17 October 2024
EMA/447042/2024
Human Medicines Division

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

Paxlovid

Nirmatrelvir / Ritonavir

Procedure no: EMEA/H/C/005973/P46/022

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	19 Aug 2024	19 Aug 2024
☐	CHMP Rapporteur Assessment Report	23 Sep 2024	23 Sep 2024
☐	CHMP members comments	07 Oct 2024	N/A
☐	Updated CHMP Rapporteur Assessment Report	10 Oct 2024	N/A
☒	CHMP adoption of conclusions:	17 Oct 2024	17 Oct 2024

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1. Introduction

On 13 May 2024, the MAH submitted a completed paediatric study for Paxlovid, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

It has to be underlined that these data from study C4671042 are expected to be submitted and assessed as part of the post-authorisation measure MEA 19.1. This current P46 procedure will only focus on paediatric data from this study (i.e. only 1 subject).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

This study is being submitted in accordance with Article 46 of the Paediatric Regulation (European Commission [EC] No 1901/2006). The MAH is submitting the CSR under Article 46 within 6 months of completion to report paediatric data. The Marketing Authorisation Holder is not proposing any amendments to the Paxlovid EU Summary of Product Characteristics to add data from Study C4671042.

2.2. Information on the pharmaceutical formulation used in the study

The currently approved formulation of Paxlovid (nirmatrelvir tablet 150 mg + ritonavir tablet 100 mg) was used in the study. An age-appropriate oral dose formulation for the treatment of COVID-19 from birth to less than 18 years of age is under investigation.

2.3. Clinical aspects

2.3.1. Introduction

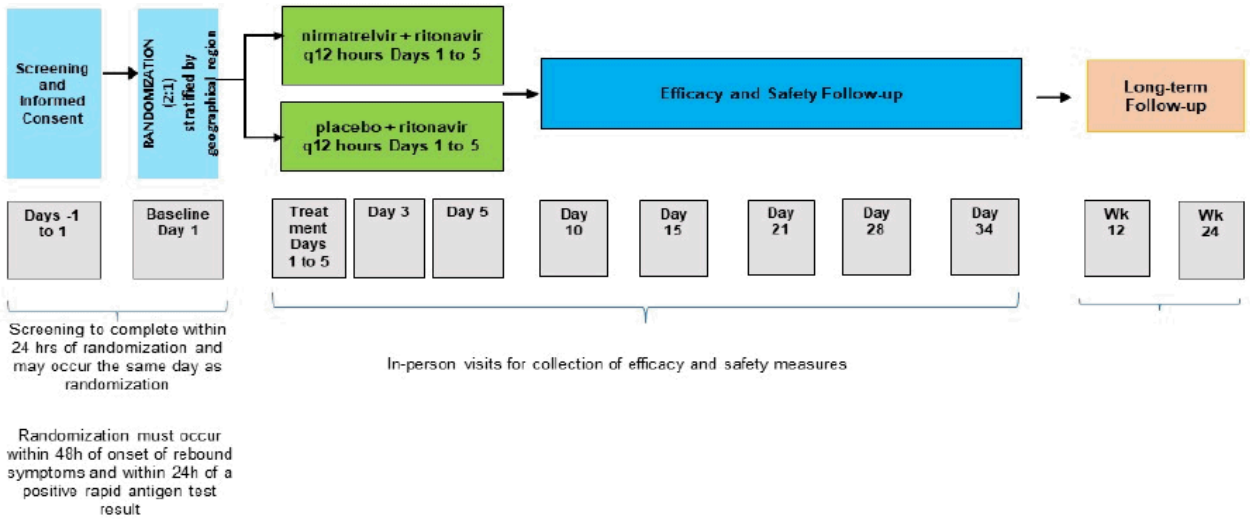
The MAH submitted a final report for study C4671042 (An Interventional, Efficacy and Safety, Phase 2, Randomized, Double-Blind, 2-Arm Study to Investigate a Repeat 5-Day Course of Nirmatrelvir/Ritonavir Compared to Placebo/Ritonavir in Participants at Least 12 Years of Age With Rebound of COVID-19 Symptoms and Rapid Antigen Test Positivity). Of the 436 participants who were assigned to treatment, 1 participant was a pediatric participant.

2.3.2. Clinical study

C4671042, An Interventional, Efficacy and Safety, Phase 2, Randomized, Double-Blind, 2-Arm Study to Investigate a Repeat 5-Day Course of Nirmatrelvir/Ritonavir Compared to Placebo/Ritonavir in Participants at Least 12 Years of Age With Rebound of COVID-19 Symptoms and Rapid Antigen Test Positivity.

Description

This is a Phase 2, randomized, double-blind, placebo-controlled study will evaluate the efficacy and safety of a repeat 5-day treatment course of nirmatrelvir/ritonavir or placebo/ritonavir for the treatment of mild-to-moderate COVID-19.



Methods

Study participants

Participants ≥12 years of age and weighing at least 40 kg at screening, with rebound of COVID-19 symptoms and rapid antigen test positivity within 2 weeks (14 days) following documented completion of an initial 5-day treatment course of nirmatrelvir/ritonavir. Participants must have had at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19. However, participants who are immunocompromised were excluded from this study as they may have had prolonged viral shedding due to their immunocompromised state. Participants were eligible for enrollment irrespective of COVID-19 vaccination/boosted status (except for time course restrictions listed in the exclusion criteria).

Treatments

The first dose of study intervention will be administered at the site.

Nirmatrelvir 150 mg tablets or placebo for nirmatrelvir will be administered with ritonavir 100 mg for 5 days.

Participants will be instructed to take:

- 2 tablets of nirmatrelvir 150 mg or placebo for nirmatrelvir q12h;

- 1 capsule of ritonavir 100 mg q12h.

Participants with moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m2 [or eCrCl ≥30 to <60 mL/min] at screening) will receive either 1 tablet of nirmatrelvir 150 mg and placebo for nirmatrelvir or 2 tablets of placebo for nirmatrelvir. The dose for ritonavir remains unchanged (ie, participants will receive 1 capsule of ritonavir 100 mg q12h).

Objective

Primary objective: To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on viral RNA level in NP swabs in participants with mild-to-moderate COVID-19.

Outcomes/endpoints

Primary endpoint: The change in viral SARS-CoV-2 RNA level as measured in NP swabs from baseline to Day 5.

Secondary and exploratory objectives include notably the comparison nirmatrelvir/ritonavir vs placebo/ritonavir on the duration of viral shedding, the duration and severity of signs and symptoms, the viral RNA level in NP swabs and plasma, the COVID-19-related hospitalization and all-cause mortality.

Sample size

A sample size of approximately 315 evaluable participants (210 participants in nirmatrelvir/ritonavir group and 105 participants in placebo/ritonavir group) is expected to provide 90% power to detect a difference of 0.7 log10 copies/mL in viral RNA between groups using a 2-sided 0.05 alpha level test. Assuming approximately 10% of participants will have a negative viral RNA result at baseline, and assuming a non-evaluable rate of 15%, approximately 411 participants will be randomized in the study to achieve approximately 315 participants evaluable for the primary efficacy endpoint.

Randomisation and blinding (masking)

Eligible participants for this study will be randomly assigned (2:1 allocation of active to placebo) to receive:

- nirmatrelvir plus ritonavir orally q12h for 5 days; or

- placebo plus ritonavir orally q12h for 5 days.

Randomization will be stratified by geographic region.

Participants must be randomized within 48 hours from the onset of the rebound COVID-19 symptoms and must be randomized within 24 hours of a positive baseline rapid antigen test.

Statistical Methods

Table 1: Analysis Sets

Participant Analysis Set	Description
Full analysis set (FAS)	All participants randomly assigned to study intervention.
Safety analysis set (SAS)	All participants randomly assigned to study intervention and who took at least 1 dose of study intervention. Participants were analyzed according to the study intervention they received.

Participant Analysis Set	Description
mITT	All participants randomly assigned to study intervention who took at least 1 dose of study intervention and who had a positive viral RNA NP swab test result (≥2.0 $\log_{10}$ copies/mL) at baseline. Participants were analyzed according to the study intervention they were randomized.
mITT1	All participants randomly assigned to study intervention who took at least 1 dose of study intervention and who had a positive rapid antigen test result at baseline. Participants were analyzed according to the study intervention they were randomized.
Per protocol (PP)	All participants in the mITT analysis set without important protocol deviations considered to impact the interpretation of the primary efficacy endpoint. Protocol deviations were reviewed to generate the list of participants with significant deviations to be excluded from the PP analysis set. The PP exclusion criteria were finalized prior to breaking the blind.

A decision was made to remove efficacy data from the analyses for Site 1020 due to GCP quality issues. A total of 41 participants were enrolled at Site 1020 and data from all 41 participants were excluded from efficacy analyses. No further participants were enrolled at this site after the GCP quality issues were identified. The pediatric participant was not enrolled at Site 1020.

Results

Participant flow

Of the 551 participants who were screened for entry into the study, 436 participants were assigned to treatment. During the treatment phase (through Day 5/6), 2 participants discontinued study intervention during the treatment period due to an AE, but none of those AEs caused the participant to be discontinued from the study. During the efficacy and safety follow-up phase (through Day 34) and long-term follow-up phase, the most frequent reason for study discontinuation was withdrawal by participant.

The one enrolled pediatric participant completed the study.

Participants from Site 1020 were excluded from efficacy analyses due to GCP quality issues.

Table 2: Participants Evaluation Groups -All Screened Participats (Protocol C4671042

	Nirmatrelvir 300 mg + Ritonavir 100 mg (N=292) n (%)	Placebo + Ritonavir 100 mg (N=144) n (%)	Total (N=436) n (%)
Screened: 551			
Screened Failure: 111			
Not Screen Failure but not Randomized: 4			
Assigned to Treatment	292 (100.0)	144 (100.0)	436 (100.0)
Treated	289 (99.0)	144 (100.0)	433 (99.3)

Table 6. Participant Evaluation Groups - All Screened Participants (Protocol C4671042)

	Nirmatrelvir 300 mg + Ritonavir 100 mg (N=292) n (%)	Placebo + Ritonavir 100 mg (N=144) n (%)	Total (N=436) n (%)
Not Treated	3 (1.0)	0	3 (0.7)
Full analysis set	292 (100.0)	144 (100.0)	436 (100.0)
Safety analysis set	289 (99.0)	144 (100.0)	433 (99.3)
mITT analysis set	225 (77.1)	117 (81.3)	342 (78.4)
mITT1 analysis set	260 (89.0)	132 (91.7)	392 (89.9)
Per-protocol analysis set	212 (72.6)	109 (75.7)	321 (73.6)

All 41 participants randomized at site 1020 were excluded from all efficacy analysis sets.
mITT analysis set: All participants randomly assigned to study intervention who take at least 1 dose of study intervention and who have a positive viral RNA NP swab test result ($\geq$ 2.0 $\log_{10}$ copies/mL) at baseline.
mITT1 analysis set: All participants randomly assigned to study intervention who take at least 1 dose of study intervention and who have a positive rapid antigen test result at baseline.
Per-protocol analysis set: All participants in the mITT analysis set without important protocol deviations considered to impact the interpretation of the primary efficacy endpoint.

Baseline data

Overall, 56.7% participants were female. 90.8% of participants were White, 4.6% were Black or African American, 3.4% were Asian, 0.2% were American Indian or Alaska Native; and 0.2% were multiracial. 53.0% of participants were Hispanic or Latino. A total of 94.0% participants had a positive serology test at baseline. A total of 72.0% of participants had a baseline SARS-CoV-2 RNA level ≥4 log10 copies/mL and 20.9% of participants had a baseline SARS-CoV-2 RNA level ≥7 log10 copies/mL.

The paediatric participant had a medical history of chronic respiratory disease and asthma. The paediatric participant had a baseline SARS-CoV-2 RNA of 4.73 log10 copies/mL.

Efficacy results

Primary endpoint: change in viral SARS-CoV-2 RNA level as measured in NP swabs from baseline to Day 5.

In the mITT population who received at least 1 dose of study intervention and who had a positive viral RNA NP swab test result (≥2.0 log10 copies/mL) at baseline, on-treatment reduction in viral RNA level (ie, change from baseline in viral RNA concentration) at Day 5 was significantly (p=0.0004) larger in the nirmatrelvir/ritonavir treatment group than in the placebo/ritonavir group.

At baseline (Day 1), the pediatric participant had an NP swab SARS-CoV-2 RNA of 4.73 log10 copies/mL but had undetectable (ie, 0.0 log10 copies/mL) viral RNA from the Day 3 through Day 10 visits, which increased to 1.7 log10 copies/mL at Day 15. Viral RNA from Day 21-28 was undetectable (ie, 0.0 log10 copies/mL). Viral RNA at Day 34 was 1.7 log10 copies/mL.

Secondary endpoints:

Table 3: Secondary endpoints

Endpoint	Results and Location in Study C4671042 LPLV CSR
Secondary Efficacy	
Time to 2 consecutive negative rapid antigen test results obtained at least 24 (-2) h apart through Day 28.	Treatment with nirmatrelvir/ritonavir reduced the median time to 2 consecutive non-missing negative RAT results obtained 24 (-2) hours apart through Day 28 in the mITT analysis set by 4 days in the nirmatrelvir/ritonavir group and 5 days in the placebo treatment group. The hazard ratio for treatment with nirmatrelvir + ritonavir versus placebo + ritonavir was 1.235 (95% CI: 0.983, 1.551, p=0.0697), indicating participants treated with nirmatrelvir ritonavir on average were 23.5% more likely to achieve negative RAT status. The difference was not statistically significant when tested in the pre-specified proportional hazard model. Module 5.3.3.5 C4671042 LPLV CSR V1.0 Table 13 and Figure 3. Similar results were seen in the mITT1 analysis set (Module 5.3.3.5 C4671042 LPLV CSR V1.0 Table 14 and Figure 4). See Module 5.3.3.5 C4671042 LPLV CSR Section 5.1.2 for more details. The pediatric participant had 2 consecutive non-missing negative RAT results on Day 3 and Day 5 (Module 5.3.3.5 C4671042 LPLV CSR V1.0 Table 16.2.6.3).
Time (days) to sustained alleviation of all targeted signs and symptoms through Day 28 where sustained alleviation is defined as the first of 2 consecutive days when any symptoms scored as moderate or severe at baseline are scored as mild or absent and any symptoms scored as mild or absent at baseline are scored as absent.	Treatment with nirmatrelvir/ritonavir reduced the median time to sustained alleviation of all targeted signs and symptoms through Day 28 in the mITT analysis set. The median time to sustained alleviation of all targeted signs and symptoms was 8 days in the nirmatrelvir/ritonavir group and 9 days in the placebo/ritonavir treatment group Module 5.3.3.5 C4671042 LPLV CSR V1.0 Table 15. Similar results were seen in the mITT1 analysis set (Module 5.3.3.5 C4671042 LPLV CSR V1.0 Table 16 and Figure 6). See Module 5.3.3.5 C4671042 LPLV CSR Section 5.1.3 for more details. The pediatric participant achieved sustained alleviation of all targeted signs and symptoms observed at baseline (ie, moderate cough, headache, low energy or tiredness, and mild muscle or body aches) by Day 8 (Module 5.3.3.5 C4671042 LPLV CSR V1.0 Table 16.2.6.2).
Exploratory	
Proportion of participants with SARS-CoV-2 RNA in NP swab below the LLOQ on Days 3, 5, 10, 15, 21, 28, and 34.	In the mITT analysis set, the proportion of participants with SARS-CoV-2 RNA in NP swabs that was <LLOQ (<2.0 $\log_{10}$ copies/mL) at Day 3 was 22.831% and 16.667% in the nirmatrelvir/ritonavir and placebo/ritonavir groups, respectively. (Module 5.3.3.5 C4671042 LPLV CSR V1.0 Table 17). • The greatest difference between treatment groups in the proportion of participants with SARS-CoV-2 RNA <LLOQ occurred at Day 5 (59.633% and 42.478% in the nirmatrelvir/ritonavir and placebo/ritonavir groups, respectively). From Day 10 through Day 34, as most (≥84.211%) participants had SARS-CoV-2 RNA NP swabs <LLOQ, a minimal difference (≤5%) was observed between the nirmatrelvir/ritonavir and placebo/ritonavir groups. See Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Section 5.1.4 for more details. The pediatric participant had NP swab SARS-CoV-2 RNA levels <2.0 $\log_{10}$ copies/mL at Days 15 and 34. At Days 3, 5, 10, 21, and 28 the pediatric participant had undetectable (0.0 $\log_{10}$ copies/mL) NP swab SARS-CoV-2 RNA levels (Module 5.3.3.5 C4671042 LPLV CSR V1.0 Table 16.2.6.1).
Proportion of participants with	The proportion of participants in the mITT analysis set with sustained NP swab SARSCoV2 RNA that was <LLOQ (<2.0 $\log_{10}$ copies/mL) from Day 5 through Day

Endpoint	Results and Location in Study C4671042 LPLV CSR
sustained NP swab SARS-CoV-2 RNA below the LLOQ (defined as <2.0 log_{10} copies/mL) from Day 5 through Day 34.	34 was 55.157% in the nirmatrelvir/ritonavir group and 40.870% in the placebo group Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Table 18. See Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Section 5.1.5 for more details. The pediatric participant did not have sustained NP swab SARS-CoV-2 RNA levels <2.0 log_{10} copies/mL from Day 5 through Day 34 (Module 5.3.3.5 C4671042 LPLV CSR V1.0 Table 16.2.6.1).
Proportion of participants with SARS-CoV-2 RNA in NP swabs below the LLOQ (defined as <2.0 log_{10} copies/mL) on both Days 5 and 10.	The proportion of participants in the mITT analysis set with NP swab SARS-CoV-2 RNA <LLOQ (<2.0 log_{10} copies/mL) on both Day 5 and Day 10 was 54.260% in the nirmatrelvir/ritonavir group and 40.870% in the placebo/ritonavir group Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Table 19. See Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Section 5.1.6 for more details. The pediatric participant had undetectable (0.0 log_{10} copies/mL) NP swab SARS-CoV-2 RNA levels on both Days 5 and 10. (Module 5.3.3.5 C4671042 LPLV CSR V1.0 Table 16.2.6.1).
The change in SARS-CoV-2 RNA level in NP swabs from baseline to Days 3, 10, 15, 21, 28, and 34.	Levels of SARS-CoV-2 RNA decreased over time in both treatment groups. A faster decrease was seen in the nirmatrelvir/ritonavir group compared to the placebo/ritonavir group. The difference in decrease was shown as early as Day 3, the first assessment after baseline, and was most apparent at Day 5 (Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Table 11). See Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Section 5.1.7 for more details. At baseline (Day 1), the pediatric participant had an NP swab SARS-CoV-2 RNA level of 4.73 log_{10} copies/mL. The change in SARS-CoV-2 RNA level in NP swabs from baseline was -4.73 log_{10} copies/mL at Days 3, 5, 10, 21, and 28 and -3.03 log_{10} copies/mL at 15 and 34 . (Module 5.3.3.5 C4671042 LPLV CSR V1.0 Table 16.2.6.1).
Time to sustained NP swab SARS-CoV-2 RNA below the LLOQ (defined as <2.0 log_{10} copies/mL) and remains below the LLOQ through Day 34 for participants with NP swab SARS-CoV-2 RNA greater than or equal to the LLOQ at baseline.	The median time to sustained NP swab SARS-CoV-2 RNA <LLOQ through Day 34 was 6 days in the nirmatrelvir/ritonavir treatment group and 10 days in the placebo/ritonavir treatment group Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Table 20. See Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Section 5.1.8 for more details. Since the pediatric participant was randomized to nirmatrelvir/ritonavir treatment group, the median time to sustained NP swab SARS-CoV-2 RNA <LLOQ through Day 34 was 6 days. As the participant had detectable RNA levels of 1.7 log_{10} copies/mL at Days 15 and 34, the pediatric participant did not achieve sustained NP swab SARS-CoV-2 RNA <LLOQ through Day 34 (Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Table 20 and Table 16.2.6.1).
Rebound in SARS-CoV-2 RNA level in NP swabs at follow-up (ie, any study visit from Day 10 to through Day 34, defined as a half (0.5) log_{10} copies/mL increase or greater in SARS-CoV-2 RNA	The proportion of participants in the mITT analysis set with a rebound (pre-defined in the protocol as a half [0.5] log_{10} copies/mL increase or greater in SARS-CoV-2 RNA level relative to SARS-CoV-2 RNA level on Day 5, with a follow-up viral RNA level ≥2.5 log_{10} copies/mL) in SARS-CoV-2 RNA level in NP swabs at follow-up (Day 10 to Day 34) was 4.147% and 1.770% in the nirmatrelvir/ritonavir and placebo treatment groups, respectively Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Table 21. See Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Section 5.1.9 for more details.

Endpoint	Results and Location in Study C4671042 LPLV CSR
level relative to SARS-CoV-2 RNA level on Day 5 and with a follow-up viral RNA level ≥2.5 log_{10} copies/mL.	The pediatric participant did not show rebound in SARS-CoV-2 RNA level in NP swabs at follow-up. At Days 3, 5, 10, 21, and 28 the pediatric participant had undetectable (0.0 log_{10} copies/mL) NP swab SARS-CoV-2 RNA levels (Module 5.3.3.5 C4671042 LPLV CSR V1.0 Table 16.2.6.1).
Change from baseline in SARS-CoV-2 viral RNA level in plasma, over time.	A total of 2 participants had SARS-CoV-2 viral RNA above the lower limit of quantification (2 log_{10} copies/mL) in their plasma at baseline or at a post-baseline visit (Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Table 14.2.15). See Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Section 5.1.10 for more details. The pediatric participant, did not have detectable SARS-CoV-2 vRNA in plasma at any time point (i.e., there was no change from baseline in SARS-CoV-2 viral RNA level in plasma over time) (Module 5.3.3.5 C4671042 LPLV CSR V1.0 Table 16.2.6.5).
Proportion of participants with COVID-19-related hospitalization >24 h or death from any cause through Day 28.	There were no hospitalizations >24 hours or deaths from any cause for all participants, including the pediatric participant, in the mITT analysis set through Day 28 (Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Table 14.2.16). See Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Section 5.1.11 for more details.
Number of COVID-19-related medical visits through Day 34.	In the mITT analysis set, a total of 6 COVID-19-related medical visits were reported in each treatment group. The number of participants with COVID-19 related medical visits was 5 participants (2.222%) and 5 participants (4.274%) in the nirmatrelvir/ritonavir and placebo/ritonavir groups, respectively Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Table 14.2.17). See Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Section 5.1.12 for more details. There were no COVID-19 related medical visits reported for the pediatric participant (Module 5.3.3.5 C4671042 LPLV CSR V1.0 Table 16.2.6.4).
Time (days) to sustained resolution of all targeted signs and symptoms through Day 28 where sustained resolution is defined as the first of two consecutive days when all targeted COVID-19 symptoms are scored as absent.	Treatment with nirmatrelvir/ritonavir reduced the median time to sustained resolution of all targeted signs and symptoms through Day 28 in the mITT analysis set. The median time to sustained resolution of all targeted signs and symptoms was 12 days in the nirmatrelvir/ritonavir group and 13 days in the placebo treatment group (Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Table 14.2.18.1). See Module 5.3.3.5 Study C4671042 LPLV CSR V1.0 Section 5.1.13 for more details. The pediatric participant had sustained resolution of all targeted signs and symptoms observed at baseline (ie, moderate cough, headache, low energy or tiredness, and mild muscle or body aches) by Day 8 (Module 5.3.3.5 C4671042 LPLV CSR V1.0 Table 16.2.6.2).

Safety results

Overview of adverse events

The following table provides an overview of adverse events reported during the study:

Table 4: Treatment -Emergent Adverse Events (All Casualties) – DAIDS Grade – Safety Analysis Set (Protocol C4671042)

Number (%) of Participants	Nirmatrelvir 300 mg + Ritonavir 100 mg n (%)	Placebo + Ritonavir 100 mg n (%)
Participants evaluable for adverse events	289	144
Number of adverse events	124	48
Participants with adverse events	77 (26.6)	30 (20.8)
Participants with serious adverse events	1 (0.3)	1 (0.7)
Participants with Maximum Grade 3 or 4 adverse events	8 (2.8)	4 (2.8)
Participants with Maximum Grade 5 adverse events	0	0
Participants discontinued from study due to adverse events[a]	0	0
Participants discontinued study drug due to AE and continue study[b]	1 (0.3)	1 (0.7)
Participants with dose reduced or temporary discontinuation due to adverse events	0	0

Overall, the proportion of participants with treatment-emergent adverse events that started on or prior to the Day 34 was higher in the nirmatrelvir/ritonavir group (26.6%) compared to the placebo/ritonavir group (20.8%). When focusing on drug-related adverse events, the differential is more marked (13.1% vs 5.6%)

Most common AEs:

As expected, the most common AEs reported in the nirmatrelvir/ritonavir group were dysgueusia (10% vs 1.4% in the placebo arm) and diarrhoea (2.4% vs 1.4%). All these events were considered related to study drug by the investigator and were non serious.

AE of cough are also reported in 4 subjects in nirmatrelvir/ritonavir group (1.4%) versus none in the placebo/ritonavir group but none of them were considered related to study intervention.

Mots of events are mild to moderate in severity. However, a participant older than 70 years of age in the nirmaterlvir/ritonavir group had a potentially life-threatening (Grade 4) adverse event of abdominal pain and a severe (Grade 3) AE of diarrhoea that started on Study Day 3 and resulted in discontinuation of study intervention and resolved after that. Both of these TEAEs were considered related to study intervention by the investigator.

Death

There were no deaths reported during the study.

Serious adverse events

Two subjects experienced SAE on or prior to the Day 34: 1 subject in each treatment group (gastrointestinal haemorrhage in nirmatrelvir/ ritonavir group and hypovolemia in the placebo/ritonavir group). None of them was considered related to study intervention by the investigator:

The SAE of gastrointestinal haemorrhage reported in the nirmaterlvir/ritonavir group concerns a participant older than 18 years of age with medical history of obesity and cardiovascular risk factors. The event occurred at Day 27 and was related to oesophageal ulcer. The patient was treated and the event resolved.

During the long-term follow-up period, two SAEs were reported, both in the nirmatrelvir/ritonavir group (B-cell lymphoma at day 65 and general anxiety disorder/major depression at Day 30, both in adults).

None were considered related to study intervention. There were considered related to pre-existing medical conditions (history of cancer in the first case and of depression/general anxiety in the second case)

Discontinuations due to AEs:

Two subjects discontinued the study medication due to an AE and continued the study, one in each treatment group (abdominal pain/ diarrhoea in nirmatrelvir/ritonavir group and one TEAE of COVID-19 in the placebo/ritonavir group)

No participant discontinued the study due to TEAEs.

Laboratory abnormalities:

The overall incidence of laboratory test abnormalities without regard to baseline abnormality was comparable between treatment groups.

Mean changes from baseline over time for laboratory parameters (including ALT/AST and creatinine) were also generally small and similar between treatment groups.

No potential Hy's law cases were identified in either treatment group.

Vital signs:

No clinically meaningful findings in the vital signs measurements were observed in this study. The assessments and observations were comparable between treatment groups.

2.3.3. Discussion on clinical aspects

Considering that only 1 paediatric subject was included in this study, the paediatric data are too limited to be discussed.

Overall, as regards efficacy data in patients who experiences COVID-19 rebound, the reduction in viral RNA level after 5 days of treatment with Paxlovid was significantly larger than in subjects who have received placebo. However, the clinical impact of this larger decrease in viral load (i.e. time to alleviation of symptoms, hospitalisation rates, COVID-19 related visits) was not demonstrated.

As regards safety aspects, no safety signal was raised from this study. The most commonly reported adverse events are in line with the known safety profile of the drug and are listed in the Product information.

As stated by MAH, the submission of safety and efficacy data from this study does not warrant any changes to the current, approved EU SmPC for nirmatrelvir/ritonavir. The benefit-risk profile remains unchanged for nirmatrelvir/ritonavir.

3. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

No further action required, however data from study C4671042 are expected to be assessed in the context of the PAM MEA 19.1.