30 January 2025
EMA/53726/2025
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Paxlovid

Nirmatrelvir / Ritonavir

Procedure no: EMEA/H/C/005973/P46/024

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	02 Dec 2024	02 Dec 2024
☐	CHMP Rapporteur Assessment Report	06 Jan 2025	02 Jan 2025
☐	CHMP members comments	20 Jan 2025	20 Jan 2025
☐	Updated CHMP Rapporteur Assessment Report	23 Jan 2025	N/A
☒	CHMP adoption of conclusions:	30 Jan 2025	30 Jan 2025

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1. Introduction

On 21 October 2024, the Marketing Authorisation Holder (MAH) submitted a completed paediatric study for Paxlovid (study C4671048), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Of note, 2 paediatric subjects were included in this study, which explains the submission of this clinical study report under the "article 46" umbrella. However, this study is not relevant to provide paediatric data for Paxlovid.

A short critical expert overview was also provided.

2. Scientific discussion

2.1. Information on the development program

This study is being submitted in accordance with Article 46 of the Paediatric Regulation (European Commission [EC] No 1901/2006). The MAH is submitting the CSR under Article 46 within 6 months of completion to report paediatric data. The MAH is not proposing any amendments to the Paxlovid EU Summary of Product Characteristics to include data from Study C4671048.

2.2. Information on the pharmaceutical formulation used in the study

Study C4671048 was a non-interventional, retrospective cohort study. Some participants had been treated with the commercial nirmatrelvir/ritonavir product (Paxlovid pack: nirmatrelvir tablet 150 mg + ritonavir tablet 100 mg) as part of their therapeutic care for COVID-19.

2.3. Clinical aspects

2.3.1. Introduction

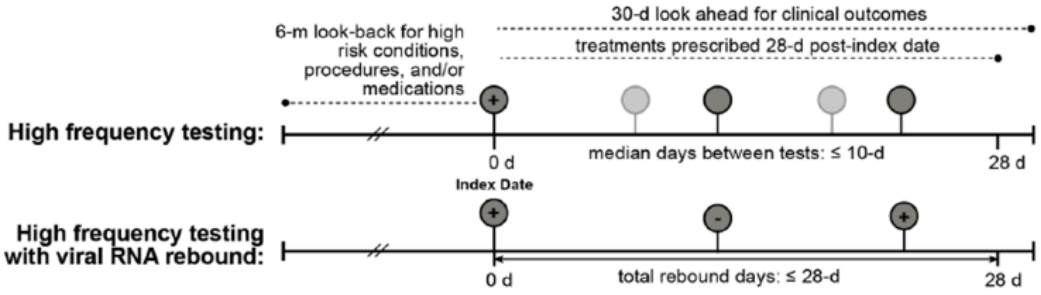
The submitted Critical Expert Overview supports the submission of the final CSR for Study C4671048, Viral SARS-CoV-2 Rebounds in Commercial Pharmacy-Based SARS-CoV-2 PCR Testing, in accordance with Article 46 of the Paediatric Regulation (EC No. 1901/2006). Of the 372 participants who received nirmatrelvir/ritonavir, 2 were paediatric patients.

2.3.2. Clinical study

Study C4671048: Viral SARS-CoV-2 rebounds in commercial pharmacy-based SARS-CoV-2 PCR testing.

Description

This was a non-interventional, retrospective cohort study using secondary data sources containing structured data from the US. This study included participants with a positive SARS-CoV-2 test.



(Upper) High-frequency testing and (Lower) High-frequency testing with viral RNA rebound, along with relevant clinical information indicated by dashed lines. Each circle represents a SARS-CoV-2 RT-qPCR test with the darker shade indicating the minimum required tests to meet the definition and the lighter shade reflecting the possibility of >3 tests. The index date is the first positive test within 28 days.

Figure 1. Schematic Representation of Study Population

Methods

This study was conducted using SARS-CoV-2 diagnostic testing data from the Helix Respiratory Registry with linkage to the Komodo Healthcare claims data during the period between 01 June 2020 and 28 February 2023.

Study participants

Participants in the main cohort were required to meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Age ≥ 12 years on the index date (i.e., first confirmed positive SARS-CoV-2 rRTPCR test within a positive - negative – positive sequence that occurs within 28 days)

2. High frequency (volume) tester, as defined as tested for SARS-CoV-2 at least 3 times (including the test on the index date) within 28 days of the index date and median time between tests (positive or negative) is at most 10 days. Alternative definitions using maximum and minimum boundaries for time between tests may be explored.

3. Sufficient enrolment and clinical encounter data in Komodo Healthcare claims, through 6-months of continuous medical and/or pharmacy claims enrolment (<= 30-day gaps allowed) were required, to allow at least 1 year of a baseline period prior to the index date to assess medical history.

Treatments

This was a non-interventional retrospective study. The nirmatrelvir/ritonavir treatment status was collected. It was assumed that participants in the nirmatrelvir/ritonavir treated group took Paxlovid as prescribed and in line with the approved product information.

Objectives

The primary objectives were as follows:

Objective 1: To estimate viral SARS-CoV-2 rebound rates (primary definition: 1. a positive test (at the index date i.e., first confirmed positive SARS-CoV-2 rRT-PCR test within a positive - negative – positive sequence that occurs within 28 days), followed by a single negative test, followed by a positive test - within 28 days, or 2. 1 or more positive tests at the index date, followed by 1 or more negative tests, followed by a positive test within same 28 day time span), prior to the Omicron era and during the Omicron era (defined as December 1, 2021 to present), in high frequency (volume) SARS-CoV-2

diagnostic testers (primary definition: 1 or more positive tests followed by 1 or more negative tests followed by 1 or more positives within same 28 day time span and median time between tests (positive or negative) is at most 10 days).

Objective 2: To estimate viral SARS-CoV-2 rebound rates (using the primary definition of viral SARS-CoV-2 rebound), prior to the Omicron era and during the Omicron era, in high frequency (volume) SARS-CoV-2 diagnostic testers (using the primary definition of high frequency testing), among those treated with Paxlovid/nirmatrelvir-ritonavir for SARS-CoV-2 versus those with no evidence of SARS-CoV-2 treatment (untreated for SARS-CoV-2), stratified by:

a. Demographics of participants

b. Time from first positive test to treatment (if treated).

c. Participants at high-risk for progression to severe SARS-CoV-2 versus those not at high-risk, if sample size allows. If sample size is limited, age (<50 years of age versus 50+ years of age) will be used as a proxy for high-risk for progression to severe SARS-CoV-2 status)

d. Co-infections

e. Vaccinated against SARS-CoV-2 (has received at least 1 dose) and time since last vaccine dose > 6 months vs. ≤ 6 months

f. Multiple SARS-CoV-2 treatment prescription status

Outcomes/endpoints

The following primary endpoint was examined:

- Viral SARS-CoV-2 rebound, where the main definition defines rebound as 1) a positive test (at the index date), followed by a single negative test, followed by a positive test - within 28 days or 2) 1 or more positive tests starting at the index date, followed by 1 or more negative tests, followed by a positive test within the same 28-day time span. The index date was defined as the first positive test date.

The following exploratory endpoints were examined:

- Clinical outcomes (within 30 days of index date), based on healthcare utilisation following viral SARS-CoV-2 rebound

- Hospitalisation

Sample size

This was a non-interventional study with no *a priori* hypotheses specified; therefore, sample size calculations are not applicable.

Statistical Methods

Unadjusted descriptive analyses were performed among high-frequency testing infections, and stratified by Omicron-era and SARS-CoV-2 treatment status to estimate the overall viral SARS-CoV-2 rebound rate. As a proxy for high-risk status, unadjusted viral rebound rates were also stratified by age group (below or above 50 years, 65 years). Analyses were also conducted among patients with ≥1 confirmed vaccination as well as patients at high-risk status for progression to severe SARS-CoV-2.

Results

Number analysed

A cohort of 30,646 unique individuals was identified who had a combined 30,766 infection periods where testing occurred at a high frequency (at least 3 tests during the infection with a median interval between tests at most 10 days). The data from this cohort of 30,646 unique individuals were then split into 3 comparison groups (untreated patients pre-Omicron, untreated patients within Omicron-era, and nirmatrelvir/ritonavir [NMV-r] treated patients).

Baseline data

The cohort is largely similar between the three comparison groups, with the NMV-r treated group skewing more female (57%), older (median age 58 years), more likely to be vaccinated (73%), and more likely to be high risk (based on underlying medical conditions) (73%).

	Untreated		NMV-r Treated
	Pre-Omicron (n = 18,005)	Omicron-Era (n = 12,281)	Omicron-Era (n = 372)
Male, n (%)	8,882 (49%)	5,584 (45%)	161 (43%)
Age, years (mean [sd])	40.1 (15.9)	44.7 (16.9)	57.6 (14.9)
<65 years	16,749 (93%)	10,588 (86%)	246 (66%)

Figure 2. Demographics and clinical characteristics of high frequency SARS-CoV-2 diagnostic testers from 2020-2022

	Untreated		NMV-r Treated
	Pre-Omicron (n = 18,005)	Omicron-Era (n = 12,281)	Omicron-Era (n = 372)
≥65 years	1,256 (7%)	1,693 (14%)	126 (34%)
Vaccinated (≥1 SARS-CoV-2 vaccine)	1,277 (7.1%)	6,593 (54%)	272 (73%)
Continuous 6-month mx and rx enrollment*	5,068 (26%)	3,479 (28%)	131 (35%)
High-risk** within those with 6-month enrollment*	2,415 (48%)	1,893 (54%)	96 (73%)
Hospitalized within 30-d of index date	154 (0.9%)	92 (0.8%)	1 (0.3%)
ED visit within 30-d of index	798 (4%)	337 (3%)	21 (13%)
Geographic Region			
Northeast	1,754 (10%)	1,047 (9%)	46 (12%)
Midwest	1,939 (11%)	1,077 (9%)	13 (4%)
South	12,091 (67%)	7,735 (63%)	235 (63%)
West	1,387 (8%)	1,897 (15%)	50 (13%)
Not Available	834 (5%)	525 (4%)	28 (8%)

*allowed for a 30-day gap in coverage
**high-risk status for progression to severe SARS-CoV-2 infection
Abbreviations: mx, medical; NMV-r, nirmatrelvir/ritonavir; rx, pharmacy; sd, standard deviation.

Efficacy results

Main efficacy endpoint

The viral rebound rate in NMV-r treated patients was 3.5% (95% CI: 2.0%, 5.7%), 1.5% (95% CI: 1.3%, 1.7%) in untreated patients in the Omicron-era, and 1.9% (95% CI: 1.7%, 2.1%) in untreated patients infected during the pre-Omicron era. The differences in the NMV-r treated viral rebound rate compared to the rate in untreated patients during the pre-Omicron and Omicron-era are statistically significant by Fisher's exact test, with p-values of 0.03 and 0.004, respectively.

This overall relationship in viral rebound rates is consistent in a sensitivity analysis using alternative definitions of high-frequency testing.

Table 1. Viral SARS-CoV-2 rebound rates and characteristics of patient cohort, stratified by risk group, Omicron era, and NMV-r treatment.

	High-Frequency Testing Cohort			High-Frequency Testing Cohort with High-Risk Status** and 6-month Continuous Healthcare Claims Enrollment*		
	Pre-Omicron, Untreated	**Omicron-Era, Untreated**	**NMV-r Treated**	**Pre-Omicron, Untreated**	**Omicron-Era, Untreated**	**NMV-r Treated**
Overall viral SARS-CoV-2 rebound rate (rebound / high frequent testing infection)	334/18,018 (1.9%)	179/12,310 (1.5%)	13/372 (3.5%)	46/2,417 (1.9%)	21/1,898 (1.1%)	4/96 (4.2%)
Viral rebound rate in vaccinated	33/1,278 (2.6%)	91/6,601 (1.3%)	10/272 (3.7%)	5/247 (2.0%)	17/1,250 (1.4%)	2/67 (3.0%)
Clinical outcomes in high frequency testing infections						
% of high frequency patients hospitalized within 30-d of index date	154/18,018 (<1%)	92/12,310 (<1%)	1/372 (<1%)	49/2,417 (2.0%)	36/1,898 (1.9%)	0/96 (0%)
% of high frequency patients who visited the ED within 30-d of index date	798/18,018 (4.4%)	337/12,310 (2.7%)	21/372 (5.6%)	193/2,417 (8.0%)	83/1,898 (4.4%)	9/96 (9.4%)
Clinical outcomes in viral rebounds						
% of viral rebound patients hospitalized within 30-d of index date	4/334 (1.2%)	0/179 (0%)	0/13 (0%)	1/46 (2.2%)	0/21 (0%)	0/4 (0%)
% of viral rebound patients who visited the ED within 30-d of index date	16/334 (4.8%)	4/179 (5.1%)	1/13 (7.7%)	3/46 (6.5%)	0/21 (0%)	1/4 (25%)

*with a 30-day allowable gap in coverage
**high-risk status for progression to severe SARS-CoV-2
Abbreviations: %, percentage; NMV-r, nirmatrelvir/ritonavir.

Sensitivity analyses with lower thresholds for the maximum median time between tests (7 or 14 days) provide comparable viral rebound rates: 2.7% to 3.5% in NMV-r treated infections, 1.4% to 1.6% in untreated patients infected during the Omicron-era, and 1.7% to 2.5% in untreated patients infected pre-Omicron.

Table 2. Supplementary table. Sensitivity analyses with alternative definitions of hight-frequency tester using a threshod for the maximum median time between tests of seven and 14-days

Viral RNA Rebound Rate (point estimate, 95% CI)	Pre-Omicron, Untreated	Omicron-Era, Untreated	Omicron-Era, NMV-r Treated
≤ 7-day median test interval	295/11,970 (2.5%, 2.2-2.8%)	163/10,298 (1.6%, 1.4-1.8%)	8/295 (2.7%, 1.3-5.1%)
≤ 14-day median test interval	363/21,431 (1.7%, 1.5-1.9%)	190/13,371 (1.4%, 1.2-1.6%)	14/404 (3.5%, 2.0-5.6%)

Subgroup analyses

- By age group:

Using age group as a proxy for high-risk status gives a slightly higher rate of viral rebound in treated patients over the age of 65, but the CIs overlap with that of treated patients below the age of 65 and of treated patients overall. For the 65+ group, the viral rebound rate in NMV-r treated infections was 4.8% (0.2% to 9.6%), 1.5% (1.0% to 2.1%) for untreated patients infected during the Omicron era, and 1.8% (1.7% to 2.1%) for untreated patients infected during the pre-Omicron era.

When the high-risk age range is expanded to 50 years and above, the viral rebound rates become more comparable to the overall cohort. The viral rebound rate in NMV-r treated 50+ patients is 3.0% (1.4% to 5.6%, n=276), while it is 1.3% (1.0% to 1.7%) for untreated patients infected during the Omicron-era, and 1.8% (1.4% to 2.2%) in untreated patients infected during the pre-Omicron era.

Stratification for the paediatric age group was not completed as this was not a planned study objective. In addition, there was an insufficient sample size for the paediatric age group (the study only enrolled 2 paediatric patients).

- By vaccination:

Among vaccinated individuals, the viral rebound rate in NMV-r treated infections is 3.7% (95% CI: 1.9%, 6.4%), 1.3% (95% CI: 1.1%, 1.7%) in untreated Omicron-era infections, and 2.6% (95% CI: 1.8%, 3.6%) in untreated pre-Omicron infections. The difference in viral rebound rate between NMV-r treated infections and untreated Omicron-era infections is statistically significant (p=0.006), while the difference in viral rebound rate between NMV-r treated infections and untreated pre-Omicron infections is not (p=0.3).

- By high-risk status:

In high-risk patients, the viral rebound rate in NMV-r treated infections is 4.2% (95% CI: 1.2%, 8.3%), 1.1% (95% CI: 0.7%, 1.6%) in untreated Omicron-era infections, and 1.9% (95% CI: 1.6%, 2.6%) in untreated pre-Omicron infections. Similar to the results in the vaccinated cohort, the difference in viral rebound rate between NMV-r treated infections and untreated Omicron-era infections is statistically significant (p=0.029), while the difference in viral rebound rate between NMV-r treated infections and untreated pre-Omicron infections was not statistically significant (p=0.12).

Rebound Viral Loads

Viral SARS-CoV-2 rebounds in NMV-r treated infections did not have higher viral loads than viral SARS-CoV-2 rebounds in untreated infections. The low viral titers in these samples suggest the majority of viral rebounds identified in this analysis are likely caused by limited test specificity towards the end of an infection, and do not represent a drastic increase in viral load. The time to viral rebound, defined as the number of days between the index date and the first positive test after the negative test(s), is also comparable between the three groups.

The high median values of the rebound Cq value (i.e. low viral load) further indicate that high viral load rebounds are, in general, rare. Using a Cq value of 28 as a threshold for high viral load rebound, we see that high viral load rebounds comprise only 8% of rebounds in NMV-r treated infections, 11% of untreated Omicron-era infections, and 5% of viral rebounds in untreated pre-Omicron infections.

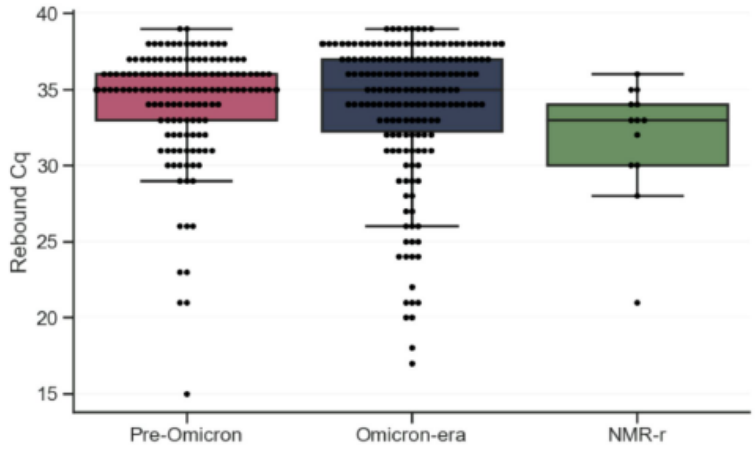


Figure 3. Cq value of first positive test after viral SARS-CoV-2 rebound negative by treatment group. Treated infections are not included in the re-Omicron and Omicron-era groups (see 'Treatment' in Definitions section).

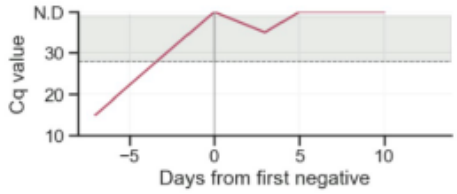
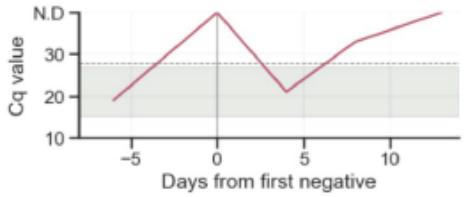
Viral rebound type	Representative viral kinetics profile	Group	Prevalence
Low viral load (Rebound Cq ⩾ 28)		Pre-Omicron Omicron-era NMV-r	95% (90-97%) 89% (84-93%) 92% (69-99%)
High viral load (Rebound Cq < 28)		Pre-Omicron Omicron-era NMV-r	5% (3-10%) 11% (7-16%) 8% (1-31%)

Figure 4. Viral SARS-CoV-2 rebounds stratified by rebound viral load and treatment groups. Gray bands indicate the range (minimum-maximum) of rebound Cq values within each category (weak or strong).

Clinical outcomes

Although the sample sizes for patients treated with NMV-r and/or exhibiting rebound are quite small for this analysis (e.g., the number of NMV-r treated viral rebound infections in this group is only 13), the rates of hospitalisation were comparable between the overall cohort and NMV-r treated infections (both were <1%), as well as between the overall cohort (<1%) and infections with the viral rebound (0%). The trend is similar for emergency department visits occurring within 30 days.

Safety results

N/A.

2.3.3. Discussion on clinical aspects

Study C4671048 was submitted in accordance with Article 46 of the Paediatric Regulation, however, no paediatric data can be discussed given only 2 paediatric patients (between 12 to less than 18 years old) were included in this study.

This study was an observational retrospective cohort study assessing the prevalence of viral SARS-CoV-2 rebound across a large cohort of patients (>30.000 US patients) from Helix Laboratories and Komodo Healthcare databases. To our knowledge, this is the larger cohort study performed to specifically assess COVID-19 viral rebound. Such study has its methodological limits for the interpretation of the results, but remains interesting, in addition to the available literature data, to further substantiate the SARS-CoV-2 rebound and the potential link with Paxlovid.

Overall, the final results of this study have reported:

- a frequency of COVID-19 viral rebound (1.5% to 3.5%) similar or lower to those reported in the literature and other clinical studies (e.g. 4-6% in EPIC-HR study);

- a higher frequency of viral rebound in subjects treated with Paxlovid in comparison to untreated subjects;

- a viral rebound usually with a low viral load and without significant clinical outcomes.

In addition, no specific individual categories (e.g. depending on the age, vaccination or high-risk status) could be highlighted to be significantly more susceptible to experience COVID-19 viral rebound.

These results are consistent with the available data from clinical studies assessing SARS-CoV-2 rebound. A hypothesis of the viral load rebound after nirmatrelvir/ritonavir treatment is that this phenomenon corresponds to a window to rebound after the end of the 5-day treatment and before the immune system can mount an effective response.

However, as correctly discussed by the MAH, several limitations of this study could impact the interpretation of these results. The nature of the study (observational retrospective) could introduce a selection bias given the retrospective inclusion of patients who satisfy certain testing patterns. Only subjects with high frequency testing were include (in order to detect the viral rebound), that could biased the results if SARS-CoV-2 positive subjects treated with nirmatrelvir/ritonavir were more likely to continue to be tested after the first negative test than subjects who were not treated, given the knowledge of the potential association between viral rebound and Paxlovid treatment. In addition, by requiring a negative test in the rebound definition, viral rebounds may be undercounted if the viral load never reaches the undetected level in an RT-qPCR test. Theoretically, this undercount of rebounds is more likely to impact viral rebound in untreated infections than NMV-r treated infections where the decrease of the viral load is greater and faster with the antiviral treatment. Furthermore, this study was not design to collect clinical outcomes data during viral rebound, limiting its interpretation for the clinical consequences of such rebound.

In conclusion, the results of this study are consistent with the current knowledge of the COVID-19 viral rebound after nirmatrelvir/ritonavir treatment. The current paragraph “viral load rebound” in section 5.1 of Paxlovid SmPC, based on study EPIC-HR data, is still considered relevant and no further modifications are considered necessary.

3. Overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.