NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	A Multicenter, Retrospective, Observational Study Using Real-world Data to Describe the Safety, Treatment Pattern and Effectiveness of Nirmatrelvir/Ritonavir among Patients treated with Nirmatrelvir/Ritonavir in China
Protocol number	C4671043
Protocol version identifier	Version 1.0
Date	05 December 2022
EU Post Authorization Study (PAS) register number	To be registered before the start of data collection
Active substance	Nirmatrelvir/Ritonavir; ATC: J05
Medicinal product	Nirmatrelvir Tablets/Ritonavir Tablets (co-packaged)
Research question and objectives	***Primary objective*** • To describe real-world safety of nirmatrelvir/ritonavir among patients treated with nirmatrelvir/ritonavir in China ***Secondary objectives*** • To describe real-world treatment patterns of patients treated with nirmatrelvir/ritonavir in China • To describe real-world effectiveness of nirmatrelvir/ritonavir among patients treated with nirmatrelvir/ritonavir in China
Author	[redacted]

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2. LIST OF ABBREVIATIONS

Abbreviatio	Definition
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BMI	Body Mass Index
CDE	Center for Drug Evaluation
CI	Confidence Interval
CLIA	Chemiluminescence Immunoassay
COVID-19	Coronavirus Disease 2019
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Cycle threshold
DCT	Data Collection Tool
DBIL	Direct bilirubin
EAS	Effectiveness Analysis Set
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPIC-HR	Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients
EPIC-SR	Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients
EUA	Emergency Use Authorization
FAS	Full Analysis Set
FDA	Food and Drug Administration
GGT	Gamma-Glutamyl Transferase
HIS	Hospital Information System
ICD	Informed Consent Document
IEC	Independent Ethics Committee
IL-6	Interleukin-6
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	Pharmacoeconomics and Outcomes Research
K-M	Kaplan-Meier
LD	L-lactate Dehydrogenase
LFIA	Lateral Flow Immunoassay
LIS	Laboratory Information System
MedDRA	Medical Dictionary for Regulatory Activities
MOD	Multiple Organ Dysfunction

Abbreviatio	Definition
MoE	Margin of Error
mITT	modified Intent-To-Treat
NAT	Nucleic Acid Test
NIS	Non-interventional study
NMPA	National Medical Products Administration
PASS	Post-Authorization Safety Study
PaO_2/FiO_2	Arterial Partial Pressure of Oxygen to Fraction of Inspired Oxygen
PCR	Polymerase Chain Reaction
PK	Pharmacokinetics
PT	Preferred Term
RR	Respiratory Rate
SAS	Safety Analysis Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SOC	System Organ Class
SpO_2	Oxygen Saturation
TCM	Traditional Chinese Medicine
TBIL	Total Bilirubin
WHO	World Health Organization
YRR	Your Reporting Responsibility

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

4. ABSTRACT

Title

- A Multicenter, Retrospective, Observational Study Using Real-world Data to Describe the Safety, Treatment Pattern and Effectiveness of Nirmatrelvir/Ritonavir among Patients treated with Nirmatrelvir/Ritonavir in China
- Version number and date: Version 1.0, 05 December 2022.
- Author: [redacted]

Rationale and background

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to threaten global health, highlighting the urgent need to develop broad-spectrum anti-coronavirus antivirals. Nirmatrelvir/ritonavir is a combination of nirmatrelvir, an oral protease inhibitor, and ritonavir, a CYP3A4 inhibitor. The combination has been developed for the treatment of patients with COVID-19. The efficacy and safety of nirmatrelvir/ritonavir in non-hospitalized, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness has been demonstrated in the global Phase 2/3 EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) study. In the final analysis of participants who commenced treatment within 3 days after symptom onset (modified Intent-To-Treat [mITT] population), the incidence of COVID-19-related hospitalization or death by day 28 was lower in the nirmatrelvir/ritonavir group than in the placebo group by -5.81 percentage points (95% confidence interval [CI], -7.78 to -3.84; P<0.0001; relative risk reduction 88.9%). There were 13 deaths reported through study Day 34 and 2 additional deaths during long-term follow-up (i.e., 15 total deaths during the study); all deaths occurred in the placebo group. Among participants who commenced treatment within 5 days after symptom onset, 9 of 1039

participants (0.87%) in the nirmatrelvir/ritonavir group and 66 of 1046 (6.31%) in the placebo group were hospitalized for COVID-19 or died from any cause through day 28 (P<0.0001), corresponding to an 86.3% relative risk reduction. The incidence of all-causality adverse events (AEs) that emerged during the treatment period was similar in the two groups (any AE, 23.1% with nirmatrelvir/ritonavir vs. 24.2% with placebo; serious adverse events [SAE], 1.7% vs 6.6%; and AEs leading to discontinuation of study treatment, 2.1% vs 4.2%, respectively).

On 11 February 2022, the National Medical Products Administration (NMPA) granted conditional approval for nirmatrelvir/ritonavir to treat mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19.

Nirmatrelvir/ritonavir has been strongly recommended for the treatment of non-severe COVID-19 among patients at the highest risk of hospitalization by the World Health Organization (WHO) and China guideline. It has been approved or authorized for conditional or emergency use in more than 65 countries across the globe as of June 30, 2022.

Under current clinical practice and epidemic prevention policy in China, all patients who had positive SAR-CoV-2 test results are to be admitted to specific hospitals for treatment or quarantine purpose, regardless of the disease severity. Patients with COVID-19 may be prescribed nirmatrelvir/ritonavir for treatment during hospitalization period.

[redacted] this study aims to retrospectively describe the safety, treatment pattern, and effectiveness of nirmatrelvir/ritonavir in treating patients with COVID-19 in the real-world clinical settings in China.

Research question and objectives

Primary objective

- To describe real-world safety of nirmatrelvir/ritonavir among patients treated with nirmatrelvir/ritonavir in China

Secondary objectives

- To describe real-world treatment patterns of patients treated with nirmatrelvir/ritonavir in China
- To describe real-world effectiveness of nirmatrelvir/ritonavir among patients treated with nirmatrelvir/ritonavir in China

Study design

This is a multicenter, single-arm, retrospective observational study to describe the safety, treatment patterns and effectiveness of nirmatrelvir/ritonavir among patients with COVID-19

in China. Approximately 5 hospitals in multiple cities are planned to be included in this study. Retrospective data abstraction will start after site ethics committee approval.

Patients who initiated nirmatrelvir/ritonavir treatment between 11 February 2022 and 31 August 2022 will be included in this study. For the purposes of analysis, the index date for an individual patient is defined as the date of initiating nirmatrelvir/ritonavir treatment. The baseline period for an individual patient is defined as the period from the first day of hospitalization to the day prior to the index date to capture the patient's baseline clinical characteristics, medical history, and comorbidity. The observation period for an individual patient is defined as the period from initiation of nirmatrelvir/ritonavir (i.e., index date) until discharge from hospital, death, or a maximum of 28 days after the last dose of nirmatrelvir/ritonavir, whichever comes first.

The study data cut-off date will be 02 October 2022. Each patient will be included in the study only once. If the patient initiated nirmatrelvir/ritonavir treatment more than once between 11 February 2022 and 31 August 2022, only the first treatment course will be included for analysis.

Population

Study population will consist of patients who initiated treatment with nirmatrelvir/ritonavir within the period from 11 February 2022 to 31 August 2022 during hospitalization. Approximately 1000 patients are planned to be included in the study. Eligible patients must meet the following inclusion criteria and none of the exclusion criteria:

Inclusion criteria

- Chinese patients aged ≥18 years on index date
- Patients initiated and took at least one dose of nirmatrelvir/ritonavir between 11 February 2022 and 31 August 2022 during hospitalization
- Patients had documented confirmed symptomatic COVID-19 with positive SARS-CoV-2 test in any specimen collected prior to or at initiation of nirmatrelvir/ritonavir
- Evidence of a personally signed and dated informed consent document (ICD) indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study if requested by study sites.

Exclusion criteria

- Patients participated in any interventional COVID-19 trials during the study period

Variables

This study will retrospectively abstract individual-level data from the Hospital Information System (HIS) and Laboratory Information System (LIS), which include electronic/paper medical records, prescription files, and laboratory testing results. Data for baseline variables will be abstracted from the baseline period. Data for safety, treatment pattern and effectiveness variables will be abstracted from the observation period.

- Safety variables:
  - AEs and SAEs with explicit attribution to nirmatrelvir/ritonavir
  - Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, lack of efficacy, and occupational exposure associated with the use of nirmatrelvir/ritonavir if applicable
- Treatment patterns variables:
  - Nirmatrelvir/ritonavir treatment: Daily dose, frequency, treatment duration, dose changes (reduction/discontinuation), and reason for dose changes
  - Concomitant COVID-19-related treatments: Generic name, dose, frequency, and treatment duration
  - Other concomitant medications: Generic name, dose, frequency, and treatment duration
- Effectiveness variables:
  - Proportion of patients with COVID-19 disease severity progressed or death from any cause during observation period
  - Time (days) to alleviation of all targeted COVID-19 signs and symptoms during observation period
  - Proportion of patients with two consecutive negative SARS-CoV-2 test results / cycle threshold (CT) ≥ 35 (specimens collected in two different calendar days) among patients with at least two SARS-CoV-2 tests after initiation of nirmatrelvir/ritonavir treatment
  - Time (days) to the first negative SARS-CoV-2 test / CT ≥ 35 from two consecutive negative SARS-CoV-2 test results / CT ≥ 35 (specimens collected in two different calendar days) among patients with at least two SARS-CoV-2 tests after initiation of nirmatrelvir/ritonavir treatment

- Demographic and clinical characteristics variables:
    - Age, sex
    - Baseline clinical characteristics: Body mass index (BMI), smoking status, COVID-19 severity at baseline, duration since first COVID-19 symptom/sign, presence and severity of any COVID-19 symptoms/signs at baseline, duration between the first positive SARS-CoV-2 test and index date, SARS-CoV-2 test status at baseline, renal and hepatic laboratory results at baseline, vaccination status, virus variant (if available), and serology status at baseline (if available)
    - Comorbidities
    - Prior COVID-19 related treatments and other prior medications

Data sources

Individual-level data will be retrospectively abstracted from the HIS and LIS to the electronic Case Report Form (eCRF). Source documents may include but are not limited to electronic/paper medical records, prescription files, and laboratory testing results. No personal identifiable information will be abstracted. Only de-identified data will be used in analysis.

Study size

There is no formal hypothesis testing for this study. This study is planned to include approximately 1000 individuals who initiated nirmatrelvir/ritonavir between 11 February 2022 and 31 August 2022.

The primary objective of the study is to describe real-world safety of nirmatrelvir/ritonavir, and one of the primary safety endpoints is the proportion of patients experiencing AEs with explicit attribution to nirmatrelvir/ritonavir. With a sample size of 1000 individuals, there will be a probability of >99.9% to observe an AE related to nirmatrelvir/ritonavir with a low incidence rate of 1% in at least one patient, and a probability of 95.0% to observe an AE related to nirmatrelvir/ritonavir with an even lower incidence rate of 0.3% in at least one patient.

For effectiveness consideration, assuming 20% of patients will have two consecutive negative SARS-CoV-2 test results from two consecutive respiratory specimens collected in two different calendar days, and accounting for non-evaluable data loss, samples of 800 and 500 evaluable individuals will provide a 95% CI with a half width of 2.77% and 3.50%, respectively.

Data analysis

This study is descriptive in nature and no formal hypothesis testing will be conducted. Individual level data from all sites participating in the study will be pooled for analysis. One interim analysis is planned to be conducted and the report is expected to be available in May 2023 to provide timely summary and analysis based on available data.

The main analysis sets are defined as the following. The full analysis set (FAS) will include all patients who meet the inclusion criteria and do not meet the exclusion criteria. The safety analysis set (SAS) will include all patients from FAS. The effectiveness analysis set 1 (EAS1) will include all patients from FAS who had at least one of the effectiveness variables collected and had the latest positive SARS-CoV-2 test result within 5 days prior to administration initiation. The effectiveness analysis set (EAS) is a subset of EAS1 and will include patients who had mild or moderate COVID-19 illness at baseline and had at least one risk factor for progression to severe COVID-19 at baseline. The safety variables will be analyzed using the SAS, treatment pattern variables will be analyzed using the FAS, and the effectiveness variables will be analyzed using the EAS and EAS1.

Continuous variables will be summarized using n, mean, median, minimum, maximum, standard deviation (SD), 25th and 75th percentiles, and in addition, 95% CI will be provided for effectiveness variables. Categorical variables will be summarized using number and percentage in each category. For continuous and categorical variables, missing data will not be imputed and will not be included in the summary statistics. Missing data will be reported with frequency and percentage of the overall patients in the analysis set. For time-to-event variables (such as time to alleviation of all targeted COVID-19 signs and symptoms), Kaplan Meier (K-M) plots will be generated, and median time will be estimated along with the corresponding 95% CI.

If data are adequate, subgroup analyses for the variables assessing safety, treatment patterns and effectiveness may be performed. Specifically,

- For safety variables, subgroup analyses will be performed by vaccination status, baseline COVID-19 severity, risk factors, renal impairment, hepatic impairment, and use of prior COVID-19-related treatments.

- For treatment patterns variables, subgroup analyses will be performed by vaccination status, baseline COVID-19 severity, risk factors, renal impairment, hepatic impairment, use of prior COVID-19-related treatment and administration time since onset of the first COVID-19 symptom/sign.

- For effectiveness variables, subgroup analyses will be performed by vaccination status, baseline COVID-19 severity, risk factors, renal impairment, hepatic impairment, use of prior COVID-19-related treatments, and administration time since onset of the first COVID-19 symptom/sign .

All statistical analyses will be performed using SAS software. Detailed methodology and methods for summarization and statistical analyses will be introduced in the statistical analysis plan (SAP).

Milestones

Milestone	Planned date*
Start of data collection	6 March 2023
End of data collection	29 November 2023
Interim analysis report	30 May 2023
Final study report	17 April 2024

*The actual dates may be adjusted based on study progress and will be reflected in the final clinical study report (CSR).

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date*
Start of data collection	6 March 2023
End of data collection	29 November 2023
Interim analysis report	30 May 2023
Final study report	17 April 2024

*The actual dates may be adjusted based on study progress and will be reflected in the final CSR.

7. RATIONALE AND BACKGROUND

COVID-19 is an infectious disease caused by SARS-CoV-2, which has reached about 565 million confirmed infections and approximately 6 million deaths worldwide as of March 2022.[1] In mainland China, there have been over 236,000 confirmed cases by August 2022, with a new outbreak of the Omicron variants since February 2022.[2]

The clinical features of COVID-19 are diverse and range from asymptomatic to critical illness and death. People with particular characteristics such as older age, current smoking or underlying clinical conditions (e.g., cardiovascular disease, diabetes, obesity or cancer) are at a high risk of developing severe COVID-19 illness.[1,2] Although vaccine development against the SARS-CoV-2 virus and mass vaccination campaigns are still going on worldwide,[3,4] developing broad-spectrum antivirals, particularly those easily administrated and non-

invasive oral antivirals, is urgently needed, since vaccinated individuals may still be infected by new variants and those immunocompromised patients may not be fully protected by vaccination.[5,6]

Nirmatrelvir/ritonavir is a SARS-CoV-2 protease inhibitor antiviral therapy, which is specifically designed to be administered orally so that it can be prescribed at the first sign of infection or at first awareness of an exposure, potentially helping patients avoid severe illness of COVID-19 which can lead to hospitalization and death. [9] Nirmatrelvir is a SARS-CoV-2 main protease (M^{pro}: also referred to as $3CL^{pro}$) inhibitor. With its essential function in virus replication and absence of closely related homologues in humans,[10] M^{pro} is an attractive antiviral drug target. Ritonavir is a CYP3A inhibitor, which can suppress the CYP3A-mediated metabolism of nirmatrelvir, so as to increase the plasma concentrations of nirmatrelvir.[11]

Results from the global Phase 2/3 clinical trials of EPIC-HR and Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients (EPIC-SR) support the efficacy profile for nirmatrelvir/ritonavir, in terms of treating patients with mild-to-moderate COVID-19 illness and with at least one risk factor for progressing to severe COVID-19 illness, regardless of vaccination status. The EPIC-HR study showed that, in the final analysis of participants who commenced treatment within 3 days after symptom onset (mITT population), the incidence of COVID-19-related hospitalization or death by day 28 was lower in the nirmatrelvir/ritonavir group than in the placebo group by -5.81 percentage points (95% CI, -7.78 to -3.84; P<0.0001; relative risk reduction 88.9%). There were 13 deaths reported through study Day 34 and 2 additional deaths during long-term follow-up (i.e., 15 total deaths during the study); all deaths occurred in the placebo group. Among participants who commenced treatment within 5 days after symptom onset, 9 of 1039 participants (0.87%) in the nirmatrelvir/ritonavir group and 66 of 1046 (6.31%) in the placebo group were hospitalized for COVID-19 or died from any cause through day 28 (P<0.0001), corresponding to an 86.3% relative risk reduction. In EPIC-SR, the analysis of vaccinated participants with at least one risk factor for progressing to severe illness showed a 57% relative risk reduction in hospitalizations or death through Day 28 (nirmatrelvir/ritonavir-treated participants: 3/361 with no death; placebo: 7/360 with 1 death).[12] An integrated analysis of data across the EPIC-HR and EPIC-SR studies reported an 84% reduction (p<0.0001) in hospitalizations or death, compared to placebo and regardless of vaccination status, in participants with at least one risk factor for progression to severe COVID-19 illness who were treated with nirmatrelvir/ritonavir (12/1400 [0.857%] nirmatrelvir/ritonavir-treated participants versus 73/1406 [5.192%] placebo recipients) within five days of symptom onset.[12] Although China did not participate in the global EPIC-HR study, analysis for Asian subpopulation in EPIC-HR study showed that the treatment effects through Day 28 demonstrated by the comparison of nirmatrelvir/ritonavir to placebo were consistent between the Asian and overall study populations. Several post-marketing publications including real-world studies in mainland China and Hong Kong are supportive of the effectiveness of nirmatrelvir/ritonavir among patients with COVID-19 illness.[13-16]

The safety profile for nirmatrelvir/ritonavir have been consistent in over 3,500 participants across the EPIC clinical development programs, including EPIC-HR, EPIC-SR, and EPIC-PEP (Evaluation of Protease Inhibition for COVID-19 in Post-Exposure Prophylaxis) studies.[12] Results from the EPIC-HR study showed that the incidence of all-causality AEs that emerged during the treatment period was similar in the two groups (any AE, 23.1% with nirmatrelvir/ritonavir vs. 24.2% with placebo; SAE, 1.7% vs 6.6%; and AEs leading to discontinuation of study treatment, 2.1% vs 4.2%, respectively). Asian subpopulation analysis showed that the treatment with nirmatrelvir /ritonavir was also safe and well tolerated in the Asian subpopulation, and no distinct safety signals were observed compared to the overall population. A China stand-alone Phase 1 study (C4671016) investigated the pharmacokinetics (PK), safety and tolerability of nirmatrelvir/ritonavir when nirmatrelvir/ritonavir was administered in healthy Chinese participants. Among the 14 participants enrolled, a total of 10 all-causality AEs were reported for 6 (42.9%) participants and four of the AEs reported by 4 (28.6%) participants were treatment related. All AEs were mild in severity except for 1 moderate AE of Rash. All AEs were resolved. No SAEs, AEs leading to discontinuation or AEs leading to dose reduction or temporary discontinuation were reported. It is indicated that nirmatrelvir/ritonavir was generally safe and well tolerated after repeated doses in healthy Chinese participants.

On 11 February 2022, the NMPA granted conditional approval for nirmatrelvir/ritonavir to treat mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19.[17]

Nirmatrelvir/ritonavir has been strongly recommended for the treatment of non-severe COVID-19 among patients at the highest risk of hospitalization by the WHO[18] and China guideline,[19] and has been approved or authorized for conditional or emergency use in more than 65 countries across the globe as of June 30, 2022.[12]

Under current clinical practice and epidemic prevention policy in China, all patients who had positive SAR-CoV-2 test results are to be admitted to specific hospitals for treatment or quarantine purpose, regardless of the disease severity. Patients with COVID-19 may be prescribed nirmatrelvir/ritonavir for treatment during hospitalization period.

[redacted] this study aims to retrospectively describe the safety, treatment pattern, and effectiveness of nirmatrelvir/ritonavir in treating patients with COVID-19 in the real-world clinical settings in China in order to provide more data and evidence for use of nirmatrelvir/ritonavir in larger Chinese population.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) [redacted].

8. RESEARCH QUESTION AND OBJECTIVES

This study will provide real-world evidence on safety, treatment patterns and effectiveness of nirmatrelvir/ritonavir for Chinese patients with COVID-19 and treated with nirmatrelvir/ritonavir.

Primary objective

- To describe real-world safety of nirmatrelvir/ritonavir among patients treated with nirmatrelvir/ritonavir in China

Secondary objectives

- To describe real-world treatment patterns of patients treated with nirmatrelvir/ritonavir in China

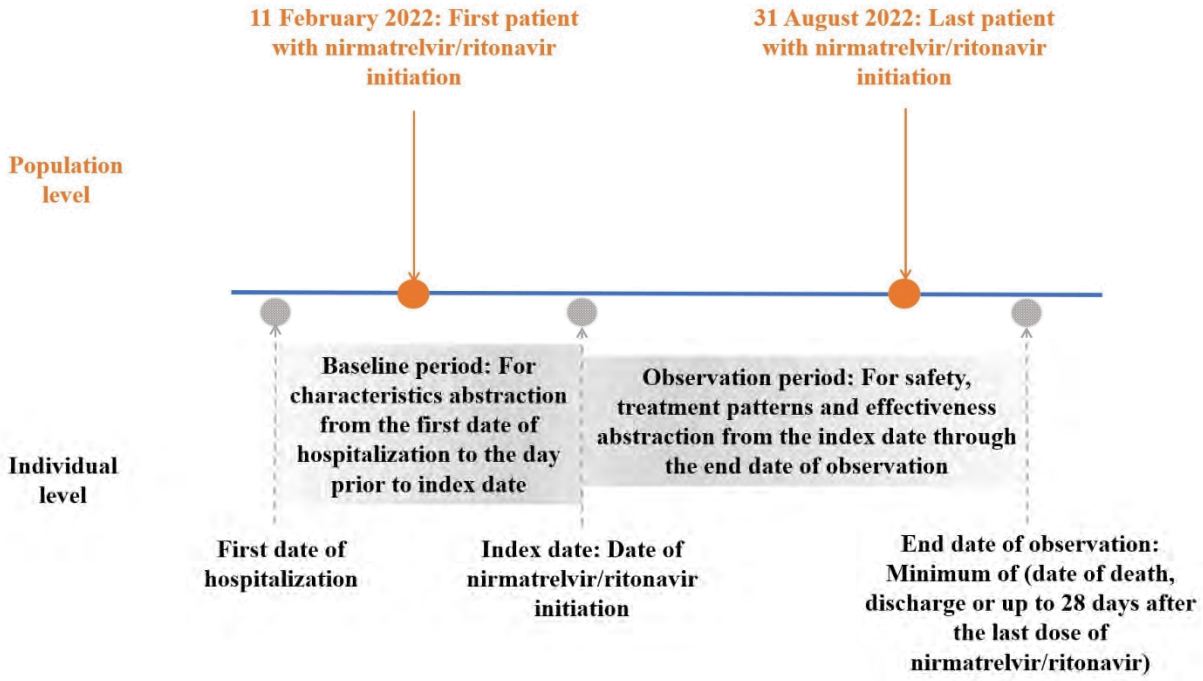
- To describe real-world effectiveness of nirmatrelvir/ritonavir among patients treated with nirmatrelvir/ritonavir in China

9. RESEARCH METHODS

9.1. Study design

This is a multicenter, single-arm, retrospective observational study to describe the safety, treatment patterns and effectiveness of nirmatrelvir/ritonavir among patients with COVID-19 in China. Approximately 5 hospitals and 1000 patients are planned to be included in this study. Retrospective data abstraction will start after site ethics committee approval. Patients who initiated nirmatrelvir/ritonavir treatment between 11 February 2022 and 31 August 2022 will be included in this study. Continuous recruitment of patients in each site will be employed. For analyzing purpose, the index date for an individual patient is defined as the date of initiating nirmatrelvir/ritonavir treatment. The baseline period for an individual patient is defined as the period from the first day of hospitalization through the index date to capture the patient's baseline clinical characteristics, medical history, and comorbidity. The observation period for an individual patient is defined as the period from initiation of nirmatrelvir/ritonavir (i.e., index date) until discharge from hospital, death, or a maximum of 28 days after the last dose of nirmatrelvir/ritonavir, whichever comes first. The study data cut-off date will be 02 October 2022. Each patient will be included in the study only once. If the patient initiated nirmatrelvir/ritonavir treatment more than once between 11 February 2022 and 31 August 2022, only the first treatment course will be included for analysis. The study design schematic is presented in Figure 1.

Figure 1. Study design schematic



9.1.1. Primary endpoints

The safety profiles for nirmatrelvir/ritonavir will be evaluated as follows:[20]

- Incidence of AEs and SAEs with explicit attribution to nirmatrelvir/ritonavir
- Proportion of patients with nirmatrelvir/ritonavir dose change (reduction/discontinuation) due to AEs with explicit attribution to nirmatrelvir/ritonavir
- Proportion of patients experiencing safety related scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, lack of efficacy, and occupational exposure associated with the use of nirmatrelvir/ritonavir

9.1.2. Secondary endpoints

The treatment patterns will be evaluated as follows:[19]

- Proportion of patients receiving nirmatrelvir/ritonavir only, or receiving nirmatrelvir/ritonavir plus concomitant COVID-19-related treatments, regardless of receiving other concomitant medications
- Treatment duration (days) of receiving nirmatrelvir/ritonavir

- Proportion of patients receiving concomitant COVID-19-related treatments by therapeutic use (including antiviral therapy, immunotherapy, and other)
- Treatment duration (days) of receiving concomitant COVID-19-related treatments by therapeutic use (including antiviral therapy, immunotherapy, and other)
- Proportion of patients receiving concomitant medications other than COVID-19 related treatments by drug class.

The effectiveness profiles of nirmatrelvir/ritonavir will be evaluated as follows:

- Proportion of patients with COVID-19 disease severity progressed or death from any cause
- Time (days) to alleviation of all targeted COVID-19 signs and symptoms during the observation period
- Proportion of patients with two consecutive negative SARS-CoV-2 test results / CT ≥ 35 (specimens collected in two different calendar days) among patients with at least two SARS-CoV-2 tests after initiation of nirmatrelvir/ritonavir treatment
- Time (days) to the first negative SARS-CoV-2 test/ CT ≥ 35 from two consecutive negative SARS-CoV-2 test results / CT ≥ 35 (specimens collected in two different calendar days) among patients with at least two SARS-CoV-2 tests after initiation of nirmatrelvir/ritonavir treatment

9.2. Setting

Study population will consist of patients who initiated treatment with nirmatrelvir/ritonavir between 11 February 2022 and 31 August 2022 during hospitalization. Approximately 1000 patients are planned to be included in the study. Eligible patients must meet the following inclusion criteria and none of the exclusion criteria:

Inclusion criteria

- Chinese patients aged ≥18 years on index date
- Patients initiated and took at least one dose of nirmatrelvir/ritonavir between 11 February 2022 and 31 August 2022 during hospitalization
- Patients had documented confirmed symptomatic COVID-19 with positive SARS-CoV-2 test in any specimen collected prior to or at initiation of nirmatrelvir/ritonavir
- Evidence of a personally signed and dated ICD indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study if requested by study sites.

Exclusion criteria

- Patients participated in any interventional COVID-19 trials during the study period.

9.3. Variables

This study will retrospectively abstract individual-level data from the HIS and LIS, which include electronic/paper medical records, prescription files, and laboratory testing results. Data for baseline variables will be abstracted from the baseline period. Data for primary and secondary endpoint variables will be abstracted from the observation period.

Table 1. List of variables and operational definitions

Variable	Role	Data source(s)	Operational definition
Age	Demographics /subgroup identifier	HIS	Age on index date. Age = Year of index date - Birth year See section 9.3.1 Risk factors for more detail.
Sex	Demographics	HIS	As recorded in medical record (male or female).
BMI	Baseline clinical characteristics / subgroup identifier	HIS	As recorded in medical record for individual height and weight or BMI. BMI = weight (kg) / [height (m)]^2. According to the WHO standard, four categories of BMI (kg/m^2) are underweight (<18.5), normal weight (18.5≤ BMI<25.0), pre-obesity (25.0 ≤BMI<30.0) and obesity (. 30.0).[21] According to China guideline, four categories of BMI (kg/m^2) are underweight (<18.5), normal weight (18.5≤BMI<24.0), pre-obesity (24.0≤BMI<28.0) and obesity (≥28.0).[22] The assessment on or closest to the index date will be used. Both BMI categorizations will be used for analysis. See section 9.3.1 Risk factors for more detail.

Table 1. List of variables and operational definitions

Variable	Role	Data source(s)	Operational definition
Smoking status	Baseline clinical characteristics / subgroup identifier	HIS	As recorded in medical record. See section 9.3.1 Risk factors for more detail.
COVID-19 severity at baseline	Baseline clinical characteristics / subgroup identifier	HIS	COVID-19 severity will be categorized into four levels. Apart from categories of severity level, severity scale used and the relevant parameters used for severity assessment will also be abstracted from medical records. See section 9.3.2 COVID-19 severity for categorization and parameters in detail. The assessment of severity level on or closest to the index date will be used.
Duration since first COVID-19 symptom/sign	Baseline clinical characteristics / subgroup identifier	HIS	It is defined as the duration between onset date of the first COVID-19 related symptom/sign and the index date. The equation will be: (Index date) – (Onset date of the first COVID-19 symptom/sign abstracted from the medical records during baseline period) + 1. See section 9.3.3 for a list of COVID-19 signs/symptoms in detail.
Presence and severity of any COVID-19 symptoms/signs at baseline	Baseline clinical characteristics	HIS	Severity level of each COVID-19 symptom/sign will be abstracted from medical records. Categories of severity levels of each COVID-19 symptom/sign will be absent, mild, moderate and severe.[20] The assessment on or closest to the index date will be used.
Duration between the first positive SARS-CoV-2 test and index date	Baseline clinical characteristics	HIS/LIS	The following information about the SARS-CoV-2 tests will be abstracted from medical

Table 1. List of variables and operational definitions

Variable	Role	Data source(s)	Operational definition
SARS-CoV-2 test status at baseline	Baseline clinical characteristics	HIS/LIS	records if available: test type (i.e., NAT [nucleic acid test] or antigen test), sampling site, sampling date and time, test result date and time, test result (positive vs. negative, and CT value if available). Duration = (Index date) – (Sampling date of the first positive SAR-CoV-2 test abstracted from the baseline period medical records) +1 Baseline test status will be the latest assessment prior to or on the index date.
Renal laboratory results at baseline	Baseline clinical characteristics / subgroup identifier	HIS/LIS	Renal laboratory results are measured by the estimated glomerular filtration rate (eGFR; mL/min/1.73m^2). The serum creatinine and the eGRF (if available) will be collected as recorded in medical records. CKD-EPI Equation:[23] $eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if Black] where: Scr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. Patients will be categorized into four groups: • eGFR ≥90 mL/min/1.73m^2 • eGFR ≥60 and <90 mL/min/1.73m^2

Table 1. List of variables and operational definitions

Variable	Role	Data source(s)	Operational definition
			• eGFR ≥30 and <60 mL/min/1.73m^2 • eGFR <30 mL/min/1.73m^2 The assessment on or closest to the index date will be used.
Hepatic laboratory results at baseline	Baseline clinical characteristics / subgroup identifier	HIS/LIS	The following lab parameters reflecting hepatic function will be abstracted from medical records: Alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), albumin and total protein, gamma-glutamyl transferase (GGT), total bilirubin (TBIL), direct bilirubin (DBIL), and L-lactate dehydrogenase (LD). If available, additional parameters including ascites, brain damage (hepatic encephalopathy) and prothrombin time/international normalized ratio for the development of the "Child Pugh score" will also be abstracted from medical records. The assessment on or closest to the index date will be used. See section 9.3.4 Development of the Child Pugh score for the assignment of the scores based on parameters, and the total score (between 5–15) corresponds with the Child Pugh score ranging from Grade A (the lowest) to Grade C (the highest).
Virus variant	Baseline clinical characteristics	HIS/LIS	As recorded in medical records.
Serology status at baseline	Baseline clinical characteristics	HIS/LIS	Serology status (positive/negative) will be abstracted from medical records. The assessment on or

Table 1. List of variables and operational definitions

Variable	Role	Data source(s)	Operational definition
			closest to the index date will be used.
Comorbidities	Baseline clinical characteristics / subgroup identifier	HIS	All comorbidities (including medical histories) will be collected from medical records, including comorbidities defined as risk factors in the nirmatrelvir/ritonavir label and any other comorbidities. See section 9.3.1 Risk factors for more detail.
Prior COVID-19-related treatments	Baseline clinical characteristics / subgroup identifier	HIS	For each prior COVID-19-related treatment, information should be abstracted as follows: generic name, start and end dates of treatment, daily dose, and frequency. See section 9.3.5 COVID-19-related treatments for details.
Other prior medications	Baseline clinical characteristics	HIS	As recorded in medical records for other prior medications. For each medication, information should be abstracted as follows: generic name, start and end dates, daily dose, and frequency.
Vaccination status	Baseline clinical characteristics / subgroup identifier	HIS	Patients' vaccination status will be abstracted and categorized as unvaccinated, vaccinated with one dose, vaccinated with two doses, vaccinated with three doses, and vaccinated with over three doses.
AE/SAE	Primary endpoint (safety)	HIS	All AEs/SAEs with explicit attribution to nirmatrelvir/ritonavir will be abstracted with information on AEs, including severity, seriousness, onset date, end date, outcome and actions for managing each AE. See section 9.3.6 Adverse event and section 11.
At risk scenarios involving drug exposure	Primary endpoint (safety)	HIS	As recorded in medical record. At risk scenarios involving drug exposure will be abstracted with information on exposure during pregnancy, exposure during breast feeding,

Table 1. List of variables and operational definitions

Variable	Role	Data source(s)	Operational definition
			medication error, overdose, misuse, lack of efficacy, and occupational exposure associated with the use of nirmatrelvir/ritonavir. See section 11 for further details.
Nirmatrelvir/ritonavir treatment	Secondary endpoint (treatment patterns)	HIS	Start and end dates of treatment, daily dose for nirmatrelvir and ritonavir treatment separately (if applicable), frequency, date of dose change (reduction/discontinuation), reasons for dose change
Concomitant COVID-19-related treatments	Secondary endpoint (treatment patterns)	HIS	For each concomitant COVID-19-related treatment, information should be abstracted as follows: generic name, start and end dates of treatment, daily dose, and frequency. See section 9.3.5 COVID-19-related treatments for details.
Other concomitant medications	Secondary endpoint (treatment patterns)	HIS	As recorded in medical records for other concomitant medications. For each medication, information should be abstracted as follows: generic name, start and end dates, daily dose, and frequency. These medications will be re-categorized using the ATC Classification System[24]
COVID-19 severity	Secondary endpoint (effectiveness)	HIS	The first occurrence of severe or critical COVID-19 illness after initiation of nirmatrelvir/ritonavir treatment during observation period, and the date of this first occurrence will be abstracted.[25] COVID-19 severity will be categorized into four levels. Apart from categories of severity level, names of the severity scale used and the relevant parameters used for severity assessment will also be

Table 1. List of variables and operational definitions

Variable	Role	Data source(s)	Operational definition
			abstracted from medical records. See section 9.3.2 COVID-19 Severity for categorization and parameters.
Death	Secondary endpoint (effectiveness)	HIS	Information on cause of death and the date of death will be abstracted.
Time to alleviation of all targeted COVID-19 signs and symptoms	Secondary endpoint (effectiveness)	HIS	Information on alleviation (yes/no) and severity level (if available, including absent, mild, moderate, and severe[20]) of each targeted sign/symptom of COVID-19 by date during the observation period will be abstracted from medical records. For a list of targeted signs and symptoms of COVID-19, see section 9.3.3 Signs/symptoms of COVID-19. For the definition of alleviation and the calculation of the time to alleviation, see section 9.3.7. Time to alleviation of all targeted COVID-19 signs and symptoms
Time to two consecutive negative SARS-CoV-2 test results / CT ≥ 35	Secondary endpoint (effectiveness)	HIS/LIS	Medical records of dates, time and results of SARS-CoV-2 tests (positive/negative and CT values) after index date will be abstracted. See section 9.3.8 for calculating the time to two consecutive negative SARS-CoV-2 test results / CT ≥ 35
Date of admission			As recorded in medical record.
Date of discharge from hospital			As recorded in medical record.

9.3.1. Risk factors

Risk factors (as defined in the nirmatrelvir/ritonavir label[26]) are as follows:

- Being overweight/obesity (e.g., BMI > 25 kg/m^2)
- Older age (e.g., age ≥ 60 years)
- Current smokers
- Immunosuppressive disease or immunosuppressive treatment

- Comorbidity
    - Chronic kidney disease
    - Diabetes
    - Cardiovascular disease (including congenital heart disease) or hypertension
    - Chronic lung diseases (e.g., chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
    - Sickle cell disease
    - Neurodevelopmental disorders (e.g., cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes, and severe congenital anomalies)
    - Active cancer
    - Medical-related technological dependence not related to COVID-19 (e.g., tracheotomy, gastrostomy, or positive pressure ventilation)

9.3.2. COVID-19 severity

According to the China Guideline on Diagnosis and Treatment Plan for Coronavirus Disease 2019 (9th Edition),[19]COVID-19 severity is categorized as follows:

- Mild illness: Mild signs and symptoms of COVID-19 but no abnormal chest imaging.
- Moderate illness: Showing evidence of signs and symptoms of COVID-19 and abnormal chest imaging.
- Severe illness: Individuals who have oxygen saturation (SpO_2) ≤93% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ≤300 mmHg, a respiratory rate (RR) ≥30/min, or lung infiltrates progression >50% within 24–48 hours.
- Critical illness: Individuals who have respiratory failure requiring mechanical ventilation, septic shock, or multiple organ dysfunction (MOD).

Note: Different scales and categorization of COVID-19 severity may be used across hospitals in real-world clinical settings, such as the WHO Ordinal Scale.[27] If a COVID-19 severity categorization different from the above China guideline is used in one participating site, the participating site's categorization will be collected via eCRF and will be mapped to the above four categories during analysis.

9.3.3. Signs/symptoms of COVID-19

Signs/symptoms of COVID-19 include cough, shortness of breath or difficulty breathing, objective fever (documented temperature >38˚C [100.4˚F]), fatigue (low energy or tiredness), subjective fever (e.g., feeling feverish), chills or shivering, muscle or body aches, diarrhea, nausea, vomiting, headache, sore throat, stuffy and runny nose.[20]

Among them, the targeted signs/symptoms of COVID-19 for analysis include cough, shortness of breath or difficulty breathing, subjective fever (e.g., feeling feverish), chills or

shivering, muscle or body aches, diarrhea, nausea, vomiting, headache, sore throat, stuffy and runny nose.[20]

9.3.4. Development of the Child Pugh score

Table 2. Assignment of the scores based on parameters

Assessment parameter	Score		
	1	**2**	**3**
Ascites	None	Mild	Moderate / severe
Encephalopathy (grade)	None	1–2	3–4
Total bilrubin (mg/dL)	<2	2–3	>3
Albumin (g/L)	>35	28–35	<28
Prothrombin time (second prolonged)	<4	4–6	>6
Or	<1.7	1.8–2.3	>2.3
International normalized ratio			

Table 3. Child Pugh scores correspond with the Child Pugh grades

Child Pugh grade	Child Pugh score	Level of dysfunction
A	5–6	Mild
B	7–9	Moderate
C	10–15	Severe

9.3.5. COVID-19-related treatments

COVID-19-related treatments are defined as any therapy that is approved and used as indicated by regulatory authority (including approvals for emergency use), or any therapy as recommended by a national (or a reputable international) scientific body (e.g., WHO, European Centre for Disease Prevention and Control, Centers for Disease Control and Prevention, or National Institute of Health) for COVID-19 treatment.

Categories of variables for COVID-19-related treatments are as follows:[19 28]

- Antiviral therapy: Monoclonal antibodies (Amubarvimab/Romlusevimab Combination, bebtelovimab, Casirivimab, Imdevimab, Regdanvimab, Bamlanivimab, Etesevimab, or any other monoclonal antiboides for COVID-19 treatment), COVID-19 Human Immunoglobulin, convalescent plasma, azvudine, remdesivir, and molnupiravird
- Immunotherapy: Glucocorticoid, Interleukin-6 (IL-6) inhibitor (tocilizumab, sarilumab), baricitinib, tofacitinib
- Any other COVID-19 related treatments: Anticoagulant, Traditional Chinese Medicine (TCM) and oxygen supplemental therapies

9.3.6. Adverse event

The observation period of AE with explicit attribution to nirmatrelvir/ritonavir is defined as the period from initiation of nirmatrelvir/ritonavir (i.e., the index date) until discharge from hospital, death, or maximally 28 days after last dose of nirmatrelvir/ritonavir, whichever comes first.

Seriousness of each AE: A SAE is any untoward medical occurrence in a participant or a patient administered a medicinal product at any dose, that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of hospitalization
- Results in a persistent or significant disability/incapacity
- Results in congenital anomaly / birth defect

Or that is considered to be:

- An important medical event

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of important medical events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; development of drug dependency or drug abuse; or development of potential drug-induced liver injury; suspected transmission of an infectious agent.

Each AE's duration: From onset to end date of each AE or till the end of observation period.
Each AE's outcome: Recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal, and unknown.
Actions for each AE: Actions made to manage each AE.
Severity of each AE will be collected.

9.3.7. Time to alleviation of all targeted COVID-19 signs and symptoms

The targeted signs and symptoms of COVID-19 (described in section 9.3.3) will be used for the analysis of time to alleviation calculation. For a patient, the targeted signs and symptoms recorded in either baseline or observation period will be evaluated.

The First Alleviation Date for a targeted sign/symptom is the date when alleviation is firstly recorded in medical records during the observation period

Event Date = The last date of (The First Alleviation Dates for ALL targeted signs/symptoms to be evaluated)

The time to alleviation of all targeted COVID-19 signs and symptoms is defined as:

- For a patient with the Event Date, it will be calculated as (Event Date) – (Index Date) +1.
- For a patient without the Event Date, it will be calculated as (End of Observation Date) – (Index Date) +1 and be considered as a censoring time. [7 12]

9.3.8. Time to two consecutive negative SARS-CoV-2 test results / CT ≥ 35

For patients with at least two SARS-CoV-2 tests (specimens collected in two different calendar days) after treatment initiation during observation period, the first day of a negative SARS-CoV-2 test / CT ≥ 35 from two consecutive negative results is considered as an Event Date.

The time to event of two consecutive negative SARS-CoV-2 test results / CT ≥ 35 in this study is defined as:

- For a patient with the Event Date, it will be calculated using (Event Date) – (Index Date) +1.
- For a patient without the Event Date, it will be calculated as (End of Observation Date) – (Index date) + 1 and be considered as a censoring time.

9.4. Data sources

Individual-level data will be retrospectively abstracted from the HIS and LIS to the eCRF from all sites participating in the study. The source of collected data will be all elements that can constitute a reliable in the patients' medical record (e.g., consultation notes, discharge summaries, laboratory test results, recorded prescription data, imaging data, and any other documentation of communication with other health care providers). Variables and data abstracted from source documents included are described in section 9.3, and will be collected by the delegated trained site personnel and entered directly into the web-based eCRFs. No personal identification information will be abstracted. Only de-identified data will be used in analysis.

9.5. Study size

There is no formal hypothesis testing for this study. This study is planned to include approximately 1000 individuals who initiated nirmatrelvir/ritonavir between 11 February 2022 and 31 August 2022. The primary objective of the study is to describe real-world safety of nirmatrelvir/ritonavir, and one of the primary safety endpoint is the proportion of patients experiencing AEs with explicit attribution to nirmatrelvir/ritonavir.

With a sample size of 1000, there will be a probability of >99.9% to observe an AE related to nirmatrelvir/ritonavir with a low incidence rate of 1% in at least one patient, and a probability of 95.0% to observe an AE related to nirmatrelvir/ritonavir with an even lower incidence rate of 0.3%[29] in at least one patient.

Table 4. Probabilities to observe an AE of different incidence rates

		Incidence rates	
Sample Size	**1%**	**0.5%**	**0.3%**
1000	> 99.9%	99.3%	95.0%

Note: The sample size and power is calculated based on the exact probabilities of the Binomial distribution, the probability of observing at least one event in n observations = $1 - (1-p)^n$.

For the effectiveness endpoint of proportion of patients with two consecutive negative SARS-CoV-2 test results, assuming that 20%[30] of patients will have negative SARS-CoV-2 test results from two consecutive respiratory specimens collected in two different calendar days, and 80% and 50% patients will be evaluable with at least one of the effectiveness endpoints data collected and in addition having at least one risk factor, samples of 800 and 500 individuals will provide a 95% CI with a half width of 2.77% and 3.50%, respectively.

Table 5. Precision for evaluating effectiveness for different numbers of evaluable patients

Scenarios	Evaluable patients	Half width of CI *
Included patients who had mild or moderate COVID-19 illness and had at least one risk factor at baseline for progression to severe COVID-19	500	3.50%
Included patients who had at least one of the effectiveness variables collected.	800	2.77%

*Note: The half width confidence interval is calculated according to the formula . $* \sqrt{p * (1-p)}/\sqrt{n}$, where z = 1.96 for a confidence level (α) of 95%, p = proportion, n = #of evaluable patients.

9.6. Data management

Patient information will be abstracted and managed by study sites on eCRFs by a web-based electronic data capture (EDC) tool. All data will be collected and entered directly into the EDC system. All participating sites will have access to the data entered regarding the individual site and its own enrolled patients. All sites will be fully trained on using the online data capture system, including eCRF completion guidelines and help files. Sites will be responsible for entering extracted patient data into a secure EDC database via the eCRF. Investigators and site personnel will be able to access their account with a username and password. All eCRFs should be completed by designated, trained personnel or the study coordinator, as appropriate. In most cases, the eCRF should be reviewed, electronically signed, and dated by the investigator. All changes or corrections to eCRFs are documented in an audit trial and an adequate explanation is required.

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed-up for resolution.

Data collection standards will be maintained, and processes and procedures utilized to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out of range or anomalous data.

9.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term CRF should be understood to refer to an electronic data record.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

9.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless CRO and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years or as required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

This study is descriptive in nature and no formal hypothesis testing will be conducted. Continuous variables will be summarized using n, mean, median, minimum, maximum, standard deviation (SD), and 25th and 75th percentiles, and in addition, 95% CI will be provided for effectiveness variables. Categorical variables will be summarized using number and percentages of each category. For continuous and categorical variables, missing data will not be imputed and will be reported as frequency and percentage. Missing data will not be included in the summary statistics. For time-to-event variables (such as time to alleviation of all targeted COVID-19 signs and symptoms), Kaplan Meier (K-M) plots will be generated, and median time will be estimated along with the corresponding 95% CI.

9.7.1. Analysis sets

- Full Analysis Set (FAS):

The FAS will include all patients who meet the inclusion criteria and do not meet the exclusion criteria described in section 9.2.

- Safety Analysis Set (SAS):

The SAS will include all patients from FAS.

- Effectiveness Analysis Set 1 (EAS1):

The EAS1 will include all patients from FAS who had at least one of the effectiveness variables collected and had the latest positive SARS-CoV-2 test result within 5 days prior to administration initiation.

- Effectiveness Analysis Set (EAS):

The EAS is a subset of EAS1 and will include patients who had mild or moderate COVID-19 illness at baseline and had at least one risk factor (defined in section 9.3.1) for progression to severe COVID-19 at baseline.

9.7.2. Analysis of primary endpoints

The analyses of primary endpoints will be based on the SAS, and following will be presented:

Number and percentage of patients experiencing at least one AE/SAE with explicit attribution to nirmatrelvir/ritonavir will be summarized.

Summary of AEs/SAEs by SOC and PT in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) will be provided; and AEs/SAEs will also be summarized by PT in descending order.

Number and percentage of patients with nirmatrelvir/ritonavir dose change (discontinuation/dose reduction) due to AEs with explicit attribution to nirmatrelvir/ritonavir will be summarized.

Number and percentage of patients experiencing safety related scenarios involving drug exposure (described in section 9.3 and 11) will be summarized in descending order.

9.7.3. Analysis of secondary endpoints

9.7.3.1. Analysis of treatment pattern endpoints

The analyses of treatment pattern endpoints will be based on FAS, and the following will be presented:

Number and percentage of patients receiving nirmatrelvir/ritonavir treatment only, and receiving nirmatrelvir/ritonavir plus concomitant COVID-19 related treatments, regardless of other concomitant medication, will be summarized.

The treatment duration (days) of nirmatrelvir/ritonavir will be summarized using n, mean, median, minimum, maximum, SD, and the 25th and 75th percentiles. This duration will also be categorized and be summarized using number and percentage for each duration category.

Number and percentage of patients receiving concomitant COVID-19 related treatments (described in section 9.3.5) will be summarized by therapeutic use (including antiviral therapy, immunotherapy, and other).

The treatment duration (days) of concomitant COVID-19 related treatments will be summarized using n, mean, median, minimum, maximum, SD, and the 25th and 75th percentiles by therapeutic use (including antiviral therapy, immunotherapy, and other), and also by subcategories of therapeutic use as listed in Section 9.3.5.

Number and percentage of patients receiving concomitant medications other than COVID-19 related treatments will be summarized by drug class.

9.7.3.2. Analysis of effectiveness endpoints

The analyses of effectiveness endpoints will be based on EAS1 and EAS, and the following will be presented:

Proportion of patients with COVID-19 disease severity (described in section 9.3.2) progressed or death from any cause and corresponding 95% CI will be summarized.

Time to alleviation of all targeted COVID-19 signs and symptoms (described in section 9.3.7) will be summarized by K-M plots with the median time and corresponding 95% CI.

Number and percentage of patients with two consecutive negative SARS-CoV-2 test results / CT ≥ 35 (specimens collected in two different calendar days) and corresponding 95% CI will be summarized for the patients with at least two SARS-CoV-2 tests after treatment initiation.

Time to the first negative SARS-CoV-2 test result / CT ≥ 35 from two consecutive negative SARS-CoV-2 test results / CT ≥ 35 (specimens collected in two different calendar days) among patients with at least two SARS-CoV-2 tests (described in section 9.3.8) will be summarized and plotted in a K-M curve with the median time and corresponding 95% CI.

9.7.4. Subgroup analysis

If data are adequate, subgroup analyses for the variables assessing safety, treatment patterns and effectiveness may be performed. Specifically,

- For safety variables, subgroup analyses will be performed by vaccination status, baseline COVID-19 severity, risk factors, renal impairment, hepatic impairment, and use of prior COVID-19-related treatments (described in section 9.3).

- For treatment patterns variables, subgroup analyses will be performed by vaccination status, baseline COVID-19 severity, risk factors, renal impairment, hepatic impairment, use of prior COVID-19-related treatments and administration time since onset of the first COVID-19 symptom/sign (described in section 9.3).

- For effectiveness variables, subgroup analyses will be performed by vaccination status, baseline COVID-19 severity, risk factors, renal impairment, hepatic impairment, use of prior COVID-19-related treatments and administration time since onse of the first COVID-19 symptom/sign (described in section 9.3).

9.7.5. Interim analyses

One interim analysis is planned to be conducted with the report expected to be available in May 2023. At this interim analysis, safety, treatment patterns and effectiveness with respect to all endpoints will be assessed.

9.8. Quality control

All participants data relating to the study will be recorded on electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or onsite monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

9.9. Limitations of the research methods

This study has the following limitations:

- Missing or incomplete data: Since data will be collected from medical records retrospectively, some of the requested information might be missing or incomplete. Safeguards against missing or incomplete data will be employed throughout the research process, which include choosing qualified sites, ensuring primary variables of interest that are routinely collected, using required fields and validation techniques in eCRFs,

and employing analytic techniques including evaluating and describing patterns of missingness.

- Generalizability of the study results: Due to the approval date of nirmatrelvir/ritonavir in China, this study will only include patients diagnosed with COVID-19 from 11 February 2022 and might only include patients infected with specific virus variants. Moreover, patients treated with COVID-19 during hospitalization in this study could have more severe COVID-19 illness and comorbidities. Therefore, our study results will be interpreted within study setting context. Furthermore, baseline characteristics of included patients in the study will be summarized and may be compared to other studies to evaluate the potential effects.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient consent

The informed consent /assent documents if requested by study sites and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/IEC before use, and available for inspection.

The investigator must ensure that each study patient, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The investigator further must ensure that each study patient or his or her legally acceptable representative, is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/IEC. If the investigator determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/IEC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (e.g., minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (e.g., parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study specific activity is performed unless a waiver of informed consent has been granted by an IRB/IEC. The investigator will retain the original of each patient's signed consent/assent document.

10.3. Patient withdrawal

For patient with a written ICD as requested by site, patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if applicable. The investigator would inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events if applicable.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

10.4. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the IRB/IEC. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.5. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR–International Society for Pharmacoepidemiology (ISPE) Special Task Force on real-world evidence in health care decision making, International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, x-rays, or narrative fields in a database. The reviewer is obligated to report AEs with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the CRF and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- For exposure during pregnancy in studies of pregnant women, data on the exposure to nirmatrelvir/ritonavir during pregnancy, are not reportable unless associated with serious or non-serious adverse events.

- For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness," "Study Drug," and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

- *"Your Reporting Responsibilities (YRR) Training for Vendors"*.

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

[redacted]

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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14. LIST OF TABLES

15. LIST OF FIGURES

16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

17. ANNEX 2. ADDITIONAL INFORMATION

None.

Document Approval Record

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