# Efficacy and safety of SIM0417 (SSD8432) plus ritonavir for COVID-19 treatment: a randomised, double-blind, placebo-controlled, phase 1b trial

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## Summary

**Background** SIM0417 (SSD8432) is an orally administered coronavirus main proteinase ($3CL^{pro}$) inhibitor with potential anti-SARS-CoV-2 activity. This study aimed to evaluate the efficacy and safety of SIM0417 plus ritonavir (a pharmacokinetic enhancer) in adults with COVID-19.

**Methods** This was a randomised, double-blind, placebo-controlled, phase 1b study in China. Adults with asymptomatic infection, mild or moderate COVID-19 were randomly assigned (3:3:2) to receive either 750 mg SIM0417 plus 100 mg ritonavir, 300 mg SIM0417 plus 100 mg ritonavir or placebo every 12 h for 10 doses. The main efficacy endpoints included SARS-CoV-2 viral load, proportion of participants with positive SARS-CoV-2 nucleic acid test and time to alleviation of COVID-19 symptoms. This trial is registered with ClinicalTrials.gov, NCT05369676.

**Findings** Between May 12 and August 29, 2022, 32 participants were enrolled and randomised to high dose group (n = 12), low dose group (n = 12) or placebo (n = 8). The viral load change from baseline in high dose group was statistically lower compared with placebo, with a maximum mean difference of −2.16 ± 0.761 $\log_{10}$ copies/mL (p = 0.0124) on Day 4. The proportion of positive SARS-CoV-2 in both active groups were lower than the placebo. The median time to sustained alleviation of COVID-19 symptoms was 2.0 days in high dose group versus 6.0 days in the placebo group (HR = 3.08, 95% CI 0.968–9.818). SIM0417 plus ritonavir were well tolerated with all adverse events in grade 1.

**Interpretation** SIM0417 plus ritonavir was generally well tolerated. The efficacy of SIM0417 showed a monotonic dose–response relationship, and the 750 mg SIM0417 plus 100 mg ritonavir was selected as the recommended clinical dose.

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**Keywords:** Covid-19; 3CL protease inhibitor; SARS-CoV-2 viral load; Alleviation of COVID-19 symptoms

## Introduction

As of May 2023, over 766 million people worldwide have been diagnosed with COVID-19, including over 6.9 million deaths, reported to WHO, according to the World Health Organization (WHO) dashboard.[1] The emergence of SARS-CoV-2 and subsequent COVID-19 pandemic has resulted in a significant global public health burden, leading to an urgent need for effective

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## Research in context

### Evidence before this study

Oral small molecule antiviral drugs are less susceptible to viral mutation, and has the advantages of lower price and higher accessibility. At present, the research and development of small molecule drugs targeted 3CL protease, an enzyme that the coronavirus needs to replicate, has become a hot spot. SIM0417, an oral antiviral candidate for the treatment of coronavirus disease 2019 (COVID-19), which is designed to block the SARS-CoV-2 main protease ($M^{pro}$, also known as $3CL^{pro}$). It can be prescribed at the first sign of infection–potentially helping patients avoid severe illness that may lead to hospitalization and death. The results of preclinical studies showed that SIM0417 is a highly active, orally available, and low toxic anti-COVID-19 drug that not only inhibits wild-type $3CL^{pro}$, but also maintains inhibitory activity against variants including Omicron. Co-administration with a low dose of ritonavir helps slow the metabolism of SIM0417 in order to remain effectiveness in the body for longer periods at higher concentrations. SIM0417 also demonstrated a good safety profile in phase 1 clinical trials in healthy adult participants (NCT05339646).

### Added value of this study

This was a phase 1b study to evaluate the safety and efficacy of SIM0417 plus ritonavir in adult Chinese patients with COVID-19. Study results have suggested that SIM0417 plus ritonavir were well tolerated and effective over placebo for asymptomatic infection, mild or moderate COVID-19. SIM0417 plus ritonavir is a potential treatment for the adult patients with COVID-19. It is worth noting that, for the viral load change from baseline in 750 mg SIM0417 plus 100 mg ritonavir group, from Day 2 to Day 7, compared with placebo group, there were statistically significant differences, with a maximum mean difference of $-2.16 \pm 0.761$ $\log_{10}$ copies/mL on Day 4.

### Implications of all the available evidence

This study, along with other studies, suggested that the SIM0417 plus ritonavir is another promising candidate for COVID-19 treatment. Currently, SIM0417 (Simnotrelvir)/ritonavir has been EUA approved in China.

therapeutic strategies. Also, the emergence of novel variants of the SARS-CoV-2 has led to a matter of great concern. SARS-CoV-2 has very strong mutation ability.[2] Omicron mutant, whose transmission rate is much higher than the pre-existing variants has been widely spread to many countries and has become dominant worldwide. Severe cases and mortality rates were less than compared prior at this time.[3]

The vaccines against SARS-CoV-2 have helped to limit the spread but has yet to eradicate it. Therefore, there are needs to be continuous development of new therapeutics as well as continuous monitoring and sequencing of the SARS-CoV-2 virus over time.[4] Since trials have shown the need for initiation of treatment as soon as possible after the onset of symptoms,[5–7] such therapies would ideally be readily available and easily administered by the patients themselves.[8] Neutralized antibodies have improved the prognosis of COVID-19 during wild type variants spreads, but the efficacy has been declined due to mutation and immune escape of SARS-CoV-2.[6,9] Compared with neutralizing antibody therapy, the activity of oral small molecule antiviral drugs is less susceptible to viral mutation, and has the advantages of lower price and higher accessibility. Development of safe and effective treatments to rapid reduce SARS-CoV-2 viral load and improve symptoms recovery, and potential to reduce the risk of progressing into severe disease and mortality rate is still an important unmet need. At present, there are two main development routes for anti-coronavirus drugs: 3CL protease inhibitors and RNA polymerase inhibitors.[10]

$3CL^{pro}$ (3-Chymotrypsin-like cysteine protease), also known as the main protease ($M^{pro}$), is a three-domain (domains I to III) cysteine protease composed of 306 amino acids.[11,12] $3CL^{pro}$ plays a crucial role in the coronavirus replication and maturation, and is highly conserved. Inhibition of $3CL^{pro}$ can effectively block viral RNA replication and transcription and further block viral proliferation. These makes it an important and promising target for developing operative and applicable antiviral drugs against COVID-19.[12,13] A series of $3CL^{pro}$ inhibitors have been developed, while few have been on the market.[14]

SIM0417 is an oral SARS-CoV-2 main protease inhibitor that exerts antiviral effects by inhibiting the replication of the virus. Co-administration with a low dose of ritonavir as a pharmacokinetic booster helps to optimize the pharmacokinetics of this anti-protease against SARS-CoV-2. The results of preclinical studies showed that SIM0417 is a highly active, orally available, and low toxic anti-COVID-19 drug that not only inhibits wild-type SARS-CoV-2 $3CL^{pro}$, but also maintains inhibitory activity against Delta and Omicron, with $IC_{50}$ <100 nM.

The phase 1 clinical trial of SIM0417 in healthy volunteers (NCT05339646) has been completed and the results showed that single/multiple oral doses of SIM0417 and SIM0417 co-administrated with ritonavir in healthy adult participants were well tolerated. The phase 2/3 clinical trial has been completed (NCT05506176) and 1208 participants has been enrolled. Currently, SIM0417 (Simnotrelvir)/ritonavir

has been EUA approved in China. Here, we reported the results of a phase 1b trial (NCT05369676) which we sought to preliminarily evaluate the efficacy and safety of SIM0417 plus ritonavir in adult patients with COVID-19, and determine the recommended clinical dose.

## Methods

### Study design and participants

This is a randomised, double-blind, placebo-controlled, phase 1b study conducted in China. Eligible participants were adult patients (age ≥18 and ≤ 75 years) with asymptomatic infection, mild or moderate COVID-19, who had initial positive SARS-CoV-2 test result within 5 days and the onset of COVID-19 symptoms within 3 days before randomisation. Women of childbearing potential and men with female partners of childbearing potential were required to use highly effective methods of contraception from inform consent to 1 month after the last dosage. Main exclusion criteria included: (1) Urgent need for nasal high-flow oxygen therapy or non-invasive ventilation, invasive mechanical ventilation, or Extra-corporeal Membrane Oxygenation (ECMO); (2) Prior SARS-CoV-2 infection by self-reported; (3) Active liver disease (except non-alcoholic fatty liver disease); (4) Undergoing dialysis or known moderate to severe renal impairment; (5) Known human immunodeficiency virus (HIV) infection; (6) Suspected or confirmed active, systemic infections other than COVID-19 that may interfere with the assessment of response to study interventions; (7) $SpO_2$ ≤93%; (8) AST >3 × ULN or (ALT) > 3 × ULN, Total bilirubin ≥1.5 × ULN; (9) Receiving COVID-19 monoclonal antibodies, convalescent plasma, or using other contraindicated concomitant drugs within 30 days. The study was approved and supervised by the ethics committee of the Third People's Hospital of Shenzhen, conducted in accordance with the protocol/protocol amendments, Good Clinical Practice, and the Declaration of Helsinki. All participants provided written informed consent before enrolment. The protocol synopsis is included in the appendix.

### Randomisation and masking

The random allocation sequence was generated with permuted blocks of fixed size by a randomisation statistician in a third party.

Eligible participants were randomly assigned (3:3:2) to receive either 750 mg SIM0417 plus 100 mg ritonavir (high dose), 300 mg SIM0417 plus 100 mg ritonavir (low dose) or placebo every 12 h for 10 doses. To ensure the safety of participants in this early phase study, the randomisation was performed within three separate cohorts. 8 participants in cohort 1 were randomised in a 3:1 ratio into low dose SIM0417 plus ritonavir or placebo group to detect potential safety signals. As the safety profile in cohort 1 didn't meet the termination criteria (2 or more subjects in one cohort reported Grade 3 or more severe adverse event(s) associated with the study drug as adjudicated by the investigator), 8 patients in cohort 2 were randomised in the same ratio into high dose SIM0417 plus ritonavir or placebo group. Finally, 16 participants in cohort 3 were randomised concurrently in a 3:3:2 ratio to receive high dose, low dose or placebo treatment.

The randomisation was implemented through an interactive web response system (IWRS) and the allocation concealment can be guaranteed. The sponsor study team, investigators, and patients were masked to treatment group assignments before study unblinding. The sponsor set up an internal review team independent of the study team and with access to unblinded data to provide support to phase 3 study designs for SIM0417.

### Procedures and outcomes

The study duration is about one month (28 ± 3 days) after randomisation, the participants received study intervention through Day 5 or Day 6 (if only 1 dose is administered on Day 1), and had efficacy and safety assessments through Day 28.

All participants were hospitalised in The Third People's Hospital of Shenzhen (the clinical centre) due to isolation treatment, and discharged after the nucleic acid test negative conversion (defined as two consecutive Ct value ≥35 or negative for both SARS-CoV-2 ORF1ab gene and N gene detected at local laboratory, at least at an interval of 24 h). Viral load below the detection limit of 200 copies/mL was regarded as negative result. Nasopharyngeal swabs were collected at baseline and every morning until discharge. Swabs were sent to the central laboratory for SARS-CoV-2 viral load detection, using a validated Real-time Quantitative SARS-CoV-2 LDT (laboratory developed test) assay developed with Sansure biotech commercial kit[15] and SARS-CoV-2 standard for quantitative analysis of nucleic acid from SARS-CoV-2 by detecting the nucleocapsid (N) genes. Participants were allowed to receive standard of care treatment, except for contraindicated medications or drugs with potential drug–drug interactions. Participants reported COVID-19 signs and symptoms twice a day during hospitalization, and continued daily after discharge if not alleviated at the time of discharge, until all COVID-19 signs and symptoms were alleviated. Vital signs, physical examinations, electrocardiogram and laboratory tests were monitored by clinicians at specific timepoints during the study. Adverse events were graded for severity by using the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0)[16] and categorised according to codes in the Medical Dictionary for Regulatory Activities (MedDRA; version 25.0). After discharge, data were collected via in-person visits or telephone visits. The investigators discussed with the participants to determine an appropriate location for the visits.

A Safety Review Committee (SRC) was set up, including sponsor medical team staff and study team representatives, and other members that may be

needed. It was responsible for blinded safety monitoring and safety data review during the study. After at least 4 participants in cohort 1 completed the 3-day (Day 9 ± 1) follow-up after the last dose, the safety of all available participants (≥4 participants) was assessed blindly by the SRC, and without reaching termination criteria, participants in cohort 2 started to be enrolled.

The primary outcome was safety which included incidence of Treatment Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs) and AEs leading to discontinuation. The secondary outcomes of efficacy included change from baseline in viral load of SARS-CoV-2 in nasopharyngeal swabs by RT-PCR at each time point, proportion of participants with positive nucleic acid test result at each time point, and time from first dose to overall symptom alleviation for COVID-19 (defined as having all 9 COVID-19 symptoms (cough, stuffy or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, low energy or tiredness, headache, fever or feeling hot, chills, muscle or body aches) of 0 (none) or 1 (mild) for at least 1 day).

Full lists of secondary efficacy endpoints are provided in the protocol.

### Statistical analyses

The statistical analysis plan was finalized before database lock and unblinding. The safety analysis set was used for the safety analyses and the full analysis set was used for efficacy analyses. As all patients enrolled took at least one dose of study drug/placebo and no switch of group occurred, both analysis sets included all patients enrolled with treatment group as randomised.

The sample size was not determined on a statistical hypothesis testing basis as the primary objective of this study focused on safety.

The AEs were summarized using frequencies and proportions. All efficacy endpoints were analyzed in an exploratory way using a nominal significance level of two-sided 0.05. Descriptive statistics were calculated for each group respectively and statistical comparisons were performed for high dose and low dose versus placebo group.

For continuous and ordinal efficacy endpoints, Wilcoxon rank sum test was used to compare the difference of treatment groups. Differences and 95% confidence intervals (CIs) of mean between groups for viral load change from baseline were provided for each visit using Analysis of Variance (ANOVA) method. Proportional odds logistic regression model was also used for some ordinal endpoints. For time-to-event efficacy endpoints, Kaplan–Meier curves were provided and hazard ratios and 95% CIs were calculated through proportional hazards (PH) cox regression model. The PH assumption is assessed by plotting the ln (-ln (S(t))) versus time. For binary efficacy endpoints, exact 95% CIs of proportions for each group were calculated by Clopper-Pearson method and group comparisons were performed using Fisher exact test. Difference of proportions between SIM0417 groups and placebo group together with exact 95% CIs were also provided. There were no planning of subgroups analyses and adjustment for variables in this study due to small sample size.

### Role of the funding source

The sponsor of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

## Results

Between May 14 and August 29, 2022, 39 potential participants who attended for screening, 7 were excluded (5 met the exclusion criteria or not met the inclusion criteria, 2 withdrew their informed consents), 32 participants were enrolled and randomly assigned to receive 750 mg SIM0417 plus 100 mg ritonavir (n = 12), 300 mg SIM0417 plus 100 mg ritonavir (n = 12) or placebo (n = 8). All participants were included in the efficacy and safety analysis population. 30 participants completed the study, 2 participants withdrew from the study (1 in the placebo group, 1 in the low dose group). The reasons were withdrawal of informed consent. In all participants enrolled, all of them were Asian, the median age was 39.5 years; 7 participants (21.9%) were female and 25 participants (78.1%) were male. Most of the participants (87.5%) were classified as mild COVID-19 (high dose group 83.3%, low dose group 83.3%, placebo group 100%). The proportions of baseline SARS-CoV-2 nucleic acid Ct values (local lab) ≤25 were 91.7%, 91.7% and 75.0%, respectively. The most frequent symptoms were fever (17 (53.1%)), Sore throat or dry throat (17 (53.1%)), cough (14 (43.8%)) and fatigue (11 (34.4%)). Except for 1 participant in the high dose group, all the others had been vaccinated against COVID-19. Among all participants, 1 (3.1%) were vaccinated with one dose, 6 (18.8%) were vaccinated with two doses, 20 (62.5%) were vaccinated with three doses and 4 (12.5%) were vaccinated with four doses. Most of the participants were received inactivated vaccines, the proportions were 83.3%, 100%, and 100%, respectively (Table 1) (Fig. 1).

Swab samples for SARS-CoV-2 viral load were collected at baseline and every day until met the discharge standards. The results showed that the viral load dramatically decreased with both doses of SIM0417 plus ritonavir even after only one day's treatment, with a mean change of −1.90 ± 0.915 (mean ± SD) and −2.08 ± 0.852 $\log_{10}$ copies/mL from baseline. The greater reduction was seen in the high dose group (Fig. 2). The baseline characteristics of the participants showed that the baseline viral load (copies/mL, $\log_{10}$-transformed) was high in each group, with a mean (SD) of 7.89 (0.558), 7.42 (0.880) and 7.44 (1.002) $\log_{10}$ copies/mL in the high dose, low dose, and placebo groups, respectively. On Day 3 of the treatment period,

| | High dose (N = 12) | Low dose (N = 12) | Placebo (N = 8) | Total (N = 32) |
|---|---|---|---|---|
| Age (years) | | | | |
| Mean (SD) | 36.3 (12.82) | 39.5 (14.80) | 43.6 (14.98) | 39.3 (13.97) |
| Median | 35.5 | 36.5 | 42.0 | 39.5 |
| Range | 22, 57 | 19, 67 | 21, 72 | 19, 72 |
| ≥18 – < 60 | 12 (100%) | 11 (91.7%) | 7 (87.5%) | 30 (93.8%) |
| ≥60 – ≤ 75 | 0 | 1 (8.3%) | 1 (12.5%) | 2 (6.3%) |
| Gender, n (%) | | | | |
| Male | 11 (91.7%) | 9 (75.0%) | 5 (62.5%) | 25 (78.1%) |
| Female | 1 (8.3%) | 3 (25.0%) | 3 (37.5%) | 7 (21.9%) |
| BMI ($kg/m^2$) | | | | |
| Mean (SD) | 24.43 (1.990) | 23.10 (3.749) | 25.08 (5.057) | 24.09 (3.583) |
| Median | 24.00 | 24.30 | 24.95 | 24.35 |
| Min, Max | 22.2, 29.2 | 17.3, 28.4 | 16.0, 31.1 | 16.0, 31.1 |
| <25 | 7 (58.3%) | 9 (75.0%) | 4 (50.0%) | 20 (62.5%) |
| ≥25 – < 30 | 5 (41.7%) | 3 (25.0%) | 2 (25.0%) | 10 (31.3%) |
| ≥30 | 0 | 0 | 2 (25.0%) | 2 (6.3%) |
| Duration since first diagnosis (Days) | | | | |
| Mean (SD) | 4.1 (0.900) | 4.2 (0.937) | 4.0 (0.756) | 4.1 (0.856) |
| Median | 4 | 4 | 4 | 4 |
| Min, Max | 3, 6 | 3, 6 | 3, 5 | 3, 6 |
| ≤3 | 3 | 3 | 2 | 8 |
| ≥3 | 9 | 9 | 6 | 24 |
| Clinical classification before enrollment, n (%) | | | | |
| Asymptomatic infection | 1 (8.3%) | 1 (8.3%) | 0 | 2 (6.3%) |
| Mild | 10 (83.3%) | 10 (83.3%) | 8 (100%) | 28 (87.5%) |
| Moderate | 1 (8.3%) | 1 (8.3%) | 0 | 2 (6.3%) |
| Duration since first symptoms to randomisation (days) | | | | |
| 1 | 1 (8.3%) | 1 (8.3%) | 2 (25.0%) | 4 (12.5%) |
| 2 | 1 (8.3%) | 3 (25.0%) | 1 (12.5%) | 5 (15.6%) |
| 3 | 3 (25.0%) | 5 (41.7%) | 4 (50.0%) | 12 (37.5%) |
| >3 | 6 (50.0%) | 1 (8.3%) | 1 (12.5%) | 8 (25.0%) |
| COVID-19 symptoms at baseline | | | | |
| Cough | 4 (33.3%) | 7 (58.3%) | 3 (37.5%) | 14 (43.8%) |
| Stuffy or runny nose | 2 (16.7%) | 2 (16.7%) | 3 (37.5%) | 7 (21.9%) |
| Sore throat or dry throat | 6 (50.0%) | 5 (41.7%) | 6 (75.0%) | 17 (53.1%) |
| Shortness of breath or difficulty breathing | 0 | 0 | 0 | 0 |
| Fatigue | 4 (33.3%) | 2 (16.7%) | 5 (62.5%) | 11 (34.4%) |
| Headache | 2 (16.7%) | 0 | 3 (37.5%) | 5 (15.6%) |
| Fever | 8 (66.7%) | 5 (41.7%) | 4 (50.0%) | 17 (53.1%) |
| Chills or shivering | 0 | 0 | 0 | 0 |
| Muscle or body aches (or soreness) | 1 (8.3%) | 2 (16.7%) | 1 (12.5%) | 4 (12.5%) |
| Nausea | 0 | 1 (8.3%) | 0 | 1 (3.1%) |
| Vomiting | 0 | 0 | 0 | 0 |
| Diarrhea | 1 (8.3%) | 0 | 1 (12.5%) | 2 (6.3%) |
| Other | 2 (16.7%) | 2 (16.7%) | 1 (12.5%) | 5 (15.6%) |
| Ct Value | | | | |
| Ct Value ≤25 | 11 (91.7%) | 11 (91.7%) | 6 (75.0%) | 28 (87.5%) |
| Ct Value >25 and SARS-CoV-2 serum IgG and IgM are negative | 0 | 0 | 1 (12.5%) | 1 (3.1%) |
| Ct value >25 and SARS-CoV-2 serum IgG-positive IgM negative | 1 (8.3%) | 1 (8.3%) | 1 (12.5%) | 3 (9.4%) |
| High-risk factors | | | | |
| Yes | 6 (50.0%) | 4 (33.3%) | 5 (62.5%) | 15 (46.9%) |
| >60 years | 0 | 1 (8.3%) | 1 (12.5%) | 2 (6.3%) |
| Comorbidities | 5 (41.7%) | 3 (25.0%) | 2 (25.0%) | 10 (31.3%) |
| Immune deficiency | 0 | 0 | 0 | 0 |

(Table 1 continues on next page)

| | High dose (N = 12) | Low dose (N = 12) | Placebo (N = 8) | Total (N = 32) |
|---|---|---|---|---|
| (Continued from previous page) | | | | |
| Obesity | 0 | 0 | 2 (25.0%) | 2 (6.3%) |
| Heavy smoker | 1 (8.3%) | 3 (25.0%) | 2 (25.0%) | 6 (18.8%) |
| No | 6 (50.0%) | 8 (66.7%) | 3 (37.5%) | 17 (53.1%) |
| Number of risk factors of interest | | | | |
| 0 | 6 (50.0%) | 8 (66.7%) | 3 (37.5%) | 17 (53.1%) |
| 1 | 6 (50.0%) | 1 (8.3%) | 3 (37.5%) | 10 (31.3%) |
| 2 | 0 | 3 (25.0%) | 2 (25.0%) | 5 (15.6%) |
| Vaccinations | | | | |
| Not vaccinated | 1 (8.3%) | 0 | 0 | 1 (3.1%) |
| 1 dose | 1 (8.3%) | 0 | 0 | 1 (3.1%) |
| 2 doses | 3 (25.0%) | 2 (16.7%) | 1 (12.5%) | 6 (18.8%) |
| 3 doses | 5 (41.7%) | 8 (66.7%) | 7 (87.5%) | 20 (62.5%) |
| 4 doses | 2 (16.7%) | 2 (16.7%) | 0 | 4 (12.5%) |
| Type of vaccine, n (%) | | | | |
| Inactivated Virus Vaccine | 10 (83.3%) | 12 (100%) | 8 (100%) | 30 (93.8%) |
| mRNA vaccine | 3 (25.0%) | 0 | 0 | 3 (9.4%) |

***Table 1:*** **Baseline characteristics of all randomised participants (Safety Analysis Population).**

the mean changes from baseline in viral load in the high dose group, low dose group and placebo group were −3.04, −3.23, and −1.01 $\log_{10}$ copies/mL (based on the Last Observation Carried Forward, LOCF). On Day 4 of the treatment period, the mean changes from baseline in viral load were −3.99, −3.41, −1.82 $\log_{10}$ copies/mL in each group, respectively (based on LOCF). On the Day 3 and Day 4, the mean viral load reduction from baseline in the high dose group was approximately 2 $\log_{10}$ copies/mL greater than that in the placebo group. Based on LOCF, the mean viral load changes from baseline in the high dose group from Day 2 to Day 7, compared with those in the placebo group, there were statistically significant differences (Day 2 $p = 0.0387$, Day 3 $p = 0.0041$, Day 4 $p = 0.0124$, Day 5 $p = 0.0096$, Day 6 $p = 0.0096$, Day 7 $p = 0.0473$). In the low dose group on Day 2 and Day 3, compared with those in the placebo group, there were statistically significant differences (Day 2 $p = 0.0124$, Day 3 $p = 0.0055$). On Day 4, in the high dose group, the mean viral load decreased the most compared to the placebo group, which was $-2.16 \pm 0.761$ $\log_{10}$ copies/mL. On Day 3, in low dose group, the mean viral load decreased the most compared to the placebo group, which was $-2.21 \pm 0.666$ $\log_{10}$ copies/mL (Table S1). The results of the analysis based on observed observations were similar to the results of LOCF imputed data analysis (Table S2).

Another virologic endpoint of this study was the proportion of participants with positive nucleic acid test at each time point. Based on the readout of the central laboratory on the Day 3 of the study, the proportion of positive nucleic acid test in the low dose group was lower than that in the placebo group. From the Day 4, the proportion of positive nucleic acid test or with N gene CT value ≤25 in the high dose group and the low dose group were both lower than that in the placebo group (Fig. 3, Table S3, Table S4). Fig. 3 shows the proportion of participants who were positive or with N gene CT value ≤25 for nucleic acid test (central lab), shown in red, at Day 1 (baseline), Day 4, Day 6 and Day 7 after treatment. Participants who were negative for nucleic acid test result are shown in blue.

Except for 1 participant in the placebo group, 31 participants were tested for viral variants and sequenced to determine the type of SARS-Cov-2 variant which they were infected. The results showed that the variants in the samples of 31 participants were all Omicron mutants. The most common subtype of variants was BA.2.2, 8 (66.7%) in the high-dose group, 9 (75.0%) in the low-dose group, and 6 (85.7%) in the placebo group (Table S5).

The median time to sustained alleviation of COVID-19 symptoms was 2.0 days (95% CI 1.0–5.0), 3.0 days (1.0–6.0), and 6.0 days (1.0–9.0) in the high dose, low dose and placebo groups, respectively. The hazard ratio (95% CI) of the high dose group and the low dose group relative to the placebo group were 3.08 (0.97–9.82) and 1.91 (0.66–5.53), respectively (Fig. 4). Among all the participants, 1 participant in the low dose group and 1 participant in placebo group were not relieved at the end of the study, and both of them were participants who withdrew early. All participants in the high dose group achieved alleviation within 6 days.

Severity of 9 target symptoms was evaluated and the change from baseline was analyzed (Fig. 5A). For respiratory symptoms, the most frequent symptoms which the participants experienced were cough, sore or dry throat, stuffy or runny nose, and no participants experienced shortness of breath or difficulty breathing. The proportion of participants with the symptom of cough changed more rapidly over time in the high dose and

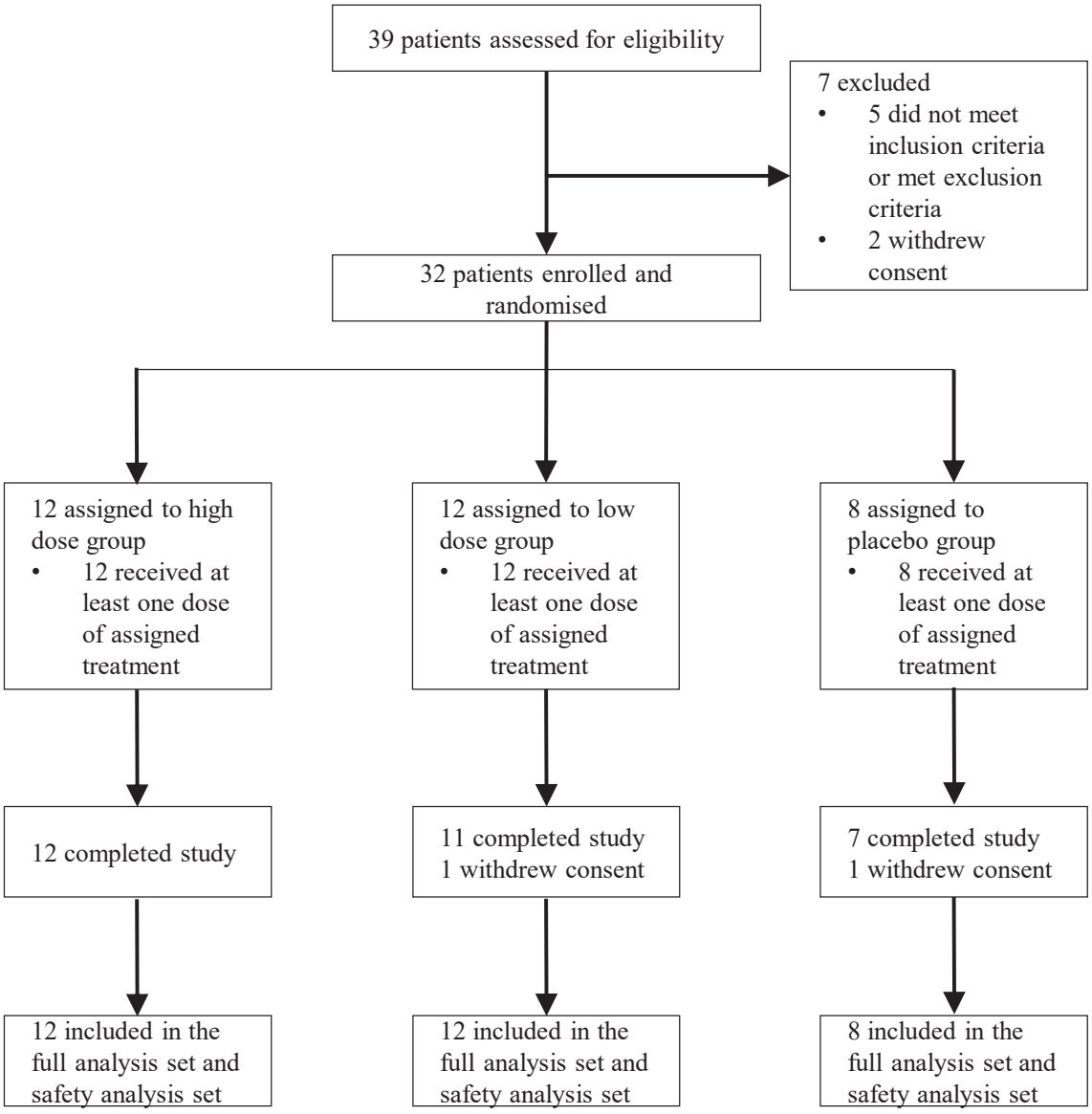



***Fig. 1:*** **Study profile.**

low dose groups compared to the placebo group, and the symptom disappeared (score of 0) on Day 12 and Day 13, respectively. The symptoms of sore throat and dry throat were disappeared on Day 3 and Day 4 in all participants of the high dose group and the low dose group, respectively. For stuffy or runny nose, the symptoms of all participants in the high dose group and the placebo group disappeared on Day 3 and Day 4, respectively. The incidence of each systemic symptoms, including low energy or tiredness, headache, fever, muscle or body aches (or soreness), was relatively low. No participants experienced chills. Except for the intermittent persistent of headache, the other 3 symptoms only lasted for 1–2 days (Fig. 5B).

During the study, a total of 22 TEAEs were reported in 13 participants. The total incidence rate of TEAEs was 40.6% (13/32). All TEAEs that were followed up till the study completion and had either recovered or improved outcome. No SAE occurred during the trial period. There was no adverse event leading to discontinuation of the investigational drugs or study withdrawal. The incidence of TEAEs among participants of high dose group, low dose group and placebo was 33.3% (4/12), 33.3% (4/12) and 62.5% (5/8). 4 participants in the high dose group experienced 6 related TEAEs, 4 participants in the low dose group experienced 7 related TEAEs, and 5 participants in placebo group experienced 9 related TEAEs (Table 2).

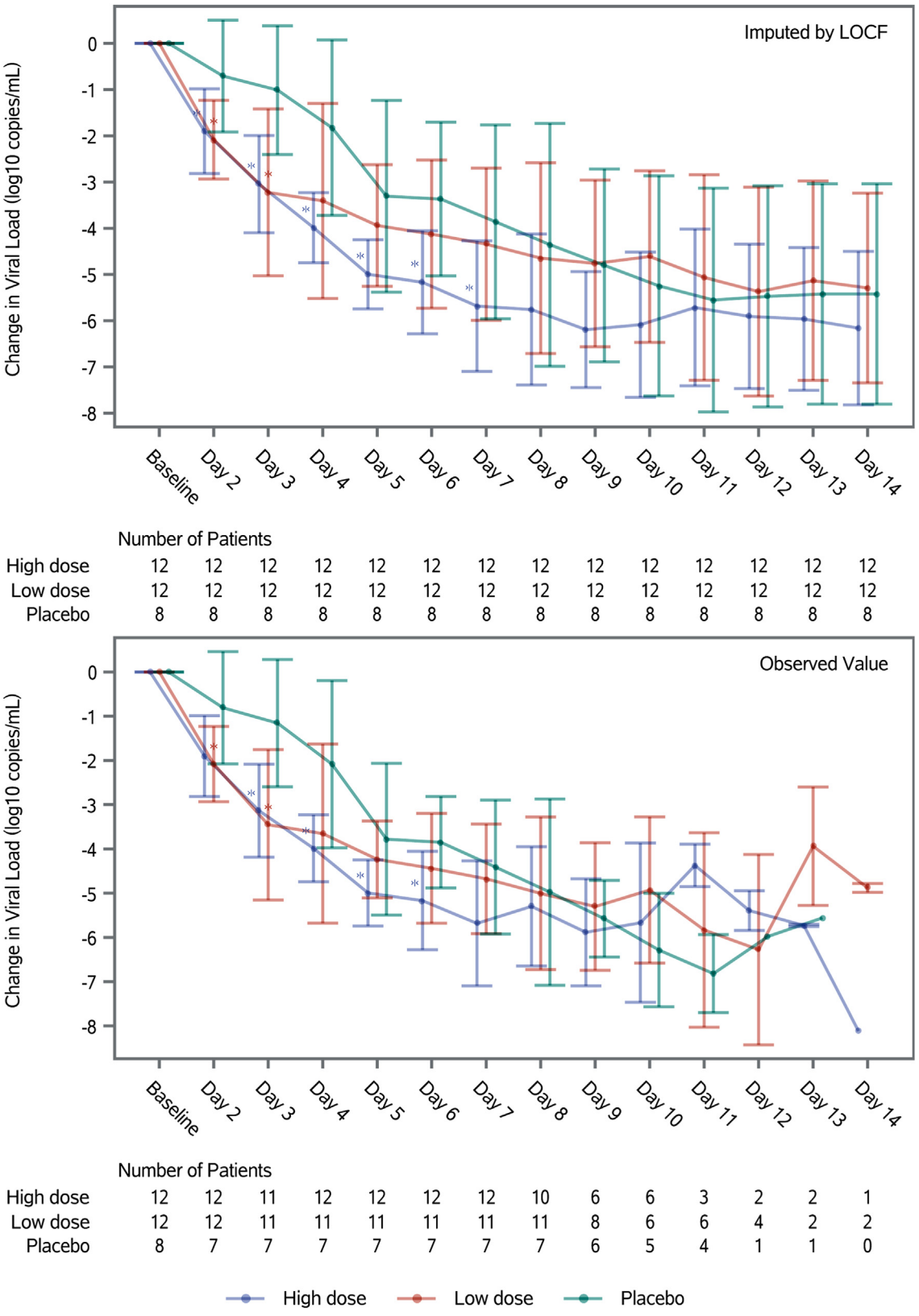
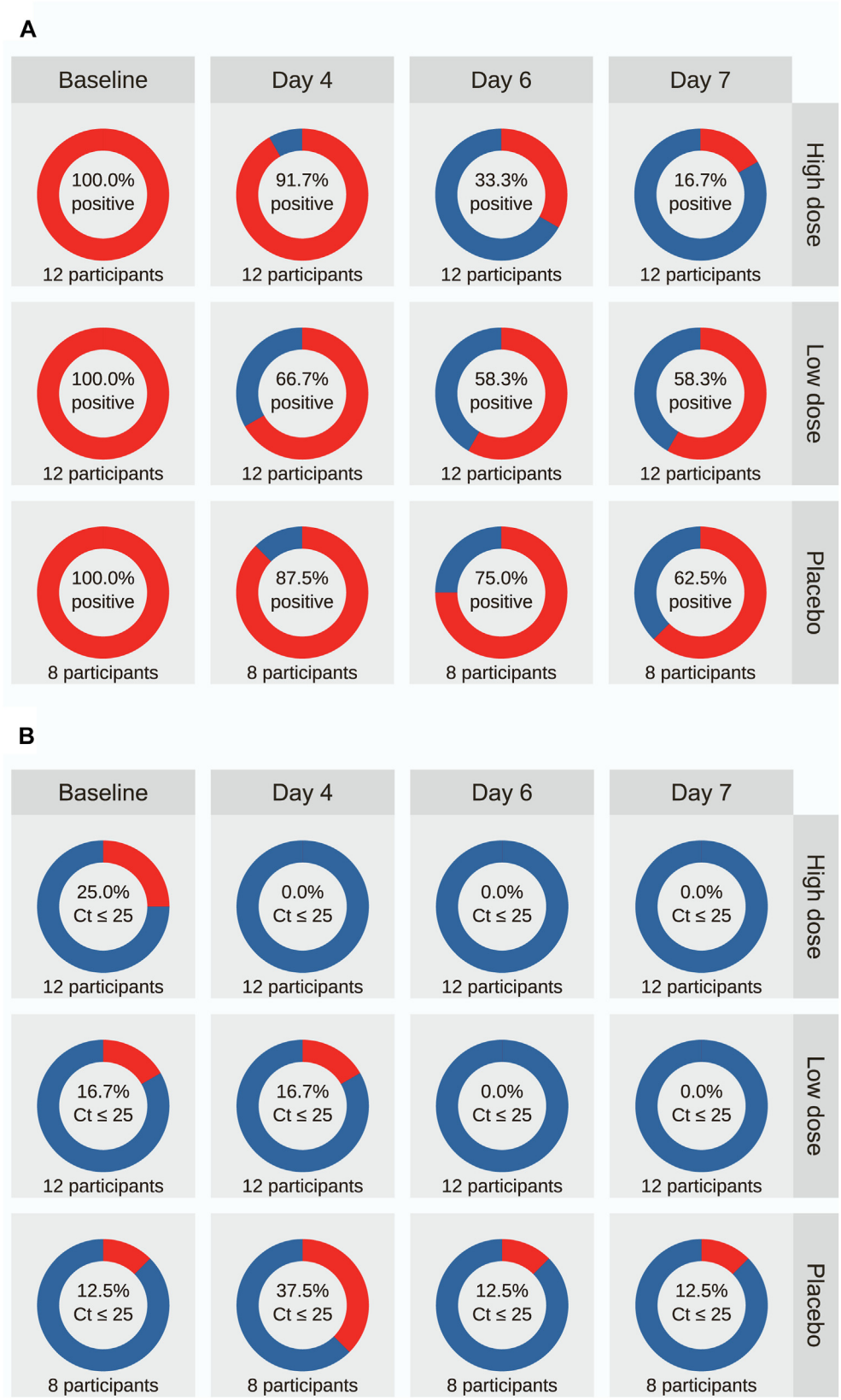



***Fig. 2:*** **Viral load change from baseline**. Data are presented as mean ± standard deviation (SD). *, P < 0.05 versus placebo.


A
Baseline
Day 4
Day 6
Day 7
High dose
100.0% positive
12 participants
91.7% positive
12 participants
33.3% positive
12 participants
16.7% positive
12 participants
Low dose
100.0% positive
12 participants
66.7% positive
12 participants
58.3% positive
12 participants
58.3% positive
12 participants
Placebo
100.0% positive
8 participants
87.5% positive
8 participants
75.0% positive
8 participants
62.5% positive
8 participants
B
Baseline
Day 4
Day 6
Day 7
High dose
25.0% Ct ≤ 25
12 participants
0.0% Ct ≤ 25
12 participants
0.0% Ct ≤ 25
12 participants
0.0% Ct ≤ 25
12 participants
Low dose
16.7% Ct ≤ 25
12 participants
16.7% Ct ≤ 25
12 participants
0.0% Ct ≤ 25
12 participants
0.0% Ct ≤ 25
12 participants
Placebo
12.5% Ct ≤ 25
8 participants
37.5% Ct ≤ 25
8 participants
12.5% Ct ≤ 25
8 participants
12.5% Ct ≤ 25
8 participants

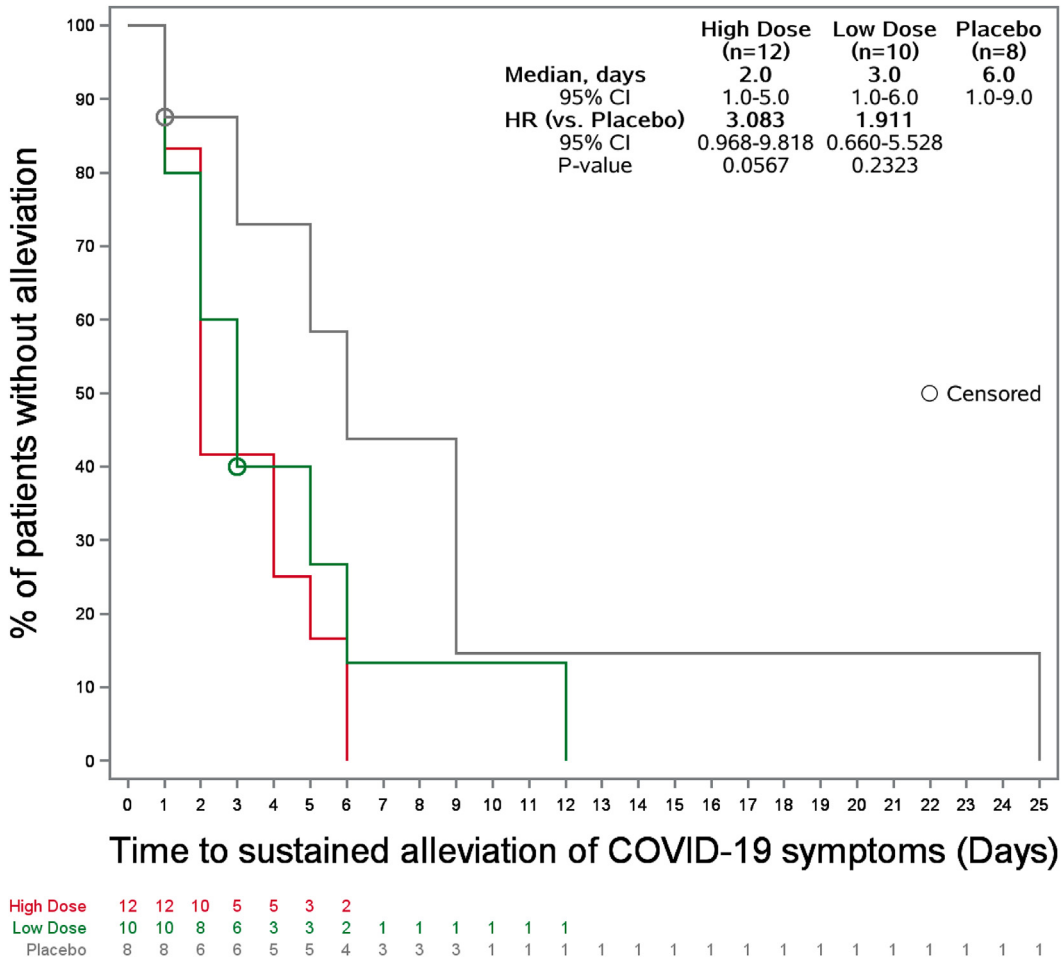



*Fig. 4:* **Time to sustained alleviation of COVID-19 symptoms (Days)**.

## Discussion

This is the first clinical study to assess the safety and efficacy of SIM0417 plus ritonavir in COVID-19 patients, and the aim is to select an optimal dosage for the intended clinical use. Although most of the patients participating in this study have been vaccinated, there is still a large outbreak in the vaccinated population due to the strong mutation and contagion of COVID-19. The two doses investigated (high dose 750 mg SIM0417/100 mg ritonavir, low dose 300 mg SIM0417/100 mg ritonavir) in this study are based on the safety, pharmacokinetics (PK) profile and dose range of Phase 1 study in the heathy volunteers. Multiple doses of SIM0417 150–750 mg co-administered with ritonavir 100 mg were well tolerated, and showed dose-dependent PK profile. Compared with SIM0417 monotherapy, there was a 5~8x increase in the exposure of SIM0417 when co-administered with ritonavir. And the PK parameters also supported the twice a day (b.i.d) dosage (Data provided in another manuscript being prepared).

In this Phase 1b study, it further demonstrated that 750 mg SIM0417/100 mg ritonavir and 300 mg SIM0417/100 mg ritonavir were safe and well tolerated in patients with COVID-19. The overall incidence of TEAEs in the two SIM0417/ritonavir dose groups were less (33.3%, 8/24) than in the placebo group (62.5%, 5/8), and the related TEAE rates were similar (33.3% vs 37.5%). The overall TEAE rates were higher in this study compared to phase 1 study in the heathy volunteers, in which the overall incidence of adverse events for subjects receiving SIM0417 or SIM0417 plus ritonavir was 22.9% (11/48). All TEAEs were grade 1, the same as in

*Fig. 3:* **The proportion of participants who were positive for nucleic acid test at day 1, day 4, day 6 and day 7 of treatment**. **(A)** The proportion of participants with N gene and/or ORF gene Ct value < 35 (red) **(B)** The proportion of participants with N gene Ct value ≤ 25 (red).

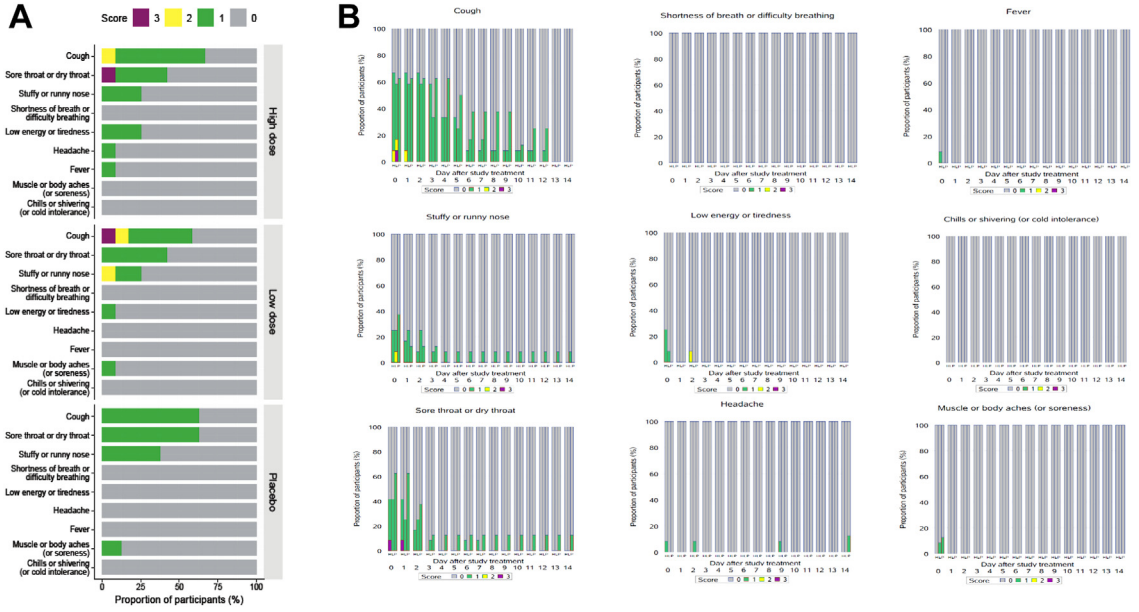



***Fig. 5:*** **Frequency and severity of 9 target COVID-19 symptoms**. (A) Severity of symptoms at baseline (B) The frequency and severity of symptoms from baseline till Day 14. Each bar interprets high dose (H), low dose (L) and placebo (P).

phase 1 study. Although the sample size was small, the high-dose group did not indicate higher risk about safety. The lab abnormal results of hypokalemia were frequently reported as TEAEs in this study rather than in the Phase 1 healthy subjects' study. It was reported that hypokalemia might be common in patients with COVID-19, which might be associated with that SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) and enhances the degradation of ACE2. ACE2 is well-known as to be a counter-regulator of the renin-angiotensin system (RAS), thus, there would be increased sodium and water reabsorption, followed by increased blood pressure and potassium (K+) excretion.[17–19] There was a rather high proportion of hypokalemia occurred among the participants of this phase 1b study: according to the investigators' judgement, the abnormal serum potassium values of 17 participants were considered to be related to the medical history, and 3 participants with hypokalemia were reported as TEAE. In other antiviral clinical studies in COVID-19 patients, there were also reported adverse events of hypokalemia or blood potassium decreased.[20,21] The safety results of this study have not yet suggested a risk signal of the decrease in serum potassium caused by the investigational drug (not reported in healthy volunteers in phase 1 study). However, based on the prevalence of hypokalemia in patients with COVID-19, changes in serum potassium should be monitored in later studies.

The baseline viral load of the enrolled participants was relatively high (mean >7 $\log_{10}$ copies/mL), which is helpful to observe the change of PD after administration of the investigational drug. The study results indicated that SIM0417 plus ritonavir can decrease the viral load

| | High dose (N = 12) n (%) | Low dose (N = 12) n (%) | Placebo (N = 8) n (%) | Total (N = 32) n (%) |
|---|---|---|---|---|
| At least one TEAE occurred | 4 (33.3) [6] | 4 (33.3) [7] | 5 (62.5) [9] | 13 (40.6) [22] |
| TEAE (highest severity) | | | | |
| Grade 1 | 4 (33.3) [6] | 4 (33.3) [7] | 5 (62.5) [9] | 13 (40.6) [22] |
| TEAE related to investigational drug (SIM0417 plus ritonavir) | 4 (33.3) [6] | 4 (33.3) [7] | 3 (37.5) [5] | 11 (34.4) [18] |
| TEAE related to SIM0417 | 4 (33.3) [6] | 4 (33.3) [7] | 3 (37.5) [5] | 11 (34.4) [18] |
| TEAE related to ritonavir | 4 (33.3) [6] | 4 (33.3) [7] | 3 (37.5) [5] | 11 (34.4) [18] |
| TEAE related to investigational drug (most severity) | | | | |
| Grade 1 | 4 (33.3) [6] | 4 (33.3) [7] | 3 (37.5) [5] | 11 (34.4) [ 18] |

The denominator of the percentage is N, followed by the number of cases of adverse events.

***Table 2:*** **Summary of TEAEs (safety analysis population).**

rapidly and the high dose group showed higher efficacy than the low dose group. At Day 2, the mean viral load change from baseline in the low dose and high dose groups reached approximately −2 $\log_{10}$ copies/mL, which were statistically significant compared with the placebo group. The mean viral load of the high dose group kept approximately −1 $\log_{10}$ copies/mL change per day from Day 3 to Day 6, with a statistically significant difference to the placebo (mean change was −1.688 to −2.163 $\log_{10}$ copies/mL), which were only observed on Day 3 in the low dose group. To investigate the relationship between the drug exposure and the pharmacodynamics (PD), we chose the viral load as the major PD indicator. Exposure-Response (E-R) analysis also indicated a relationship between the viral load change from baseline and the plasma exposure of SIM0417 where the viral load change increased with SIM0417 trough concentrations and approached the plateau at the concentration range associated with the high dose (750 mg). It is reported by some studies that the viral load of SARS-CoV-2 is related with the disease progression, disease severity and risk of mortality.[22] Chen et al. found that the elevated viral load is very likely to be the key factor leading to the overloading of the body's immune response and resulting in the disease progression into severe disease.[23] Liu et al. found that the viral load of severe cases was higher than that of mild cases.[24] It suggested that the higher viral loads are associated with poor clinical outcomes. In order to improve the accuracy of detection, nasal swabs were collected uniformly in this study and the samples were continuously collected every day from randomization, and the same sample was tested at local lab for Ct values, while a copy was saved and sent to the central lab for unified testing. In this way, we can monitor the Ct value change of patients, and ensure that the central lab can also detect the change curve of viral load over time.

In terms of the COVID-19 overall symptoms alleviation, SIM0417 plus ritonavir demonstrated strong efficacy signals consistent with the effect observed on the viral load (median alleviation time: 2 days, 3 days and 6 days for the high dose, low dose and placebo respectively). This suggests SIM0417 has the potential treatment of COVID-19 by decreasing viral load timely. As the trend of the epidemics, in the enrollment period of this trial, the major circulating strain was Omicron, which has been confirmed by sequencing the samples collected in 31 participants. The most commonly variants of concern were BA.2.2 (74.2%), BA.5.2 (12.9%). Due to the lower pathogenic characteristics of the Omicron BA strains, as well as the strict COVID-19 prevention policy in China at that time, most of the patients were identified by large-scale PCR testing at the very early stages with asymptomatic or mild symptoms. Under the Zero-COVID policy in China during the study, all the participants needed to be isolated in the hospital after being PCR positive tests. Most of the participants enrolled in the study had milder clinical manifestations, mainly respiratory symptoms. Therefore, nine major COVID-19 respiratory and systemic symptoms and sustained alleviation of these symptoms was observed as the secondary efficacy endpoint. Despite the low incidence of symptoms, we observed that 750 mg SIM0417 combined with ritonavir shortened 4 days of the time to symptom alleviation comparing to the placebo.

This trial has several limitations. First, the sample size was small to confirm the efficacy and safety of SIM0417 plus ritonavir because this was an exploratory early phase study. A late stage phase 2/3 pivotal study with a larger sample size initiated in Aug, 2022 has further confirmed the potential efficacy, safety and virologic reductions. Second, most of the participants enrolled in this study were asymptomatic or mild symptoms, and population with at least one moderate symptom need to be included to gain more clinical benefit. Third, the randomisation was not performed concurrently among three treatment groups to protect the safety of patients so the ability of balance through randomisation would be compromised although it would also be challenging for a small-sized trial even with concurrent randomisation. Despite those limitations, the study results indicated the preliminary safety and efficacy of SIM0417 plus ritonavir in patients with COVID-19, and the high dose group showed better efficacy.

Overall, based on the safety and efficacy preliminary data on this Phase 1b study, 750 mg SIM0417 plus 100 mg ritonavir was recommended for the further Phase 2/3 study. The preliminary safety and efficacy shown in COVID-19 patients in this study has been further confirmed in a phase 2/3 clinical trial (a placebo controlled and superiority designed study) with a large sample size.

#### Contributors

HZL, FXW, RHT, YMY, JXT, YSH, YY and WW designed the trial. HZL was the study site principal investigator. FXW, YMT, MLC, WX and DS contributed to the data collection. The underlying data were verified by HZL, JSS and RHT. YSH and JXT leaded the data analyses and figure table generation. FXW, WX, YMT, YSH, WW, JXT, YY and YMY contributed to writing the original draft manuscript. TA, YCX, XRJ and LKZ reviewed the data and edited the manuscript. All the authors had full access to all the data in the study. All the authors interpreted data, provided critical review and revision of the text, and approved the final version of the manuscript.

#### Data sharing statement

The study protocol is provided in this manuscript appendix. Aggregate data are available within the manuscript and in the appendix.

#### Declaration of interests

RHT, YMY, WW, JXT, YSH and YY are employees of Jiangsu Simcere Pharmaceutical Co., Ltd.

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the medical writer of the manuscript. Qingxian Zhang reviewed and edited the manuscript. We dedicate this paper to the memory of Prof. Hualiang Jiang (1965–2022) from Shanghai Institute of Materia Medical, Chinese Academy of Sciences for his extraordinary contribution and support to the drug discovery project of SIM0417.

### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100835.

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