[12] The second interim analysis of the primary end point met the prespecified efficacy criterion.

In this trial, the time to resolution of symptoms was compared between the simnotrelvir group and the placebo group with the use of a Peto–Prentice generalized Wilcoxon test with geographic region, age group, and Covid-19 vaccination status used as stratifying variables (see the Supplementary Appendix). The Peto–Prentice generalized Wilcoxon test was also used for prespecified subgroup analyses of the primary efficacy end point and time to alleviation of 11 symptoms. Mixed models for repeated measures were used for $\log_{10}$ transformation of the changes from baseline in viral load. A post hoc comparison of the time to resolution of respiratory, fever, and systemic symptoms (excluding fever) between the simnotrelvir group and the placebo group was conducted. All P values are two-sided and were calculated with SAS software, version 9.4 (SAS Institute). Additional details of the statistical analyses, including the handling of missing data, are provided in the protocol.

RESULTS

PATIENTS

From August 19, 2022, to December 16, 2022, a total of 1208 patients were enrolled at 35 research sites in China; 603 were assigned to receive simnotrelvir plus ritonavir, and 605 were assigned to receive placebo (Fig. 1). After randomization, 1139 patients received trial drug or placebo and were included in the full analysis population. Of the 1139 patients in the full analysis population, 95.5% of those in the simnotrelvir group and 97.0% of those in the placebo group had good adherence (i.e., they took >80% of the intended doses); the mean (±SD) number of doses taken was 9.7±1.4 (9.7±1.5 in the simnotrelvir group and 9.8±1.3 in the placebo group).

The characteristics of the patients were generally similar in the two groups (Table 1). The median age was 35 years. Overall, the trial recruited a fully vaccinated and relatively young population, with approximately half the patients (609 [53.5%]) having at least one risk factor for severe Covid-19 (Table S6). The most common risk factors were overweight or obesity (35.7%), current or former smoking (22.7%), and cardiovascular disease (4.5%). The percentage of the patients with moderate disease was higher in the simnotrelvir group than in the placebo group (67.5% vs. 61.3%). Almost all the patients (1092 [95.9%]) had completed primary vaccination, and 874 patients (76.7%) had received a booster dose. A total of 1007 patients received trial drug or placebo within 72 hours after symptom onset and were included in the modified intention-to-treat–1 population (Fig. 1). Approximately half the patients (49.6%) received trial drug or placebo within 48 hours after symptom onset. The most frequent Covid-19 symptoms at baseline were sore or dry throat (76.2%), cough (73.4%), stuffy or runny nose (55.9%), headache (52.9%), and fever (52.9%) (Table S7). The percentage of patients who used treatment for symptoms was similar in the two groups (Table S8).

EFFICACY

In the modified intention-to-treat–1 population, the median time to sustained resolution of Covid-19 symptoms (i.e., symptom scores of 0) was significantly shorter in the simnotrelvir group than in the placebo group (180.1 hours [95% confidence interval {CI}, 162.1 to 201.6] vs. 216.0 hours [95% CI, 203.4 to 228.1]; median difference, −35.8 hours [95% CI, −60.1 to −12.4]; P=0.006 by Peto–Prentice test) (Fig. 2A). The results were similar in the sensitivity analysis in which baseline disease severity was added as a covariate in the model (P=0.005 by Peto–Prentice test). In the subgroup of patients with risk factors for severe Covid-19, the median difference in the time to sustained resolution was −60.4 hours (95% CI, −84.3 to −23.2) (Fig. 2B). The efficacy in the modified intention-to-treat and per-protocol populations was similar to that in the modified intention-to-treat–1 population (Fig. S1).

The median time to sustained alleviation of symptoms (i.e., symptom scores of ≤1) was also significantly shorter in the simnotrelvir group than in the placebo group in the modified intention-to-treat–1 population (120.4 hours [95% CI, 119.4 to 132.8] vs. 168.3 hours [95% CI, 155.0 to 191.2]; median difference, −47.9 hours [95% CI, −69.8 to −24.0]) (Fig. S2). In addition, simnotrelvir significantly accelerated the resolution of respiratory symptoms (median between-group dif-

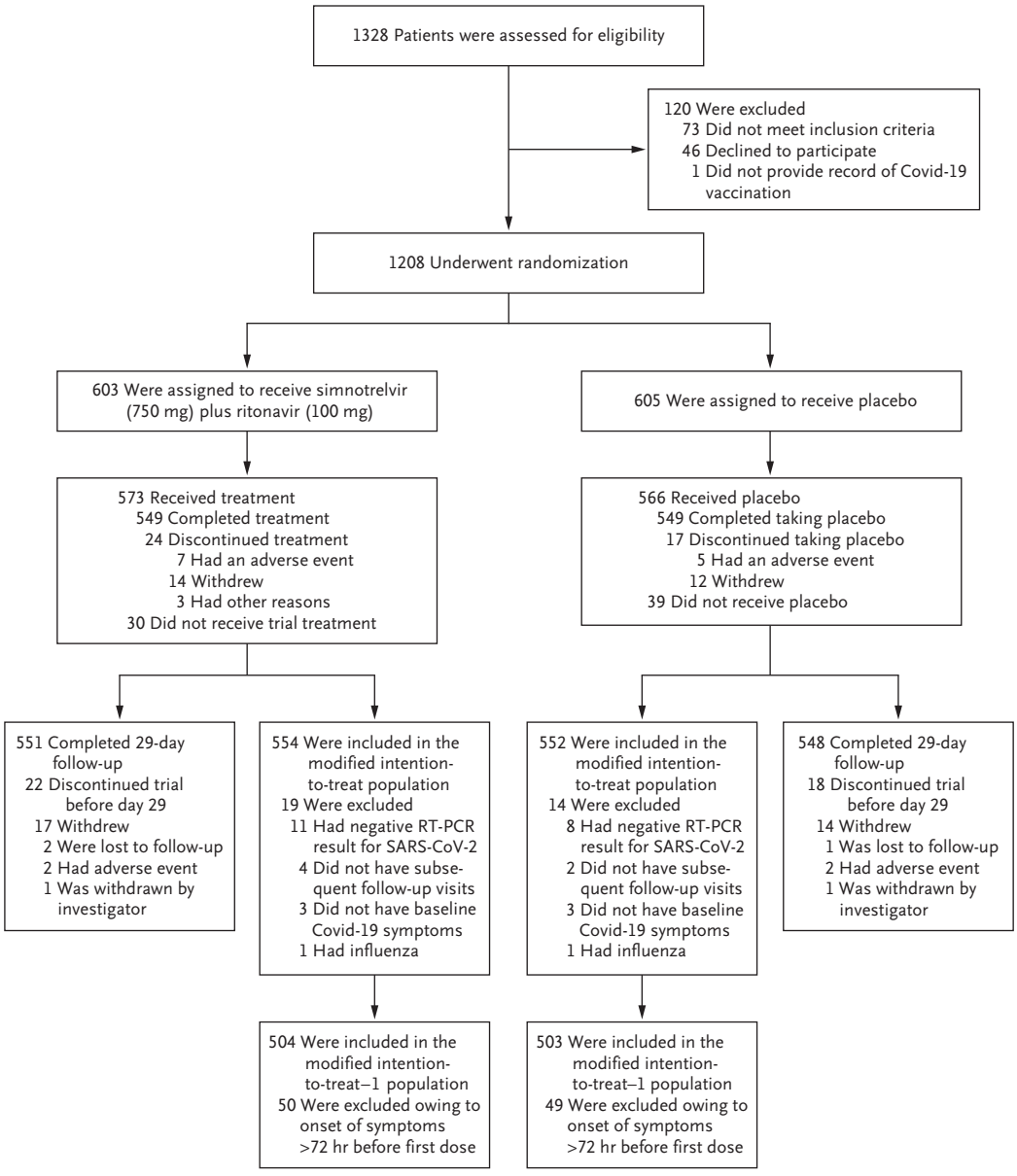


Figure 1. Screening, Randomization, and 29-Day Follow-up.

The modified intention-to-treat population included all patients who received at least one dose of trial drug or placebo and had a diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection confirmed by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay, no influenza virus infection, at least one coronavirus disease 2019 (Covid-19)–related symptom at baseline, and at least one postbaseline visit. Patients in the modified intention-to-treat population who received the first dose of trial drug or placebo within 72 hours after Covid-19 symptom onset were included in the modified intention-to-treat–1 population.

ference, –41.4 hours; 95% CI, –70.7 to –13.3) (Fig. S3A). The time to resolution of systemic symptoms and fever was similar in the two groups (Fig. S3B and S3C). According to the daily score for each of the 11 Covid-19 symptoms and signs, resolution of cough, stuffy or runny nose, and sore or dry throat was the main contributor to the resolution of Covid-19 symptoms. In addition,

fever, chill, headache, stuffy or runny nose, shortness of breath, and muscle or body aches showed substantially greater abatement on the first day of treatment in the simnotrelvir group than in the placebo group (Fig. S4). The GIQ results also showed a shorter time to usual health status in the simnotrelvir group than in the placebo group (Table S9). At day 29, severe Covid-19 had not developed in any patient. No patient in either group died.

VIROLOGY

The baseline viral load was similar in the two groups (Table 1 and Fig. 3). On day 3, the mean (±SE) additional change in viral load from baseline in the simnotrelvir group as compared with the placebo group was –1.10±0.13 $\log_{10}$ copies per milliliter (95% CI, –1.36 to –0.84) (Fig. 3). On day 5, the additional change in viral load with simnotrelvir as compared with placebo was –1.51±0.14 $\log_{10}$ copies per milliliter (95% CI, –1.79 to –1.24) (Fig. 3). The viral load changes at day 7 and day 9 were also greater with simnotrelvir than with placebo. Among the patients in the modified intention-to-treat–1 population who received trial drug or placebo within 48 hours after symptom onset, simnotrelvir also led to greater reductions in viral load than placebo until day 9, with the largest between-group difference observed on day 5 (–1.74±0.18 $\log_{10}$ copies per milliliter; 95% CI, –2.10 to –1.38) (Fig. S5A). Among the patients in the modified intention-to-treat–1 population who received trial drug or placebo between 48 and 72 hours after symptom onset, differences in the decrease in viral load were also maintained until day 9 (Fig. S5B). In the modified intention-to-treat population, differences in the decrease in viral load were similar to those in the modified intention-to-treat–1 population (Fig. S5C).

Among the patients in the modified intention-to-treat–1 population who had available respiratory samples, more than 99% (607 of 611) had the same type of sample obtained at every time point. At baseline, 273 had nasopharyngeal swab specimens, and 338 had oropharyngeal swab specimens. The change from baseline in viral load in the simnotrelvir group as compared with the placebo group was similar for nasopharyngeal and oropharyngeal swabs (Fig. S5D and S5E). After the exclusion of the 4 patients from the modified intention-to-treat–1 population who had both types of swab specimens obtained, the results of viral load analysis remained consistent (Fig. S5F).

REBOUND AND RESISTANCE ASSESSMENT

All 750 patients in the full analysis population who had respiratory samples available (379 in the simnotrelvir group and 371 in the placebo group) were included in the assessment of viral and symptom rebound. Viral rebound occurred in 18 of the 379 patients (4.7%) in the simnotrelvir group and 18 of the 371 patients (4.9%) in the placebo group. Among the patients who had sustained resolution of symptoms by day 14, symptom rebound occurred in 1 of 425 patients (0.2%) in the simnotrelvir group and 2 of 420 patients (0.5%) in the placebo group. No patient had both viral and symptom rebound. Additional details of the results for viral and symptom rebound are provided in Table S10. We did not identify any evidence of drug resistance (see Supplementary Results).

SAFETY

During the period from the first dose through day 29, the incidence of adverse events was higher in the simnotrelvir group than in the placebo group (29.0% vs. 21.6%) (Table 2 and Table S11). These adverse events were mostly of grade 1 or 2. No serious adverse event occurred in the simnotrelvir group, whereas two serious adverse events occurred in two patients in the placebo group. One 28-year-old woman had abdominal pain that was diagnosed as acute appendicitis, and a 46-year-old woman had vaginal bleeding that was diagnosed as adenomyosis. Adverse events during treatment that were considered by the site investigator to be related to trial drug or placebo occurred more frequently in the simnotrelvir group than in the placebo group (17.5% vs. 10.2%). The top three adverse events that were reported as being related to simnotrelvir were an increase in blood triglyceride levels (in 4.3% of the patients in the simnotrelvir group and 2.1% in the placebo group), a decrease in neutrophil count (1.9% and 0.2%), and diarrhea (1.7% and 1.1%).

DISCUSSION

In this phase 2–3 trial of treatment for mild-to-moderate Covid-19, simnotrelvir plus ritonavir shortened the time to sustained symptom resolution by approximately 1.5 days among patients

Table 1. Demographic and Clinical Characteristics of the Patients (Full Analysis Population).*

Characteristic	Simnotrelvir plus Ritonavir (N=573)	Placebo (N=566)	Total (N=1139)
Median age (IQR) — yr	35 (28–47)	35 (28–47)	35 (28–47)
Male sex — no. (%)	333 (58.1)	340 (60.1)	673 (59.1)
Risk factors for severe Covid-19 — no. (%)			
At least one risk factor	302 (52.7)	307 (54.2)	609 (53.5)
Overweight or obesity†	214 (37.3)	193 (34.1)	407 (35.7)
Overweight	182 (31.8)	154 (27.2)	336 (29.5)
Obesity	32 (5.6)	39 (6.9)	71 (6.2)
Current smoking or former smoking	132 (23.0)	127 (22.4)	259 (22.7)
Current smoking	122 (21.3)	122 (21.6)	244 (21.4)
Former smoking	10 (1.7)	5 (0.9)	15 (1.3)
Cardiovascular disease, including hypertension	21 (3.7)	30 (5.3)	51 (4.5)
Chronic liver disease	24 (4.2)	22 (3.9)	46 (4.0)
Age ≥60 yr	18 (3.1)	20 (3.5)	38 (3.3)
Diabetes mellitus	14 (2.4)	15 (2.7)	29 (2.5)
Chronic lung disease	3 (0.5)	6 (1.1)	9 (0.8)
Stroke or cerebrovascular disease	0	1 (0.2)	1 (0.1)
Other risk factors	2 (0.3)	1 (0.2)	3 (0.3)
Covid-19 severity — no. (%)			
Mild	186 (32.5)	219 (38.7)	405 (35.6)
Moderate‡	387 (67.5)	347 (61.3)	734 (64.4)
SARS-CoV-2 strain genotype — no./total no. (%)			
WHO label			
Omicron	62/62 (100)	78/78 (100)	140/140 (100)
Pango lineage			
BA.2.76	2/62 (3)	6/78 (8)	8/140 (6)
BA.4.1	1/62 (2)	0/78	1/140 (1)
BA.5.1.30	0/62	1/78 (1)	1/140 (1)
BA.5.2	15/62 (24)	19/78 (24)	34/140 (24)
BA.5.2.1	2/62 (3)	5/78 (6)	7/140 (5)
BA.5.2.48	29/62 (47)	27/78 (35)	56/140 (40)
BA.5.2.49	8/62 (13)	7/78 (9)	15/140 (11)
BA.5.6	0/62	1/78 (1)	1/140 (1)
BF.21	0/62	2/78 (3)	2/140 (1)
BF.7	0/62	1/78 (1)	1/140 (1)
BF.7.14	4/62 (6)	8/78 (10)	12/140 (9)
BN.1.3	1/62 (2)	0/78	1/140 (1)
XBB.1.4	0/62	1/78 (1)	1/140 (1)
Median total score for 11 targeted symptoms at baseline (IQR)§	6.0 (4.0–8.0)	6.0 (4.0–8.0)	6.0 (4.0–8.0)

Table 1. (Continued.)

Characteristic	Simnotrelvir plus Ritonavir (N=573)	Placebo (N=566)	Total (N=1139)
Time from symptom onset to initiation of trial drug or placebo			
≤48 hr — no. (%)	294 (51.3)	271 (47.9)	565 (49.6)
>48 hr — no. (%)	279 (48.7)	295 (52.1)	574 (50.4)
Median (IQR) — hr	47.5 (32.8–60.7)	51.1 (33.0–63.5)	48.9 (32.9–61.5)
Covid-19 vaccination status — no. (%)¶			
Not fully vaccinated	24 (4.2)	23 (4.1)	47 (4.1)
Primary vaccination	109 (19.0)	109 (19.3)	218 (19.1)
Boosted vaccination	440 (76.8)	434 (76.7)	874 (76.7)
Viral load — $\log_{10}$ copies per milliliter	6.25±2.10	6.36±1.91	6.30±2.01

* Plus–minus values are means ±SD. The full analysis population included all patients who underwent randomization and received at least one dose of trial drug or placebo, included in the analysis according to the intention-to-treat principle. Covid-19 denotes coronavirus disease 2019, IQR interquartile range, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, and WHO World Health Organization.

† Overweight was defined as a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 25 to 29, and obesity was defined as a BMI of 30 or greater.

‡ Patients were defined as having moderate Covid-19 if they did not meet criteria for severe Covid-19, had an oxygen saturation of more than 93% while breathing room air, and met one or more of the following criteria: shortness of breath with activity or exercise, respiratory rate of 20 to 29 breaths per minute, or heart rate of 90 to 124 beats per minute.

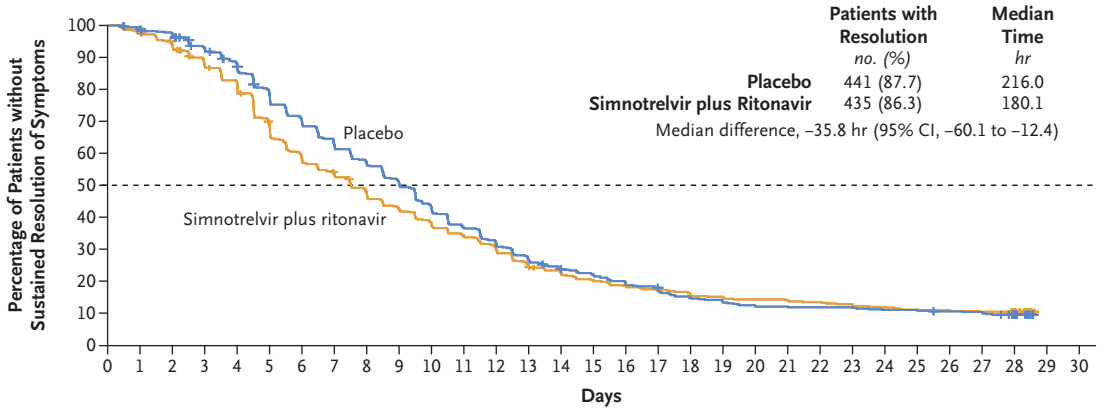
§ Patients assessed the severity of each of 11 Covid-19–associated signs and symptoms (listed in the protocol) on a 4-point scale, with 0 indicating no symptoms, 1 mild symptoms, 2 moderate symptoms, and 3 severe symptoms.

¶ Most of the vaccinated patients (83.6%) received either the Sinopharm Vero cell inactivated vaccine (58.4%) or the Sinovac Vero cell inactivated vaccine (25.2%), and 5.5% received the Anhui Zhifei Longcom recombinant subunit vaccine; the remainder received the Biokangtai Vero cell inactivated vaccine (2.3%), the CanSino adenovirus vector vaccine (1.9%), the Pfizer–BioNTech mRNA vaccine (1.0%), the Moderna mRNA vaccine (0.8%), or another vaccine (2.9%).

who received treatment within 3 days after symptom onset. Simnotrelvir had more benefits for the alleviation of respiratory symptoms than placebo. In addition, simnotrelvir was associated with an additional decrease in viral load until day 9. The most pronounced antiviral effect occurred on day 5, when the decrease in viral load in the simnotrelvir group was 1.51 $\log_{10}$ copies per milliliter greater than that in the placebo group. Most adverse events were mild or moderate.

For patients with mild-to-moderate Covid-19, viral replication and direct viral damage are important drivers of disease.[13] Persistent Covid-19 symptoms have been found to be associated with poor quality of life.[14,15] However, the benefits of antiviral medications in shortening the disease course have still not been fully determined. In the Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients (EPIC-SR) trial, nirmatrelvir plus ritonavir did not accelerate sustained alleviation of 11 symptoms.[16,17] However, data from the Stopping COVID-19 Progression with Early Protease Inhibitor Treatment in Standard-Risk Patients (SCORPIO-SR) trial and the Platform Adaptive Trial of Novel Antivirals for Early Treatment of COVID-19 in the Community (PANORAMIC) suggested that oral small-molecule antiviral drugs could provide clinical benefits in shortening the duration of symptoms.[18,19] Nirmatrelvir, ensitrelvir, and simnotrelvir were associated with a maximum difference from placebo of approximately 1, 1.4, and 1.5 $\log_{10}$ copies per milliliter, respectively, in viral-load decrease.[16,18] Various factors may contribute to the disparity in the aforementioned clinical and antiviral effects, including research settings, blinding status, definitions of outcomes, patient characteristics, dose of the medications, and techniques used in obtaining and testing the respiratory samples. A direct comparison in the same trial will be nec-

A Time to Sustained Resolution of Covid-19 Symptoms



No. at Risk

Placebo	503	495	484	457	425	379	337	304	274	244	207	179	152	129	114	106	91	85	70	63	57	56	56	55	52	52	49	48	38	0
Simnotrelvir plus ritonavir	504	489	463	429	394	329	281	258	227	205	182	164	145	119	106	95	87	82	73	70	67	66	63	57	56	52	51	49	45	0

B Subgroup Analysis of Time to Sustained Resolution of Symptoms

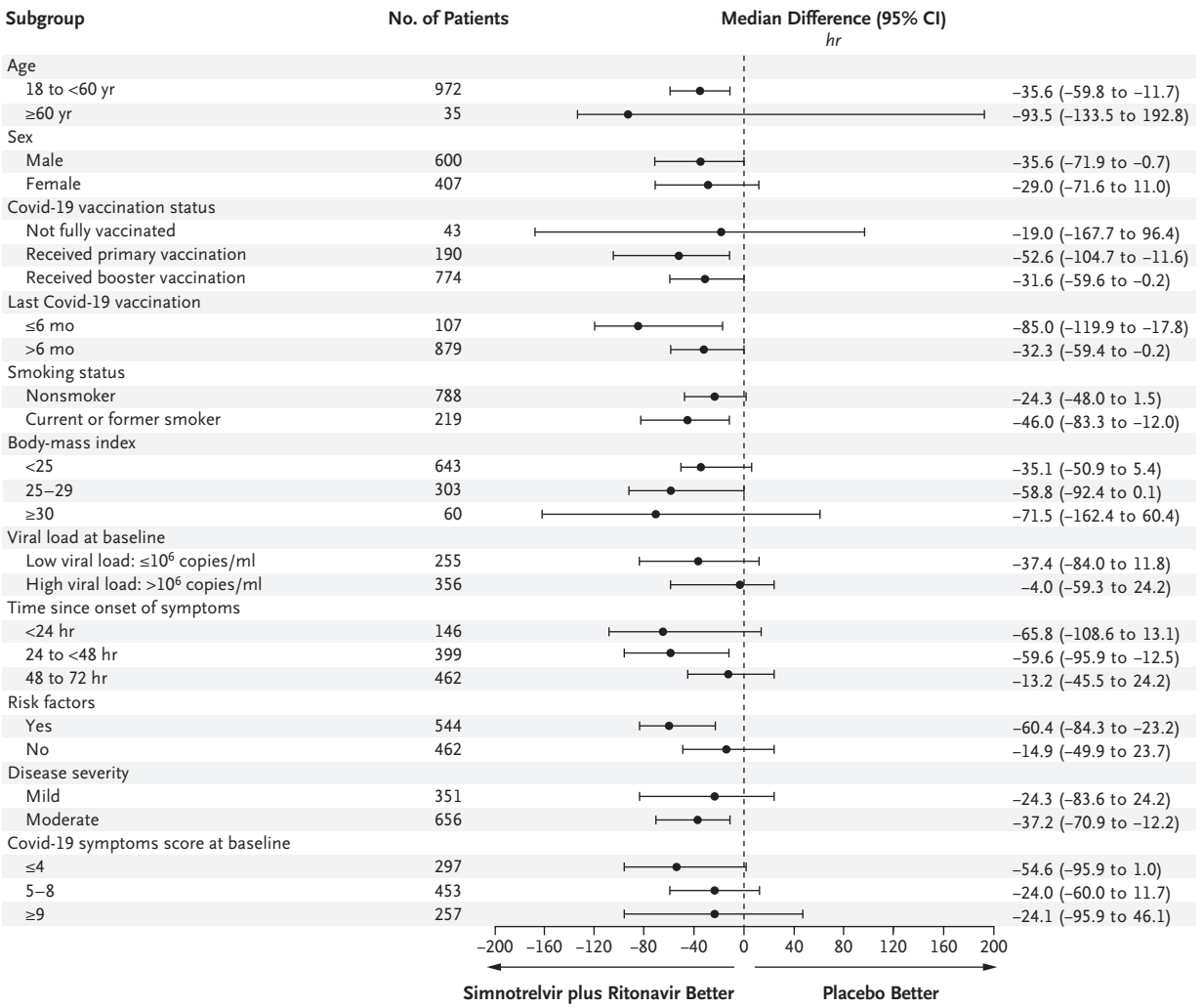


Figure 2 (facing page). Time to Sustained Resolution of Covid-19 Symptoms.

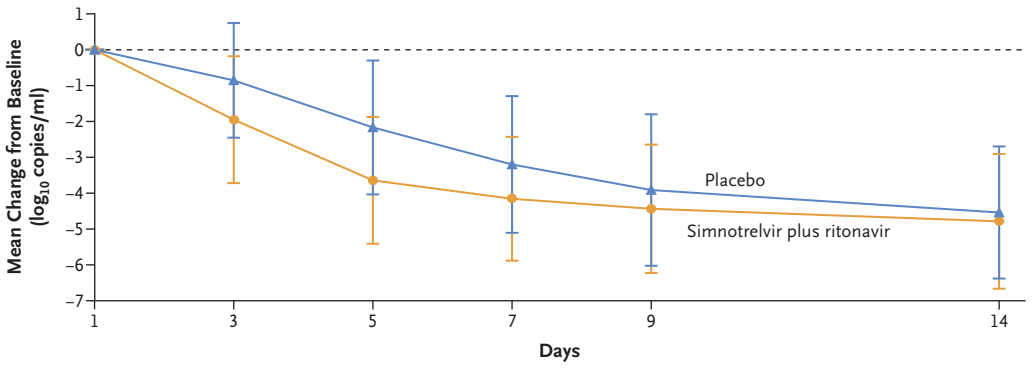
Panel A shows the Kaplan–Meier curve for the time to sustained resolution of 11 targeted Covid-19 symptoms in the modified intention-to-treat–1 population. Panel B shows the results of the subgroup analysis of this end point. The confidence intervals in Panel B have not been adjusted for multiplicity, and therefore inferences drawn from the intervals may not be reproducible. The body-mass index is the weight in kilograms divided by the square of the height in meters; values were rounded to whole numbers.

essary to infer the actual differences in efficacy among these antiviral agents.

Observational studies have indicated that even in the vaccinated population, nirmatrelvir use is associated with lower mortality among older persons or persons at increased risk for disease progression.[20,21] Because of the absence of events, we cannot assess the effect of simnotrelvir on reducing the risk of disease progression in this trial. Because the subgroup analyses in the trial were not adequately powered and were not corrected for type I error, they should not be used to draw definitive conclusions about efficacy, and the apparent difference in the point estimates in different subgroups should be interpreted with caution. We plan to undertake real-world observational studies as well as phase 4 trials to further evaluate end points such as death and disease progression, as well as to determine the efficacy in different subgroups.

The most frequent adverse event that occurred at a higher incidence in the simnotrelvir group than in the placebo group was an increase in the blood triglyceride level. This adverse event is also common in association with other 3CLpro inhibitors, including nirmatrelvir[22] and ensitrelvir.[18] Post-authorization pharmacovigilance is important, as is close monitoring of the safety profile of the drug in larger populations in real-world clinical settings.

The trial has strengths and limitations. First, we recruited vaccinated people, approximately half of whom had risk factors for severe Covid-19. The trial population is similar to the general population in terms of immunity against SARS-CoV-2 and risk-factor status. Second, although the double-blind design of the trial decreases the placebo effect in symptom evaluation, the placebo contained only excipients; therefore, unblinding may have occurred in some patients, given the unique taste of ritonavir. Third, the recruited population was relatively young. The efficacy and safety among older patients still warrants investigations



No. at Risk						
Placebo	311	297	283	273	232	82
Simnotrelvir plus ritonavir	300	288	284	249	201	48
Change from Baseline						
Mean (±SE)		−1.10±0.13	−1.51±0.14	−0.98±0.14	−0.55±0.15	−0.27±0.27
95% CI		−1.36 to −0.84	−1.79 to −1.24	−1.24 to −0.71	−0.86 to −0.25	−0.81 to −0.26

Figure 3. Change from Baseline in Viral Load over Time among Patients Treated within 72 Hours after Symptom Onset.

Mean changes are shown for 300 patients in the simnotrelvir group and 311 in the placebo group; I bars indicate standard errors. The mean (±SD) viral loads on day 1 were 6.25±2.02 $\log_{10}$ copies per milliliter in the simnotrelvir group and 6.33±1.91 $\log_{10}$ copies per milliliter in the placebo group in the modified intention-to-treat–1 population. I bars indicate standard deviations.

Table 2. Adverse Events That Emerged during the Treatment or Follow-up Period (Safety Population).*

Adverse Event	Simnotrelvir plus Ritonavir (N=573)	Placebo (N=566)
Events that emerged during treatment or follow-up		
No. of events	255	169
Patients with an event — no. (%)		
Any adverse event	166 (29.0)	122 (21.6)
Serious adverse event	0	2 (0.4)
Grade 3 adverse event	12 (2.1)	7 (1.2)
Grade 4 or 5 adverse event	0	0
Discontinued trial drug or placebo because of adverse event	7 (1.2)	5 (0.9)
Had temporary discontinuation owing to adverse event	0	0
Events considered to be related to trial drug or placebo		
No. of events	140	79
Patients with an event — no. (%)		
Any adverse event	100 (17.5)	58 (10.2)
Serious adverse event	0	0
Grade 3 adverse event	5 (0.9)	1 (0.2)
Grade 4 or 5 adverse event	0	0
Discontinued trial drug or placebo because of adverse event	7 (1.2)	3 (0.5)
Had temporary discontinuation owing to adverse event	0	0
Specific types of adverse events related to trial drug or placebo		
Increase in blood triglyceride level	25 (4.3)	12 (2.1)
Decrease in neutrophil count†	11 (1.9)	1 (0.2)
Diarrhea	10 (1.7)	6 (1.1)

* The safety population included all patients who received at least one dose of trial drug or placebo, included in the analysis according to the as-treated principle. Events that occurred on or before day 29 were included in the analysis.
† No patients in the simnotrelvir group had a decrease in neutrophil count to lower than 1.0×10^9 per liter.

in future research. Finally, both nasopharyngeal and oropharyngeal swabs were used in this trial. However, the sampling method was consistent in nearly all patients (excluding four) across the trial visits. The sensitivity analysis showed a limited effect on the virologic analysis.

In this trial, early administration of simnotrelvir plus ritonavir was effective in shortening the time to symptom resolution among adult patients with Covid-19, without evident safety concerns.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

The authors' affiliations are as follows: the Departments of Pulmonary and Critical Care Medicine (B.C., Y.W., L.S., J.X., Chen Wang) and Clinical Research and Data Management (X.G.), Institute of Respiratory Medicine in the Chinese Academy of Medical Sciences, National Clinical Research Center for Respiratory Diseases, National Center for Respiratory Medicine, China–Japan Friendship Hospital, Changping Laboratory (B.C., Chen Wang), the Department of Medicine, Non-oncology, Jiangsu Simcere Pharmaceutical (Y.Y.), Clinical and Research Center of Infectious Diseases Beijing Ditan Hospital, Capital Medical University (R.J.), and Chinese Academy of Medical Sciences and Peking Union Medical College (Chen Wang), Beijing, the Department of Infectious Diseases, Third People's Hospital of

Shenzhen, National Clinical Research Center for Infectious Diseases, Shenzhen (H.L., F.W.), Jin Yin-tan Hospital (C.H., F.G.) and Wuhan Institute of Virology, Chinese Academy of Sciences (L.Z.), Wuhan, the Public Health Clinical Center of Chengdu, Chengdu (Z.C.), Tianjin First Central Hospital, Tianjin (Y.L.), the Department of Cardiology, Hainan Third People's Hospital, Sanya (L.L.), the Department of Respiratory Medicine, Guangzhou Eighth People's Hospital, Guangzhou (P.P.), the Department of Clinical Statistics and Data Management, Jiangsu Simcere Pharmaceutical (H.H.), the Department of Infection and Immunity, Shanghai Public Health Clinical Center (Y.S.), and the Department of Infectious Diseases, Zhongshan Hospital (B.H.), Fudan University, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences (J.S., Y.X.), and the Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, and Key Laboratory of Carcinogenesis and Cancer Invasion of the Ministry of Education (J.F.), Shanghai, the Second Hospital of Nanjing (C.C.), Jiangsu Simcere Pharmaceutical (R.T.), and State Key Laboratory of Neurology and Oncology Drug Development (R.T.), Nanjing, the First Affiliated Hospital of Xiamen University, Xiamen (X. Yao), Guizhou Provincial People's Hospital, Guiyang (X. Ye, H.Z.), the Second Department of Infection, Shandong Public Health Clinical Center, Jinan (C.L.), Xuzhou Infectious Diseases Hospital, Xuzhou (Chunying Wang), and Central People's Hospital of Zhanjiang, Zhanjiang (Z.Y.) — all in China.

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