

ORIGINAL ARTICLE

VV116 versus Nirmatrelvir–Ritonavir for Oral Treatment of Covid-19

Z. Cao, W. Gao, H. Bao, H. Feng, S. Mei, P. Chen, Yueqiu Gao, Z. Cui, Q. Zhang, X. Meng, H. Gui, W. Wang, Y. Jiang, Z. Song, Y. Shi, J. Sun, Y. Zhang, Q. Xie, Y. Xu, G. Ning, Yuan Gao, and R. Zhao

ABSTRACT

BACKGROUND

Nirmatrelvir–ritonavir has been authorized for emergency use by many countries for the treatment of coronavirus disease 2019 (Covid-19). However, the supply falls short of the global demand, which creates a need for more options. VV116 is an oral antiviral agent with potent activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

METHODS

We conducted a phase 3, noninferiority, observer-blinded, randomized trial during the outbreak caused by the B.1.1.529 (omicron) variant of SARS-CoV-2. Symptomatic adults with mild-to-moderate Covid-19 with a high risk of progression were assigned to receive a 5-day course of either VV116 or nirmatrelvir–ritonavir. The primary end point was the time to sustained clinical recovery through day 28. Sustained clinical recovery was defined as the alleviation of all Covid-19–related target symptoms to a total score of 0 or 1 for the sum of each symptom (on a scale from 0 to 3, with higher scores indicating greater severity; total scores on the 11-item scale range from 0 to 33) for 2 consecutive days. A lower boundary of the two-sided 95% confidence interval for the hazard ratio of more than 0.8 was considered to indicate noninferiority (with a hazard ratio of >1 indicating a shorter time to sustained clinical recovery with VV116 than with nirmatrelvir–ritonavir).

RESULTS

A total of 822 participants underwent randomization, and 771 received VV116 (384 participants) or nirmatrelvir–ritonavir (387 participants). The noninferiority of VV116 to nirmatrelvir–ritonavir with respect to the time to sustained clinical recovery was established in the primary analysis (hazard ratio, 1.17; 95% confidence interval [CI], 1.01 to 1.35) and was maintained in the final analysis (median, 4 days with VV116 and 5 days with nirmatrelvir–ritonavir; hazard ratio, 1.17; 95% CI, 1.02 to 1.36). In the final analysis, the time to sustained symptom resolution (score of 0 for each of the 11 Covid-19–related target symptoms for 2 consecutive days) and to a first negative SARS-CoV-2 test did not differ substantially between the two groups. No participants in either group had died or had had progression to severe Covid-19 by day 28. The incidence of adverse events was lower in the VV116 group than in the nirmatrelvir–ritonavir group (67.4% vs. 77.3%).

CONCLUSIONS

Among adults with mild-to-moderate Covid-19 who were at risk for progression, VV116 was noninferior to nirmatrelvir–ritonavir with respect to the time to sustained clinical recovery, with fewer safety concerns. (Funded by Vigonvita Life Sciences and others; ClinicalTrials.gov number, NCT05341609; Chinese Clinical Trial Registry number, ChiCTR2200057856.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Zhao can be contacted at zhaorensurgeon@aliyun.com or at the Department of General Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 197 2nd Ruijin Rd., Shanghai, China.

Drs. Cao, W. Gao, Bao, Feng, and Mei and Drs. Xie, Xu, Ning, Yuan Gao, and Zhao contributed equally to this article.

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THE CORONAVIRUS DISEASE 2019 (COVID-19) pandemic continues to spread rapidly worldwide,^{1,2} and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has evolved into variants with increasing transmissibility and capability of evading human immunity (e.g., the B.1.1.529 [omicron] variant).³⁻⁵ A widespread and timely distribution of efficacious antiviral therapy is an important part of the response.^{6,7}

Currently, nirmatrelvir-ritonavir⁸ is recommended by World Health Organization (WHO) guideline for treating mild-to-moderate Covid-19.⁹ Nirmatrelvir is an oral inhibitor of the SARS-CoV-2 3-chymotrypsin-like cysteine protease enzyme that can be dispensed at community pharmacies and has been authorized for emergency use by many countries. However, access to nirmatrelvir is limited worldwide, and its effectiveness depends on ritonavir,¹⁰ which has multiple drug-drug interactions warranting specialized assessment before prescription. Remdesivir is also recommended¹¹ but needs to be administered intravenously, which limits its widespread use during the pandemic. Therefore, several oral analogues of remdesivir have been developed to address this issue, including GS-621763,¹² ATV006,¹³ and VV116.^{14,15}

VV116 is a deuterated remdesivir hydrobromide with oral bioavailability and potent activity against SARS-CoV-2 in studies in animals¹⁵ and satisfactory safety and side-effect profiles in phase 1 trials.¹⁶ A preliminary small-scale study has shown a shorter viral shedding time in patients with Covid-19 who received VV116 within 5 days after the first positive test than in those who received regular care.¹⁷ However, the efficacy of VV116 for clinical recovery, symptom resolution, and prevention of disease progression remains unknown, particularly as compared with nirmatrelvir-ritonavir. In addition, the safety profiles of VV116 have not been fully assessed. Here, we report the results of a phase 3 trial of VV116 as compared with nirmatrelvir-ritonavir for oral treatment of symptomatic participants at high risk for progression to severe Covid-19 during the omicron outbreak.

METHODS

TRIAL DESIGN AND RANDOMIZATION

In this multicenter, observer-blinded, randomized, controlled trial, symptomatic participants at high risk for progression to severe Covid-19 were randomly assigned in a 1:1 ratio to receive either oral VV116 (600 mg every 12 hours on day 1 and 300 mg every 12 hours on days 2 through 5) or oral nirmatrelvir-ritonavir (300 mg of nirmatrelvir plus 100 mg of ritonavir every 12 hours for 5 days) (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). VV116 was manufactured and provided by Vigonvita Life Sciences. The selection of nirmatrelvir-ritonavir as the active control for comparison with VV116 was based on the established superiority of nirmatrelvir-ritonavir to placebo¹² and on its recommendation as the standard treatment for our target population by the WHO guideline.¹¹

Randomization was performed with the use of a centralized, interactive Web response system. All the site investigators, site staff (except for those who administered the trial drugs), and those who were involved in end-point assessments were unaware of the trial-group assignments until unblinding on May 20, 2022. Participants remained aware of the trial-group assignments throughout the trial. Additional details are provided in the Supplementary Appendix.

The data-cutoff date for the primary analysis was May 13, 2022, when the target number of primary end-point events (>724 events) was reached in the full analysis population. The data-cutoff date for the final analysis was August 18, 2022.

TRIAL OVERSIGHT

The trial was approved by the National Human Genetic Resources Committee in China and the institutional review board or ethics committee at each trial site before the start of recruitment and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. One of the sponsors, Vigonvita Life Sciences, designed and monitored the trial and collected and analyzed the data in collaboration with the site investigators. Safety oversight was



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performed by Vigonvita Life Sciences and the institutional review board or ethics committee at each site. The first author drafted the manuscript, and the writing committee revised the manuscript and made the decision to submit it for publication. All the authors had data confidentiality agreements with Vigonvita Life Sciences and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org.

PARTICIPANTS

After written informed consent was obtained, participants from seven hospitals in Shanghai, China, that were designated by the Chinese government for the treatment of Covid-19 were assessed for eligibility between April 4, 2022, and May 2, 2022. Adults 18 years of age or older were eligible if they had mild-to-moderate Covid-19 with a total symptom score of 2 or more as determined on the basis of definitions adapted from the Food and Drug Administration.¹⁸ Symptom scores range from 0 to 3 (with higher scores indicating greater severity) for each of 11 symptoms; total symptom scores range from 0 to 33 (Table S1). Other key inclusion criteria were a positive SARS-CoV-2 reverse-transcriptase–polymerase-chain-reaction (RT-PCR) test with an additional finding indicating early infection or high viral activity (the findings are listed in the Supplementary Appendix), and at least one risk factor for progression to severe Covid-19.

Key exclusion criteria were confirmed or suspected severe or critical Covid-19 or an anticipated need for mechanical ventilation before randomization, an alanine aminotransferase or aspartate aminotransferase level that was more than 1.5 times the upper limit of the normal range, an estimated glomerular filtration rate (eGFR) of less than 60 ml per minute, or the use of contraindicated drugs listed in the package insert of nirmatrelvir–ritonavir. Although nirmatrelvir–ritonavir is not contradicted in persons with an eGFR of 30 to less than 60 ml per minute, we excluded these participants to avoid a potential overdose in the updated protocol (version 3.0; April 10, 2022). Before that date, a total of 38 participants with an eGFR of 30 to less than 60 ml per minute had been enrolled in the trial (16 in the VV116 group and 22 in the nirmatrelvir–ritonavir group). Full eligibility cri-

teria are provided in the Supplementary Appendix and protocol.

ASSESSMENT

Covid-19–related symptom scores (described above) and scores on the WHO Clinical Progression Scale (range, 0 to 10, with higher scores indicating a worse clinical condition) (Table S2) were determined by investigators on day 1 before the trial-drug administration, followed by assessment at approximately the same time every day until the resolution of Covid-19–related target symptoms or day 28, whichever was earlier. SARS-CoV-2 RNA from nasopharyngeal swabs was measured by RT-PCR assay at each site, with both qualitative data (positive or negative) and quantitative data (cycle-threshold value) obtained if available. More details of assessment and data collection are provided in the protocol.

END POINTS

The primary efficacy end point was the time from randomization to sustained clinical recovery through day 28. Sustained clinical recovery was defined as the alleviation of all Covid-19–related target symptoms to a total symptom score of 0 or 1 (range, 0 to 33, with higher scores indicating greater severity) for 2 consecutive days. The first day of the 2-consecutive-day period was considered to be the event date. Secondary efficacy end points included progression to severe or critical Covid-19 or death from any cause; the change in Covid-19–related symptom score and the score on the WHO Clinical Progression Scale through day 28, the time to sustained resolution of all target symptoms and to a first negative SARS-CoV-2 test, and clinical recovery, symptom resolution, and a negative SARS-CoV-2 test by prespecified days. Safety end points included adverse events and serious adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Any adverse event that emerged or worsened from the time of informed consent through day 28 was actively recorded and reported for trial-regimen recipients. Details of the end points are provided in the Supplementary Appendix and Table S3. The primary end point was assessed in the primary analysis (data-cutoff date, May 13, 2022), and the data were updated in the final analysis (data-cutoff date, August 18, 2022).

STATISTICAL ANALYSIS

The primary efficacy hypothesis was that VV116 would be noninferior to nirmatrelvir–ritonavir with respect to sustained clinical recovery. Owing to the lack of data on the time to clinical recovery in participants with omicron infection treated with nirmatrelvir–ritonavir, the reference duration of 5.5 days was estimated on the basis of the duration of acute symptoms in persons infected with SARS-CoV-2 during the omicron wave¹⁹ and an overall vaccination rate of more than 90% in the general population in Shanghai.²⁰ To satisfy the noninferiority hypothesis, the lower boundary of the two-sided 95% confidence interval for the hazard ratio of the primary end point had to be above 0.8. The noninferiority margin corresponds to a duration of 6.875 days to sustained clinical recovery, which is 25% longer than 5.5 days. A minimum of 724 events were required to ensure a statistical power of 85%.

The noninferiority hypothesis was tested in the full analysis population — that is, the modified intention-to-treat population (all the participants who underwent randomization and received at least one dose of VV116 or nirmatrelvir–ritonavir). Sensitivity analyses involved participants who started a trial regimen within 5 days after symptom onset and the per-protocol population. The intention-to-treat population (all the participants who underwent randomization) was analyzed post hoc. Details of the analysis populations are provided in Tables S4 and S5.

For all the other efficacy analyses, data were analyzed in the full analysis population. The Kaplan–Meier method was used to estimate the median time to sustained clinical recovery, with the 95% confidence interval estimated by means of the Brookmeyer–Crowley method with log–log transformation. The hazard ratio for time to sustained clinical recovery and its 95% confidence interval were estimated with the use of the Cox proportional-hazards model. Data for participants without sustained clinical recovery were censored on the last day on which Covid-19–related symptoms or signs were recorded. Participants with missing end-point data were considered to have not had clinical recovery on that day, and a sensitivity analysis was performed with the use of the multiple-imputation method. Subgroup analyses of the primary end point were prespecified to assess the consistency of

the intervention effect. For efficacy results other than the primary end point in the full analysis population, 95% confidence intervals have not been adjusted for multiplicity and should not be used to infer treatment effects. Additional details are provided in the statistical analysis plan, available with the protocol.

RESULTS

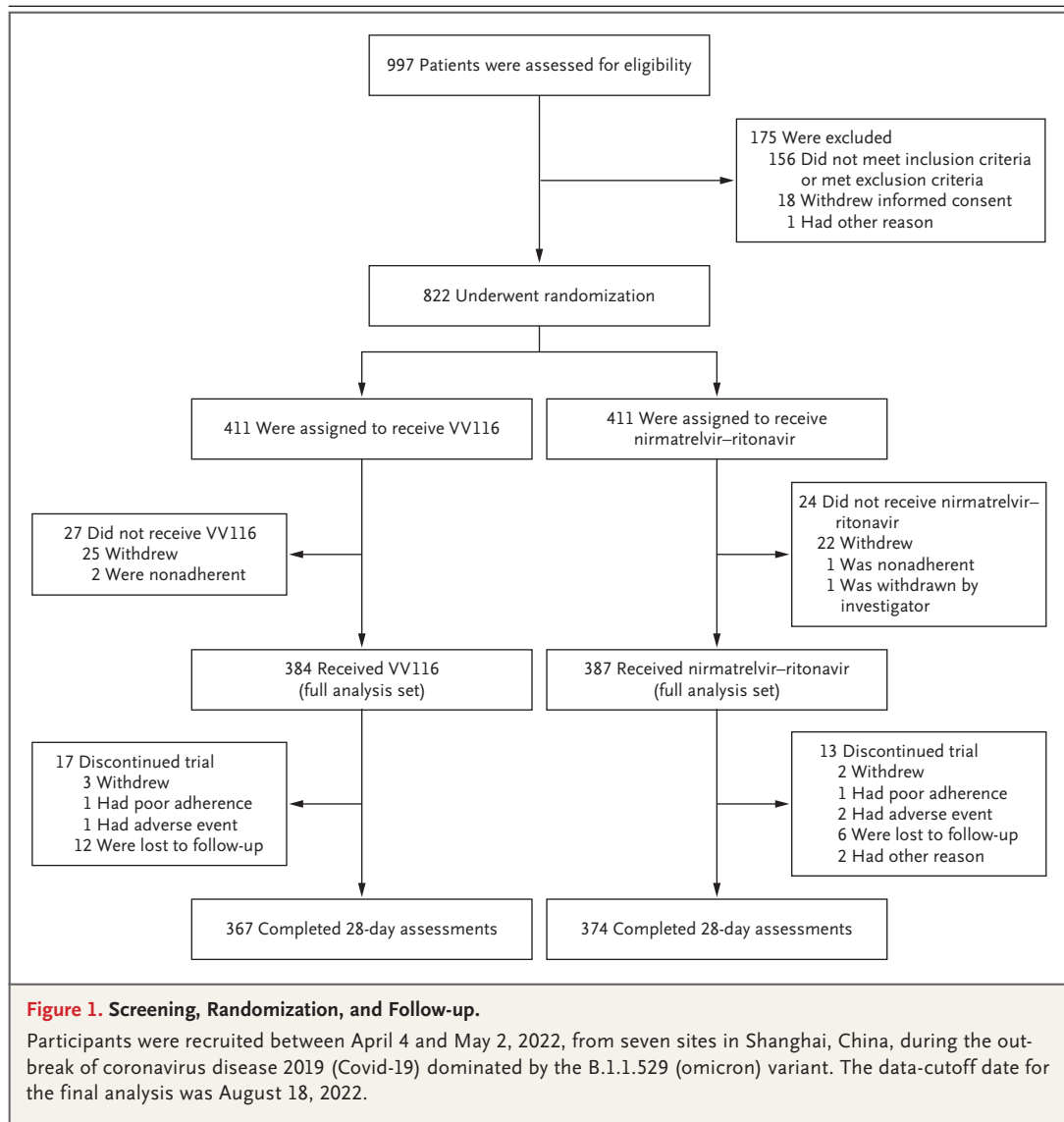
PARTICIPANTS

A total of 997 participants were screened from April 4 through May 2, 2022, and 822 were randomly assigned to receive VV116 (411 participants) or nirmatrelvir–ritonavir (411 participants). Of these 822 participants, 741 (90.1%) completed 28-day follow-up, 51 (6.2%) did not receive VV116 or nirmatrelvir–ritonavir, and 30 (3.6%) had discontinued the trial by the time of the final analysis (data-cutoff date, August 18, 2022) (Fig. 1 and Table S6).

The characteristics of the full analysis population at baseline were balanced between the VV116 group (384 participants) and the nirmatrelvir–ritonavir group (387 participants) (Table 1) and were largely representative of the expected patient population (Table S7). The median age of the participants was 53 years (interquartile range, 38 to 66), and approximately half were women. Most participants (92.1%) had mild Covid-19, and three quarters were fully vaccinated or boosted. The most common risk factor for progression to severe Covid-19 at baseline was an age of 60 years or older (37.7%), followed by cardiovascular disease (including hypertension) (35.1%), a body-mass index (weight in kilograms divided by the square of the height in meters) of 25 or higher (32.9%), current smoking (12.5%), and diabetes (10.1%). Most participants (77.3%) received trial regimens within 5 days after symptom onset. Medication adherence was similar in the two groups, with a mean (\pm SD) of 9.7 ± 1.6 doses taken in the VV116 group and 9.4 ± 2.0 doses taken in the nirmatrelvir–ritonavir group. More information on received vaccines, coexisting conditions, and adherence is provided in Tables S8, S9, and S10.

PRIMARY END POINT

In the primary analysis involving the full analysis population, sustained clinical recovery occurred in 377 participants in the VV116 group



and 378 participants in the nirmatrelvir–ritonavir group. The hazard ratio for the time from randomization to sustained clinical recovery (VV116 vs. nirmatrelvir–ritonavir) was 1.17 (95% confidence interval [CI], 1.01 to 1.35; lower boundary, >0.8), which indicates that the noninferiority of VV116 to nirmatrelvir–ritonavir was established.

In the final analysis of this population, the hazard ratio for the time to sustained clinical recovery (VV116 vs. nirmatrelvir–ritonavir) was 1.17 (95% CI, 1.02 to 1.36; lower boundary, >0.8); the estimated median time to sustained

clinical recovery was 4 days and 5 days, respectively, and the 25th percentile of the time to sustained clinical recovery was 4 days (95% CI, 3 to 4) in both groups (Fig. 2A and Table 2). Consistent results were also found in a sensitivity analysis with imputation of missing endpoint data (hazard ratio, 1.17; 95% CI, 1.01 to 1.35). Noninferiority of VV116 to nirmatrelvir–ritonavir was also observed in the per-protocol population (Fig. 2B), among participants who started treatment within 5 days after symptom onset (Fig. 2C), and in the intention-to-treat population (Fig. S2). In most prespecified sub-

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

Characteristic	VV116 (N=384)	Nirmatrelvir–Ritonavir (N=387)	Total (N=771)
Median age at randomization (range) — yr	53.0 (18–94)	53.0 (18–91)	53.0 (18–94)
Sex — no. (%)			
Male	185 (48.2)	199 (51.4)	384 (49.8)
Female	199 (51.8)	188 (48.6)	387 (50.2)
Ethnic group — no. (%)†			
Han	384 (100)	385 (99.5)	769 (99.7)
Other	0	2 (0.5)	2 (0.3)
Vaccination status — no. (%)			
Unvaccinated	94 (24.5)	93 (24.0)	187 (24.3)
Standard course	117 (30.5)	121 (31.3)	238 (30.9)
Boosted course	173 (45.1)	173 (44.7)	346 (44.9)
Covid-19 severity — no. (%)			
Mild	355 (92.4)	355 (91.7)	710 (92.1)
Moderate	29 (7.6)	32 (8.3)	61 (7.9)
Covid-19–related symptoms			
Median time from onset of first symptom to first dose (IQR) — days	4 (3–5)	4 (3–5)	4 (3–5)
Median total score for Covid-19–related target symptoms (IQR) — points‡	3.0 (3.0–5.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)
Risk factors for severe illness from Covid-19 — no. (%)			
Age of ≥60 yr	144 (37.5)	147 (38.0)	291 (37.7)
Cardiovascular disease, including hypertension	129 (33.6)	142 (36.7)	271 (35.1)
Obesity§	124 (32.3)	130 (33.6)	254 (32.9)
Current smoking	46 (12.0)	50 (12.9)	96 (12.5)
Diabetes mellitus	35 (9.1)	43 (11.1)	78 (10.1)
Chronic lung disease	21 (5.5)	23 (5.9)	44 (5.7)
Active cancer	15 (3.9)	17 (4.4)	32 (4.2)
Chronic kidney disease	2 (0.5)	9 (2.3)	11 (1.4)
Immunosuppressive disease or use of immunosuppressive treatment	0	1 (0.3)	1 (0.1)
Virology			
Median time from first RT-PCR confirmation of SARS-CoV-2 to first dose (IQR) — days	4 (3–5)	4 (3–5)	4 (3–5)
Median SARS-CoV-2 RNA cycle-threshold value from nasopharyngeal swab (IQR)¶	21.5 (18.5–25.6)	21.9 (18.9–26.1)	21.7 (18.6–25.8)

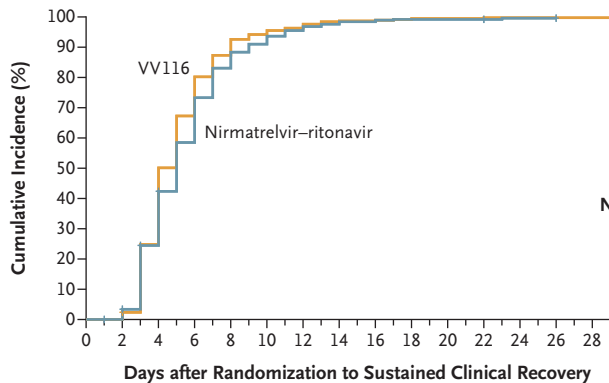
* Shown are participants who underwent randomization and received at least one dose of VV116 or nirmatrelvir–ritonavir. Participants were grouped according to treatment assignment. Percentages may not total 100 because of rounding. Covid-19 denotes coronavirus disease 2019, IQR interquartile range, RT-PCR reverse-transcriptase–polymerase chain reaction, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

† Ethnic group was reported by the participant.

‡ Symptom scores range from 0 to 3 (with higher scores indicating greater severity) for each of 11 symptoms; total symptom scores range from 0 to 33.

§ Obesity was defined as a body-mass index of 25 or higher in accordance with World Health Organization (WHO) criteria for adult Asians.

¶ Data were available for 291 participants in the VV116 group and 307 participants in the nirmatrelvir–ritonavir group.

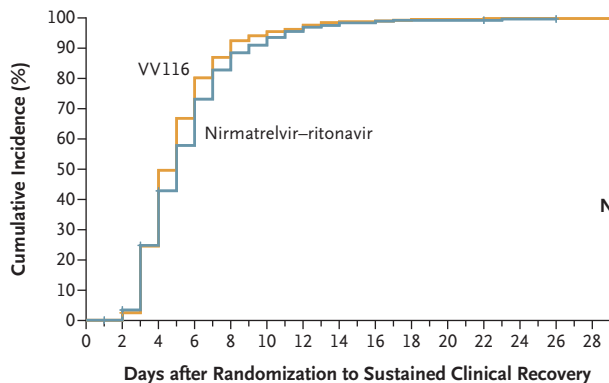
A Sustained Clinical Recovery, Full Analysis Population

	No. of Participants	No. of Events (%)	25th Percentile (95% CI) days	Median days
VV116	384	378 (98.4)	4.0 (3.0–4.0)	4.0
Nirmatrelvir– Ritonavir	387	378 (97.7)	4.0 (3.0–4.0)	5.0

Hazard ratio, 1.17 (95% CI, 1.02–1.36)

No. at Risk

VV116	384	384	285	124	48	22	14	6	5	3	2	2	1	1	1	1
Nirmatrelvir-ritonavir	387	386	287	157	64	34	17	9	6	3	3	3	1	1	0	0

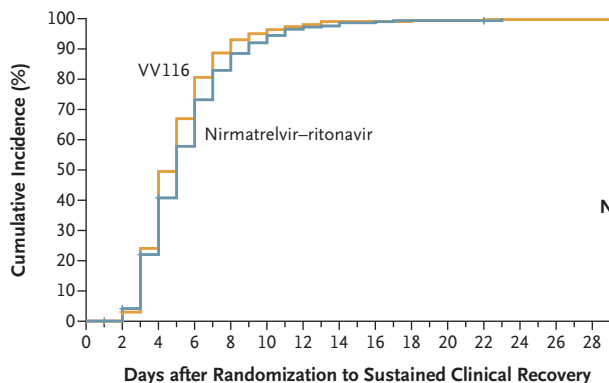
B Sustained Clinical Recovery, Per-Protocol Population

	No. of Participants	No. of Events (%)	25th Percentile (95% CI) days	Median days
VV116	371	366 (98.7)	4.0 (3.0–4.0)	5.0
Nirmatrelvir– Ritonavir	358	352 (98.3)	4.0 (3.0–4.0)	5.0

Hazard ratio, 1.17 (95% CI, 1.01–1.35)

No. at Risk

VV116	371	371	277	122	48	22	14	6	5	3	2	2	1	1	1	1
Nirmatrelvir-ritonavir	358	357	267	149	61	32	16	9	6	3	3	3	1	1	0	0

C Sustained Clinical Recovery, Participants Who Started Trial Regimen within 5 Days after Symptom Onset

	No. of Participants	No. of Events (%)	25th Percentile (95% CI) days	Median days
VV116	303	298 (98.3)	4.0 (3.0–4.0)	5.0
Nirmatrelvir– Ritonavir	293	287 (98.0)	4.0 (3.0–4.0)	5.0

Hazard ratio, 1.21 (95% CI, 1.02–1.42)

No. at Risk

VV116	303	303	227	99	34	15	8	3	3	3	2	2	1	1	1	1
Nirmatrelvir-ritonavir	293	292	225	121	49	23	10	7	4	2	2	2	0	0	0	0

Figure 2 (facing page). Time to Sustained Clinical Recovery.

Shown are the results of the final analysis (data-cutoff date, August 18, 2022) of the time to sustained clinical recovery, estimated by means of the Kaplan–Meier method, in the full analysis population (771 participants) (Panel A), per-protocol population (729 participants) (Panel B), and participants who started a trial regimen within 5 days after symptom onset (596 participants) (Panel C). Sustained clinical recovery was defined as the alleviation of all Covid-19–related target symptoms to a total score of 0 or 1 for the sum of each symptom (on a scale from 0 to 3, with higher scores indicating greater severity; total scores on the 11-item scale range from 0 to 33) for 2 consecutive days. The first day of the 2-consecutive-day period was considered to be the event date. The 95% confidence intervals were estimated with the use of normal approximation (Brookmeyer–Crowley method) on the basis of log–log transformation. Hazard ratios were calculated with the use of the Cox proportional-hazards model. A lower boundary of the two-sided 95% confidence interval for the hazard ratio of more than 0.8 was considered to indicate non-inferiority (with a hazard ratio of >1 suggesting that participants receiving VV116 had a shorter time to sustained clinical recovery than those receiving nirmatrelvir–ritonavir).

groups, the point estimates of the hazard ratio were greater than 1 regardless of age, sex, and vaccination status (Fig. S3).

SECONDARY END POINTS

By the time of the final analysis, no participants in this trial had died or had had progression to severe Covid-19. The estimated median time from randomization to sustained resolution of Covid-19–related target symptoms was 7 days (95% CI, 7 to 8) in both groups (hazard ratio, 1.06; 95% CI, 0.91 to 1.22) (Table 2 and Fig. S4). The percentage of participants with sustained clinical recovery was higher in the VV116 group than in the nirmatrelvir–ritonavir group by each prespecified time point (Table 2). The median time from randomization to a first negative SARS-CoV-2 test was 7 days (95% CI, 6 to 7) in both groups (hazard ratio, 0.99; 95% CI, 0.85 to 1.14) (Fig. S5). The percentages of participants with negative SARS-CoV-2 tests by prespecified time points and the changes in viral cycle-threshold values and target symptom scores from baseline were similar in the two groups (Table 2 and Tables S11 and S12).

SAFETY

Through 28 days of follow-up, participants who received VV116 reported fewer adverse events than those who received nirmatrelvir–ritonavir (67.4% vs. 77.3%), as well as fewer grade 3 or 4 adverse events (2.6% vs. 5.7%) (Table 3). Seven participants in the VV116 group were taking concomitant medications that have potential drug interactions with ritonavir (three were taking estazolam, one diazepam, and three nifedipine), and four of them (one taking estazolam and three nifedipine) had concomitant medications withheld during the active treatment phase. Seven participants in the nirmatrelvir–ritonavir group were taking concomitant medications that have potential drug interactions with ritonavir (three were taking estazolam and four nifedipine), and three of them (one taking estazolam and two nifedipine) had concomitant medications withheld during the active treatment phase. Two serious adverse events (acute cerebral infarction and a deterioration of the preexisting interstitial lung disease) were reported in two participants in the nirmatrelvir–ritonavir group. One serious adverse event was reported in a participant in the VV116 group who was readmitted for repeat positivity for SARS-CoV-2 on RT-PCR assay. None of the three serious adverse events were considered by the investigators to be related to the assigned drugs (Table 3). The most frequently reported adverse events (occurring in $\geq 5\%$ of the participants in either group) were dysgeusia (3.6% with VV116 and 25.8% with nirmatrelvir–ritonavir), hypertriglyceridemia (10.7% and 20.9%, respectively), and hyperlipidemia (3.1% and 9.6%) (Table S13); all these frequent adverse events were nonserious.

DISCUSSION

In light of the preliminary positive findings of a reduction in viral shedding time among patients with SARS-CoV-2 infection who were taking VV116,¹⁷ the current trial compared VV116 with nirmatrelvir–ritonavir to assess clinical end points and adverse events. This trial showed that in symptomatic adults hospitalized with mild-to-moderate Covid-19 who were at high risk for severe disease, a 5-day course of oral treatment with VV116 was noninferior to nirmatrelvir–ritonavir.

Table 2. Primary and Secondary Efficacy End Points (Full Analysis Population).*

End Point	VV116 (N=384)	Nirmatrelvir–Ritonavir (N=387)
Primary end point†		
25th percentile of time to sustained clinical recovery (95% CI) — days	4.0 (3.0–4.0)	4.0 (3.0–4.0)
Median time to sustained clinical recovery — days	4.0	5.0
Hazard ratio vs. nirmatrelvir–ritonavir (95% CI)‡	1.17 (1.02–1.36)	—
Secondary end points		
Progression to severe Covid-19 or death by day 28 — no. (%)	0	0
Median time to sustained symptom resolution (95% CI) — days§	7.0 (7.0–8.0)	7.0 (7.0–8.0)
Hazard ratio vs. nirmatrelvir–ritonavir (95% CI)‡	1.06 (0.91–1.22)	—
Clinical recovery — no. (%)		
By day 5	255 (66.4)	223 (57.6)
By day 7	331 (86.2)	316 (81.7)
By day 10	362 (94.3)	356 (92.0)
By day 14	374 (97.4)	374 (96.6)
By day 28	378 (98.4)	378 (97.7)
Symptom resolution — no. (%)		
By day 5	109 (28.4)	94 (24.3)
By day 7	207 (53.9)	191 (49.4)
By day 10	283 (73.7)	276 (71.3)
By day 14	334 (87.0)	334 (86.3)
By day 28	364 (94.8)	370 (95.6)
SARS-CoV-2 clearance — no. (%)		
By day 5	186 (48.4)	183 (47.3)
By day 7	288 (75.0)	275 (71.1)
By day 10	337 (87.8)	345 (89.1)
By day 14	364 (94.8)	358 (92.5)

* The primary end point was assessed in the primary analysis (data-cutoff date, May 13, 2022), and the data were updated in the final analysis (data-cutoff date, August 18, 2022). The updated data are reported here. Participants were those who underwent randomization and received at least one dose of VV116 or nirmatrelvir–ritonavir. Participants were grouped according to treatment assignment. CI denotes confidence interval.

† Sustained clinical recovery was defined as the alleviation of all Covid-19–related target symptoms to a total score of 0 or 1 for the sum of each symptom (on a scale from 0 to 3, with higher scores indicating greater severity; total scores on the 11-item scale range from 0 to 33) for 2 consecutive days. The first day of the 2-consecutive-day period was considered to be the event date.

‡ Hazard ratios were calculated by means of a Cox proportional-hazards model. A hazard ratio of more than 1 suggests that participants receiving VV116 had a shorter time to sustained clinical recovery or sustained symptom resolution than those receiving nirmatrelvir–ritonavir.

§ Sustained symptom resolution was defined as a score of 0 for each of the 11 Covid-19–related target symptoms for 2 consecutive days.

navir in shortening the time to sustained clinical recovery. This noninferiority in efficacy was seen in the full analysis population, the per-protocol population, and in participants who started treatment within 5 days after symptom onset. The point estimates of secondary end points also suggested that VV116 was better than or similar to nirmatrelvir–ritonavir with respect to the

time to sustained symptom resolution and to a first negative SARS-CoV-2 test. No participants in either group died or had progression to severe or critical Covid-19. Participants in the VV116 group had a lower incidence of adverse events than those in the nirmatrelvir–ritonavir group.

The administration of oral antiviral agents is feasible early in infection. Such therapies, if

Table 3. Adverse Events (Safety Population).*

Table 3. Adverse Events (Safety Population).*		
Adverse Event	VV116 (N = 384)	Nirmatrelvir–Ritonavir (N = 387)
	no. of participants (%)	
Adverse events overall		
Any adverse event	259 (67.4)	299 (77.3)
Adverse event with maximum grade of ≥3†	10 (2.6)	22 (5.7)
Serious adverse event‡	1 (0.3)	2 (0.5)
Adverse event leading to discontinuation of trial regimen	6 (1.6)	9 (2.3)
Adverse event leading to dose reduction or temporary discontinuation of trial regimen	5 (1.3)	4 (1.0)
Adverse events considered by the investigator to be related to the assigned regimen		
Any adverse event	199 (51.8)	260 (67.2)
Adverse event with maximum grade of ≥3†	7 (1.8)	20 (5.2)
Serious adverse event	0	0
Adverse event leading to discontinuation of trial regimen	6 (1.6)	9 (2.3)
Adverse event leading to dose reduction or temporary discontinuation of trial regimen	4 (1.0)	4 (1.0)

* Shown are results (data-cutoff date, August 18, 2022) for all the adverse events as coded according to the *Medical Dictionary for Regulatory Activities*, version 25.0, from the time of consent through 28-day follow-up. Participants were those who received at least one dose of VV116 or nirmatrelvir–ritonavir as grouped according to actual intervention.

† Severity grades were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0. For events not listed in the NCI CTCAE, version 5.0, severity was determined according to prespecified criteria listed in the protocol.

‡ Serious adverse events included readmission for a newly positive RT-PCR result for SARS-CoV-2 (one participant in the VV116 group), acute cerebral infarction (one participant in the nirmatrelvir–ritonavir group), and deterioration of preexisting interstitial lung disease (one participant in the nirmatrelvir–ritonavir group). None of the events were considered by the investigator to be related to the assigned regimen.

given promptly, could help mitigate hospitalization burden, facilitate postexposure prophylaxis, and potentially minimize household transmission.

This trial was performed in Shanghai, China, during an outbreak of Covid-19 (March through June 2022) involving more than 600,000 infections.²¹ SARS-CoV-2 genomic analysis of specimens from 129 patients in this period showed the BA.2.2 sublineage in all of them,²⁰ which suggests that the major variant involved in our trial was omicron. In this population, the median time to sustained clinical recovery or symptom resolution in both trial groups was shorter than those reported in other trials, such as those evaluating REGEN-COV (14 days)²² and bamlanivimab with or without etesevimab (8 days).²³

Another feature of this trial is that 75.7% of the participants had been vaccinated against SARS-CoV-2, which reflects the current reality of

population immunity; vaccinated persons have been excluded from most trials, given the rapidly changing landscape of the Covid-19 response.⁸ Therefore, we prespecified and conducted subgroup analyses according to vaccination status. The results were similar in participants with previous vaccination and those without previous vaccination. Recent studies have shown that treatment with nirmatrelvir–ritonavir in vaccinated patients with Covid-19 is associated with a reduced risk of hospitalization or progression to severe Covid-19, as well.^{24–26}

In this trial, fewer adverse events occurred in the VV116 group than in the nirmatrelvir–ritonavir group. Unlike nirmatrelvir–ritonavir, which has drug–drug interactions with multiple medications,⁹ VV116 does not inhibit or induce major drug-metabolizing enzymes or inhibit major drug transporters, so interaction with concomitant medications is less likely. Transient dysgeu-

sia was reported in one quarter of the participants receiving nirmatrelvir–ritonavir in this trial, a proportion higher than that previously reported in the EPIC-HR (Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients) trial (5.6%)⁹; this adverse event warrants more attention in future trials. In addition, the incidence of dyslipidemia was relatively high among both nirmatrelvir–ritonavir recipients and VV116 recipients. Although this adverse reaction has been noted with long-term use of ritonavir in patients with human immunodeficiency virus infection,²⁷ the possible effect of nirmatrelvir or VV116 on lipid metabolism needs further investigation.

The trial has several limitations. First, we were not able to conduct this trial with a double-blind and double-dummy design because the production of the placebo tablet for nirmatrelvir–ritonavir was not completed before the trial began owing to the omicron outbreak. Second, the trial involved Chinese adults infected with omicron subvariants in a single geographic area, so the results require validation in more heterogeneous populations with greater diversity of viral variants. Third, it is possible that symptoms could have recurred after 2 consecutive days without symptoms. Fourth, the WHO ordinal scale that was used to evaluate outcomes was not ideal for detecting differences among participants with mild Covid-19, especially when discharge decisions may be driven by factors other than clinical improvement. Fifth, no con-

clusions can be made about the efficacy of VV116 for the prevention of progression to severe or critical Covid-19 or death, because no events occurred in either group. Possible efficacy for this outcome is planned to be evaluated in a separate trial (ClinicalTrials.gov number, NCT05242042). Sixth, we did not recognize SARS-CoV-2 rebound after nirmatrelvir–ritonavir treatment until the release of the Centers for Disease Control and Prevention advisory on May 24, 2022.²⁸ Data on such rebounds were very limited and not suitable for analysis in our trial.

In this trial, early administration of oral VV116 was noninferior to nirmatrelvir–ritonavir in shortening the time to sustained clinical recovery in participants with mild-to-moderate Covid-19 who were at high risk for progression to severe disease. VV116 also had fewer safety concerns than nirmatrelvir–ritonavir.

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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' full names and academic degrees are as follows: Zhujun Cao, M.D., Ph.D., Weiyi Gao, M.D., Ph.D., Hong Bao, M.D., Ph.D., Haiyan Feng, M.D., Shuya Mei, M.D., Ph.D., Peizhan Chen, Ph.D., Yueqiu Gao, M.D., Ph.D., Zhilei Cui, M.D., Ph.D., Qin Zhang, M.D., Ph.D., Xianmin Meng, Ph.D., Honglian Gui, M.D., Ph.D., Weijing Wang, M.D., Ph.D., Yimei Jiang, M.D., Zijia Song, M.D., Ph.D., Yiqing Shi, M.D., Jing Sun, M.D., Ph.D., Yifei Zhang, M.D., Ph.D., Qing Xie, M.D., Ph.D., Yiping Xu, Ph.D., Guang Ning, M.D., Yuan Gao, M.D., Ph.D., and Ren Zhao, M.D., Ph.D.

The authors' affiliations are as follows: the Department of Infectious Diseases, Shanghai Institute of Virology (Z. Cao, H.G., W.W., Q.X.), the Department of Emergency Medicine, Shanghai Innovation Center for Digital Medicine (W.G.), the Clinical Research Center, Shanghai National Center for Translational Medicine, State Key Laboratory of Medical Genomics (P.C., Y.X.), the Departments of General Surgery (Y.J., Z.S., Y.S., R.Z.) and Gastroenterology (J.S.), the Department of Endocrine and Metabolic Diseases, Shanghai Institute of Endocrine and Metabolic Diseases (Y.Z., G.N.), and Shanghai National Clinical Research Center for Metabolic Diseases, Key Laboratory for Endocrine and Metabolic Diseases of the National Health Commission of the People's Republic of China, Shanghai Key Laboratory for Endocrine Tumors (Y.Z., G.N.), Ruijin Hospital, the Department of Critical Care Medicine, Renji Hospital (S.M., Yuan Gao), the Department of Respiratory Medicine, Xinhua Hospital (Z. Cui), and the Department of Good Clinical Practice Office and Phase I Unit, Tongren Hospital (Q.Z.), Shanghai Jiao Tong University School of Medicine, the Department of Respiratory and Critical Medicine, Shanghai Pudong Hospital, Fudan University Pudong Medical Center (H.B.), the Departments of Pain Rehabilitation (H.F.) and Pharmacology (X.M.), Shanghai Public Health Clinical Center, Fudan University, and the Department of Liver Disease, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine (Yueqiu Gao) — all in Shanghai, China.

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