NON-INTERVENTIONAL STUDY
FINAL STUDY REPORT ABSTRACT

Title: A Multicenter, Retrospective, Observational Study Using Real-World Data to Describe the Safety, Treatment Pattern and Effectiveness of Nirmatrelvir/Ritonavir Among Patients Treated with Nirmatrelvir/Ritonavir in China

Date: 07 June 2024

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Keywords:
Nirmatrelvir/Ritonavir; Safety; Treatment Pattern; Effectiveness; COVID-19; Chinese Patients

Rationale and background:
Nirmatrelvir/ritonavir is an oral antiviral therapy approved for treatment of adults with mild to moderate coronavirus disease 2019 (COVID-19) at a high risk of progression to severe disease. [redacted] This study was designated as a Post-Authorization Safety Study (PASS) [redacted].

This final study report presents the results of the final analysis, including 1,047 patients' data from seven active study sites. 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, 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).

Research question and objectives:
To describe real-world safety, treatment pattern and effectiveness of nirmatrelvir/ritonavir among patients treated with nirmatrelvir/ritonavir in China.

Study design:
This study was a multicenter, retrospective, observational study. Patients who initiated nirmatrelvir/ritonavir treatment between 11 February 2022 and 31 August 2022 were included in this study.

Setting:
Study population consisted of patients who initiated treatment with nirmatrelvir/ritonavir between 11 February 2022 and 31 August 2022 during hospitalization. In the final analysis, 1,047 patients were included from seven sites.

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.

Subjects and study size:
Patients who either signed a dated informed consent document (ICD) or met the criteria of ICD waiver were continuously identified using the initiation date of nirmatrelvir/ritonavir (abstracted from the physician prescription records in hospitals). This final analysis included 1,047 eligible patients. These eligible patients must meet the following inclusion criteria and none of the exclusion criteria:

Inclusion criteria

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

Exclusion criteria

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

Variables and data sources:
Safety endpoints:

- Incidence of adverse events (AEs) and serious adverse events (SAEs) with explicit attribution to nirmatrelvir/ritonavir
- Proportion of patients with nirmatrelvir/ritonavir dose change due to AEs with explicit attribution to nirmatrelvir/ritonavir
- Proportion of patients experiencing safety related scenarios involving drug exposure

Treatment pattern endpoints:

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

- Treatment duration (days) of receiving nirmatrelvir/ritonavir

- Proportion of patients receiving concomitant COVID-19-related treatments by therapeutic use (including antiviral therapy, immunotherapy, and other)

- Treatment duration (days) of receiving concomitant COVID-19-related treatments by therapeutic use (including antiviral therapy, immunotherapy, and other)

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

Effectiveness endpoints:

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

- Time (days) to alleviation of all targeted COVID-19 signs and symptoms during the observation period

- Proportion of patients with two consecutive negative SARS-CoV-2 test results / cycle threshold (Ct) ≥ 35 (specimens collected in two different calendar days) among patients with at least two SARS-CoV-2 tests after initiation of nirmatrelvir/ritonavir treatment

- Time (days) to the first negative SARS-CoV-2 test / Ct ≥ 35 from two consecutive negative SARS-CoV-2 test results / Ct ≥ 35 (specimens collected in two different calendar days) among patients with at least two SARS-CoV-2 tests after initiation of nirmatrelvir/ritonavir treatment

Demographic and clinical characteristics:

- 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

Individual data were retrospectively abstracted from the hospital information system and laboratory information system to the electronic case report form from seven sites participating in the study (i.e., Sites 1002, 1003, 1004, 1006, 1007, 1008, and 1009).

Analysis methods:
Four analysis sets were generated. Specifically,

- The full analysis set (FAS) included all eligible patients.
- The safety analysis set (SAS) included all patients from FAS.
- The effectiveness analysis set 1 (EAS1) included all patients from FAS who had at least one of the effectiveness variables collected (see Variables and data sources section) and had the latest positive SARS-CoV-2 test result within 5 days prior to administration initiation. The EAS1 reflected the patients treated under clinical practice.
- 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 (as listed in the product label) for progression to severe COVID-19 at baseline. The EAS reflected the patients treated under clinical practice, and who had mild-to-moderate COVID-19 with at least one of the risk factors as listed in the product label.

During data extraction, the AEs/SAEs with explicit attribution to nirmatrelvir/ritonavir 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.

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

Due to partial ICD waiver (which applied to 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), 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% confidence intervals (CIs), in which site was considered as a cluster factor. Inverse probability of treatment weighting (IPTW) was employed to assign different weights to patients who died, and patients who did not die in the hospitals.

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 symptoms and signs), 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.

Results:

Patients:

In the final analysis, 1,047 eligible patients were included, with 58.4% being included with ICD waiver and 41.6% with signed and dated ICDs. All of them were evaluable for safety and treatment pattern analyses. Of 1,047 patients, 982 and 796 patients were included in the EAS1 and EAS, respectively.

- The median (range) age of the patients 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 ($24.0 \leq BMI < 28.0$ 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, Traditional Chinese

Medicine (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.

Safety:

- During a median (range) observation period of 10.0 (1.0, 50.0) days, of 1,047 patients,15.8% (165) experienced at least one AE with explicit attribution to nirmatrelvir/ritonavir. No SAEs with explicit attribution to nirmatrelvir/ritonavir were reported.
    - 0.6% (6) experienced severe AEs. 5 patients experienced Hypertension (all had ongoing medical history of hypertension and experienced exacerbation of hypertension 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.
    - 0.6% (6) of the total patients discontinued nirmatrelvir/ritonavir treatment due to AEs. By preferred term, 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 one 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.
    - Dysgeusia was the most frequently reported AE (5.0%), followed by Diarrhoea (2.4%) and Hypoalbuminaemia (2.0%).
- Of the 1,047 patients, 8.1% (85) were reported to have nirmatrelvir/ritonavir overdose 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 (0.1%) patient experienced nirmatrelvir/ritonavir exposure during breast feeding. No scenarios were associated with any AEs or SAEs.
- Of the total 1,047 patients, the sampling weight adjusted death rate was 1.9% (60).
    - No deaths were due to AEs that were explicitly attributed to nirmatrelvir/ritonavir.
    - Of the 60 patients, the sampling weight adjusted death rate was 0.2% (7) for COVID-19 being one of the causes.
    - 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).

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 with nirmatrelvir/ritonavir and 4.3% received interrupted courses 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 5-6 days for the uninterrupted treatment course, and 11.0 (2.0, 18.0) days with 65.9% (29/44) patients being treated for over 10 days for the interrupted treatment course.

- During a median (range) observation period of 10.0 (1.0, 50.0) days, of the total of 1,047 patients, 24.5% and 75.5% received nirmatrelvir/ritonavir as monotherapy and combination therapy with other COVID-19 related medications, respectively. 84.8% (190/224) of the patients with monotherapy and 82.0% (588/717) of the patients with combination therapy received a full course of nirmatrelvir/ritonavir treatment for 5-6 days.

- For the other COVID-19 related treatments, of the total of 1,047 patients, 0.4% received antiviral therapies other than nirmatrelvir/ritonavir (i.e., COVID-19 human immunoglobulin), 10.5% received immunotherapies (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.

Effectiveness:

- After treatment with nirmatrelvir/ritonavir, during a median (range) observation period of 10.0 (1.0, 50.0) days, the sampling weight adjusted proportion of patients with COVID-19 progression to severe/critical or death from any cause was 5.3% (95% CI: 0.0%-11.8%) in EAS1 and 5.8% (95% CI: 0.0%-13.1%) in EAS.

    - Among them, 33 patients in EAS1 and 26 patients in EAS experienced COVID-19 progression from mild/moderate to severe/critical illness and none of these cases resulted in death; and another 47 patients in EAS1 and 37 patients in EAS died from any cause.

    - Additionally, among these death cases, 6 patients in EAS1 and 3 patients in EAS died with COVID-19 being one of the causes.

- 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% [95% CI: 0.8% to 17.0%] in EAS1 and 9.0% [95% CI: 0.00% to 18.11%] in EAS for ≥ 70 to < 80 years, 10.8% [95% CI: 0% to 22.9%] in EAS1 and 11.0% [95% CI: 0.00% to 23.24%] in EAS for ≥ 80 years vs. 0.7% [95% CI: 0% to 1.9%] in EAS1 and 0.9% [95% CI: 0.00% to 2.65%] in EAS for < 60 years and 2.8%

[95% CI: 0% to 7.1%] in EAS1 and 2.9% [95% CI: 0.00% to 7.50%] in EAS for ≥ 60 to < 70 years).

- Over 50% of patients in both EAS1 (54.0% of the 769 patients) and EAS (55.2% of the 609 patients) had alleviation of all targeted COVID-19 signs and symptoms during a median (range) observation period of 11.0 (1.0, 37.0) days (for both EAS and EAS1).
    - The median time to alleviation of all targeted COVID-19 signs and symptoms was 9.0 (95% CI: 8.0-10.0) days in both EAS1 and EAS.
- Over 95% of the patients in EAS1 and EAS had achieved two consecutive negative SARS-CoV-2 test results after nirmatrelvir/ritonavir initiation, during a median (range) observation period of 11.0 (3.0, 50.0) days (for both EAS and EAS1).
    - The median time to two consecutive negative SARS-CoV-2 test results was 7.0 (95% CI: 7.0-8.0) days in EAS1 and 8.0 (95% CI: 7.0-8.0) days in EAS.

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 patient 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 s observed in patients aged 70 years or above (8.9% [95% CI: 0.8%-17.0%] for ≥ 70 to < 80 and 10.8% [95% CI: 0%-22.9%] for ≥ 80) than those aged less 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.

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