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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/P46/021

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	27 May 2024	27 May 2024
☐	CHMP Rapporteur Assessment Report	01 Jul 2024	24 Jun 2024
☐	CHMP members comments	15 Jul 2024	15 Jul 2024
☐	Updated CHMP Rapporteur Assessment Report	18 Jul 2024	N/A
☒	CHMP adoption of conclusions:	25 Jul 2024	25 Jul 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.

In the study C4671034, 1 paediatric subject was included. Overall, the results of the study C4671034 were already discussed within the procedure MEA 20.1, with a list of requests for the forthcoming submission. However, as these requests were not related to paediatric data, their responses will not be discussed within this procedure, but should be the scope and the focus of a type II variation.

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 C4671034.

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.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for study C4671034 (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). Of the 156 participants who were assigned to treatment, 1 participant was a pediatric participant.

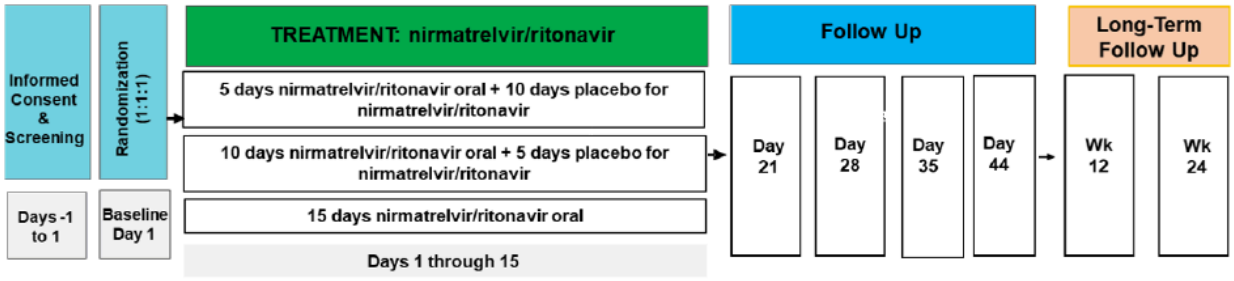
2.3.2. Clinical study

C4671034, 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

Description

This is a Phase 2, randomized, double-blind, study will 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.

Figure 1 Study Design Schema



In addition, this study will also evaluate a second treatment course of nirmatrelvir/ritonavir (5-, 10-, or 15-days) in an additional immunocompromised population with a rebound in COVID-19 within 14 days following completion of an initial 5-day treatment course of nirmatrelvir/ritonavir.

Methods

Study participants

The study will enroll approximately 150 participants + 50 participants with COVID-19 rebound. Non-hospitalized, 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.

Inclusion criteria

1. Participants aged 12 years or older and weighing ≥40 kg at screening.

2. Confirmed SARS-CoV-2 infection as determined by RT-PCR or other acceptable test method in any specimen collected.

3. ≥1 sign/symptom attributable to COVID-19 present on the day of randomization.

4. Immunocompromised, defined as follow:

    1) *Solid organ (eg, liver, heart, lung or kidney) transplant recipient who is receiving immunosuppressive therapy;*

    2) *Receipt of CAR-T-cell therapy or HCT either within 2 years of transplantation or who are receiving immunosuppressive therapy;*

    3) *Moderate or severe primary immunodeficiency (eg, DiGeorge syndrome, Wiskott-Aldrich syndrome);*

    4) *Use of at least 1 of the following immune-weakening medications:*

        a) *Recent treatment with corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days, all of which must have been within the last 30 days prior to study entry OR are currently receiving ≥20 mg daily that must have been administered for at least 14 consecutive days at the time of study entry.*

        b) *Active treatment causing significant immunosuppression, including alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer*

chemotherapeutic agents, TNF blockers, or other highly immunosuppressive drugs such as biologics (eg, ustekinumab, anti-CD20).

5) *Active immunosuppressive treatment for solid tumor or hematological malignancy (including leukemia, lymphoma, and myeloma).*

6) *HIV infection with CD4 cell count <200 mm3 from known medical history within the past 6 months of screening.*

In addition, the following inclusion criteria only apply to the additional population with rebound:

5. Presenting with documented, symptomatic COVID-19 rebound within 14 days following completion of an initial 5-day treatment course with nirmatrelvir/ritonavir

Exclusion criteria comprise notably pregnancy, need for hospitalization, oxygen saturation of <92% on room air, severe chronic liver disease, severe renal impairment, active systemic infection other than COVID-19, current use of any prohibited concomitant medication.

Rapporteur's comment:

The study population is consistent with Paxlovid indication, i.e. subjects who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19. Adolescent subjects (≥12 years of age and weighing ≥40 kg) may be included, since Paxlovid is already indicated in this population in US.

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 or placebo for ritonavir capsules for 15 days. Participants will be instructed to take 2 tablets of nirmatrelvir 150 mg or placebo for nirmatrelvir q12h + 1 capsule of ritonavir 100 mg or placebo for ritonavir 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.

Participants may receive concomitant medications, including SoC therapy for COVID-19, in addition to study intervention. However, use of antiviral therapy, including monoclonal antibody therapy, is prohibited through the entire treatment period, except for participants who progress to severe or critical COVID-19.

Objectives and endpoints

Primary objective: To describe the effect of nirmatrelvir/ritonavir on viral RNA levels in NP swabs over time for the treatment of COVID-19 in non-hospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.

Primary 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.

Secondary and exploratory objectives include notably the effect of nirmatrelvir/ritonavir treatment duration on the rate of sustained virologic clearance, the effect of nirmatrelvir/ritonavir on hospitalization and all-cause mortality.

Statistical Methods

Up to approximately 200 participants will be enrolled in this study.

Analyses will be conducted after the main study population is fully enrolled and have completed the Day 44 visit regardless of the number of randomized participants in the population with rebound. There will be 2 analysis time points for reporting the results of this study. The primary analysis will be performed after all participants in the main study population have completed the Day 44 visit. The follow-up analysis will be performed after all participants in the main study population have completed the Week 24 visit. In addition, both analyses (primary and follow-up) will include separate results for the main study population and the additional population with rebound.

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. For the main study population, the goal of the primary analysis is to estimate the treatment effect for each duration of nirmatrelvir/ritonavir.

Bioanalysis

Nirmatrelvir and ritonavir concentrations in plasma were analyzed using a validated HPLC-MS/MS method developed and validated at York Bioanalytical Solutions (York, United Kingdom). Briefly, the method used K2-EDTA as anticoagulant, Nirmatrelvir and Ritonavir-d6 (both stable isotope labeled) as internal standards. The lower and upper limits of quantification of the method are 10.0 ng/mL and 10000 ng/mL, for nirmatrelvir and 5.00 ng/mL and 5000 ng/mL for ritonavir. Long term stability was demonstrated at 543 days when stored at -20°C or -80°C.

A total of 595 samples were received from 19 Aug 2022 to 28 Jul 2023 and analysed from 28 Sept 2022 to 31 Jul 2023. Samples were received frozen (approximately at -20°C), and were analysed within 362 days of collection. 23 runs were performed from which 4 were considered as invalid for various documented reasons and all were re-runed. ISR were performed on 60 samples with 100% provided satisfactory results.

Rapporteur's comment:

The developed method for PF-07321332 and ritonavir quantification in human plasma is adequate and comply with the ICHM10 Guideline on bioanalytical method validation and study sample analysis (EMA/CHMP ICH/172948/2019). ISR data for the current Study C4671034 were provided with satisfactory results (100%).

Results

Participant flow

As of the data cutoff (09 Aug 2023), 163 participants in the main study population were screened, of which 156 participants were randomized and 4 participants did not fulfil all eligibility criteria at screening. A decision was made to remove one site efficacy data from analyses due to GCP quality issues. A total of 5 participants, all in the main study population including 1 pediatric participant, were enrolled at that site and excluded from all efficacy analyses.

Table 1. Participant Evaluation Groups – All Enrolled participants, main study population (Protocol C4671034)

	Nirmatrelvir + Ritonavir 5 Day (N=54) n (%)	Nirmatrelvir + Ritonavir 10 Day (N=51) n (%)	Nirmatrelvir + Ritonavir 15 Day (N=51) n (%)	Total (N=156) n (%)
Screened: 163 Screened Failure: 4 Not Screen Failure but not Randomized: 3				
Assigned to Treatment	54 (100.0)	51 (100.0)	51 (100.0)	156 (100.0)
Treated	53 (98.1)	51 (100.0)	51 (100.0)	155 (99.4)
Not Treated	1 (1.9)	0	0	1 (0.6)
Full analysis set	54 (100.0)	51 (100.0)	51 (100.0)	156 (100.0)
Evaluable analysis set	52 (96.3)	48 (94.1)	50 (98.0)	150 (96.2)
Safety analysis set	53 (98.1)	51 (100.0)	51 (100.0)	155 (99.4)

5 patients from one site were excluded from evaluable analysis set

The most frequent reason for discontinuation of study intervention during the treatment phase was withdrawal by subject:

Number (%) of Participants	Nirmatrelvir + Ritonavir 5 Day (N=54) n (%)	Nirmatrelvir + Ritonavir 10 Day (N=51) n (%)	Nirmatrelvir + Ritonavir 15 Day (N=51) n (%)	Total (N=156) n (%)
Disposition phase: Treatment				
Participants Entered:	54 (100.0)	51 (100.0)	51 (100.0)	156 (100.0)
Discontinued	5 (9.3)	3 (5.9)	8 (15.7)	16 (10.3)
Reason for discontinuation				
Adverse event	2 (3.7)	1 (2.0)	3 (5.9)	6 (3.8)
Death	0	0	0	0
Lost to follow-Up	0	0	0	0
Withdrawal by subject	2 (3.7)	1 (2.0)	4 (7.8)	7 (4.5)
No longer meets eligibility criteria	0	1 (2.0)	0	1 (0.6)
Other	1 (1.9)	0	1 (2.0)	2 (1.3)
Completed	49 (90.7)	48 (94.1)	43 (84.3)	140 (89.7)
Ongoing	0	0	0	0
Disposition phase: Follow-up				
Participants Entered:	54 (100.0)	51 (100.0)	51 (100.0)	156 (100.0)
Discontinued	5 (9.3)	2 (3.9)	6 (11.8)	13 (8.3)
Reason for discontinuation				
Adverse event	1 (1.9)	0	0	1 (0.6)
Death	0	0	0	0
Lost to follow-Up	0	0	0	0
Withdrawal by subject	3 (5.6)	2 (3.9)	6 (11.8)	11 (7.1)
No longer meets eligibility criteria	0	0	0	0
Other	1 (1.9)	0	0	1 (0.6)
Completed	49 (90.7)	49 (96.1)	45 (88.2)	143 (91.7)
Ongoing	0	0	0	0

Baseline data

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

Table 2. Demographic and baseline characteristics – full analysis set, main study population (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:

Although this study could include adolescent subjects from 12 years of age, only 1 paediatric subject was included (in the arm "10 days of treatment"). This subject was immunocompromised due to receiving immunosuppressant drug therapy. However, this subject was enrolled at site where GCP quality issues were observed. Although the paediatric participant's data were excluded from all efficacy analyses, its efficacy, safety, and PK results are nevertheless presented in accordance with Article 46 of the Paediatric Regulation.

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 in group 3. However, almost all subjects in the 3 groups (94%) were treated in the 5 days since first symptom, in accordance to Paxlovid SmPC.

Efficacy results

- **Overall 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 3. 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.

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 4. Proportion of participants with sustained SARS-CoV-2 RNA (NP) <LLOQ from Day 15 to Day 44, Anti-Viral or mAB as failure, by immunocompomised 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).

- **Paediatric results (1 subject)**

Primary Efficacy Endpoint: At baseline, the pediatric participant had an NP swab SARS-CoV-2 RNA of 4.12 log10 copies/mL but had undetectable (ie, 0.0 log10 copies/mL) viral RNA from the Day 10 through Day 28 visits, which increased to 2.56 log10 copies/mL at Day 35 before returning to undetectable levels at Day 44.

Secondary Efficacy Endpoints: The pediatric participant had:

- A time to first NP swab SARS-CoV-2 RNA<LLOQ of 10 days.

- A sustained NP swab SARS-CoV-2 RNA<LLOQ from Day 10 through Day 28, but a detectable SARS-CoV-2 RNA level of 2.56 log10 copies/mL at Day 35.

- An undetectable SARS-CoV-2 RNA level in plasma at baseline and all visits during the 24-week study.

The pediatric participant did not report any moderate or severe targeted COVID-19-related signs/symptoms during the study, but did report mild severity for chills or shivering, cough, low energy or tiredness, muscle or body aches, sore throat, and stuffy or runny nose and also reported a less than usual sense of smell and taste at baseline (Day 1). Chills or shivering, sore throat, stuffy or runny nose resolved on Day 4. Cough, low energy or tiredness, muscle or body aches resolved on Day 9. Sense of taste and sense of smell were reported as the same as usual on Day 13 and Day 20, respectively. The pediatric participant did not experience any COVID-19-related hospitalization.

Rapporteur's comment:

The paediatric patient was treated during 10 days and had reported a virologic rebound in NP swab at Day 35 after an undetectable viral load in NP swab from Day 10 to Day 28. However, no moderate/severe symptoms were reported, nor any increased of symptoms after the end of treatment.

Safety results

The proportion of participants in the main study population with all-causality TEAEs that started on or prior to the Day 44 visit ranged from 52.8% to 66.7% across the treatment groups:

Table 5. Treatment-Emergent Adverse Events (All causalitites) – 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]	0	0	0
Participants discontinued study drug due to AE and continue study[b]	2 (3.8)	1 (2.0)	3 (5.9)
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

There was no increase in SAEs as a result of treatment duration. All SAEs were reported in 1 participant each, including 1 participant in the 5-day nirmatrelvir/ritonavir treatment group with an SAE of COVID-19.

The proportion of participants with all-causality Grade 3 or Grade 4 TEAEs increased with longer durations of treatment, ranging from 3.8% to 11.8%.

The most frequently reported all-causality TEAEs (≥20% in any group) by SOC were: Nervous system disorders (5-day: 7 [13.2%]; 10-day: 17 [33.3%]; 15-day: 16 [31.4%]) and Gastrointestinal disorders (5-day: 8 [15.1%]; 10-day: 9 [17.6%]; 15-day: 15 [29.4%]).

The most frequently reported all-causality TEAEs (≥5% in any group) by PT were:

- Dysgeusia (5-day: 6 [11.3%]; 10-day: 11 [21.6%]; 15-day: 14 [27.5%])

- Diarrhoea (5-day: 5 [9.4%]; 10-day: 4 [7.8%]; 15-day: 4 [7.8%])

- Nausea (5-day: 1 [1.9%]; 10-day: 2 [3.9%]; 15-day: 5 [9.8%])

- Headache (5-day: 1 [1.9%]; 10-day: 3 [5.9%]; 15-day: 1 [2.0%])

- Blood thyroid stimulating hormone increased: (5-day and 10-day: 0 participants; 15-day: 3 [5.9%]).

No TEAEs were observed in the pediatric participant.

Rapporteur's comment:

No new safety concern was observed. Based on these safety data, 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.

Pharmacokinetics results

PK sampling consisted of one T 1-2h after dose administration in Day 1, and one sample collected at any time during the visit at Day 5, 10 and 15. At end of treatment (ET), a last PK sample will be collected if the ET visit occurs within 2 days (48h) of the last dose of study intervention.

PK data were collected from 154 patients aged 12 years and older, contributing to 595 PK plasma samples. 52, 51 and 51 were treated following a 5, 10, 15 days schedule, respectively.

Individual nirmatrelvir plasma concentrations ranged from <LLOQ (<10.0 ng/mL) to 12,400 ng/mL at 1 to 2 hours postdose on Day 1. Individual ritonavir plasma concentrations ranged from <LLOQ (<5.0 ng/mL) to 2980 ng/mL at 1 to 2 hours postdose on Day 1.

Participants with rebound had nirmatrelvir and ritonavir plasma concentrations within the range of the concentrations observed in the main study population.

One patient aged between 12 and 18 years old was treated for 10 days. Nirmatrelvir concentration was 1220 ng/mL at Day 1 and < LLOQ (10 ng/mL) at Day 5 and Day 9. Ritonavir concentration was 8.66 ng/mL at Day 1 and < LLOQ (10 ng/mL) at Day 5 and Day 9.

2.3.3. Discussion on clinical aspects

Overall, the results of the study C4671034 were already discussed within the procedure MEA 20.1, with a list of requests for the forthcoming submission. Therefore, the MAH responses to these requests (which are outside the scope of this paediatric procedure) will be discussed within a type II variation.

As regards the paediatric data, only 1 paediatric subject was included in this study. Furthermore, this subject was enrolled in a site where GCP quality issues were observed, excluding its efficacy data from the final analyses of this study.

In conclusion, no relevant paediatric data was available from this study. The MAH should clarify its intentions for an extension of indication in paediatric patients (with corresponding timelines)

3. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

Based on the MAH responses to CHMP requests related to the procedure MEA 20.1, the MAH should submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004.

In addition, The MAH should clarify its intentions for an extension of indication in paediatric patients (with corresponding timelines).