EMA/CHMP/214389/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMEA/H/C/005973/II/0042

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.

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	26 Apr 2023	26 Apr 2023
☐	CHMP Rapporteur Assessment Report	10 May 2023	10 May 2023
☐	CHMP members comments	15 May 2023	15 May 2023
☐	Updated CHMP Rapporteur Assessment Report	17 May 2023	17 May 2023
☐	Request for supplementary information	25 May 2023	25 May 2023
☐	Submission of responses	20 June 2023	20 June 2023
☐	Restart	21 June 2023	21 June 2023
☐	CHMP Rapporteur Assessment Report	05 July 2023	05 July 2023
☐	CHMP members comments	10 July 2023	10 July 2023
☐	Updated CHMP Rapporteur Assessment Report	13 July 2023	N/A
☒	Opinion	20 July 2023	20 July 2023

Table of contents

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 2023 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of sections 4.8, 5.1 and 5.2 of the SmPC in order to update efficacy, safety and pharmacokinetic information, based on updated results from studies C4671005 (EPIC-HR), C4671002 (EPIC-SR) and C4671006 (EPIC-PEP) as well as a supplemental report to Pop PK analysis PMAR-EQDD-C467a-DP4-1323, following the reanalysis of data after the removal of data related to four sites from the Paxlovid data analysis.

The requested variation proposed amendments to the Summary of Product Characteristics.

GLP/GCP inspections

This type II variation relies on the outcome of a systematic FDA inspection during the review process of the MAA (after the Emergency Use Authorisation).

2. Introduction

Nirmatrelvir (PF-07321332) is a peptidomimetic inhibitor of the coronavirus 19, including the SARS-CoV-2 M^{pro}. Inhibition of the M^{pro} renders the protein incapable of processing polyprotein precursors which leads to inhibit viral replication.

Nirmatrelvir is co-administered with ritonavir (acting as a PK enhancer) to achieve and maintain exposures greater than the in vitro antiviral EC90 throughout the duration of the dosing interval. Ritonavir is not active against SARS-CoV-2 M^{pro} and is not expected to have any antiviral activity against the SARS-CoV-2 virus. Ritonavir inhibits the CYP3A mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.

PAXLOVID (nirmatrelvir tablets; ritonavir tablets) is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

The recommended oral dose is 300 mg PF-07321332 (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily (BID) for 5 days. The dose is adjusted to PF-07321332 (single 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet) in patients with moderate renal impairment.

The drug product is available as a film-coated tablets containing PF-07321332 (one single strength 150 mg) and film-coated tablets containing ritonavir (one single 100 mg strength).

In the current type II variation, the marketing authorization holder (MAH) proposed to update the Product Information removing data from sites with GCP and data anomaly issues following interactions and correspondence with US FDA and US FDA site inspections.

3. Clinical Pharmacology aspects

3.1. Methods – analysis of data submitted

A new Pop PK analysis of nirmatrelvir (PF-07321332) was submitted (Report PMAR-EQDD-C467a-DP4-1323-Supplement). This analysis follows two type II variations where a Pop-PK model was developed on a limited PK dataset, (please refer to EMEA/H/C/005973/II/0008, Report PMAR-EQDD-C467a-DP4-1323) and a full PK dataset (please refer to EMEA/H/C/005973/II/0037, Report PMAR-EQDD-C467a-Other-1463).

Therefore, the methodology used for the PopPK model development and qualification in the current submission is the same as previously described as part of EMEA/H/C/005973/II/0008 and EMEA/H/C/005973/II/0037 and will not be detailed in this report (full information contained in assessment reports for these specific variations).

Then, in addition to update a previously developed Pop PK model (without PK data from 2 study sites) an objective of this analysis was to:

- generate post-hoc predictions of plasma nimatrelvir exposures co-administered with RTV and compute secondary PK parameters as Cmin, Cmax and AUC tau at steady state for adults with COVID-19 in the EPIC-HR study C4671005 (Study 1005), and
- calculate the percentage of participants achieving Cmin≥ 90% of EC90 for adults with COVID-19 in the EPIC-HR study 1005.

3.2. Results

In the EPIC-HR study 1005, 71 participants enrolled (48 in 1 site and 23 in another) accounting for n=210 observations (144 in 1 site and 66 in another) were excluded.

The total PK dataset consisted of 1166 participants, including 150 healthy subjects from Phase 1 studies and 1016 patients from Phase 2/3 study 1005 contributing 4249 PK samples (Table 1).

Table 1: Demographics summary of the Population PK analysis dataset

	All	COVID-19	Healthy
Number (%) of Participants	1166	1016 (87.1%)	150 (12.9%)
Number (%) of Plasma Samples	4941	2280 (46.1%)	2661 (53.9%)
Sex			
Number (%) of Males	617 (52.9%)	506 (43.4%)	111 (9.52%)
Number (%) of Females	549 (47.1%)	510 (43.7%)	39 (3.34%)
Race			
Number (%) of White	801 (68.7%)	713 (61.1%)	88 (7.55%)
Number (%) of Black/African American	98 (8.40%)	49 (4.20%)	49 (4.20%)
Number (%) of Asian	162 (13.9%)	152 (13.0%)	10 (0.858%)
Number (%) of American Indian/Alaska Native	95 (8.15%)	95 (8.15%)	0
Number (%) of Other	4 (0.343%)	1 (0.0858%)	3 (0.257%)
Number (%) of Unknown	6 (0.515%)	6 (0.515%)	0
Body Weight (kg)			
Median	79.0	79.4	77.3
Range	42.0-158	42.0-158	52.7-114
Age (years)			
Median	45.0	44.0	49.0
Range	18.0-86.0	18.0-86.0	20.0-76.0
Baseline CL_{cr} (mL/min)			
Median	128	133	103
Range	19.5-421	20.7-421	19.5-277
Baseline BSA-normalized CL_{cr} (mL/min/1.73 m^2)			
Median	119	124	95.8
Range	15.8-318	22.8-318	15.8-247
Baseline Body Mass Index			
Median	27.8	28.1	26.5
Range	16.6-58.1	16.6-58.1	19.7-40.3

Final PK parameter estimates with and without exclusion of subjects are provided in Table 2. In comparison to the previous Pop PK model parameter estimates reported in PMAR-EQDD-C467a-DP4-1323 (refer to EMEA/H/C/005973/II/0008), the parameter estimates from the updated Pop PK model with exclusion of participants enrolled in the EPIC-HR Study 1005 did not deviate more than 10%.

The exceptions are for the nCLCR breakpoint (from 70.1 to 84.1 mL/min/1.73 m2), the exponent of the power model for nCLCR effect on CL (from 1.05 to 0.812), and IIV in V2 (from 27.3% to 31.7%) and ka (60.7% to 69.6%). It is anticipated that these changes would have minimal impact on the nirmatrelvir exposure predictions.

Table 2: Final PK parameter estimates with/without exclusion of sites in Study 1005

	Run 104 (CP1:ST-28773188) [1] No Site Exclusion			Run 4 (CP1:ST-36301803) With Site Exclusions[a]		
	Parameter	Estimate	%RSE	Parameter	Estimate	%RSE
CL (θ_1) [L/h]	9.09	3.64	-	9.17	3.64	-
V_2 (θ_2) [L]	56.9	4.32	-	57.3	4.09	-
Q (θ_3) [L/h]	1.28	14.2	-	1.28	15.2	-
V_3 (θ_4) [L]	12.8	11.1	-	12.9	10.3	-
k_a (θ_5) [1/h]	0.873	8.94	-	0.895	8.12	-
$nCLCR_{breakpoint}$ (θ_8) [mL/min/1.73 m^2]	70.1	0.0300	-	84.1	0.174	-
$nCLCR_{power}$ (θ_9) <$nCLCR_{breakpoint}$	1.05	8.44	-	0.812	9.97	-
$F1_{power}$ (θ_{11})	-0.409	8.70	-	-0.412	9.37	-
Effect of Carbamazepine on CL (θ_{13})	0.740	27.1	-	0.742	27.1	-
Effect of Itraconazole on CL (θ_{14})	-0.308	7.19	-	-0.327	8.71	-
Effect of 150 mg Tablet on F1 (θ_{15})	-0.379	10.1	-	-0.372	10.4	-
Power of Age effect on V_2 (θ_{16})	-0.425	17.6	-	-0.436	17.6	-
Effect of COVID-19 on CL (θ_{17})	-0.341	10.7	-	-0.366	9.60	-
Proportional Error Phase 1 (θ_6) [%]	32.4	5.69	6.28	32.1	5.63	7.29
Proportional Error Phase 2/3[b] (θ_{12}) [%]	139	3.81	-	134	4.43	-
$\omega^2_{1,1}$ IIV_{CL} [%CV]	35.9	48.8	55.9	36.2	48.2	54.9
$\omega^2_{2,2}$ IIV_{V_2} [%CV]	27.3	17.6	68.8	31.7	14.6	67.7
$\omega^2_{3,3}$ IIV_{k_a} [%CV]	60.7	20.9	63.1	69.6	22.9	61.1
$\omega^2_{4,4}$ IIV_{V_3} [%CV]	58.7	26.6	79.2	58.4	25.3	78.7

Model-based simulations

The studied dosing regimen nirmatrelvir/RTV 300 mg/100 mg BID for 5 days was simulated for participants in Study 1005 using the updated Pop PK model and individual's post hoc PK parameters. Table 3 and Table 4 show the predicted nirmatrelvir exposure parameters and the percentage of subjects achieving Cmin_EC90 of 292 ng/mL on Day 1 and Day 5. Predictions based on the Pop PK model without site exclusions are available in Table 3 and Table 4 for references.

Table 3: Predicted Day 5 nirmatrelvir exposure parameters for adults in study 1005 following BID dosing of Paxlovid with (up) and without (down) exclusion of the data

		AUC_τ (ng·h/mL)			C_{max} (ng/mL)			C_{min} (ng/mL)		
	Dose[a]		Percentile			Percentile			Percentile	
Group	(mg)	Geomean	10th	90th	Geomean	10th	90th	Geomean	10th	90th
Adult	300	30399	22932	39788	3427	2592	4521	1566	1159	2098

Repository artifact ID FI-38530213. Lines 1-3 substitued.
AUC_τ = area under the plasma concentration-time profile from time 0 to 12 hours for BID dosing; BID=twice daily; C_{max} = maximum concentration; C_{min} - maximum concentration; RTV = ritonavir.
[a]Nirmatrelvir 150mg table gives as BID with RTV 100mg for 5 days.
Based on 1016 subjects with their post hoc PK parameters. Excluded participants enrolled at sites in the EPIC-HR Study C4671005.

		AUC_τ (ng·h/mL)			C_{max} (ng/mL)			C_{min} (ng/mL)		
	Dose[a]		Percentile			Percentile			Percentile	
Group	(mg)	Geomean	10th	90th	Geomean	10th	90th	Geomean	10th	90th
Adult	300	28804	22089	36942	3283	2506	4250	1447	1074	1914

Repository artifact ID FI-38691647. Lines 1–3 substituted.
AUC_τ = area under the plasma concentration-time profile from time 0 to 12 hours for BID dosing; BID = twice daily; C_{max} = maximum concentration; C_{min} = minimum concentration; RTV = ritonavir.
[a]Nirmatrelvir 150 mg tablet given as BID with RTV 100 mg for 5 days.
Based on 1087 subjects with their post hoc PK parameters. No site exclusion in the EPIC-HR Study C4671005.

Table 4: Predicted Cmin and percentage of adults in study 1005 achieving the PK/PD target following BID dosing of Paxlovid, with (up) and without (down) exclusion of the data

Group	Dose[a] (mg)	Dose Number	C_{min} (ng/mL) Median	10^{th} percentile	90^{th} percentile	% Subjects Achieved $C_{min} \geq EC_{90}$
Adult	300	1st (Day 1)	920	687	1211	99.9
	300	10^{th} (Day 5)	1577	1159	2098	100

Repository artifact ID FI-38530221. Lines 1-2 substituted.
BID = twice daily; C_{min} = minimum concentration; EC_{90} = in vitro 90% maximal effective concentration; RTV=ritonavir.
|[a]Nirmatrelvir 150 mg tablet given as BID with RTV 100mg for 5 days.
Based on 1016 subjects with their post hoc PK parameters. Excluded participants enrolled at sites in the EPIC-HR Study C4671005.

Group	Dose[a] (mg)	Dose Number	C_{min} (ng/mL) Median	10^{th} percentile	90^{th} percentile	% Subjects Achieved $C_{min} \geq EC_{90}$
Adult	300	1st (Day 1)	877	663	1135	99.8
	300	10^{th} (Day 5)	1457	1074	1914	99.9

Repository artifact ID FI-38691655. Lines 1–2 substituted.
BID = twice daily; C_{min} = minimum concentration; EC_{90} = in vitro 90% maximal effective concentration; RTV = ritonavir.
[a]Nirmatrelvir 150 mg tablet given as BID with RTV 100 mg for 5 days.
Based on 1087 subjects with their post hoc PK parameters. No site exclusion in the EPIC-HR Study C4671005.

In comparison to the previous nirmatrelvir exposure predictions for nirmatrelvir/RTV 300 mg/100 mg reported in PMAR-EQDD-C467a-DP4-1323, the geometric mean of the predicted Day 5 nirmatrelvir exposure parameters (Cmin, Cmax, AUCt) using the updated Pop PK model were higher but within the previously reported 10th and 90th percentile range. Similar to the previous predictions, >99% of participants in the EPIC-HR Study 1005 following a dose of nirmatrelvir/RTV 300 mg/100 mg BID achieve Cmin_EC90 of 292 ng/mL on Day 1 after the first dose and on Day 5.

3.3. Discussion on clinical pharmacology

The current report is a supplemental report to PMAR-EQDD-C467a-DP4-1323 and presents the results of updating the final PopPK model PMAR-EQDD-C467a-DP4-1323 by removing data from participants enrolled in 2 sites in the EPIC HR study 1005.

Report PMAR-EQDD-C467a-DP4-1323 was submitted as part of **EMEA/H/C/005973/II/0008**, and the CHMP concluded that the developed PopPK model and model-based simulations were not considered valid. During this submission several critical issues have been raised (High RUV >100%, High Eta-shrinkage >50%, biased pcVPC, exclusion of the RUV during the model-based simulations) and remained unsolved. As part of **EMEA/H/C/005973/II/0037**, where an update PopPK model was submitted, despite significant efforts made by the applicant, these same several critical issues remained and the developed PoPK model was again not considered valid.

Then, it appears obvious that discarding PK data of 71 subjects from the 2 study sites of study 1005 would have minimal impact on both the fixed and random effects, as demonstrated by the applicant with less than 10% of deviation between PK parameter estimates (Table 2). Similarly, RUV and eta-shrinkage were slightly decreased (RUV of 134% vs 139% and eta-shr > 54% vs 55%) and diagnostic plots were not provided.

In conclusion, given the preceding as part of this submission, the proposed PopPK model and model-based simulations are not considered valid. Therefore, the MAH was asked, in the first round, to delete the predicted exposure metrics at steady-state (model-based simulations) from patients of EPIC-HR reported in section 5.2 of the SmPC. This was agreed and the SmPC has been revised according to this recommendation.

4. Clinical Efficacy aspects

4.1. Methods – analysis of submitted data

The pivotal clinical development for the treatment of non-hospitalized, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illnesses was supported by one Phase 2/3 trial: Study C4671005 (abbreviated Study 1005).

During the clinical study conduct of Study 1002, Pfizer conducted an audit and noted that a site not reported to the US FDA was used for data collection and that the Principal Investigator's (PI) oversight of the study was inadequate. Pfizer decided to terminate this site for GCP noncompliance and participants were transferred to another site. The termination of the site from Study 1002 in common with Study 1005 was previously communicated in the interim Study 1002 CSR dated 16 June 2022 and in both the interim 1005 and in LPLV CSR's, dated 21 November 2021 and 6 June 2022, respectively submitted to the US FDA and EMA. The US FDA also inspected this site and following the inspection requested that all clinical and safety data from this site be excluded from Study 1005 and Study 1002 analyses.

In addition, the US FDA performed a marketing application GCP inspection for studies 1005 and 1002 in 3 sites . The FDA noted unusual patterns of SARS-CoV-2 viral RNA and/or COVID-19 symptom diary data from these sites. Based on the findings, Pfizer conducted a review of all site data in the Study 1005 and Study 1002 to identify unexpected data patterns related to SARS CoV-2 viral RNA, COVID-19 symptom data, vital signs, adverse events, laboratory safety data, demographics, PK parameter and ECG parameter data. No unusual patterns of symptom diary data were identified. Differences in virology and patient symptom data were observed in 1 site. Pfizer performed an in-depth review of the differences and noted a level of homogeneity between virology results which could not be biologically explained. The data differences in virology and symptom data were assessed and determined to not be the result of vendor or technical issues. Pfizer performed a review of safety laboratory data, and this review did not identify any concerns. Based on a review of data from all sites, Pfizer identified no additional sites with unusual data patterns.

Following interactions and correspondence with US FDA and US FDA site inspections, a decision was made to remove data from the analysis for 2 sites (1 site due to GCP noncompliance and 1 site due to data anomaly issues) in Study 1005. Of note, data from the analysis were removed for 4 sites in Study C4671002 (abbreviated Study 1002), and 2 sites in Study C4671006.

Reanalysis of the data was performed without data from the excluded sites (including those participants who transferred to another site) for Study 1005.

4.2. Results

The following section presents the main results before and after the exclusion of the sites in order to compare the changes removing the data.

Events Summary

Table 5. Disposition Events Summary - Full Analysis Set (Protocol C4671005) – BEFORE exclusion sites

Number (%) of Participants	Nirmatrelvir 300 mg + Ritonavir 100 mg (N=1120) n (%)	Placebo (N=1126) n (%)	Total (N=2246) n (%)
Disposition phase: Treatment			
Participants Entered:	1120 (100.0)	1126 (100.0)	2246 (100.0)
Discontinued	67 (6.0)	87 (7.7)	154 (6.9)
Reason for discontinuation			
Adverse event	23 (2.1)	47 (4.2)	70 (3.1)
Death	0	0	0
Lack of efficacy	0	0	0
Lost to follow-up	0	0	0
Noncompliance with study drug	0	0	0
Pregnancy	0	0	0
Protocol deviation	0	0	0
Study terminated by sponsor	0	0	0
Withdrawal by subject	32 (2.9)	27 (2.4)	59 (2.6)
Medication error without associated adverse event	0	1 (<0.1)	1 (<0.1)
No longer meets eligibility criteria	3 (0.3)	1 (<0.1)	4 (0.2)
Other	9 (0.8)	11 (1.0)	20 (0.9)
Completed	1053 (94.0)	1039 (92.3)	2092 (93.1)
Ongoing	0	0	0
Disposition phase: Follow-up			
Participants Entered:	1120 (100.0)	1126 (100.0)	2246 (100.0)
Discontinued	67 (6.0)	77 (6.8)	144 (6.4)
Reason for discontinuation			
Death	0	13 (1.2)	13 (0.6)
Lost to follow-up	10 (0.9)	9 (0.8)	19 (0.8)
Study terminated by sponsor	0	0	0
Withdrawal by subject	43 (3.8)	43 (3.8)	86 (3.8)
Other	14 (1.3)	12 (1.1)	26 (1.2)
Completed	1053 (94.0)	1049 (93.2)	2102 (93.6)
Ongoing	0	0	0
Disposition phase: Long-term follow-up			
Participants Entered:	1120 (100.0)	1126 (100.0)	2246 (100.0)
Discontinued	75 (6.7)	87 (7.7)	162 (7.2)
Reason for discontinuation			
Adverse event	0	0	0
Death	0	15 (1.3)	15 (0.7)
Lost to follow-up	20 (1.8)	17 (1.5)	37 (1.6)
Study terminated by sponsor	0	0	0
Withdrawal by subject	43 (3.8)	45 (4.0)	88 (3.9)
Other	12 (1.1)	10 (0.9)	22 (1.0)
Completed	1045 (93.3)	1039 (92.3)	2084 (92.8)
Ongoing	0	0	0

Table 6. Disposition Events Summary - Full Analysis Set (Protocol C4671005) – AFTER exclusion sites

Number (%) of Participants	Nirmatrelvir 300 mg + Ritonavir 100 mg (N=1049) n (%)	Placebo (N=1064) n (%)	Total (N=2113) n (%)
Disposition phase: Treatment			
Participants Entered:	1049 (100.0)	1064 (100.0)	2113 (100.0)
Discontinued	63 (6.0)	85 (8.0)	148 (7.0)
Reason for discontinuation			
Adverse event	21 (2.0)	45 (4.2)	66 (3.1)
Death	0	0	0
Lack of efficacy	0	0	0
Lost to follow-up	0	0	0
Noncompliance with study drug	0	0	0
Pregnancy	0	0	0
Protocol deviation	0	0	0
Study terminated by sponsor	0	0	0
Withdrawal by subject	30 (2.9)	27 (2.5)	57 (2.7)
Medication error without associated adverse event	0	1 (<0.1)	1 (<0.1)
No longer meets eligibility criteria	3 (0.3)	1 (<0.1)	4 (0.2)
Other	9 (0.9)	11 (1.0)	20 (0.9)
Completed	986 (94.0)	979 (92.0)	1965 (93.0)
Ongoing	0	0	0
Disposition phase: Follow-up			
Participants Entered:	1049 (100.0)	1064 (100.0)	2113 (100.0)
Discontinued	65 (6.2)	74 (7.0)	139 (6.6)
Reason for discontinuation			
Death	0	13 (1.2)	13 (0.6)
Lost to follow-up	10 (1.0)	9 (0.8)	19 (0.9)
Study terminated by sponsor	0	0	0
Withdrawal by subject	41 (3.9)	42 (3.9)	83 (3.9)
Other	14 (1.3)	10 (0.9)	24 (1.1)
Completed	984 (93.8)	990 (93.0)	1974 (93.4)
Ongoing	0	0	0
Disposition phase: Long-term follow-up			
Participants Entered:	1049 (100.0)	1064 (100.0)	2113 (100.0)
Discontinued	73 (7.0)	85 (8.0)	158 (7.5)
Reason for discontinuation			
Adverse event	0	0	0
Death	0	15 (1.4)	15 (0.7)
Lost to follow-up	20 (1.9)	16 (1.5)	36 (1.7)
Study terminated by sponsor	0	0	0
Withdrawal by subject	41 (3.9)	44 (4.1)	85 (4.0)
Other	12 (1.1)	10 (0.9)	22 (1.0)
Completed	976 (93.0)	979 (92.0)	1955 (92.5)
Ongoing	0	0	0

Number analysed

Table 7. Participant Evaluation Groups - All Screened Participants (Protocol C4671005) – BEFORE exclusion sites

	Nirmatrelvir 300 mg + Ritonavir 100 mg (N=1120) n (%)	Placebo (N=1126) n (%)	Total (N=2246) n (%)
Screened: 2396			
Screened failure: 137			
Not screen failure but not randomized: 13			
Assigned to treatment	1120 (100.0)	1126 (100.0)	2246 (100.0)
Treated	1109 (99.0)	1115 (99.0)	2224 (99.0)
Not treated	11 (1.0)	11 (1.0)	22 (1.0)
Safety analysis set	1109 (99.0)	1115 (99.0)	2224 (99.0)
Full analysis set	1120 (100.0)	1126 (100.0)	2246 (100.0)
mITT analysis set	697 (62.2)	682 (60.6)	1379 (61.4)
mITT1 analysis set	1039 (92.8)	1046 (92.9)	2085 (92.8)
mITT2 analysis set	1109 (99.0)	1115 (99.0)	2224 (99.0)
Per-protocol analysis set	670 (59.8)	649 (57.6)	1319 (58.7)

Table 8. Participant Evaluation Groups - All Screened Participants (Protocol C4671005) – AFTER exclusion sites

	Nirmatrelvir 300 mg + Ritonavir 100 mg (N=1049) n (%)	Placebo (N=1064) n (%)	Total (N=2113) n (%)
Screened: 2256			
Screened failure: 130			
Not screen failure but not randomized: 13			
Assigned to treatment	1049 (100.0)	1064 (100.0)	2113 (100.0)
Treated	1038 (99.0)	1053 (99.0)	2091 (99.0)
Not treated	11 (1.0)	11 (1.0)	22 (1.0)
Safety analysis set	1038 (99.0)	1053 (99.0)	2091 (99.0)
Full analysis set	1049 (100.0)	1064 (100.0)	2113 (100.0)
mITT analysis set	671 (64.0)	647 (60.8)	1318 (62.4)
mITT1 analysis set	977 (93.1)	989 (93.0)	1966 (93.0)
mITT2 analysis set	1038 (99.0)	1053 (99.0)	2091 (99.0)
Per-protocol analysis set	646 (61.6)	616 (57.9)	1262 (59.7)

Demographic and Baseline Characteristics

Table 9. Demographic and Baseline Characteristics - Full Analysis Set (Protocol C4671005) – BEFORE exclusion sites

	Nirmatrelvir 300 mg + Ritonavir 100 mg (N=1120)	Placebo (N=1126)	Total (N=2246)
Age (Years), n (%)			
< 18	0	0	0
18 - 44	556 (49.6)	517 (45.9)	1073 (47.8)
45 - 59	338 (30.2)	349 (31.0)	687 (30.6)
60 - 64	86 (7.7)	112 (9.9)	198 (8.8)
65 - 74	104 (9.3)	117 (10.4)	221 (9.8)
≥ 75	36 (3.2)	31 (2.8)	67 (3.0)
Mean (SD)	45.33 (15.40)	46.34 (15.51)	45.84 (15.46)
Median (range)	45.00 (18.00, 86.00)	46.50 (18.00, 88.00)	46.00 (18.00, 88.00)
Gender, n (%)			
Male	566 (50.5)	582 (51.7)	1148 (51.1)
Female	554 (49.5)	544 (48.3)	1098 (48.9)
Race, n (%)			
White	800 (71.4)	808 (71.8)	1608 (71.6)
Black or African American	60 (5.4)	50 (4.4)	110 (4.9)
Asian	154 (13.8)	160 (14.2)	314 (14.0)
American Indian or Alaska Native	96 (8.6)	95 (8.4)	191 (8.5)
Native Hawaiian or other Pacific Islander	0	0	0
Multiracial	1 (<0.1)	2 (0.2)	3 (0.1)
Other	0	0	0
Not reported	8 (0.7)	9 (0.8)	17 (0.8)
Unknown	1 (<0.1)	2 (0.2)	3 (0.1)
Ethnicity, n (%)			
Hispanic or Latino	499 (44.6)	505 (44.8)	1004 (44.7)
Not Hispanic or Latino	616 (55.0)	614 (54.5)	1230 (54.8)
Not reported	5 (0.4)	7 (0.6)	12 (0.5)
Unknown	0	0	0
Weight (kg)			
Mean (SD)	81.39 (17.51)	82.28 (18.85)	81.84 (18.19)
Median (range)	80.00 (42.00, 158.3)	80.00 (42.00, 173.0)	80.00 (42.00, 173.0)
Height (cm)			
Mean (SD)	167.1 (9.64)	167.5 (10.24)	167.3 (9.94)

	Nirmatrelvir 300 mg + Ritonavir 100 mg (N=1120)	Placebo (N=1126)	Total (N=2246)
Median (range)	167.0 (136.9, 196.0)	167.6 (125.2, 207.3)	167.6 (125.2, 207.3)
BMI (kg/m²), n (%)			
< 25	220 (19.6)	217 (19.3)	437 (19.5)
25 - < 30	492 (43.9)	489 (43.4)	981 (43.7)
30 - < 35	276 (24.6)	268 (23.8)	544 (24.2)
35 - < 40	78 (7.0)	88 (7.8)	166 (7.4)
≥ 40	53 (4.7)	63 (5.6)	116 (5.2)
Mean (SD)	29.09 (5.50)	29.25 (5.74)	29.17 (5.62)
Median (range)	28.20 (16.58, 58.07)	28.34 (16.05, 59.07)	28.30 (16.05, 59.07)
Duration since first diagnosis (Days), n (%)			
≤ 3	1044 (93.2)	1071 (95.1)	2115 (94.2)
> 3	76 (6.8)	55 (4.9)	131 (5.8)
Mean (SD)	1.30 (1.30)	1.31 (1.23)	1.31 (1.26)
Median (range)	1.00 (0.00, 5.00)	1.00 (0.00, 9.00)	1.00 (0.00, 9.00)
Duration since first symptom (Days), n (%)			
≤ 3	754 (67.3)	735 (65.3)	1489 (66.3)
> 3	366 (32.7)	391 (34.7)	757 (33.7)
Mean (SD)	2.93 (1.12)	2.99 (1.09)	2.96 (1.10)
Median (range)	3.00 (0.00, 7.00)	3.00 (0.00, 9.00)	3.00 (0.00, 9.00)
Number of risk factors of interest, n (%)			
0	2 (0.2)	0	2 (<0.1)
1	449 (40.1)	424 (37.7)	873 (38.9)
2	392 (35.0)	409 (36.3)	801 (35.7)
3	184 (16.4)	192 (17.1)	376 (16.7)
4	77 (6.9)	75 (6.7)	152 (6.8)
> 4	16 (1.4)	26 (2.3)	42 (1.9)
Comorbidities, n (%)			
Cardiovascular disorder	42 (3.8)	50 (4.4)	92 (4.1)
Chronic kidney disease	6 (0.5)	8 (0.7)	14 (0.6)
Chronic lung disease	62 (5.5)	41 (3.6)	103 (4.6)
Cigarette smoker	428 (38.2)	448 (39.8)	876 (39.0)
Diabetes mellitus	136 (12.1)	138 (12.3)	274 (12.2)
Hypertension	359 (32.1)	381 (33.8)	740 (32.9)
Immunosuppression	6 (0.5)	7 (0.6)	13 (0.6)

	Nirmatrelvir 300 mg + Ritonavir 100 mg (N=1120)	Placebo (N=1126)	Total (N=2246)
Cancer	5 (0.4)	6 (0.5)	11 (0.5)
Neurodevelopmental disorder	2 (0.2)	1 (<0.1)	3 (0.1)
Sickle cell disease	0	0	0
HIV infection	0	1 (<0.1)	1 (<0.1)
Device dependence	4 (0.4)	3 (0.3)	7 (0.3)
COVID-19 mAb treatment, n (%)			
Received/expected to receive	70 (6.3)	70 (6.2)	140 (6.2)
Not received/not expected to receive	1050 (93.8)	1056 (93.8)	2106 (93.8)
Geographic region, n (%)			
United States	463 (41.3)	465 (41.3)	928 (41.3)
Europe	334 (29.8)	335 (29.8)	669 (29.8)
India	95 (8.5)	98 (8.7)	193 (8.6)
Rest of World	228 (20.4)	228 (20.2)	456 (20.3)
Serology status, n (%)			
Negative	518 (46.3)	537 (47.7)	1055 (47.0)
Positive	581 (51.9)	568 (50.4)	1149 (51.2)
Unknown	21 (1.9)	21 (1.9)	42 (1.9)
Viral load (Log_{10} copies/mL), n (%)			
0	191 (17.1)	184 (16.3)	375 (16.7)
< 2.7	300 (26.8)	332 (29.5)	632 (28.1)
< 4	406 (36.3)	413 (36.7)	819 (36.5)
≥ 4	677 (60.4)	676 (60.0)	1353 (60.2)
≥ 5	583 (52.1)	582 (51.7)	1165 (51.9)
≥ 6	442 (39.5)	441 (39.2)	883 (39.3)
< 7	783 (69.9)	814 (72.3)	1597 (71.1)
≥ 7	300 (26.8)	275 (24.4)	575 (25.6)
≥ 8	118 (10.5)	113 (10.0)	231 (10.3)
≥ 9	4 (0.4)	5 (0.4)	9 (0.4)
≥ 10	0	0	0
Mean (SD)	4.67 (2.88)	4.59 (2.86)	4.63 (2.87)
Median (range)	5.41 (0.00, 9.16)	5.30 (0.00, 9.15)	5.35 (0.00, 9.16)

Age at Screening (years) = (date of given informed consent - date of birth + 1)/365.25.
The denominator to calculate percentages is N, the number of participants in the analysis set within each treatment group.
Risk Factors include Age ≥ 60, BMI > 25 and Verbatims from pre-specified Medical History (Cigarette Smoker, Immunosuppression, Chronic Kidney Disease,Hypertension, Diabetes Mellitus, Cardiovascular Disorder, Chronic Lung Disease, HIV Infection, Sickle Cell Disease, Neurodevelopmental Disorder, Cancer and Device Dependence).
Duration since First Diagnosis is days from qualifying positive SARS-CoV-2 test.
Duration since first diagnosis and duration since first symptom are computed from the start of dosing.
Missing category is not included in the table.
Rest of World: Argentina, Brazil, Colombia, Japan, Malaysia, Mexico, Peru, Russian Federation, South Africa, Republic of Korea, Taiwan, Thailand, and Turkey.

Table 10. Demographic and Baseline Characteristics - Full Analysis Set (Protocol C4671005) – AFTER exclusion sites

	Nirmatrelvir 300 mg + Ritonavir 100 mg (N=1049)	Placebo (N=1064)	Total (N=2113)
Age (Years), n (%)			
< 18	0	0	0
18 - 44	540 (51.5)	505 (47.5)	1045 (49.5)
45 - 59	310 (29.6)	320 (30.1)	630 (29.8)
60 - 64	70 (6.7)	105 (9.9)	175 (8.3)
65 - 74	96 (9.2)	103 (9.7)	199 (9.4)
≥ 75	33 (3.1)	31 (2.9)	64 (3.0)
Mean (SD)	44.82 (15.35)	45.91 (15.56)	45.37 (15.46)
Median (range)	44.00 (18.00, 86.00)	46.00 (18.00, 88.00)	45.00 (18.00, 88.00)
Gender, n (%)			
Male	526 (50.1)	543 (51.0)	1069 (50.6)
Female	523 (49.9)	521 (49.0)	1044 (49.4)
Race, n (%)			
White	736 (70.2)	760 (71.4)	1496 (70.8)
Black or African American	53 (5.1)	36 (3.4)	89 (4.2)
Asian	154 (14.7)	160 (15.0)	314 (14.9)
American Indian or Alaska Native	96 (9.2)	95 (8.9)	191 (9.0)
Native Hawaiian or other Pacific Islander	0	0	0
Multiracial	1 (<0.1)	2 (0.2)	3 (0.1)
Other	0	0	0
Not reported	8 (0.8)	9 (0.8)	17 (0.8)
Unknown	1 (<0.1)	2 (0.2)	3 (0.1)
Ethnicity, n (%)			
Hispanic or Latino	429 (40.9)	443 (41.6)	872 (41.3)
Not Hispanic or Latino	615 (58.6)	614 (57.7)	1229 (58.2)
Not reported	5 (0.5)	7 (0.7)	12 (0.6)
Unknown	0	0	0
Weight (kg)			
Mean (SD)	81.11 (17.48)	81.87 (18.60)	81.49 (18.05)
Median (range)	79.50 (42.00, 158.3)	79.50 (42.00, 166.0)	79.50 (42.00, 166.0)
Height (cm)			
Mean (SD)	167.2 (9.70)	167.3 (10.12)	167.3 (9.91)

	Nirmatrelvir 300 mg + Ritonavir 100 mg (N=1049)	Placebo (N=1064)	Total (N=2113)
Median (range)	167.0 (136.9, 196.0)	167.6 (125.2, 207.3)	167.0 (125.2, 207.3)
BMI (kg/m^2), n (%)			
< 25	210 (20.0)	210 (19.7)	420 (19.9)
25 - < 30	471 (44.9)	466 (43.8)	937 (44.3)
30 - < 35	250 (23.8)	250 (23.5)	500 (23.7)
35 - < 40	71 (6.8)	79 (7.4)	150 (7.1)
≥ 40	47 (4.5)	58 (5.5)	105 (5.0)
Mean (SD)	28.95 (5.43)	29.15 (5.69)	29.05 (5.56)
Median (range)	28.12 (16.58, 58.07)	28.26 (16.05, 59.07)	28.16 (16.05, 59.07)
Duration since first diagnosis (Days), n (%)			
≤ 3	988 (94.2)	1017 (95.6)	2005 (94.9)
> 3	61 (5.8)	47 (4.4)	108 (5.1)
Mean (SD)	1.20 (1.25)	1.25 (1.22)	1.23 (1.23)
Median (range)	1.00 (0.00, 5.00)	1.00 (0.00, 9.00)	1.00 (0.00, 9.00)
Duration since first symptom (Days), n (%)			
≤ 3	722 (68.8)	696 (65.4)	1418 (67.1)
> 3	327 (31.2)	368 (34.6)	695 (32.9)
Mean (SD)	2.89 (1.10)	2.98 (1.09)	2.93 (1.10)
Median (range)	3.00 (0.00, 5.00)	3.00 (0.00, 9.00)	3.00 (0.00, 9.00)
Number of risk factors of interest, n (%)			
0	1 (<0.1)	0	1 (<0.1)
1	440 (41.9)	409 (38.4)	849 (40.2)
2	368 (35.1)	387 (36.4)	755 (35.7)
3	162 (15.4)	180 (16.9)	342 (16.2)
4	65 (6.2)	65 (6.1)	130 (6.2)
> 4	13 (1.2)	23 (2.2)	36 (1.7)
Comorbidities, n (%)			
Cardiovascular disorder	39 (3.7)	48 (4.5)	87 (4.1)
Chronic kidney disease	5 (0.5)	7 (0.7)	12 (0.6)
Chronic lung disease	60 (5.7)	40 (3.8)	100 (4.7)
Cigarette smoker	402 (38.3)	424 (39.8)	826 (39.1)
Diabetes mellitus	109 (10.4)	119 (11.2)	228 (10.8)
Hypertension	319 (30.4)	352 (33.1)	671 (31.8)
Immunosuppression	6 (0.6)	7 (0.7)	13 (0.6)

	Nirmatrelvir 300 mg + Ritonavir 100 mg (N=1049)	Placebo (N=1064)	Total (N=2113)
Cancer	5 (0.5)	6 (0.6)	11 (0.5)
Neurodevelopmental disorder	2 (0.2)	1 (<0.1)	3 (0.1)
Sickle cell disease	0	0	0
HIV infection	0	1 (<0.1)	1 (<0.1)
Device dependence	4 (0.4)	3 (0.3)	7 (0.3)
COVID-19 mAb treatment, n (%)			
Received/expected to receive	61 (5.8)	65 (6.1)	126 (6.0)
Not received/not expected to receive	988 (94.2)	999 (93.9)	1987 (94.0)
Geographic region, n (%)			
United States	392 (37.4)	403 (37.9)	795 (37.6)
Europe	334 (31.8)	335 (31.5)	669 (31.7)
India	95 (9.1)	98 (9.2)	193 (9.1)
Rest of World	228 (21.7)	228 (21.4)	456 (21.6)
Serology status, n (%)			
Negative	505 (48.1)	529 (49.7)	1034 (48.9)
Positive	523 (49.9)	514 (48.3)	1037 (49.1)
Unknown	21 (2.0)	21 (2.0)	42 (2.0)
Viral load (Log_{10} copies/mL), n (%)			
0	178 (17.0)	173 (16.3)	351 (16.6)
< 2.7	270 (25.7)	302 (28.4)	572 (27.1)
< 4	359 (34.2)	374 (35.2)	733 (34.7)
≥ 4	654 (62.3)	653 (61.4)	1307 (61.9)
≥ 5	563 (53.7)	561 (52.7)	1124 (53.2)
≥ 6	427 (40.7)	427 (40.1)	854 (40.4)
< 7	718 (68.4)	753 (70.8)	1471 (69.6)
≥ 7	295 (28.1)	274 (25.8)	569 (26.9)
≥ 8	117 (11.2)	113 (10.6)	230 (10.9)
≥ 9	4 (0.4)	5 (0.5)	9 (0.4)
≥ 10	0	0	0
Mean (SD)	4.76 (2.89)	4.67 (2.88)	4.71 (2.89)
Median (range)	5.52 (0.00, 9.16)	5.39 (0.00, 9.15)	5.44 (0.00, 9.16)

Age at Screening (years) = (date of given informed consent - date of birth + 1)/365.25.
The denominator to calculate percentages is N, the number of participants in the analysis set within each treatment group.
Risk Factors include Age ≥ 60, BMI > 25 and Verbatims from pre-specified Medical History (Cigarette Smoker, Immunosuppression, Chronic Kidney Disease,Hypertension, Diabetes Mellitus, Cardiovascular Disorder, Chronic Lung Disease, HIV Infection, Sickle Cell Disease, Neurodevelopmental Disorder, Cancer and Device Dependence).
Duration since First Diagnosis is days from qualifying positive SARS-CoV-2 test.
Duration since first diagnosis and duration since first symptom are computed from the start of dosing.
Missing category is not included in the table.
Rest of World: Argentina, Brazil, Colombia, Japan, Malaysia, Mexico, Peru, Russian Federation, South Africa, Republic of Korea, Taiwan, Thailand, and Turkey

Primary analysis: Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 in mITT

This analysis was conducted in patients who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 onset.

Table 11. Primary Analysis of Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28 - mITT, Kaplan-Meier Method (Protocol C4671005) – BEFORE exclusion sites

	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo
N	697	682
Participants with event, n (%)	5 (0.717)	44 (6.452)
Participants with COVID-19 hospitalization	5 (0.717)	44 (6.452)
Participants with death	0	9 (1.320)
Average time at risk for event (Days)[a]	27.296	26.189
Average study follow-up (Days)[b]	27.455	27.284
Estimated proportion (95% CI), %	0.723 (0.302, 1.729)	6.531 (4.901, 8.676)
Difference from Placebo (SE)	-5.807 (1.005)	
95% CI of difference	-7.777, -3.837	
p-value	<.0001	

N = number of participants in the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.

Table 12. Primary Analysis of Proportion of Participants With COVID-19-Related-Hospitalization or Death From Any Cause Through Day 28 - mITT, Kaplan-Meier Method (Protocol C4671005) – AFTER exclusion sites

	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo
N	671	647
Participants with event, n (%)	5 (0.745)	44 (6.801)
Participants with COVID-19 hospitalization	5 (0.745)	44 (6.801)
Participants with death	0	9 (1.391)
Average time at risk for event (Days)[a]	27.268	26.091
Average study follow-up (Days)[b]	27.434	27.246
Estimated proportion (95% CI), %	0.752 (0.313, 1.796)	6.888 (5.172, 9.146)
Difference from Placebo (SE)	-6.137 (1.057)	
95% CI of difference	-8.208, -4.066	
p-value	<.0001	

N=number of participants in the analysis set.
The cumulative proportion of participants hospitalised for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time for first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.
Participants enrolled at sites (including those switched) are excluded.

First secondary analysis: Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 in mITT-1

This secondary analysis was to assess the treatment effect in a population including participants who have received treatment within 3 days of symptom onset and those who have received treatment after 3 days.

Table 13. Secondary Analysis of Proportion of Participants With COVID-19- Related-Hospitalization or Death From Any Cause Through Day 28 - mITT1, Kaplan-Meier Method (Protocol C4671005) – BEFORE exclusion sites

	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo
N	1039	1046
Participants with event, n (%)	9 (0.866)	66 (6.310)
Participants with COVID-19 hospitalization	9 (0.866)	65 (6.214)
Participants with death	0	12 (1.147)
Average time at risk for event (Days)[a]	27.033	25.974
Average study follow-up (Days)[b]	27.213	27.098
Estimated proportion (95% CI), %	0.878 (0.458, 1.680)	6.400 (5.063, 8.075)
Difference from Placebo (SE)	-5.522 (0.816)	
95% CI of difference	-7.122, -3.923	
p-value	<.0001	

N = number of participants in the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.

Table 14. Secondary Analysis of Proportion of Participants With COVID-19- Related-Hospitalization or Death From Any Cause Through Day 28 - mITT1, Kaplan-Meier Method (Protocol C4671005) – AFTER exclusion sites

	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo
N	977	989
Participants with event, n (%)	9 (0.921)	64 (6.471)
Participants with COVID-19 hospitalization	9 (0.921)	63 (6.370)
Participants with death	0	12 (1.213)
Average time at risk for event (Days)[a]	27.019	25.907
Average study follow-up (Days)[b]	27.211	27.046
Estimated proportion (95% CI), %	0.933 (0.487, 1.786)	6.571 (5.180, 8.318)
Difference from Placebo (SE)	-5.638 (0.852)	
95% CI of difference	-7.308, -3.967	
p-value	<.0001	

N=number of participants in the analysis set.
The cumulative proportion of participants hospitalised for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time for first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.
Participants enrolled at sites (including those switched) are excluded.

4.3. Discussion

The pivotal clinical development of Paxlovid was based on a single Phase 2/3 trial conducted in participants with COVID-19 who are at increased risk of progressing to severe disease: Study C467-1005. Two additional studies were also conducted by the MAH: Study C4671002 (treatment of participants with COVID-19 who are at low risk of progressing to severe illness) and Study C4671006 (preventing symptomatic SARS-CoV-2 infection in adult household contacts of individuals with symptomatic COVID-19). These studies are out of the scope of the current indication and did not meet the primary endpoints, therefore they are not considered further.

Following the MAH's audit of a study site during the conduct of the Study 1002 (this study site was common to both Study 1005 and Study 1002), and a US FDA routine marketing application GCP inspection for studies 1005 and 1002, 2 sites included in Study 1005 were identified by US FDA as presenting major issues.

Considering that there were no apparent signs towards a systemic nature of the issues identified and that it was rather judged that the inadequacy of the study process was confined to the 2 sites, it was decided to remove the data from the two sites. This removal was anticipated as being of limited impact on the study results considering the total number of sites (2 sites among n=343) and the total number of participants (133 participants among N=2246).

The results after the sites exclusion are largely consistent with the results on the totality of the data, and efficacy outcomes are only marginally impacted by removing the data. No case of death was removed from the results in mITT as well as in mITT1 (mITT1 is considered as the population of interest). However, 2 cases of hospitalization due do COVID-19 were coming from the 2 identified sites in the mITT1. Nonetheless, the size effect as well as the 95% confidence interval remain very close: the estimated difference from placebo in proportion of participants with COVID-19-related-hospitalization or

death from any cause through day 28 in mITT1 was -5.522 (95%CI: -7.122, -3.923) before sites exclusion, and -5.638 (95%CI: -7.308, -3.967) after sites exclusion.

Therefore, it is acceptable to update the Product Information with results after sites exclusion. However, considering that study site was not a stratification factor at randomisation, some blocks of randomisation may be incomplete. Thus, the information indicating that data from 2 sites were removed after completion of the study should be mentioned in describing Study C4671005 in section 5.1 of the SmPC.

5. Clinical Safety aspects

5.1. Methods – analysis of data submitted

The datasets used to determine ADR frequencies for nirmatrelvir/ritonavir were Studies C4671005 (LPLV), C4671002 (LPLV), and C4671006 (LPLV) with data from the aforementioned sites excluded (Section 2.5). These 3 data sets consisted of a total of 3515 participants who were treated with nirmatrelvir/ritonavir and 2585 participants who received placebo.

The ADR is coded based on MedDRA, Version 25.0. Based on the determination of ADR frequencies with the site exclusions and the inclusion of final C4671002 data, the frequencies for Hypersensitivity, Anaphylaxis, Dysgeusia, Headache, Diarrhoea, Nausea, Vomiting, Abdominal Pain, Malaise, and Hypertension have been updated. However, based on these updates there were no changes to frequency category for any of the ADRs.

5.2. Results

An overview of the ADR frequencies and categories are provided in Table 6 and Table 7.

Across the 3 studies, 3515 participants received a dose of nirmatrelvir/ritonavir and 2585 participants received a dose of placebo. The most common adverse reactions (≥1% incidence in the nirmatrelvir/ritonavir group and occurring at a greater frequency than in the placebo group) were dysgeusia (5.9% and 0.4%, respectively) and diarrhoea (2.9% and 1.9%, respectively).

Table 15. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class

System Organ Class	ADR Term	Frequency n/N (%)	Category	CDS Version (frequency last updated)	Comments
Immune system disorders	Hypersensitivity*	21/3515 (0.60%)	Uncommon	5.0	PTs from the Hypersensitivity SMQ (v25.0) broad and narrow): Acute respiratory failure (1), Allergic cough (1), Allergic sinusitis (1), Asthma (1), Bronchospasm (1), Eosinophilia (2), Interstitial lung disease (1), Pruritus (3), Rash (3), Rash maculo-papular (1), Respiratory distress (1), Rhinitis allergic (1) Seasonal allergy (1), Skin exfoliation (2), Skin oedema (1)
	Anaphylaxis*	3/3515 (0.09%)	Rare	6.0	PTs from the MedDRA (v25.0) SMQ Anaphylactic reaction (narrow) and SMQ Anaphylactic/anaphylactoid shock conditions (narrow): No relevant PTs identified - statistical 3/X rule applied
Nervous system disorders	Dysgeusia[a]	208/3515 (5.92%)	Common	5.0	PTs: Dysgeusia (208)
	Headache[a]	50/3515 (1.42%)	Common	5.0	PTs: Headache (*50*)
Gastrointestinal disorders	Diarrhoea[a]	102/3515 (2.90%)	Common	5.0	PTs: Diarrhoea (102)
	Nausea*	63/3515 (1.79%)	Common	5.0	PTs: Nausea (*63*)
	Vomiting[a]	33/3515 (0.94%)	Uncommon	5.0	PTs: Vomiting (*33*)
	Abdominal Pain*	11/3515 (0.31%)	Uncommon	5.0	PTs: Abdominal pain (2), Abdominal pain lower (1), Abdominal pain upper (8)
General disorders and administration site conditions	Malaise*	1/3515 (0.03%)	Rare	5.0	PTs: Malaise (1), Feeling abnormal (0)
Vascular disorders	Hypertension*	18/3515 (0.51%)	Uncommon	7.0	PTs from the MedDRA (v25.0) SMQ Hypertension (narrow): Blood pressure increased (4), Blood pressure systolic increased (1), Hypertension (*12*), Hypertensive crisis (1)

* ADR identified post-marketing.
a. Occurring at a ≥1% frequency in the nirmatrelvir/ritonavir group and at a greater frequency than in the placebo group and/or likely associated with nirmatrelvir/ritonavir based on available data and causality assessment.

Table 16. ADRs by System Organ Class and CIOMS Frequency Category Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	Frequency not Known (cannot be estimated from the available data)
Immune system disorders	--	--	Hypersensitivity*	Anaphylaxis*	--	--
Nervous system disorders	--	Dysgeusia[a], Headache[a]	--	--	--	--
Vascular disorders	--	--	Hypertension*	--	--	--
Gastrointestinal disorders	--	Diarrhoea[a], Nausea*	Vomiting[a] Abdominal pain*	--	--	--
General disorders and administration site conditions	--	--	--	Malaise*	--	--

* ADR identified post-marketing.
a. Occurring at a ≥1% frequency in the nirmatrelvir/ritonavir group and at a greater frequency than in the placebo group and/or likely associated with nirmatrelvir/ritonavir based on available data and causality assessment.

5.3. Discussion

The safety reanalysis was based on the subjects included in studies C4671005, C4671002, and C4671006 with data from the aforementioned sites excluded and included a dataset of 3515 subjects treated with nirmatrelvir/ritonavir and 2585 participants who received placebo. In comparison, the latest safety analysis used a safety pool including both studies C4671005, C4671002 and C4671006 with a total of 3643 participants who received nirmatrelvir/ritonavir and 2668 participants who received placebo.

Overall, the safety profile remains consistent between the primary safety analysis and the reanalysis, with no changes of frequency *category* for the ADRs. The impact of the exclusion of the identified sites for the analysis of the safety profile of Paxlovid is minor.

The PI has been slightly modified with the updated ADRs frequencies of dysgeusia (4.6%), diarrhoea (3.0%), headache (1.2%) and vomiting (1.2%) based on the frequency reported in the pivotal study C4671005, which is endorsed. For consistency with the assessment of the variation II/0026/G (i.e., not supporting that the population included in studies C4671005, C4671002 and C4671006 was homogeneous considering that study C4671002 targeted a population at standard risk ,and C4671006 a population for a post exposure prophylaxis with a treatment duration up to 10 days while the current indication is the high risk population with a treatment duration of 5 days, the ADR frequencies of the pivotal study C4671005 were used in section 4.8 of the SmPC instead of the pooled safety data for the ADRs already identified during the MAA, and the pooled safety data was used for the frequency of new emerging ADRs. The safety profile from these 3 studies was comparable which support the use of the pooled data for the estimation of ADR frequency for new emerging ADRs. Nevertheless since "vomiting" was already identified as an ADR in the pivotal study targeting the intended population and treatment duration, the frequency should remain "common".

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

The pivotal clinical development for the treatment of non-hospitalized, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illnesses was supported by one Phase 2/3 trial: Study C4671005 (abbreviated Study 1005).

Following interactions and correspondence with the US FDA and US FDA site inspections, a decision was made to remove data from the analysis for 2 sites (1 site due to GCP noncompliance and 1 site due to data anomaly issues) in Study C4671005.

This Type II variation includes a reanalysis of the data performed without data from the excluded sites (including those participants who transferred to another site) for Study 1005, accordingly with identified site by US FDA.

Similarly, from a clinical pharmacology perspective, the MAH submitted a Pop-PK analysis (Report PMAR-EQDD-C467a-DP4-1323-Supplement), developed without PK data collected in patients from the excluded sites from Study 1005.

This analysis is an update of a Pop-PK model (Report PMAR-EQDD-C467a-1323) submitted as part of EMEA/H/C/005973/II/0008 where the CHMP considered that the Pop-PK model and model-based simulations were not valid / reliable. Therefore, the same limitation raised as part of EMEA/H/C/005973/II/0008 remains in this current submission. Consequently, the applicant was asked to delete the predicted exposure metrics (model-based simulations) from patients of EPIC-HR reported in section 5.2 of the SmPC.

Overall, the updated clinical results with excluded sites are consistent with the results submitted at the time of the marketing authorization. It is thus agreed to update the Product Information accordingly. The MAH was requested to mention the sites exclusion in section 5.1 of the SmPC. This reference was included.

7. Recommendations

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

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy, safety and pharmacokinetic information based on updated results from studies C4671005 (EPIC-HR), C4671002 (EPIC-SR) and C4671006 (EPIC-PEP) as well as a supplemental report to Pop PK analysis PMAR-EQDD-C467a-DP4-1323 following the reanalysis of data after the removal of data related to four sites from the Paxlovid data analysis.

☒is recommended for approval.

Amendments to the marketing authorisation

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