NON-INTERVENTIONAL (NI) STUDY

FINAL STUDY REPORT

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
Version identifier of the study report	Version 1.0
Date	07 June 2024
EU Post Authorization Study (PAS) register number	EUPAS103409
Active substance	Nirmatrelvir and ritonavir; ATC: J05AE30
Medicinal product	Nirmatrelvir Tablets/Ritonavir Tablets (co-packaged)
Marketing Authorization Holder (MAH)	Pfizer Limited/Pfizer Investment CO., Ltd.
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 pattern of patients treated with nirmatrelvir/ritonavir in China • To describe real-world effectiveness of nirmatrelvir/ritonavir among patients treated with nirmatrelvir/ritonavir in China
Country(-ies) of study	China

Author	[redacted]

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
Ct	Cycle Threshold
DCT	Data Collection Tool
EAS	Effectiveness Analysis Set
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
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
EPIC-PEP	Evaluation of Protease Inhibition for COVID-19 in Post-Exposure Prophylaxis
FAS	Full Analysis Set
FDA	Food and Drug Administration

GPP	Good Pharmacoepidemiology Practices
HIS	Hospital Information System
ICD	Informed Consent Document
IEC	Independent Ethics Committee
I/E	Inclusion and Exclusion Criteria
IL-6	Interleukin-6
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IPTW	Inverse Probability of Treatment Weighting
K-M	Kaplan-Meier
LIS	Laboratory Information System
MedDRA	Medical Dictionary for Regulatory Activities
[N]	Nucleocapsid Protein
NAT	Nucleic Acid Test
NMPA	National Medical Products Administration
ORF	Open Reading Frame
PACL	Protocol Administrative Change Letter
PASS	Post-Authorization Safety Study
PaO_2/FiO_2	Arterial Partial Pressure of Oxygen to Fraction of Inspired Oxygen
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
RCT	Randomized Controlled Trial

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Safety Analysis Set
SD	Standard Deviation
SOC	System Organ Class
SpO_2	Oxygen Saturation
TAS2R	Bitter Taste-Sensing Type 2 Receptors
TCM	Traditional Chinese Medicine
WHO	World Health Organization

3. INVESTIGATORS

The names, affiliations, and contact information of the investigators at each study site are listed in Appendix 3.1.

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
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Lead Country Investigator(s) of the Protocol

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4. OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in the study
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of independent ethics committee (IEC) or institutional review board (IRB) approval of protocol The IEC/IRB approval dates for the protocol are provided in Appendix 3.2.	Not applicable	First approval: 27 December 2022; Last approval: 31 August 2023	
Start of data collection	06 March 2023	10 April 2023	Adjusted based on actual study progress
End of data collection	29 November 2023	08 January 2024	Adjusted based on actual study progress
Registration in the EU PAS register	Not applicable	16 March 2023	
Interim report	30 May 2023	25 July 2023	Adjusted based on actual study progress
Final report of study results	17 April 2024	07 June 2024	Adjusted based on actual study progress

6. RATIONALE AND BACKGROUND

Nirmatrelvir/ritonavir is a severe acute respiratory syndrome coronavirus 2 (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, potentially helping patients avoid severe illness of coronavirus disease 2019 (COVID-19) which can lead to hospitalization and death.[1] 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 the absence of closely related homologues in humans,[2] M^{pro} is an attractive antiviral drug target. Ritonavir is a CYP3A inhibitor, that can suppress the CYP3A-mediated metabolism of nirmatrelvir, so as to increase the plasma concentrations of nirmatrelvir.[3]

Results from the global Phase 2/3 clinical trials of Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (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.[4] The safety profile for nirmatrelvir/ritonavir has been consistent in over 3,500 patients across the EPIC clinical development programs, including EPIC-HR, EPIC-SR, and Evaluation of Protease Inhibition for COVID-19 in Post-Exposure Prophylaxis (EPIC-PEP) studies.[5] A China stand-alone Phase 1 study (C4671016) conducted in healthy Chinese participants also indicated that nirmatrelvir/ritonavir was generally safe and well tolerated after repeated doses in healthy Chinese participants.

Nirmatrelvir/ritonavir has been strongly recommended for treating mild to moderate COVID-19 among patients at the highest risk of hospitalization by the World Health Organization (WHO).[6] In the latest China guideline, it has also been recommended as an antiviral medication for adults with mild or moderate COVID-19 at high risk of progression to severe disease within five days of onset.[7]

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

This final study report presents the results of the final analysis, including 1,047 patients' data from seven active study sites (Sites 1002, 1003, 1004, 1006, 1007, 1008, and 1009). Data were collected from patients who initiated nirmatrelvir/ritonavir between 11 February 2022 and 31 August 2022. The study database freeze date for the final analysis was 26 February 2024 (i.e., when data entry and cleaning were completed).

The patients included into this study was reflective of the clinical practice and pandemic prevention policy in China in 2022. Before December 2022,[9, 10] all patients who had positive SAR-CoV-2 test results were required to be admitted to designated hospitals for treatment, regardless of the disease severity. Nirmatrelvir/ritonavir was supplied to the designated hospitals per pandemic demands and prescribed to patients with COVID-19 based on treating

physicians' assessment. Therefore, patients in this study were all inpatients, and data were collected during patients' hospitalization period. The analyses related to COVID-19 severity were based on the China Guideline on Diagnosis and Treatment Plan for Coronavirus Disease 2019 (9th version).

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

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to provide real-world evidence on the safety, treatment pattern and effectiveness of nirmatrelvir/ritonavir in the treatment of COVID-19 among Chinese patients.

Primary objective

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

Secondary objectives

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

8. AMENDMENTS AND UPDATES

The original protocol (version 1.0) was finalized on 05 December 2022, and there were no protocol amendments afterwards. Two Protocol Administrative Change Letters (PACLs) were issued for administrative changes/clarifications to the original protocol. These changes/clarifications were not considered substantial by the sponsor. Please refer to Appendix 2.2 for further details.

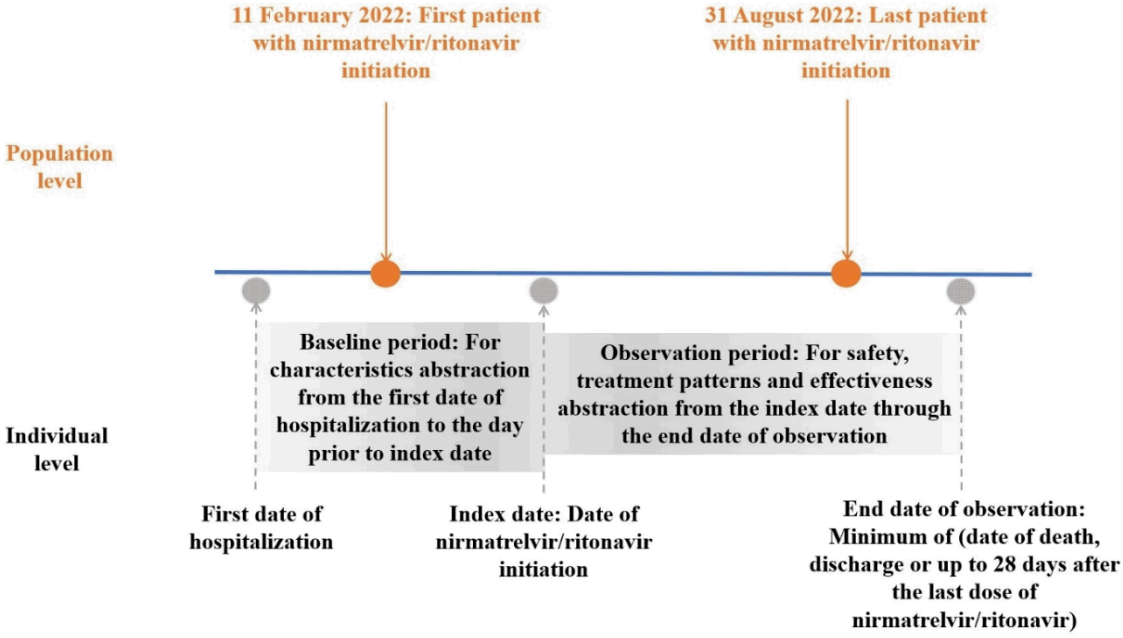
9. RESEARCH METHODS

9.1. Study design

This study was a multicenter, retrospective observational study to describe the safety, treatment pattern and effectiveness of nirmatrelvir/ritonavir among patients with COVID-19 in China. Approximately 1,000 patients were planned to be included in this study. Retrospective data abstraction started after ethics committee approval at each site. Patients who initiated nirmatrelvir/ritonavir treatment between 11 February 2022 and 31 August 2022 were included in this study. Continuous identification and entry of patients in each site were employed. For analysis purposes, an **index date** for an individual patient was defined as the date of initiating nirmatrelvir/ritonavir treatment. The **baseline period** for an individual patient was defined as the period from the first day of hospitalization to the day prior to the index date to capture the patient's baseline characteristics, medical history, and comorbidity. The **observation period** for an individual patient was defined as the period from initiation of nirmatrelvir/ritonavir (i.e., index date) until discharge from the hospital, death, or a maximum of 28 days after the last dose of nirmatrelvir/ritonavir, whichever occurred first. The study data cut-off date (i.e., the

last data point date) was 2 October 2022. The study design schematic is presented in Figure 1.

Figure 1. Study Design Schematic



9.2. Setting

The study population consisted of patients who initiated treatment with nirmatrelvir/ritonavir between 11 February 2022 and 31 August 2022, which was approximately 6 months post the Paxlovid approval in China. During this time, per clinical practice and epidemic prevention policy, patients with positive SAR-CoV-2 test results were admitted to the government designated hospitals for the treatment of COVID-19, and therefore, patients included in this study were all inpatients. In total, nine sites from Shanghai, Beijing, Jilin, and Guangzhou were selected based on the epidemiology of COVID-19, drug availability during the study period, feasibility assessments on patients' pool and site operations, as well as the physicians and hospitals' experiences. These sites located in the areas where outbreak happened in 2022, including Jilin and Shanghai. The site from Beijing is a specialized infectious disease hospital where patients with COVID-19 were treated during the outbreak in 2022. Eventually patients were enrolled from seven sites, and the other two sites (including the leading site in Guangzhou [Site 1001] and one site in Shanghai [Site 1011]) turned out to have none or very few eligible nirmatrelvir/ritonavir treated patients during the data collection period. In the final analysis, 1,047 patients were included from seven active sites in Shanghai, Beijing, and Jilin (Sites 1002, 1003, 1004, 1006, 1007, 1008, and 1009). See Section 9.3 for inclusion and exclusion (I/E) criteria of eligible patients.

9.3. Subjects

People with positive SAR-CoV-2 test results were required to be admitted to designated hospitals and were prescribed with nirmatrelvir/ritonavir in hospitals during the study period. At each site, the use of nirmatrelvir/ritonavir for an individual patient was verified across multiple available source records including stat/standing medication orders and medical

charts. Patients who were not prescribed with nirmatrelvir/ritonavir, and those who were prescribed with nirmatrelvir/ritonavir but the use could not be verified by site personnel were not considered to be enrolled in this study. Under this setting, eligible patients were designed to 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.

Partial ICD waivers were applied for this study, considering that this is a retrospective observational study with minimal risk to patients. Partial ICD waivers were applied to those patients who signed the general ICD when they were admitted to the hospital, as well as those who died or were lost to follow-up. Consequently, the probability of being enrolled into the study was 100% for patients who died in hospitals, which was higher than the probability for those who did not die. All study sites have fully reviewed and approved the application of partial ICD waiver.

The following process was followed to enroll study patients. Firstly, patients were continuously identified by site personnel based on the initiation date of nirmatrelvir/ritonavir. Patients who met all the inclusion criteria were kept and those who met the exclusion criterion were excluded. Then, patients were contacted for informed consent. Patients who either signed and dated the ICDs or met the criteria of ICD waiver were included in this study.

9.4. Variables

This study retrospectively abstracted individual-level data from the Hospital Information System (HIS) and the Laboratory Information System (LIS), which included electronic/paper medical records, prescription files, and laboratory testing results. Data for baseline variables were abstracted from the baseline period. Data for primary and secondary endpoint variables were abstracted from the observation period.

9.4.1. Primary endpoints – safety

The following endpoints were analyzed to evaluate the safety profiles of nirmatrelvir/ritonavir among patients who received nirmatrelvir/ritonavir in the real-world clinical practice:

- Incidence of adverse events (AEs) and serious adverse events (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

Procedure of AE/SAE data review, entry, and reporting:

During data extraction, the AEs/SAEs with explicit attribution to nirmatrelvir/ritonavir, as documented in the medical records, were collected. Further, the investigators reviewed the medical records and assessed if there was any AE/SAE with explicit attribution to nirmatrelvir/ritonavir based on available information in medical records per the investigators' medical and scientific judgement. The management and reporting of AEs/SAEs and safety related scenarios meeting protocol requirement is detailed in Section 11 of Appendix 2.1 PROTOCOL.

9.4.2. Secondary endpoints – treatment pattern

The treatment pattern was evaluated using the following endpoints:

- Proportion of patients receiving nirmatrelvir/ritonavir only, or receiving nirmatrelvir/ritonavir plus concomitant COVID-19-related treatments (including antiviral therapies [monoclonal antibodies, COVID-19 Human Immunoglobulin, convalescent plasma, azvudine, remdesivir and molnupiravir], immunotherapies [glucocorticoid, Interleukin-6 [IL-6] inhibitor, baricitinib, and tofacitinib] and any other COVID-19 related treatments [anticoagulant, Traditional Chinese Medicine [TCM], and oxygen supplemental therapy], see details in Section 9.3.5 in Appendix 2.1 PROTOCOL), regardless of receiving other concomitant medications

- Treatment duration (days) of receiving nirmatrelvir/ritonavir

    - Uninterrupted treatment course indicated that patients received nirmatrelvir/ritonavir for consecutive days. The treatment duration was calculated using (latest end date) – (index date) + 1.

    - Interrupted treatment course indicated that patients received nirmatrelvir/ritonavir with gaps in between consecutive days of treatment. The treatment duration was calculated using [sum of (end date of each consecutive treatment day – start date of each consecutive treatment day + 1)].

      In clinical practice in China, an inpatient could be prescribed with nirmatrelvir/ritonavir daily per treating physician's assessment regarding the patient's symptoms, timing of the treatment start, laboratory test results, etc. Therefore, patients may receive nirmatrelvir/ritonavir repeatedly but with a total duration being shorter than 5 days.

- 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)

    - If the patient had a single record of a specific drug label, the treatment duration was calculated using (end date – start date + 1)

    - If the patient had multiple records of a specific drug label, the following calculation methods were proceeded:

        1) if the records were overlapped, the treatment duration was calculated using (latest end date – earliest start date + 1)

        2) if records were separated, the treatment duration was calculated using [sum (each end date – each start date + 1)]

        3) if records contained both case 1) and case 2), firstly, approach 1) was used to calculate the duration of the overlapped records; secondly, approach 2) was used to calculate the duration of each separated record; lastly, these durations were summed together

        For instance, a patient took 3 concomitant treatments. If the treatment dates were 1/1 to 1/5 for Drug A, 1/20 to 1/26 for Drug B, and 1/3 to 1/12 for Drug C, then the duration of concomitant treatments was calculated as sum of (1/1 to 1/12; 1/20 to 1/26).

    See data curation plan for further details.

- Proportion of patients receiving concomitant medications other than COVID-19 related treatments by drug class

Definitions of dose reduction and dose discontinuation

Dose reduction was only captured if occurred during the observation period. It must involve an adjustment during the course of treatment. For instance, compared to the preceding record, if a patient's second dose record of nirmatrelvir was reduced from 300 mg to 150 mg (or if the dosing frequency changed from twice daily to once per day), these instances would be qualified as dose reductions during observation. If a dose reduction was collected into the treatment case report form (CRF), the patient should have at least two or more medication records reflecting such changes. Reasons for dose reduction were collected based on medical orders and records, and were reviewed by investigators to confirm the occurrence of dose reduction.

Dose discontinuation should be supported by definite wording of ‘stop’ or ‘discontinuation’, or health condition description indicating a need of nirmatrelvir/ritonavir discontinuation in the medical records, and/or be reviewed by the investigators.

See data curation plan for further details.

9.4.3. Secondary endpoints – effectiveness

The effectiveness profiles of nirmatrelvir/ritonavir were evaluated using the following endpoints:

- Proportion of patients with COVID-19 disease severity progressed or death from any cause

  Note that COVID-19 disease severity progressed or death from any cause was defined as:

  - Patients with mild to moderate COVID-19 at baseline and (1) progressed to severe/critical COVID-19 or (2) death in the observation period
  - Patients with severe/critical COVID-19 at baseline and death in the observation period

- Time (days) to alleviation of all targeted COVID-19 signs and symptoms during the observation period (see Section 9.3.3 in Appendix 2.1 PROTOCOL for a detailed list of the targeted COVID-19 signs and symptoms)

  See Section 5.3.3 in Appendix 4 STATISTICAL ANALYSIS PLAN for details of the endpoint definition.

- 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

  See Section 5.3.4 in Appendix 4 STATISTICAL ANALYSIS PLAN for details of the endpoint definition.

Derivation criteria for two consecutive negative SARS-CoV-2 test results:

Endpoints related to two consecutive negative SARS-CoV-2 test results / Ct ≥ 35 were set with reference to the China Guideline on Diagnosis and Treatment Plan for Coronavirus Disease 2019 (9th version), which was the effective local guideline during the study period. During data collection, for some patients, multiple SARS-CoV-2 test results (e.g., based on different types of tests) were available on the same date. The following derivation criteria for the two consecutive negative SARS-CoV-2 tests were applied:

a) The date and time of specimen collection were used as the test date and time. If the date and time were missing, then the date and time when the test result was released were used instead.

b) For patients who had more than one Nucleic Acid Test (NAT) results on the same date and the durations between any two tests [calculated based on the date and time defined in **a)**] were beyond one hour, then the latest NAT result on that date was used as the NAT result on that day.

c) For patients who had more than one NAT results within one hour on the same day, these results were considered as one test. The latest NAT result within that hour were used.

d) For patients who had more than one type of NAT results (i.e., Ct values of open reading frame [ORF] /nucleocapsid protein [N] gene, a Ct value of unspecified gene, a qualitative NAT result), the following rules in descending order of priority are used for deriving a SARS-CoV-2 test result, and this derived SARS-CoV-2 test result (Positive/Negative) were used in analyses:

   - If the Ct for ORF or N gene was < 35, the ORF/N gene result was defined as Positive.
   - If the Ct for both ORF and N gene were ≥ 35, the ORF/N gene result was defined as Negative.
   - If either the Ct for ORF or N gene was ≥ 35, and the other one was documented as undetermined, the ORF/N gene finding was defined as Negative.
   - If the Ct for ORF or N gene was missing, but an unspecified Ct result was available, then Ct < 35 was defined as Positive; otherwise, the result was Negative.
   - If the Ct for both ORF/N gene and unspecified Ct result was missing, but a qualitative NAT result was available, then this qualitative NAT result was used as the test result.
   - If the Ct for both ORF/N gene, unspecified Ct result and qualitative NAT result was all missing, then the antigen test result was used as the test result.

e) For patients who had more than one NAT results on the same date but missing time of these NAT results, the NAT result on that day were defined as positive if there was at least one positive NAT result.

f) The antigen result was only used when the NAT results were unknown or missing on the same day.

9.4.4. Demographic and clinical characteristics

Below demographic and clinical characteristic variables were collected and derived:

- Age, sex
- Clinical characteristics: Body mass index (BMI), smoking status, COVID-19 severity at baseline, duration between onset date of the first COVID-19 symptom/sign and index

date, 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, and serology status at baseline

- Comorbidities
- Prior COVID-19 related treatments and other prior medications (those that were used before nirmatrelvir/ritonavir initiation and were not used with in combination with nirmatrelvir/ritonavir [i.e., end dates of treatments were before nirmatrelvir/ritonavir initiation])

See Section 9.3 in Appendix 2.1 PROTOCOL for a detailed list of the variables.

Derivation criteria for serology results based on IgM and IgG results:

a) If any value of IgG, IgM or unspecified serology type equaled to 'Positive' then set serology to 'Positive';

b) If not a), then set to 'Negative'.

Mapping criteria for COVID-19 severity at both baseline and during the observation period:

Endpoints related to COVID-19 severity progression and description of baseline COVID-19 severity were set with reference to the China Guideline on Diagnosis and Treatment Plan for Coronavirus Disease 2019 (9th version), which was the effective local guideline during the study period. The severity was 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 ≥ 30/min, or lung infiltrates progression > 50% within 24-48 hours.
- Critical illness: Individuals who have respiratory failure requiring mechanical ventilation, shock, or multiple organ dysfunction with intensive care unit care.

During data abstraction, some patients' medical records showed that the 8th version [11] or the revised 8th version [12] of the guideline was used instead for COVID-19 severity assessments. Thus, relevant COVID-19 severity information referring to the 8th version or the revised 8th version was entered into the electronic case report form (eCRF) with investigator's review. Comparing these guideline versions, only the definition of the moderate level of COVID-19 severity is slightly different. The following mapping criterion was applied:

The "*Moderate illness: showing fever, respiratory symptoms, etc. and abnormal chest imaging*" in the 8th or the revised 8th version was mapped to be the same level of moderate illness as the 9th version "*Moderate illness: showing evidence of signs and symptoms of COVID-19 and abnormal chest imaging*".

Furthermore, following the eCRF Completion Guidelines, '999' was entered into eCRF to indicate that a patient's information on the COVID-19 severity level was insufficient while this patient's COVID-19 condition was stated as 'improved/recovered' during the observation period in the medical records.

9.5. Data sources and measurement

Individual-level data were retrospectively abstracted from the HIS and LIS to the eCRF (see Appendix 5 for details) from the seven sites with patient enrollment (i.e., Sites 1002, 1003, 1004, 1006, 1007, 1008, and 1009). Data were collected from a variety of medical records, including consultation notes, discharge summaries, laboratory test results, recorded prescription data, imaging data, and other related documents. Data for the prespecified variables (see Section 9.4) were abstracted from source documents by the delegated trained site personnel and were entered directly into the web-based eCRFs. Only de-identified data were abstracted and used in the analysis. Detailed rules for eCRF data entry were specified in the eCRF Completion Guidelines.

9.6. Minimization of bias

The following strategies were applied to minimize selection bias.

Firstly, to ensure representativeness of the study population, the government designated hospitals for COVID-19 treatment in China during the pandemic (i.e., between 11 February 2022 and 31 August 2022) were selected for data collection.

Secondly, continuous identification and inclusion of patients were attained through applying both individual consent and partial ICD waiver. The partial ICD waiver allowed this study to include patients who signed the general ICD when they admitted to hospital, as well as those who died or were lost to follow up.

Thirdly, statistical method for survey data analysis was used, in which site was considered as a cluster factor and the inverse probability of treatment weighting (IPTW) was used to estimate the death rate, the proportion involving death (i.e., proportion of patients with COVID-19 severity progressed or death from any cause), as well as the corresponding 95% confidence intervals (CIs). Among the patients who met the I/E criteria, some patients consented to be included in the study, some patients were included via the partial ICD waiver, and other patients declined to participate in the study. Therefore, patients who died in the hospitals were all enrolled with partial ICD waiver and thus they were more likely to be included into the final analysis than those who did not die.

9.7. Study size

There was no formal hypothesis testing for this study. This study aimed to extract information from approximately 1,000 patients. With 1,000 patients, there was a probability of > 99.9% to observe an AE related to nirmatrelvir/ritonavir with a 1% incidence rate from at least one

patient, and a probability of 95.0% to observe an AE related to nirmatrelvir/ritonavir with a 0.3%[13] incidence rate from at least one patient.

Assuming that 20%[14] of the 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, the sample sizes of 800 and 500 evaluable individuals provided a 95% CI with a half-width of 2.77% and 3.50%, respectively (See Section 9.5 in Appendix 2.1 PROTOCOL for more details).

9.8. Data transformation

Detailed methodology for data transformations (e.g., many raw variables used to derive an analysis variable), are documented in the statistical analysis plan (SAP; Appendix 4).

Source data were abstracted and managed by study sites on eCRFs by a web-based electronic data capture (EDC) tool. All eCRFs were completed by designated, trained personnel or the study coordinator. The eCRF was reviewed, electronically signed, and dated by the investigator. All changes or corrections to eCRFs have been documented in an audit trail and an adequate explanation has been added.

Data management plan was in place before the start of data collection and described all functions, processes, and specifications for data collection, cleaning, and validation. The eCRF Completion Guidelines containing detailed instructions were also used to guide the data entry into eCRFs. The eCRFs included programmable edits to obtain immediate feedback if data were missing, out of range, illogical or potentially erroneous. Concurrent manual data review was performed based on parameters dictated by the plan. Queries were generated within the EDC system and followed-up for resolution.

Data collection standards were maintained, measures were taken to ensure data accuracy. Data quality was enhanced through manual checks, and a series of programmed data quality checks that automatically detect out of range or anomalous data.

9.9. Statistical methods

This study was descriptive, and no formal hypothesis testing was conducted.

9.9.1. General analysis methodologies

Continuous variables were summarized using n, mean, median, minimum, maximum, standard deviation (SD), and first quartile (Q1) and third quartile (Q3). Categorical variables were summarized using the number and percentage of each category.

Due to partial ICD waiver, patients who died in the hospitals were all enrolled and thus were more likely to be included into the final analysis than those who did not die in the hospitals. To adjust for sampling bias, survey data analysis method was used to estimate the death rate, the proportion involving death (i.e., proportion of patients with COVID-19 severity progressed or death from any cause), as well as the corresponding 95% CIs, in which site was considered as a cluster factor and the IPTW was applied for assigning different weights for patients who died and patients who did not die in the hospitals:

Equation 1 Calculation of Weight

$$weight = \frac{1}{\text{probability of being included in the study}}$$
$$= \begin{cases} \frac{1}{100\%}, if\ a\ patient\ died \\ \frac{1}{\text{\# alive patients in final analysis sample/\# alive patients satisfied I/E criteria}}, if\ a\ patient\ did\ not\ die \end{cases}$$

Missing data were not imputed and were reported by frequency and percentage (the number of missing cases / the total number of cases).

For a time-to-event variable (such as time to alleviation of all targeted COVID-19 signs and symptoms), estimates for the Q1, median, and Q3 and corresponding 95% CIs were generated based on Kaplan-Meier (K-M) method; a K-M plot was generated with number of events, number of censoring, and number at risk across time.

9.9.2. Analysis sets

- Full Analysis Set (FAS):

  The FAS included all patients who met the inclusion criteria and did not meet the exclusion criteria described in Section 9.3.

- Safety Analysis Set (SAS):

  The SAS included all patients from FAS.

- Effectiveness Analysis Set 1 (EAS1):

  The EAS1 included all patients from FAS who had at least one of the effectiveness variables collected (see Section 9.4.3) and had the latest positive SARS-CoV-2 test result within 5 days prior to administration initiation.

- Effectiveness Analysis Set (EAS):

  The EAS was a subset of EAS1 and included patients who had mild or moderate COVID-19 illness at baseline and had at least one risk factor (defined in Section 9.3.1 Risk factors in Appendix 2.1 PROTOCOL) for progression to severe COVID-19 at baseline.

9.9.3. Summary of analyses

The patient disposition, baseline demographic and disease characteristics, baseline COVID-19 symptoms/signs, prior treatments, and comorbidities at baseline were descriptively summarized.

The primary safety endpoints were analyzed using SAS. AEs with explicit attribution to nirmatrelvir/ritonavir were presented with overall summary. AEs/SAEs were also presented by System Organ Class (SOC) and Preferred Term (PT). Patients who experienced nirmatrelvir/ritonavir dose change (discontinuation/dose reduction) due to AEs with explicit

attribution to nirmatrelvir/ritonavir, and safety-related scenarios involving drug exposure were presented with an overall summary. Deaths from any causes were also summarized.

The secondary endpoints of the treatment pattern were summarized using FAS. The numbers and percentages of patients by types of treatment course (uninterrupted treatment course with nirmatrelvir/ritonavir versus interrupted treatment course with nirmatrelvir/ritonavir, see Section 9.4.2 for definitions), and whether on nirmatrelvir/ritonavir alone or in combination with COVID-19 related concomitant treatments were summarized.

The overall treatment duration (days) of nirmatrelvir/ritonavir, treatment duration of nirmatrelvir/ritonavir by types of treatment course, treatment duration of nirmatrelvir/ritonavir for nirmatrelvir/ritonavir administered alone and in combination with COVID-19 related concomitant treatments were all summarized descriptively with n, mean, median, quantiles, and range, as well as by categories (1 to 4 days / 5 to 6 days / 7 to 10 days / >10 days). The category of 5-6 days duration is to reflect the 5-day standard treatment course as recommended by nirmatrelvir/ritonavir label since patients may start treatment in the afternoon. In addition, the treatment duration (days) of concomitant COVID-19 related medications (including antiviral therapy, immunotherapy, and others) were also summarized descriptively with n, mean, median, quantiles, and range. Other concomitant medications were summarized by numbers and percentages according to the Anatomical Therapeutic Chemical (ATC) level 2 and PT.

The secondary endpoints of treatment effectiveness were analyzed using EAS1 and EAS. The numbers and percentages of patients with COVID-19 disease severity progressed or death from any cause, and patients with two consecutive negative SARS-CoV-2 test results / Ct ≥ 35 post-baseline were summarized. Time to alleviation of all targeted COVID-19 signs and symptoms, and time to the first negative SARS-CoV-2 test result / Ct ≥ 35 from two consecutive negative SARS-CoV-2 test results / Ct ≥ 35 were summarized and plotted using the K-M method.

9.9.4. Subgroup analyses

For key safety endpoints in SAS and key treatment pattern endpoints in FAS, subgroup analyses were performed by vaccination status (unvaccinated; vaccinated), baseline COVID-19 severity (mild to moderate illness; severe to critical illness), and baseline eGFR level [mL/min/1.73m^2] (eGFR < 30; 30 ≤ eGFR < 60; 60 ≤ eGFR < 90; eGFR ≥ 90). Death was summarized by age groups (< 60; ≥ 60 to < 70; ≥ 70 to < 80; ≥ 80 years).

For key effectiveness endpoints in EAS1, subgroup analyses were performed by age group (< 60 years, 60 to < 70 years, 70 to < 80 years, ≥ 80 years), vaccination status (unvaccinated; vaccinated), baseline COVID-19 severity (mild to moderate illness; severe to critical illness), baseline eGFR level [mL/min/1.73m^2] (eGFR < 30; 30 ≤ eGFR < 60; 60 ≤ eGFR < 90; eGFR ≥ 90), and duration since the earliest on-record COVID-19 symptom/sign till nirmatrelvir/ritonavir treatment (≤ 5 days; > 5 days). For the same key effectiveness endpoints in EAS, subgroup analyses were performed by vaccination status (unvaccinated; vaccinated), nirmatrelvir/ritonavir label defined risk factors, baseline eGFR level [mL/min/1.73m^2] (eGFR < 30; 30 ≤ eGFR < 60; 60 ≤ eGFR < 90; eGFR ≥ 90), and duration since the earliest on-record COVID-19 symptom/sign till nirmatrelvir/ritonavir treatment (≤ 5 days; > 5 days).

See more details in Section 4.5 in Appendix 4 STATISTICAL ANALYSIS PLAN.

9.9.5. Amendments to the statistical analysis plan

There was an original SAP (version 1.0, on 25 April 2023) without any amendments.

During data analysis, some changes to the planned analyses in SAP were made and are shown in Table 1 below.

Table 1. Change to the planned analyses

Planned analysis	Change to analysis	Rationale
In Section 7.2.4, the number and percentage of patients with COVID-19 severity progressed or death from any cause will be summarized. The normal approximation will be used to provide relevant 95% CIs.	The survey data analysis method was used to estimate the death rate, the proportion of patients with COVID-19 severity progressed or death from any cause, as well as the corresponding 95% CIs, in which site was considered as a cluster factor and the IPTW was applied.	To minimize the sampling bias in death related estimates.
In Section 5.4.2, duration since the first positive SARS-CoV-2 test and duration since the first COVID-19 symptom/sign onset till the index date will be analyzed.	The duration since the earliest on-record positive SARS-CoV-2 test and the duration since the earliest on-record COVID-19 symptom/sign onset were presented instead.	The earliest time observed in medical records might not be the real time of the first positive test or the first symptom/sign onset time. The real time might occur before patient's admission and was not recorded in medical records. Therefore, these two variables were named as earliest on-record durations for appropriateness.
In Section 4.5, the age group will be categorized as < 60 years and ≥ 60 years.	The age group was recategorized as < 60 years, 60 to < 70 years, 70 to < 80 years, and ≥ 80 years.	To show older patients' safety and effectiveness results.
In Section 5.2.1, for the treatment duration of nirmatrelvir/ritonavir, if a patient discontinued and then reinitiated nirmatrelvir/ritonavir treatment during the observation period, only the first treatment course will be included for analysis.	The treatment duration of nirmatrelvir/ritonavir was calculated for uninterrupted treatment course and interrupted treatment course.	To reflect the actual administration pattern of nirmatrelvir/ritonavir in the real-world clinical setting.

Table 1. Change to the planned analyses		
Planned analysis	**Change to analysis**	**Rationale**
In Section 7.2.3, the treatment duration of nirmatrelvir/ritonavir will be categorized as 1 to 4 days, 5 days and > 5 days.	The treatment duration of nirmatrelvir/ritonavir was recategorized as 1 to 4 days, 5 to 6 days, 7 to 10 days and > 10 days.	To take into account that a 5-day treatment started in the afternoon of a day may be calculated with a duration being 6 days based only on available dates information in medical records.

9.10. Quality control

Participants' data relating to the study were recorded on eCRF. The investigator was responsible for verifying that data entries being accurate and correct by electronically signing the CRF. Guidance on completion of CRFs was provided in the CRF Completion Requirements document.

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

Institutional Review Board (IRB)/Independent Ethics Committee (IEC) reviewed and approved the protocol and other relevant documents (e.g., informed consent forms if applicable) before study initiation at each site. Investigator staff training was provided by IQVIA during investigator meeting, initiation, and routine monitoring visits.

IQVIA is responsible for the data management of this study and oversighted by sponsor. Specific data management activities for data collection, cleaning, and validation were conducted following the data management plan, the eCRF Completion Guidelines, and the ad hoc file notes to sites. The eCRFs included programmable edits to obtain immediate feedback if data were missing, out of range, illogical or potentially erroneous. Concurrent manual data review was performed based on parameters dictated by the plan. Ad hoc queries were also generated within the EDC system and followed-up for resolution.

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.

Audit of this study was included as part of the independent sponsor quality assessment performed by sponsor Quality Assurance.

See Sections 9.6, 9.8, and 10 in Appendix 2.1 PROTOCOL for more details.

9.11. Protection of human subjects

Subject information and consent

Partial ICD waiver was applied in this retrospective study and was approved by the study sites with patient enrollment before use. Partial ICD waiver applied to patients who signed the

general ICD of the designated hospital when they admitted to hospital seeking for medical care, and also applied to those who died or lost to follow up (defined by each site). Written informed consent (reference Appendix 6) was obtained prior to the patient entering the study (before initiation of data extraction procedure) by study personnel. Except for those patients who were enrolled under partial ICD waiver, the nature, purpose, and duration of the study was explained to each patient, the patients who signed the ICD were informed that they could withdraw from the study at any time and for any reason; each patient who signed the ICD was given sufficient time to consider the implications of the study before deciding whether to participate; patients who chose to participate signed an ICD.

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

The final protocol, PACLs, partial ICD waiver approval, and ICD were reviewed and approved by EC for each site participating in the study.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and followed generally accepted research practices described in Guidelines for Good Clinical Practice (GCP), 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.

10. RESULTS

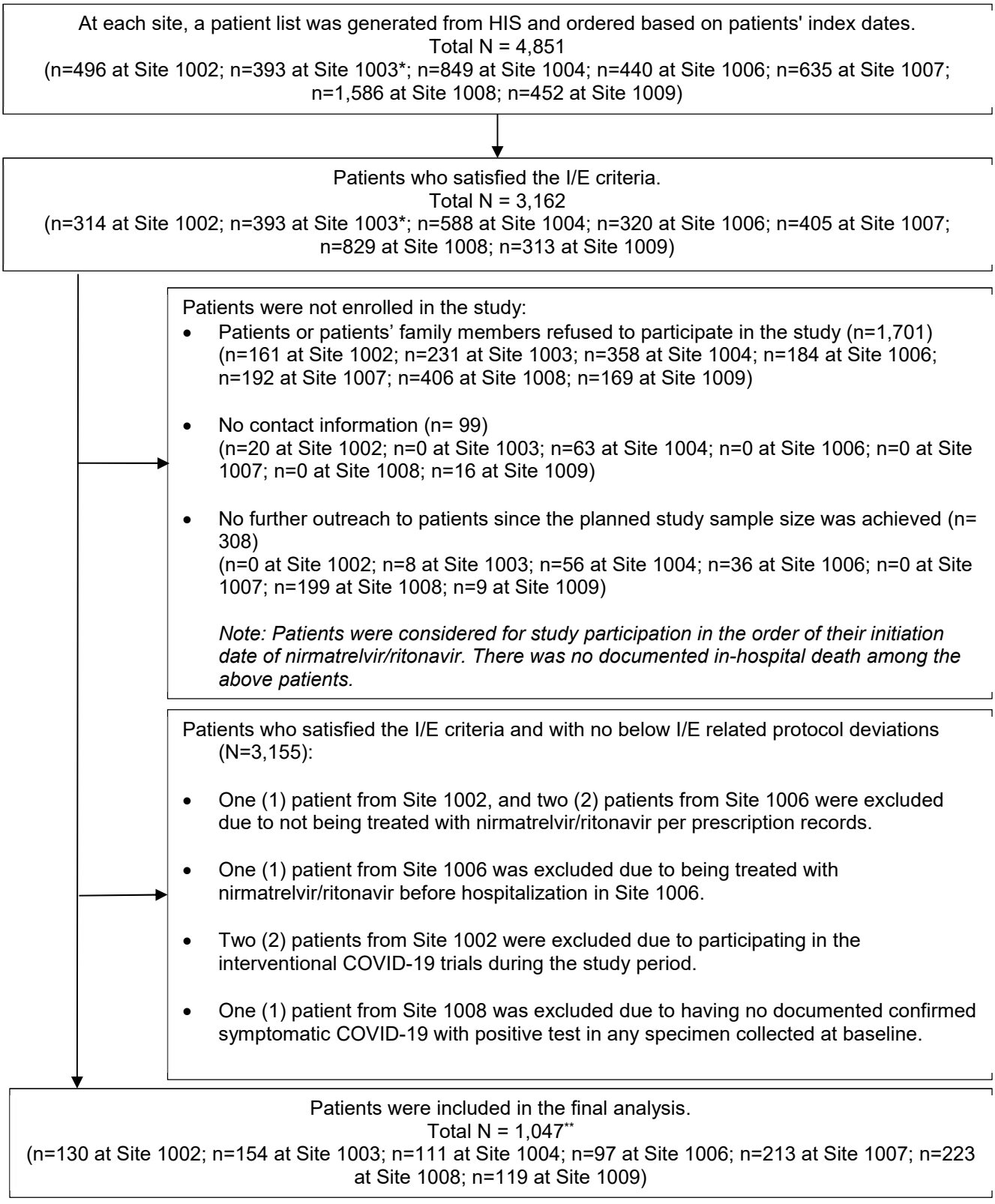
10.1. Participants

10.1.1. Procedure of data extraction

Initially, the patient lists of 4,851 patients from seven hospitals were identified according to their nirmatrelvir/ritonavir initiation dates and were reviewed by site personnel at each hospital. Of these, 3,162 patients were kept based on I/E criteria. Next, 2,108 patients were not included into the study due to refusal to study participation (1,701), missing of contact information (99), and achievement of the planned study sample size (308). There was no documented in-hospital death among the 2,108 patients. During data entry into EDC, 7 patients were excluded due to protocol deviations related to I/E criteria violation: 3 patients were identified as not being treated with nirmatrelvir/ritonavir, 1 patient was treated with nirmatrelvir/ritonavir before admission to the study site, 2 patients met the exclusion criterion of participating in other interventional COVID-19 trials during the study period, and 1 patient had no confirmed symptomatic COVID-19 with positive SARS-CoV-2 test documented (See Appendix 7.2 Protocol Deviations for more details).

As a result, among the 3,155 patients who satisfied the I/E criteria (excluding the 7 patients with protocol deviations related to I/E criteria), a total of 1,047 eligible patients were included in the final analysis. See Figure 2 for more details.

Figure 2. Flow Chart of Data Extraction



HIS: Hospital Information System; I/E criteria: Inclusion and Exclusion criteria
[*]Steps one and two were combined at the Site 1003.
[**]Enrollment with:

- *ICD obtained: n=28 at Site 1002, n=114 at Site 1003, n=56 at Site 1004, n=37 at Site 1006, n=88 at Site 1007, n=51 at Site 1008, and n=62 at Site 1009*
- *ICD waiver: n=102 at Site 1002, n=40 at Site 1003, n=55 at Site 1004, n=60 at Site 1006, n=125 at Site 1007, n=172 at Site 1008, and n=57 at Site 1009*

10.1.2. Patient disposition

A total of 1,047 eligible patients were included in the final analysis with 58.4% being included based on the ICD waiver (Table 2). All the patients were included in the FAS and SAS, with 982 and 796 patients being included in the EAS1 and EAS respectively. Further details on patient disposition for all enrolled patients are provided in Listing 15.1.

Table 2. Patient Disposition - All Enrolled Participants

	Total (N=1,047)
Eligible Patients, n (%)	1,047 (100.0)
Patients Whose ICD Waiver is Acquired	611 (58.4)
Patients Whose ICD is Collected	436 (41.6)
FAS, n (%)	1,047 (100.0)
SAS, n (%)	1,047 (100.0)
EAS1, n (%)	982 (93.8)
EAS, n (%)	796 (76.0)

ICD: Informed Consent Document; FAS: Full Analysis Set; SAS: Safety Analysis Set; EAS1: Effectiveness Analysis Set 1; EAS: Effectiveness Analysis Set
The FAS includes all patients who meet the inclusion criteria and do not meet the exclusion criteria.
The SAS includes all patients from the FAS.
The EAS1 includes all patients from the 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 EAS is a subset of EAS1 and includes 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.
Source: Table 15.1

Among the 1,047 patients in the FAS, the median (range) duration of the baseline period (excluding the index date) and the observation period (including the index date) were 2.0 (0.0, 31.0) days and 10.0 (1.0, 50.0) days, respectively. See Table 3 below and Listings 15.2. Adverse Events (AEs) with Explicit Attribution to Nirmatrelvir/Ritonavir - SAS, 15.3. Nirmatrelvir and Ritonavir Treatment - FAS, 15.4. Demographics and Baseline Characteristics - FAS, 15.5. SARS-CoV-2 Test - FAS, 15.6. COVID-19 Severity - FAS, 15.9. Prior/Concomitant Medications - FAS, and 15.12. Medical History - FAS in Section 15 for more details.

Two (2) patients in this study had an observation period being longer than 40 days, which was cut off by 28 days post the last dose of nirmatrelvir/ritonavir. Specifically:

One patient was with a 50-day observation period. This patient was an 88-year-old unvaccinated male with mild COVID-19 at baseline. There was no medical history recorded, however, before taking nirmatrelvir/ritonavir 300/100 mg BID, in addition to prior COVID-19 related oxygen, methylprednisolone and Lianhua Qingwen granule, the patient also took prior medications including bisoprolol, amiodarone, nifedipine, several antibacterials and nutrients, etc. The patient received nirmatrelvir/ritonavir 300/100 mg BID from 24 April 2022 to 4 May 2022. On 11 May 2022, medical records indicated that the patients' disease severity became critical, and the patient received further treatment with nirmatrelvir/ritonavir 300/100 mg BID from 9 May 2022 to 15 May 2022. Concomitant COVID-19 related oxygen supplemental therapies, glucocorticoid, TCM, and anticoagulant were also given. The patient was recorded to have two consecutive negative SARS-CoV-2 tests on 12 May 2022 and 13 May 2022. The observation period ended on 12 June 2022. No AE with explicit attribution to nirmatrelvir/ritonavir was reported for this patient. See Listings 15.1. Patient Disposition - All Enrolled Patients, 15.3. Nirmatrelvir and Ritonavir Treatment - FAS, 15.4. Demographics and Baseline Characteristics - FAS, 15.5. SARS-CoV-2 Test - FAS, 15.6. COVID-19 Severity - FAS, and 15.9. Concomitant Treatments - FAS in Section 15.

Another patient was with a 49-day observation period. This patient was a 53-year-old male, received 3 doses of vaccines, and had moderate COVID-19, ongoing diabetes, ongoing lung transplantation status, and ongoing bilateral bronchial stenosis at baseline. The patient received nirmatrelvir/ritonavir 300/100 mg Q12H from 13 April 2022 to 18 April 2022, and the disease was recorded as moderate during the treatment. On 20 April 2022, records indicated that the patient's disease severity became severe. Further treatment with nirmatrelvir/ritonavir 300/100 mg was given to this patient from 29 April 2022 to 3 May 2022. Concomitant COVID-19 related oxygen supplemental therapies, glucocorticoid, and anticoagulant were also given. The patient had negative SARS-CoV-2 test results on 11 May 2022 and 15 May 2022, and then achieved 2 consecutive negative results starting on 18 May 2022. The observation period ended on 31 May 2022. No AE with explicit attribution to nirmatrelvir/ritonavir was reported for this patient. See Listings 15.1. Patient Disposition - All Enrolled Patients, 15.3. Nirmatrelvir and Ritonavir Treatment - FAS, 15.4. Demographics and Baseline Characteristics - FAS, 15.5. SARS-CoV-2 Test - FAS, 15.6. COVID-19 Severity - FAS, and 15.9. Concomitant Treatments - FAS in Section 15.

Table 3. Summary of Analysis Period - FAS

	Total (N=1,047)
Duration of Baseline Period (Days) [1]	

Table 3. Summary of Analysis Period - FAS

	Total (N=1,047)
n (%)	1,047 (100.0)
Mean (SD)	2.9 (3.76)
Median	2.0
Q1, Q3	1.0, 3.0
Min, Max	0.0, 31.0
Duration of Observation Period (Days) [2]	
n (%)	1,047 (100.0)
Mean (SD)	11.4 (5.86)
Median	10.0
Q1, Q3	7.0, 14.0
Min, Max	1.0, 50.0

SD: Standard Deviation; Q1: First Quartile; Q3: Third Quartile.
Percentages are calculated using the number of total patients in the Full Analysis Set (N) as the denominator.
[1] Duration of baseline period (Days) = (Index date) – (First day of hospitalization)
[2] Duration of observation period (Days) = (End of observation date) – (Index date) + 1, in which the end of observation date is defined as the date of discharge from hospital, death, or a maximum of 28 days after the last dose of nirmatrelvir/ritonavir, whichever comes first.
Source: Table 15.1.1

10.1.3. Protocol deviation

Overall, the protocol deviations were reported from 27 patients (Table 4).

There were 4 (0.4%) patients who did not initiate the nirmatrelvir/ritonavir treatment during hospitalization (i.e., not meeting the inclusion criteria 2). One (1) of them received nirmatrelvir/ritonavir treatment before hospitalization, and another 3 patients were not treated with nirmatrelvir/ritonavir. Two (2) patients (0.2%) participated in other clinical trials during nirmatrelvir/ritonavir treatment (i.e., meeting the exclusion criterion), and one (1, 0.1%) patient had no documented confirmed symptomatic COVID-19 with positive SARS-CoV-2 test result in any specimen collected at baseline (i.e., not meeting the inclusion criteria 3). These 7 patients were considered critical protocol deviations that were related to I/E criteria, and were not included in any analysis set.

Moreover, 15 (1.4%) patients were reported to have major protocol deviations due to AEs not being reported to the sponsor within 24 hours of the investigators' awareness (n=14) and the signee's name on the ICD being recorded wrongly (n=1).

Additionally, minor protocol deviations were reported for five (0.5%) patients as patient-reported AEs were recorded during patients' signatures for informed consent.

Due to the nature of the retrospective data abstraction, the reported protocol deviations are not considered to place participants at risk, invalidate data or jeopardize this study's scientific integrity.

Further details on the protocol deviations are provided in Listing 15.8. Protocol Deviations - All Screened Participants in Section 15.

Table 4. Protocol Deviation - All Screened Participants

Protocol Deviation Severity*	Number of Patients (N=1,054)
Patients with Any Critical Protocol Deviation, n (%)**	7 (0.7)
Not Meeting Inclusion Criteria 2 [1]	4 (0.4)
Not Meeting Inclusion Criteria 3 [2]	1 (0.1)
Meeting Exclusion Criterion [3]	2 (0.2)
Patients with Any Major Protocol Deviation, n (%)	15 (1.4)
Study Procedures [4]	14 (1.3)
Informed Consent and Process [5]	1 (0.1)
Patients with Any Minor Protocol Deviation, n (%)	5 (0.5)
Study Procedures [6]	5 (0.5)

[1] Three patients were not treated with nirmatrelvir/ritonavir and one patient was treated with nirmatrelvir/ritonavir before admission to the study site.
[2] No documented confirmed symptomatic COVID-19 with positive SARS-CoV-2 test in any specimen collected at baseline.
[3] Participating in other clinical trials during nirmatrelvir/ritonavir treatment.
[4] AEs were not reported to the sponsor within 24 hours of the investigators' awareness.
[5] The signee's name on the informed consent document was recorded wrongly. The participant's name was recorded while an immediate family member signed the form on behalf of the participant.

[6] Patient-reported AEs were recorded during patients' signature for informed consent.
** Severity of protocol deviation is classified below:*
- Critical Protocol Deviation: A deviation from Protocol-related procedures that threatens integrity of data, adversely affects subjects and/or could invalidate acceptability of a project (or part of it). Such deviations require immediate action.
- Major Protocol Deviation: A deviation from Protocol-related procedures that could affect integrity of the data or adversely affect subjects. Such deviations require timely action.
- Minor Protocol Deviation: A deviation from accepted procedures that will not adversely affect subjects or data integrity but should be dealt with appropriately.
*** These patients were not involved in the final analysis.*
Source: Listing 15.8

10.2. Descriptive data

10.2.1. Baseline demographics

Baseline demographic characteristics of all 1,047 patients in the FAS are summarized in Table 5.

- The median (range) age of the patients was 68 (18, 103) years. The proportion of patients older than 70 years of age were 46.6%, with 20.3% aged between 70 and 79 years and 26.3% aged 80 years or older at the time of nirmatrelvir/ritonavir initiation.
- Patients' sex was about evenly distributed with 52.9% being male.
- The mean (SD) BMI was 24.7 (4.35) kg/m^2. Among patients with BMI available (n=616), 33.4% and 19.3% of them had pre-obesity and obesity, respectively, based on the China guideline for BMI categorization.[15] The corresponding proportions were 32.5% and 10.7%, based on the WHO standard for BMI categorization.[16]
- Of the 678 patients with smoking status available, the majority (84.2%) were non-smokers; only 5.0% were ex-smokers and 10.8% were current smokers.
- Of the 912 (87.1%) patients with baseline eGFR recorded, 47.6% had a baseline eGFR of 90 mL/min/1.73m^2 or greater, 35.2% had a baseline eGFR between 60 and 90 mL/min/1.73m^2, 13.5% had a baseline eGFR between 30 and 60 mL/min/1.73m^2, and 3.7% of the patients had a baseline eGFR of less than 30 mL/min/1.73m^2.

Table 5. Baseline Demographic Characteristics - FAS

	Total (N=1,047)
Age at Treatment Initiation (Years)	
n (%) [1]	1,047 (100.0)
Mean (SD)	65.9 (19.08)
Median	68
Q1, Q3	53, 81
Min, Max	18, 103
18 ≤ Age <60 [2]	332 (31.7)
60 ≤ Age < 70 [2]	227 (21.7)
70 ≤ Age < 80 [2]	213 (20.3)
Age ≥ 80 [2]	275 (26.3)
Sex, n (%) [1]	1,047 (100.0)
Male	554 (52.9)
Female	493 (47.1)

Table 5. Baseline Demographic Characteristics - FAS

	Total (N=1,047)
BMI (kg/m^2)	
n (%) [1]	616 (58.8)
Mean (SD)	24.7 (4.35)
Median	24.2
Q1, Q3	21.6, 27.2
Min, Max	13.7, 48.9
Underweight (<18.5) a [2]	30 (4.9)
Normal Weight (18.5≤BMI<25.0) a [2]	320 (51.9)
Pre-Obesity (25.0≤BMI<30.0) a [2]	200 (32.5)
Obesity (≥30.0) a [2]	66 (10.7)
Underweight (<18.5) b [2]	30 (4.9)
Normal Weight (18.5≤BMI<24.0) b [2]	261 (42.4)
Pre-Obesity (24.0≤BMI<28.0) b [2]	206 (33.4)
Obesity (≥28.0) b [2]	119 (19.3)
Smoking Status, n (%) [1]	678 (64.8)
Non-Smoker [2]	571 (84.2)
Ex-Smoker [2]	34 (5.0)
Current Smoker [2]	73 (10.8)
Baseline eGFR Level [mL/min/1.73m^2], n (%) [1]	912 (87.1)
eGFR < 30 [2]	34 (3.7)
30 ≤ eGFR < 60 [2]	123 (13.5)
60 ≤ eGFR < 90 [2]	321 (35.2)
eGFR ≥ 90 [2]	434 (47.6)
Hepatic Impairment (Child Pugh Grade), n (%) [1] [3]	4 (0.4)
A – Mild [2]	1 (25.0)
B – Moderate [2]	2 (50.0)
C – Severe [2]	1 (25.0)

SD: Standard Deviation; Q1: First Quartile; Q3: Third Quartile; BMI: Body Mass Index.
[1] Percentages are calculated using the number of total patients in the Full Analysis Set (N) as the denominator.
[2] Percentages are calculated using number of non-missing value (n) as the denominator.
A: Based on the WHO standard (2010).
B: Based on the Criteria of Weight for Adults (2013) by the National Health Commission of the People's Republic of China.
[3] For patients with a medical history of liver cirrhosis only.
Source: Table 15.2

10.2.2. Baseline disease characteristics

Baseline disease characteristics of all 1,047 patients in the FAS are summarized in Table 6.

- The majority (96.0%) of the patients had COVID-19 severity as assessed by treating physicians and reviewed by study investigators, at baseline with 64.5% being mild and 29.3% being moderate. There were also 4.9% severe and 0.8% critical COVID-19 cases.

- The duration from the earliest on-record COVID-19 symptom/sign to patients initiating nirmatrelvir/ritonavir was calculated for 94.3% of the overall patients. Among them, the median (range) duration was 4.0 (1.0, 32.0) days, with 38.2% and 60.8% initiating nirmatrelvir/ritonavir within 3 and 5 days since the earliest on-record symptom/sign onset, respectively.

- The majority of the patients (90.5%) had positive SARS-CoV-2 test results at baseline, and 9.5% of the patients had a change in the latest baseline SARS-CoV-2 test to negative from an earlier positive test.

- The duration from the earliest on-record positive SARS-CoV-2 test result to patients initiating nirmatrelvir/ritonavir was calculated for 99.1% of the overall patients. Among them, the median (range) duration was 4.0 (1.0, 49.0) days.

- Of the 427 (40.8%) patients with serology status recorded at baseline, 46.8% were tested positive.

- Of the 768 (73.4%) patients with vaccination status recorded, the majority were vaccinated, with 3.0%, 26.0%, and 34.5% receiving one, two, and three or more doses of COVID-19 vaccine, respectively.

Table 6. Baseline Disease Characteristics - FAS

	Total (N=1,047)
Mapped COVID-19 Severity at Baseline, n (%) [1]	1,005 (96.0)
Mild [2]	648 (64.5)
Moderate [2]	294 (29.3)
Severe [2]	49 (4.9)
Critical [2]	8 (0.8)
Unknown [2]	6 (0.6)
Duration Since the Earliest On-Record COVID-19 Symptom/Sign (Days) [3]	
n (%) [1]	987 (94.3)
Mean (SD)	5.8 (4.55)
Median	4.0
Q1, Q3	3.0, 7.0
Min, Max	1.0, 32.0
≤3 Days (%) [2]	377 (38.2)

Table 6. Baseline Disease Characteristics - FAS

	Total (N=1,047)
>3 Days (%) [2]	610 (61.8)
≤5 Days (%) [2]	600 (60.8)
>5 Days (%) [2]	387 (39.2)
Baseline SARS-CoV-2 Test Status, n (%) [1] [4]	1,045 (99.8)
Positive [2]	946 (90.5)
Negative [2]	99 (9.5)
Duration Since the Earliest On-Record Positive SARS-CoV-2 Test (Days) [5]	
n (%) [1]	1,038 (99.1)
Mean (SD)	6.0 (5.26)
Median	4.0
Q1, Q3	2.0, 8.0
Min, Max	1.0, 49.0
Virus Variant, n (%) [1]	2 (0.2)
Alpha [2]	0 (-)
Beta [2]	2 (100.0)
Gamma [2]	0 (-)
Delta [2]	0 (-)
Omicron [2]	0 (-)
Other [2]	0 (-)
Unknown [2]	0 (-)
Serology Status, n (%) [1]	427 (40.8)
Positive [2]	200 (46.8)
Negative [2]	227 (53.2)
Vaccination Status, n (%) [1]	768 (73.4)
Unvaccinated [2]	247 (32.2)
Vaccinated with One Dose [2]	23 (3.0)
Vaccinated with Two Doses [2]	200 (26.0)
Vaccinated with Three Doses or More Than Three Doses [2]	265 (34.5)
Vaccinated with Unknown Doses [2]	13 (1.7)
Unspecified Vaccination Status [2]	20 (2.6)

SD: Standard Deviation; Q1: First Quartile; Q3: Third Quartile; eGFR: estimated Glomerular Filtration Rate
[1] Percentages are calculated using the number of total patients in the Full Analysis Set (N) as the denominator.

[2] Percentages are calculated using the number of non-missing value (n) as the denominator.
[3] Duration since the earliest on-record COVID-19 symptom/sign during baseline period (Days) = (Index date) – (Onset date of the first COVID-19 symptom/sign abstracted from the medical records during baseline period) +1
[4] The following rules in descending priority are used for derived SARS-CoV-2 test result:
- If the Ct for ORF or N gene is < 35, the ORF/N gene result is defined as Positive.
- If the Ct for both ORF and N gene is ≥ 35, the ORF/N gene result is defined as Negative.
- If either the Ct for ORF or N gene is ≥ 35, and the other one is documented as undetermined, the ORF/N gene finding is defined as Negative.
- If the Ct for ORF or N gene is missing, but an unspecified Ct result is available, then Ct < 35 is defined as Positive; otherwise, the result is Negative.
- If the Ct for both ORF/N gene and unspecified Ct result is missing, but a qualitative NAT result is available, then this qualitative NAT result is used as the test result.
- If the Ct for both ORF/N gene, unspecified Ct result and qualitative NAT result is all missing, then the antigen test result is used as the test result.
[5] Duration since the earliest on-record SARS-CoV-2 test during baseline period (Days) = (Index date) – (Specimen collection date of the earliest on-record positive SARS-CoV-2 test abstracted from the medical record) +1 if specimen collection date is available; otherwise, it is imputed by the test result date.
[6] The following rules are used for derived serology result based on IgM and IgG result:
a) If any value of IgG, IgM or unspecified serology type equaled to 'Positive' then set serology to 'Positive'.
b) If not a), then set to 'Negative'.
Source: Table 15.3

10.2.3. Baseline COVID-19 symptoms and signs

Symptoms/signs of COVID-19 defined in this study included 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. Among them, the targeted signs/symptoms of COVID-19 for analysis included 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.[4] Please refer to Section 9.3.3 of Appendix 2.1 PROTOCOL for further details.

Among all 1,047 patients in the FAS, 82.7% (866) were recorded as having at least one COVID-19 symptom/sign, and 78.9% (826) had at least one targeted COVID-19 symptom/sign at baseline.

Among the 866 patients with any COVID-19 symptoms/signs, Cough (77.6%) was the most frequently reported symptom/sign at baseline. Other frequently reported COVID-19 symptoms/signs were Sore Throat (26.2%), Fatigue (17.7%), Shortness of Breath or Difficulty Breathing (16.7%), Objective Fever (13.0%), Muscle or Body Aches (11.4%), Stuffy and Runny Nose (11.3%), and Subjective Fever (11.1%). Detailed severity distributions for these symptoms and signs based on medical records documented by treating physician are shown in Table 7.

Table 7. Baseline COVID-19 Symptoms/Signs - FAS

COVID-19 Symptoms/Signs at Baseline	Total (N=1,047)
Patients with Any COVID-19 Symptoms/Signs, N1 (%) [1]	866 (82.7)
Patients with Any Targeted COVID-19 Symptoms/Signs, N2 (%) [1]	826 (78.9)
[Cough], n (%) [2]	672 (77.6)
Mild [3]	30 (4.5)
Moderate [3]	0 (-)
Severe [3]	1 (0.1)
Unknown [3]	641 (95.4)
[Shortness of Breath or Difficulty Breathing], n (%) [2]	145 (16.7)
Mild [3]	6 (4.1)
Moderate [3]	1 (0.7)
Severe [3]	1 (0.7)
Unknown [3]	137 (94.5)
[Objective Fever], n (%) [2][4]	113 (13.0)
Mild [3]	1 (0.9)
Moderate [3]	2 (1.8)
Severe [3]	0 (-)
Unknown [3]	110 (97.3)

Table 7. Baseline COVID-19 Symptoms/Signs - FAS

COVID-19 Symptoms/Signs at Baseline	Total (N=1,047)
[Subjective Fever (e.g., Feeling Feverish)], n (%) [2]	96 (11.1)
Mild [3]	1 (1.0)
Moderate [3]	0 (-)
Severe [3]	0 (-)
Unknown [3]	95 (99.0)
[Fatigue], n (%) [2]	153 (17.7)
Mild [3]	3 (2.0)
Moderate [3]	1 (0.7)
Severe [3]	1 (0.7)
Unknown [3]	148 (96.7)
[Chills or Shivering], n (%) [2]	20 (2.3)
Mild [3]	1 (5.0)
Moderate [3]	0 (-)
Severe [3]	0 (-)
Unknown [3]	19 (95.0)
[Muscle or Body Aches], n (%) [2]	99 (11.4)
Mild [3]	0 (-)
Moderate [3]	0 (-)
Severe [3]	1 (1.0)
Unknown [3]	98 (99.0)
[Diarrhea], n (%) [2]	30 (3.5)
Mild [3]	1 (3.3)
Moderate [3]	0 (-)
Severe [3]	0 (-)
Unknown [3]	29 (96.7)
[Nausea], n (%) [2]	19 (2.2)
Mild [3]	1 (5.3)
Moderate [3]	0 (-)
Severe [3]	0 (-)
Unknown [3]	18 (94.7)
[Vomiting], n (%) [2]	22 (2.5)
Mild [3]	2 (9.1)
Moderate [3]	0 (-)
Severe [3]	0 (-)
Unknown [3]	20 (90.9)

Table 7. Baseline COVID-19 Symptoms/Signs - FAS

COVID-19 Symptoms/Signs at Baseline	Total (N=1,047)
[Headache], n (%) [2]	38 (4.4)
Mild [3]	1 (2.6)
Moderate [3]	0 (-)
Severe [3]	0 (-)
Unknown [3]	37 (97.4)
[Sore Throat], n (%) [2]	227 (26.2)
Mild [3]	4 (1.8)
Moderate [3]	0 (-)
Severe [3]	0 (-)
Unknown [3]	223 (98.2)
[Stuffy and Runny Nose], n (%) [2]	98 (11.3)
Mild [3]	1 (1.0)
Moderate [3]	0 (-)
Severe [3]	0 (-)
Unknown [3]	97 (99.0)

Unknown implies that a sign/symptom is recorded in the medical records, but the severity is not recorded.
COVID-19 Symptoms/Signs with partial or missing onset dates were identified as Baseline information based on assessment dates or hospitalization dates.
[1] Percentages are calculated using the number of total patients in the Full Analysis Set (N) as the denominator.
[2] Percentages are calculated using the number of patients with any COVID-19 symptoms/signs (N1) as the denominator.
[3] Percentages are calculated using the number of non-missing value (n) as the denominator.
[4] Objective fever reflects that patient had documented temperatures > 38 ˚C.
Source: Table 15.4

10.2.4. Prior treatment

The prior treatment information at baseline for the 1,047 patients in the FAS is summarized in Table 8.

COVID-19 related treatments were pre-defined and categorized in Section 9.3.5 of Appendix 2.1 PROTOCOL, mainly following the China Guideline on Diagnosis and Treatment Plan for Coronavirus Disease 2019 (9th version). Among 754 patients who had prior treatment information in the medical records, 18.0% (136) of them received COVID-19 related prior treatments. Specifically:

- No patients received antiviral therapies.
- 0.7% (5) patients received glucocorticoids.
- 17.9% (135) patients received COVID-19 related treatments other than antiviral therapies or immunotherapies. Among them, the majority (86.7%) received TCM. Oxygen supplemental therapies and anticoagulants were prescribed for 10.4% and 8.9% of the 135 patients, respectively.

Additionally, 43.1% (325) of the 754 patients reported utilization of other prior medications, including medications used for the treatment of conditions other than COVID-19 and those used for COVID-19 treatments by sites but were not protocol specified medication categories. Of note, there were 6.8% (22) of the 325 patients receiving prior corticosteroids for systemic use for health conditions other than COVID-19. See Table 15.5. Prior Treatment at Baseline – FAS in Section 15 for further details.

Table 8. Prior Treatment at Baseline - FAS

	Total (N=1,047)
Number of Patients without Prior Treatment Information Collected from Medical Records, N1	293
Number of Patients with Prior Treatment Information Collected from Medical Records, N2	754
Use of Prior COVID-19 Related Treatments, n (%) [1]	**136 (18.0)**
Antiviral Therapy, n (%) [1]	**0 (-)**
Monoclonal Antibodies (Amubarvimab/Romlusevimab Combination, Bebtelovimab, Casirivimab, Imdevimab, Regdanvimab, Bamlanivimab, Etesevimab, or Any Other Monoclonal Antibodies for COVID-19 Treatment) [2]	0 (-)
COVID-19 Human Immunoglobulin [2]	0 (-)
Convalescent Plasma [2]	0 (-)
Azvudine [2]	0 (-)
Remdesivir [2]	0 (-)
Molnupiravir [2]	0 (-)
Immunotherapy, n (%) [1]	**5 (0.7)**
Glucocorticoid [2]	5 (100.0)

Table 8. Prior Treatment at Baseline - FAS

	Total (N=1,047)
IL-6 Inhibitor (Tocilizumab, Sarilumab) [2]	0 (-)
Baricitinib, Tofacitinib [2]	0 (-)
Any Other COVID-19 Related Treatments, n (%) [1] [3]	**135 (17.9)**
Anticoagulant [2]	12 (8.9)
TCM [2]	117 (86.7)
Oxygen Supplemental Therapies [2]	14 (10.4)
Use of Other Prior Medication, n (%) [1][4]	**325 (43.1)**

IL-6: Interleukin 6; TCM: Traditional Chinese Medicine
Categorization of the prior COVID-19 related treatments is mainly based on the China Guideline on Diagnosis and Treatment Plan for Coronavirus Disease 2019 (9th version).
[1] Percentage of each category is calculated using N2 as the denominator.
[2] Percentage of each medication is calculated using the number of non-missing value (n) as the denominator.
[3] Any other COVID-19 related medications are recategorized following the definition in protocol.
[4] ATC level 2 is used for reporting 'Use of Other Prior Medication'.
Source: Table 15.5

10.2.5. Baseline comorbidities

The protocol specified baseline comorbidities of the 1,047 patients in the FAS are summarized in Table 9.

Over 70% (737) of the patients had at least one of the protocol specified comorbidities, which were the health condition related risk factors stated in the nirmatrelvir/ritonavir label. There were also 30.2% (316) and 7.1% (74) of the patients with at least two and three protocol specified comorbidities, respectively.

The majority of the patients had cardiovascular disease or hypertension (56.9%) or diabetes (22.1%). Chronic lung diseases (13.1%) were the third commonly recorded comorbidities, however, over a half of the 1,047 patients had no information on whether they had chronic lung diseases in the medical records.

The general medical histories of the 1,047 patients in the FAS are summarized by SOC and PT (see Table 15.18. Medical History by System Organ Class (SOC) and Preferred Term (PT) in Descending Frequency - FAS in Section 15). Also see Listing 15.12. Medical History - FAS in Section 15 for more details.

Table 9. Comorbidities at Baseline - FAS

Comorbidities	Total (N=1,047)
Number of Patients with Any Comorbidities, n (%)	737 (70.4)
Number of Patients with ≥2 Comorbidities, n (%)	316 (30.2)
Number of Patients with ≥3 Comorbidities, n (%)	74 (7.1)
Chronic Kidney Disease, n (%)	
Yes	57 (5.4)
No	183 (17.5)
No Information	807 (77.1)
Immunosuppression, n (%)	
Yes	11 (1.1)
No	159 (15.2)
No Information	877 (83.8)
Diabetes, n (%)	
Yes	231 (22.1)
No	537 (51.3)
No Information	279 (26.6)
Cardiovascular Disease or Hypertension, n (%)	
Yes	596 (56.9)
No	320 (30.6)

Table 9. Comorbidities at Baseline - FAS

Comorbidities	Total (N=1,047)
No Information	131 (12.5)
Chronic Lung Diseases, n (%)	
Yes	137 (13.1)
No	336 (32.1)
No Information	574 (54.8)
Sickle Cell Disease, n (%)	
Yes	0 (-)
No	89 (8.5)
No Information	958 (91.5)
Neurodevelopmental Disorders or Other Conditions that Confer Medical Complexity, n (%)	
Yes	11 (1.1)
No	95 (9.1)
No Information	941 (89.9)
Active Cancer, n (%)	
Yes	71 (6.8)
No	170 (16.2)
No Information	806 (77.0)
Medical-Related Technological Dependence Not Related to COVID-19, n (%)	
Yes	22 (2.1)
No	99 (9.5)
No Information	926 (88.4)

Percentages are calculated using the number of total patients in the Full Analysis Set (N) as the denominator.
Source: Table 15.6

10.3. Outcome data

The SAS consisted of all the 1,047 patients in the FAS (Table 2). Overall, 15.8% (165) of the patients in the SAS experienced AE with explicit attribution to nirmatrelvir/ritonavir (Table 10).

In the FAS, 95.7% (1,002) of the patients received uninterrupted single course of nirmatrelvir/ritonavir treatment and 4.3% (45) received interrupted treatment with nirmatrelvir/ritonavir (i.e., there were gaps in between consecutive days of treatment). Regarding monotherapy or combination therapy, 24.5% (256) of the patients received nirmatrelvir/ritonavir only and 75.5% (791) received nirmatrelvir/ritonavir in combination with COVID-19 related concomitant treatments (Table 14).

A total of 982 and 796 patients were included in the EAS1 and EAS, respectively (Table 2). The number of patients with available COVID-19 disease severity information at both baseline and observation periods were 941 in the EAS1 and 795 in the EAS (Table 16), respectively. 954 patients in the EAS1 and 772 patients in the EAS had positive SARS-CoV-2 test results at baseline and at least two post-baseline SARS-CoV-2 tests (Table 17). The number of patients with at least one targeted COVID-19 sign/symptom at baseline was 769 in the EAS1 and 609 in the EAS (Table 18).

The following sections present main results of safety, treatment patterns, and effectiveness of nirmatrelvir/ritonavir in the treatment of COVID-19 among adult Chinese patients in a real-world clinical setting.

10.4. Main results

10.4.1. Primary endpoints – safety

All safety results below were analyzed based on the SAS (n=1,047).

10.4.1.1. Adverse events with explicit attribution to nirmatrelvir/ritonavir

All AEs/SAEs with explicit attribution to nirmatrelvir/ritonavir were collected and reported as specified in Appendix 2.1 PROTOCOL. The AEs/SAEs with explicit attribution to nirmatrelvir/ritonavir as documented in the medical records by the treating physician and/or identified by investigators during their review were collected and reported. For further details on AE/SAE definition and assessment, see Section 9.4.1 of this report and Section 9.3.6 and Section 11 of Appendix 2.1 PROTOCOL.

All AEs mentioned within this section refer to AEs with explicit attribution to nirmatrelvir/ritonavir unless otherwise specified.

10.4.1.1.1. Overall summary of adverse events

An overall summary of AEs and SAEs with explicit attribution to nirmatrelvir/ritonavir is presented in Table 10.

During the observation period spanning a median (range) of 10.0 (1.0, 50.0) days (Table 3), 15.8% (165) of the 1,047 patients experienced at least one AE based on their medical records and investigators' review (see Section 9.4.1 for the procedure of AE/SAE data review, entry, and reporting).

Severe AEs occurred in 0.6% (6) of the patients, among whom 5 patients experienced Hypertension (All of them had an ongoing medical history of hypertension and experienced exacerbation of hypertension [investigator reported term] after nirmatrelvir/ritonavir initiation) and 1 experienced Diarrhoea. All these AEs were recovered/resolved except for 1 AE of Hypertension, which was recorded as ongoing. None of these AEs were serious. See Listing 15.2. Adverse Events (AEs) with Explicit Attribution to Nirmatrelvir/Ritonavir - SAS and Listing 15.12. Medical History - FAS in Section 15 for further details.

In addition, 0.6% (6) of the patients experienced AEs that led to discontinuation of nirmatrelvir/ritonavir treatment. By PT, 2 patients experienced Diarrhoea, 1 patient experienced Dizziness and Nausea, and 1 patient experienced Cough and Nausea. For the remaining 2 patients, one experienced Anaphylactic reaction and the other experienced Hepatic Function Abnormal. All these AEs were mild or moderate except for 1 Nausea and 1 Cough, for which the intensity information was missing. All these AEs were recovered/resolved. See Listing 15.2. Adverse Events (AEs) with Explicit Attribution to Nirmatrelvir/Ritonavir - SAS in Section 15 for further details.

There were no SAEs with explicit attribution to nirmatrelvir/ritonavir reported in this study.

Table 10. Overall Summary of Adverse Events (AEs) and Serious Adverse Events (SAEs) with Explicit Attribution to Nirmatrelvir/Ritonavir - SAS

	Total (N=1,047)
Number of AEs with Explicit Attribution to Nirmatrelvir/Ritonavir, n	362
Patients Experiencing AEs with Explicit Attribution to Nirmatrelvir/Ritonavir, n (%)	165 (15.8)
Patients Experiencing SAEs with Explicit Attribution to Nirmatrelvir/Ritonavir, n (%)	0 (-)
Patients Experiencing Severe AEs with Explicit Attribution to Nirmatrelvir/Ritonavir, n (%)	6 (0.6)
Patients with Nirmatrelvir/Ritonavir Discontinuation Due to AEs with Explicit Attribution to Nirmatrelvir/Ritonavir, n (%) [1]	6 (0.6)
Patients with Nirmatrelvir/Ritonavir Dose Reduction Due to AEs with Explicit Attribution to Nirmatrelvir/Ritonavir, n (%) [2]	0 (-)

AE: Adverse Event; SAE: Serious Adverse Event
Percentages are calculated using the number of total patients in the Safety Analysis Set (N) as the denominator.
[1] Dose discontinuation is defined by the wording of "stop", "discontinuation", or health condition description indicating a need of study drug discontinuation in the medical records, and/or be reviewed by the study investigator.
[2] Dose reductions are only recognized if they occur during the observation period, comparing with patient's initial dose.
Source: Table 15.7

10.4.1.1.2. Adverse events by System Organ Class and Preferred Term

The AEs with explicit attribution to nirmatrelvir/ritonavir (frequency ≥ 5 patients) based on medical records and investigators' assessment by SOC and PT are presented in Table 11.

Overall, AEs were frequently reported (≥ 4% of the patients) in the SOCs of Investigations (6.1%), Nervous System Disorders (5.9%), and Gastrointestinal Disorders (4.5%).

The most frequently reported AEs (≥ 2%) by PT were Dysgeusia (5.0%), Diarrhoea (2.4%) and Hypoalbuminaemia (2.0%) as assessed by investigators.

All these Hypoalbuminaemia AEs were reported from one site. Hypoalbuminaemia has been reported in patients with COVID-19 in several publications.[17, 18] A previous study among 663 patients with COVID-19 showed that 67.0% of the patients had a low level of serum albumin concentration. The reduced serum albumin concentration was associated with the aggravation of COVID-19.[19] It is considered that Hypoalbuminaemia in patients with COVID-19 might occur due to pulmonary capillary leakage of albumin,[20] or decreased hepatic synthesis of albumin and its increased catabolism after oxidation during the acute inflammation and COVID-19.[21] COVID-19 per se might serve as an alternative explanation for the reported Hypoalbuminaemia.

See Table 15.8 in Section 15 for a complete list of AEs by SOC and PT reported during the observation period.

Table 11. Adverse Events with Explicit Attribution to Nirmatrelvir/Ritonavir by System Organ Class and Preferred Term (≥ 5 patients) in Descending Order of Frequency - SAS

	Total (N=1,047)
	Number (%) of patients
Any AEs with Explicit Attribution to Nirmatrelvir/ritonavir	165 (15.8)
Investigations	64 (6.1)
Alanine aminotransferase increased	11 (1.1)
Platelet count increased	11 (1.1)
Lymphocyte count decreased	9 (0.9)
Aspartate aminotransferase increased	8 (0.8)
Prealbumin decreased	6 (0.6)
Blood creatinine increased	5 (0.5)
Gamma-glutamyltransferase increased	5 (0.5)
Neutrophil count decreased	5 (0.5)
Nervous System Disorders	62 (5.9)
Dysgeusia	52 (5.0)
Dizziness	7 (0.7)
Headache	5 (0.5)
Gastrointestinal Disorders	47 (4.5)
Diarrhoea	25 (2.4)

Table 11. Adverse Events with Explicit Attribution to Nirmatrelvir/Ritonavir by System Organ Class and Preferred Term (≥ 5 patients) in Descending Order of Frequency - SAS

	Total (N=1,047)
	Number (%) of patients
Nausea	7 (0.7)
Constipation	6 (0.6)
Metabolism and Nutrition Disorders	38 (3.6)
Hypoalbuminaemia	21 (2.0)
Hyperuricaemia	8 (0.8)
Hypoproteinaemia	5 (0.5)
Vascular Disorders	6 (0.6)
Hypertension	6 (0.6)

Medical Dictionary for Regulatory Activities (MedDRA) dictionary <MedDRA v26.0 - Mar 2023>.
Frequency is sorted in descending order by System Organ Class (SOC); within each SOC, frequency is sorted in descending order by preferred terms (PTs).
The patients with AEs SOC frequency ≥ 5 are included in this table.
A patient can have one or more PTs.
Percentages are calculated using the number of total patients in the Safety Analysis Set (N) as the denominator.
Source: Table 15.8

10.4.1.2. Summary of at-risk scenarios

A total of 86 (8.2%) patients experienced safety-related scenarios, as shown in Table 12.

Of these 1,047 patients, 8.1% (85) were reported to have overdose of nirmatrelvir/ritonavir based on the medical records and investigator review, with records of treatment duration showing longer than a 5-day course (which might span over 6 calendar days) or prescriptions of more than one carton (i.e., over 20 tablets for nirmatrelvir and/or 10 tablets for ritonavir cumulatively). One (1) patient was also recorded to receive three times daily use, while further dose information for nirmatrelvir and ritonavir was missing.

One (0.1%) patient experienced nirmatrelvir/ritonavir exposure during breast feeding.

No scenarios were associated with any AEs or SAEs.

No other at-risk scenarios were reported. Also see Table 15.10, Listing 3. Nirmatrelvir and Ritonavir Treatment - FAS and Listing 15.11. At-Risk Scenarios - SAS in Section 15.

Table 12. Summary of At-Risk Scenarios Involving Drug Exposure in Descending Order - SAS

Safety Related Scenarios	Total (N=1,047)
Patients Experience Safety Related Scenarios, n (%)	86 (8.2)
Patients Without Any Safety Related Scenarios, n (%)	958 (91.5)
Overdose, n (%)	85 (8.1)
Exposure During Breast Feeding, n (%)	1 (0.1)
Exposure During Pregnancy, n (%)	0 (-)
Lack of Efficacy, n (%)	0 (-)
Medication Error, n (%)	0 (-)
Misuse, n (%)	0 (-)
Occupational Exposure Associated with the Use of Nirmatrelvir/Ritonavir, n (%)	0 (-)

Percentages are calculated using the number of total patients in the Safety Analysis Set (N) as the denominator.
Overdose is administration of a quantity of a medicinal product per administration or cumulatively that is above the maximum recommended dose according to the approved product labelling.
Source: Table 15.10

10.4.1.3. Summary of deaths from any cause

Associated with the ICD waiver/data extraction (Figure 2), the sample selection process appeared to have included all 60 deaths that occurred during the observation period among the 3,155 (excluding 7 protocol deviations due to I/E criteria) eligible patients. Therefore, the IPTW method was applied to assign different weights based on Equation 1 (see Section 9.9.1) and patients extraction flow (see Figure 2) for dead patients and alive patients in the sample.

Of the total 1,047 patients in SAS, the sampling weight adjusted all-cause death rate was 1.9% (60) during the observation period.

- Regarding the death relationship to the AEs, of the 60 deaths, no death (0) was due to AEs with explicit attribution to nirmatrelvir/ritonavir. All deaths were associated with other health conditions including COVID-19.

- Regarding the death causes, of the 60 deaths, the sampling weight adjusted death rate was 0.2% (7) for COVID-19 being one of the causes, and 1.7% (53) for other causes, respectively.

Looking at the all-cause death rate by age subcategories, the sampling weight adjusted all-cause death rates were 5.1% in patients aged 80 years or older, 2.4% in patients aged between 70 and 79 years, 0.4% in patients aged between 60 and 69 years, and 0.2% in patients younger than 60 years, respectively.

It is worth noting that the death cases in this study were generally of older age. They also had several underlying comorbidities, and most of them were unvaccinated. See Listing 15.10. Deaths - SAS in Section 15 for further details.

Table 13. Summary of Deaths from Any Causes - SAS

	Total (N=1,047)
Number of Deaths from Any Cause, n (%) [1]	60 (1.9)
Death due to AEs with Explicit Attribution to Nirmatrelvir/Ritonavir [1] [2]	
Yes	0 (-)
No	60 (1.9)
Deaths with COVID-19 as One of Causes of Death [1] [3]	
Yes	7 (0.2)
No	53 (1.7)
Deaths from Any Causes by Age Group, n/N1 (%) [4]	
Age < 60 Years	2/332 (0.2)
60 ≤ Age < 70 Years	3/227 (0.4)
70 ≤ Age < 80 Years	15/213 (2.4)
Age ≥ 80 Years	40/275 (5.1)

Table 13. Summary of Deaths from Any Causes - SAS

	Total (N=1,047)

Due to partial ICD wavier, patients who died were more likely to be enrolled into the study than those who did not die. All deaths within the 3,155 eligible patients (who satisfied the I/E criteria and were included for sample selection) were included. To adjust for sampling bias, percentages are calculated using site as cluster factor and different sampling weights for alive and death patients.
[1] Adjusted percentages out of N.
[2] A death is counted if the patient had any AE with explicit attribution to nirmatrelvir/ritonavir and "resulted in death" as collected via the AE CRF.
[3] A death is counted if the patient with cause of death including "COVID-19" as collected via the Disposition CRF.
[4] Adjusted percentages out of N1.
Source: Table 15.17

10.4.2. Secondary endpoints – treatment pattern

10.4.2.1. Treatment pattern of nirmatrelvir/ritonavir

The treatment pattern of nirmatrelvir/ritonavir is summarized using FAS in Table 14.

In total, based on the total 941 patients with treatment dates available, 82.7% were treated with nirmatrelvir/ritonavir for a full course (5-6 days) and the median (range) treatment duration was 6.0 (1.0, 19.0) days.

Of the total 1,047 patients, 95.7% (1,002) patients received an uninterrupted single course of treatment with nirmatrelvir/ritonavir. Among the 897 patients with treatment dates available, the median (range) treatment duration of nirmatrelvir/ritonavir was 6.0 (1.0, 19.0) days with the majority (86.5%, 776 out of 897) being treated for 5 to 6 days.

Of the total 1,047 patients, 4.3% (45) patients received interrupted course of treatment with nirmatrelvir/ritonavir. Among the 44 patients with treatment dates available, the median (range) treatment duration was 11.0 (2.0, 18.0) days with the majority (65.9%, 29 out of 44) being treated for over 10 days. Patients with the interrupted treatment course were generally older (76 years of mean age and 81 years of median age) and had cardiovascular disease or hypertension (60.0%) (see Listing 15.3. Nirmatrelvir and Ritonavir Treatment - FAS in Section 15). Of the 45 patients with interrupted treatment course, 20 patients' disease progression details were available and all of them experienced disease progression or death from any cause (see Listing 15.6. COVID-19 Severity – FAS in Section 15). Thus, the longer term of nirmatrelvir/ritonavir treatment mainly occurred in older adults with comorbidities and might be due to disease progression during the observation period.

Furthermore, 24.5% (256) of the 1,047 patients received nirmatrelvir/ritonavir treatment only. Among the 224 patients with treatment dates available, the median (range) treatment duration of nirmatrelvir/ritonavir was 6.0 (2.0, 19.0) days with the majority (84.8%, 190 out of 224) being treated for 5 to 6 days.

The majority (75.5%; 791) of the 1,047 patients received nirmatrelvir/ritonavir in combination with other concomitant COVID-19 related treatments. Among the 717 patients with treatment dates available, the median (range) treatment duration of nirmatrelvir/ritonavir was 6.0 (1.0, 18.0) days with the majority (82.0%, 588 out of 717) being treated for 5 to 6 days.

Of note, the 5-6 days of treatment duration summarized above and in Table 14 is reflective of the 5-day treatment course as recommended by the nirmatrelvir/ritonavir label (i.e., 10 total doses). Patients with only 1 dose of nirmatrelvir/ritonavir on the index date (e.g., starting with the evening dose) had received the last dose on the 6th day from the index date, which counted 10 total doses to form a 5-day treatment course in compliant with the label.

It is also worth noting that 43 patients discontinued nirmatrelvir/ritonavir treatment due to reasons including AE with explicit attribution to nirmatrelvir/ritonavir (Table 10), death, physician decision, patient decision or other (e.g., underlying disease, use of other drugs/therapies). Regarding dose reduction, 9 patients were recorded to have dose reduction for nirmatrelvir due to physician decision and other reasons (e.g., hemodialysis or CCr < 60 ml/min) and 2 patients had dose reduction for ritonavir due to physician decision. Please refer to Listing 15.3. Nirmatrelvir and Ritonavir Treatment - FAS in Section 15 for further details.

Table 14. Treatment Pattern of Nirmatrelvir/Ritonavir - FAS

Treatment Pattern of Nirmatrelvir/Ritonavir	Total (N=1,047)
Patients Receiving Uninterrupted Treatment Course with Nirmatrelvir/Ritonavir, n (%) [1] [2]	1,002 (95.7)
Patients Receiving Interrupted Treatment Course with Nirmatrelvir/Ritonavir, n (%) [1] [3]	45 (4.3)
Patients Receiving Nirmatrelvir/Ritonavir Treatment Only, n (%) [1]	256 (24.5)
Patients Receiving Nirmatrelvir/Ritonavir with Concomitant COVID-19 Related Treatments, n (%) [1]	791 (75.5)
Overall Treatment Duration of Nirmatrelvir/Ritonavir (Without Regard to Treatment Course) (Days) [4]	
n (%) [1]	941 (89.9)
Mean (SD)	5.9 (2.03)
Median	6.0
Q1, Q3	5.0, 6.0
Min, Max	1.0, 19.0
1 to 4 Days [5]	79 (8.4)
5 to 6 Days [5]	778 (82.7)
7 to 10 Days [5]	31 (3.3)
>10 Days [5]	53 (5.6)
Treatment Duration of Nirmatrelvir/Ritonavir with Uninterrupted Treatment Course (Days) [2] [4]	
n (%) [1]	897 (85.7)
Mean (SD)	5.6 (1.51)
Median	6.0
Q1, Q3	5.0, 6.0
Min, Max	1.0, 19.0
1 to 4 Days [5]	78 (8.7)
5 to 6 Days [5]	776 (86.5)
7 to 10 Days [5]	19 (2.1)
>10 Days [5]	24 (2.7)
Treatment Duration of Nirmatrelvir/Ritonavir with Interrupted Treatment Course (Days) [3] [4]	
n (%) [1]	44 (4.2)
Mean (SD)	11.3 (3.27)
Median	11.0
Q1, Q3	10.0, 12.0
Min, Max	2.0, 18.0

[redacted]

Table 14. Treatment Pattern of Nirmatrelvir/Ritonavir - FAS

Treatment Pattern of Nirmatrelvir/Ritonavir	Total (N=1,047)
1 to 4 Days [5]	1 (2.3)
5 to 6 Days [5]	2 (4.5)
7 to 10 Days [5]	12 (27.3)
>10 Days [5]	29 (65.9)
Treatment Duration of Nirmatrelvir/Ritonavir (Only vs. with Concomitant COVID-19 Related Treatments)	
Nirmatrelvir/Ritonavir Only (Days) [4]	
n (%) [1]	224 (21.4)
Mean (SD)	5.9 (1.91)
Median	6.0
Q1, Q3	5.0, 6.0
Min, Max	2.0, 19.0
1 to 4 Days [5]	17 (7.6)
5 to 6 Days [5]	190 (84.8)
7 to 10 Days [5]	6 (2.7)
>10 Days [5]	11 (4.9)
Nirmatrelvir/Ritonavir with Concomitant COVID-19 Related Treatments (Days) [4]	
n (%) [1]	717 (68.5)
Mean (SD)	5.9 (2.06)
Median	6.0
Q1, Q3	5.0, 6.0
Min, Max	1.0, 18.0
1 to 4 Days [5]	62 (8.6)
5 to 6 Days [5]	588 (82.0)
7 to 10 Days [5]	25 (3.5)
>10 Days [5]	42 (5.9)

SD: Standard Deviation; Q1: First Quartile; Q3: Third Quartile.
[1] Percentages are calculated using the number of total patients in the Full Analysis Set (N) as the denominator.
[2] Uninterrupted treatment course indicates that patients received nirmatrelvir/ritonavir for consecutive days.
[3] Interrupted treatment course indicates that patients received nirmatrelvir/ritonavir with gaps in between consecutive days of treatment.
[4] Treatment duration = (End date of nirmatrelvir/ritonavir treatment) – (Index date) +1.
If there are overlaps between the treatment records and following records, the latest treatment end date will be selected as the end date of this treatment course for treatment duration calculation. The treatment duration of patients with interrupted treatment course is calculated by sum the treatment

duration of each treatment course. For patients with missing treatment end dates, this duration is not calculated.
[5] Percentages are calculated using the number of non-missing value (n) as the denominator.

Source: Table 15.11

10.4.2.2. Concomitant COVID-19 related treatments

In the FAS, 75.5% (791) of the patients received concomitant COVID-19 related treatments as pre-specified in protocol, as shown in Table 14. COVID-19 related treatments were pre-defined and categorized in Section 9.3.5 of Appendix 2.1 PROTOCOL, mainly following the China Guideline on Diagnosis and Treatment Plan for Coronavirus Disease 2019 (9th version).

Table 15 shows further details of the concomitant COVID-19 related treatments among the 791 patients. Specially, among the total 1,047 patients:

- 0.4% (4) patients received COVID-19 human immunoglobulin, with a median (range) treatment duration of 5.0 (4.0, 6.0) days.
- 10.5% (110) patients were treated with glucocorticoid for COVID-19, with a median (range) treatment duration of 4.0 (1.0, 49.0) days among the 99 patients with available information on treatment duration.
- 62.2% (651) received other COVID-19 related treatments. TCM was the most frequently used treatment by 55.4% of the total patients, and the median (range) treatment duration was 5.0 (1.0, 33.0) days. Anticoagulant and oxygen supplemental therapies were prescribed for 28.8% and 21.2% of the total patients during the observation period, with a median treatment duration being 9.0 (1.0, 42.0) and 10.0 (1.0, 50.0) days, respectively.

See Listing 15.9. Concomitant Treatments - FAS in Section 15 for more details on concomitant COVID-19 related treatments.

Table 15. Concomitant COVID-19 Related Treatments - FAS

	Total (N=1,047)
Patients Receiving Concomitant COVID-19 Related Treatments, n (%)	791 (75.5)
Antiviral therapy	4 (0.4)
[COVID-19 Human Immunoglobulin]	4 (0.4)
Treatment duration (days)	
n (%)	4 (0.4)
Mean (SD)	5.0 (1.15)
Median	5.0
Q1, Q3	4.0, 6.0
Min, Max	4.0, 6.0
Immunotherapy	110 (10.5)
[Glucocorticoid]	110 (10.5)
Treatment duration (days)	
n (%)	99 (9.5)
Mean (SD)	5.9 (6.68)

Table 15. Concomitant COVID-19 Related Treatments - FAS

	Total (N=1,047)
Median	4.0
Q1, Q3	2.0, 7.0
Min, Max	1.0, 49.0
Any other COVID-19 related treatments	651 (62.2)
[Anticoagulant]	302 (28.8)
Treatment duration (days)	
n (%)	298 (28.5)
Mean (SD)	9.8 (6.25)
Median	9.0
Q1, Q3	5.0, 13.0
Min, Max	1.0, 42.0
[Traditional Chinese Medicine (TCM)]	580 (55.4)
Treatment duration (days)	
n (%)	452 (43.2)
Mean (SD)	6.5 (5.39)
Median	5.0
Q1, Q3	2.0, 10.0
Min, Max	1.0, 33.0
[Oxygen supplemental therapies]	222 (21.2)
Treatment duration (days)	
n (%)	218 (20.8)
Mean (SD)	11.3 (7.65)
Median	10.0
Q1, Q3	6.0, 15.0
Min, Max	1.0, 50.0

SD: Standard Deviation; Q1: First Quartile; Q3: Third Quartile.
Categorization of the concomitant COVID-19 related treatments is mainly based on the China Guideline on Diagnosis and Treatment Plan for Coronavirus Disease 2019 (9th version).
Percentages are calculated using the number of total patients in the Full Analysis Set (N) as the denominator.
Source: Table 15.12

10.4.2.3. Other concomitant medications

See Table 15.13. Other Concomitant Medications in Descending Frequency - FAS in Section 15 for other concomitant medications of the 1,047 patients in the FAS. In the FAS, 94.0% (984) patients received other concomitant medications including medications used for the treatment of conditions other than COVID-19 and those used for COVID-19 treatments by sites but were not protocol specified medication categories. Specifically, cough and cold preparations (45.2%), unspecified herbal and traditional medicine (45.0%), and antithrombotic agents (35.8%) were the top three frequently used medication categories.

Of note, there were patients receiving heparin (i.e., anticoagulants), corticosteroids (for systemic use), and oxygen supplement therapies for health conditions other than COVID-19. See Listing 15.9. Concomitant Treatments – FAS in Section 15 for more details.

10.4.3. Secondary endpoints – effectiveness

The EAS1 and EAS were used to summarize the effectiveness results in this study. See Section 9.9.2 for definitions of EAS1 and EAS in detail.

10.4.3.1. COVID-19 disease severity progression

Results of COVID-19 severity progression are summarized in Table 16.

Of the 941 patients who had COVID-19 disease severity at both baseline and observation periods in the EAS1, the sampling weight adjusted proportion of patients with COVID-19 disease progression to severe/critical or death from any cause was 5.3% (n=80, 95% CI: 0.0%–11.8%). Among them,

- Thirty-three (33) patients experienced COVID-19 progression from mild/moderate to severe/critical illness and none of these cases resulted in death.
- Another 47 patients died from any cause, with 30, 7, 8, and 2 being mild, moderate, severe, and critical COVID-19 at baseline, respectively. Similar to the death rate findings in SAS (see Section 10.4.1), most of the death cases in EAS1 were older people who had several comorbidities/complications.
    - Among the 47 death cases, 6 patients (3 mild and 3 severe COVID-19 at baseline) died withCOVID-19 being one of the causes. See Listings 15.6. COVID-19 Severity - FAS and 15.10. Death - SAS.

Among all the 796 patients who had COVID-19 disease severity at both baseline and observation periods in the EAS, the sampling weight adjusted proportion of patients with COVID-19 disease progression to severe/critical or death was 5.8% (n=70, 95% CI: 0.0%–13.1%). Among them,

- Thirty-three (33) patients experienced COVID-19 progression from mild/moderate to severe/critical illness and none of these cases resulted in death.
- Another 37 patients died from any cause, with 30 and 7 being classified as mild and moderate COVID-19 at baseline, respectively. Similar to the death rate findings in SAS

(see Section 10.4.1), most of the death cases in EAS were older (i.e., ≥ 70 years of age) and had several comorbidities/complications.

- Among the 37 death cases, 3 patients (all with mild COVID-19 at baseline) died with COVID-19 being one of the causes. See Listings 15.6. COVID-19 Severity - FAS and 15.10. Death - SAS.

10.4.3.2. Two consecutive negative SARS-CoV-2 test results / cycle threshold (Ct) ≥ 35

There were 954 and 772 patients with positive SARS-CoV-2 test results at baseline and at least two post-baseline SARS-CoV-2 tests in EAS1 and EAS, respectively. In EAS1, 95.1% (907) of the 954 patients achieved two consecutive negative SARS-CoV-2 test results / Ct value ≥ 35 after nirmatrelvir/ritonavir initiation. In EAS, the corresponding proportion was 95.9% (740) (see Table 16).

Table 16. Proportions of Patients with COVID-19 Disease Severity Progressed or Death from Any Cause and Patients with Two Consecutive Negative SARS-CoV-2 Tests - EAS1/EAS

	EAS1 (N=982)	EAS (N=796)
Patients with COVID-19 Disease Severity Information at Baseline and COVID-19 Disease Severity/Death Information in Observation Period, N1	941	796
Patients with COVID-19 Disease Progressed to Severe/Critical or Death from Any Cause [1]		
n	80	70
Adjusted proportion (95% CI), % [2]	5.3 (0.0-11.8)	5.8 (0.0-13.1)
Patients with COVID-19 Disease Progressed to Severe/Critical, n	33	33
Mild/Moderate Progressed to Severe	26	26
Mild/Moderate Progressed to Critical	7	7
Patients with Death from Any Cause, n	47	37
Mild at Baseline	30	30
Moderate at Baseline	7	7
Severe at Baseline	8	-
Critical at Baseline	2	-
Patients with Positive Baseline and At Least Two Post-Baseline SARS-CoV-2 Tests, N2 [3]	954	772
Patients with Two Consecutive Negative SARS-CoV-2 Test Results / Ct ≥ 35 Post-Baseline, n (%) [4]	907 (95.1)	740 (95.9)

CI: Confidence Interval; Ct: Cycle threshold; EAS1: Effectiveness Analysis Set 1; EAS: Effectiveness Analysis Set
Baseline is defined as the severity level / derived SARS-CoV-2 test assessed on or closest prior to the index date.
[1] Patients with COVID-19 disease severity progressed/death are counted only once at the maximum severity.
[2] Due to partial ICD wavier, patients who died were more likely to be enrolled into the study than those who did not die. Percentages and confidence intervals out of N1 are calculated using site as cluster factor and different sampling weights for alive and death patients to adjust for sampling bias.
[3] The following rules in descending priority are used for derived SARS-CoV-2 test result:
- If the Ct for ORF or N gene is < 35, the ORF/N gene result is defined as Positive.
- If the Ct for both ORF and N gene is ⩾ 35, the ORF/N gene result is defined as Negative.

- If either the Ct for ORF or N gene is ≥ 35, and the other one is documented as undetermined, the ORF/N gene finding is defined as Negative.
- If the Ct for ORF or N gene is missing, but an unspecified Ct result is available, then Ct < 35 is defined as Positive; otherwise, the result is Negative.
- If the Ct for both ORF/N gene and unspecified Ct result is missing, but a qualitative NAT result is available, then this qualitative NAT result is used as the test result.
- If the Ct for both ORF/N gene, unspecified Ct result and qualitative NAT result is all missing, then the antigen test result is used as the test result.
[4] Percentages are calculated using N2 as the denominator.
Source: Table 15.14

10.4.3.3. Time to two consecutive negative SARS-CoV-2 test results

The time to two consecutive negative SARS-CoV-2 test results / Ct ≥ 35 in EAS1 and EAS are summarized in Table 17 and Figure 3.

Of 954 patients with positive SARS-CoV-2 test results at baseline and at least two post-baseline SARS-CoV-2 tests in EAS1, 95.1% (907) patients achieved two consecutive negative SARS-CoV-2 test results, while 4.9% (47) patients were censored (i.e., those who died during hospitalization with only one or none negative test results, had only one negative test record but was discharged, had two negative test records but on the same calendar day, or had two test records but missing test results). The median (Q1, Q3) time to two consecutive negative SARS-CoV-2 test results was 7.0 (5.0, 11.0) days within a median (range) observation period of 11.0 (3.0, 50.0) days.

In EAS, 772 patients had both positive SARS-CoV-2 tests at baseline and at least two post-baseline SARS-CoV-2 tests, of which 95.9% (740) achieved two consecutive negative SARS-CoV-2 test results and 4.1% (32) were censored (i.e., those who died during hospitalization with only one or none negative test results, had only one negative test record but was discharged, had two negative test records but on the same calendar day, or had two tests records but missing test results). The median (Q1, Q3) time to two consecutive negative SARS-CoV-2 test results was 8.0 (5.0, 11.0) days within a median (range) observation period of 11.0 (3.0, 50.0) days.

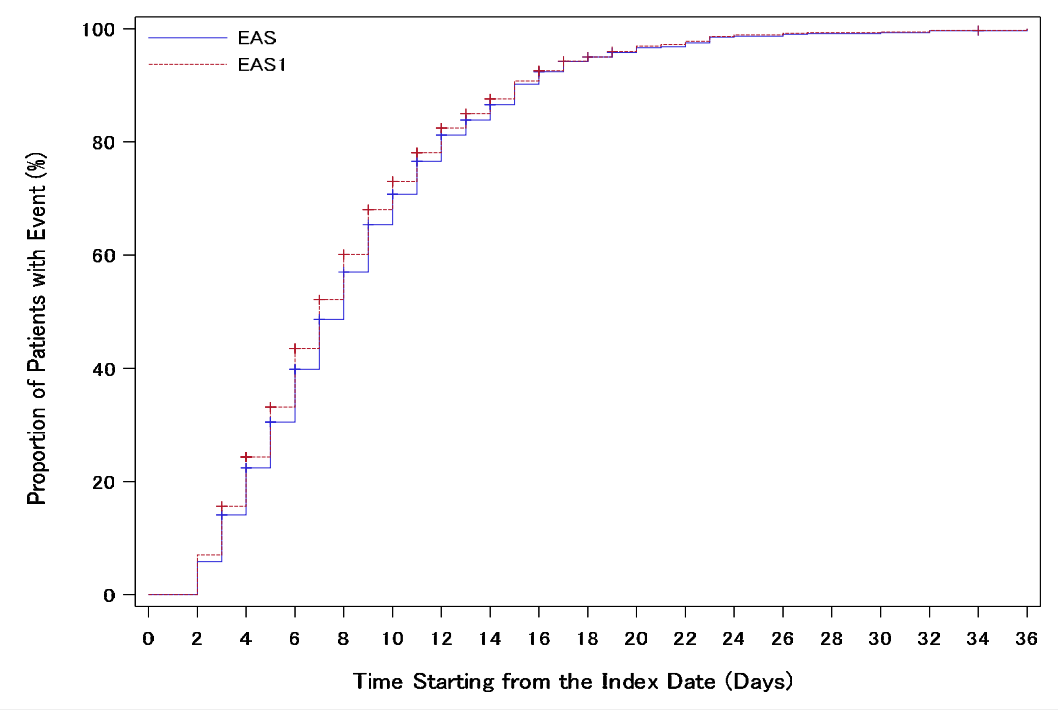
Both analysis sets indicated that 75% of the patients returned to negative SARS-CoV-2 test by 11 days post initiation of nirmatrelvir/ritonavir.

Table 17. Time to Two Consecutive Negative SARS-CoV-2 Test Results / Ct ≥ 35 Summary - EAS1/EAS

	EAS1 (N=982)	EAS (N=796)
Two Consecutive Negative SARS-CoV-2 Test Results / Ct ≥ 35		
Number of Patients with Positive Baseline and At Least Two Post-Baseline SARS-CoV-2 Tests, N1	954	772
Cumulative Number of Patients with Two Consecutive Negative SARS-CoV-2 Test Results Post Baseline, n (%) [1]	907 (95.1)	740 (95.9)
Cumulative Number of Patients Censored, n (%) [1]	47 (4.9)	32 (4.1)
Time to Event (Days) [2] [3]		
Q3 (95% CI)	11.0 (10.0; 11.0)	11.0 (11.0; 12.0)
Median (95% CI)	7.0 (7.0; 8.0)	8.0 (7.0; 8.0)
Q1 (95% CI)	5.0 (4.0; 5.0)	5.0 (4.0; 5.0)
Duration of Observation Period (Days) [4]		
Median	11.0	11.0
Q1, Q3	8.0, 15.0	8.0, 15.0
Min, Max	3.0, 50.0	3.0, 50.0

Ct: Cycle threshold; Q1: First Quartile; Q3: Third Quartile; CI: Confidence Interval; EAS1: Effectiveness Analysis Set 1; EAS: Effectiveness Analysis Set
The following rules in descending priority are used for derived SARS-CoV-2 test result:
- If the Ct for ORF or N gene is < 35, the ORF/N gene result is defined as Positive.
- If the Ct for both ORF and N gene is ≥ 35, the ORF/N gene result is defined as Negative.
- If either the Ct for ORF or N gene is ≥ 35, and the other one is documented as undetermined, the ORF/N gene finding is defined as Negative.
- If the Ct for ORF or N gene is missing, but an unspecified Ct result is available, then Ct < 35 is defined as Positive; otherwise, the result is Negative.
- If the Ct for both ORF/N gene and unspecified Ct result is missing, but a qualitative NAT result is available, then this qualitative NAT result is used as the test result.
- If the Ct for both ORF/N gene, unspecified Ct result and qualitative NAT result is all missing, then the antigen test result is used as the test result.
[1] Percentages are calculated using N1 as the denominator.
[2] Time to event (Days) is the time to two consecutive negative SARS-CoV-2 test results / Ct ≥ 35 , which is calculated as (the first date of negative SARS-CoV-2 test/ Ct ≥ 35 from two consecutive negative SARS-CoV-2 test results / Ct ≥ 35 that specimens collected in two different calendar days) - (Index date) +1 for patients with at least two SARS-CoV-2 tests after initiation of nirmatrelvir/ritonavir treatment. For a patient without the event, it will be calculated as (End of observation date) – (Index date) +1 and be considered as a censoring time.
[3] Q1, Median and Q3 are obtained from Kaplan Meier (KM) method and CI is based on the Brookmeyer-Crowley method.
[4] Duration of Observation Period (Days) = (End of observation date) – (Index date) + 1.
Source: Table 15.15

Figure 3. Time to Two Consecutive Negative SARS-CoV-2 Test Results / Ct ≥ 35 (Days) (EAS and EAS1)



	Study day	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
EAS1	Number of patients at risk	954	954	803	626	443	291	192	127	76	44	29	20	10	8	5	5	4	2	1
	Number of patients with event	0	0	149	315	492	639	730	790	838	866	879	888	898	900	903	903	904	906	906
	Number of patients censored	0	0	2	13	19	24	32	37	40	44	46	46	46	46	46	46	46	46	47
EAS	Number of patients at risk	772	772	661	530	387	259	171	114	67	37	25	19	9	8	5	5	4	2	1
	Number of patients with event	0	0	109	235	373	499	582	635	679	706	716	722	732	733	736	736	737	739	739
	Number of patients censored	0	0	2	7	12	14	19	23	26	29	31	31	31	31	31	31	31	31	32

Source: Figure 15.1

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

The time to alleviation of all targeted COVID-19 signs and symptoms in EAS1 and EAS are summarized in Table 18 and Figure 4.

In EAS1, among the 796 patients with at least one targeted COVID-19 symptom/sign at baseline, 54.0% of the patients achieved alleviation of all the baseline targeted symptoms and signs, while 46.0% were censored (i.e., alleviation of all targeted COVID-19 signs and symptoms was not observed). The median time to alleviation of all targeted COVID-19 symptoms and signs was 9.0 (95% CI: 8.0-10.0) days during the observation period with a median (range) of 11.0 (1.0, 37.0) days.

In EAS, among the 609 patients with at least one targeted COVID-19 symptom/sign at baseline, 55.2% of the patients achieved alleviation of all the baseline targeted symptoms and signs, while 44.8% were censored (i.e., alleviation of all targeted COVID-19 signs and symptoms was not observed). The median time to alleviation of all targeted COVID-19 symptoms and signs was 9.0 (95% CI: 8.0-10.0) days during the observation period with median (range) of 11.0 (1.0, 37.0) days.

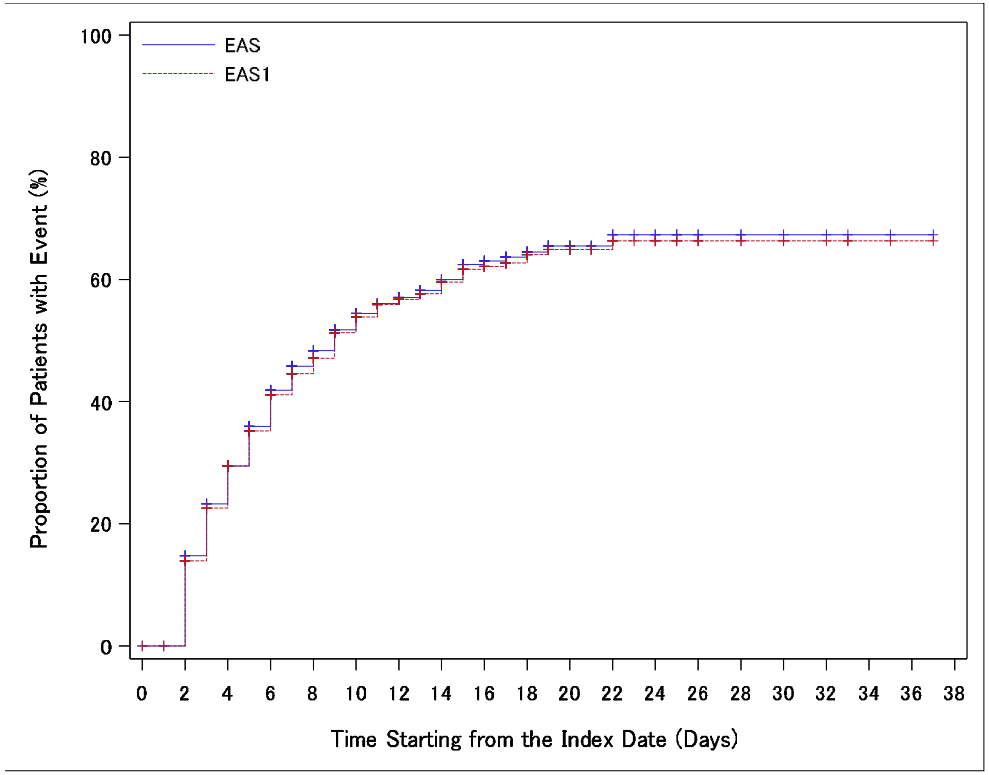
Table 18. Time to Alleviation of All Targeted COVID-19 Signs and Symptoms Summary - EAS1/EAS

	EAS1 (N=982)	EAS (N=796)
All Targeted COVID-19 Signs and Symptoms		
Number of Patients with At Least One Targeted COVID-19 Sign and Symptom at Baseline, N1	769	609
Cumulative Number of Patients with Alleviation of All the Baseline Targeted Signs/Symptoms, n (%) [1]	415 (54.0)	336 (55.2)
Cumulative Number of Patients Censored, n (%) [1]	354 (46.0)	273 (44.8)
Time to Event (Days) [2] [3]		
Q3 (95% CI)	NA (NA; NA) [4]	NA (NA; NA) [4]
Median (95% CI)	9.0 (8.0; 10.0)	9.0 (8.0; 10.0)
Q1 (95% CI)	4.0 (3.0; 4.0)	4.0 (3.0; 4.0)
Duration of Observation Period (Days) [5]		
Median	11.0	11.0
Q1, Q3	8.0, 14.0	8.0, 15.0
Min, Max	1.0, 37.0	1.0, 37.0

Q1: First Quartile; Q3: Third Quartile; CI: Confidence Interval; EAS1: Effectiveness Analysis Set 1; EAS: Effectiveness Analysis Set
COVID-19 signs/symptoms with partial or missing onset dates were identified onset at baseline based on assessment dates or hospitalization dates.
[1] Percentages are calculated using N1 as the denominator.
[2] Time to event (Days) is the time to alleviation of all baseline targeted COVID-19 signs and symptoms, which is calculated as the last date of (Alleviation dates for all targeted COVID-19 signs and symptoms observed at baseline) - (Index date) +1 for patient with alleviation of all baseline

targeted signs and symptoms observed. For a patient without the event, it will be calculated as (End of observation date) – (Index date) +1 and be considered as a censoring time.
[3] Q1, Median and Q3 are obtained from Kaplan Meier (KM) method and CI is based on the Brookmeyer-Crowley method.
[4] NA = not available. The observation period is not long enough to observe the point estimator and upper bound of the 95% CI.
[5] Duration of Observation Period (Days) = (End of observation date) – (Index date) + 1.
Source: Table 15.16

Figure 4. Time to Alleviation of All Targeted COVID-19 Signs and Symptoms (EAS and EAS1)



	Study day	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38
EAS1	Number of patients at risk	769	768	586	449	350	247	159	111	81	54	35	25	18	12	9	7	5	2	1	0
	Number of patients with event	0	0	173	267	331	371	393	399	409	411	414	414	415	415	415	415	415	415	415	415
	Number of patients censored	0	1	10	53	88	151	217	259	279	304	320	330	336	342	345	347	349	352	353	354
EAS	Number of patients at risk	609	608	460	357	274	200	132	93	66	45	27	19	14	9	7	5	4	2	1	0
	Number of patients with event	0	0	141	216	270	299	316	322	331	333	335	335	336	336	336	336	336	336	336	336
	Number of patients censored	0	1	8	36	65	110	161	194	212	231	247	255	259	264	266	268	269	271	272	273

Source: Figure 15.2

10.5. Other analyses

10.5.1. Subgroup analyses

Subgroup analyses were performed based on baseline vaccination status (vaccinated, unvaccinated), baseline COVID-19 severity (mild to moderate, severe to critical), and baseline eGFR levels (< 30, ≥ 30 to < 60, ≥ 60 to < 90, ≥ 90 [mL/min/1.73m^2]) for key safety and treatment pattern endpoints. For key effectiveness endpoints, subgroup analyses were additionally performed based on age groups (< 60, ≥ 60 to < 70, ≥ 70 to < 80, ≥ 80 years), duration since the earliest on-record COVID-19 symptom/sign till nirmatrelvir/ritonavir treatment (≤ 5 days, > 5 days) and a series of COVID-19 risk factors as defined in Section 9.9.4.

10.5.1.1. Subgroup analysis for adverse events and serious adverse events

Table 19 shows subgroup analysis results for the summary of AEs and SAEs with explicit attribution to nirmatrelvir/ritonavir.

The proportions of patients experiencing AEs with explicit attribution to nirmatrelvir/ritonavir were 11.7% in the unvaccinated subgroup and 22.4% in the vaccinated subgroup, mainly because the majority of AEs with explicit attribution to nirmatrelvir/ritonavir were reported by the site with a higher proportion of vaccinated patients. The proportions of severe AEs and AEs leading to nirmatrelvir/ritonavir discontinuation observed in both subgroups were low and similar. No SAEs reported in either subgroup.

AEs occurred in 9.8%, 20.2%, and 19.1% of the patients within the subgroups of 30 ≤ eGFR < 60 mL/min/1.73m^2, 60 ≤ eGFR < 90 mL/min/1.73m^2, and eGFR ≥ 90 mL/min/1.73m^2, respectively. In a small sample size of patients with baseline eGFR < 30 mL/min/1.73m^2 (N1=34), no AEs were reported.

Table 19. Summary of Adverse Events (AEs) and Serious Adverse Events (SAEs) with Explicit Attribution to Nirmatrelvir/Ritonavir - Subgroup Analysis SAS

	Number of Patients in Each Subgroup, N1	Patients Experiencing AEs with Explicit Attribution to Nirmatrelvir/Ritonavir, n (%)	Patients Experiencing SAEs with Explicit Attribution to Nirmatrelvir/Ritonavir, n (%)	Patients Experiencing Severe AEs with Explicit Attribution to Nirmatrelvir/Ritonavir, n (%)	Patients with Nirmatrelvir/ritonavir Discontinuation Due to AEs with Explicit Attribution to Nirmatrelvir/Ritonavir, n (%) [1]	Patients with Nirmatrelvir/ritonavir Dose Reduction Due to AEs with Explicit Attribution to Nirmatrelvir/Ritonavir, n (%) [2]
Vaccination Status						
Unvaccinated	247	29 (11.7)	0 (-)	2 (0.8)	2 (0.8)	0 (-)
Vaccinated	501	112 (22.4)	0 (-)	3 (0.6)	4 (0.8)	0 (-)
Mapped COVID-19 Severity at Baseline						
Mild to Moderate	942	156 (16.6)	0 (-)	5 (0.5)	5 (0.5)	0 (-)
Severe to Critical	57	7 (12.3)	0 (-)	1 (1.8)	1 (1.8)	0 (-)
Baseline eGFR Level [mL/min/1.73m^2]						
eGFR＜30	34	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)
30 ≤ eGFR＜60	123	12 (9.8)	0 (-)	1 (0.8)	1 (0.8)	0 (-)
60 ≤ eGFR＜90	321	65 (20.2)	0 (-)	5 (1.6)	4 (1.2)	0 (-)
eGFR ≥ 90	434	83 (19.1)	0 (-)	0 (-)	1 (0.2)	0 (-)

SAE: Serious Adverse Event; eGFR: estimated Glomerular Filtration Rate
Percentages are calculated using the number of patients in each subgroup (N1) as denominator.

[1] Dose discontinuation is defined by the wording of "stop", "discontinuation", or health condition description indicating a need of study drug discontinuation in the medical records, and/or be reviewed by the study investigator.
[2] Dose reductions are only recognized if they occur during the observation period, comparing with patient's initial dose.
Source: Table 15.7.1

10.5.1.2. Subgroup analysis for treatment pattern

Table 15.11.1. Treatment Pattern of Nirmatrelvir/Ritonavir - Subgroup Analysis - FAS in Section 15 shows subgroup analysis results for treatment patterns of nirmatrelvir/ritonavir.

The median treatment duration of nirmatrelvir/ritonavir ranged from 5 to 6 days across subgroups of patients with different baseline vaccination status (vaccinated, unvaccinated), baseline COVID-19 severity (mild to moderate, severe to critical), and baseline eGFR level (< 30, ≥ 30 to < 60, ≥ 60 to < 90, ≥ 90 [mL/min/1.73m^2]).

The proportion of patients receiving nirmatrelvir/ritonavir with COVID-19 related concomitant treatments was higher among baseline vaccinated patients (80.8% compared to 69.6% among unvaccinated patients) and patients with mild to moderate baseline COVID-19 (77.3% compared to 59.6% among patients with severe/critical COVID-19]), while this proportion was lower (55.9%) among patients with baseline eGFR < 30 mL/min/1.73m^{2}compared to patients with higher baseline eGFR levels (72.4%, 75.1%, 77.9% for patients with eGFR being ≥ 30 to < 60, ≥ 60 to < 90, ≥ 90 mL/min/1.73m^2, respectively).

10.5.1.3. Subgroup analysis for effectiveness

Subgroup analysis results based on EAS1

Table 20 shows the subgroup analysis results for COVID-19 severity progression or death from any cause and post-baseline SARS-CoV-2 tests in EAS1.

- As expected, the sampling weight adjusted proportions of patients with COVID-19 disease progression or death from any cause were higher among patients:
    - aged 70 years or older (8.9% [95% CI: 0.8% to 17.0%] for ≥ 70 to < 80 years and 10.8% [95% CI: 0% to 22.9%] for ≥ 80 years, compared to 0.7% [95% CI: 0% to 1.9%] and 2.8% [95% CI: 0% to 7.1%] for < 60 years and ≥ 60 to < 70 years, respectively),
    - unvaccinated patients (6.3% [95% CI: 0.12% to 12.49%] compared to 1.6% [95% CI: 0.00% to 4.17%] for vaccinated patients),
    - patients with severe to critical COVID-19 at baseline (7.1% [95% CI: 0.00% to 16.37%] compared to 5.2% [95% CI: 0.00% to 11.82%] for mild to moderate illness patients), and
    - patients with baseline eGFR <60 (20.2% [95% CI: 2.75% to 37.62%] for eGFR < 30 and 12.9% [95% CI: 0.00% to 27.98%] for eGFR 30 ≤ eGFR < 60 compared to 5.8% [95% CI: 0.00% to 12.87%] for 60 ≤ eGFR < 90 and 2.1% [95% CI: 0.00% to 5.36%] for eGFR ≥ 90 mL/min/1.73m^2).
- No evident difference was seen between patients initiating nirmatrelvir/ritonavir within 5 days from the onset of COVID-19 symptoms/signs (analyzed per the earliest on-record onset dates) and those initiating nirmatrelvir/ritonavir later.

Regarding proportion of patients achieving two consecutive negative SARS-CoV-2 test results / Ct ≥ 35 during the observation period, the proportion appeared to be lower for patients with severe to critical baseline COVID-19 (84.0% compared to 96.1% for patients with mild to moderate COVID-19) and patients with baseline eGFR < 30 mL/min/1.73m^2 (82.1% compared to 95.5%, 92.8%, and 97% for patients with baseline eGFR being ≥ 30 to < 60, ≥ 60 to < 90, ≥ 90 mL/min/1.73m^2, respectively). No evident differences were seen among subgroups of patients by age, vaccination status, and duration of nirmatrelvir/ritonavir treatment since onset of the earliest on-record COVID-19 symptoms/signs.

Regarding time to two consecutive negative results, consistent with the natural decline in viral loads over a longer baseline period, patients initiating nirmatrelvir/ritonavir more than 5 days after onset of COVID-9 symptoms/signs, per the medical records, had a shorter median time (5.0 days [95% CI: 5.0 to 6.0] compared to 8.0 days [95% CI: 7.0 to 8.0 days] for ≤ 5 days). (Table 15.15.1. Time to Two Consecutive Negative SARS-CoV-2 Test Results / Ct ⩾ 35 Summary - Subgroup Analysis 1 - EAS1 in Section 15). A similar median time to two consecutive negative results (ranging from 6.5 to 8.0 days) was observed across subgroups of baseline vaccination status, baseline COVID-19 severity, and baseline eGFR level. See Table 15.15.1. Time to Two Consecutive Negative SARS-CoV-2 Test Results / Ct ≥ 35 Summary - Subgroup Analysis 1 - EAS1 in Section 15.

Table 20. Proportions of Patients with COVID-19 Disease Severity Progressed or Death from Any Cause and Patients with Two Consecutive Negative SARS-CoV-2 Tests - Subgroup Analysis 1 - EAS1

	Number of Patients with COVID-19 Disease Severity Information at Baseline and COVID-19 Disease Severity/Death Information in Observation Period in Each Subgroup	Patients with COVID-19 Disease Progressed to Severe/Critical or Death from Any Cause		Number of Patients with Positive Baseline and At Least Two Post-baseline SARS-CoV-2 Tests [2]	Patients with Two Consecutive Negative SARS-CoV-2 Test Results / Ct ≥ 35 Post-Baseline [2]
	N1	n (%) [1]	95% CI [1]	N2	n (%) [3]
Age Group					
Age < 60 Years	311	3 (0.7)	(0.00 - 1.90)	318	311 (97.8)
60 ≤ Age < 70 Years	194	6 (2.8)	(0.00 – 7.06)	202	193 (95.5)
70 ≤ Age < 80 Years	194	26 (8.9)	(0.81 – 17.04)	192	184 (95.8)
Age ≥ 80 Years	242	45 (10.8)	(0.00 – 22.88)	242	219 (90.5)
Vaccination Status					
Unvaccinated	220	26 (6.3)	(0.12-12.49)	224	205 (91.5)
Vaccinated	462	8 (1.6)	(0.00-4.17)	466	455 (97.6)
Mapped COVID-19 Severity at Baseline					
Mild to Moderate	889	70 (5.2)	(0.00-11.82)	865	830 (96.1)
Severe to Critical	52	10 (7.1)	(0.00-16.37)	50	42 (84.0)
Baseline eGFR Level [mL/min/1.73m^2]					
eGFR < 30	28	10 (20.2)	(2.75-37.62)	28	23 (82.1)
30 ≤ eGFR < 60	109	23 (12.9)	(0.00-27.98)	111	106 (95.5)
60 ≤ eGFR < 90	293	28 (5.8)	(0.00-12.87)	293	272 (92.8)

Table 20. Proportions of Patients with COVID-19 Disease Severity Progressed or Death from Any Cause and Patients with Two Consecutive Negative SARS-CoV-2 Tests - Subgroup Analysis 1 - EAS1

	Number of Patients with COVID-19 Disease Severity Information at Baseline and COVID-19 Disease Severity/Death Information in Observation Period in Each Subgroup	Patients with COVID-19 Disease Progressed to Severe/Critical or Death from Any Cause		Number of Patients with Positive Baseline and At Least Two Post-baseline SARS-CoV-2 Tests [2]	Patients with Two Consecutive Negative SARS-CoV-2 Test Results / Ct ≥ 35 Post-Baseline [2]
	N1	n (%) [1]	95% CI [1]	N2	n (%) [3]
eGFR ≥ 90	403	11 (2.1)	(0.00-5.36)	403	391 (97.0)
Duration Since the Earliest On-Record COVID-19 Symptom/Sign (Days)					
≤5 days	553	41 (5.1)	(0.00-11.49)	568	546 (96.1)
>5 days	330	34 (5.4)	(0.00-12.94)	329	305 (92.7)

eGFR: estimated Glomerular Filtration Rate; CI: Confidence Interval; Ct: Cycle threshold; EAS1: Effectiveness Analysis Set 1
Baseline is defined as the severity level / derived SARS-CoV-2 test assessed on or closest prior to the index date.
[1] Due to partial ICD wavier, patients who died were more likely to be enrolled into the study than those who did not die. Percentages and confidence intervals out of N1 are calculated using site as cluster factor and different sampling weights for alive and death patients to adjust for sampling bias.
[2] The following rules in descending priority are used for derived SARS-CoV-2 test result:
- If the Ct for ORF or N gene is < 35, the ORF/N gene result is defined as Positive.
- If the Ct for both ORF and N gene is ⩾ 35, the ORF/N gene result is defined as Negative.
- If either the Ct for ORF or N gene is ⩾ 35, and the other one is documented as undetermined, the ORF/N gene finding is defined as Negative.
- If the Ct for ORF or N gene is missing, but an unspecified Ct result is available, then Ct < 35 is defined as Positive; otherwise, the result is Negative.
- If the Ct for both ORF/N gene and unspecified Ct result is missing, but a qualitative NAT result is available, then this qualitative NAT result is used as the test result.
- If the Ct for both ORF/N gene, unspecified Ct result and qualitative NAT result is all missing, then the antigen test result is used as the test result.
[3] Percentages are calculated using N2 as the denominator.
Source: Table 15.14.1

Subgroup analysis results based on EAS

Table 21 shows the subgroup analysis results for COVID-19 severity progression or death from any cause and post-baseline SARS-CoV-2 tests in EAS.

- Similar to the results for subgroup analysis in EAS1, the sampling weight adjusted proportions of patients with COVID-19 disease progression or death from any cause were higher among patients:
  - aged 70 years or older (9.0% [95% CI: 0.00% to 18.11%] for ≥ 70 to < 80 years and 11.0% [95% CI: 0.00% to 23.24%] for ≥ 80 years, compared to 0.9% [95% CI: 0.00% to 2.65%] and 2.9% [95% CI: 0.00% to 7.50%] for < 60 years and ≥ 60 to < 70 years, respectively),
  - unvaccinated patients (6.6% [95% CI: 0.00% to 13.50%] compared to 1.9% [95% CI: 0.00% to 5.06%] for vaccinated patients),
  - patients with baseline eGFR <60 (26.2% [95% CI: 14.99% to 37.49%] for eGFR < 30 and 12.5% [95% CI: 0.00% to 28.39%] for 30 ≤ eGFR < 60, compared to 6.0% [95% CI: 0.00% to 13.22%] and 2.5% [95% CI: 0.00% to 6.62%] for 60 ≤ eGFR < 90 and eGFR ≥ 90 mL/min/1.73m^2, respectively),
  - patients with BMI ≤ 25 kg/m^2 (3.7% [95% CI: 0.00% to 8.67% for BMI ≤ 25 compared to 1.2% [95% CI: 0.00% to 3.86%] for BMI > 25),
  - non-smokers and ex-smokers (3.5% [95% CI: 0.00% to 9.60%] for non-smokers and 3.4% [95% CI: 0.00% to 15.33%] for ex-smokers compared to 1.4% [95% CI: 0.00% to 5.35%] for current smokers),
  - patients with chronic kidney disease (12.9% [95% CI: 0.59% to 25.23%] compared to 2.9% [95% CI: 0.00% to 7.28%] for without),
  - patients with diabetes (8.1% [95% CI: 0.00% to 16.40%] compared to 2.2% [95% CI: 0.00% to 5.93%] for without),
  - patients with cardiovascular disease or hypertension (6.3% [95% CI: 0.00% to 14.33%] compared to 3.4% [95% CI: 0.00% to 8.88%] for patients without cardiovascular disease and hypertension),
  - patients with chronic lung diseases (11.8% [95% CI: 0.00% to 26.40%] compared to 4.1% [95% CI: 0.00% to 10.49%] for patients without chronic lung disease), and
  - patients with active cancer (6.1% [95% CI: 0.00% to 15.93%] compared to 1.8% [95% CI: 0.00% to 5.16%] for patients without active cancer).
- No evident difference was seen between patients initiating nirmatrelvir/ritonavir within 5 days from the onset of COVID-19 symptoms/signs (analyzed per the earliest on-record onset dates) and those initiating nirmatrelvir/ritonavir later.

Regarding achieving two consecutive negative SARS-CoV-2 test results / Ct ≥ 35 during the observation period, the proportion appeared to be smaller among patients aged ≥ 80 years on the index date (92.7% compared to 98.1%. 96.7%, and 96.0% for patients aged < 60, ≥ 60 to < 70, and ≥ 70 to < 80, respectively), unvaccinated patients (92.6% compared to 97.6% for unvaccinated patients) and patients with baseline eGFR < 30 mL/min/1.73m^2 (82.4% compared to 97.9%, 94.2%, and 97.2% for patients with eGFR being ≥ 30 to < 60, ≥ 60 to < 90, and ≥ 90 mL/min/1.73m^2, respectively). Similar proportions (ranging from 94.1% to 100%) were observed among subgroups of patients with different baseline risk factors and duration since the earliest on-record COVID-19 symptom/sign onset till start of nirmatrelvir/ritonavir treatment, except for the subgroups of patients with immunosuppressive disease or immunosuppressive treatment, sickle cell disease, and neurodevelopmental disorders or other conditions that confer medical complexity, in which few patients had risk factors reported.

Regarding the time to two consecutive negative test results, similar to the results observed in EAS1, the median time was shorter for patients initiating nirmatrelvir/ritonavir more than 5 days after onset of COVID-19 symptoms/signs (6.0 days [95% CI: 5.0 to 6.0 days] compared to 8.0 days [95%CI: 8.0 to 9.0 days] for patients initiating treatment within 5 days) and this may likely due to the natural decline in viral loads over a longer baseline period Similar median time to two consecutive negative results (ranging from 6.0 to 8.5 days) was observed among subgroups of patients by baseline vaccination status, baseline eGFR level and other baseline risk factors (except for the subgroups of patients with immunosuppressive disease or immunosuppressive treatment, sickle cell disease, and neurodevelopmental disorders or other conditions that confer medical complexity, in which few patients had risk factors reported). See Table 15.15.2. Time to Two Consecutive Negative SARS-CoV-2 Test Results / Ct ≥ 35 Summary - Subgroup Analysis 2 - EAS in Section 15.

Table 21. Proportions of Patients with COVID-19 Disease Severity Progressed or Death from Any Cause and Patients with Two Consecutive Negative SARS-CoV-2 Tests - Subgroup Analysis 2 - EAS

	Number of Patients with COVID-19 Disease Severity Information at Baseline and COVID-19 Disease Severity/Death Information in Observation Period in Each Subgroup	Patients with COVID-19 Disease Progressed to Severe/Critical or Death from Any Cause		Number of Patients with Positive Baseline and At Least Two Post-baseline SARS-CoV-2 Tests [2]	Patients with Two Consecutive Negative SARS-CoV-2 Test Results / Ct ≥ 35 Post-Baseline [2]
	N1	n (%) [1]	95% CI [1]	N2	n (%) [3]
Age Group					
Age < 60 Years	214	2 (0.9)	(0.00-2.65)	210	206 (98.1)
60 ≤ Age < 70 Years	186	5 (2.9)	(0.00-7.50)	183	177 (96.7)
70 ≤ Age < 80 Years	179	23 (9.0)	(0.00-18.11)	174	167 (96.0)
Age ≥ 80 Years	217	39 (11.0)	(0.00-23.24)	205	190 (92.7)
Vaccination Status					
Unvaccinated	193	23 (6.6)	(0.00-13.50)	188	174 (92.6)
Vaccinated	376	7 (1.9)	(0.00-5.06)	368	359 (97.6)
Baseline eGFR Level [mL/min/1.73m^2]					
eGFR < 30	19	8 (26.2)	(14.99-37.49)	17	14 (82.4)
30 ≤ eGFR < 60	96	18 (12.5)	(0.00-28.39)	94	92 (97.9)
60 ≤ eGFR < 90	268	25 (6.0)	(0.00-13.22)	259	244 (94.2)
eGFR ≥ 90	335	11 (2.5)	(0.00-6.62)	324	315 (97.2)

Table 21. Proportions of Patients with COVID-19 Disease Severity Progressed or Death from Any Cause and Patients with Two Consecutive Negative SARS-CoV-2 Tests - Subgroup Analysis 2 - EAS

	Number of Patients with COVID-19 Disease Severity Information at Baseline and COVID-19 Disease Severity/Death Information in Observation Period in Each Subgroup	Patients with COVID-19 Disease Progressed to Severe/Critical or Death from Any Cause		Number of Patients with Positive Baseline and At Least Two Post-baseline SARS-CoV-2 Tests [2]	Patients with Two Consecutive Negative SARS-CoV-2 Test Results / Ct ≥ 35 Post-Baseline [2]
	N1	n (%) [1]	95% CI [1]	N2	n (%) [3]
Risk Factors					
BMI (WHO Standard [kg/m^2]) ≤ 25	271	12 (3.7)	(0.00-8.67)	267	259 (97.0)
BMI (WHO Standard [kg/m^2]) > 25	247	3 (1.2)	(0.00-3.86)	242	239 (98.8)
Age < 60 Years	214	2 (0.9)	(0.00-2.65)	210	206 (98.1)
Age ≥ 60 Years	582	68 (7.7)	(0.00-15.81)	561	533 (95.0)
Non-Smoker	440	18 (3.5)	(0.00-9.60)	423	408 (96.5)
Ex-Smoker	29	1 (3.4)	(0.00-15.33)	29	29 (100.0)
Current Smoker	70	1 (1.4)	(0.00-5.35)	70	70 (100.0)
With Immunosuppressive Disease or Immunosuppressive Treatment	9	2 (15.9)	(0.00-46.88)	9	8 (88.9)
Without Immunosuppressive Disease	121	2 (1.7)	(0.00-5.59)	117	117 (100.0)

Table 21. Proportions of Patients with COVID-19 Disease Severity Progressed or Death from Any Cause and Patients with Two Consecutive Negative SARS-CoV-2 Tests - Subgroup Analysis 2 - EAS

	Number of Patients with COVID-19 Disease Severity Information at Baseline and COVID-19 Disease Severity/Death Information in Observation Period in Each Subgroup	Patients with COVID-19 Disease Progressed to Severe/Critical or Death from Any Cause		Number of Patients with Positive Baseline and At Least Two Post-baseline SARS-CoV-2 Tests [2]	Patients with Two Consecutive Negative SARS-CoV-2 Test Results / Ct ≥ 35 Post-Baseline [2]
	N1	n (%) [1]	95% CI [1]	N2	n (%) [3]
or Immunosuppressive Treatment					
With Chronic Kidney Disease	39	8 (12.9)	(0.59-25.23)	38	36 (94.7)
Without Chronic Kidney Disease	139	4 (2.9)	(0.00-7.28)	134	134 (100.0)
With Diabetes	194	22 (8.1)	(0.00-16.40)	183	175 (95.6)
Without Diabetes	403	11 (2.2)	(0.00-5.93)	395	383 (97.0)
With Cardiovascular Disease or Hypertension	492	47 (6.3)	(0.00-14.33)	475	449 (94.5)
Without Cardiovascular Disease or Hypertension	225	9 (3.4)	(0.00-8.88)	220	216 (98.2)
With Chronic Lung Diseases	103	17 (11.8)	(0.00-26.40)	102	96 (94.1)
Without Chronic Lung Diseases	244	12 (4.1)	(0.00-10.49)	228	218 (95.6)
With Sickle Cell Disease	0	0 (-)	-	0	0 (-)

Table 21. Proportions of Patients with COVID-19 Disease Severity Progressed or Death from Any Cause and Patients with Two Consecutive Negative SARS-CoV-2 Tests - Subgroup Analysis 2 - EAS

	Number of Patients with COVID-19 Disease Severity Information at Baseline and COVID-19 Disease Severity/Death Information in Observation Period in Each Subgroup	Patients with COVID-19 Disease Progressed to Severe/Critical or Death from Any Cause		Number of Patients with Positive Baseline and At Least Two Post-baseline SARS-CoV-2 Tests [2]	Patients with Two Consecutive Negative SARS-CoV-2 Test Results / Ct ≥ 35 Post-Baseline [2]
	N1	n (%) [1]	95% CI [1]	N2	n (%) [3]
Without Sickle Cell Disease	71	4 (3.8)	(2.74-4.83)	66	66 (100.0)
With Neurodevelopmental Disorders or Other Conditions that Confer Medical Complexity	9	1 (11.1)	(0.00-28.25)	9	9 (100.0)
Without Neurodevelopmental Disorders or Other Conditions that Confer Medical Complexity	75	3 (3.1)	(1.31-4.93)	68	68 (100.0)
With Active Cancer	58	8 (6.1)	(0.00-13.17)	54	51 (94.4)
Without Active Cancer	130	3 (1.8)	(0.00-5.16)	125	125 (100.0)
With Medical-related Technological Dependence Not Related to COVID-19	11	1 (3.1)	(0.00-15.93)	10	10 (100.0)
Without Medical-related Technological Dependence Not Related to COVID-19	73	3 (3.2)	(1.80-4.61)	68	67 (98.5)

Table 21. Proportions of Patients with COVID-19 Disease Severity Progressed or Death from Any Cause and Patients with Two Consecutive Negative SARS-CoV-2 Tests - Subgroup Analysis 2 - EAS

	Number of Patients with COVID-19 Disease Severity Information at Baseline and COVID-19 Disease Severity/Death Information in Observation Period in Each Subgroup	Patients with COVID-19 Disease Progressed to Severe/Critical or Death from Any Cause		Number of Patients with Positive Baseline and At Least Two Post-baseline SARS-CoV-2 Tests [2]	Patients with Two Consecutive Negative SARS-CoV-2 Test Results / Ct ≥ 35 Post-Baseline [2]
	N1	n (%) [1]	95% CI [1]	N2	n (%) [3]
Duration Since the Earliest On-Record COVID-19 Symptom/Sign (Days)					
≤5 days	468	36 (5.6)	(0.00-12.83)	459	444 (96.7)
>5 days	276	29 (5.9)	(0.00-14.02)	261	245 (93.9)

eGFR: estimated Glomerular Filtration Rate; CI: Confidence Interval; Ct: Cycle threshold; EAS: Effectiveness Analysis Set
Baseline is defined as the severity level / derived SARS-CoV-2 test assessed on or closest prior to the index date.
[1] Due to partial ICD wavier, patients who died were more likely to be enrolled into the study than those who did not die. Percentages and confidence intervals out of N1 are calculated using site as cluster factor and different sampling weights for alive and death patients to adjust for sampling bias.
[2] The following rules in descending priority are used for derived SARS-CoV-2 test result:
- If the Ct for ORF or N gene is < 35, the ORF/N gene result is defined as Positive.
- If the Ct for both ORF and N gene is ⩾ 35, the ORF/N gene result is defined as Negative.
- If either the Ct for ORF or N gene is ⩾ 35, and the other one is documented as undetermined, the ORF/N gene finding is defined as Negative.
- If the Ct for ORF or N gene is missing, but an unspecified Ct result is available, then Ct < 35 is defined as Positive; otherwise, the result is Negative.
- If the Ct for both ORF/N gene and unspecified Ct result is missing, but a qualitative NAT result is available, then this qualitative NAT result is used as the test result.
- If the Ct for both ORF/N gene, unspecified Ct result and qualitative NAT result is all missing, then the antigen test result is used as the test result.
[3] Percentages are calculated using N2 as the denominator.
Source: Table 15.14.2

11. DISCUSSION

11.1. Key results

11.1.1. Results of baseline patient characteristics

- The median (range) age of patients in this study was 68 (18, 103) years, with 20.3% aged between 70 and 79 years and 26.3% aged 80 years and above at the time of nirmatrelvir/ritonavir initiation.

- Of 616 patients with BMI available, the mean (SD) was 24.7 (4.35) kg/m^2 with 33.4% being pre-obesity (24.0 ≤ BMI < 28.0 kg/m^2) and 19.3% being obesity (≥ 28.0 kg/m^2) based on the China guideline for BMI categorization.

- Of 678 patients with smoking status available, the majority (84.2%) were non-smokers; 5.0% were ex-smokers and 10.8% were current smokers.

- Of 912 patients with baseline eGFR available, 13.5% had a baseline eGFR being ≥30 to <60 mL/min/1.73m^2, and 3.7% had a baseline eGFR being less than 30 mL/min/1.73m^2.

- Of patients with baseline disease characteristics available, 93.7% (942/1005) patients had mild to moderate COVID-19 and 5.7% had severe to critical COVID-19; 65.2% (501/768) were vaccinated with 3.0%, 26.0%, and 34.5% patients receiving one, two, and three or more doses, respectively.

- Of 866 patients with baseline COVID-19 symptoms/signs recorded, cough (77.6%), sore throat (26.2%), fatigue (17.7%), and shortness of breath or difficulty breathing (16.7%) were the most frequently reported symptoms/signs (≥ 15% relative frequency).

- Among the 987 patients with nirmatrelvir/ritonavir initiation dates and baseline COVID-19 symptom/sign onset dates available, the median (range) duration since the earliest on-record COVID-19 symptoms/signs until start of nirmatrelvir/ritonavir treatment was 4.0 (1.0, 32.0) days, with 38.2% and 60.8% initiating nirmatrelvir/ritonavir within 3 and 5 days, respectively.

- Of the 1,047 patients, 70.4% had at least one protocol specified comorbidity at baseline. The most frequently recorded comorbidities were cardiovascular disease or hypertension (56.9%) and diabetes (22.1%).

- Of 754 patients with prior treatment information, 18.0% received COVID-19 related treatments including glucocorticoids (0.7%) and COVID-19 related treatments other than antiviral or immune- therapies (17.9%). Among the latter, TCM, oxygen supplemental therapies, and anticoagulants were prescribed for 86.7%,10.4%, and 8.9% patients, respectively. No antiviral therapies before taking nirmatrelvir/ritonavir initiation were recorded.

11.1.2. Results of safety

- Of the 1,047 patients, 15.8% experienced AEs with explicit attribution to nirmatrelvir/ritonavir, 0.6% experienced severe AEs, and 0.6% discontinued nirmatrelvir/ritonavir treatment due to AEs with explicit attribution to nirmatrelvir/ritonavir during the observation period with a median (range) of 10.0 (1.0, 50.0) days.

- No SAEs with explicit attribution to nirmatrelvir/ritonavir were reported.

- Dysgeusia was the most frequently reported AE with explicit attribution to nirmatrelvir/ritonavir (5.0%), followed by Diarrhoea (2.4%) and Hypoalbuminaemia (2.0%).

- Among the 86 patients who experienced safety-related scenarios, nirmatrelvir/ritonavir overdose was reported in 85 patients based on the medical records and investigator review, with records of treatment duration showing longer than a 5-day course (which might span over 6 calendar days) or prescriptions of more than one carton (i.e., over 20 tablets for nirmatrelvir and/or 10 tablets for ritonavir cumulatively). One patient experienced nirmatrelvir/ritonavir exposure during breast feeding. No scenarios were associated with any AEs or SAEs.

- Of the 1,047 patients, the sampling weight adjusted all-cause death rate was 1.9% (60) during the observation period. No deaths were resulted from AEs with explicit attribution to nirmatrelvir/ritonavir. Of the 60 deaths, the sampling weight adjusted death rate was 0.2% (7) for COVID-19 being one of the causes, and 1.7% (53) for other causes, respectively. The sampling weight adjusted all-cause death rates by age group were 5.1% (aged 80 years or older), 2.4% (between 70 and 79 years), 0.4% (between 60 and 69 years), and 0.2% (younger than 60 years).

- For subgroups of patients, it appeared that the proportion of patients experiencing AEs with explicit attribution to nirmatrelvir/ritonavir was higher among patients vaccinated at baseline (22.4% vs. 11.7% in unvaccinated patients) and with higher baseline eGFR levels (20.2% and 19.1% in eGFR ≥ 60 to < 90 and ≥ 90 mL/min/1.73m^2 vs. 0.0% and 9.8% in eGFR < 30 and ≥ 30 to < 60 mL/min/1.73m^2).

11.1.3. Results of treatment pattern

- Among 941 patients with treatment dates available, the median (range) treatment duration spanned 6.0 (1.0, 19.0) calendar days with 82.7% receiving nirmatrelvir/ritonavir for a full course (5–6 days).

- Of the total of 1,047 patients, 95.7% received an uninterrupted course of treatment and 4.3% received interrupted course of treatment with nirmatrelvir/ritonavir (i.e., gaps occurred in between consecutive days of treatment). Based on patients with treatment dates available, the median (range) duration of nirmatrelvir/ritonavir treatment was 6.0 (1.0, 19.0) days with 86.5% (776/897) patients being treated for 5 to 6 days, and 11.0 (2.0, 18.0) days with 65.9% (29/44) patients being treated for over 10 days for the uninterrupted and interrupted treatment courses, respectively. Of the total of 1,047 patients, 24.5% and 75.5% patients received nirmatrelvir/ritonavir as monotherapy and

combination therapy with other COVID-19 related medications, respectively. Based on patients with treatment dates available, the median (range) duration of nirmatrelvir/ritonavir treatment was 6.0 (2.0, 19.0) days and 6.0 (1.0, 18.0) days with the proportion of patients receiving 5-6 day full course treatment being 84.8% (190/224) and 82.0% (588/717) for monotherapy and combination therapy, respectively.

- Of the total of 1,047 patients, 0.4% patients received antiviral therapy other than nirmatrelvir/ritonavir (i.e., COVID-19 human immunoglobulin), 10.5% received immunotherapy (i.e., glucocorticoid), and 62.2% received other COVID-19 related treatments while taking nirmatrelvir/ritonavir. More specifically, TCM (55.4%), anticoagulant (28.8%), and oxygen supplemental therapies (21.2%) were the other COVID-19 related treatments prescribed.

- For subgroups of patients, the median duration of nirmatrelvir/ritonavir treatment, regardless of treatment course and mono-/combination therapy, ranged from 5 to 6 days across all subgroups. The proportion of patients receiving nirmatrelvir/ritonavir with COVID-19 related concomitant medications was higher among vaccinated patients (80.8% vs. 69.6% in unvaccinated patients) and patients with mild/moderate COVID-19 at baseline (77.3% vs. 59.6% among patients with severe/critical COVID-19), while lower among patients with baseline eGFR < 30 mL/min/1.73m^2 (55.9% vs. 72.4%, 75.1%, 77.9% in patients with eGFR ≥ 30 to < 60, ≥ 60 to < 90, ≥ 90 mL/min/1.73m^2, respectively).

11.1.4. Results of effectiveness

The following results were observed with a median (range) observation period of 10.0 (1.0, 50.0) days for the final analysis.

Among patients treated under clinical practice (patients included in the EAS1):

- The sampling weight adjusted proportion of patients with COVID-19 progression to severe/critical illness or all-cause death was 5.3% (95% CI: 0.0% to 11.8%).
  - Thirty-three (33/80) patients experienced COVID-19 progression from mild/moderate to severe/critical illness.
  - Forty-seven (47/80) patients died from any cause with 30, 7, 8, and 2 being mild, moderate, severe, and critical COVID-19 at baseline, respectively. Of the 47 deaths, 6 patients died for COVID-19 being one of the causes.

- During the observation period, 95.1% patients achieved two consecutive SARS-CoV-2 negative test results, and the median time to two consecutive negative results was 7.0 (95% CI: 7.0 to 8.0) days.

- During the observation period, 54.0% patients achieved alleviation of all targeted COVID-19 symptoms and signs with a median time of 9.0 (95% CI: 8.0 to 10.0) days.

- For subgroups of patients,

- The sampling weight adjusted proportions of patients with COVID-19 severity progression to severe/critical or all-cause death were higher in patients aged 70 years and above (8.9% and 10.8% for ≥ 70 to < 80 and ≥ 80 years vs. 0.7% and 2.8% for < 60 and ≥ 60 to < 70 years), unvaccinated patients (6.3% vs. 1.6% in vaccinated patients), patients with severe/critical illness at baseline (7.1% vs. 5.2% in patients with mild/moderate COVID-19), and patients with poor kidney function at baseline (20.2% and 12.9% in patients with eGFR < 30 and ≥ 30 to < 60 mL/min/1.73m^2 vs. 5.8% and 2.1% in patients with eGFR ≥ 60 to < 90 and ≥ 90 mL/min/1.73m^2). No evident difference was seen between patients initiating nirmatrelvir/ritonavir within and exceeding 5 days since the earliest on-record COVID-19 symptoms/signs.

- The proportions of patients achieving two consecutive negative SARS-CoV-2 test results / Ct ≥ 35 appeared to be lower among patients with severe/critical illness at baseline (84.0% vs. 96.1% in patients with mild/moderate COVID-19) and patients with baseline eGFR < 30 mL/min/1.73m^2 (82.1% vs. > 90% among patients with eGFR ≥ 30 mL/min/1.73m^2). No evident differences were seen by age, vaccination status, and duration of initiating nirmatrelvir/ritonavir since the earliest on-record COVID-19 symptoms/signs.

- The median time to two consecutive negative results was shorter in patients initiating nirmatrelvir/ritonavir more than 5 days (5.0 days, 95% CI: 5.0 to 6.0 days) since the earliest on-record COVID-19 symptoms/signs than patients treated sooner (8.0 days, 95% CI: 7.0 to 8.0 days), which may be due to the natural declining in viral loads over time. A similar median time to two consecutive negative results (ranging from 6.5 to 8.0 days) was observed among patients by vaccination status, baseline COVID-19 severity, and baseline eGFR level.

Similar results were observed among patients who were treated under clinical practice and had mild-to-moderate COVID-19 with at least one of the risk factors as listed in the nirmatrelvir/ritonavir label (patients included in the EAS):

- The sampling weight adjusted proportion of patients with COVID-19 progression to severe/critical illness or all-cause death was 5.8% (95% CI: 0.0% to 13.1%).
  - Thirty-three (33/70) patients experienced COVID-19 progression from mild/moderate to severe/critical illness.
  - Thirty-seven (37/70) patients died from any causes, with 30 and 7 being classified as mild and moderate COVID-19 at baseline, respectively. Of the 37 deaths, 3 patients died for COVID-19 being one of the causes.
- During the observation period, 95.9% patients achieved two consecutive SARS-Cov-2 negative test results, and the median time to two consecutive negative results was 8.0 (95% CI: 7.0 to 8.0) days.
- During the observation period, 55.2% patients achieved alleviation of all targeted COVID-19 symptoms and signs with a median time of 9.0 (95% CI: 8.0 to 10.0) days.

- For subgroups of patients,
  - The sampling weight adjusted proportions of patients with COVID-19 severity progression to severe/critical or all-cause death were higher in patients aged 70 years and above (9.0% and 11.0% for ≥ 70 to < 80 years and ≥ 80 years vs. 0.9% and 2.9% for < 60 years and ≥ 60 to < 70 years), unvaccinated patients (6.6% vs. 1.9% in vaccinated patients), patients with poor kidney function at baseline (26.2% and 12.5% in patients with eGFR < 30 and ≥ 30 to <60 mL/min/1.73m^2 vs. 6.0% and 2.5% in patients with eGFR ≥ 60 to < 90 and ≥ 90 mL/min/1.73m^2), patients with BMI ≤ 25 kg/m^2 at baseline (3.7% vs. 1.2% for BMI > 25), and non-smokers and ex-smokers (3.5% for non-smokers and 3.4% for ex-smokers vs. 1.4% for current smokers). For other baseline risk factors, the corresponding sampling weight adjusted proportions appeared to be higher in patients with chronic kidney disease (12.9% vs. 2.9% for patients without chronic kidney disease), diabetes (8.1% vs. 2.2% for patients without diabetes), cardiovascular disease or hypertension (6.3% vs. 3.4% for patients without cardiovascular disease or hypertension), chronic lung diseases (11.8% vs. 4.1% for patients without chronic lung disease), and active cancer (6.1% vs. 1.8% for patients without active cancer). No evident difference was seen between patients initiating nirmatrelvir/ritonavir within and exceeding 5 days since the earliest on-record COVID-19 symptom/signs.
  - The proportions of patients achieving two consecutive negative SARS-CoV-2 test results / Ct ≥ 35 appeared to be lower among patients aged ≥ 80 years (92.7% vs. 96.0% in ≥ 70 to < 80 years, 96.7% in ≥ 60 to < 70 years, and 98.1% in < 60 years), unvaccinated patients (92.6% vs. 97.6% in vaccinated patients) and patients with baseline eGFR < 30 mL/min/1.73m^2 (82.4% vs. >94% in eGFR ≥ 30 mL/min/1.73m^2). No evident differences were seen by other baseline risk factors and duration of initiating nirmatrelvir/ritonavir since the earliest on-record COVID-19 symptoms/signs.
  - The median time to two consecutive negative results was shorter in patients initiating nirmatrelvir/ritonavir more than 5 days (6.0 days, 95% CI: 5.0 to 6.0 days) since the earliest on-record COVID-19 symptoms/signs than patients treated within 5 days (8.0 days, 95% CI: 8.0 to 9.0 days), which may be due to the natural declining in viral loads. A similar median time to two consecutive negative results (ranging from 6.0 to 8.5 days) was observed among patients by baseline vaccination status, baseline eGFR level, and other risk factors.

11.2. Limitations

This study presents the safety, treatment pattern, and effectiveness profiles of nirmatrelvir/ritonavir among adult patients with symptomatic COVID-19 in China. Strategies have been undertaken to reduce missing data and selection bias during study design and data abstraction. Unavoidably, this retrospective observational study still has limitations.

Firstly, different from the clinical practice after 2022, during the study period, patients with positive SAR-CoV-2 test results were required to be admitted to the designated hospitals for treatment, regardless of the disease severity, reflecting China's clinical practice and pandemic prevention policy in 2022.

Secondly, since the data was retrospectively abstracted from medical records, some of the information might not be available if they were not recorded during patients' hospitalization. Strategies to reduce incomplete data included: selecting the qualified sites which had a high capacity of recording patients' characteristics and care information during their hospital visits, using the required fields and validation techniques in eCRFs for sufficient and accurate information abstraction, and setting up precise derivation and mapping rules for supplementary information generation to enhance the data quality. In the final analysis, most of the baseline variables had low rates of missing data. However, certain variables, such as the virus variants and the specific comorbidities (e.g., sickle cell disease and immunosuppression), still showed a higher level of missingness. This might be a genuine reflection of how medical information is routinely recorded in clinical practice in China during the pandemic. Results for these variables were cautiously interpreted, considering the missing rates.

Thirdly, the treatment start and end dates of nirmatrelvir/ritonavir could not be directly collected from the medical records; instead, they were collected based on the prescription records. These dates were used to calculate the treatment duration. Some patients' treatment duration might be slightly longer than the actual duration since their drug interruption information was not recorded in the prescription records. However, since this study used the inpatient data, treatment duration calculation based on the prescription data could be considered close to actual.

Fourthly, similar to treatment information, some patients' data for the assessments of alleviation and exacerbation of COVID-19 targeted symptoms/signs was insufficient. COVID-19 symptoms and signs might not be entirely recorded under routine clinical practice. Some symptoms/signs were recorded as symptom/sign alleviations post-treatment but were missing at baseline, and some were recorded at baseline but had no further information until patients were discharged. Thus, in this study, the proportion of patients achieving alleviation of all the baseline targeted symptoms/signs might be underestimated, and the time to alleviation might be overestimated since around 45% of the patients were censored (Table 18).

Finally, to mitigate the potential underreporting of AEs/SAEs in real-world clinical settings, investigator review was applied to assess AEs/SAEs with explicit attribution to nirmatrelvir/ritonavir. Heterogeneity might also exist in investigators' evaluations of AEs/SAEs. Considering that the investigators made these assessments per their medical knowledge and clinical experiences, and AE findings were generally consistent with the label and many previous real-world studies (see Section 11.3 for more details), the possibility of AEs/SAEs being underreported could have been minimized in this study. The findings of this study could reflect the practicing physicians' perceptions towards the real-world safety profile of nirmatrelvir/ritonavir.

11.3. Interpretation

This final analysis provided real-world evidence on the safety, treatment pattern, and effectiveness of nirmatrelvir/ritonavir among patients with COVID-19 in China.

11.3.1. Interpretation of safety findings

Safety results indicated that the nirmatrelvir/ritonavir treatment was safe and well-tolerated in Chinese adult patients with COVID-19. In this study, no SAEs with explicit attribution to nirmatrelvir/ritonavir occurred during the observation period (Table 10 and Listing 15.2 in

Section 15). In line with the nirmatrelvir/ritonavir label,[22] Dysgeusia (5.0%) and Diarrhoea (2.4%) were two frequently reported AEs with explicit attribution to nirmatrelvir/ritonavir. In addition, 2.0% of the patients experienced Hypoalbuminaemia as an AE with explicit attribution to nirmatrelvir/ritonavir (Table 11). Nirmatrelvir/ritonavir overdose was reported among 85 patients based on the medical records and investigator review, with records of treatment duration showing longer than a 5-day course (which might span over 6 calendar days) or prescriptions of more than one carton (i.e., over 20 tablets for nirmatrelvir and/or 10 tablets for ritonavir cumulatively) (Listing 15.3 in Section 15). One patient experienced nirmatrelvir/ritonavir exposure during breast feeding. Although none were associated with AEs with explicit attribution to nirmatrelvir/ritonavir (Listing 15.2 in Section 15), the recommendation is to adhere to the labelled recommended dose[22] and avoid breast feeding during treatment with nirmatrelvir/ritonavir and for seven days after the last dose.[23]

This study retrospectively collected AEs with explicit attribution to nirmatrelvir/ritonavir based on medical records and investigator review among symptomatic COVID-19 patients treating with nirmatrelvir/ritonavir in China with a median age of 68 years old. The incidence of AEs with explicit attribution to nirmatrelvir/ritonavir (15.8%) was higher than in the EPIC-HR trial (7.8%; median age: 46 years for all patients and 45 years for patients treated with nirmatrelvir/ritonavir).[4] However, the incidence was in line with findings from two previous real-world studies under a similar setting in China. In these two retrospective observational studies (one involving 364 inpatients with a median age of 60 years from Beijing and the other with 81 inpatients with a median age of 78 years from Shanghai), AEs associated with nirmatrelvir/ritonavir were observed in 13.2% (48/364) and 14.6% (12/82) of patients within 7 and 17 days of observation after nirmatrelvir/ritonavir initiation, respectively.[24, 25]

The EPIC-HR trial[4], two real-world studies in China[26] and Korea,[27] and the other real-world studies in Italy[28] and Spain[29], all reported that the most common AE or side effect was Dysgeusia (36.4% [94/258] in China, 23.8% [57/240] in Korea, 41.9% [99/236] in Italy, but data were not shown in Spain), which was the same as findings from this study. In a real-world pharmacovigilance study, Dysgeusia was also the most frequently reported AE (17.5%) out of the 15,140 AEs screened related to nirmatrelvir/ritonavir.[30] Although the mechanism of Dysgeusia associated with nirmatrelvir/ritonavir has yet to be fully elucidated, the *in vitro* research has shown that the plasma and saliva concentration of nirmatrelvir metabolites activates bitter taste-sensing type 2 receptors (TAS2R), leading to persistent Dysgeusia.[31]

This study showed that Hypoalbuminaemia was also a frequently reported AE, which was not reported in the global Phase 2/3 studies or listed in the nirmatrelvir/ritonavir label. All these AEs were reported from one site. It is noted that Hypoalbuminaemia in patients with COVID-19 has been reported [17, 18] and was reported to be possibly due to pulmonary capillary leakage of albumin,[20] or decreased hepatic synthesis of albumin and its increased catabolism after oxidation during the acute inflammation and COVID-19.[21] COVID-19 per se might serve as an alternative explanation for the reported Hypoalbuminaemia.

No SAEs with explicit attribution to nirmatrelvir/ritonavir were reported in this study, which was in line with three Chinese studies (0%),[24-26] one Japanese study (0%),[32] the EPIC-HR trial (<0.1%, 1/1038), and one Italian study (1.21%, 2/165).[33] In the EPIC-HR trial, only one subject experienced SAE considered to be related to ritonavir treatment (<0.1%, 1/1038; grade 3 Dysgeusia). In the Italian study, two SAEs (1.21%, 2/165) were reported, including one case of Reversible Bradycardia and another case of Extensive Rash.[33]

In this study, 0.6% of the patients experienced severe AEs, consistent with findings from the EPIC-HR trial, where 0.5% experienced treatment-related severe AEs (grade 3 events). Only a few previous real-world studies assessed the severity of AE. One Korean study reported 0% of severe AEs,[27] while one study in Italy reported one severe AE (0.2%, 1/502) attributed to an allergy related to nirmatrelvir/ritonavir.[34]

In the EPIC-HR trial (median age: 45 years for patients treated with nirmatrelvir/ritonavir), there was no reported death following nirmatrelvir/ritonavir treatment. However, in this study (median age: 68 years and mean age: 65.9 years), 60 patients (the sampling weight adjusted rate: 1.9%) died from any cause during the observation period (Table 13 and Figure 2). This death rate was lower than that observed in the other RCT and real-world studies in China. An open-label, multicenter RCT involving mild or moderate COVID-19 adult patients with severe comorbidities (mean age: 70 years) in Shanghai reported a 28-day all-cause death rate of 3.79% (5/132) following nirmatrelvir/ritonavir treatment, compared with 6.06% (8/132) in standard treatment group.[35] One retrospective cohort study among hospitalized patients not requiring supplemental oxygen admission in Hong Kong, China (where hospitalization policy may be different from that in mainland China) showed an all-cause death rate of 3.6% (32/890) of inpatients who received nirmatrelvir/ritonavir (mean age: 77 years) during a mean follow-up of 41 days after nirmatrelvir/ritonavir initiation, compared with 10.3% (92/890) among the matched controls.[36] Compared to the Shanghai and Hong Kong studies, patients enrolled in the final analysis of this study were relatively younger. Still, they were older than in the EPIC-HR trial, reflecting heterogeneity in death rates across studies. The differences in death rate by age were also seen in the current study. The sampling weight adjusted all-cause death rates were 5.1% in patients aged 80 years or older but 0.2% and 0.4% in patients aged less than 60 years and between 60 and 69 years, respectively (Table 13). In addition, notably, patients who died also tended to have other comorbidities in this study. Over 68% of them had cardiovascular disease or hypertension. Besides, over 83% of them were unvaccinated, and the mean duration since the earliest on-record positive SARS-CoV-2 test results until treatment of nirmatrelvir/ritonavir was 9 days (Listing 15.10 in Section 15). Therefore, most of these dead patients were not protected by vaccine and/or did not initiate nirmatrelvir/ritonavir within 5 days after a positive test per recommendation in the nirmatrelvir/ritonavir label. Furthermore, it is essential to note that none of these reported deaths were resulted from AEs/SAEs with explicit attribution to nirmatrelvir/ritonavir in this study. This finding aligned with findings from three real-world studies conducted in Beijing (mean age: 60 years),[24] Xiamen (mean age: 78 years),[25] and Jilin (mean age: 54 years) in China,[26] where no SAEs or deaths were explicitly associated with the use of nirmatrelvir/ritonavir.

As for subgroup analysis for safety endpoints, this study showed that the proportions of patients experiencing AEs were slightly higher in baseline vaccinated patients but lower in patients with a low eGFR level at baseline. Similarly, the single-site prospective observational study from Jilin province of China also suggested that vaccinated patients (45.7%) were more likely to report side effects of nirmatrelvir/ritonavir than unvaccinated patients (16.0%).[26] Previous studies also found a low proportion of AE occurrence in patients with severe renal insufficiency. One retrospective multicenter observational study among 40 Chinese patients with allogeneic transplantation with severe renal dysfunction (eGFR < 30 mL/min/1.73m^2) at baseline experienced a 10% AE occurrence related to nirmatrelvir/ritonavir during the observation period.[37] In another prospective, single-arm trial in Hong Kong, researchers found that the proportion of AEs associated with nirmatrelvir/ritonavir was 9.2% in the low-GFR group (<30 mL/min/1.73m^2).[38] Taken together, findings of the previous studies and this study

provide safety related data on the use of nirmatrelvir/ritonavir for treating COVID-19 in patients with severe renal insufficiency.

11.3.2. Interpretation of treatment pattern findings

As for the treatment pattern, this study revealed the use pattern of nirmatrelvir/ritonavir and concomitant treatments among patients with COVID-19 in the real-world clinical setting in China. In this study, the majority (82.7%; 778 out of 941 patients with treatment dates available) had a treatment duration of 5 to 6 days (Table 14), indicating that the recommendation in the nirmatrelvir/ritonavir label was well followed.[22] Patients with a treatment duration of 6 days might represent a situation when the treatment of nirmatrelvir/ritonavir was prescribed in the afternoon and completed in the morning of the sixth day. This high proportion of full course completion was in line with the proportions in two retrospective cohort studies. Wong *et al.* reported that 98.9% of all inpatients in Hong Kong completed the 5-day regimen of nirmatrelvir/ritonavir,[36] and Arbel *et al.* found that 97% of patients completed the 5-day treatment course in Israel.[39]

Among the 1,002 patients who received an uninterrupted single course of treatment with nirmatrelvir/ritonavir, 86.5% received a full course of nirmatrelvir/ritonavir treatment for 5-6 days; while among the other 45 patients who underwent interrupted treatment course with nirmatrelvir/ritonavir, the majority (65.9%) received nirmatrelvir/ritonavir treatment for over 10 days (Table 14). Data of this study showed that, of the 45 patients with interrupted treatment course, 20 patients' disease progression details were available and all of them experienced disease progression or death from any cause (see Listing 15.3. Nirmatrelvir and Ritonavir Treatment - FAS and Listing 15.6. COVID-19 Severity - FAS in Section 15). Thus, one reason for receiving a long-term nirmatrelvir/ritonavir treatment could be due to COVID-19 disease progression during the observation period.

Over 60% of patients initiated nirmatrelvir/ritonavir within five days since the earliest on-record COVID-19 symptom/sign onset, and the median time to nirmatrelvir/ritonavir initiation was 4 (95% CI: 1-32) days (Table 6), which was within the label-recommended window.[40] However, notably, the earliest on-record symptom/sign onset date might be later than the actual earliest date, leading to an overestimation of the real proportion of patients initiating nirmatrelvir/ritonavir within five days. In a previous multicenter retrospective cohort study in Beijing, only 35.1% (319/909) of the patients initiated nirmatrelvir/ritonavir within five days since COVID-19 symptoms onset and the median time from symptom onset to nirmatrelvir/ritonavir initiation was 8 (95% CI: 4-13) days.[41] This longer duration likely reflected the real-world clinical treatment pattern, delayed diagnosis since COVID-19 symptom/sign onset, or the supply issue of nirmatrelvir/ritonavir in China during the study period.

The concomitant COVID-19 related treatments, to some extent, reflected the treatment pattern of COVID-19 in China. Specifically, four patients (0.4%) received COVID-19 human immunoglobulin, 110 patients (10.5%) received glucocorticoid, and 651 patients (62.2%) received other concomitant COVID-19 related treatments (including anticoagulant, TCM and oxygen support therapy). TCM accounted for the highest proportion of this study's concomitant COVID-19 related treatments. Overall, 55.4% of the total 1,047 patients used TCM after initiation of their treatments with nirmatrelvir/ritonavir (Table 15). Previous randomized control trials (RCTs) showed that TCM such as Shenhuang Granule and Lianhuaqingwen capsules were effective in reducing disease progression or alleviating clinical symptoms of COVID-19.[42, 43] A review concluded that TCM, in general, is effective in

preventing COVID-19 and has an outstanding curative effect on COVID-19.[44] Limited studies on nirmatrelvir/ritonavir treatment reported the concomitant therapies of TCM. One non-randomized, controlled trial in Shanghai, China, also showed that 72.54% (103/142) of the patients treated with nirmatrelvir/ritonavir had concomitant TCM.[45]

11.3.3. Interpretation of effectiveness findings

This study also explored the effectiveness of nirmatrelvir/ritonavir under routine clinical practice in China. The sampling weight adjusted proportions of patients with COVID-19 disease progressed to severe/critical or death from any cause were 5.3% (95% CI: 0.0%–11.8%) in EAS1 and 5.8% (95% CI: 0.0%–13.1%) in EAS (Table 16. Proportions of Patients with COVID-19 Disease Severity Progressed or Death from Any Cause and Patients with Two Consecutive Negative SARS-CoV-2 Tests - EAS1/EAS). However, disease progression or death from any cause occurred mainly in older patients aged 70 years or over. The proportions were only 0.7% in EAS1 and 0.9% in EAS among patients aged less than 60 years and 2.8% in EAS1 and 2.9% in EAS among those aged between 60 and 69 years (Table 20 and Table 21). Previous real-world studies also reported low proportions of disease progression following nirmatrelvir/ritonavir treatment in younger age groups. One study conducted among 198 inpatients acquiring COVID-19 between 6 April and 11 May 2022 in Shanghai (median age: 52 years, ranging from 32 to 68 years) reported that 1% of the 198 patients treated with nirmatrelvir/ritonavir had radiographic progressions on the 7th day after symptom onset.[46] Another study reported that 1.2% of the 774 patients (median age: 62 years with over half aged ≤ 65 years) receiving nirmatrelvir/ritonavir progressed to severe disease by 30 days after treatment during Omicron BA.2 epoch in the US.[47]

Similar to discussion in Section 11.3.1, patients with baseline mild to moderate COVID-19 but progression to all-cause death were older and tended to have other comorbidities. Their mean age was 85 years, with over 67% having cardiovascular disease or hypertension, nearly 30% having diabetes, and nearly 20% having active cancer (see Listing 15.10 in Section 15). Thus, subgroup analysis by age (Table 20 and Table 21) still supported the general expectation that COVID-19 patients with severe health conditions at baseline would have a higher disease progression/death rate based on the sampling weight adjusted results during the observation period.[35]

Furthermore, the weight adjusted proportions of patients with COVID-19 severity progression or death from any cause appeared to be higher in unvaccinated patients (6.3% in EAS1 and 6.6% in EAS). Previous real-world studies in both China and other countries have also shown that unvaccinated patients were more likely to experience disease progression or all-cause death after nirmatrelvir/ritonavir initiation than vaccinated patients.[48-50]. Vaccination leads to a profound risk reduction in adverse outcomes caused by COVID-19.[51, 52] The vaccination uptake would be essential to provide protection against severe COVID-19 and death.

Most patients (over 95%) achieved two consecutive negative SARS-CoV-2 test results after nirmatrelvir/ritonavir initiation, and the median time to this event was 7 (in EAS1) or 8 (in EAS) days (Table 17). Previous studies on time to virus clearance in China had different definitions for the start time points; thus, the results of these studies could not be directly compared with the results of this study. The non-randomized, controlled trial in Shanghai reported a median time to nucleic acid shedding of 9.32 days, which was calculated from the date of the first positive NAT.[45] Liu *et al.* found a median time to SARS-CoV-2 RNA clearance of 10 days in the RCT from Shanghai, which was defined as the duration from admission to negative

conversion.[35] The median time from admission to reach a Ct value of ≥ 35 was 13.74 days in a retrospective cohort study in Fujian, China.[53] Considering the gap between positive NAT/hospital admission and treatment initiation, overall, the result of virus clearance in this study is generally consistent with other studies in China.

Cough (77.6%) was the most frequently reported symptom/sign at baseline (Table 7). About 55% of the patients with at least one targeted COVID-19 symptom or sign at baseline achieved alleviation of these symptoms/signs after nirmatrelvir/ritonavir initiation, and the median time to this event was 9 (95% CI: 8.0-10.0) days (Table 18). Definitions of symptom/sign alleviation in previous studies were different thus the results could not be directly compared across studies. In this study, alleviation for a targeted sign/symptom was defined as alleviation firstly recorded in the medical documents. In the EPIC-HR trial (median age of patients treated with nirmatrelvir/ritonavir: 45 years), the median time to symptom/sign alleviation was 12 days. In a single-site prospective observational study among 220 patients with COVID-19 in Beijing (mean age: 59.7 years), the clinical recovery was defined as achieving more than 3-day normal temperature, remission of respiratory symptoms, improvement of acute lung infiltrates on imaging, and two consecutive negative test results after nirmatrelvir/ritonavir treatment, and the median time to clinical recovery was 10 days.[54] Compared to patients in these trial and real-world studies, patients in this study tended to be older (median age: 68 years). Thus, findings of this study enhanced the profile of the effectiveness of nirmatrelvir/ritonavir in terms of achieving symptom alleviation among the older adult patients under routine clinical practice.

As for subgroup analysis for effectiveness endpoints, there was a higher sampling weight adjusted proportion of COVID-19 severity progression or death from any cause in patients with baseline eGFR < 30 (20.2% in EAS1 and 26.2% in EAS) and 30 ≤ eGFR < 60 mL/min/1.73m^2 (12.9% in EAS1 and 12.5% in EAS). The proportion of achieving two consecutive negative tests during the observation period was smaller in patients with eGFR < 30 mL/min/1.73m^2 (82.1% in EAS1 and 82.4% in EAS). Studies on subgroup analysis for the effectiveness of nirmatrelvir/ritonavir by eGFR levels were limited in the literature. A systematic review revealed that patients with kidney diseases (who had lower eGFRs) are more likely to experience disease progression for hospitalization or all-cause death after nirmatrelvir/ritonavir initiation than those without kidney diseases in the real-world clinical setting.[50] Though the effectiveness of nirmatrelvir/ritonavir in treating COVID-19 might differ across eGFR levels, the majority of the patients within each eGFR subgroup still experienced no disease progression and achieved two consecutive negative tests in this study. Previous retrospective cohort studies in China also showed a remarkable reduction in death risk after nirmatrelvir/ritonavir initiation among COVID-19 inpatients with chronic kidney diseases[55] or severe renal dysfunction.[37]

For other risk factors, in EAS, this study found that patients with protocol specified comorbidities tended to be more likely to experience disease progression or all-cause death than those without comorbidities, which was in line with findings from previous real-world studies.[48-50] However, this study showed that the sampling weight adjusted proportion of disease progression or all-cause death tended to be higher in patients with BMI ≤ 25 kg/m^2 (3.7%) than those with BMI > 25 kg/m^2 (1.2%), and in non-smokers (3.5%) and ex-smokers (3.4%) than current smokers (1.4%). Compared to the general population with COVID-19 in China, the study sample tended to be older in this study. According to the literature, the BMI in older adults has a different interpretation. Older adults with BMI < 25 kg/m^2 or BMI > 35 kg/m^2 were at a higher risk of experiencing functional capacity reduction, gait and balance problems, fall, decrease in muscle strength, and malnutrition.[56] Therefore, older patients within

the subgroup of BMI < 25 kg/m^2 in this study might have been frail with a higher risk of experiencing disease progression or all-cause death. Besides, patients who were non-smokers or ex-smokers (mean age for each subgroup: 63 years) tended to be older than those who were current smokers (mean age: 56 years). The subgroup of non-smokers (12.32%) also had a higher proportion of diabetes than the subgroup of current smokers (1.05%). Therefore, the higher proportions of disease progression or all-cause death in non-smoker and ex-smoker subgroups could be due to an unequal age and comorbidity distribution across subgroups of smoking status in this study.

11.4. Generalizability

This multicenter, retrospective observational study aimed to describe the safety, treatment pattern, and effectiveness of nirmatrelvir/ritonavir among patients with COVID-19 in China. To maximize the generalizability of the study results, this study applied only four necessary inclusion criteria to identify the study population. Participating in any interventional trials of COVID-19 was set as the only exclusion criterion. Per clinical practice and epidemic prevention policy in 2022, patients with positive SAR-CoV-2 test results were admitted to designated hospitals for the treatment of COVID-19 regardless of severity, and therefore, patients included in this study were all inpatients.[10] In this case, unlike in other countries, distinct differences in patient characteristics between outpatients and inpatients during the study period were not anticipated in China.

Patient enrollment was conducted in seven sites which were designated to admit patients with COVID-19 in three of the largest cities in China (Shanghai, Jilin, and Beijing) during the outbreak in 2022. Sites in Shanghai and Jilin are located in the main areas with COVID-19 outbreak in 2022. The site from Beijing is a specialized infectious disease hospital where patients with COVID-19 were treated during the outbreak in 2022. Patients treated with nirmatrelvir/ritonavir and met I/E criteria were identified. Attempts were made to collect ICD from individual patients. Partial ICD waivers were additionally applied to patients who signed the general ICD when they were admitted to the hospital, and then died or were lost of contact after discharge from hospitals.

Consequently, the probability of being enrolled into the study (N=1,047) was 100% for patients who died in hospitals (60 deaths recorded in HIS were all included in the study), which was higher than the probability for those who did not die (987 patients of the 1,047 study sample who did not die in the hospital were sampled from 3,095 alive patients of the total 3,155 patients satisfying I/E criteria, see Section 10.1.1). To minimize the sampling selection bias in death related estimates, the statistical method of IPTW was used for assigning different weights for patients who died and patients who did not die in the hospital. After applying IPTW, the overall death rate, the death rates by age group, and the proportions of COVID-19 disease progression and death from any cause could be considered generalizable to all patients treated with nirmatrelvir/ritonavir in China during the study observation period. These endpoints may be relatively more reflective for the all nirmatrelvir/ritonavir treated Chinese patients compared to other endpoints in the study.

While given the limited availability of nirmatrelvir/ritonavir during the study period, which happened to be right after the drug approval by NMPA and outbreak in China, the Chinese patients treated with nirmatrelvir/ritonavir in this study, as defined by the age, demographics, underlying disease characteristics, were different from the target population (i.e., Chinese patients with COVID-19). Apart from following the China guidelines for treating COVID-19,

physicians also prescribed nirmatrelvir/ritonavir for patients who genuinely needed this treatment per their clinical assessments. Patients included for the final analyses of this study tended to be older with a median (range) age of 68 (18, 103) years; and over 70% of them had at least one protocol specified comorbidity, such as cardiovascular disease or hypertension, or diabetes. Therefore, findings of this study could be more appropriately generalized to patients treated with nirmatrelvir/ritonavir in China and are older with several comorbidities.

Considering the differences in patient characteristics between the study sample and the target population, the association between patient characteristics and endpoint estimates, the endpoint estimates with proper statistical adjustment, as well as previous study findings in the literature referred to and discussed in above subsections, it is anticipated that no significant drug safety signals of nirmatrelvir/ritonavir would occur in the target population. Compared to what was in the current study, the overall all-cause death rate and the proportion of disease progression after nirmatrelvir/ritonavir initiation would be lower in the target population, which had larger proportion of young and middle-aged patients (aged between 18-69 years).[57]

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

Patients initiated with nirmatrelvir/ritonavir between 11 February 2022 and 31 August 2022 were included in this report. The median age of the study patients was 68 (ranging from 18 to 103) years. Of patients with relevant baseline characteristics data available, 52.7% (325/616) were pre-obese or obese with BMI ≥ 24 kg/m^2, 15.8% (107/678) were current or ex-smokers, 60.5% (465/768) were vaccinated with at least two doses, and the median duration of nirmatrelvir/ritonavir initiation since the earliest on-record COVID-19 sign/symptom was 4.0 (ranging from 1.0 to 32.0) days.

No significant drug safety signals were observed, suggesting that nirmatrelvir/ritonavir was safe and well-tolerated in Chinese adults with COVID-19. No SAEs with explicit attribution to nirmatrelvir/ritonavir were reported. The sampling weight adjusted all-cause death rate was 1.9% during the observation period, and no deaths were resulted from AEs with explicit attribution to nirmatrelvir/ritonavir.

Most patients (82.7%) received a full course (5-6 days) of nirmatrelvir/ritonavir treatment. The majority (75.5%) were treated with nirmatrelvir/ritonavir in combination with other COVID-19 related medications. Concomitant COVID-19 related treatments included COVID-19 human immunoglobulin (0.4%), glucocorticoid (10.5%), oxygen supplemental therapies (21.2%), anticoagulant (28.8%), and TCM (55.4%).

With a median observation period of 10.0 (ranging from 1.0 to 50.0) days, among patients treated under clinical practice, 5.3% (95% CI: 0.0%-11.8%) experienced COVID-19 progression to severe/critical illness or all-cause death, with higher rates observed in patients aged 70 years and above (8.9% [95% CI: 0.8%-17.0%] for ≥ 70 to < 80 and 10.8% [95% CI: 0%-22.9%] for ≥ 80 years) than those younger than 70 years (0.7% [95% CI: 0%-1.9%] for <60 and 2.8% [95% CI: 0%-7.1%] for ≥ 60 to < 70 years). The median time to alleviation of all targeted COVID-19 symptoms/signs was 9.0 (95% CI: 8.0-10.0) days, and the median time to two consecutive negative SARS-CoV-2 test results was 7.0 (95% CI: 7.0-8.0) days. Similar

results for effectiveness were observed among patients treated under routine clinical practice and those with mild-to-moderate COVID-19 and at least one of the risk factors listed on the nirmatrelvir/ritonavir label.

14. REFERENCES

1. Pfizer Inc. Pfizer's Novel COVID-19 Oral Antiviral Treatment Candidate Reduced Risk of Hospitalization or Death by 89% in Interim Analysis of Phase 2/3 EPIC-HR Study 2021 [Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate.
2. Anand K, Ziebuhr J, Wadhwani P, Mesters JR, Hilgenfeld R. Coronavirus main proteinase (3CLpro) structure: basis for design of anti-SARS drugs. Science. 2003;300(5626):1763-7.
3. Administration US Food and Drug. Emergency use authorization 105 2022 [Available from: https://www.fda.gov/media/155049/download.
4. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med. 2022;386(15):1397-408.
5. Pfizer Inc. Pfizer Announces Submission of New Drug Application to the U.S. FDA for PAXLOVID™ 2022 [Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-submission-new-drug-application-us-fda.
6. World Health Organization. Therapeutics and COVID-19: living guideline 2022 [Available from: https://app.magicapp.org/#/guideline/nBkO1E/rec/LwrMyv.
7. National Health Commission of the People's Republic of China. China Guideline on Diagnosis and Treatment Plan for Coronavirus Disease 2019 (10th Edition) 2023 [Available from: http://www.nhc.gov.cn/xcs/zhengcwj/202301/32de5b2ff9bf4eaa88e75bdf7223a65a.shtml.
8. Administration National Medical Products. Center for Drug Evaluation conditionally approves Pfizer's oral COVID-19 Therapy nirmatrelvir/ritonavir to treat COVID 19 2022 [Available from: https://www.nmpa.gov.cn/zhuanti/yqyjzxd/yqyjxd/20220212085753142.html.
9. National Health Commission of the People's Republic of China. Notice on Further Optimizing the Implementation of Epidemic Prevention and Control Measures for New Coronary Pneumonia 2022 [Available from: https://www.gov.cn/xinwen/2022-12/07/content_5730443.htm.
10. Hospital Authority. Key Points for Revision of Diagnosis and Treatment Plan for New Corona Virus Pneumonia (Ninth Edition for Trial Implementation) 2022 [Available from: http://www.nhc.gov.cn/yzygj/s7653p/202203/a354cb3151b74cfdbac6b2e909f311e6.shtml.
11. National Health Commission of the People's Republic of China. China Guideline on Diagnosis and Treatment Plan for Coronavirus Disease 2019 (Tentative 8th Edition) 2020 [Available from: http://www.nhc.gov.cn/yzygj/s7653p/202008/0a7bdf12bd4b46e5bd28ca7f9a7f5e5a.shtml.
12. National Health Commission of the People's Republic of China. China Guideline on Diagnosis and Treatment Plan for Coronavirus Disease 2019 (Tentative 8th Edition; Revision) 2021 [Available from: https://www.gov.cn/zhengce/zhengceku/2021-04/15/content_5599795.htm.
13. Pfizer. Pfizer Reports Additional Data on Paxlovid™ Supporting Upcoming New Drug Application Submission to U.S. FDA 2022 [Available from: http://www.pfizer.com/news/press-release/press-release-detail/pfizer-reports-additional-data-paxlovidtm-supporting.
14. PhIRDA. Are Pfizer Paxlovid and Merck Molnupiravir Cost-Effective? China Pharmaceutical Innovation and Research Development Association (PhIRDA) 2022 [Available from: http://www.phirda.com/artilce_27429.html?cId=1.

15. National Health Commission of the People's Republic of China. Criteria of weight for adults 2013 [Available from: http://www.nhc.gov.cn/wjw/yingyang/201308/a233d450fdbc47c5ad4f08b7e394d1e8.shtml.
16. World Health Organization. A healthy lifestyle - WHO recommendations 2010 [Available from: https://www.who.int/europe/news-room/fact-sheets/item/a-healthy-lifestyle---who-recommendations.
17. Paliogiannis P, Mangoni AA, Cangemi M, Fois AG, Carru C, Zinellu A. Serum albumin concentrations are associated with disease severity and outcomes in coronavirus 19 disease (COVID-19): a systematic review and meta-analysis. Clin Exp Med. 2021;21(3):343-54.
18. Chen C, Zhang Y, Zhao X, Tao M, Yan W, Fu Y. Hypoalbuminemia - An Indicator of the Severity and Prognosis of COVID-19 Patients: A Multicentre Retrospective Analysis. Infect Drug Resist. 2021;14:3699-710.
19. Zhang J, Wang X, Jia X, Li J, Hu K, Chen G, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clin Microbiol Infect. 2020;26(6):767-72.
20. Wu MA, Fossali T, Pandolfi L, Carsana L, Ottolina D, Frangipane V, et al. Hypoalbuminemia in COVID-19: assessing the hypothesis for underlying pulmonary capillary leakage. J Intern Med. 2021;289(6):861-72.
21. Lapenna D. Regarding: Hypoalbuminemia in COVID-19. J Intern Med. 2022;291(3):388-9.
22. Pfizer Laboratories Div Pfizer Inc. Fact Sheet for Nirmatrelvir Tablets/Ritonavir Tablets (co-packaged). Approval Number: HJ20220006. Date of Approval: February 11, 2022.
23. National Health Service. Pregnancy, breastfeeding and fertility while taking Paxlovid 2022 [Available from: https://www.nhs.uk/medicines/paxlovid/pregnancy-breastfeeding-and-fertility-while-taking-paxlovid/.
24. Jin'e P, Hui L, Xiao L, Lijun W, Shuo W, Haofan S, et al. Safety analysis of nirmatrelvir/ritonavir in the treatment of coronavirus disease 2019. ADRJ. 2023;25(1):11-6.
25. Weng C, Xie R, Han G, Yuan Y, Li S, Wang C, et al. Safety and Efficacy of Paxlovid Against Omicron Variants of Coronavirus Disease 2019 in Elderly Patients. Infect Dis Ther. 2023;12(2):649-62.
26. Li H, Gao M, You H, Zhang P, Pan Y, Li N, et al. Association of Nirmatrelvir/Ritonavir Treatment on Upper Respiratory Severe Acute Respiratory Syndrome Coronavirus 2 Reverse Transcription-Polymerase Chain Reaction (SARS-Cov-2 RT-PCR) Negative Conversion Rates Among High-Risk Patients With Coronavirus Disease 2019 (COVID-19). Clin Infect Dis. 2023;76(3):e148-e54.
27. Park JJ, Kim H, Kim YK, Lee SS, Jung E, Lee JS, et al. Effectiveness and Adverse Events of Nirmatrelvir/Ritonavir Versus Molnupiravir for COVID-19 in Outpatient Setting: Multicenter Prospective Observational Study. J Korean Med Sci. 2023;38(42):e347.
28. Tiseo G, Barbieri C, Galfo V, Occhineri S, Matucci T, Almerigogna F, et al. Efficacy and Safety of Nirmatrelvir/Ritonavir, Molnupiravir, and Remdesivir in a Real-World Cohort of Outpatients with COVID-19 at High Risk of Progression: The PISA Outpatient Clinic Experience. Infect Dis Ther. 2023;12(1):257-71.
29. Pinargote-Celorio H, Otero-Rodriguez S, Gonzalez-de-la-Aleja P, Rodriguez-Diaz JC, Climent E, Chico-Sanchez P, et al. Mild SARS-CoV-2 infection in vulnerable patients: implementation of a clinical pathway for early treatment. Enferm Infecc Microbiol Clin (Engl Ed). 2023.

30. Cvancara DJ, Baertsch HC, Lehmann AE, Humphreys IM, Farrell NF, Marshall TB, et al. Postmarketing Reporting of Paxlovid-Related Dysgeusia: A Real-World Pharmacovigilance Study. Otolaryngol Head Neck Surg. 2023;169(1):55-61.
31. Caronia L, Xi R, Margolskee RF, Jiang P. Paxlovid mouth likely is mediated by activation of the TAS2R1 bitter receptor by nirmatrelvir. Biochem Biophys Res Commun. 2023;682:138-40.
32. Mutoh Y, Umemura T, Nishikawa T, Kondo K, Nishina Y, Soejima K, et al. Real-World Experience of the Comparative Effectiveness and Safety of Molnupiravir and Nirmatrelvir/Ritonavir in High-Risk Patients with COVID-19 in a Community Setting. Viruses. 2023;15(3).
33. Bruno G, Giotta M, Perelli S, De Vita G, Bartolomeo N, Buccoliero GB. Early Access to Oral Antivirals in High-Risk Outpatients: Good Weapons to Fight COVID-19. Viruses. 2022;14(11).
34. Mazzitelli M, Mengato D, Sasset L, Ferrari A, Gardin S, Scaglione V, et al. Molnupiravir and Nirmatrelvir/Ritonavir: Tolerability, Safety, and Adherence in a Retrospective Cohort Study. Viruses. 2023;15(2).
35. Liu J, Pan X, Zhang S, Li M, Ma K, Fan C, et al. Efficacy and safety of Paxlovid in severe adult patients with SARS-Cov-2 infection: a multicenter randomized controlled study. Lancet Reg Health West Pac. 2023;33:100694.
36. Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of early molnupiravir or nirmatrelvir-ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2 wave: a retrospective cohort study. Lancet Infect Dis. 2022;22(12):1681-93.
37. Yang H, Yu X, Hou W, Liu X, Chen J, Zhang Y, et al. Effectiveness and safety of nirmatrelvir-ritonavir in kidney transplant recipients with severe kidney dysfunction infected with COVID-19. Antimicrob Agents Chemother. 2024;68(3):e0138423.
38. Chan GCK, Lui GCY, Wong CNS, Yip SST, Li TCM, Cheung CSK, et al. Safety Profile and Clinical and Virological Outcomes of Nirmatrelvir-Ritonavir Treatment in Patients With Advanced Chronic Kidney Disease and Coronavirus Disease 2019. Clin Infect Dis. 2023;77(10):1406-12.
39. Arbel R, Wolff Sagy Y, Hoshen M, Battat E, Lavie G, Sergienko R, et al. Nirmatrelvir Use and Severe Covid-19 Outcomes during the Omicron Surge. N Engl J Med. 2022;387(9):790-8.
40. Pfizer Laboratories Div Pfizer Inc. FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVID™ 2021 [Available from: https://labeling.pfizer.com/ShowLabeling.aspx?id=16474.
41. Han X, Gao D, Li C, Yuan X, Cui J, Zhao W, et al. Real-world effectiveness of nirmatrelvir-ritonavir versus azvudine in hospitalized patients with COVID-19 during the omicron wave in Beijing: a multicenter retrospective cohort study. BMC Infect Dis. 2024;24(1):57.
42. Zhou S, Feng J, Xie Q, Huang T, Xu X, Zhou D, et al. Traditional Chinese medicine shenhuang granule in patients with severe/critical COVID-19: A randomized controlled multicenter trial. Phytomedicine. 2021;89:153612.
43. Hu K, Guan WJ, Bi Y, Zhang W, Li L, Zhang B, et al. Efficacy and Safety of Lianhuaqingwen Capsules, a repurposed Chinese Herb, in Patients with Coronavirus disease 2019: A multicenter, prospective, randomized controlled trial [Phytomedicine 85 (2021) 153242]. Phytomedicine. 2021;93:153775.
44. Zhao Z, Li Y, Zhou L, Zhou X, Xie B, Zhang W, et al. Prevention and treatment of COVID-19 using Traditional Chinese Medicine: A review. Phytomedicine. 2021;85:153308.

45. Zhong W, Jiang X, Yang X, Feng T, Duan Z, Wang W, et al. The efficacy of paxlovid in elderly patients infected with SARS-CoV-2 omicron variants: Results of a non-randomized clinical trial. Front Med (Lausanne). 2022;9:980002.
46. Shao J, Fan R, Hu J, Zhang T, Lee C, Huang X, et al. Clinical Progression and Outcome of Hospitalized Patients Infected with SARS-CoV-2 Omicron Variant in Shanghai, China. Vaccines (Basel). 2022;10(9).
47. Razonable RR, O'Horo JC, Hanson SN, Arndt RF, Speicher LL, Seville TA, et al. Comparable Outcomes for Bebtelovimab and Ritonavir-Boosted Nirmatrelvir Treatment in High-Risk Patients With Coronavirus Disease-2019 During Severe Acute Respiratory Syndrome Coronavirus 2 BA.2 Omicron Epoch. J Infect Dis. 2022;226(10):1683-7.
48. Wan EYF, Yan VKC, Wong ZCT, Chui CSL, Lai FTT, Li X, et al. Effectiveness of molnupiravir vs nirmatrelvir-ritonavir in non-hospitalised and hospitalised patients with COVID-19: a target trial emulation study. EClinicalMedicine. 2023;64:102225.
49. Souza KM, Carrasco G, Rojas-Cortés R, Michel Barbosa M, Bambirra EHF, Castro JL, et al. Effectiveness of nirmatrelvir-ritonavir for the treatment of patients with mild to moderate COVID-19 and at high risk of hospitalization: Systematic review and meta-analyses of observational studies. PLoS One. 2023;18(10):e0284006.
50. Ombelet S, Castanares-Zapatero D, Desimpel F, Hulstaert F, Stordeur S, Roberfroid D. Effectiveness of nirmatrelvir-ritonavir on severe outcomes of COVID-19 in the era of vaccination and Omicron: An updated meta-analysis. J Med Virol. 2024;96(2):e29434.
51. Paraskevis D, Gkova M, Mellou K, Gerolymatos G, Psalida N, Gkolfinopoulou K, et al. Real-world Effectiveness of Molnupiravir and Nirmatrelvir/Ritonavir as Treatments for COVID-19 in Patients at High Risk. The Journal of Infectious Diseases. 2023;228(12):1667-74.
52. Paraskevis D, Gkova M, Mellou K, Mellou K, Gkolfinopoulou K, Kostaki EG, et al. 547. Molnupiravir and Nirmatrelvir/Ritonavir Effectiveness in Reducing the Risk for COVID-19 Disease Progression and Death: Open Forum Infect Dis. 2023 Nov 27;10(Suppl 2):ofad500.616. doi: 10.1093/ofid/ofad500.616. eCollection 2023 Dec.
53. Zheng J, Hong W, Zhou C, Hong D, Yan H, Shen Y. A retrospective analysis of factors associated with the length of hospital stay in COVID-19 patients treated with Nirmatrelvir / Ritonavir. Frontiers in Pharmacology. 2023;14.
54. Liu W, Song Q, Li F, Cao Y, Han Y, Wu J, et al. Real-World Effectiveness of Nirmatrelvir/Ritonavir and Dexamethasone Among Hospitalized Patients with COVID-19: A Prospective Cohort Study. Infect Drug Resist. 2023;16:5223-31.
55. Cheng FWT, Yan VKC, Wan EYF, Chui CSL, Lai FTT, Wong CKH, et al. Effectiveness of Molnupiravir and Nirmatrelvir-Ritonavir in CKD Patients With COVID-19. Kidney Int Rep. 2024;9(5):1244-53.
56. Kıskaç M, Soysal P, Smith L, Capar E, Zorlu M. What is the Optimal Body Mass Index Range for Older Adults? Ann Geriatr Med Res. 2022;26(1):49-57.
57. Statista. Population distribution in China in 2022, by five-year age group 2023 [Available from: https://www.statista.com/statistics/1101677/population-distribution-by-detailed-age-group-in-china/.

15. LIST OF SOURCE TABLES AND FIGURES

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