EMADOC-1700519818-2050861
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMA/VR/0000262540

Invented name: Paxlovid

International non-proprietary name: nirmatrelvir / ritonavir

Marketing authorisation holder (MAH): Pfizer Europe MA EEIG

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**
☐	Submission deadline	28 March 2025	24 March 2025
☐	Validation	13 April 2025	8 April 2025
☐	Start date	14 April 2025	14 April 2025
☐	CHMP Rapporteur AR	19 May 2025	20 May 2025
☐	CHMP Comments	2 June 2025	2 June 2025
☐	Updated CHMP Rapporteur AR	5 June 2025	5 June 2025
☐	Start of CHMP written procedure	10 June 2025	10 June 2025
☐	CHMP Outcome - RSI	12 June 2025	12 June 2025
☐	TT extension request	14 July 2025	14 July 2025
☐	Submission of responses	02 Sep 2025	02 Sep 2025
☐	Restart	03 Sep 2025	03 Sep 2025
☐	CHMP Rapporteur AR	17 Sep 2025	17 Sep 2025
☐	CHMP Comments	22 Sep 2025	22 Sep 2025
☐	Updated CHMP Rapporteur AR	25 Sep 2025	30 Sep 2025
☐	Start of CHMP written procedure	30 Sep 2025	30 Sep 2025
☒	CHMP Outcome	02 Oct 2025	02 Oct 2025

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 24 March 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		Type
C.I.13	C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Variation type II

Submission of the final efficacy, safety, and PK analyses from study C4671034 following CHMP outcome for procedure EMA/H/C/005973/P46. This is an Interventional Efficacy and Safety, Phase 2, Randomized, Double-Blind, 3-Arm Study to Investigate Nirmatrelvir/Ritonavir in Nonhospitalized Participants at Least 12 Years of Age With Symptomatic COVID-19 Who Are Immunocompromised.

The requested variation(s) proposed no amendments to the Product information.

GLP/GCP inspections

The following clinical study site was inspected in connection to this variation:

Site name	Address	Outcome
Site 1001	Tampa, FL, United States	GCP quality issues, efficacy data from this site were excluded (n=5 subjects)

2. Overall conclusion and impact on the benefit/risk balance

Study C4671034 was a Phase II study comparing 3 dosing durations of Paxlovid (5, 10 and 15 days) in immunocompromised subjects with symptomatic COVID-19. Indeed, there is a need to assess higher treatment duration of Paxlovid in this population, for whom higher viral clearance is expected. Of note, this study was not powered to statistically compare these 3 doses regimen, without formal comparative statistical analyses, and the efficacy results are expected to be rather informative than statistically significant.

A total of 156 patients were randomized. The demographic and disease characteristics at baseline are overall similar across the 3 treatment duration groups. Almost all subjects in the 3 groups (94%) were treated in the 5 days since first symptom, in accordance to Paxlovid SmPC, but more subjects in the group 3 (15 days treatment duration) were treated earlier (54.9% <3 days since first symptom vs 37% and 39% in the other groups) which could favour the efficacy results in this group.

As regards the preliminary efficacy results, there is no significant differences between the 3 treatment duration groups. However, a trend to higher antiviral efficacy could be highlighted in the 2 higher treatment duration groups (10 and 15 days) in comparison to the currently approved treatment duration group (5 days). Furthermore, the 4 subjects who had still detectable SARS-CoV-2 RNA levels at Day 44 were all in the 5 days group, supporting this hypothesis of higher antiviral efficacy of treatment duration >5 days for immunocompromised subjects. In addition, the MAH has provided a post-hoc analysis reporting in severely immunocompromised patients a higher number of subjects with prolonged periods of viral replication and viral rebound following the end of treatment in the 5 days treatment group vs the 10 days and the 15 days treatment groups. Of note, no differences between the 10 days and the 15 days treatment groups was reported. These data suggest that a prolonged

period of treatment could be of interest to mitigate the risk of viral rebound after the end of treatment in severely immunocompromised patients. The clinical relevancy of this higher duration of treatment is unknown.

No new safety concern was observed during this study. No conclusion can be drawn whether longer treatment durations are associated to an increase in the frequency and/or severity of Paxlovid-related AEs. Although no significant safety concern is highlighted, it could however be noted that the proportion of Grade 3-4 TEAEs is increased with the duration of treatment, with higher rates of nervous system disorders (notably dysgeusia and headache) and gastrointestinal disorders (notably nausea and vomiting) in the longer treatment duration group. Therefore, considering the efficacy and safety data, a 15 days duration of treatment cannot be privileged compared to the 10 days duration of treatment.

In conclusion, the CHMP considers it appropriate to state in the SmPC that for patients with severe immunosuppression (e.g. active haematologic malignancies, haematopoietic stem cell transplantation, CAR T-cell therapy or B-cell depleting therapies), the data suggest that a total treatment duration up to 10 days might mitigate the risk of virological rebound.

The benefit-risk balance of Paxlovid remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		**Type**
C.I.13	C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Variation type II

Update of sections 4.2 and 5.1 of the SmPC in order to include information on the treatment of patients with severe immunosuppression, based on the final efficacy, safety, and PK analyses from study C4671034 following CHMP outcome for procedure EMA/H/C/005973/P46. This is an Interventional Efficacy and Safety, Phase 2, Randomized, Double-Blind, 3-Arm Study to Investigate Nirmatrelvir/Ritonavir in Nonhospitalized Participants at Least 12 Years of Age With Symptomatic COVID-19 Who Are Immunocompromised.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex I are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

SmPC new text

Section 4.2

(…)

Special populations

(…)

Severely immunocompromised population

Data are limited in severely immunocompromised individuals. A treatment duration of 10 days may help to mitigate the risk of virological rebound in patients with severe immunodepression (e.g. active haematologic malignancies, haematopoietic stem cell transplantation, CAR Tcell therapy or Bcell depleting therapies) (see section 5.1).

Section 5.1

Clinical efficacy

Posthoc subgroup analysis in severely immunocompromised participants

A post-hoc subgroup analysis in severely immunocompromised participants (e.g., active haematologic malignancies, haematopoietic stem cell transplantation, CAR T-cell therapy or B-cell depleting therapies) has been performed and was derived from EPIC-IC (C4671034) study in immunocompromised participants. In participants who were severely immunocompromised, the median time to achieving NP swab SARS-CoV-2 RNA <LLOQ was numerically longer in the 5-day treatment group (28 days) compared with the 10-day (13 days) and 15-day (15 days) treatment groups. The proportion of participants with both a positive SARS-CoV-2 rapid antigen test and any selfreported targeted symptom of COVID 19 from Day 15 through Day 44 was 33.3% (6 of 18 participants), 6.3% (1 of 16 participants), and 0% (0 of 16 participants) in the 5-, 10- and 15-day nirmatrelvir/ritonavir treatment groups, respectively. The incidence of viral RNA rebound observed in the severely immunocompromised participants was 25% (5 of 20 participants), 0% (0 of 17 participants) and 5% (1 of 20 participants) in the 5-, 10-, and 15day Paxlovid treatment groups, respectively.

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Following CHMP outcome for Procedure EMA/H/C/005973/P46, the MAH is hereby submitting a Type II variation including the C4671034 data, to investigate nirmatrelvir/ritonavir in non-hospitalized subjects with symptomatic COVID-19 who are immunocompromised. Patients with COVID-19 who are immunocompromised are at increased risk of progressing to severe illness due to prolonged infection, limited contribution by the immune system in clearing the infection, and increased potential for viral resistance. Therefore, patients who are immunocompromised may benefit from extended treatment durations.

Study C4671034 is a Phase II study comparing 3 dosing durations of nirmatrelvir/ritonavir in immunocompromised subjects with symptomatic COVID-19. The purpose of this study is to evaluate the efficacy and safety of nirmatrelvir/ritonavir (5, 10, and 15-day dosing durations) for the treatment of COVID-19 in non-hospitalized symptomatic participants who are immunocompromised. The topline results of study C4671034 were already assessed within the procedure MEA 20.1, and the responses to requests received following this procedure are included in this procedure.

6. Clinical Pharmacology aspects

6.1. Methods – analysis of data submitted

The final PK analyses from study C4671034 were provided (*see below Clinical Efficacy section for details of study C4671034*). Blood samples were collected at pre-specified time points in the study protocols. Plasma samples were analyzed for nirmatrelvir concentrations using a validated analytical method in compliance with Pfizer standard operating procedures.

These PK data were compared to those previously available from the pivotal study C4671005 (EPIC-HR), a Phase 2/3, double-blind, 2-arm study assessing nirmatrelvir/rtv vs placebo in non-hospitalized symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness.

For both studies, nirmatrelvir samples were analyzed at York Bioanalytical Solutions (York, UK) using a validated LC-MS/MS using turbo ion spray ionization with multiple reaction monitoring detection mode. The LLOQ for nirmatrelvir plasma sample was 10 ng/mL.

To further compare nirmatrelvir exposure in immunocompromised versus non-immunocompromised patients, a previously developed PopPK model from combined 13 Phase 1/2/3 studies was utilized to generate the 90% CI for 100 subjects. Covariates were sampled from a multivariate normal density based on the covariance of age, weight and nCLCR observed in the PopPK data in participants with COVID-19 and nCLCR ≥60 mL/min/1.73 m2 in Study C4671005. Only sampled subjects with nCLCR ≥90 mL/min/1.73 m2 were retained, and body weight was truncated to the range observed from the adults with COVID-19 data (Study C4671005). Nirmatrelvir plasma concentration profiles were simulated (1000 subproblems) using the parameter estimates from the PopPK model incorporating inter-individual variability and random effects to compute nirmatrelvir exposures on Day 5. Thereafter, the observed data from Study C4671034 was overlaid on the 90% CI generated.

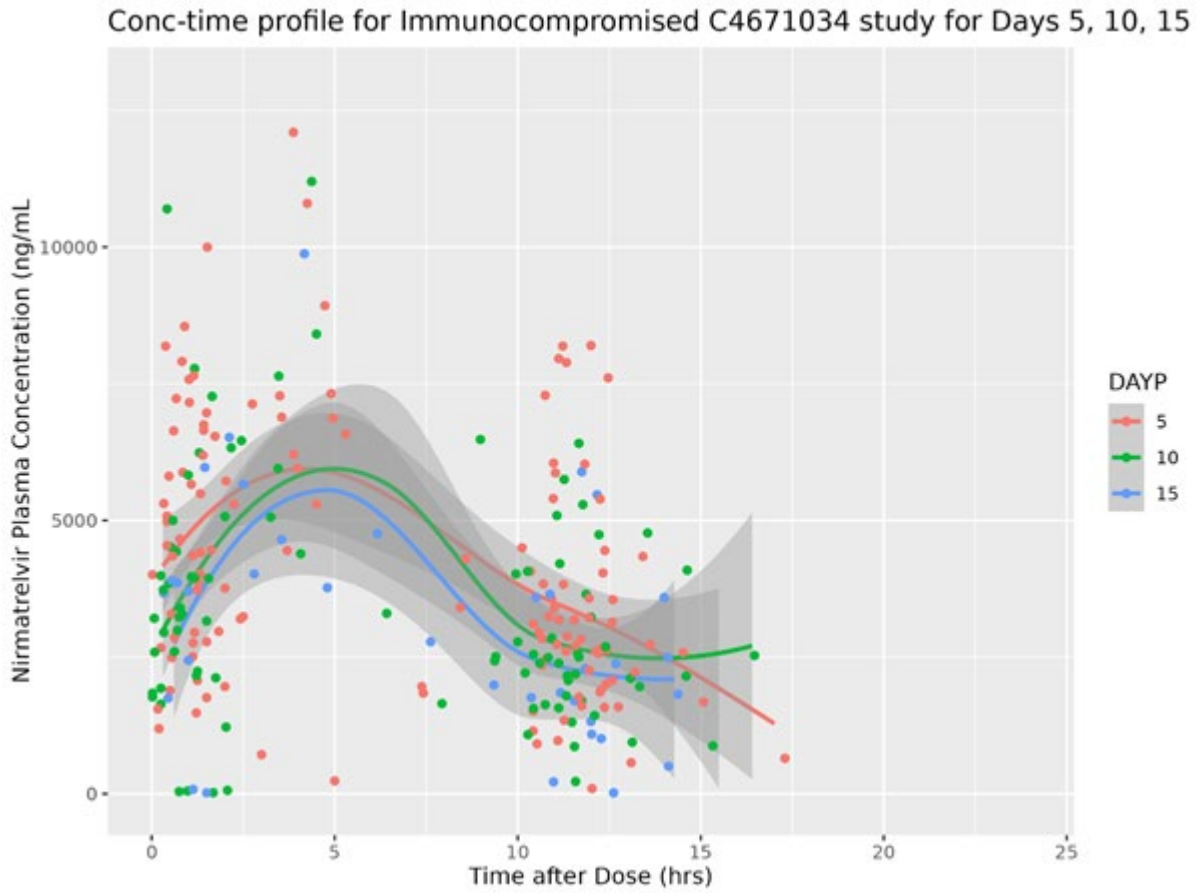
6.2. Results

Observed PK data

In study C4671034, a total of 156 subjects had received nirmatrelvir/rtv. In the main study population, individual nirmatrelvir plasma concentrations ranged from <LLOQ (<10.0 ng/mL) to 12,400 ng/mL at 1 to 2 hours post-dose on Day 1. Individual ritonavir plasma concentrations ranged from <LLOQ (<5.0 ng/mL) to 2980 ng/mL at 1 to 2 hours post-dose on Day 1. Nirmatrelvir and ritonavir plasma concentrations on Days 5, 10, and 15 were collected at any time within the corresponding study day.

A graphical comparison of Study C4671034 plasma concentrations on Days 5, 10, and 15 is shown in Figure 1. This comparison shows that nirmatrelvir/ritonavir exposure from PK samples collected on Days 5, 10, and 15 were comparable. Although higher nirmatrelvir concentrations were observed for some patients, which may have been due to underlying medical conditions, the observed data indicates steady state is reached by Day 5 in this population.

Figure 1. Observed Plasma Steady State Concentration versus Time Profile for Immunocompromised Patients in Study C4671034 Overlaying Samples Colected on Days 5, 10, and 15



The symbols represent observed steady state nirmatrelvir concentrations on Days 5, 10, and 15 across the 3 treatment arms from Study C4671034 (Day 1 data were excluded). Thirty BLQ samples (below LLOQ of 10 ng/mL) across Day 5, 10, and 15 PK samples were excluded from this figure. Grey shaded areas represent the 90% confidence interval for Day 5, 10, and 15 PK samples, and the solid lines represent the median concentration for Day 5, 10, and 15 PK samples, respectively.

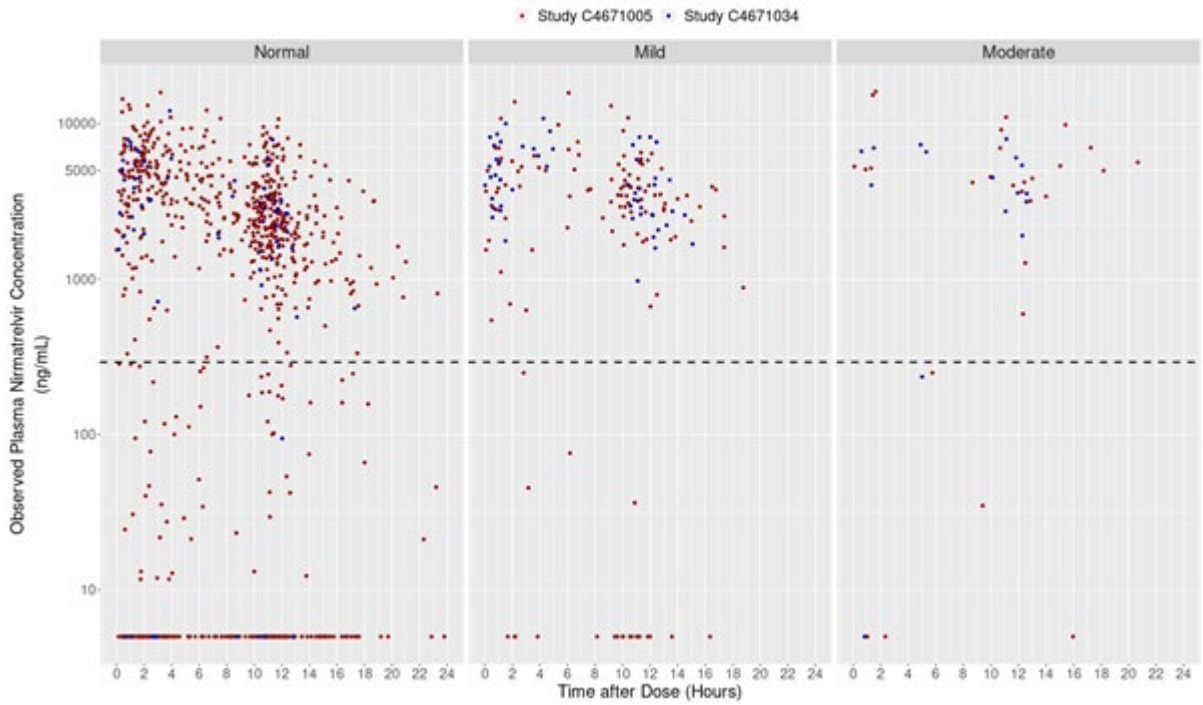
Comparison with study C4671005 PK data

These PK data were compared to those from the pivotal study C4671005 (227 nirmatrelvir steady-state data on Day 5 from 227 patients). For Study C4671034, 139 evaluable plasma observations

(including 12 BLQ observations) were collected on Day 5 from 139 participants across the 3 treatment arms; 93 evaluable plasma observations (including 10 BLQ observations) were collected on Day 10 from 93 participants in the nirmatrelvir/ritonavir 10 day and 15 day treatment arms; and 46 evaluable plasma observations (including 8 BLQ observations) were collected on Day 15 from 46 participants in the nirmatrelvir/ritonavir 15 day treatment arm. Since there was a minimal number of immunocompromised participants (13) in Study C4671005, the analysis provided does not present them separately from other participants in Study C4671005.

Figure 2 shows the observed plasma nirmatrelvir concentration versus time after dose for Studies C4671005 (normal, mild, and moderate renal function only on Day 5) and C4671034 (normal, mild, and moderate renal function PK samples collected on Day 5) stratified by renal function category. The BLQ samples are shown below the LLOQ of 10 ng/mL.

Figure 2. Observed Day 5 Plasma Nirmatrelvir Concentration versus Time After Dose for Study C4671005 and Study C4671034 Stratified by Renal Function



Symbols represent individual observations from both studies with normal, mild and moderate renal function only using Day 5 PK samples. Dashed horizontal line represents the target exposure in vitro EC_{90} of 292 ng/mL.
Only observations up to 24 hours were included in the figure. Six observations with time after dose >24 hours from Study C4671034 were excluded.
BLQ samples are shown below the nirmatrelvir LLOQ of 10 ng/mL.
Renal function: Normal = nCLCR ≥90 mL/min/1.73 m^2; Mild = 60≤ nCLCR <90 mL/min/1.73 m^2; Moderate = 30≤ nCLCR <60 mL/min/1.73 m^2. Participants with moderate renal impairment in Study C4671005 received 300 mg/100 mg nirmatrelvir/ritonavir, whereas participants with moderate renal impairment in Study C4671034 received 150 mg/100 mg nirmatrelvir/ritonavir.

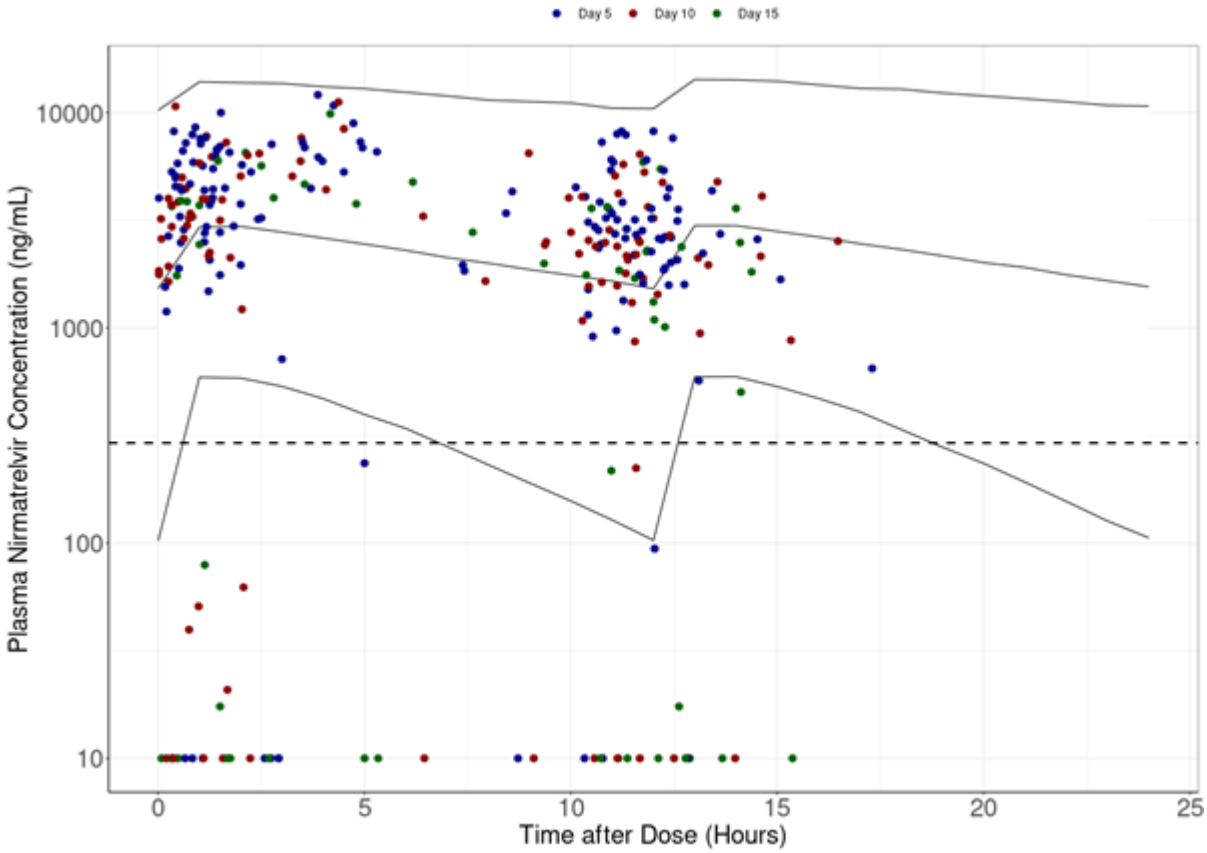
With the data from non-hospitalized immunocompromised participants of at least 12 years of age with symptomatic COVID-19, a graphical exploration of the observed data indicates that nirmatrelvir exposure in the immunocompromised study is consistent with the Study C4671005 high-risk COVID-19 patient population with normal, mild, and moderate renal function as seen Figure 2. Of note, there were 18 adults with moderate renal function in Study C4671034 receiving 150 mg/100 mg

nirmatrelvir/ritonavir BID and 29 adults with moderate renal function in Study C4671005 receiving 300 mg/100 mg nirmatrelvir/ritonavir BID.

PopPK modeling

Using the PopPK model-predicted profile in normal renal function patients with sampled covariates from Study C4671005 (300 mg/100 mg nirmatrelvir/ritonavir BID for 5 days), the 90% confidence intervals were overlaid on steady-state Day 5, Day 10, and Day 15 observed data from Study C4671034 (Figure 3). Most of the observed steady-state data in C4671034 were within the predicted interval, which demonstrates a good agreement with prediction in Study C4671005.

Figure 3. Visual Predictive Check for Observed Study C4671034 Data Overlaid on the Prediction Interval Using the Sampled Covariates in Study C4671005 with Normal Renal Function



PopPK model-predicted Day 5 concentration versus time profile in normal renal function patients based on sampled covariates (age, body weight, and nCLCR) from Study C4671005 (300 mg/100 mg BID nirmatrelvir/ritonavir). Symbols represent observed steady state nirmatrelvir concentrations on Days 5, 10, and 15 from all 3 treatment arms from Study C4671034, excluding Day 1 data (300 mg/100 mg nirmatrelvir/ritonavir BID for normal/mild renal function or 150 mg/100 mg nirmatrelvir/ritonavir BID for moderate renal function). Black broken lines represent the EC90 of 292 ng/mL, and the black solid lines represent the median, 5th, 95th percentiles from 1000 simulations.

6.3. Discussion

Considering the observed PK values and the popPK modelling, the Rapporteur is agreed with the Applicant that no significant differences are expected between nirmatrelvir exposures in immunocompetent and immunocompromised patients. Furthermore, nirmatrelvir exposure is not

expected to be significantly modified when co-administered with immunosuppressants. Therefore, similar nirmatrelvir/rtv doses should be administered in both populations.

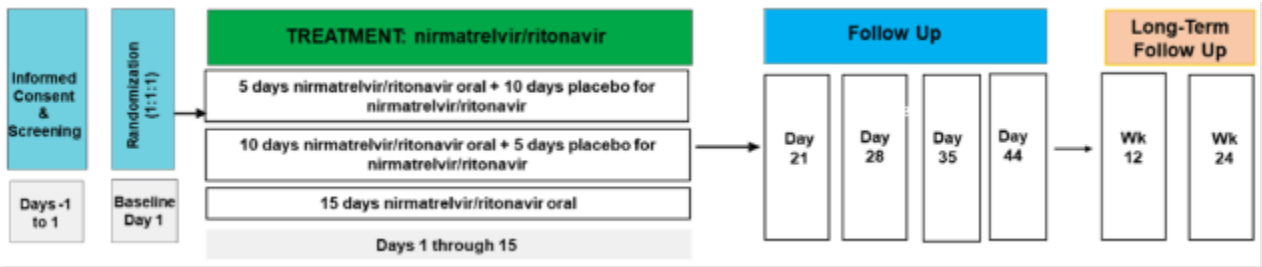
7. Clinical Efficacy aspects

Rapporteur's comment:

As efficacy data are similar to those previously assessed within the procedure MEA 20.1, the data and comments in this section are therefore similar.

7.1. Methods – analysis of data submitted

Design



Study C4671034, a Phase 2, randomized, double-blind study, evaluated the efficacy and safety of nirmatrelvir/ritonavir (5-, 10-, and 15-day dosing durations) for the treatment of COVID-19 in nonhospitalized symptomatic participants ≥12 years of age and weighing ≥40 kg who are immunocompromised (main study population). This study also evaluated the efficacy and safety of a second treatment course of nirmatrelvir/ritonavir (5-, 10-, or 15-day dosing durations) in an additional population of nonhospitalized symptomatic participants who are immunocompromised with a rebound in COVID-19 within 14 days following completion of an initial 5-day treatment course of nirmatrelvir/ritonavir (population with rebound).

The total study duration was up to 24 weeks, including study intervention administration through Day 15 or Day 16, safety assessments through Day 44, efficacy assessments through Week 24, and long-term follow-up at Weeks 12 and 24.

Eligible participants (main study population and additional population with rebound) for this study were assigned (1:1:1) to receive:

- nirmatrelvir plus ritonavir orally q12h for 5 days followed by placebo for nirmatrelvir plus placebo for ritonavir q12h for 10 days; or
- nirmatrelvir plus ritonavir orally q12h for 10 days followed by placebo for nirmatrelvir plus placebo for ritonavir q12h for 5 days; or
- nirmatrelvir plus ritonavir orally q12h for 15 days.

Objectives and endpoints

The primary efficacy objective was to describe the effect of nirmatrelvir/ritonavir on viral RNA levels in NP swabs over time for the treatment of COVID-19 in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised. The primary endpoint was the proportion

of participants with sustained NP swab SARS- CoV- 2 RNA<LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44 (ie, 28 days following the end of the 15-day treatment).

The safety objective was to describe the safety and tolerability of nirmatrelvir/ritonavir for the treatment of COVID-19 in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised as measured by the incidence of TEAEs as well as the incidence of SAEs and AEs leading to discontinuation.

Study population

Nonhospitalized, symptomatic, immunocompromised participants ≥12 years of age and weighing ≥40 kg with COVID-19 were enrolled in this study. Participants included in the trial had a confirmed SARS-CoV-2 infection within 5 days of randomization and were experiencing at least 1 symptom of COVID-19. To adequately capture a representative range of participants who were immunocompromised, enrollment was stratified and capped for participants with corticosteroid or TNF blocker use as the sole form of immunosuppression.

Statistical methods

No formal hypothesis testing will be performed for this study.

The primary descriptive analysis will summarize the number and proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 log10 copies/mL) from the end of active treatment through Day 44 for each treatment arm in the Evaluable Analysis Set and FAS. In addition, 95% CIs for the proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ from the end of active treatment through Day 44 for each treatment arm will be calculated. The difference in proportions for the primary endpoint and associated 95% CI will be calculated for each pairwise comparison of the treatment arms.

Supplemental analyses will be performed for the primary efficacy endpoint:

1. An analysis of the primary endpoint will be conducted where participants that received non-study antiviral or mAb treatment post-baseline for the treatment of COVID-19 will be considered to have NP swab SARS-CoV-2 RNA level ≥2.5 log10 copies/mL for all timepoints after the date of non-study antiviral or mAb treatment start.

2. An analysis of the primary endpoint will be conducted to include all NP swab SARS-CoV-2 RNA data regardless of whether participants received non-study antiviral or mAb treatment post-baseline for the treatment of COVID-19.

No formal interim analysis will be conducted for this study.

As no formal hypothesis testing will be performed for this study, no power calculation was carried out to assess the number of participants required for each treatment arm. The goal of the primary analysis is to estimate the treatment effect for each duration of nirmatrelvir/ritonavir. The smaller numbers of participants in these groups will be reflected in the precision of the estimate of the primary endpoint.

Rapporteur's comment:

Overall, the design, population and schedule of assessment of this study are acceptable to compare 3 treatment durations of Paxlovid in immunocompromised subjects. Importantly, as this study was not powered to statistically compare these 3 doses regimen, without formal comparative statistical analyses, the efficacy results are expected to be rather informative than statistically significant.

7.2. Results

7.2.1. Participants population

A total of 163 participants in the main study population were screened, of which 156 participants were randomized. 5 participants from one site (site 1001) were excluded from the evaluable analysis set for all efficacy analyses due to GCP issues. In the population with rebound, a total of 2 participants were enrolled and treated: 1 participant each in the 5- and 10-day treatment groups.

Demographic and baseline characteristics of the main study population for the FAS were similar across treatment groups:

Table 3. Demographic and Baseline Characteristics - Full Analysis Set, Main Study Population (Protocol C4671034)

	Nirmatrelvir + Ritonavir 5 Day (N=54)	Nirmatrelvir + Ritonavir 10 Day (N=51)	Nirmatrelvir + Ritonavir 15 Day (N=51)	Total (N=156)
Age (Years), n (%)				
< 12	0	0	0	0
12 - 17	0	1 (2.0)	0	1 (0.6)
18 - 44	12 (22.2)	9 (17.6)	11 (21.6)	32 (20.5)
45 - 59	19 (35.2)	18 (35.3)	17 (33.3)	54 (34.6)
60 - 64	4 (7.4)	7 (13.7)	10 (19.6)	21 (13.5)
65 - 74	13 (24.1)	11 (21.6)	8 (15.7)	32 (20.5)
≥ 75	6 (11.1)	5 (9.8)	5 (9.8)	16 (10.3)
Mean (SD)	56.48 (14.86)	54.90 (16.33)	55.63 (14.44)	55.69 (15.14)
Median (range)	58.00 (19, 80)	58.00 (16, 82)	58.00 (28, 80)	58.00 (16, 82)
Sex, n (%)				
Male	26 (48.1)	21 (41.2)	25 (49.0)	72 (46.2)
Female	28 (51.9)	30 (58.8)	26 (51.0)	84 (53.8)
Race, n (%)				
White	50 (92.6)	47 (92.2)	44 (86.3)	141 (90.4)
Black or African American	1 (1.9)	0	1 (2.0)	2 (1.3)
Asian	0	0	0	0
American Indian or Alaska Native	1 (1.9)	3 (5.9)	3 (5.9)	7 (4.5)
Native Hawaiian or Other Pacific Islander	0	0	0	0
Not reported	2 (3.7)	1 (2.0)	3 (5.9)	6 (3.8)
Unknown	0	0	0	0
Ethnicity, n (%)				
Hispanic or Latino	37 (68.5)	33 (64.7)	32 (62.7)	102 (65.4)
Not Hispanic or Latino	15 (27.8)	18 (35.3)	19 (37.3)	52 (33.3)
Not Reported	2 (3.7)	0	0	2 (1.3)
Weight (kg)				
Mean (SD)	78.38 (15.65)	80.46 (21.42)	74.47 (20.09)	77.76 (19.17)
Median (range)	77.55 (51, 121)	78.80 (41, 182)	68.00 (50, 133)	75.39 (41, 182)
Height (cm)				
Mean (SD)	167.1 (9.25)	167.0 (10.49)	166.7 (10.75)	166.9 (10.10)
Median (range)	166.0 (150, 189)	166.1 (146, 196)	167.0 (146, 195)	166.8 (146, 196)

	Nirmatrelvir + Ritonavir 5 Day (N=54)	Nirmatrelvir + Ritonavir 10 Day (N=51)	Nirmatrelvir + Ritonavir 15 Day (N=51)	Total (N=156)
BMI (kg/m^2), n (%)				
< 25	15 (27.8)	11 (21.6)	25 (49.0)	51 (32.7)
25 - < 30	18 (33.3)	25 (49.0)	14 (27.5)	57 (36.5)
30 - < 35	15 (27.8)	7 (13.7)	8 (15.7)	30 (19.2)
35 - < 40	4 (7.4)	3 (5.9)	1 (2.0)	8 (5.1)
≥ 40	1 (1.9)	4 (7.8)	3 (5.9)	8 (5.1)
Mean (SD)	28.27 (5.58)	28.69 (5.93)	26.64 (6.12)	27.87 (5.90)
Median (range)	27.60 (18, 45)	27.95 (17, 48)	25.00 (16, 46)	27.30 (16, 48)
Duration since first diagnosis (Days), n (%)				
< 3	46 (85.2)	44 (86.3)	43 (84.3)	133 (85.3)
3 - 5	8 (14.8)	7 (13.7)	8 (15.7)	23 (14.7)
6 - 7	0	0	0	0
8 - 15	0	0	0	0
16 - 29	0	0	0	0
≥ 30	0	0	0	0
Mean (SD)	1.50 (0.86)	1.51 (0.86)	1.41 (0.90)	1.47 (0.87)
Median (range)	1.00 (1, 5)	1.00 (1, 5)	1.00 (1, 4)	1.00 (1, 5)
Duration since first symptom (Days), n (%)				
< 3	20 (37.0)	20 (39.2)	28 (54.9)	68 (43.6)
3 - 5	31 (57.4)	28 (54.9)	20 (39.2)	79 (50.6)
6 - 7	2 (3.7)	0	2 (3.9)	4 (2.6)
8 - 15	0	1 (2.0)	0	1 (0.6)
16 - 29	0	1 (2.0)	0	1 (0.6)
≥ 30	1 (1.9)	0	1 (2.0)	2 (1.3)
≤ 5	51 (94.4)	48 (94.1)	48 (94.1)	147 (94.2)
> 5 - ≤ 30	2 (3.7)	2 (3.9)	2 (3.9)	6 (3.8)
> 30	1 (1.9)	0	1 (2.0)	2 (1.3)
Mean (SD)	5.31 (16.38)	3.42 (3.70)	6.08 (24.02)	4.95 (16.89)
Median (range)	3.00 (1, 123)	3.00 (1, 27)	2.00 (1, 174)	3.00 (1, 174)
Country, n (%)				
Australia	0	1 (2.0)	1 (2.0)	2 (1.3)
Brazil	4 (7.4)	0	0	4 (2.6)
Bulgaria	0	0	1 (2.0)	1 (0.6)
Canada	4 (7.4)	5 (9.8)	2 (3.9)	11 (7.1)
Hungary	0	0	0	0
Mexico	8 (14.8)	5 (9.8)	11 (21.6)	24 (15.4)

	Nirmatrelvir + Ritonavir 5 Day (N=54)	Nirmatrelvir + Ritonavir 10 Day (N=51)	Nirmatrelvir + Ritonavir 15 Day (N=51)	Total (N=156)
Slovakia	7 (13.0)	8 (15.7)	10 (19.6)	25 (16.0)
Spain	19 (35.2)	17 (33.3)	15 (29.4)	51 (32.7)
United States	12 (22.2)	15 (29.4)	11 (21.6)	38 (24.4)
Vaccination status, n (%)				
Vaccinated within 6 months prior to randomization	7 (13.0)	8 (15.7)	9 (17.6)	24 (15.4)
Not vaccinated within 6 months prior to randomization	47 (87.0)	43 (84.3)	42 (82.4)	132 (84.6)
Renal function eGFR/eCrCl (mL/min/1.73 m^2 / mL/min), n (%)				
Normal (≥90)	35 (64.8)	36 (70.6)	27 (52.9)	98 (62.8)
Mild Impairment (≥60 to <90)	11 (20.4)	12 (23.5)	21 (41.2)	44 (28.2)
Moderate Impairment (≥30 to <60)	7 (13.0)	3 (5.9)	3 (5.9)	13 (8.3)
Severe Impairment (<30)	0	0	0	0
Rapid antigen test (RAT), n (%)				
Positive	19 (35.2)	18 (35.3)	21 (41.2)	58 (37.2)
Negative	0	0	0	0
CRF Immunocompromised categories[a], n (%)				
Solid organ transplant	1 (1.9)	1 (2.0)	0	2 (1.3)
CAR-T-cell therapy / hematopoietic stem cell transplant infusion	7 (13.0)	7 (13.7)	6 (11.8)	20 (12.8)
Moderate or severe primary immunodeficiency / HIV infection CDC group III < 200 CD4 count	1 (1.9)	1 (2.0)	2 (3.9)	4 (2.6)
Solid tumor	8 (14.8)	6 (11.8)	6 (11.8)	20 (12.8)
Hematological malignancy	19 (35.2)	15 (29.4)	20 (39.2)	54 (34.6)
Immunosuppressant drug therapy	46 (85.2)	46 (90.2)	46 (90.2)	138 (88.5)
Not meeting any CRF category	0	1 (2.0)	1 (2.0)	2 (1.3)
Immunocompromised based solely on corticosteroids or TNF blockers[b], n (%)				
Yes	11 (20.4)	9 (17.6)	10 (19.6)	30 (19.2)
No	43 (79.6)	41 (80.4)	40 (78.4)	124 (79.5)
Not Immunocompromised	0	1 (2.0)	1 (2.0)	2 (1.3)
SARS-CoV-2 RNA NP level (Log_{10} copies/mL), n (%)				
< 2	3 (5.6)	4 (7.8)	2 (3.9)	9 (5.8)
≥ 2	49 (90.7)	47 (92.2)	48 (94.1)	144 (92.3)
< 4	9 (16.7)	6 (11.8)	9 (17.6)	24 (15.4)
≥ 4	43 (79.6)	45 (88.2)	41 (80.4)	129 (82.7)
< 7	32 (59.3)	29 (56.9)	22 (43.1)	83 (53.2)
≥ 7	20 (37.0)	22 (43.1)	28 (54.9)	70 (44.9)
Mean (SD)	6.03 (2.19)	6.09 (2.32)	6.42 (2.20)	6.18 (2.23)
Median (range)	6.64 (0, 9)	6.81 (0, 9)	7.29 (0, 9)	6.82 (0, 9)

Overall, the median age was 58 years, 53.8% of participants were female, 90.4% of participants were White, 65.4% of participants were Hispanic or Latino. Most participants had a qualifying SARS-CoV-2 positive test collected within 3 days of the first dose of study intervention (85.3%), did not receive a COVID-19 vaccination within 6 months prior to randomization (84.6%) and were receiving

immunosuppressant drug therapy (88.5%). Nearly 20% of participants were immunocompromised solely because of receiving either systemic corticosteroids or TNF blockers. Because these participants were considered less severely immunocompromised, their enrolment was capped at 25%.

Concomitant medications reported by participants up to Day 44 are mainly:

- immunosuppressants (39.6%, 43.1%, and 33.3% for the nirmatrelvir/ritonavir 5-day, 10-day, and 15-day treatment groups, respectively), with the most frequently (>5% in any treatment group) reported concomitant medications: azathioprine, ciclosporin, infliximab, leflunomide, lenalidomide, methotrexate, and methotrexate sodium.

- corticosteroids for systemic use (30.2%, 35.3%, and 35.3% for the nirmatrelvir/ritonavir 5-day, 10-day, and 15-day treatment groups, respectively).

5.7%, 3.9%, and 2.0% of participants in the 5-day, 10-day, and 15-day treatment groups, respectively, reported use of an immune sera and immunoglobulins. In addition, there were 2 reports in the 5-day treatment group of concomitant use of SARS-CoV-2 antivirals (remdesivir and sotrovimab).

Rapporteur's comment:

As stated by the Applicant, the demographic and disease characteristics at baseline are overall similar across the 3 treatment duration groups. Of note, it could be highlighted that more subjects in the group 3 (15 day treatment duration) were treated earlier (54.9% <3 days since first symptom vs 37% and 39% in the other groups) which could favour the efficacy results in this group, as Paxlovid should be administered as soon as possible (accordingly to section 4.2). Contrarily, a larger proportion of patients in this group had > 7 log viral load. However, almost all subjects in the 3 groups (94%) were treated in the 5 days since first symptom, in accordance to Paxlovid SmPC.

7.2.2. Efficacy results

As a reminder, there was no formal statistical analyses to compare the three treatment groups.

Primary efficacy endpoint: Proportion of Participants with Sustained NP Swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 log10 copies/mL) From Day 15 Through Day 44.

The proportion of participants with sustained NP swab SARS-CoV-2 RNA<LLOQ were 61.54% for the 5-day treatment group, 70.83% for the 10-day treatment group, and 66.00% for the 15-day treatment group. A total of 4 participants (all in the nirmatrelvir/ritonavir 5-day treatment group) had a detectable SARS-CoV-2 RNA levels (ie, ≥2 log10 copies/mL) at Day 44.

Table 5. Proportion of Participants With Sustained SARS-CoV-2 RNA (NP) < LLOQ from Day 15 to Day 44, Anti-Viral or mAB as Failure - Evaluable Analysis Set, Main Study Population (Protocol C4671034)

	Nirmatrelvir + Ritonavir 5 Day (N=52)	Nirmatrelvir + Ritonavir 10 Day (N=48)	Nirmatrelvir + Ritonavir 15 Day (N=50)
N1	52	48	50
Participants with event, n (%)	32 (61.54)	34 (70.83)	33 (66.00)
95% CI	0.483, 0.748	0.580, 0.837	0.529, 0.791
Difference in Proportion (95% CI) versus Day 5		0.093 (-0.091, 0.277)	0.045 (-0.142, 0.231)
Difference in Proportion (95% CI) versus Day 10			-0.048 (-0.232, 0.135)

N and N1 = number of participants in the analysis set.
The lower limit of quantification (LLOQ) is
5 participants from site 1001 were excluded from evaluable analysis set.

Secondary efficacy endpoints:

Endpoint	Main Study Population Results
Time to first NP swab SARS-CoV-2 RNA <LLOQ (<2.0 $\log_{10}$ copies/mL) for participants with NP swab SARS-CoV-2 RNA ≥LLOQ at baseline.	For participants with NP swab SARS-CoV-2 RNA ≥LLOQ at baseline, the median time to first NP swab SARS-CoV-2 RNA <LLOQ (<2.0 $\log_{10}$ copies/mL) was 9.5 days, 11.0 days, and 9.0 days in the nirmatrelvir/ritonavir 5-day, 10-day, and 15-day treatment groups, respectively.
Time to sustained NP swab SARS-CoV-2 RNA <LLOQ (<2.0 $\log_{10}$ copies/mL) through Day 44 for participants with NP swab SARS-CoV-2 RNA ≥LLOQ at baseline.	The median time to achieving NP swab SARS-CoV-2 RNA <LLOQ that was sustained through Day 44 was numerically longer in the 5-day treatment group (15 days) compared with the 10-day (11 days) and 15-day (10 days) treatment groups.
Proportion of participants with SARS-CoV-2 RNA <LLOQ in plasma over time.	SARS-CoV-2 RNA level in plasma was <LLOQ at baseline in 92.00% to 98.08% of participants across treatment groups. • Across treatment groups, SARS-CoV-2 RNA level in plasma was >LLOQ in a study visit through Day 44 for 4 participants. o At Week 12, two participants in the 5-day treatment group had detectable (≥1.7◦$\log_{10}$◦copies/mL) SARS-CoV-2 RNA level in plasma o At Week 24, one participant each in the 10- and 15-day treatment groups, had detectable (>1.7 $\log_{10}$ copies/ml) SARS-CoV-2 RNA level in plasma.
Proportion of participants with SARS-CoV-2 RNA level in NP swabs <2.0 $\log_{10}$ copies/mL at each study visit through Day 44.	• At baseline, 3 (5.77%), 4 (8.33%), and 2 (4.00%) participants in the 5-, 10-, and 15-day treatment groups had SARS-CoV-2 RNA NP swab <LLOQ. • At Day 44, 41 (78.85%), 44 (91.67%), and 44 (88.00%) participants in the 5-, 10-, and 15-day treatment groups had SARS-CoV-2 RNA NP swab <LLOQ.
Change from baseline in SARS-CoV-2 RNA level in NP swabs and in plasma over time.	Mean (SD) baseline SARS-CoV-2 RNA (NP swab) level was 6.454 (1.615), 6.733 (1.489), and 6.591 (2.020) $\log_{10}$ copies/mL in the 5-, 10-, and 15-day treatment groups, respectively, in participants with detectable RNA in NP swab at baseline. The mean SARS-CoV-2 RNA (NP swab) level decreased over time for all treatment groups. • At Day 15, the mean change from baseline SARS-CoV-2 RNA (NP swab) level was lower in the 5-day treatment group than the 10- or 15-day treatment groups (-4.827 vs -5.773 and -6.009 $\log_{10}$ copies/mL, respectively).

	• At Day 44, the mean change from baseline SARS-CoV-2 RNA (NP swab) level was -5.916, -6.597, and -6.707 log_{10} copies/mL in the 5-, 10-, and 15-day treatment groups, respectively. At baseline, 8, 10, and 15 participants in the 5-, 10-, and 15-day treatment groups, respectively, had detectable SARS-CoV-2 RNA levels in plasma. From Days 15 through 44, no participant had detectable SARS-CoV-2 RNA levels in plasma.
Rebound in SARS-CoV-2 RNA level in NP swabs at follow-up (ie, any study visit after EOT through Day 44) that is defined as a half (0.5) log_{10} copies/mL increase or greater in SARS-CoV-2 RNA level relative to EOT SARS-CoV-2 RNA level based on treatment regimen, with a follow-up viral RNA level ≥2.5 log_{10} copies/mL.	The incidence of rebound (defined as ≥0.5 log_{10} copies/mL increase in SARS-CoV-2 RNA level relative to the SARS-CoV-2 RNA level at the end of active treatment, with a follow-up viral RNA level ≥2.5 log_{10} copies/mL) in SARS-CoV-2 RNA level (NP swab) up to Day 44 was 17.31%, 2.08%, and 2.00% in the 5-, 10-, and 15-day treatment groups, respectively.
Proportion of participants with COVID-19-related hospitalization >24 hours or death from any cause through Day 28.	No death from any cause was reported through Day 28. 2 participants in the 5-day treatment group were hospitalized for >24 hours due to COVID-19 through Day 28. No COVID-19-related hospitalizations >24 hours were reported for participants in the 10- and 15-day treatment groups through Day 28.
Proportion of participants with death (all cause) through Week 24.	There was 1 death in the 5-day treatment group and none in the 10-, or 15-day treatment groups through Week 24 (Day 168). 1 participant in the 15-day treatment group died after Week 24 (Day 175)
Proportion of participants with COVID-19-related hospitalization of any duration.	Two participants in the 5-day treatment group were hospitalized due to COVID-19 through Day 44. Both participants were admitted before the Day 44 visit.
Proportion of participants with COVID-19-related ICU admission of any duration.	One participant in the 5-day treatment group had COVID-19-related ICU admission during the 24-week study and was admitted to the ICU before the Day 44 visit.
Proportion of participants requiring IMV or ECMO.	No participants required IMV or ECMO with COVID-19-related hospitalization during the 24-week study.
Number of days in hospital and ICU stay in participants with COVID-19-related hospitalization.	No COVID-19-related hospitalizations were reported for participants in the 10- and 15-day treatment groups during the 24-week study. Two participants in the 5-day treatment group were hospitalized for >24 hours due to COVID 19; of which, 1 participant was admitted on Day 6 and discharged on Day 15. The other participant was admitted on Day 25, was in the ICU from Days 29 to 37, and discharged on Day 47.
Number of COVID-19-related medical visits through Day 44 and through Week 24.	During the 24-week study, there were a total of 5 COVID-19-related medical visits (inclusive of hospitalizations) in 3 participants. • Two participants in the 5-day treatment group had a total of 4 COVID-19-related medical visits. All 4 medical visits occurred before the Day 44 visit. • One participant in the 15-day treatment group had a COVID-19-related medical visit on Day 85.

Duration of each targeted COVID-19 signs/symptoms.	80% to 100% of participants across treatment groups achieved first alleviation of any targeted COVID-19 sign or symptom that they reported at baseline, through Day 44. • The most frequently reported COVID-19 signs and symptoms at baseline across treatment groups in the main study population were stuffy or runny nose (139 out of 150 participants), cough (138 out of 150 participants), and low energy or tiredness (137 out of 150 participants). • The median time to first alleviation of any targeted COVID-19 sign or symptom ranged from 4 to 10 days across treatment groups • The median time to first resolution of any targeted COVID-19 sign or symptom ranged from 4 to 27 days across treatment groups
Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 44.	Over the study period from Day 1 through Day 44, 28.85%, 31.25%, and 38.00% of participants in the 5-, 10-, and 15-day treatment groups, respectively, had severe signs and symptoms attributed to COVID-19. • 40.38%, 64.58%, and 38.00% of participants in the 5-, 10-, and 15-day treatment groups, respectively, had severe signs and symptoms at baseline. • Over the study period from Day 2 through end of active treatment (Day 15), 17.31%, 29.17%, and 30.00% of participants in the 5-, 10-, and 15-day treatment groups, respectively, had severe signs and symptoms. • Over the study period from end of active treatment (Day 15) through Day 44, 28.85%, 16.67%, and 20.00% of participants in the 5-, 10-, and 15-day treatment groups, respectively, had severe signs and symptoms.

In addition, no emergent M^{pro} and cleavage mutations were observed in ≥2 participants in the main study population.

Subgroup analysis by immunocompromised category

The proportion of participants with sustained SARS-CoV-2 RNA (NP) <LLOQ (defined as <2.0 log10 copies/mL) was numerically higher in participants who were immunocompromised based solely on corticosteroids or TNF blockers at baseline than in those participants who were immunocompromised based on other criteria at baseline.

Table 6. Proportion of Participants With Sustained SARS-CoV-2 RNA (NP) < LLOQ from Day 15 to Day 44, Anti-Viral or mAB as Failure, by Immunocompromised Status - Evaluable Analysis Set, Main Study Population (Protocol C4671034)

Immunocompromised based solely on corticosteroids or TNF blockers (based on CRF data)		Nirmatrelvir + Ritonavir 5 Day (N=52)	Nirmatrelvir + Ritonavir 10 Day (N=48)	Nirmatrelvir + Ritonavir 15 Day (N=50)
Yes	N1	10	8	10
	Participants with event, n(%)	7 (70.00)	7 (87.50)	8 (80.00)
No	N1	42	39	39
	Participants with event, n(%)	25 (59.52)	27 (69.23)	24 (61.54)
Not Immunocompromised	N1	0	1	1
	Participants with event, n(%)	0	0	1 (100.0)

Rapporteur's comment:

Overall, there is no significant efficacy differences between the 3 treatment duration groups. However, a trend to higher antiviral efficacy could be highlighted in the 2 higher treatment duration groups (10 and 15 days) in comparison to the currently approved treatment duration group (5 days). Furthermore, the 4 subjects who had still detectable SARS-CoV-2 RNA levels at Day 44 were all in the 5 days group, supporting this hypothesis of higher antiviral efficacy of treatment duration >5 days for immunocompromised subjects. However, these data must be mitigated with the clinical efficacy of higher treatment duration (i.e. duration and severity of symptoms, including oxygen requirement), which is unknown at this stage.

The subgroup analysis suggests that, as expected, antiviral treatment is probably less effective in subjects with high level of immunodeficiency (i.e. not only based on corticosteroids/anti-TNF).

7.3. Discussion

Study C4671034 is a Phase II study comparing 3 dosing durations of Paxlovid (5, 10 and 15 days) in immunocompromised subjects with symptomatic COVID-19. Indeed, there is a need to assess higher treatment duration of Paxlovid in this population, for whom higher viral clearance is expected.

Most included participants had positive test collected within 3 days of the first dose of study intervention, did not receive a COVID-19 vaccination within 6 months prior to randomization and were receiving immunosuppressant drug therapy. In accordance to the protocol, the rate of subjects immunocompromised solely because of corticosteroids or TNF blockers treatment – i.e. subjects less severely immunocompromised - was capped at 25%.

The demographic and disease characteristics at baseline are overall similar across the 3 treatment duration groups. Of note, it could be highlighted that more subjects in the group 3 (15 days treatment duration) were treated earlier (54.9% <3 days since first symptom vs 37% and 39% in the other groups) which could favour the efficacy results in this group, as Paxlovid should be administered as soon as possible (accordingly to section 4.2). This potential bias should be considered to mitigate the efficacy results in this group, although almost all subjects in the 3 groups (94%) were treated in the 5 days since first symptom, in accordance to Paxlovid SmPC.

As regards the preliminary efficacy results, there is no significant differences between the 3 treatment duration groups (of note, this study had a descriptive primary endpoint and was not intended to perform a powerful statistical comparison between the 3 arms). However, a trend to higher antiviral efficacy could be highlighted in the 2 higher treatment duration groups (10 and 15 days) in comparison to the currently approved treatment duration group (5 days). Furthermore, the 4 subjects who had still detectable SARS-CoV-2 RNA levels at Day 44 were all in the 5 days group, supporting this hypothesis of higher antiviral efficacy of treatment duration >5 days for immunocompromised subjects. However, these data must be mitigated by the potential bias in the 15 days-treatment group, and reflect only the antiviral activity of Paxlovid. In conclusion, the clinical efficacy of higher treatment duration (i.e. duration and severity of symptoms, including oxygen requirement) is unknown at this stage based on these data.

See also below (Section 9) the discussion of the MAH Response to CHMP Comments (Request 5) on PAM MEA 20.1

8. Clinical Safety aspects

8.1. Exposure

In study C4671034, 156 participants were assigned to treatment and 155 participants took at least 1 dose of study treatment.

8.2. Results

TEAEs

The proportion of participants with all-causality TEAEs that started on or prior to the Day 44 visit were 52.8%, 66.7%, and 60.8% for the 5-, 10-, and 15-day treatment groups, respectively. Most of these TEAEs were Grade 1 or 2 in severity groups. The most frequently reported (≥5% in any treatment group) all-causality TEAEs by preferred term in the 5-, 10-, and 15-day treatment groups were Dysgeusia (11.3%, 21.6%, and 27.5%, respectively), Diarrhoea (9.4%, 7.8%, and 7.8%, respectively), Nausea (1.9%, 3.9%, and 9.8%, respectively), Headache (1.9%, 5.9%, and 2.0%, respectively), and Blood thyroid stimulating hormone increased (0, 0, and 5.9%, respectively). These TEAEs were all nonserious and mild (Grade 1) or moderate (Grade 2). No participants discontinued treatment or the study due to any of the TEAEs listed above. One participant in the 5-day treatment group discontinued the study due to an all-causality TEAE of Grade 1 Urticaria.

The proportion of participants with an all-causality SAE was ≤9.4% across treatment groups. There was no increase in the incidence of SAEs as a result of longer treatment duration.

The proportion of participants with severe (Grade 3) or potentially life-threatening TEAEs (Grade 4) was 3.8%. 9.8%, 11.8% in the 5-, 10-, and 15-day treatment groups respectively.

Table 1.Treatment-Emergent Adverse Events (All Causalities) - DAIDS Grade - Safety Analysis Set, Main Study Population (Protocol C4671034)

Number (%) of Participants	Nirmatrelvir + Ritonavir 5 Day (N=53) n (%)	Nirmatrelvir + Ritonavir 10 Day (N=51) n (%)	Nirmatrelvir + Ritonavir 15 Day (N=51) n (%)
Participants evaluable for adverse events	53	51	51
Number of adverse events	46	71	97
Participants with adverse events	28 (52.8)	34 (66.7)	31 (60.8)
Participants with serious adverse events	5 (9.4)	1 (2.0)	4 (7.8)
Participants with Maximum Grade 3 or 4 adverse events	2 (3.8)	5 (9.8)	6 (11.8)
Participants with Maximum Grade 5 adverse events	0	0	0
Participants discontinued from study due to adverse events[a]	1 (1.9)	0	0
Participants discontinued study drug due to AE and continue study[b]	1 (1.9)	1 (2.0)	4 (7.8)

Participants with temporary study drug discontinuation due to adverse events	0	0	0

Includes AEs that started on or prior to Day 44.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study
b. Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Participant to be discontinued from Study
MedDRA v26.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 02FEB2024 (11:27) Source Data: adae Table Generation: 15FEB2024 (14:27) (Database snapshot date : 02FEB2024) Output File: ./nda ph23/C4671034 LPLV CSR/adae s020
Table 14.3.1.2.1.1 Nirmatrelvir/ritonavir is for Pfizer internal use.

Treatment-Related AEs

The proportion of participants with treatment-related TEAEs increased with longer durations of treatment (22.6%, 33.3%, and 41.2% in the 5-, 10-, and 15-day treatment groups, respectively). The proportion of participants with treatment-related severe (Grade 3) or potentially life-threatening TEAEs (Grade 4) was 0, 0, and 3.9% in the 5-, 10-, and 15-day treatment groups, respectively. Two participants in the 15-day treatment group had nonserious, Grade 3 events of Dyspepsia and ALT increased. No participants in any treatment group experienced treatment-related SAEs.

The most frequently reported treatment-related TEAEs across treatment groups (≥2 participants in any treatment group) were Dysgeusia (11.3%, 21.6%, and 27.5% in the 5-, 10-, and 15-day treatment groups), Diarrhoea (1.9%, 3.9%, and 5.9% in the 5-, 10-, and 15-day treatment groups), Nausea 1.9%, 3.9%, and 5.9% in the 5-, 10-, and 15-day treatment groups), Dyspepsia (3.8%, 2.0%, and 2.0% in the 5-, 10-, and 15-day treatment groups), Blood thyroid stimulating hormone increased (5.9% in the 15-day treatment group), and Dry mouth (3.9% in the 15 day treatment group).

The proportion of participants who discontinued study intervention due to at least 1 treatment-related AE and continued the study was similar across treatment groups (1.9%, 2.0%, and 5.9% in the 5-, 10-, and 15-day treatment groups, respectively). One participant discontinued the study due to a treatment-related TEAE of Diarrhoea.

SAEs and Deaths

The proportion of participants with an all-causality SAE was 9.4%, 2.0%, and 7.8% for the 5-day, 10-day, and 15-day treatment groups, respectively. There was no increase in the incidence of SAEs as a result of longer treatment duration. One participant in the 5-day treatment group had an SAE of COVID-19. No SAE was considered related to study intervention by the investigator.

No AEs resulting in death (Grade 5) were reported in any treatment group on or prior to Day 44. Two deaths occurred after the Day 44 visit. Both deaths were due to complications of the participants underlying conditions of acute lymphocytic leukaemia and acute myeloid leukemia.

Clinical laboratory evaluations

No clinically meaningful differences by treatment durations were observed with respect to hematology and clinical chemistry laboratory test results.

A higher incidence of Blood thyroid stimulating hormone increased was reported in the 15-day treatment group. However the incidence of relevant (thyrotropin or thyroxine) laboratory abnormalities was similar across the 3 treatment groups. Furthermore, the proportion of participants who shifted from normal (baseline value) to high levels of thyrotropin through Day 44, were similar across the

treatment groups and no participant in any treatment group, shifted from a normal level of free T4 (thyroxine) at baseline to a high level of thyroxine through Day 44.

Vital signs

No clinically meaningful findings in the vital sign measurements were observed in this study. The assessments and observations were similar across treatment groups.

Rapporteur's comment:

Overall, no new safety concern was observed in comparison to the known safety profile of Paxlovid. However, it could be noted that the proportion of Grade 3-4 TEAEs and treatment-related TEAEs are increased with the duration of treatment, with higher rates of nervous system disorders (notably dysgeusia and headache) and gastrointestinal disorders (notably nausea and vomiting) in the longer treatment duration group.

Drug interactions

Patients taking concomitant medications that are contraindicated with nirmatrelvir/ritonavir were excluded from Study C4671034. The nirmatrelvir/ritonavir DDI risk profile is not anticipated to be different in immunocompromised versus non-immunocompromised patients.

Rapporteur's comment:

As highlighted in the MEA 20.1 procedure, it was asked to the MAH to scrutinize whether there was any safety issue in relation to drug drug interaction with immununosuppressants and with the prolonged treatment duration. See below section 9 for MAH answer.

Overdose

There were 6 participants (3.8%) who received an incorrect dose of nirmatrelvir due to incorrect calculation or entry of eGFR/eCrCl; Four participants received an increased dose of nirmatrelvir (300 mg instead of 150 mg) and 2 participants received a reduced dose of nirmatrelvir (150 mg instead of 300 mg). These dosing errors were captured as important protocol deviations.

Post-marketing data

Post-marketing safety data regarding the use of nirmatrelvir/ritonavir in immunocompromised patients has been assessed through 31 December 2024, by searching for nirmatrelvir/ritonavir cases reported in patients with a medical history which includes any of the MedDRA (version 27.1) Preferred Terms (PTs) from the following:

- SMQs (narrow and broad): Malignancy related conditions, Malignancy related therapeutic and diagnostic procedures and Malignant or unspecified tumours
- HLGT (primary path): Immunodeficiency syndromes
- HLT (primary path): Retroviral infections
- PTs: Allogenic bone marrow transplantation therapy, Allogenic stem cell transplantation, Autologous bone marrow transplantation therapy, Autologous haematopoietic stem cell transplant, Bone marrow transplant, Cord blood transplant therapy, Heart transplant, Liver transplant, Lung transplant, Pancreas islet cell transplant, Renal transplant, Small intestine transplant, Stem cell transplant.

Using this search strategy, a total of 3885 cases has been retrieved which is equivalent to 6.5% of the total nirmatrelvir/ritonavir dataset of 59,600 cases. Of these 3885 cases, 904 (23.3%) were serious and 2981 (76.7%) were nonserious, and they reported a total of 10,979 events. A summary overview of the cases is presented in Table 3:

Table 3. Summary of Case Characteristics in Immunocompromised Patients (N = 3885)

		Number of Cases	Percentage (%)
Sex			
	Female	2298	59.2 %
	Male	1375	35.4 %
	No data	212	5.5 %
Age Range			
Min = 3.0 Years Max = 102.0 Years Mean = 62.9 Median = 65.0 Standard Deviation = 13.81 n = 3459	Less than or equal to 17 years	23	0.6 %
	18 - 30 years	59	1.5 %
	31 - 50 years	526	13.5 %
	51 - 64 years	1059	27.3 %
	65 - 74 years	1167	30.0 %
	Greater than or equal to 75 years	663	17.1 %
	Unknown	388	10.0 %
Case Outcome			
	Fatal	76	2.0 %
	Not recovered/not resolved	1040	26.8 %
	Recovered/resolved	907	23.3 %
	Recovered/resolved with sequelae	36	0.9 %
	Recovering/resolving	826	21.3 %
	Unknown	1000	25.7 %
Country Where Event Occurred (Top 10)			
	United States	2179	56.1 %
	United Kingdom	296	7.6 %
	France	262	6.7 %

	Japan	211	5.4 %
	China	176	4.5 %
	Germany	169	4.4 %
	Italy	106	2.7 %
	Canada	83	2.1 %
	Australia	65	1.7 %
	Spain	46	1.2 %
Source			
	Clinical Study	85	2.2 %
	Literature - Non Study	169	4.4 %
	Literature - Study	39	1.0 %
	Solicited	23	0.6 %
	Spontaneous	3569	91.9 %
Case Seriousness			
	Serious	904	23.3 %
	Nonserious	2981	76.7 %

The most frequently reported AEs (≥5%) were COVID-19 (38.6%), Disease recurrence (36.9%), Dysgeusia (13.4%), Diarrhoea (10.5%), Off label use (7.8%), Nausea (6.7%) and Drug interaction (6.5%). The above mentioned clinical AEs are consistent with those reported in the general population and with the known safety profile of nirmatrelvir/ritonavir. This review of post-marketing data has not identified any new or unexpected safety issues with the use of nirmatrelvir/ritonavir in immunocompromised patients.

Published Literature Reports

Table 4.Summary of Published Literature Reports

Author & Year	Patient Population	Study Description Treatment Regimen	Safety Summary	Author's Conclusions
Bernardi et al 2024[1]	Pediatric patients with COVID-19 (N=85) a*nd* with either cancer and primary or secondary immunodeficiency who received N/R.	Retrospective analysis N/R: 5-days treatment N: 7.5 mg/kg per dose if <40 kg or 300 mg BID if >40 kg R: 75 mg/m^2 BID	Adverse events were reported by 4 (4.7%) patients (hypertriglyceridemia [2], nausea, vomiting, and hypertransaminasemia [1 each]); the single patient with nausea and vomiting had to discontinue N/R treatment.	The study showed a good tolerance of N/R administration in children. There were no significant sequelae upon follow up for at least 30 days. No significant adverse reactions were noted, except for 1 patient with nausea and vomiting, who had to discontinue N/R. The single

			Drug-drug interactions (increased levels of sirolimus [1] and ciclosporin [2]) were noted in 3 (3.5%) patients, leading to discontinuation of sirolimus and dose reduction of ciclosporin.	occurrence of laboratory evidence of hypertransaminasemia was possibly related to the drug. Our study shows that N/R is reasonably safe in the pediatric population and could favor viral clearance, thus reducing the duration of SARS-CoV-2 positivity. The study is limited by its retrospective design and was under-sampled for the detection of rarer adverse reactions to N/R; larger studies with control groups would be needed to further evaluate the safety of N/R administration in children. Studies with a longer follow-up may also investigate the role of N/R administration in alleviating the emergence of post-COVID-19 conditions in children. The limited availability of some lab-oratory parameters may reduce the generalizability of the findings.
Haddad et al 2024[2]	Adult patients with mild-to-moderate COVID-19 (N=240) and with a hematologic malignancy or solid tumours who received antiviral therapy.	Retrospective study Patients received either N/R (n=160) or molnupiravir (n=80) N/R: 300 mg/100 mg BID, 5 days Molnupiravir: 800 mg BID, 5 days	There was no significant difference between the 2 groups in AEs (N/R: 4% versus molnupiravir: 0%; p=0.18). Patients who received N/R were more likely than those who received molnupiravir to have AEs or have stopped another medication before starting the COVID-19 antiviral to avoid DDIs (N/R: 30% versus molnupiravir: 0%; p<0.0001).	This study showed that in the treatment of mild-to-moderate COVID-19 among cancer patients with hematologic malignancy or solid tumours, molnupiravir and N/R exhibited equivalent efficacy in terms of preventing progression to severe disease and mortality. Molnupiravir showed a superior safety profile as measured by the incidence of DDIs and AEs. Limitations include the retrospective design of this study; patients were not prospectively followed, therefore, some data pertaining to AEs may be lacking. Study drug administration could not be verified, and it was assumed that the patient had received the medication if not otherwise stated in the chart. Physicians followed NIH treatment guidelines for mild-to-moderate COVID-19, which may have introduced a confounding bias in the selection of patients who were prescribed molnupiravir.

Aiello et al 2024[3]	Adult patients with COVID-19 [omicron] (N=83) and with high-risk hematologic malignancies[a] who received antiviral treatment.	Non-interventional chart review Patients received either N/R (n=41) or remdesivir (n=42)	Neither severe AEs nor significant interactions were documented in patients on either of the treatment regimens. There was 1 death in the remdesivir group, of a patient in palliative care for end-stage renal cell carcinoma and Hodgkin lymphoma who died of multiple organ failure and septic shock.	This study suggests that early administration of N/R in patients with high-risk hematological malignancies is an excellent option to promote a faster viral load decrease and improve COVID-19 outcomes. This antiviral helped prevent hospital admissions, without significant side effects, a need of mechanical ventilation or intensive care unit admission and/or death. Limitations included the nature of the study design.
Li et al 2023[4]	Pediatric patients with COVID-19 infection (N=20) and with haematological diseases who received N/R.	Retrospective comparison of 2 groups: Group A: patients with hematologic neoplastic diseases and with 2 high-risk factors for developing severe and critical illness and who were treated with N/R (n=9). Group B: patients with haematological malignancies and 1 risk factor for haematological malignancies and no other risk factors for severe or critical illness and who were not treated with N/R (n=11).	In the patients treated with N/R (Group A), there were 2 cases (22.2%) of “bitter taste” which improved spontaneously after a few days and 1 case (11.1%) of diarrhoea.	In conclusion, Paxlovid is recommended for children with hematologic underlying immunosuppression or pneumonia infected with SARS-CoV-2 before severe disease develops. According to this study, there is no apparent adverse reaction when the drug is used in children aged 12 and under. Because the liver’s metabolic function in children is different from that in adults, further research is needed on the effect of drugs on interactions.
Piñana et al 2023[5]	Adult patients with SARS-CoV-2 omicron infection (N=466) and who were IC with haematological diseases including cell therapy recipients, who	Retrospective registry Patients were treated with N/R (n=223) or remdesivir (n=243)	There was no significant difference between the 2 groups in AEs of grade ≥3 (N/R: 1.3% versus remdesivir: 0.5%; p=0.3). The risk of DDIs was significantly higher in the N/R group compared to the remdesivir group. The proportion of patients who required either baseline treatment modification,	This study provides valuable insights into the safety of antiviral drugs in treating COVID-19 in IC patients with hematological diseases. As expected, N/R was significantly associated with higher drug–drug interactions, although severe AEs did not differ between the groups. In line with the current guidelines, remdesivir was the

	received antiviral therapy.		antiviral dose modification or early antiviral interruption was 14.9% in the N/R group versus 23.3% in the remdesivir group (p=0.001).	treatment of choice for severe cases. There was also a higher non-COVID mortality in the remdesivir group, attributed to a relapse or progression of haematological diseases.
Caso et al 2023[6]	Adult patients diagnosed with COVID-19 (N=110), and who fulfilled pre-specified criteria[b] for immunosuppression, who received N/R.	Retrospective observational study N/R: 300 mg/100 mg BID for 5 days or 150 mg/100mg BID for 5 days for patients with eGFR 30-60 mL/min/1.73m^2	A total of 12 (10.9%) patients experienced at least one TEAE attributable to N/R therapy. The most frequently reported were GI in nature (diarrhoea, nausea, or vomiting), and occurred in 4 (3.6%) patients. At least one drug combination potentially resulting in a DDI was detected in 62 (56.4%) patients. TEAEs attributed to DDIs occurred in 8 (7.3%) patients. The most common putative interacting drugs were tamsulosin (3 patients; 2.7%) which resulted in diarrhoea (n=2) and hypotension leading to acute kidney failure (n=1) and amlodipine (2; 1.8% patients) which resulted in hypotension (n=1) and oedema (n=1).	N/R represents a promising treatment choice for IC patients in the early phase of SARS-CoV-2 infection. Early initiation of N/R therapy should be considered in IC patients with COVID-19, with particular attention to interacting medications. Limitations of this study included the “benign” course of the omicron variant, making it difficult to analyses he effectiveness of antiviral therapies. The study lacked a control group so the role of N/R in IC patients must be interpreted with caution.

a. High-risk hematologic malignancies were acute leukemia under intensive chemotherapy; lymphoma in either treatment or remission with rituximab therapy; multiple myeloma under active treatment; chronic lymphocytic leukemia with targeted therapies; high-risk myelodysplastic syndrome in active treatment; and primary high-risk myelofibrosis. Individuals receiving CAR T-cell therapies and patients either within the first year of an allogenic HSCT or the initial 6 months of an autologous stem cell transplant were also deemed as high risk
b.Immunosuppression criteria: HSCT, solid organ transplantation, CAR T-cell therapy, primary immunodeficiency, solid or hematological malignancy receiving active chemotherapy, human immunodeficiency virus infection, Down's syndrome, use of immunosuppressive therapies including glucocorticoids at a daily prednisone dose >7.5 mg (or equivalent) for ≥4 weeks or Janus kinase inhibitors, and/or receipt of anti-CD20 or anti-CD38 monoclonal antibodies in the previous 6 months.

8.3. Discussion

As stated by the MAH, nirmatrelvir/ritonavir was found to be safe and well tolerated in Study C4671034 in participants at least 12 years of age with symptomatic COVID-19 who are immunocompromised. No new safety findings were observed, including in post-marketing data and published literature. However, it could be noted that the proportion of Grade 3-4 TEAEs and treatment-related TEAEs are increased with the duration of treatment, with higher rates of nervous system disorders (notably dysgeusia and headache) and gastrointestinal disorders (notably nausea and vomiting) in the longer treatment duration group. Although no conclusion can be drawn from these data whether longer treatment durations are associated to an increase in the frequency and/or severity of Paxlovid-related AEs, this should be

considered in case of higher treatment duration of Paxlovid for the treatment of immunocompromised patients.

9. MAH Response to CHMP Comments on PAM MEA 20.1

REQUEST 1

Specify whether the site where the 5 participants were excluded from is part of the sites that were affected by the GCP issues on the pivotal EPIC-HR study from the original Marketing Application

Response to Request 1

No, the 5 participants excluded from analyses in Study C4671034 originated from site 1001 (PIs: Lisa Patel, Tampa, FL, United States) due to GCP quality issues. In EPIC-HR sites 1274 (PIs: Martinez, Cutler Bay, FL, United States) and 1470 (PIs: Hernandez, Sunrise, FL, United States) were removed from efficacy, safety, and virology analyses due to data quality and GCP compliance issues, respectively. Neither of these 2 sites participated in Study C4671034.

Rapporteur's comment:

Point solved.

REQUEST 2

Scrutinize the subgroups of patients under corticosteroids and under [TNF-alpha] immunosuppressants in terms of baseline characteristics (VL>2 >4 and >7 log)

Response to Request 2

To adequately capture a representative range of participants who were immunocompromised, enrolment was stratified and capped for participants with corticosteroid or TNF blocker use as the sole form of immunosuppression. The Section 5.1.1.3 of the LPLV CSR provides an analysis of the primary endpoint for participants who were immunocompromised based on corticosteroids or TNF blocker use which is consistent with primary endpoint outcome in the main study population. We have also provided an analysis of this subpopulation (N = 30 full analysis set; 28 evaluable) with respect to baseline demographic characteristics (Table 14.1.2.1.2), and the primary endpoint sub-grouped by baseline VL of ≥2, 4, or 7 logs (Table 14.2.1.1.1.7.2). Given the relatively small number of participants in these analyses, there is no clear relationship between the initial VL and success in the primary endpoint.

In addition, the reviewer's inquiry could also be interpreted to request an analysis in the subpopulation of all participants receiving immunosuppressive therapy at baseline. We provided the demographic tables (Table 14.1.2.1.1), primary endpoint (Table 14.2.1.1.1) and the primary endpoint sub-grouped by baseline VL of ≥2, 4, or 7 logs (Table 14.2.1.1.1.7.1). The outcomes of the analyses in this subgroup are similar to the main study population.

Rapporteur's comment:

As requested, the proportion of participants with sustained SARS-CoV-2 RNA< LLOQ from Day 15 to Day 44, by Baseline viral load level, in the subgroups of patients with immunosuppressant drug therapy, is as follows:

Baseline Viral Load		Nirmatrelvir + Ritonavir 5 Day (N=44)	Nirmatrelvir + Ritonavir 10 Day (N=44)	Nirmatrelvir + Ritonavir 15 Day (N=45)
<2	N1	3	3	1
	Participants with event, n(%)	3 (100.0)	2 (66.67)	1 (100.0)
>=2	N1	40	41	43
	Participants with event, n(%)	25 (62.50)	29 (70.73)	28 (65.12)
<4	N1	7	5	8
	Participants with event, n(%)	7 (100.0)	4 (80.00)	7 (87.50)
>=4	N1	36	39	36
	Participants with event, n(%)	21 (58.33)	27 (69.23)	22 (61.11)
<7	N1	27	23	19
	Participants with event, n(%)	19 (70.37)	18 (78.26)	12 (63.16)
>=7	N1	16	21	25
	Participants with event, n(%)	9 (56.25)	13 (61.90)	17 (68.00)

Focusing on the subgroup of patients treated with only corticosteroids/TNF blocker, the results are difficult to interpret, given the relatively small number of participants:

Baseline Viral Load		Nirmatrelvir + Ritonavir 5 Day (N=10)	Nirmatrelvir + Ritonavir 10 Day (N=8)	Nirmatrelvir + Ritonavir 15 Day (N=10)
<2	N1	3	1	0
	Participants with event, n(%)	3 (100.0)	1 (100.0)	0
>=2	N1	7	7	10
	Participants with event, n(%)	4 (57.14)	6 (85.71)	8 (80.00)
<4	N1	5	1	2
	Participants with event, n(%)	5 (100.0)	1 (100.0)	2 (100.0)
>=4	N1	5	7	8
	Participants with event, n(%)	2 (40.00)	6 (85.71)	6 (75.00)
<7	N1	9	5	6
	Participants with event, n(%)	7 (77.78)	4 (80.00)	5 (83.33)
>=7	N1	1	3	4
	Participants with event, n(%)	0	3 (100.0)	3 (75.00)

Overall, no differences could be highlighted between the 3 groups of patients treated with immunosuppressant drugs, whatever the level of baseline viral load.

Point solved.

REQUEST 3

Detail the characteristics of patients failing to meet the primary endpoint in each subgroup (viral load strata, specific cause of immunosuppression, delay between first symptom and treatment initiation, time to first negativation)

Response to Request 3

The demographic information for study participants who did not achieve the primary endpoint (N = 51) is summarised in Table 14.1.2.1.3. The baseline characteristics of participants who did not achieve the primary endpoint were similar in pattern to the main study population (LPLV CSR Table 8). Please note that participants could have multiple causes for being considered immunocompromised.

With regard to time to first NP swab <LLOQ, Table 14.2.2.1 provides the data for participants who did not achieve the primary endpoint (non-responder population). In the non-responder population, the median time to first NP swab SARS-CoV-2 RNA <LLOQ was 22.0, 20.0, and 21.0 days in the 5-, 10-, and 15-day treatment groups respectively, whereas in the main study population, the median time to first NP swab SARS-CoV-2 RNA <LLOQ was 9.5, 11.0, and 9.0 days in the 5-, 10-, and 15-day treatment groups respectively, for participants with NP swab SARS-CoV-2 RNA ≥LLOQ at baseline.

Rapporteur's comment:

The requested data are as follows:

Demographic and Baseline Characteristics - Full Analysis Set, Main Study Population - Subset with non Responders (Protocol C4671034)

	Nirmatrelvir + Ritonavir 5 Day (N=20)	Nirmatrelvir + Ritonavir 10 Day (N=14)	Nirmatrelvir + Ritonavir 15 Day (N=17)	Total (N=51)
Immunocompromised based solely on corticosteroids or TNF blockers [b], n (%)				
Yes	3 (15.0)	1 (7.1)	2 (11.8)	6 (11.8)
No	17 (85.0)	12 (85.7)	15 (88.2)	44 (86.3)
Not Immunocompromised	0	1 (7.1)	0	1 (2.0)
SARS-CoV-2 RNA NP level (Log_{10} copies/mL), n (%)				
< 2	0	2 (14.3)	1 (5.9)	3 (5.9)
≥ 2	19 (95.0)	12 (85.7)	16 (94.1)	47 (92.2)
< 4	0	2 (14.3)	2 (11.8)	4 (7.8)
≥ 4	19 (95.0)	12 (85.7)	15 (88.2)	46 (90.2)
< 7	8 (40.0)	6 (42.9)	8 (47.1)	22 (43.1)
≥ 7	11 (55.0)	8 (57.1)	9 (52.9)	28 (54.9)
Mean (SD)	7.02 (1.23)	6.21 (2.89)	6.60 (2.00)	6.65 (2.05)
Median (range)	7.05 (5, 9)	7.37 (0, 9)	7.26 (2, 9)	7.17 (0, 9)

	Nirmatrelvir + Ritonavir 5 Day (N=20)	Nirmatrelvir + Ritonavir 10 Day (N=14)	Nirmatrelvir + Ritonavir 15 Day (N=17)	Total (N=51)
Unknown	0	0	0	0
Ethnicity, n (%)				
Hispanic or Latino	14 (70.0)	9 (64.3)	10 (58.8)	33 (64.7)
Not Hispanic or Latino	5 (25.0)	5 (35.7)	7 (41.2)	17 (33.3)
Not Reported	1 (5.0)	0	0	1 (2.0)
Weight (kg)				
Mean (SD)	77.57 (15.52)	85.20 (31.26)	73.29 (21.11)	78.10 (22.35)
Median (range)	72.70 (60, 115)	79.00 (58, 182)	67.00 (50, 133)	72.00 (50, 182)
Height (cm)				
Mean (SD)	167.8 (9.60)	167.7 (11.36)	167.8 (8.95)	167.8 (9.67)
Median (range)	165.6 (154, 189)	167.0 (152, 196)	169.0 (155, 182)	166.8 (152, 196)
BMI (kg/m²), n (%)				
< 25	7 (35.0)	4 (28.6)	10 (58.8)	21 (41.2)
25 - < 30	7 (35.0)	4 (28.6)	4 (23.5)	15 (29.4)
30 - < 35	4 (20.0)	2 (14.3)	2 (11.8)	8 (15.7)
35 - < 40	2 (10.0)	1 (7.1)	0	3 (5.9)
≥ 40	0	2 (14.3)	1 (5.9)	3 (5.9)
Mean (SD)	27.50 (4.78)	29.93 (7.59)	25.63 (5.07)	27.50 (5.84)
Median (range)	25.70 (22, 40)	28.30 (21, 48)	23.80 (19, 41)	25.70 (19, 48)
Duration since first diagnosis (Days), n (%)				
< 3	17 (85.0)	12 (85.7)	12 (70.6)	41 (80.4)
3 - 5	3 (15.0)	2 (14.3)	5 (29.4)	10 (19.6)
6 - 7	0	0	0	0
8 - 15	0	0	0	0
16 - 29	0	0	0	0
≥ 30	0	0	0	0
Mean (SD)	1.45 (0.76)	1.50 (1.16)	1.82 (1.13)	1.59 (1.00)
Median (range)	1.00 (1, 3)	1.00 (1, 5)	1.00 (1, 4)	1.00 (1, 5)
Duration since first symptom (Days), n (%)				
< 3	7 (35.0)	6 (42.9)	8 (47.1)	21 (41.2)
3 - 5	11 (55.0)	7 (50.0)	7 (41.2)	25 (49.0)
6 - 7	1 (5.0)	0	1 (5.9)	2 (3.9)
8 - 15	0	1 (7.1)	0	1 (2.0)
16 - 29	0	0	0	0
≥ 30	1 (5.0)	0	1 (5.9)	2 (3.9)
≤ 5	18 (90.0)	13 (92.9)	15 (88.2)	46 (90.2)
> 5 - ≤ 30	1 (5.0)	1 (7.1)	1 (5.9)	3 (5.9)
> 30	1 (5.0)	0	1 (5.9)	2 (3.9)
Mean (SD)	9.05 (26.86)	3.21 (1.97)	13.12 (41.49)	8.80 (29.00)

	Nirmatrelvir + Ritonavir 5 Day (N=20)	Nirmatrelvir + Ritonavir 10 Day (N=14)	Nirmatrelvir + Ritonavir 15 Day (N=17)	Total (N=51)
Median (range)	3.00 (1, 123)	3.00 (1, 8)	3.00 (1, 174)	3.00 (1, 174)
Country, n (%)				
Australia	0	0	0	0
Brazil	4 (20.0)	0	0	4 (7.8)
Bulgaria	0	0	0	0
Canada	3 (15.0)	2 (14.3)	2 (11.8)	7 (13.7)
Hungary	0	0	0	0
Mexico	1 (5.0)	1 (7.1)	3 (17.6)	5 (9.8)
Slovakia	1 (5.0)	2 (14.3)	2 (11.8)	5 (9.8)
Spain	7 (35.0)	6 (42.9)	9 (52.9)	22 (43.1)
United States	4 (20.0)	3 (21.4)	1 (5.9)	8 (15.7)
Vaccination status, n (%)				
Vaccinated within 6 months prior to randomization	3 (15.0)	4 (28.6)	5 (29.4)	12 (23.5)
Vaccinated more than 6 months prior to randomization	14 (70.0)	9 (64.3)	12 (70.6)	35 (68.6)
Not vaccinated at all prior to randomization	3 (15.0)	1 (7.1)	0	4 (7.8)
Serology status, n (%)				
Negative	0	0	0	0
Positive	20 (100.0)	14 (100.0)	17 (100.0)	51 (100.0)
Renal function eGFR/eCrCl (mL/min/1.73 m^2 / mL/min), n (%)				
Normal (≥90)	10 (50.0)	11 (78.6)	8 (47.1)	29 (56.9)
Mild Impairment (≥60 to <90)	4 (20.0)	2 (14.3)	7 (41.2)	13 (25.5)
Moderate Impairment (≥30 to <60)	5 (25.0)	1 (7.1)	2 (11.8)	8 (15.7)
Severe Impairment (<30)	0	0	0	0
Rapid antigen test (RAT), n (%)				
Positive	6 (30.0)	5 (35.7)	4 (23.5)	15 (29.4)
Negative	0	0	0	0
CRF Immunocompromised categories [a], n (%)				
Solid organ transplant	1 (5.0)	1 (7.1)	0	2 (3.9)
CAR-T-cell therapy / hematopoietic stem cell transplant infusion	4 (20.0)	2 (14.3)	4 (23.5)	10 (19.6)
Moderate or severe primary immunodeficiency / HIV infection CDC group III < 200 CD4 count	1 (5.0)	0	1 (5.9)	2 (3.9)
Solid tumor	0	0	0	0
Hematological malignancy	12 (60.0)	6 (42.9)	12 (70.6)	30 (58.8)
Immunosuppressant drug therapy	16 (80.0)	13 (92.9)	15 (88.2)	44 (86.3)
Not meeting any CRF category	0	1 (7.1)	0	1 (2.0)
Immunocompromised based solely on corticosteroids or TNF blockers [b], n (%)				
Yes	3 (15.0)	1 (7.1)	2 (11.8)	6 (11.8)
No	17 (85.0)	12 (85.7)	15 (88.2)	44 (86.3)
Not Immunocompromised	0	1 (7.1)	0	1 (2.0)
SARS-CoV-2 RNA NP level (Log $_{10}$ copies/mL), n (%)				
< 2	0	2 (14.3)	1 (5.9)	3 (5.9)
≥ 2	19 (95.0)	12 (85.7)	16 (94.1)	47 (92.2)
< 4	0	2 (14.3)	2 (11.8)	4 (7.8)
≥ 4	19 (95.0)	12 (85.7)	15 (88.2)	46 (90.2)
< 7	8 (40.0)	6 (42.9)	8 (47.1)	22 (43.1)
≥ 7	11 (55.0)	8 (57.1)	9 (52.9)	28 (54.9)
Mean (SD)	7.02 (1.23)	6.21 (2.89)	6.60 (2.00)	6.65 (2.05)
Median (range)	7.05 (5, 9)	7.37 (0, 9)	7.26 (2, 9)	7.17 (0, 9)

Overall, these data did not highlight any trend of treatment duration on the lack of virological response, whatever the baseline characteristics subgroups (notably viral load strata, specific cause of immunosuppression, delay between first symptom and treatment initiation).

Point solved.

REQUEST 4

Scrutinize whether there was any safety issue in relation to drug drug interaction with immununosuppressants and with the prolonged treatment duration.

Response to Request 4

There were no adverse events reported for drug-drug interactions between nirmatrelvir/ritonavir and immunosuppressive therapies. Participants taking any interacting drugs that might have resulted in a clinically significant interaction of concern (eg, simvastatin, carbamazepine, ergotamine) were excluded from the trial. In some cases, the interacting drug was discontinued before enrolment and restarted after completion of treatment with nirmatrelvir/ritonavir. The decision of whether a concomitant medication needed to be discontinued was taken by the investigator, according to their assessment of potential risks and benefits. Participants taking interacting drugs that could be managed through appropriate dosage adjustments or therapeutic drug monitoring were allowed in the study.

Calcineurin inhibitors and mTOR inhibitors were infrequently reported as baseline medications, and were managed as follows:

- Two participants on sirolimus stopped medication prior to nirmatrelvir/ritonavir initiation, while one participant discontinued sirolimus 4 days after nirmatrelvir/ritonavir initiation.
- Of 4 participants on tacrolimus, 2 had discontinued medication long before enrolment, 1 discontinued and restarted after treatment completion with nirmatrelvir/ritonavir and 1 was taking a topical formulation (mouth washes) that did not need dose adjustment.
- Of 6 participants on cyclosporine: 4 had discontinued medication before enrolment and 2 remained on it without safety issues.

Rapporteur's comment:

There was no safety issue in relation to drug interaction with immunosuppressants. Some subjects were initially treated with sirolimus, tacrolimus or cyclosporine when Paxlovid was introduced. The management of the risk of DDI for these patients was different according to the subject (discontinuation treatment or not), in accordance to Paxlovid SmPC section 4.5 and without safety consequences.

Point solved.

REQUEST 5

It is finally expected that the applicant will discuss the merit of prolonging treatment duration in immunocompromised patients.

Response to Request 5

Immunocompromised individuals are a particular patient population recognised to be at high-risk for disease progression. Current NIH treatment and CDC isolation guidelines note that patients who are immunocompromised may experience prolonged COVID-19 symptoms with viral shedding beyond 20 days and a prolonged course of antiviral therapy may be necessary. The optimal duration of PAXLOVID (nirmatrelvir/ritonavir) therapy in patients who are immunocompromised is uncertain and Study C4671034 (EPIC-IC) was conducted as a post-marketing commitment to address this question. A virologic endpoint was considered most feasible as a primary endpoint. Additional virologic and clinical outcomes were selected as secondary and exploratory endpoints. The topline study report provided

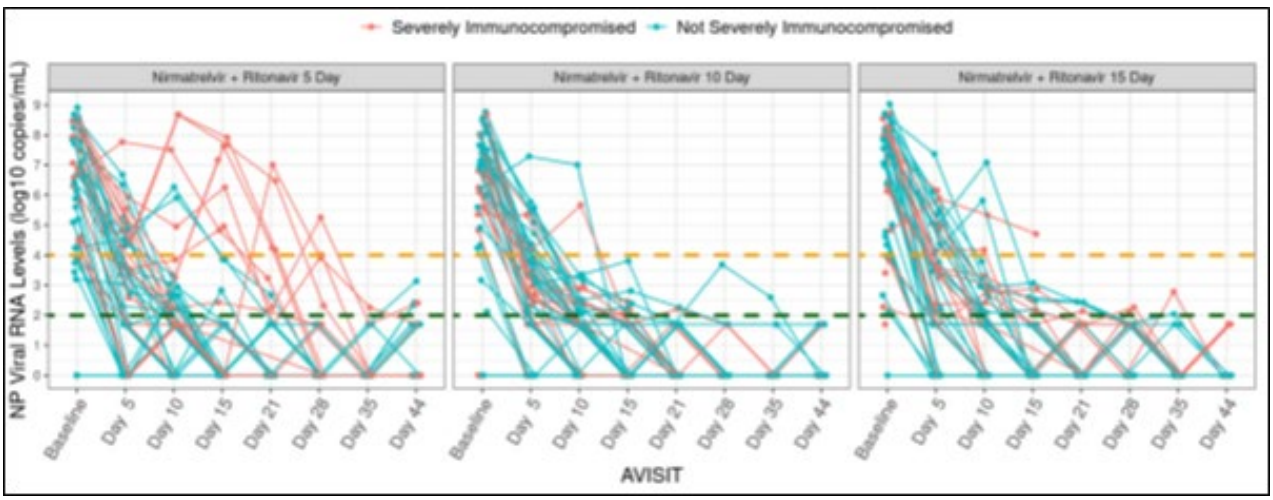
results through study Day 44; the final study report includes long term follow-up data with study visits at Weeks 12 and 24.

The overall results suggest that the currently labelled 5-day treatment duration is adequate for the overall immunocompromised population. The primary endpoint was the proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44 (ie, 28 days following the end of the 15-day treatment). The 3 treatment durations for nirmatrelvir/ritonavir were associated with similar outcomes for the primary endpoint. The proportions of participants with sustained NP swab SARS-CoV-2 RNA<LLOQ were 61.54% for the 5-day treatment group, 70.83% for the 10-day treatment group, and 66.00% for the 15-day treatment group. Prespecified secondary analyses did not reveal significant differences in outcomes among the treatment groups.

Following the completion of the study, the MAH conducted a series of post-hoc analyses to explore treatment outcomes in participants who were severely immunocompromised. Severe immunocompromise was defined as individuals with active haematologic malignancies and/or receipt of haematopoietic stem cell transplantation, CAR T-cell therapy or B-cell depleting therapies (eg, rituximab). Of the 150 participants enrolled into the main study population FAS (ie, all participants randomly assigned to study intervention), 57 participants met the criteria for being severely immunocompromised. In post-hoc subgroup analyses of these participants who were severely immunocompromised, evidence suggests 5 days of nirmatrelvir/ritonavir treatment did not control SARS-CoV-2 viral replication as well as 10 or 15 days of therapy in the subpopulation of severely immunocompromised participants (Figure 1).

A plot of individual participant's NP SARS-CoV-2 RNA levels by study visit (Figure 1) shows that more participants who were severely IC in the 5-day treatment group experienced prolonged periods of viral replication (SARS-CoV-2 RNA level >LLOQ) relative to participants who were not severely immunocompromised in the 5-day treatment group. Some participants who were severely immunocompromised in the 5-day treatment group exhibited an increase in viral RNA levels following the end of treatment on Day 5 (Figure 1). These data suggest that participants who were severely IC and received 10-days or 15-days of treatment experienced better virologic control than participants who were severely IC and received 5-days of treatment.

Figure 1. C4671034 Individual NP Viral RNA Levels, Main Study Population



In participants who were severely immunocompromised, the median time to achieving NP swab SARS-CoV-2 RNA <LLOQ was numerically longer in the 5-day treatment group (28 days) compared with the 10-day (13 days) and 15-day (15 days) treatment groups. The proportion of participants who were

severely immunocompromised with both a positive SARS-CoV-2 rapid antigen test and any self-reported targeted symptom of COVID-19 from Day 15 (end of treatment) through Day 44 was 33.3% (6 of 18 participants), 6.3% (1 of 16 participants), and 0% (0 of 16 participants) in the 5-, 10- and 15-day nirmatrelvir/ritonavir treatment groups, respectively. Importantly, there were 2 participants who were severely immunocompromised in the 5-day nirmatrelvir/ritonavir treatment group who experienced COVID-19 related hospitalisations through Day 44. No COVID-19-related hospitalisations occurred with longer nirmatrelvir/ritonavir treatment durations in participants who were severely immunocompromised or in participants who were not severely immunocompromised.

The burden of COVID-19 in patients with severe immunocompromise remains significant. A longer treatment duration that improves virologic control may reduce the risk of progression to severe COVID-19, avoid delays to other planned medical interventions, and minimize risk of emergence of variants with mutations/substitutions associated with reduced susceptibility to nirmatrelvir. Symptomatic, severely immunocompromised patients with evidence of viral replication would be expected to receive additional antiviral therapy given the risk for disease progression, as has been consistent with healthcare provider requests for expanded access to nirmatrelvir/ritonavir. The MAH considers the strength of the above data in severe IC patients, coupled with the high burden of disease, to be adequate to inform labeling for extended treatment durations (ie, up to 15 days) in this vulnerable patient population, and would value the CHMPs perspective.

Rapporteur's comment:

We acknowledge the MAH for this discussion and the potential benefit to prolong treatment duration up to 15 days for patients with severe immunosuppression based on a post-hoc analysis. The interest in higher treatment duration for IC patients is solely based on virologic endpoint at this stage, as this study is not sufficiently powerful to highlight any impact of the treatment on COVID-19 related hospitalizations. In patients who were severely immunocompromised (i.e. haematologic malignancies and/or receipt of HSCT, CAR T-cell therapy or B-cell depleting therapies), it is acknowledged that SARS-CoV-2 viral clearance is significantly prolonged in these patients, and the data from the post-hoc analyses report a higher rate of virologic rebound and positive SARS-CoV-2 viral load after the end of a 5-days treatment in comparison to 10-days or 15-days treatments. The clinical impact of such differences (i.e. higher rate/duration of COVID-19 related hospitalization with a 5-days treatment in these severely IC patients) cannot be estimated.

A comparison could be made with oseltamivir for the treatment of influenza, for which the recommended treatment duration for IC patients is prolonged to 10 days (vs 5 days for other patients). This extension of treatment duration was based on a study comparing the standard dose (75 mg BID) vs a double dose (150 mg BID), both for a longer treatment duration (10 days). No comparison 5 days vs 10 days was performed, but this duration of treatment was proposed based on PK/PD modelling in IC subjects suggesting a risk of viral rebound with a 5 days treatment, which can be reduced by using a 10 day treatment regimen. As the clinical study had not provided any improve of clinical response with the double dose, it was concluded that the dose for treatment of influenza in IC subjects with the best benefit-to-risk balance seems to be 75 mg BID for 10 days.

In conclusion for Paxlovid, a trend to higher antiviral efficacy was highlighted in the 2 higher treatment duration groups (10 and 15 days) in comparison to the currently approved treatment duration group (5 days). Furthermore, the 4 subjects who had still detectable SARS-CoV-2 RNA levels at Day 44 were all in the 5 days group, supporting this hypothesis of higher antiviral efficacy of treatment duration >5 days for immunocompromised subjects. This is also supported by the additional post-hoc analyses provided by the MAH and reporting in severely IC patients a higher number of subjects with prolonged periods of viral replication and viral rebound following the end of treatment in the 5 days treatment

group vs the 10 days and the 15 days treatment groups. Of note, no differences between the 10 days and the 15 days treatment groups was reported. Considering the safety data reporting an increased proportion of Grade 3-4 TEAEs and treatment-related TEAEs in the longer treatment duration group, a 15 days duration of treatment cannot be privileged compared to the 10 days duration of treatment.

Therefore, without imposing a treatment duration in the population of severely IC patients, we suggest to add the following statement in section 4.2 ("Special populations" sub-heading):

Severely immunocompromised patients

A treatment duration of 10 days may help to mitigate the risk of virological rebound in patients with severe immunodepression (e.g. active haematologic malignancies, haematopoietic stem cell transplantation, CAR T-cell therapy or B-cell depleting therapies) (see section 5.1)

In section 5.1, a short paragraph should be added to report the virologic data from study C4671034, e.g.:

Post-hoc subgroup analysis in severely immunocompromised patients

In participants who were severely immunocompromised in study C4671034, the median time to achieving NP swab SARS-CoV-2 RNA <LLOQ was numerically longer in the 5-day treatment group (28 days) compared with the 10-day (13 days) and 15-day (15 days) treatment groups. The proportion of participants with both a positive SARS-CoV-2 rapid antigen test and any self-reported targeted symptom of COVID 19 from Day 15 through Day 44 was 33.3% (6 of 18 participants), 6.3% (1 of 16 participants), and 0% (0 of 16 participants) in the 5-, 10- and 15-day nirmatrelvir/ritonavir treatment groups, respectively.

Point resulting in SmPC update.

10. Request for supplementary information

10.1. Other concerns

Clinical aspects

1) The following statement is proposed to be added in section 4.2 ("Special populations" sub-heading) of Paxlovid SmPC:

Severely immunocompromised patients

A treatment duration of 10 days may help to mitigate the risk of virological rebound in patients with severe immunodepression (e.g. active haematologic malignancies, haematopoietic stem cell transplantation, CAR T-cell therapy or B-cell depleting therapies) (see section 5.1)

In addition, a short paragraph should be added in section 5.1 to report the virologic data from study C4671034, e.g.:

Post-hoc subgroup analysis in severely immunocompromised patients

In participants who were severely immunocompromised in study C4671034, the median time to achieving NP swab SARS-CoV-2 RNA <LLOQ was numerically longer in the 5-day treatment group (28 days) compared with the 10-day (13 days) and 15-day (15 days) treatment groups. The proportion of participants with both a positive SARS-CoV-2 rapid antigen test and any self-reported targeted symptom of COVID 19 from Day 15 through Day 44 was 33.3% (6 of 18 participants), 6.3% (1 of 16 participants), and 0% (0 of 16 participants) in the 5-, 10- and 15-day nirmatrelvir/ritonavir treatment groups, respectively.

11. Assessment of the responses to the request for supplementary information

11.1. Other concerns

Clinical aspects

Question 1

Summary of the MAH's response

The Marketing Authorisation Holder (MAH) agrees to add information regarding Study C4671034 (EPIC-IC) to the Paxlovid Summary of Product Characteristics (SmPC) and proposes to include information in Section 4.2 and Section 5.1 as outlined below.

Section 4.2

The MAH has included a sub-heading of "*Severely immunocompromised population*" and a cross-reference to Section 5.1. The added text in Section 4.2 is intended to point the prescriber to Section 5.1 for further information regarding data that are available for 5-, 10- and 15-day treatment duration in severely immunocompromised patients, including efficacy and safety data from the EPIC-IC study.

Section 5.1

The MAH proposes to include information regarding the EPIC-IC study in Section 5.1 so that the prescriber can make a clinical judgement on the benefit-risk for their individual patient. The proposed label update includes a summary of efficacy and safety in immunocompromised patients from this study, in the subsection entitled "*EPIC-IC study in immunocompromised participants*". In a further subsection entitled "*Post-hoc subgroup analysis in severely immunocompromised participants (e.g., active haematologic malignancies, haematopoietic stem cell transplantation, CAR T-cell therapy or B-cell depleting therapies)*" efficacy and viral rebound data are provided for severely immunocompromised patients.

Assessment of the MAH's response

Overall, while the Rapporteur can agree to add some factual information in section 5.1 on the study to introduce the post-hoc analysis, this should be confined to very limited information given that the CHMP purpose was not to reflect the whole outcome of this study but just to reflect the post-hoc analysis in a sub-population of this study to alert on the potential need to extend the treatment duration in patients severely immunocompromised as a conservative measure to potentially mitigate the risk of virologic rebound.

Moreover, the applicant's proposed revision of the CHMP paragraph in section 4.2 cannot be endorsed since it leaves open the choice of extending the treatment duration to 10 or 15 days, while in the absence of apparent difference in between both extended treatment durations, 10 days should be recommended in line with the prior CHMP conclusion.

Overall the prior CHMP recommended addition in sections 4.2 and 5.1 can be slightly revised to partially take into account the applicant's proposal as follows:

Severely immunocompromised patients

Data are limited in those patients. A treatment duration of 10 days may help to mitigate the risk of virological rebound in patients with severe immunodepression (e.g. active haematologic malignancies, haematopoietic stem cell transplantation, CAR T-cell therapy or B-cell depleting therapies) (see section 5.1).

Post-hoc subgroup analysis in severely immunocompromised patients

A post-hoc subgroup analysis in severely immunocompromised participants (e.g., active haematologic malignancies, haematopoietic stem cell transplantation, CAR T-cell therapy or B-cell depleting therapies) has been performed and was derived from EPIC-IC (C4671034) *study in immunocompromised participants.* In participants who were severely immunocompromised, the median time to achieving NP swab SARS-CoV-2 RNA <LLOQ was numerically longer in the 5-day treatment group (28 days) compared with the 10-day (13 days) and 15-day (15 days) treatment groups. The proportion of participants with both a positive SARS-CoV-2 rapid antigen test and any self-reported targeted symptom of COVID 19 from Day 15 through Day 44 was 33.3% (6 of 18 participants), 6.3% (1 of 16 participants), and 0% (0 of 16 participants) in the 5-, 10- and 15-day nirmatrelvir/ritonavir treatment groups, respectively.

Conclusion

After circulating this proposed changes to the SmPC, the MAH has endorsed this update with nevertheless the addition in section 5.1 of the incidence of viral RNA rebound in the post-hoc subgroup analysis: *The incidence of viral RNA rebound observed in the severely immunocompromised participants was 25% (5 of 20 participants), 0% (0 of 17 participants) and 5% (1 of 20 participants) in the 5-, 10-, and 15-day Paxlovid treatment groups, respectively.*

This is endorsed.

☒Overall, no need to update overall conclusion and impact on benefit-risk balance