Oral VV116 versus placebo in patients with mild-to-moderate COVID-19 in China: a multicentre, double-blind, phase 3, randomised controlled study

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Summary

Background Spread of SARS-CoV-2 led to a global pandemic, and there remains unmet medical needs in the treatment of Omicron infections. VV116, an oral antiviral agent that has potent activity against SARS-CoV-2, was compared with a placebo in this phase 3 study to investigate its efficacy and safety in patients with mild-to-moderate COVID-19.

Methods This multicentre, double-blind, phase 3, randomised controlled study enrolled adults in hospitals for infectious diseases and tertiary general hospitals in China. Eligible patients were randomly assigned in a 1:1 ratio using permuted block randomisation to receive oral VV116 (0·6 g every 12 h on day 1 and 0·3 g every 12 h on days 2–5) or oral placebo (on the same schedule as VV116) for 5 days. Randomisation stratification factors included SARS-CoV-2 vaccination status and the presence of high-risk factors for progression to severe COVID-19. Inclusion criteria were a positive SARS-CoV-2 test, an initial onset of COVID-19 symptoms 3 days or less before the first study dose, and a score of 2 or more for any target COVID-19-related symptoms in the 24 h before the first dose. Patients who had severe or critical COVID-19 or who had taken any antiviral drugs were excluded from the study. The primary endpoint was the time to clinical symptom resolution for 2 consecutive days. Efficacy analyses were performed on a modified intention-to-treat population, comprising all patients who received at least one dose of VV116 or placebo, tested positive for SARS-CoV-2 nucleic acid, and did not test positive for influenza virus before the first dose. Safety analyses were done on all participants who received at least one dose of VV116 or placebo. This study was registered with ClinicalTrials.gov, NCT05582629, and has been completed.

Findings A total of 1369 patients were randomly assigned to treatment groups and 1347 received either VV116 (n=674) or placebo (n=673). At the interim analysis, VV116 was superior to placebo in reducing the time to sustained clinical symptom resolution among 1229 patients (hazard ratio [HR] 1·21, 95% CI 1·04–1·40; p=0·0023). At the final analysis, a substantial reduction in time to sustained clinical symptom resolution was observed for VV116 compared with placebo among 1296 patients (HR 1·17, 95% CI 1·04–1·33; p=0·0009), consistent with the interim analysis. The incidence of adverse events was similar between groups (242 [35·9%] of 674 patients *vs* 283 [42·1%] of 673 patients).

Interpretation Among patients with mild-to-moderate COVID-19, VV116 significantly reduced the time to sustained clinical symptom resolution compared with placebo, with no observed safety concerns.

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For the Chinese translation of the abstract see **Online** for appendix 1

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Introduction

The COVID-19 pandemic, caused by SARS-CoV-2, has posed a global threat to public health.[1] According to WHO statistics, there have been approximately 768 million confirmed COVID-19 cases and more than 6·9 million deaths as of June 27, 2023.[2] Common symptoms include fever, cough, fatigue, respiratory distress, pneumonia, and muscle pain.[3–5] Advancing age, obesity, and pre-existing comorbidities are key risk factors for severe COVID-19.[6,7]

PINETREE, a phase 3 study among 562 outpatients with severe COVID-19, revealed that a 3-day course of intravenous remdesivir treatment could lower the risk of hospitalisation (defined as ≥24 hours of acute care) or death compared with placebo (hazard ratio [HR] 0·13; 95% CI 0·03–0·59), with an acceptable safety profile,[8] leading to a prompt supplemental US Food and Drug Administration (FDA) label approval for patients with mild-to-moderate COVID-19 with one or more risk factors for progression. However, remdesivir requires intravenous administration and PINETREE excluded patients who had been vaccinated, with the study conducted before widespread infection by the omicron variant. The US FDA also issued Emergency Use

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Research in context

Evidence before this study

We searched PubMed with the terms "('remdesivir'[Title]) AND (clinicaltrial[Filter])", "((((nirmatrelvir[Title/Abstract]) AND (ritonavir[Title/Abstract])) OR (((nirmatrelvir–ritonavir[Title/Abstract]) OR (paxlovid[Title/Abstract])) OR (nirmatrelvir[Title/Abstract]))))) NOT ((((review[Filter]) OR (meta-analysis[Filter])) OR (casereport[Filter]))))", and "((((molnupiravir[Title/Abstract]) NOT (nirmatrelvir[Title/Abstract])) NOT (reivew[Filter])) NOT (case report[Title])) NOT (case[Title])" for articles published in any language from database inception to Sept 7, 2023. Our search identified 1105 results. These articles suggested that remdesivir, nirmatrelvir–ritonavir, or molnupiravir could reduce the overall risk of hospitalisation or death in patients at high risk with mild-to-moderate COVID-19. For instance, a phase 3 study (PINETREE) among 562 outpatients with severe COVID-19 found that a 3-day course of intravenous remdesivir treatment could lower the risk of hospitalisation or death compared with placebo (hazard ratio [HR] 0·13, 95% CI 0·03–0·59), with an acceptable safety profile. In terms of reducing the duration of COVID-19-related symptoms, the recently published active comparator-controlled phase 3 study by Cao and colleagues showed that VV116 was non-inferior to nirmatrelvir–ritonavir in reducing the time to sustained clinical symptom resolution among patients with mild-to-moderate COVID-19 at risk for progression (median time 7 days *vs* 7 days, HR 1·06; 95% CI 0·91–1·22). However, there are no reported data comparing VV116 with placebo.

Added value of this study

Compared with placebo, a 5-day treatment of VV116 significantly shortened the time to sustained clinical symptom resolution and clinical symptom alleviation in patients with mild-to-moderate COVID-19, regardless of the presence of high-risk factors for progression to severe COVID-19 or SARS-CoV-2 vaccination status. The treatment effects in subgroups were consistent with those in the total population, including the subgroups of those aged 60 years and older, and those aged younger than 60 years.

Implications of all the available evidence

VV116 was significantly superior to placebo and has been shown to be non-inferior to nirmatrelvir–ritonavir in time to sustained clinical symptom resolution and SARS-CoV-2 clearance, with a favourable safety profile in patients with mild-to-moderate COVID-19. Based on the completed evidence, VV116 was conditionally approved to treat mild-to-moderate COVID-19 by the National Medical Products Administration in China. These findings support the use of VV116 as a valuable treatment option for COVID-19, especially for patients with multiple comorbidities due to fewer drug interaction concerns. Furthermore, as SARS-CoV-2 is constantly mutating, in vitro studies to verify the efficacy of VV116 on predominate variants will be developed constantly.

Authorizations to other drugs for COVID-19 treatment, including neutralising monoclonal antibodies targeting the SARS-CoV-2 spike protein, the viral mutagen, molnupiravir, and, eventually, full approval of the small molecule antiviral combination drug nirmatrelvir–ritonavir, for patients who are at high risk for progression to severe COVID-19, including hospitalisation or death.[9–11] However, neutralising antibodies are limited by high drug costs, require strict transport and storage conditions, can only be intravenously administered, and are susceptible to viral escape mutations. By December, 2022, the treatment-authorised neutralising antibodies that were no longer effective against the omicron variants had lost their US Emergency Use Authorizations.[9] Meanwhile, phase 2 and phase 3 studies have revealed that molnupiravir, an oral small-molecule drug, can more effectively accelerate SARS-CoV2 RNA clearance in patients with mild-to-moderate COVID-19 compared with control groups.[12,13] Ongoing concerns exist regarding the tautomerising molnupiravir, an N-hydroxycytidine nucleoside derivative, with respect to genotoxicity and viral mutagenicity. The interim analysis of a phase 2–3 study done before the Omicron variant pandemic showed that nirmatrelvir–ritonavir reduced the incidence of COVID-19-related hospitalisation and death until day 28 by 6·32% (95% CI −9·04 to −3·59; p<0·001; relative risk reduction 89·1%) compared with placebo among 774 patients at high risk who were not hospitalised.[14] Moreover, the viral load was lower in the nirmatrelvir–ritonavir group than the placebo group by day 5 of treatment, with a mean difference of −0·868 log_{10} copies per mL.[13] However, nirmatrelvir–ritonavir contains ritonavir, a potent CYP3A inhibitor that potentiates multiple known drug–drug interactions.[15] Approximately 15% of patients with severe COVID-19 have medical contraindications for nirmatrelvir–ritonavir, with numbers reaching 26·9% in patients older than 65 years.[16] There is a growing demand for a safer and more effective oral agent with broad-spectrum antiviral activity for the treatment of COVID-19. In China, three antivirals were licensed for COVID-19 treatment at the time of this study, including amubarvimab–romlusevimab, nirmatrelvir–ritonavir, and azvudine tablets.

VV116 (known as mindeudesivir) is a deuterated remdesivir hydrobromide with improved oral bioavailability and potent anti-SARS-CoV-2 activity.[17] VV116 targets the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), and its mechanism of action is expected to be the same as remdesivir. The active triphosphate form of VV116 acts as a nucleoside analog and is incorporated into nascent RNA chains by the SARS-CoV-2 RdRp, which results in RdRp stalling after three more nucleotide extensions. VV116 is mainly

metabolised through hydrolysis and oxidative deamination. In human plasma and urine, the main metabolite is 116-N1, which is metabolically stable in vivo and widely distributed in tissues, with a low plasma protein binding rate and no significant species differences; the clearance rate of 116-N1 is moderate in vivo and is mainly excreted in urine.[18] Preclinical and clinical studies have shown that VV116 has substantial antiviral effects against the original and evolving strains of COVID-19, including alpha (B.1.1.7), beta (B.1.351), delta (B.1.617.2), and omicron (omicron BA.2, BA.2.12.1, BA.4, and BA.5), without causing genotoxicity.[19] Moreover, three phase 1 studies among healthy volunteers revealed satisfactory safety and pharmacokinetic profiles for VV116.[20] A phase 3 study involving 771 patients (NCT05341609) has indicated that VV116 was non-inferior to nirmatrelvir–ritonavir in terms of the time to sustained clinical recovery in patients with mild-to-moderate COVID-19 who were at high risk for severe or critical disease (HR 1·17, 95% CI 1·01–1·35), with fewer drug–drug interaction concerns.[21]

During the Omicron outbreak, to further verify the efficacy and safety of VV116 in COVID-19 patients with or without high-risk factors, we did a double-blind, placebo-controlled, phase 3 study among patients with mild-to-moderate COVID-19 in China (NCT05582629). On Jan 28, 2023, the China National Medical Products Administration conditionally approved VV116 for the treatment of patients with mild-to-moderate COVID-19 based on the interim analysis of this phase 3 study. Here, we present the final analyses, evaluating the efficacy and safety of VV116 in patients with mild-to-moderate COVID-19.

Methods

Study design

This multicentre, double-blind, phase 3, randomised controlled trial was done across 31 sites (16 hospitals for infectious diseases and 15 tertiary general hospitals) in China (appendix 2 p 2). Both VV116 and the placebo were manufactured and provided by Shanghai DESANO Biopharmaceutical (Shanghai, China).

An electronic data capture system was used for data collection. The study was implemented and overseen by Shanghai Junshi Biosciences. An external independent data monitoring committee was established by the funder for safety evaluation and interim analysis. The protocol and all amendments were approved by the institutional review board or ethics committee at each study site, and were in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable laws and regulations.

This study was approved by the Clinical Trial Ethics Committee of Shulan (Hangzhou) Hospital and collaborating hospitals, under approval number YW2022–037-X1. All enrolled patients provided written informed consent.

Patients

For inclusion, patients had to be 18 years or older at the time of consent, have a positive SARS-CoV-2 test, have the initial onset of COVID-19 symptoms no more than 3 days before the first dose of the study drug, and have a score of 2 or greater for at least one target COVID-19-related symptom (appendix 2 p 6) within the 24 h before the first dose of the study drug. Key exclusion criteria included severe or critical COVID-19, use of any antiviral drugs, SpO_2 of 93% or less on room air at sea level, PaO_2:FiO_2 of 300 or less (with oxygen inhalation), respiratory rate of 30 or more breaths per minute, heart rate of 125 or more beats per minute, need or anticipated need for mechanical ventilation, or serious infections. Detailed information on the inclusion and exclusion criteria can be found in the study protocol (appendix 2 pp 35–36).

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to receive VV116 or placebo. Random assignment was done by a computer-generated random sequence using an Interactive Response Technology by an independent vendor and stratified based on SARS-CoV-2 vaccination status (≤1 dose *vs* 2 doses *vs* ≥3 doses) and the presence of high-risk factors for progression to severe COVID-19 (yes or no).

Investigators were responsible for participant enrolment. Patients, care providers, investigators, and the funder's study team were masked to the study assignment. Tablets with identical appearance were used for both VV116 and placebo. In an emergency, the investigator could unblind a patient's treatment assignment via the Interactive Response Technology; the investigator had the sole responsibility for deciding if the unblinding of a patient's treatment assignment was warranted.

Procedures

For those assigned to receive VV116, VV116 was administered at 0·6 g every 12 h on day 1 and 0·3 g every 12 h on days 2–5. Those assigned to receive placebo were given the placebo on the same schedule as for VV116 for 5 days. The study consisted of a screening period of up to 3 days and a treatment and assessment period of 28 days, including the 5-day treatment period.

See Online for appendix 2

To assess the patients' clinical symptoms, COVID-19-related symptom scores were collected via a mobile application (ePData version 1.18) by means of patient-reported outcomes on day 1 before the first dose, then every 24 h until day 28, with higher scores indicating a worse clinical condition. Nasopharyngeal swabs were collected on day 1 before the first dose (ie, baseline) and days 5 and 7 to quantify the SARS-CoV-2 viral load through RT-PCR at a central laboratory; day 1 samples were also used to sequence the viral genome using next-generation sequencing. At each study site, SARS-CoV-2 nucleic acid tests were done at screening, on day 1 before

	VV116 (n=646)	Placebo (n=650)
Age		
Median (IQR)	35·0 (29·0–46·0)	35·0 (28·0–47·0)
<60 years	600 (92·9%)	603 (92·8%)
≥60 years	46 (7·1%)	47 (7·2%)
Sex		
Male	368 (57·0%)	372 (57·2%)
Female	278 (43·0%)	278 (42·8%)
Race		
Asian	646 (100%)	649 (99·9%)
White	0	1 (0·2%)
COVID-19 symptoms score		
Collected	644 (99·6%)	649 (99·9%)
Median (IQR)	10·0 (6·0–14·0)	10·0 (6·0–14·0)
≤10	356 (55·1%)	350 (53·9%)
>10	288 (44·6%)	299 (46·0%)
Unknown	2 (0·3%)	1 (0·2%)
Hospitalisation type at baseline		
Outpatient	242 (37·5%)	241 (37·1%)
Inpatient	404 (62·5%)	409 (62·9%)
Days from the onset of COVID-19 symptom to first dose		
≤2	522 (80·8%)	521 (80·2%)
≥3	124 (19·2%)	129 (19·9%)
Days from first positive SARS-CoV-2 result to first dose		
≤2	484 (74·9%)	489 (75·2%)
≥3	162 (25·1%)	161 (24·8%)
SARS-CoV-2 vaccine or prevention antibody history		
Yes	626 (96·9%)	628 (96·6%)
No	20 (3·1%)	22 (3·4%)
SARS-CoV-2 vaccine injection status		
≤1 dose	34 (5·3%)	37 (5·7%)
2 doses	116 (18·0%)	114 (17·5%)
≥3 doses	496 (76·8%)	499 (76·8%)
Concomitant medication		
Yes	374 (57·9%)	366 (56·3%)
No	272 (42·1%)	284 (43·7%)
High-risk factor for severe COVID-19 or death		
Yes	284 (44·0%)	274 (42·2%)
No	362 (56·0%)	376 (57·9%)
Overweight or obesity (BMI >25 kg/m^2)	204 (31·6%)	193 (29·7%)
Current smoker	74 (11·5%)	62 (9·5%)
Cardiovascular disease	62 (9·6%)	62 (9·5%)
Diabetes	19 (2·9%)	25 (3·8%)
Chronic lung disease	2 (0·3%)	7 (1·1%)
Need relevant medical support	4 (0·6%)	3 (0·5%)
Immunosuppressive disease or immunosuppressive treatment	1 (0·2%)	1 (0·2%)
Chronic kidney disease	2 (0·3%)	0
Active cancer	0	1 (0·2%)

Data are median (IQR) and n (%) and are for the modified intention-to-treat population. For continuous variables, descriptive statistics are only summarised from patients who have test results available.

Table 1: **Baseline characteristics**

the first dose, day 3, day 5, day 7, day 14, day 21, and day 28 to determine the cycle threshold value with RT-PCR. Safety was assessed in terms of adverse events, abnormalities in clinical laboratory tests, vital signs, physical examinations, and electrocardiograms during the study. Sex data were taken from medical records.

Outcomes

The primary endpoint was the time to sustained clinical symptom resolution for 2 days, defined as the number of days from the first dose to the first of 2 consecutive days when symptoms scored 0. The primary endpoint was referenced from a study design for influenza treatment[22] and considered applicable to this study due to the similar pathogenic characteristics of the Omicron variant of SARS-CoV-2 and influenza virus.[23]

Secondary endpoints included the time to sustained clinical symptom resolution for 3 days (defined as the number of days from the first dose to the first of 3 consecutive days when symptoms scored 0), time to sustained clinical symptom alleviation (defined as symptoms scored ≤1), percentage of patients who had disease progression by day 28 (consisting of COVID-19-related hospitalisation of non-hospitalised patients, progression to severe COVID-19, progression to critical COVID-19, and death from any cause), percentage of patients who maintained SARS-CoV-2 negativity through days 5–7, and changes in SARS-CoV-2 cycle threshold value and viral load from baseline to day 5 and day 7. The exploratory endpoint included SARS-CoV-2 viral genetic variation. All other endpoints are listed in the study protocol (appendix 2 p 31).

The safety endpoints were the incidence of adverse events and abnormalities of laboratory tests, vital signs, physical examinations, and electrocardiograms. Adverse events were captured throughout the study and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Adverse events were coded using the Medical Dictionary for Regulatory Activities terms (version 25.1).

Statistical analysis

According to Menni and colleagues,[24] the median time to acute symptoms resolution was around 5 days, and reducing the median time to sustained symptoms resolution by 1 day was regarded as clinically meaningful. For the primary endpoint, based on the conservative assumption that the median time of sustained symptoms with the placebo would be 5·5 days and that VV116 would would have a median time to sustained symptom resolution of 4·5 days, 900 events were warranted to achieve 85% power to compare VV116 with placebo, limiting controlled type I error to less than 0·025 (one-sided). Assuming 15% of patients would be excluded from the primary analysis set due to negative SARS-CoV-2 tests or positive influenza virus tests before the first dose, and that events would not be observed among 10% of

patients, the study aimed to recruit approximately 1200 patients. One interim analysis was planned and done using the O'Brien-Fleming α-spending function (approximated with the Lan-DeMets method) to control the overall type I error rate.

Efficacy was assessed in the modified intent-to-treat population (appendix 2 p 6), which included all patients who received at least one dose of the study drug, tested positive for SARS-CoV-2 nucleic acid, and tested negative for influenza virus before the first dose. The following analyses were done for the primary endpoint. Patients who took prohibited medication (ie, drugs with an antiviral effect on COVID-19 and drugs that interfere with the evaluation of the treatment effect of VV116) before sustained clinical symptom resolution were considered not recovered and were censored on day 28 after the first dose of the study treatment. The stratified Peto-Peto-Prentice test[25,26] was the primary testing method used to compare the difference in survival functions between the two groups. The Kaplan-Meier method was used to estimate the median time to sustained clinical symptom resolution for each group, and the 95% CI was estimated using the Brookmeyer-Crowley method with log–log transformation for normal approximation. The HR for

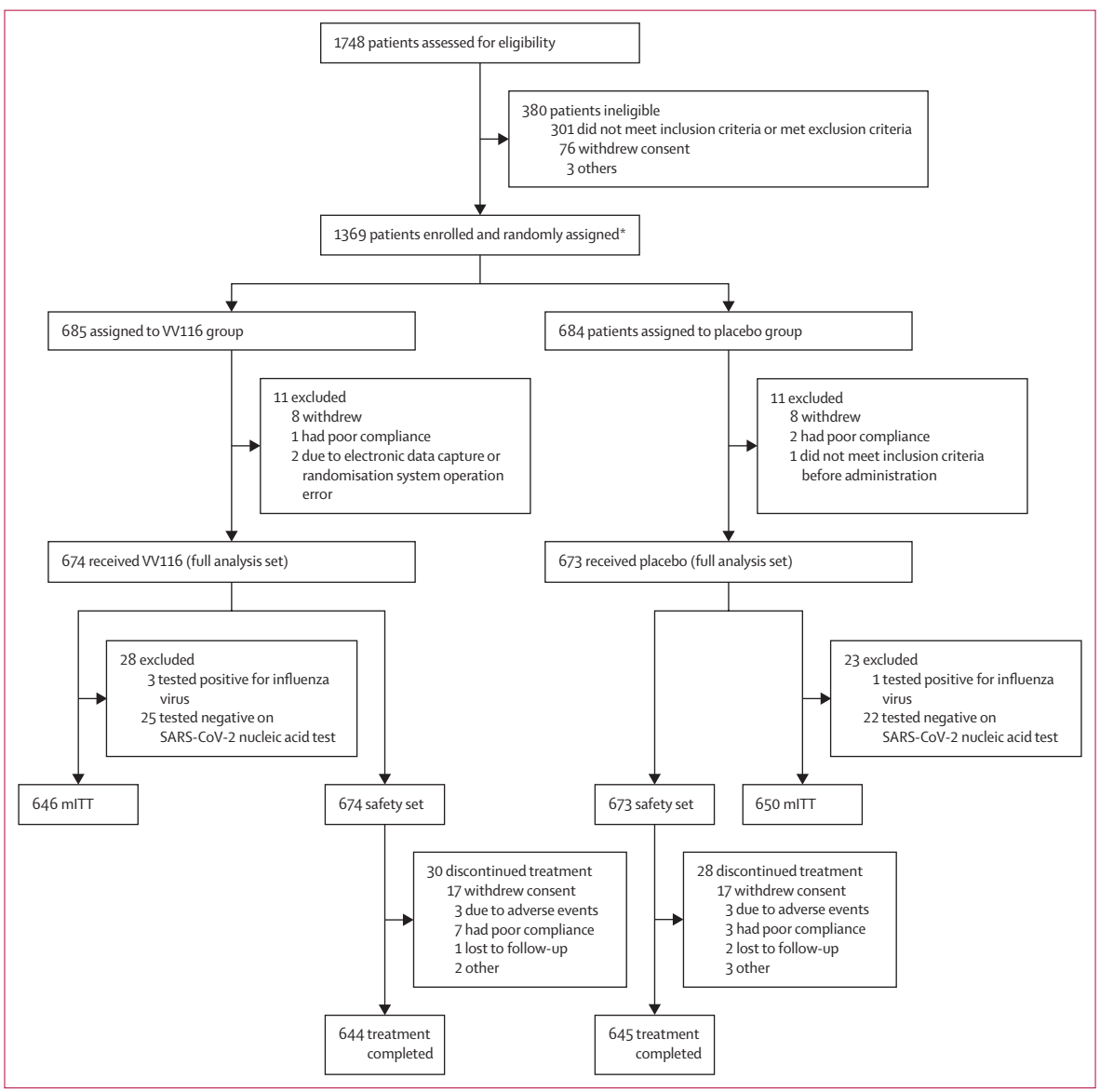

Figure 1: **Trial profile**
During the study, 37 patients in the VV116 group and 33 patients in the placebo group reported important protocol deviations that did not preclude them from mITT analysis but did from per-protocol, including inclusion criteria not met (20 in the VV116 group *vs* 13 patients in the placebo group), use of prohibited medications (18 in the VV116 group *vs* 20 patients in the placebo group), and study management (1 in each group). mITT=modified intention-to-treat. *One patient who was ineligible on screening was randomly assigned to the VV116 group and was not given the study drug.

time to sustained clinical symptom resolution and its 95% CI were estimated using a stratified Cox proportional hazards model. The stratification factors used for the analyses were the same as the ones used for randomisation. A stratified log-rank test was also done as a sensitivity analysis. A subgroup analysis was also done for the primary endpoint. The same methods as for the primary endpoint were used for the analysis of time-to-event secondary endpoints. The percentage of patients who obtained negative SARS-CoV-2 test results, changes in SARS-CoV-2 cycle threshold value, and changes in viral load from baseline were analysed in the modified intention-to-treat population and presented in a line chart. Viral genetic variation was also analysed. Once the statistical significance of the primary endpoint was ascertained, hierarchical testing was done for the secondary endpoints in the order they were presented in the statistical analysis plan.

Safety analysis was done in the safety set, and data were collected on the incidence and severity of treatment-emergent adverse events, treatment-related adverse events, serious adverse events, adverse events with an outcome of death, adverse events of special interest (ie, potential severe drug-induced liver injury), and adverse events leading to study intervention discontinuation. Statistical analyses were done with the statistical analysis software SAS 9.4.

This study is registered with ClinicalTrials.gov (NCT05582629).

Role of the funding source

All aspects of this study were done by one funder: Shanghai Junshi Biosciences. The study's other funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Oct 21, 2022, and Jan 18, 2023, a total of 1748 patients were screened for eligibility, of whom 1369 were enrolled and randomly assigned to study groups. Follow-up completed on Feb 14, 2023. 1347 participants received study treatments (674 [50·0%] in the VV116 group and 673 [50·0%] in the placebo group). Among the 1347 patients, 1296 (96·2%) were included in the modified intention-to-treat population (table 1, figure 1). Among the modified intention-to-treat population, 1243 (95·9%) patients completed treatment and 1254 (96·8%) patients completed the study (defined as completing the 28-day follow-up). The median number of VV116 or placebo administrations was ten in both groups. Important protocol deviations occurred in 37 (5·7%) of 646 patients in the VV116 group and 33 (5·1%) of 650 patients in the placebo group. The number of patients among analysis sets and patient disposition are available in appendix 2 (pp 6–7).

Demographic characteristics and other baseline characteristics were similar between the two groups among the modified intention-to-treat population, with a median age of 35·0 years (IQR 29·0–47·0; table 1). 1254 (96·8%) patients had received SARS-CoV-2 vaccination. The most common high-risk factor for COVID-19 was obesity or overweight (ie, BMI >25 kg/m²), accounting for 30·6% (n=397) of patients. A total of 150 patients were tested for SARS-CoV-2 genetic variation at enrolment and all were found to be infected with the SARS-CoV-2 Omicron variants, with BA.5.2.48 (n=88, 58·7%) and BF.7.14 (n=46, 30·7%) as the leading subvariants (appendix 2 p 5).

At the interim analysis, among those that completed follow-up and reached the primary endpoint in the modified intention-to-treat population, 369 (60·2%) of 613 patients in the VV116 group and 342 (55·5%) of 616 patients in the placebo group had sustained clinical symptom resolution for 2 consecutive days. The median time to sustained clinical symptom resolution for 2 consecutive days was 10·9 days (IQR 5·6–20·3) in the VV116 group and 12·9 days (IQR 6·8–22·6) in the placebo group (stratified HR 1·21, 95% CI 1·04–1·40, p=0·0023). The sensitivity analysis using a stratified log-rank test provided consistent results (p=0·012).

At the final analysis, among the modified intention-to-treat population, 513 (79·4%) of 646 patients in the VV116 group and 494 (76·0%) of 650 patients in the placebo group had sustained clinical symptom resolution for 2 consecutive days. The median time to sustained clinical symptom resolution for 2 consecutive days was 10·9 days (IQR 5·6–20·8) for the VV116 group and 12·9 days (IQR 7·0–23·6) for the placebo group (p=0·0009 using Peto-Peto-Prentice test and p=0·012 using log-rank test, stratified HR 1·17, 95% CI 1·04–1·33; figure 2A), consistent with the interim analysis results. Similar trends favouring VV116 were observed across subgroups. Specifically, among the 93 patients aged 60 years and older, the time to sustained clinical symptom resolution was shorter in the VV116 group compared with the placebo group (HR 1·22, 95% CI 0·74–2·01), consistent with the overall population (appendix 2 p 3). Among the 740 men, the time to sustained clinical symptom resolution was shorter in the VV116 group compared with the placebo group (HR 1·23, 95% CI 1·05–1·45); the same trend was observed among the 556 women (HR 1·13, 95% CI 0·93–1·37). In addition, the median time to sustained clinical symptom resolution for 3 consecutive days was 11·9 days (IQR 5·9–21·9) in the VV116 group and 13·9 days (IQR 7·7–24·8) in the placebo group (stratified HR 1·15, 95% CI 1·02–1·31, p=0·0069; figure 2B). The analysis of the time to sustained clinical symptom alleviation revealed similar results to those of the primary endpoint (appendix 2 pp 4–5).

Patients with a total target COVID-19 symptoms score of 10 or less had a substantial reduction in time to sustained clinical symptoms resolution compared with those who had a score of more than 10 in both the VV116

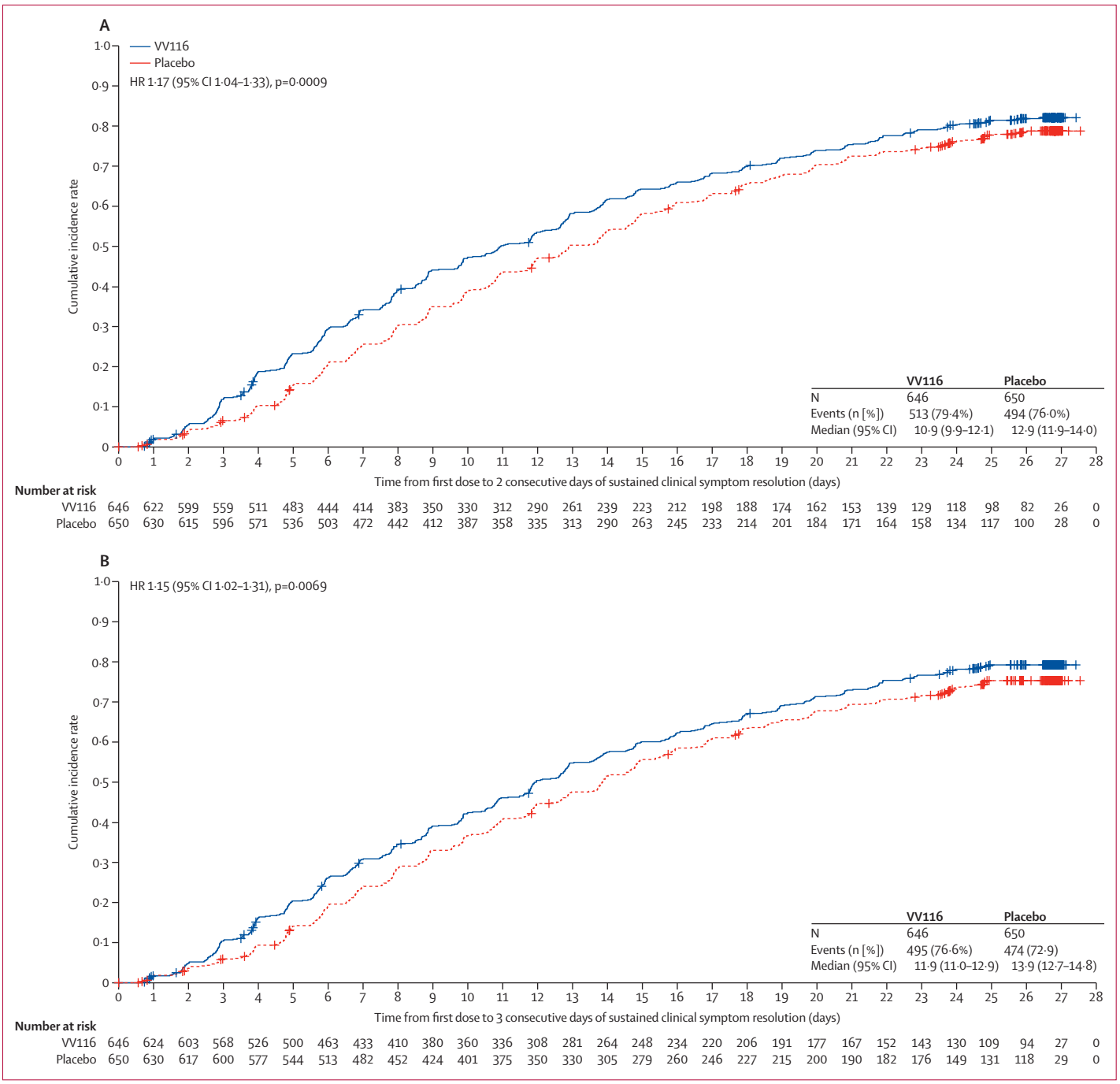

Figure 2: **Time to sustained clinical symptom resolution**
The final analysis of the time to sustained clinical symptom resolution for 2 consecutive days (A) and 3 consecutive days (B) in the modified intent-to-treat population (1296 patients), estimated using the Kaplan-Meier method. P values were estimated with Peto-Peto-Prentice, HRs were analysed using the stratified Cox proportional hazard model, and 95% CIs were analysed using the Brookmeyer-Crowley method. The stratification factors were SARS-CoV-2 vaccination status (≤1 dose *vs* 2 doses *vs* ≥3 doses) and the presence of high-risk factors for progression to severe COVID-19 (yes *vs* no). HR=hazard ratio.

group (median 7·9 days, 95% CI 6·6–8·8 for those scoring ≤10 *vs* 14·7 days, 13·5–16·8 for those scoring >10) and the placebo group (10·6 days, 8·9–11·9 *vs* 16·6, 14·8–17·9). Outpatients were also found to take longer to recover than inpatients in both the VV116 group (13·9 days, 12·8–15·8 for outpatients *vs* 8·0, 7·5–9·8 for inpatients) and the placebo group (17·8 days, 15·8–19·6 *vs* 10·6, 8·9–11·9).

During the study, only one (0·2%, 95% CI –0·9 to 0·4; p=0·32) patient in the placebo group and none in

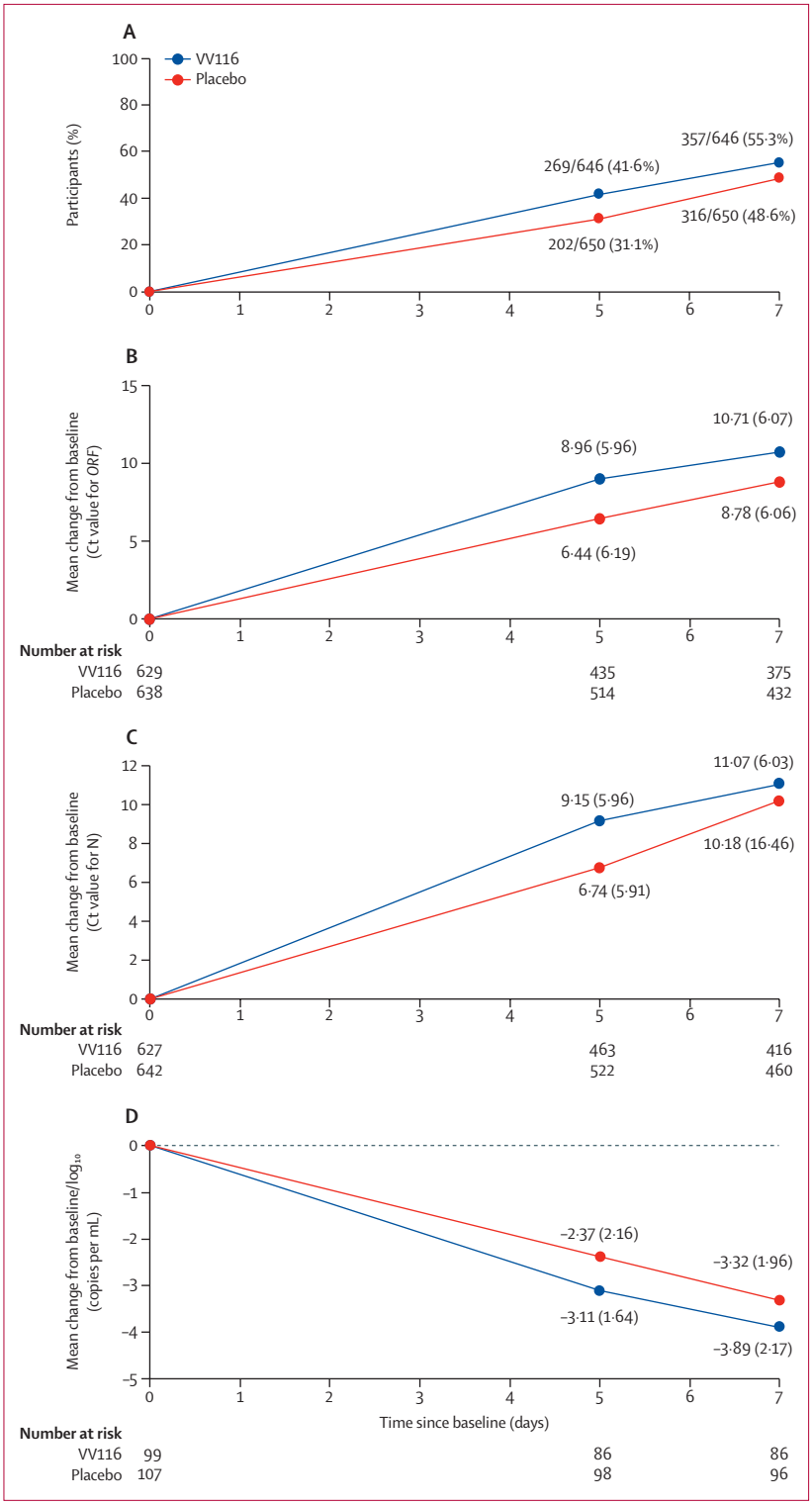

Figure 3: **Changes from baseline in the modified intention-to-treat population**
Data next to points are n/N (%) or mean (SD). (A) Percentage of patients who had SARS-CoV-2 negativity by day 5 and day 7. (B) Mean change in SARS-CoV-2 cycle threshold value for *ORF* gene from baseline to day 5 and day 7. (C) Mean change in SARS-CoV-2 Ct value for *N* gene from baseline to day 5 and day 7. (D) Mean change of SARS-CoV-2 viral RNA copy number from baseline. Ct=cycle threshold.

the VV116 group progressed to severe COVID-19. No patients in either group died or developed critical COVID-19. In the VV116 group, a higher proportion of patients had SARS-CoV-2 negativity by day 5 than in the placebo group (41·6%, 95% CI 37·8–45·4, n=269 *vs* 31·1%, 27·5–34·6, n=202; p<0·0001; figure 3A).

By day 5 of the study treatment, a substantial increase in the SARS-CoV-2 cycle threshold value (both open reading frame and N gene; figure 3B, 3C) and a more rapid decrease in viral load were observed in the VV116 group compared with the placebo group (figure 3D).

Among the 1347 patients in the safety dataset, the incidence of treatment-emergent adverse events of any grade was similar between groups (242 [35·9%] of 674 patients in the VV116 group and 283 [42·1%] of 673 patients in the placebo group). 117 (17·4%) patients in the VV116 group had treatment-related adverse events assessed by the investigator, as did 156 (23·2%) patients in the placebo group (table 2). The most common (incidence ≥5% in either group) treatment-emergent adverse events included hypertriglyceridaemia (39 [5·8%] patients in the VV116 group *vs* 48 [7·0%] patients in the placebo group) and blood pressure increase (30 [4·5%] *vs* 40 [5·9%]; appendix 2 p 8). Most (667 [99·0%] of 674 in the VV116 group and 659 [97·9%] of 673 in the placebo

	VV116 (n=674)	Placebo (n=673)	Total (n=1347)
Treatment-emergent adverse events	242 (35·9%)	283 (42·1%)	525 (39·0%)
Drug-related	117 (17·4%)	156 (23·2%)	273 (20·3%)
Treatment-emergent adverse events with NCI-CTCAE grade ≥3	7 (1·0%)	14 (2·1%)	21 (1·6%)
Drug-related	3 (0·5%)	2 (0·3%)	5 (0·4%)
Serious treatment-emergent adverse events	0	2 (0·3%)	2 (0·2%)
Drug-related	0	0	0
Treatment-emergent adverse events leading to interruption of study drug	1 (0·2%)	1 (0·2%)	2 (0·2%)
Drug-related	1 (0·2%)	1 (0·2%)	2 (0·2%)
Treatment-emergent adverse events leading to permanent discontinuation of study drug	3 (0·5%)	3 (0·5%)	6 (0·5%)
Drug-related	3 (0·5%)	3 (0·5%)	6 (0·5%)
Treatment-emergent adverse events of special interest	0	1 (0·2%)	1 (0·1%)
Drug-related	0	0	0
Treatment-emergent adverse events leading to death	0	0	0
Drug-related	0	0	0

Data are n (%) and are for the safety analysis set. A treatment-emergent adverse event is defined as any adverse event occurring or worsening relative to the baseline from the first dose of the study drug to day 28. Patients are counted only once per treatment per event category. NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 2: **Treatment-emergent adverse events**

group) of the treatment-emergent adverse events were grade 1 or 2. Grade 3 or higher treatment-emergent adverse events occurred in only seven (1·0%) patients in the VV116 group and 14 (2·1%) patients in the placebo group. The incidence of grade 3 or higher treatment-related adverse events was similar between groups (three [0·4%] patients *vs* two [0·3%] patients).

Two patients had serious adverse events, and both were in the placebo group: one had an intracranial haemorrhage and the other had a transient ischaemic attack. No treatment-emergent adverse events with an outcome of death occurred in the study. The number of treatment-emergent adverse events leading to study drug discontinuation was similar between groups (three [0·4%] patients for VV116 *vs* three [0·4%] patients for placebo). One patient from the placebo group had an adverse event of special interest: abnormal hepatic function.

Among the 97 patients aged 60 years and older who received at least one dose of VV116 or placebo (49 patients in the VV116 group and 48 in the placebo group), the incidences of treatment-emergent adverse events (21 [42·9%] patients in the VV116 group *vs* 28 [58·3%] patients in the placebo group) and treatment-related adverse events (11 [22·4%] patients *vs* 14 [29·2%] patients) were similar between the two groups (appendix 2 p 9). Treatment-emergent adverse events leading to permanent discontinuation of the investigational interventions were similar between the two groups (one [2·0%] of 49 patients in the VV116 group and one [2·1%] of 48 patients in the placebo group).

Discussion

This double-blind, phase 3, placebo-controlled randomised study has shown that, compared with placebo, a 5-day treatment with VV116 significantly shortened the time to sustained clinical symptom resolution and clinical symptom alleviation in patients with mild-to-moderate COVID-19. At the start of the trial, although three antivirals were already licensed or conditionally licensed in China for treating COVID-19 in adults, they had not been evaluated in patients infected with the Omicron variant. In this study, only one (0·2%) patient in the placebo group progressed to severe COVID-19, and no deaths occurred. Approximately 60% of participants were inpatients and 40% were outpatients. However, the health conditions of some outpatients were worse than for inpatients, as COVID-19 regulations changed through the course of the study. Before December, 2022, COVID-19 patients in China were required to be admitted to hospital regardless of their condition. After the policy changed, patients with COVID-19 could decide whether to go to hospital or not, and the doctors would judge whether the patient needed to be admitted. Our study enrolled individuals from October, 2022, to January, 2023, so the participants were almost all inpatients in the earlier stage, and most were outpatients in the later period. Therefore, the incidence of hospital admission could not be used as a surrogate endpoint for disease progression, and hospital admission did not indicate severe conditions.

The final analysis showed that the time to sustained clinical symptom resolution for 2 consecutive days was substantially reduced in the VV116 group compared with the placebo group (median time 10·9 days *vs* 12·9 days; p=0·0009), consistent with the interim analysis results. A previous active comparator-controlled phase 3 study by Cao and colleagues[21] showed that VV116 was non-inferior to nirmatrelvir–ritonavir in reducing the time to sustained clinical symptom resolution among patients with mild-to-moderate COVID-19 at risk for progression (median time: 7 days *vs* 7 days; HR 1·06, 95% CI 0·91–1·22). The longer time to sustained clinical symptom resolution observed in the present study compared with the previous study could be attributed to the higher electronic patient-reported outcome total score of the patients at study entry (median score of 10 in this study *vs* 3 in the previous study). The combined positive results from the two phase 3 studies indicate that VV116 effectively reduced the time to sustained clinical symptom resolution compared with placebo and is non-inferior to nirmatrelvir–ritonavir.

The treatment effects were consistent across subgroups. Patients with a total target COVID-19 symptoms score of 10 or less had a substantially lower time to sustained clinical symptom resolution compared with those who had a score of more than 10 in both groups. These results indicated that a higher COVID-19 symptoms score at baseline is associated with a longer time to clinical recovery. Furthermore, similar differences were observed between those who were admitted to hospital and those who were not, with outpatients taking longer to recover than inpatients (consistent with the worse baseline condition of outpatients due to policy changes mentioned previously). Among patients aged 60 years and older, the median time to sustained clinical symptom resolution and sustained clinical symptom alleviation was shorter in the VV116 group compared with the placebo group, which is consistent with the overall population. Meanwhile, the subgroup analysis in male and female patients showed similar treatment efficacy. In addition, for VV116, the rapid decrease in SARS-CoV-2 viral load from baseline was consistent with that of nirmatrelvir–ritonavir (–0·75 $\log_{10}$ copies per mL *vs* –0·87 $\log_{10}$ copies per mL lower than placebo on day 5, respectively).[12,14]

In this study, only one patient from the placebo group progressed to severe COVID-19. The potential effect of VV116 on death, disease progression, or COVID-19-related hospital admissions needs to be further explored in larger real-world studies. Overall, VV116 was well tolerated in patients with mild-to-moderate COVID-19. The incidence of treatment-emergent adverse events was 35·9% in the VV116 group and 42·1% in the placebo group and the incidence of treatment-related adverse

events was 17·4% in the VV116 group and 23·2% in the placebo group, which could be attributed to VV116's ability to inhibit viral replication, potentially reducing illness or symptoms caused by the SARS-CoV-2 infection. The incidence of treatment-emergent adverse events in the present study was lower than in Cao and colleagues' study (259 [67·4%] of 384 patients in the VV116 group and 299 [77·3%] of 387 patients in the nirmatrelvir–ritonavir group).[21] One reasonable explanation for the lower incidence of treatment-emergent adverse events was the higher proportion of patients with concomitant medications in the previous study than in the present study (611 [79·2%] of 771 *vs* 740 [57·1%] of 1296). Most of the treatment-emergent adverse events in this study were laboratory abnormalities and ranged between grades 1 and 2. The incidence of serious adverse events was low in the present study, with only two patients having severe adverse events (both in the placebo group). Among patients aged 60 years and older, the incidence of treatment-emergent adverse events was similar to that in the overall population. Increased blood pressure was the most frequently reported treatment-emergent adverse event in both the overall population and patients aged 60 years and older. No new safety signals were found in patients aged 60 years and older.

This placebo-controlled, phase 3 study provided substantial clinical evidence to support the use of VV116 in patients with mild-to-moderate COVID-19. However, there are certain limitations that should be considered when interpreting the data. Firstly, this is not a non-inferiority double-blinded randomised trial comparing VV116 with the current standard oral antiviral treatment. Second, this study was conducted only in China during the Omicron variant outbreak. The antiviral effect and safety of VV116 in other populations warrant further exploration. Finally, a low number of patients completed the sample collection for viral load and viral variant test due to COVID-19 quarantine and prevention measures, meaning that the results for viral load only stated the change in trend of SARS-CoV-2 viral load.

In summary, VV116 produced a significant reduction in the time to sustained clinical symptom resolution compared with placebo in patients with mild-to-moderate COVID-19, with a low incidence of adverse events and a favourable safety profile.

Contributors

LL, XF, and JM conceived and designed the study. YLin, LW, LT, and KZ were responsible for supervision and project administration. All authors were responsible for acquisition of data. LL, XF, YunL, JM, and BX analysed and interpreted the data. JM, BX, and YLin reviewed the manuscript. All authors participated in the critical review and final approval of the manuscript. XF, YLin, XD, LW, and LT accessed and verified the data. All authors were responsible for the decision to submit the manuscript for publication and had full access to the data in the study.

Declaration of interests

JM, BX, and KZ are employees of Shanghai Junshi Biosciences. Shanghai JunTop Biosciences is an affiliated company of Shanghai Junshi Biosciences; Shanghai Vinnerna Biosciences, the sponsor of this study, is the subsidiary of Shanghai JunTop Biosciences and Vigonvita Life Sciences. All aspects of this study were done by Shanghai Junshi Biosciences. The remaining authors declare no competing interests.

Data sharing

De-identified individual patient data collected during the study and the study protocol will be provided upon request approval. Currently, there is no expiration date for data requests. Access is granted after a proposal has been approved by an independent review committee designated for this purpose and after receiving a signed data-sharing agreement. Data and documents will be provided in a secure data-sharing environment. Proposals should be directed to the corresponding author.

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