16 October 2025
EMA/CHMP/308349/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on group of variations including an extension of indication

Invented name: Paxlovid

International non-proprietary name: nirmatrelvir / ritonavir

Procedure No. EMEA/H/C/005973/II/0061/G

Marketing authorisation holder (MAH) Pfizer Europe MA EEIG

Note

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

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1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 19 December 2024 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	I, IIIA, IIIB and A
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

A grouped application comprised of a Type II Variation and a Type IB Variation, as follows:

Type II (C.I.6.a): Extension of indication to include treatment of coronavirus disease 2019 (COVID-19) in paediatric patients 6 years of age and older weighing at least 20 kg for PAXLOVID, based on the final analysis of Cohorts 1 and 2 from pivotal Study C4671026; this is a Phase 2/3, Interventional Safety, Pharmacokinetics, and Efficacy, Open-Label, Multi-Center, Single-Arm Study to Investigate Orally Administered PF 07321332 (Nirmatrelvir)/Ritonavir in Nonhospitalized Symptomatic Pediatric Participants With COVID-19 Who Are at Risk of Progression to Severe Disease. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor changes to the PI. As part of the application, the MAH is requesting a 1-year extension of the market protection.

Type IB (B.II.e.5.a.2): To add a new pack-size of 10 film-coated tablets (5 nirmatrelvir tablets + 5 ritonavir tablets) specific to paediatric patients 6 years and older weighing 20 kg to less than 40 kg and moderate renal impaired patients (EU/1/22/1625/003); the Package Leaflet and Labelling are updated accordingly.

The group of variations requested amendments to the Summary of Product Characteristics, Labelling, Package Leaflet and Annex A and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) EMA/PE/0000225184 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMA/PE/0000225184 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Please refer to the One-year additional market protection for new indication assessment report.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Nicolas Beix Co-Rapporteur: Fátima Ventura

Timetable	Actual dates
Submission date	19 December 2024
Start of procedure	26 January 2025
CHMP Rapporteur Assessment Report	21 March 2025
PRAC Rapporteur Assessment Report	24 March 2025
CHMP Co-Rapporteur Assessment	31 March 2025
PRAC members comments	2 April 2025
Updated PRAC Rapporteur Assessment Report	3 April 2025
PRAC Outcome	10 April 2025
CHMP members comments	14 April 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 April 2025
Request for supplementary information (RSI)	25 April 2025
CHMP Rapporteur Assessment Report	16 September 2025
PRAC Rapporteur Assessment Report	19 September 2025
PRAC members comments	25 September 2025
Updated PRAC Rapporteur Assessment Report	25 September 2025
PRAC Outcome	2 October 2025
CHMP members comments	7 October 2025

Timetable	Actual dates
Updated CHMP Rapporteur Assessment Report	13 October 2025
Opinion	16 October 2025
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Paxlovid in comparison with existing therapies (Appendix 1)	16 October 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

While most children are at lower risk for COVID-19 progression to severe outcomes, children with some underlying medical conditions and comorbidities remain at increased risk for hospitalisation, death, and morbidity.

Although there are symptomatic and/or supportive treatments for COVID-19, few antiviral drugs are available to treat COVID-19 in children. Remdesivir is approved in the EU for the treatment of COVID-19 in adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia who require supplemental oxygen, as well as adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. Some monoclonal antibodies are approved in EU in paediatric populations for the treatment of COVID-19, but they have lost their neutralising activity against the current circulating SARS-CoV-2 variants.

Therefore, there is an unmet need for oral antiviral agents that could be used for the treatment of nonhospitalised paediatric patients who are at increased risk for severe COVID-19.

2.1.2. About the product

Nirmatrelvir/ritonavir is the only oral antiviral currently approved in EU for the treatment of COVID-19. Nirmatrelvir/ritonavir is currently indicated in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro), leading to the inhibition of viral replication. Ritonavir is used as a PK enhancer, inhibiting the CYP3A-mediated metabolism of nirmatrelvir and thereby increasing plasma concentrations of nirmatrelvir.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The nirmatrelvir/ritonavir clinical development program was designed to evaluate efficacy and safety in the treatment of non-hospitalised patients with mild-to-moderate COVID-19. As of 30 June 2024, there has been a total of 7545 participants (adults and paediatric patients) exposed to nirmatrelvir/ritonavir across the clinical development program.

Approval of nirmatrelvir/ritonavir was granted on the basis of results from C4671005 (EPIC-HR; referred to as Study 1005) conducted in unvaccinated adults (18 years of age and older) with risk

factors for severe COVID-19 and was supported by data from Study C4671002 (EPIC-SR; referred to as Study 1002) which enrolled adults (18 years of age and older) with at least 1 risk factor for severe disease who were fully vaccinated, or patients without risk factors for severe disease irrespective of vaccination status.

The paediatric development program (in accordance with the nirmatrelvir/ritonavir PIP) includes the pivotal Phase 2/3 open-label, interventional study C4671026 conducted in participants from birth through < 18 years of age. Dose selection in paediatric patients with mild-to-moderate COVID-19 is primarily based on matching exposure to adult COVID-19 patients (ie, extrapolation from adults to paediatric patients).

2.2. Quality aspects

2.2.1. Introduction

A new dose pack is being introduced to be utilised for both moderate renal impairment and paediatric patients 6 years and older weighing 20 kg to less than 40 kg. The MAH proposes to differentiate the standard dose pack from the new dose pack by referring to them as "Paxlovid 150 mg: 100 mg Twice Daily Standard Dose Pack" and "Paxlovid 150 mg: 100 mg Twice Daily Modified Dose Pack", respectively.

Module 3 is being updated in accordance.

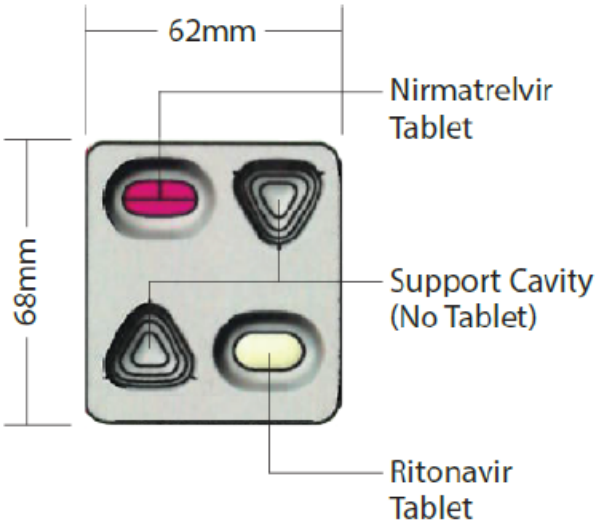
Module 3

3.2.P.7

The alternate blister packaging for reduced dose will use the currently approved packaging components. Description has been updated to include the reduced dose blister. The updates include a statement that the same blister packaging components are used for all three presentations along with the drawings to support the reduced dose blister.

The Standard blister (originally approved) and the new proposed reduced dose blister use identical materials and have cavity dimension which are designed to be identical.

Reduced dose blister layout (2 count card):

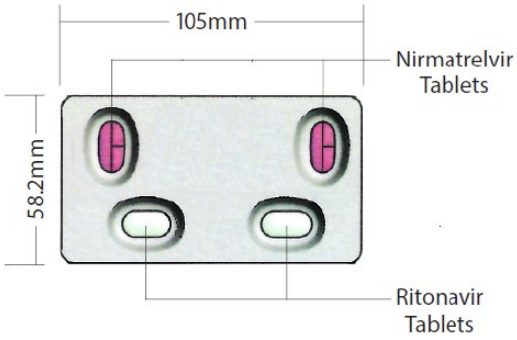


With the blister cavities being the same size and using the same blister packaging materials for all presentations no separate stability studies have been performed to support the reduced dose blister pack.

A discrepancy concerning the description of the new alternative pack size in the product information and in Module 3 was identified by the CHMP assessors.

The MAH updated the drawing within Section 3.2.P.7.1 Container Closure System to align with the description of the reduced dose blister pack in the product information.

Drawing of reduced dose blister layout (4 count card) given in section 3.2.P.7:



2.2.2. Overall conclusion

The proposed addition of new pack-size of 20 film-coated tablets (Pack size of 5 blister cards each containing two nirmatrelvir tablets and two ritonavir tablets for morning and evening doses) specific to paediatric patients 6 years and older weighing 20 kg to less than 40 kg and moderate renal impaired patients can be accepted from the Quality point of view.

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.1. Introduction

No new non-clinical data have been submitted in this application to support the paediatric indication and no discussion of the need of study in juvenile animals was submitted. A justification for not performing additional studies for ERA is submitted.

The global spread of SARS-CoV-2, the virus responsible for COVID-19, has created an urgent need for effective treatments. SARS-CoV-2 belongs to the coronavirus family and primarily infects lung and bronchial epithelial cells by binding to the ACE2 receptor. Like other coronaviruses, SARS-CoV-2 relies on a main protease (Mpro), also known as 3C-like protease (3CLpro), to process viral polyproteins essential for replication.

Mpro is a particularly attractive antiviral target because it plays a critical role in viral replication and has no close human analogue, minimising the risk of off-target effects. This combination of essential function and viral specificity makes Mpro a key focus for antiviral drug development.

Nirmatrelvir is a potent and selective oral inhibitor of Mpro, designed to block its activity and thereby disrupt viral replication. It demonstrates broad-spectrum activity across the *Coronaviridae* family, highlighting its potential effectiveness beyond SARS-CoV-2.

Because nirmatrelvir is metabolised by CYP3A enzymes, it is co-administered with ritonavir, a known CYP3A inhibitor, which boosts plasma concentrations of nirmatrelvir, ensuring sustained antiviral activity.

The proposed indication for this combination covers the treatment of COVID-19 in adults and paediatric patients aged 6 years and older, weighing at least 20 kg, who are at high or increased risk of progressing to severe disease. This extension of indication seeks to expand the existing approval to younger patients, ensuring that high-risk children have access to this important therapeutic option.

No new non-clinical studies were submitted, and no updated non-clinical information was included in the SmPC, which is considered acceptable. Nonetheless, to ensure completeness of the AR, a summary of the main available studies and their respective conclusions is provided below.

2.3.2. Pharmacology

Nirmatrelvir is an orally bioavailable inhibitor of the SARS-CoV-2 main protease (Mpro), with a Ki of 0.00311 μM in biochemical assays. Due to the structural similarity and high conservation of the Mpro active site across human coronaviruses, nirmatrelvir also effectively inhibited the Mpro of SARS-CoV-1, HCoV-229E, MERS-CoV, HCoV-OC43, HCoV-HKU1, and HCoV-NL63, supporting its broad-spectrum anti-coronavirus potential. Nirmatrelvir demonstrated high selectivity for coronavirus Mpro, showing minimal or no activity against human proteases or HIV protease.

The antiviral activity of nirmatrelvir against SARS-CoV-2 was evaluated in several cell lines, including differentiated normal human bronchial epithelial (dNHBE) cells, considered physiologically relevant. In these cells, the mean EC50 was 61.8 nM and the EC90 was 181 nM at 3 days post-infection. Nirmatrelvir maintained nanomolar antiviral potency against all tested SARS-CoV-2 variants, with susceptibility shifts of no more than 1.8-fold compared to the USA-WA1/2020 strain, except for the Beta (K90R) variant, which showed approximately 3.7-fold reduced susceptibility.

Following FDA guidelines on antiviral drug development and COVID-19 product development guidance, the MAH conducted *in vitro* resistance studies, including potency evaluation against a panel of Mpro mutants, resistance selection studies in Vero E6 P-gp KO and A549-ACE2 cells, and susceptibility testing using reverse-engineered viruses with Mpro mutations. These studies identified mutations that reduced susceptibility to nirmatrelvir and also demonstrated cross-resistance to other Mpro inhibitors.

In *in vivo* studies, nirmatrelvir alone or in combination with ritonavir reduced lung viral titers and improved weight loss and lung pathology in BALB/c and AG-129 mice infected with mouse-adapted SARS-CoV-2. When administered orally at 300 mg/kg or 1000 mg/kg twice daily, starting 4 hours or 12 hours post-inoculation, nirmatrelvir significantly reduced viral load and disease severity. Ritonavir alone showed no antiviral effect or improvement in disease pathology, but when combined with nirmatrelvir, ritonavir enhanced lung protection and further reduced viral titers, consistent with its role in boosting nirmatrelvir exposure.

Studies on the secondary pharmacology evaluated *in vitro* activity of nirmatrelvir against a wide panel of receptors, transporters, ion channels and enzyme assays, and the results indicated no significant inhibition (>50%) of functional or enzyme activity.

Safety pharmacology studies evaluated the effects of nirmatrelvir on the central nervous, cardiovascular, and respiratory systems in rats and monkeys. In rats, high doses (1000 mg/kg) caused minor and transient changes in locomotor activity and respiratory parameters, with uncertain relevance to humans. In monkeys, doses of 150 mg/kg/day led to small, transient increases in blood pressure, reduced heart rate, and minor changes in ECG intervals, all resolving within 24 hours.

Nirmatrelvir showed no significant effects on hERG channels, isolated heart, or vascular tissues, and no lasting safety concerns were observed in repeat-dose toxicity studies of up to 1 month. These effects are monitorable in clinical settings, and overall, the data support a favourable safety profile for nirmatrelvir at therapeutic doses.

2.3.3. Pharmacokinetics

Nirmatrelvir has low passive permeability, moderate plasma protein binding, and preferentially partitions into plasma over red blood cells in rats, monkeys, and humans. It does not significantly cross the blood-brain barrier in rats due to being a P-gp substrate. Its metabolism is primarily mediated by CYP3A4 (fm = 0.99), and ritonavir is co-administered to inhibit CYP3A4, increasing nirmatrelvir plasma levels. In vivo, unchanged nirmatrelvir is the main circulating form in plasma, with M4 as a key metabolite in monkeys. In humans, most nirmatrelvir is excreted unchanged (55% in urine, 28% in faeces). Nirmatrelvir/ritonavir acts as a CYP3A4 and P-gp DDI perpetrator, but the effect does not exceed that of ritonavir alone. Other transporter DDI risks are minimal.

2.3.4. Toxicology

No new toxicological studies have been submitted, and the available non-clinical data includes no studies in juvenile animals (with nirmatrelvir or ritonavir).

A non-clinical discussion was reported in the initial version of the PIP (EMEA-003081-PIP01-21, 2021); however, no clear conclusion on the need of study in juvenile animals was reported in the following PIP modifications (2022 and 2023).

In the initial assessment of the PIP (2021), it is mentioned that: Concerning the non-clinical development, in view of the already available non-clinical data (e.g. no specific targets identified in adult rats and monkeys studies, at least 10 fold safety margin based on NOAEL, treatment duration of

14 days covered by the non-clinical studies in rats + monkeys), it was considered that the study in adolescents could start without additional data however since the results of the rat pre- and post-natal developmental toxicity (PPND) study and 1-month repeat dose toxicity studies (rats and monkeys) were not yet available at the time of the submission of the responses, it was not possible to conclude with certainty whether any specific safety concern was anticipated for the paediatric population below 12 years of age and whether a juvenile toxicity study was needed to support the development of the product in the paediatric population below 12 years of age. In view of this, it was decided to specify in the opinion that paediatric patients from birth to less than 12 years of age must be included in the clinical study only after supportive results from study the PPND and 1-month repeat dose toxicity studies (in rats and monkeys) are available and confirm that there is no need to carry out a juvenile toxicity study.

In the context of the initial marketing authorisation application (Article (5), end of 2021), the 1-month repeated dose toxicity studies in rats and in monkeys did not reveal any new concern for paediatric population. The target organs identified in these 4-week studies were identical to those identified in the 2-week studies which were assessed in the initial PIP. Results of PPND study was assessed during variation EMEA/H/C/005973/II/12/G and no adverse effect were observed. Therefore, it could be concluded that the mentioned studies missing at the time of initial assessment of the PIP did not raise any concern for paediatric population and no study in juvenile animals is confirmed. Finally, clinical experience in the intended paediatric population is now available and the safety profile determined in this population is discussed in the clinical part of this AR. From non-clinical perspective, although the MAH has not discussed the non-clinical data in regard to the intended paediatric population, no question is raised.

No amendments have been made to non-clinical information in sections 5.3 or 4.6 of the SmPC. This is acceptable.

2.3.5. Ecotoxicity/environmental risk assessment

The rationale presented by the MAH for not providing an updated ERA is considered valid.

Following the Guideline on the environmental risk assessment of medicinal products for human use EMEA/CHMP/SWP/4447/00 Rev. 1, 2024, an increase in environmental exposure may be anticipated with this extension of the application to the paediatric population. Nevertheless, as the default FPEN was employed in the previously submitted ERA in 2024 and the maximum daily dose remains unchanged, the risk assessment outcome will not be altered.

Nonetheless, after further discussion, the following table was provided to update ERA information:

Substance (INN/Invented Name): Nirmatrelvir			
CAS-number (if available): 2628280-40-8			
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	Log Dow (pH 5) = 1.63 ± 0.051 Log Dow (pH 7) = 1.63 ± 0.067 Log Dow (pH 9) = 1.57 ± 0.075	Potential PBT: N
PBT-assessment			

Parameter	Result relevant for conclusion	Study/Result	Conclusion
Bioaccumulation	log K_{ow}	<3.0	not B
	BCF	NA	
Persistence	DT50 (12 °C)	OECD 308 $DT_{50\text{-water}}$ >60 d	vP
Toxicity	NOEC/EC_{10}	>0.01 mg a.i./L	not T
PBT-statement:	Nirmatrelvir is not considered to be PBT, nor vPvB		

Phase I

Calculation	**Value**	**Unit**	**Conclusion**
PECsw, default	0.041	µg/L	≥ 0.01 threshold: Y
Other concerns (e.g. chemical class)			N

Phase II Physical-chemical properties and fate

Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption Soil 1 = Silt clay loam Soil 2 = Loamy sand Sediment 1 = Silt Loam Sediment 2 = Sand Sludge 1 = Denton Sludge 2 = Easton	OECD 106	**Solid** / **KF_{ads}** / **$KFoc_{ads}$** / **1/n** Soil 1 / 2.75 / 51.0 / 0.9814 Soil 2 / 0.83 / 92.5 / 0.9883 Sediment 1 / 2.32 / 70.2 / 0.8998 Sediment 2 / 0.32 / 105 / 0.8399 Sludge 1 / 3.99 / 10.4 / 0.9440 Sludge 2 / 4.01 / 10.3 / 0.9550	Study with two soils, two sediments and two sludges
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	**DT50 (days)** / **20 °C (measured)** / **12 °C (calculated)** **HOM system:** DT50-water / 111 / 237	HOM: Foc = 2.84% LOM: Foc= 0.31%

<table>
<tr><td>Sediment 1 = HOM
Silt loam
Sediment 2 = LOM
Sand</td><td></td><td>
<table>
<tr><td>DT50-total</td><td>181</td><td>386</td></tr>
<tr><td>Total AR</td><td>%max</td><td>Day</td></tr>
<tr><td>%shift to sediment</td><td>22.4</td><td>56</td></tr>
<tr><td>%CO_2</td><td>5.1</td><td>182</td></tr>
<tr><td>%NER</td><td>23.3</td><td>182</td></tr>
</table>
Transformation products >10% = N
<table>
<tr><td>DT50 (days)</td><td>20 °C (measured)</td><td>12 °C (calculated)</td></tr>
<tr><td colspan="3">LOM system:</td></tr>
<tr><td>DT50-water</td><td>127</td><td>271</td></tr>
<tr><td>DT50-total</td><td>167</td><td>356</td></tr>
<tr><td>Total AR</td><td>%max</td><td>Day</td></tr>
<tr><td>%shift to sediment</td><td>17.3</td><td>56</td></tr>
<tr><td>%CO_2</td><td>6.6</td><td>182</td></tr>
<tr><td>%NER</td><td>15.1</td><td>182</td></tr>
<tr><td colspan="3">Transformation products >10% = N; but two TPs have an increasing trend in water: M5 (hydrolysis of amide next to nitrile) and M8 (hydrolysis of amide with TFA release)</td></tr>
</table>
</td><td></td></tr>
<tr><td>Biodegradation in Surface Water</td><td>OECD 309</td><td>DT_{50} could not be calculated (>56 d)</td><td></td></tr>
<tr><td>Biodegradation in activated sludge</td><td>OECD 314B</td><td>1.7% mineralisation after 28 days
DT_{50} = ~ 182 days</td><td></td></tr>
<tr><td colspan="4">Phase IIa Effect studies</td></tr>
</table>

Study type	**Test protocol**	**Result**	**Value**	**Unit**	**Remarks**
Algae, Growth	OECD 201	LOEC NOEC	>2.0 2.0	mg/L	growth rate

Inhibition Test (*Raphidocelis subcapitata*)					
Daphnia magna, Reproduction Test	OECD 211	LOEC NOEC	>2.0 2	mg/L	Survival, reproduction, length
Fish, Early Life Stage Toxicity Test (*Pimephales promelas*)	OECD 210	EC_5 LOEC NOEC	0.29 0.48 0.23	mg/L	Growth (weight)
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50} NOEC	>1000 1000	mg/L	respiration
Phase IIb Studies					
Sediment dwelling organism (*Chronomus riparius*)	OECD 218	LOEC NOEC	2667 1167	mg/kg_{dw}	Recalculated for standard sediment (%foc = 10%). Study sediment %foc = 1.2%

Substance (INN/Invented Name): Ritonavir			
CAS-number (if available): 155213-67-5			
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	Log Dow (pH 5) = 3.56 ± 0.10 Log Dow (pH 7) = 3.63 ± 0.12 Log Dow (pH 9) = 3.33 ± 0.16	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**	**Study/Result**	**Conclusion**
Bioaccumulation	BCF	OECD 305 BCF < 2 L/kg	Not B
Persistence	DT50 (12 °C)	OECD 308 $DT_{50\text{-water}}$ >60 d	vP

<table>
<tr><td>Toxicity</td><td>NOEC/EC_{10}</td><td>>0.01 mg a.i./L</td><td>not T</td></tr>
<tr><td>PBT-statement:</td><td colspan="3">Nirmatrelvir is not considered to be PBT, nor vPvB</td></tr>
<tr><td colspan="4">Phase I</td></tr>
<tr><td>Calculation</td><td>Value</td><td>Unit</td><td>Conclusion</td></tr>
<tr><td>PECsw, default</td><td>0.014</td><td>µg/L</td><td>≥ 0.01 threshold: Y</td></tr>
<tr><td>Other concerns (e.g.
chemical class)</td><td></td><td></td><td>N</td></tr>
<tr><td colspan="4">Phase II Physical-chemical properties and fate</td></tr>
<tr><td>Study type</td><td>Test protocol</td><td>Results</td><td>Remarks</td></tr>
<tr><td>Adsorption-Desorption
Soil 1 = Silt clay loam
Soil 2 = Loamy sand
Sediment 1 = Loam
Sediment 2 = Sand
Sludge 1 = Denton
Sludge 2 = Easton</td><td>OECD 106</td><td>
<table>
<tr><th>Solid</th><th>KF_{ads}</th><th>$KFoc_{ads}$</th><th>1/n</th></tr>
<tr><td>Soil 1</td><td>150.5</td><td>2787</td><td>0.9966</td></tr>
<tr><td>Soil 2</td><td>40.0</td><td>4446</td><td>0.8794</td></tr>
<tr><td>Sediment 1</td><td>755.6</td><td>17451</td><td>0.7849</td></tr>
<tr><td>Sediment 2</td><td>56.4</td><td>8169</td><td>0.7752</td></tr>
<tr><td>Sludge 1</td><td>347.8</td><td>924</td><td>0.9503</td></tr>
<tr><td>Sludge 2</td><td>446.2</td><td>1112</td><td>0.9312</td></tr>
</table>
</td><td>Study with two soils, two sediments and two sludges</td></tr>
<tr><td>Aerobic and Anaerobic
Transformation in Aquatic Sediment systems
Sediment 1 = HOM
Silt loam
Sediment 2 = LOM
Sand</td><td>OECD 308</td><td>
<table>
<tr><th>DT50 (days)</th><th>20 °C (measured)</th><th>12 °C (calculated)</th></tr>
<tr><td colspan="3">HOM system:</td></tr>
<tr><td>DT50-water</td><td>9.1</td><td>19.5</td></tr>
<tr><td>DT50-total</td><td>240</td><td>512</td></tr>
<tr><th>Total AR</th><th>%max</th><th>Day</th></tr>
<tr><td>%shift to sediment</td><td>67.9</td><td>28</td></tr>
</table>
</td><td>HOM: Foc = 4.44%
LOM:
Foc= 0.84%</td></tr>
</table>

$\%CO_2$	2.2	181
%NER	24.5	120-181

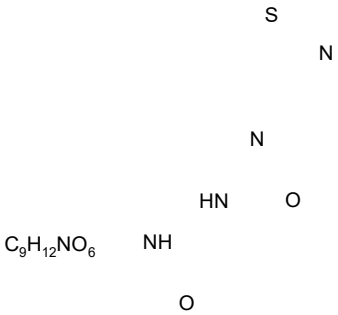
Transformation products >10% = N

DT50 (days)	**20 °C (measured)**	**12 °C (calculated)**
LOM system:		
DT50-water	33.1	70.7
DT50-total	18.3	181
Total AR	**%max**	**Day**
%shift to sediment	56.9	56
$\%CO_2$	6.4	181
%NER	18.3	181

Transformation products >10% = Y

TP1 = 10.9% at day 181

DT_{50} T1: not calculable TP1 structure:



$C_9H_{12}NO_6$

Biodegradation in Surface Water	OECD 309	DT_{50} could not be calculated (>28 d)	
Biodegradation in activated sludge	OECD 314B	22.2% mineralisation after 34 days DT_{50} = 3 days	
Phase IIa Effect studies			

Study type	Test protocol	Result	Value	Unit	Remarks
Algae, Growth Inhibition Test (*Raphidocelis subcapitata*)	OECD 201	LOEC NOEC	>0.66 0.66	mg/L	growth rate
Daphnia magna, Reproduction Test	OECD 211	LOEC NOEC	>0.54 0.54	mg/L	Survival, reproduction, length
Fish, Early Life Stage Toxicity Test (*Pimephales promelas*)	OECD 210	LOEC NOEC	>0.60 0.60	mg/L	Hatching success
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50} NOEC	>1000 1000	mg/L	respiration
Phase IIb Studies					
Bioaccumulation (bluegill sunfish) (*Lepomis macrochirus*)	OECD 305	BCF_{KmLG} BCF_{ssL}	1.0-1.9 1.5-1.6	L/kg_{ww} L/kg_{ww}	%lipids: 5.0%
Sediment dwelling organism (*Chronomus riparius*)	OECD 218	LOEC NOEC	>3750 3750	mg/kg_{dw}	Recalculated for standard sediment (%foc = 10%). Study sediment %foc = 1.8%

2.3.6. Discussion on non-clinical aspects

The global spread of SARS-CoV-2 created an urgent need for effective treatments. SARS-CoV-2 infects lung and bronchial cells via the ACE2 receptor and relies on the main protease (Mpro) for replication, making Mpro an ideal antiviral target due to its essential role and lack of human homologues. Nirmatrelvir is a selective oral inhibitor of Mpro, designed to block viral replication, with broad-spectrum activity across coronaviruses. Because it is metabolised by CYP3A, it is co-administered with ritonavir to boost its plasma levels. This extension of indication seeks to extend the approved indication for nirmatrelvir/ritonavir to treat COVID-19 in paediatric patients aged 6 years and older, weighing at least 20 kg, who are at high risk of severe disease. No new non-clinical studies were presented, and no

updated NC information was introduced in the SmPC, which is considered acceptable

Nirmatrelvir is an orally bioavailable inhibitor of the SARS-CoV-2 main protease (Mpro), with a Ki of 0.00311 μM in biochemical assays. Due to the structural similarity and high conservation of the Mpro active site across human coronaviruses, nirmatrelvir also effectively inhibited the Mpro of SARS-CoV-1, HCoV-229E, MERS-CoV, HCoV-OC43, HCoV-HKU1, and HCoV-NL63, supporting its broad-spectrum anti-coronavirus potential. Nirmatrelvir demonstrated high selectivity for coronavirus Mpro, showing minimal or no activity against human proteases or HIV protease. The antiviral activity of nirmatrelvir against SARS-CoV-2 was evaluated in several cell lines, including differentiated normal human bronchial epithelial (dNHBE) cells, considered physiologically relevant. In these cells, the mean EC50 was 61.8 nM and the EC90 was 181 nM at 3 days post-infection. Nirmatrelvir maintained nanomolar antiviral potency against all tested SARS-CoV-2 variants, with susceptibility shifts of no more than 1.8-fold compared to the USA-WA1/2020 strain, except for the Beta (K90R) variant, which showed approximately 3.7-fold reduced susceptibility. Following FDA guidelines on antiviral drug development and COVID-19 product development guidance, the MAH conducted *in vitro* resistance studies, including potency evaluation against a panel of Mpro mutants, resistance selection studies in Vero E6 P-gp KO and A549-ACE2 cells, and susceptibility testing using reverse-engineered viruses with Mpro mutations. These studies identified mutations that reduced susceptibility to nirmatrelvir and also demonstrated cross-resistance to other Mpro inhibitors. In *in vivo* studies, nirmatrelvir alone or in combination with ritonavir reduced lung viral titers and improved weight loss and lung pathology in BALB/c and AG-129 mice infected with mouse-adapted SARS-CoV-2. When administered orally at 300 mg/kg or 1000 mg/kg twice daily, starting 4 hours or 12 hours post-inoculation, nirmatrelvir significantly reduced viral load and disease severity. Ritonavir alone showed no antiviral effect or improvement in disease pathology, but when combined with nirmatrelvir, ritonavir enhanced lung protection and further reduced viral titers, consistent with its role in boosting nirmatrelvir exposure.

Studies on the secondary pharmacology evaluated *in vitro* activity of nirmatrelvir against a wide panel of receptors, transporters, ion channels and enzyme assays, and the results indicated no significant inhibition (>50%) of functional or enzyme activity.

Safety pharmacology studies evaluated the effects of nirmatrelvir on the central nervous, cardiovascular, and respiratory systems in rats and monkeys. In rats, high doses (1000 mg/kg) caused minor and transient changes in locomotor activity and respiratory parameters, with uncertain relevance to humans. In monkeys, doses of 150 mg/kg/day led to small, transient increases in blood pressure, reduced heart rate, and minor changes in ECG intervals, all resolving within 24 hours. Nirmatrelvir showed no significant effects on hERG channels, isolated heart, or vascular tissues, and no lasting safety concerns were observed in repeat-dose toxicity studies of up to 1 month. These effects are monitorable in clinical settings, and overall, the data support a favourable safety profile for nirmatrelvir at therapeutic doses.

No pharmacodynamic drug interaction studies have been conducted.

Nirmatrelvir has low passive permeability, moderate plasma protein binding, and preferentially partitions into plasma over red blood cells in rats, monkeys, and humans. It does not significantly cross the blood-brain barrier in rats due to being a P-gp substrate. Its metabolism is primarily mediated by CYP3A4 (fm = 0.99), and ritonavir is co-administered to inhibit CYP3A4, increasing nirmatrelvir plasma levels. *In vivo*, unchanged nirmatrelvir is the main circulating form in plasma, with M4 as a key metabolite in monkeys. In humans, most nirmatrelvir is excreted unchanged (55% in urine, 28% in faeces). Nirmatrelvir/ritonavir acts as a CYP3A4 and P-gp DDI perpetrator, but the effect does not exceed that of ritonavir alone. Other transporter DDI risks are minimal.

2.3.7. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of nirmatrelvir / ritonavir.

- Considering the above data, nirmatrelvir / ritonavir is not expected to pose a risk to the environment.

2.4. Clinical aspects

GCP

The Clinical trial C4671026 was performed in accordance with GCP as claimed by the MAH.

- Tabular overview of clinical studies

Study C47671026 was the pivotal study for this paediatric extension.

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Participants Randomized/ Treated/ Completed	Gender: M/F; Age: Mean (Min/Max); Race[b]: W/B/A/O	Duration of Treatment	Study Initiation/ Status	Study Synopsis
C4671026 (Bulgaria; Hungary; Mexico; Puerto Rico; South Africa; United Kingdom; United States)	A Phase 2/3, interventional safety, pharmacokinetics, and efficacy, open-label, multi-center, single-arm study to investigate orally administered PF-07321332 (Nirmatrelvir)/Ritonavir in nonhospitalized symptomatic pediatric participants with COVID-19 who are at risk of progression to severe disease Primary Objectives: • To determine the PK of nirmatrelvir/ritonavir in pediatric participants from birth to <18 years of age, using modeling and simulation approaches, in order to identify the appropriate dose for each pediatric age group that will achieve systemic exposures comparable to adults. • To describe the safety and tolerability of nirmatrelvir/ritonavir in the treatment of nonhospitalized symptomatic pediatric participants with COVID-19 who are at risk of progression to severe disease.	Cohort 1 (Cohorts 1a and 1b): nirmatrelvir/ritonavir 300 mg/100 mg q12h or nirmatrelvir/ritonavir 150 mg/100 mg q12h Cohort 2: nirmatrelvir/ritonavir 150 mg/100 mg q12h	77/75/73 Randomized: Cohort 1 (Cohorts 1a and 1b): 61 Cohort 2: 16 Treated: Cohort 1 (Cohorts 1a and 1b): 61 Cohort 2: 14	36 M/ 41 F 12.39 44 W/ 16 B/ 3 A / 0 O	5 days	07 March 2022/Ongoing	C4671026 Module 5.3.5.1

Additionally, two Phase 2 clinical trials within the development program allowed for enrolment of adolescent participants (12 years of age and older): C4671034 and C4671042. Study C4671034 was conducted in immunocompromised participants and Study C4671042 was conducted in participants with COVID-19 rebound following treatment with nirmatrelvir/ritonavir.

Phase 2 Studies							
C4671034 (Australia, Brazil, Bulgaria, Canada, Hungary, Mexico, Slovakia, Spain, United States)	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 To describe the effect of nirmatrelvir/ritonavir on viral RNA levels in NP swabs over time for the treatment of COVID-19 in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	Nirmatrelvir/ritonavir 300/100 mg administered orally q12h for 5, 10, or 15 days PBO orally (to match nirmatrelvir/ritonavir for the 5-day and 10-day treatment groups)	156/155/136	72 M/84 F 55.69 (16, 82) yrs 141W/2B/0A/0O (6 participants not reported) *(Number of Pediatric Participants: 1)*	5, 10, or 15 days	03 August 2022 completed (13 November 2023)	C4671034 Module 5.3.3.5
C4671042 (Canada, Germany, Greece, Italy, Taiwan, United States)	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. 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.	Two tablets of nirmatrelvir 150 mg and 1 capsule of ritonavir 100 mg q12h PO for 5 days; or Two tablets of placebo for nirmatrelvir and 1 capsule of ritonavir 100 mg q12h PO for 5 days.	Treated/Completed: 433/427 Excluding efficacy data from Site 1020 (41 participants)	189 M/247 F 53.5 396 W/ 20 B/ 15 A/ 0 O *(Number of Pediatric Participants: 1)*	5 days	Completed (09 February 2024)	C4671042 Module 5.3.5.1

2.4.1. Introduction

Paxlovid (nirmatrelvir/ritonavir) is currently indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19. Paxlovid should be administered as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset.

The recommended dosage is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally every 12 hours for 5 days.

The pharmacokinetic (PK) properties of Paxlovid were sufficiently characterised in the initial MAA and subsequent type II variations.

In the current type II variation, the MAH seeks an extension of the indication to include treatment of paediatric patients aged at least 6 years and weighing more than 20 kg.

This application is covered by a PIP submitted in 2021 (EMEA-003081-PIP01-21), and to date four requests for modification has been performed in 2021 (EMEA-003081-PIP01-21-M01 but withdrawn), 2022 (EMEA-003081-PIP01-21-M02), 2023 (EMEA-003081-PIP01-21-M03) and 2024 (EMA/PE/0000225184 dated 6 Dec 2024).

The PK data provided in support of this submission rely on the PK results from a Phase 2/3 study **C4671026** and an updated Population Pharmacokinetic (PPK) analysis, in order to recommend a dosing schedule in this target population.

SmPC sections 4.1, 4.2 and 5.2 has been updated accordingly.

2.4.2. Study C4671026

2.4.2.1. Bioanalysis

In study **C4671026**, nirmatrelvir and ritonavir were quantified in human plasma using a validated HPLC-MS/MS method (Report YDP/228/V10) developed and validated at York Bioanalytical Solutions.

The method used K2-EDTA as anticoagulant, Nirmatrelvir and Ritonavir-d6 (both stable isotope labelled) 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. For each analytes 4 QCs were considered (30, 300, 5000 and 8000 ng/mL for nirmatrelvir; 15, 150, 2500 and 4000 ng/mL for ritonavir). Long term stability was demonstrated at 543 days when stored at -20°C and 754 days at -80°C.

A total of 163 samples were received from 1st July 2022 until 12 Feb 2024, frozen on dry ice. 162 were analysed. The maximum days from collection to analysis was 46 days. 20 runs were performed with 2 rejected (Run 11 and 21). For ritonavir results from 147 samples were available.

ISR were performed on 25 samples with 100 % provided satisfactory results for both drugs.

2.4.2.2. Design

Study **C4671026** is a Phase 2/3, interventional safety, PK and efficacy, open-label, multi-center, single arm study to investigate orally administered Paxlovid in nonhospitalised symptomatic paediatric participants with COVID-19 who are at risk of progression to severe disease. Participants were planned to be enrolled into 5 cohorts in a tiered scheme based on age and/or weight:

- Cohort 1: Weight ≥ 40 kg, a) 12 to < 18 years, b) 6 to < 12 years
- Cohort 2: Weight 20 to < 40 kg, 6 to <18 years
- Cohort 3: 2 to < 6 years
- Cohort 4: 1 month to <2 years
- Cohort 5: < 1 month

Approximately 160 participants were planned to be enrolled with 70 in Cohort 1, 50 in cohort 2, 20 in Cohort 3 and 4 and 2 for Cohort 5.

The investigated dosing schedule consisted of:

- 300 mg/ 100 mg nirmatrelvir/ritonavir administered BID during 5 consecutive days in subjects aged 6 to 18 years and weighing at least 40 kg, and
- 150 mg/ 100 mg nirmatrelvir/ritonavir administered BID during 5 consecutive days in subjects aged 6 to 18 years and weighing 20 to 40 kg

These dosing schedules were selected by simulation using a PPK model using PK data from healthy and COVID-19 adult subjects (please refer to the initial MAA or subsequent type II variation).

Results of these simulations (which used population fixed effects and their IIV with a RUV effect fixed to 0 [RUV largely above 70% in the initial PPK model]) are presented in *Table 1* for predicted PK parameters at Day 5, and percent of participants achieving a C_{min} ≥ 90% EC90 (292 ng/mL) in *Table 2*.

PK sampling consisted for Cohort 1 and 2, of 9 PK samples performed by venous or Tasso blood sampling at Day 1 (T 1h), Day 4 (just before the next dose = T72 h), and at Day 5 (T0 , 1, 2, 4, 6, 8 and 10 h).

As stated in section 1.3.1 of the Study protocol, these sampling times are exclusive for the Tasso sampling device. Venous PK sample were only performed at Day 1 (T1h) and Day 5 (T0, 1 and 2h).

Table 1: Initial PPK simulations, Predicted Day 5 Nirmatrelvir exposure parameters for Paediatric participants with COVID-19 and normal renal function

Age Group	Weight Group	Dose[a] (mg)	AUC_τ (ng·h/mL) Percentile			C_{max} (ng/mL) Percentile			C_{min} (ng/mL) Percentile		
			Geomean	10th	90th	Geomean	10th	90th	Geomean	10th	90th
Adult	≥40 kg	300	27345	16399	45382	3160	2069	4820	1327	593	2731
12 to <18 years	20 to <40 kg	150	33276	20826	52273	3557	2436	5196	1861	928	3443
		300	50136	31378	78758	5360	3670	7829	2804	1398	5188
	≥40 kg	150	24099	14678	38818	2550	1669	3837	1372	693	2581
		300	36309	22115	58486	3843	2515	5781	2066	1044	3889
6 to <12 years	10 to <20 kg	100	43288	27302	67991	4502	3087	6546	2537	1309	4628
	20 to <40 kg	150	40104	24805	64848	4187	2812	6252	2340	1212	4401
		300	60423	37373	97704	6308	4236	9419	3526	1826	6631
	≥40 kg	150	27428	17093	44060	2842	1910	4263	1621	830	3015
		300	41325	25754	66385	4283	2877	6423	2442	1250	4542
2 to <6 years	10 to <20 kg	100	50315	31358	80231	5035	3381	7521	3149	1700	5615

Table 2: Initial PPK simulations, Predicted Day 5 C_{min} and percentage of simulated Paediatric participants with COVID-19 and normal renal function achieving C_{min} above in vitro EC90 of 292 ng/mL

Age Group	Weight Group	Dose[a] (mg)	Dose Number	C_{min} (ng/mL)			Ratio of Median to Adult	% Participants Achieved $C_{min} \geq EC_{90}$
				Median	10th percentile	90th percentile		
Adult	≥40 kg	300	1st (Day 1)	827	445	1313	-	96.7
			10th (Day 5)	1417	593	2731	-	98.0
12 to <18 years	20 to <40	300	1st (Day 1)	1522	975	2142	1.84	99.8
			10th (Day 5)	2944	1398	5188	2.08	99.9
		150	1st (Day 1)	1010	647	1422	1.22	99.3
			10th (Day 5)	1954	928	3443	1.38	99.7
	≥40 kg	300	1st (Day 1)	1093	680	1574	1.32	99.6
			10th (Day 5)	2177	1044	3889	1.54	99.8
		150	1st (Day 1)	725	452	1045	0.877	98.0
			10th (Day 5)	1445	693	2581	1.02	99.3
6 to <12 years	10 to <20	100	1st (Day 1)	1288	866	1777	1.56	99.8
			10th (Day 5)	2626	1309	4628	1.85	99.9
	20 to <40	300	1st (Day 1)	1784	1164	2538	2.16	99.9
			10th (Day 5)	3657	1826	6631	2.58	100
		150	1st (Day 1)	1184	772	1685	1.43	99.8
			10th (Day 5)	2427	1212	4401	1.71	99.9
	≥40 kg	300	1st (Day 1)	1209	792	1696	1.46	99.8
			10th (Day 5)	2547	1250	4542	1.80	99.9
		150	1st (Day 1)	802	525	1126	0.970	99.2
			10th (Day 5)	1691	830	3015	1.19	99.7
2 to <6 years	10 to <20 kg	100	1st (Day 1)	1392	977	1922	1.68	100
			10th (Day 5)	3234	1700	5615	2.28	100

The Primary PK objective are presented in Table 3 below.

Table 3: PK Study C4671026 objectives

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary**
• To determine the PK of nirmatrelvir/ritonavir in pediatric participants from birth to <18 years of age, using modeling and simulation approaches, in order to identify the appropriate dose for each pediatric age group that will achieve systemic exposures comparable to adults.	• PK parameters including C_{max} and $AUC_{0\text{-}tau}$ (and if the data permit $t_{1/2}$, C_{trough}) of nirmatrelvir and ritonavir. In adolescents (≥12 years to <18 years of age), robust PK sampling will be performed. A sparser approach will be incorporated for younger participants as PK samples are more difficult to obtain.	• PK1: The primary PK estimand will be the geometric mean of the derived and/or population predicted PK parameters (C_{max}, and $AUC_{0\text{-}tau}$ (and if the data permit $t_{1/2}$, C_{trough}) for nirmatrelvir/ritonavir in pediatric participants from birth to <18 years of age.

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints	Tertiary/Exploratory Estimands
• To estimate appropriate doses that match exposures in adults based on PK and PK/PD modeling (ie, viral load reduction)	• Integrated PK and PK/PD model in adults and pediatric participants with nirmatrelvir PK in dried blood and plasma (if feasible)	• Not applicable

As stated in the protocol, given the planned PK sampling it was expected that Pharmacokinetic parameters will be evaluated in this study, either by non-compartmental analysis or via a population PK approach. Robust samples may be evaluated via a non-compartment approach, and sparse samples will be evaluated via population PK approach. PK data from this study may be combined with other studies and analysed using the population PK approach.

2.4.2.3. Results

A total of 77 participants were enrolled in study **C4671026** with 50 subjects aged 12 to < 18 years and 27 aged 6 to < 12 years with a median age (min-max) of 13 years (6-17). Gender male/female was 36/41, subjects were mainly White (57.1%). Median (min-max) BW was 54.6 (20.3-200) kg.

A total of 162 plasma PK samples were collected and consisted of:

- 84 planned sparse PK samples (as detailed in section 5.3.2.2) and,
- 80 additional PK samples collected per protocol for specified protein research that were later analysed for drug concentration.

Predicted PK exposure parameters

Given the sparse PK sampling, the total amount of PK data (162) collected in children was combined with the amount of PK data collected as part of Paxlovid clinical development in a PPK model (please refer to section 5.3.3) from which predicted PK exposure metrics are presented in Table 4 below.

Table 4: Descriptive summary of plasma Nirmatrelvir PK parameters (Predicted)

Parameter (Unit)[a]	Cohort 1a 150mg (N=8)	Cohort 1a 300mg (N=37)	Cohort 1b 300mg (N=12)	Cohort 2 150mg (N=11)
N2	8	37	12	11
AUC_{tau} (ng.hr/mL)	23970 (19)	34330 (36)	31160 (81)	30990 (89)
C_{max} (ng/mL)	2605 (18)	3773 (28)	3835 (43)	3553 (53)
C_{min} (ng/mL)	1431 (24)	1986 (53)	1315 (498)	1439 (316)

Source: Table 14.4.5.1.1
N = Total number of participants in each cohort group in the indicated population.
N2 = Number of participants contributing to the summary statistics.
a. Geometric mean (geometric %CV) for all parameters.
PK parameters could not be determined for participants with no recorded SCR, as this is a covariate in the population PK modeling.
Cohort 1a: ≥ 40 kg, ≥ 12 to < 18 years, Cohort 1b: ≥ 40 kg, ≥ 6 to < 12 years, Cohort 2: ≥ 20 to < 40 kg, ≥ 6 to < 18 years.
PFIZER CONFIDENTIAL SDTM Creation: 07NOV2024 (00:11) Source Data: adpp Table Generation: 08NOV2024 (02:20) (Database snapshot date : 07JUN2024) Output File: ./nda_ph23/C4671026_sNDA_PKP/adpp_s101_i

Nirmatrelvir exposures based on geometric mean AUC_{tau} and C_{max} were comparable across Cohort 1 participants receiving the nirmatrelvir 300 mg dose and Cohort 2 participants (with an AUC_{tau} of 34330, 31160, and 30990 ng.hr/mL and a C_{max} of 3773, 3835, and 3553 ng/mL in Cohort 1a and 1b participants receiving nirmatrelvir 300 mg dose and Cohort 2 participants, respectively). Greater than 90% of participants enrolled achieved a C_{min} greater than the EC90, regardless of cohort or dose.

Observed Nirmatrelvir Concentrations

Table 5 presented the plasma concentration of nirmatrelvir concentration per dose cohort.

Table 5: Observed nirmatrelvir concentrations per dose cohort

Cohort Group: Cohort 1a 150mg

Visit	Planned Time Post Dose	N	NALQ	Mean (SD)	CV (%)	Median (Range)	Geometric Mean
DAY1	1H	6	6	2254 (662.40)	29	2425 (986, 2770)	2139
DAY5	0MIN	8	8	1262 (748.59)	59	1070 (481, 2370)	1077
	1H	8	8	3091 (1595.6)	52	3300 (540, 5000)	2564
	2H	8	8	3371 (1474.0)	44	3450 (519, 5170)	2870

Cohort Group: Cohort 1a 300mg

Visit	Planned Time Post Dose	N	NALQ	Mean (SD)	CV (%)	Median (Range)	Geometric Mean
DAY1	1H	34	28	2784 (2217.2)	80	2670 (0.000, 7600)	2456

Cohort Group: Cohort 1b 300mg

Visit	Planned Time Post Dose	N	NALQ	Mean (SD)	CV (%)	Median (Range)	Geometric Mean
DAY1	1H	10	8	2674 (2584.3)	97	2340 (0.000, 7660)	2136

Cohort Group: Cohort 2 150mg

Visit	Planned Time Post Dose	N	NALQ	Mean (SD)	CV (%)	Median (Range)	Geometric Mean
DAY1	1H	10	7	1149 (1816.6)	158	397.0 (0.000, 5500)	685.4

2.4.3. Population Pharmacokinetic analysis

2.4.3.1. Background

As part of a type II variation (EMEA/H/C/005973/II/) to fulfil a PAM 25 (LEG) as adopted by the CHMP from the initial CMA procedure, the MAH submitted a PPK analysis of nirmatrelvir concentrations after oral administration of Paxlovid (Report pmar-eqdd-c467a-other-1463) in adult and paediatric participants. Paediatric participants were from the ongoing study **C4671026**, where PK data were collected from 38 children aged 12-18 years and weighing ≥ 40 kg (cut-off date of 25 Oct 2022) with the Tasso M20 sampling technique.

At that time the PPK model used PK data collected by venous or capillary dried blood from:

- 9 completed phase 1 studies in healthy adult participants **C4671001**, **C4671010**, **C4671011**, **C4671012**, **C4671013**, **C4671014**, **C4671015**, **C4671016** and **C4671019** (rich PK sampling) and
- 3 Phase 2/3 outpatient studies in adult household contacts of an individual with symptomatic COVID-19 (Study **C4671006**), in non-hospitalised symptomatic adults with COVID-19 who were at low risk (Study **C4671002**) and who were at increased risk (Study **C4671005**) of progressing to severe illness (sparse PK sampling), and
- 1 phase 2/3 ongoing study **C4671026** in paediatric participants where PK samples were collected exclusively by Tasso M20 sampling.

A total 3937 subjects were included, paediatric PK data accounted of 306 samples (2.57%) as detailed in *Table 6* below.

Table 6: PK dataset (Type II-37 PPK analysis)

	All	Healthy Adult	Adult Household Contacts	Adult COVID-19	Pediatric COVID-19
Number (%) of Participants	3937	176 (4.47%)	1938 (49.2%)	1785 (45.3%)	38 (0.965%)
Number (%) of Samples	11920	3543 (29.7%)	3947 (33.1%)	4124 (34.6%)	306 (2.57%)
Number (%) of Plasma Samples	11160 (93.6%)	3304 (27.7%)	3794 (31.8%)	4062 (34.1%)	0
Number (%) of Tasso Samples	760 (6.38%)	239 (2.01%)	153 (1.28%)	62 (0.520%)	306 (2.57%)

Subsequently higher than expected nirmatrelvir exposure derived from Tasso M20 sampling were observed in 52 paediatric participants in Cohort 1 (≥6 to <18 years, weight ≥40 kg; data cutoff date 07 Feb 2023) of Study **C4671026**. A Tasso to plasma bridging analysis in approximately 10 participants was then implemented in the protocol amendment 3 to determine nirmatrelvir and ritonavir blood-to-plasma ratio in paediatric participants. When comparing the plasma concentrations derived from Tasso M20 samples with the paired venous plasma samples, the preliminary results in 9 paediatric participants in Cohort 1a (≥12 to <18 years, weight ≥40 kg; cutoff date 26 Jan 2024) showed discordance (>20% difference) between the paired Tasso and plasma samples.

Consequently, the final adult PPK model in pmar-eqdd-c467a-other-1463 was updated by adding the available PK data from study **C4671026** (cut-off date 04 Apr 2024) and by removing:

- Tasso M20 data from all Phase 1 and 2/3 studies, and
- GCP noncompliance PK data (please refer to II-42)

Based on this new PPK analysis (Report **pmar-eqdd-c467e-other-1546**), the objectives are twice:

- Simulations were performed to support dose recommendations for the paediatric population.
- Generate EBE post-hoc predictions of plasma nirmatrelvir exposures co-administered with ritonavir and compute secondary PK parameters (C_{min}, C_{max}, AUC_{tau}) at steady-state for adult and paediatric participants with COVID-19 from studies **C4671005**, **C4671002** and **C4671026**.

2.4.3.2. Methods

The same methodology as already described in the initial CMA submission and subsequent type II variations II-37, II-42 and II-57 has been applied.

Nonlinear mixed effects modelling (NONMEM) version 7.5.0 was used for all model estimations through improve M&S versions 4.0.4-14 and 4.0.7-10. Perl-speaks-NONMEM (PsN) version 5.3.0 was used for prediction corrected visual predictive check (pcVPC) and sampling importance resampling (SIR). R version 4.2.1 or 4.3.1 was used for pre-and post-processing and for summarising and plotting results.

First, a predictive check (simulation) approach was used to examine the consistency of the observed nirmatrelvir plasma PK data from paediatric participants in Cohorts 1 and 2 of the ongoing Study **C4671026** with the final adult plasma Pop PK model described in pmar-eqdd-c467a-other-1463.

The model prediction interval was constructed from a simulation with 1000 subproblems using the parameter estimates from the adult plasma Pop PK model for 100 adults infected with COVID-19 and with normal renal function (nCLCR ≥90 mL/min/1.73 m^2), covariates sampled from participants in Study **C4671005**, and assuming a dose regimen of nirmatrelvir/ritonavir 300 mg/100 mg BID given orally for 5 days.

Subsequently, the adult plasma Pop PK model was updated with the available paediatric data. All covariates included in the adult Pop PK model were retained and parameters were re-estimated. Based on previous analysis with preliminary paediatric Tasso M20 data, a separate formulation effect on F1 for paediatric population was tested.

2.4.3.3. Results

The final PK dataset consisted of 3696 participants, with 3627 adults from 12 pooled Studies and 69 paediatric participants from Cohort 1 and Cohort 2 of study **C4671026**. Evaluable PK data from adults accounted for 8355 and paediatric PK data for 131 samples (1.56%). *Table 7* presented the demographic of all participants.

Table 7: Demographic for all participants in the PPK analysis

	All	Healthy Adult	Adult Household Contacts	Adult COVID-19	Pediatric COVID-19
Number (%) of Participants	3696	176 (4.76%)	1803 (48.8%)	1648 (44.6%)	69 (1.87%)
Number (%) of Plasma Samples	10671	3304 (31.0%)	3526 (33.0%)	3691 (34.6%)	150 (1.41%)
Number (%) of Evaluable Plasma Samples	8355 (78.3%)	3005 (28.2%)	2217 (20.8%)	3002 (28.1%)	131 (1.23%)
Number (%) of BLQ Plasma Samples	2316 (21.7%)	299 (2.80%)	1309 (12.3%)	689 (6.46%)	19 (0.178%)
Sex					
Number (%) of Males	1801 (48.7%)	125 (3.38%)	834 (22.6%)	807 (21.8%)	35 (0.947%)
Number (%) of Females	1895 (51.3%)	51 (1.38%)	969 (26.2%)	841 (22.8%)	34 (0.920%)

Race					
Number (%) of White	2741 (74.2%)	93 (2.52%)	1403 (38.0%)	1205 (32.6%)	40 (1.08%)
Number (%) of Black/African American	408 (11.0%)	53 (1.43%)	263 (7.12%)	77 (2.08%)	15 (0.406%)
Number (%) of Asian	269 (7.28%)	26 (0.703%)	22 (0.595%)	220 (5.95%)	1 (0.0271%)
Number (%) of American Indian/Alaska Native	253 (6.85%)	0	110 (2.98%)	134 (3.63%)	9 (0.244%)
Number (%) of Other	7 (0.189%)	4 (0.108%)	2 (0.0541%)	1 (0.0271%)	0
Number (%) of Unknown/Missing	18 (0.487%)	0	3 (0.0812%)	11 (0.298%)	4 (0.108%)
Body Weight (kg)					
Median	76.0	75.2	76.2	76.3	55.3
Range	20.5-200	51.4-118	39.0-182	42.0-170	20.5-200
Age (years)					
Median	42.0	46.5	42.0	42.0	13.0
Range	6.00-91.0	20.0-76.0	18.0-91.0	18.0-87.0	6.00-17.0
Baseline CL_{cr} (mL/min)					
Median	128	103	128	130	147
Range	19.5-622	19.5-277	23.1-622	20.7-426	32.3-488

	All	**Healthy Adult**	**Adult Household Contacts**	**Adult COVID-19**	**Pediatric COVID-19**
Baseline BSA-normalized CL_{cr} (mL/min/1.73 m^2)					
Median	121	98.2	121	123	159
Range	15.8-518	15.8-247	24.1-518	22.8-370	56.4-312
Baseline Body Mass Index					
Median	27.1	26.2	27.2	27.2	22.9
Range	13.6-76.2	19.7-40.3	15.7-65.0	16.6-58.8	13.6-76.2

Paediatric PK data

For study **C4671026**, there were 75 participants received at least one dose of Paxlovid (Table 8). Due to:

- Missing BSCR (nCLCR is a key covariate in the PPK model), 6 participants were excluded.
- Missing race (race was not a key covariate), 4 participants were retained.
- 1 participant who had only dosing records, no plasma sample collected, and Tasso samples excluded) was retained.

There were 3 participants who received less than 10 doses of Paxlovid.

In total, 50 participants received Paxlovid 300 mg/100 mg with:

- 38 from Cohort 1a (12-<18 y ≥ 40 kg) with one who have only dosing records
- 12 from Cohort 1b (6-<12 y ≥ 40 kg)

And 19 who received Paxlovid 150mg/100mg with:

- 8 from Cohort 1a (12-<18 y ≥ 40 kg)
- 11 from Cohort 2 (6-<12 y 20-<40 kg)

Table 8: Demographic for Paediatric participants (Study C4671026)

	All	Cohort 1a[a] ≥12 to <18 years ≥40 kg	Cohort 1b ≥6 to <12 years ≥40 kg	Cohort 2 ≥6 to <18 years ≥20 to <40 kg
Number (%) of Participants	69	46 (1.24%)	12 (0.325%)	11 (0.298%)
Number (%) of Plasma Samples	150	109 (72.7%)	22 (14.7%)	19 (12.7%)
Number (%) of Evaluable Plasma PK Samples	69 (46.0%)	54 (36.0%)	8 (5.33%)	7 (4.67%)
Number (%) of Evaluable Plasma Biomarker Samples[b]	57 (38.0%)	39 (26.0%)	10 (6.67%)	8 (5.33%)
Number (%) of BLQ Plasma PK Samples	13 (8.67%)	6 (4.00%)	4 (2.67%)	3 (2.00%)
Number (%) of BLQ Plasma Biomarker Samples[b]	6 (4.00%)	5 (3.33%)	0	1 (0.667%)
Number (%) of Non-compliant Plasma PK Samples	3 (2.00%)	3 (2.00%)	0	0
Number (%) of Non-compliant Plasma Biomarker Samples[b]	2 (1.33%)	2 (1.33%)	0	0
Sex				
Number (%) of Males	35 (50.7%)	21 (30.4%)	7 (10.1%)	7 (10.1%)
Number (%) of Females	34 (49.3%)	25 (36.2%)	5 (7.25%)	4 (5.80%)
Race				
Number (%) of White	40 (58.0%)	23 (33.3%)	8 (11.6%)	9 (13.0%)
Number (%) of Black/African American	15 (21.7%)	12 (17.4%)	1 (1.45%)	2 (2.90%)
Number (%) of Asian	1 (1.45%)	1 (1.45%)	0	0
Number (%) of American Indian/Alaska Native	9 (13.0%)	7 (10.1%)	2 (2.90%)	0
Number (%) of Unknown/Missing	4 (5.80%)	3 (4.35%)	1 (1.45%)	0
Body Weight (kg)				
Median	55.3	68.4	46.3	29.5
Range	20.5-200	40.4-200	40.0-57.0	20.5-39.4
Age (years)				
Median	13.0	14.0	10.0	7.00
Range	6.00-17.0	12.0-17.0	8.00-11.0	6.00-14.0
Baseline CL_{cr} (mL/min)				
Median	147	171	97.8	72.4
Range	32.3-488	95.0-488	65.0-147	32.3-125
Baseline BSA-normalized CL_{cr} (mL/min/1.73 m^2)				
Median	159	174	133	128
Range	56.4-312	110-312	90.0-193	56.4-254
Baseline Body Mass Index				
Median	22.9	24.8	22.6	18.4
Range	13.6-76.2	16.2-76.2	19.8-26.8	13.6-23.7

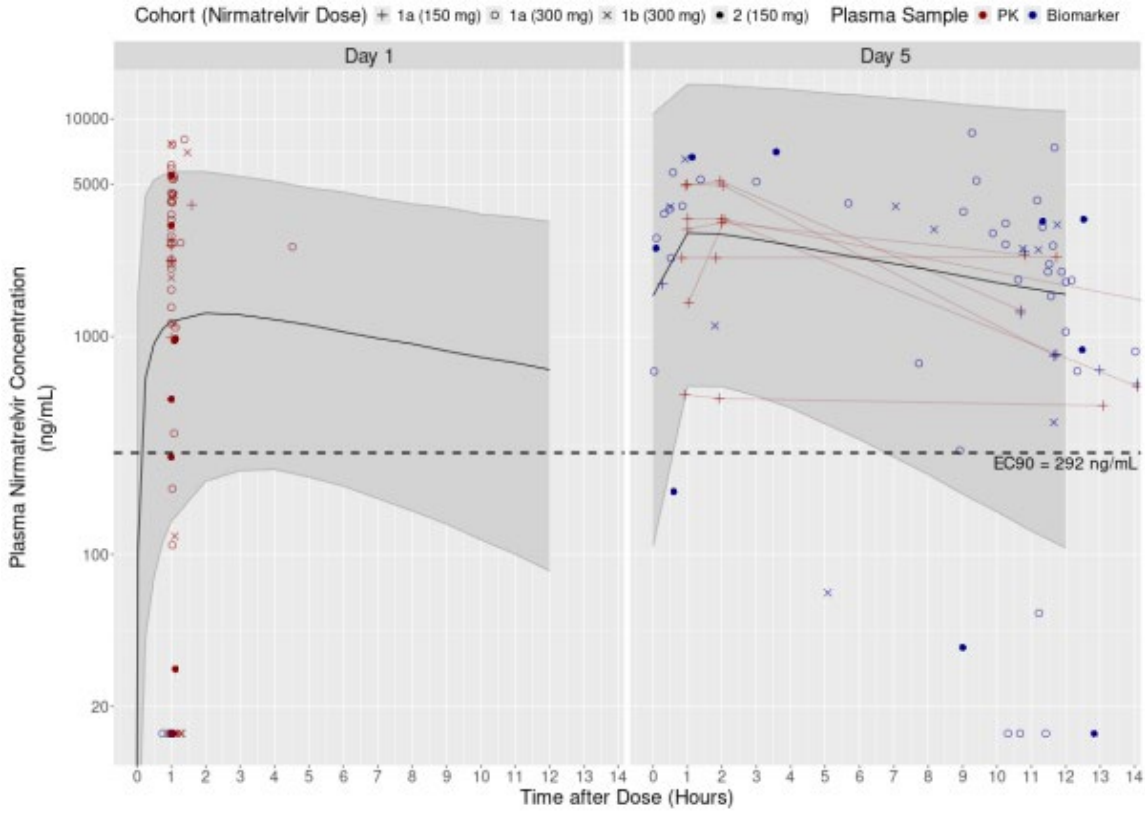
The available PK dataset consisted of 150 plasma samples (69 from sampling protocol and 57 additional from biomarker plasma samples) with 19 BQL samples (15 at Day 1, 4 at Day 5). 6 subjects has no evaluable PK samples (all were BQL).

There were 9 plasma observations (including 5 evaluable and 4 BQL samples) from 6 participants where ritonavir concentrations on Day 5 were below LLOQ (sign of non-compliance).

Predictive check

Figure 1 presented the median and 90% PI of plasma nirmatrelvir concentration versus TAD after the first dose on Day 1 and at steady state (Day 5) generated using the previous adult plasma PPK model.

Figure 1: Median and 90% Prediction intervals (5th and 95th percentile) for adult nirmatrelvir concentration based on 1000 simulations (Paxlovid 300 mg/100 mg BID) overlaid with observed data from Paediatric study C4671026



Final PPK model

Table 9 presented the final PPK model parameter estimates, *Figure 2* the associated the pcVPCs split by populations (GOF plots can be retrieved from the report).

PK parameter estimates were closed to that reported previously (please refer to II-37). BW allometric scaling (normalised to 70 kg) was considered on clearances and volumes with a power function and fixed exponents (0.75 for CL & Q, and 1 for V2 & V3). The effect of nCLCR on CL was retained with a power function (normalised to a fixed breakpoint of 84.4 mL/min/1.73m^2). The combined adult and paediatric model with exclusion of non-compliant paediatric PK data was chosen as the final model for subsequent nirmatrelvir exposure simulation.

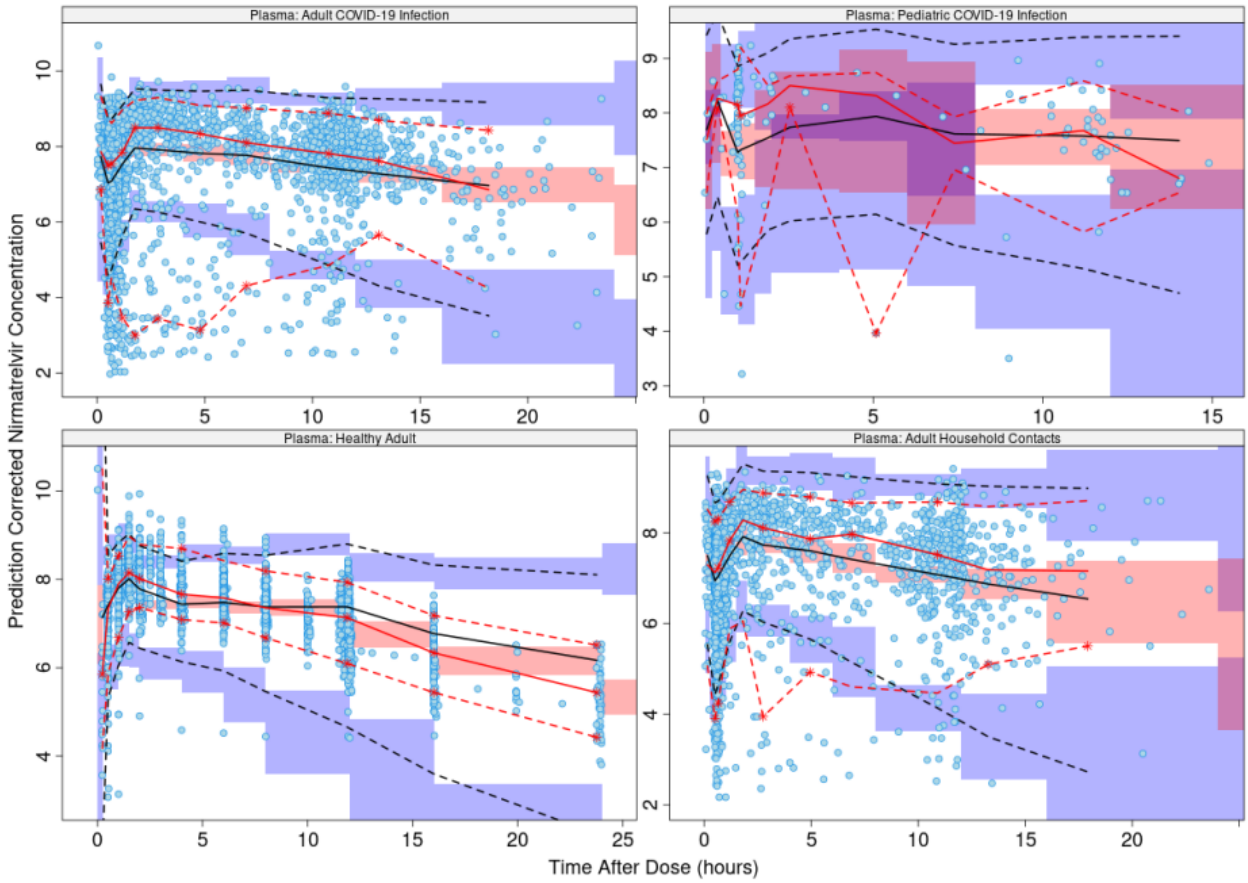
The mean, %relative standard error (RSE), median, 2.5th and 97.5th percentiles generated from 1000 SIR samples (3 iterations with resampling size of 200, 400 and 500) are also shown. In general, fixed and random effects parameters are well estimated with %RSE <30%, other than IIV on V3 (%RSE = 38.1%). All η shrinkage are >30% due to majority of the data coming from the Phase 2/3 outpatient

studies where a sparse sampling approach was implemented. RUV was moderate on Phase 1 data (34.7%) and remain higher for Phase 2/3 PK data (77.4%).

Table 9: PK parameter estimates of the final PPK model

	Final Run 13 (CP1:ST-59180461)			SIR[a] Run Statistics				
Parameter	**Estimate**	**%RSE**	**Shrinkage (%)**	**Mean**	**%RSE**	**Median**	**Lower 2.5%**	**Upper 97.5%**
CL (θ_1) [L/h]	7.11	4.03	-	7.13	4.03	7.11	6.58	7.71
V_2 (θ_2) [L]	72.8	3.70	-	72.9	3.28	72.9	68.3	77.8
Q (θ_3) [L/h]	0.558	15.8	-	0.555	8.65	0.557	0.450	0.643
V_3 (θ_4) [L]	9.61	16.7	-	9.78	12.5	9.74	7.50	12.1
k_a (θ_5) [1/h]	1.92	0.215	-	1.92	0.294	1.92	1.91	1.93
nCLCR$_{power}$ (θ_{10}) <nCLCR$_{breakpoint}$	0.633	23.9	-	0.631	19.5	0.629	0.401	0.875
F1$_{power}$ (θ_{12})	-0.474	8.83	-	-0.476	8.25	-0.475	-0.553	-0.402
Effect of Carbamazepine on CL (θ_{15})	0.728	27.8	-	0.737	11.2	0.736	0.592	0.908
Effect of Itraconazole on CL (θ_{16})	-0.322	8.91	-	-0.320	5.34	-0.320	-0.350	-0.283
Effect of COVID-19 on CL (θ_{23})	-0.253	12.1	-	-0.253	10.8	-0.253	-0.306	-0.198
Effect of 150 mg Tablet on F1 Adult (θ_{25})	-0.440	5.17	-	-0.440	4.45	-0.439	-0.478	-0.402
Power of Age effect on V_2 (θ_{27})	-0.230	23.9	-	-0.224	20.9	-0.226	-0.318	-0.130
Proportional Error Phase 1 Plasma (θ_6) [%]	34.7	6.12	22.7	34.8	1.78	34.8	33.5	36.0
Proportional Error Phase 2/3 Plasma[b] (θ_7) [%]	77.4	3.89	-	77.0	2.45	77.2	73.1	80.5
$\omega^2_{1,1}$ IIV$_{CL}$ [%CV]	79.9	6.73	35.2	80.3	5.39	80.1	76.3	84.9
$\omega^2_{2,2}$ IIV$_{V_2}$ [%CV]	36.5	11.8	66.3	36.4	10.1	36.3	32.7	40.0
$\omega^2_{3,3}$ IIV$_{k_a}$ [%CV]	175	6.87	43.5	175	4.88	175	167	183
$\omega^2_{4,4}$ IIV$_{V_3}$ [%CV]	87.6	38.1	88.7	90.6	31.8	89.3	63.0	116

Figure 2: pcVPC for final PPK model stratified by population



Repository artifact ID FI-59290626.
Symbols = observed nirmatrelvir concentrations;
Red solid and broken lines = median, 5^{th} & 95^{th} confidence intervals of the observed data;
Black solid and broken lines = median, 5^{th} & 95^{th} confidence intervals from 1000 simulations with surrounding 95% shaded area in pink and blue.
Excluded observations with time after dose ≥24 hours.

Simulations

Table 10 and *Table 11* presented the predicted Day 5 nirmatrelvir exposure parameters and the percentage of simulated subjects achieving a C_{min} at Day 1 and Day 5 for paediatric subjects aged 6 to 18 years and weighing ≥40 kg or 20-<40 kg. *Figure 3* displays the distribution of the predicted Day 5 plasma nirmatrelvir C_{min} in simulated paediatric subjects for the proposed dosing regimens stratified by age and weight group.

Table 10: Predicted Day 5 Nirmatrelvir exposure parameters for simulated adult and paediatric subjects with COVID-19 and normal renal function following proposed BID dosing Paxlovid for 5 days

Age Group	Weight Group	Dose[a] (mg)	AUC_τ (ng·h/mL) Geometric mean	AUC_τ Percentile 10^{th}	AUC_τ Percentile 90^{th}	C_{max} (ng/mL) Geometric mean	C_{max} Percentile 10^{th}	C_{max} Percentile 90^{th}	C_{min} (ng/mL) Geometric mean	C_{min} Percentile 10^{th}	C_{min} Percentile 90^{th}
Adult	≥40 kg	300	27738	10058	73986	3222	1491	6973	1361	282	5290
12 to <18 years	20 to <40 kg	150	34286	12311	88119	3908	1854	8218	1742	381	6402
	≥40 kg	300	34027	12601	89349	3842	1818	8380	1760	396	6447
6 to <12 years	10 to <20 kg	75	38214	13701	101627	4390	2108	9424	1907	400	7355
	20 to <40 kg	150	40577	14808	106022	4606	2195	9903	2078	430	7702
	≥40 kg	300	39304	14138	100472	4377	2019	9271	2073	464	7299
2 to <6 years	10 to <20 kg	50	36551	13166	94542	4092	1937	8815	1921	428	6814
		75	45235	16294	117006	5064	2397	10909	2377	530	8433

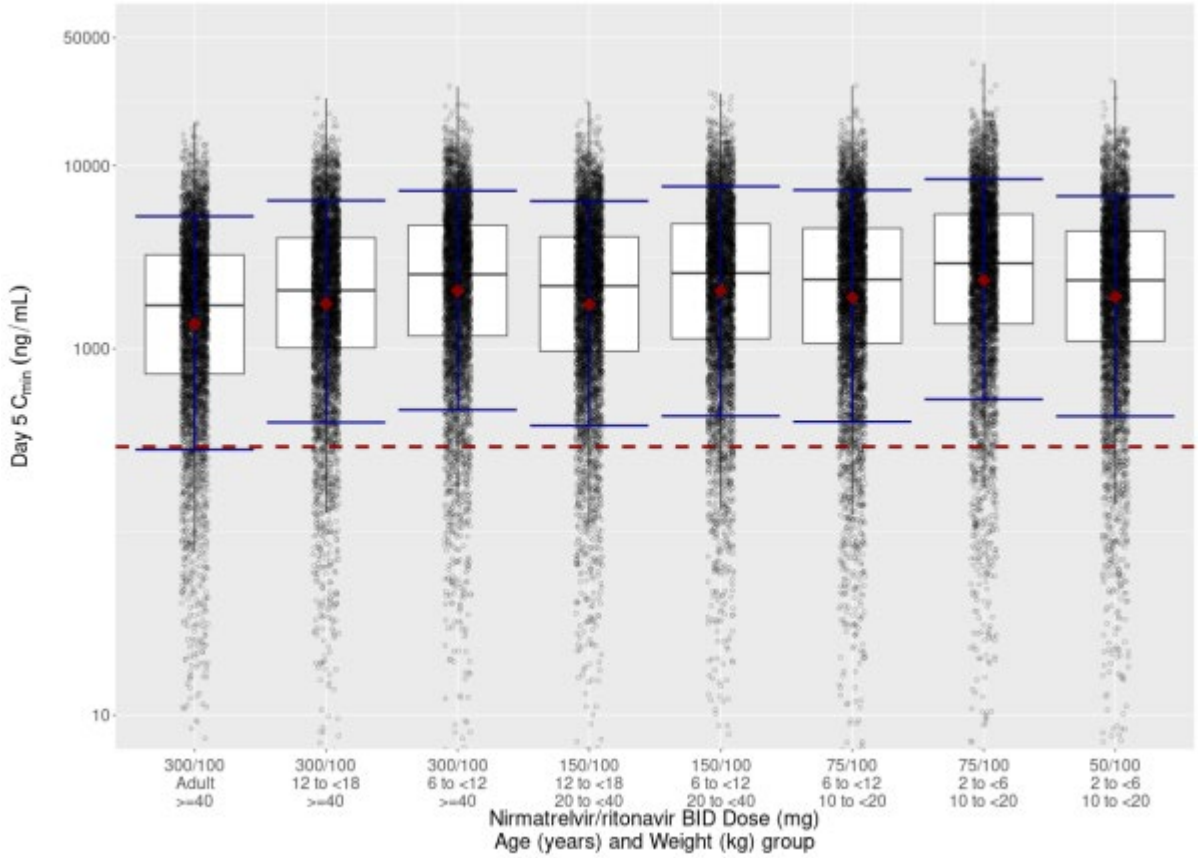
Age Group	Weight Group	Dose[a] (mg)	AUC_τ (ng·h/mL) Geometric mean	AUC_τ Percentile 10^{th}	AUC_τ Percentile 90^{th}	C_{max} (ng/mL) Geometric mean	C_{max} Percentile 10^{th}	C_{max} Percentile 90^{th}	C_{min} (ng/mL) Geometric mean	C_{min} Percentile 10^{th}	C_{min} Percentile 90^{th}
Adult	≥40 kg	300	27738	10058	73986	3222	1491	6973	1361	282	5290
6 to <18 years	20 to <40 kg	150	37299	13506	98064	4242	2003	9078	1903	403	7032
6 to <18 years	≥40 kg	300	36571	13314	95600	4100	1905	8861	1910	425	6932

Table 11: Predicted Day 1 and Day 5 C_{min} and percentage of simulated adult and paediatric subjects with COVID-19 and normal renal function achieving C_{min} above in vitro EC90 of 292 ng/mL following proposed BID dosing Paxlovid for 5 days.

Age Group	Weight Group	Dose[a] (mg)	Dose Number	C_{min} (ng/mL) Median	C_{min} 10^{th} percentile	C_{min} 90^{th} percentile	Ratio of Median to Adult	% Subjects Achieved $C_{min} \geq EC_{90}$
Adult	≥40 kg	300	1^{st} (Day 1)	797	228	1545	-	86.4
			10^{th} (Day 5)	1726	282	5290	-	89.5
12 to <18 years	20 to <40 kg	150	1^{st} (Day 1)	982	296	1774	1.23	90.2
			10^{th} (Day 5)	2202	381	6402	1.28	92.4
	≥40 kg	300	1^{st} (Day 1)	949	302	1785	1.19	90.4
			10^{th} (Day 5)	2085	396	6447	1.21	92.9
6 to <12 years	10 to <20 kg	75	1^{st} (Day 1)	1117	316	2006	1.40	91.0
			10^{th} (Day 5)	2387	400	7355	1.38	92.7
	20 to <40 kg	150	1^{st} (Day 1)	1164	339	2154	1.46	91.6
			10^{th} (Day 5)	2591	430	7702	1.50	93.2
	≥40 kg	300	1^{st} (Day 1)	1107	347	2000	1.39	91.7
			10^{th} (Day 5)	2551	464	7299	1.48	93.6
2 to <6 years	10 to <20 kg	50	1^{st} (Day 1)	1034	331	1887	1.30	91.5
			10^{th} (Day 5)	2367	428	6814	1.37	93.1
		75	1^{st} (Day 1)	1279	410	2335	1.60	93.3
			10^{th} (Day 5)	2929	530	8433	1.70	94.3

Age Group	Weight Group	Dose[a] (mg)	Dose Number	C_{min} (ng/mL) Median	C_{min} 10^{th} percentile	C_{min} 90^{th} percentile	Ratio of Median to Adult	% Subjects Achieved $C_{min} \geq EC_{90}$
Adult	≥40 kg	300	1^{st} (Day 1)	797	228	1545	-	86.4
			10^{th} (Day 5)	1726	282	5290	-	89.5
6 to <18 years	20 to <40 kg	150	1^{st} (Day 1)	1064	315	1976	1.33	90.9
			10^{th} (Day 5)	2375	403	7032	1.38	92.8
6 to <18 years	≥40 kg	300	1^{st} (Day 1)	1021	319	1897	1.28	91.1
			10^{th} (Day 5)	2317	425	6932	1.34	93.2

Figure 3: Predicted Day 5 Plasma Nirmatrelvir C_{min} in Simulated Adult and Paediatric Subjects with COVID-19 and Normal Renal Function by Proposed Dosing Regimen, Age and Weight Group



Simulations with various degrees of Renal function

Table 12 and *Table 13* presented the predicted Day 5 nirmatrelvir exposure parameters and the percentage of simulated subjects achieving a C_{min} at Day 1 and Day 5 for paediatric subjects aged 6 to 18 years and weighing ≥40 kg.

Table 12: Predicted Day 5 Nirmatrelvir exposure parameters for simulated adult and paediatric subjects with COVID-19 and various renal function following proposed BID dosing Paxlovid for 5 days

Renal Function	Age Group	Nirmatrelvir Dose[a] & Frequency	AUC_{24} (ng·h/mL) Geometric mean	AUC_{24} (ng·h/mL) Percentile 10^{th}	AUC_{24} (ng·h/mL) Percentile 90^{th}	C_{max} (ng/mL) Geometric mean	C_{max} (ng/mL) Percentile 10^{th}	C_{max} (ng/mL) Percentile 90^{th}	C_{min} (ng/mL) Geometric mean	C_{min} (ng/mL) Percentile 10^{th}	C_{min} (ng/mL) Percentile 90^{th}
Normal	Adult	300 mg BID	55477	20115	147973	3222	1491	6973	1361	282	5290
Normal	6 to <12 years	300 mg BID	79204	29233	204631	4406	2080	9519	2103	465	7446
	12 to <18 years	300 mg BID	68055	25202	178698	3842	1818	8380	1760	396	6447
Mild	6 to <12 years	300 mg BID	84933	30478	219464	4655	2174	10041	2311	522	8042
	12 to <18 years	300 mg BID	75923	27709	195477	4175	1955	9010	2061	493	7052
Moderate	6 to <12 years	150 mg BID	78724	30897	187031	4031	1886	8391	2407	720	6923
	12 to <18 years	150 mg BID	69519	26001	164864	3577	1676	7396	2111	595	6121
Severe	6 to <12 years	300 mg on Day 1 follow by 150 mg QD on Days 2-5	62020	25907	133659	3399	1807	6256	1679	499	4481
	12 to <18 years	300 mg on Day 1 follow by 150 mg QD on Days 2-5	55316	22980	118511	3044	1589	5657	1484	443	3953

Table 13: Predicted Day 1 and Day 5 C_{min} and percentage of simulated adult and paediatric subjects with COVID-19 and various renal function achieving C_{min} above in vitro EC90 of 292 ng/mL following proposed BID dosing Paxlovid for 5 days.

Renal Function	Age Group	Nirmatrelvir Dose[a] & Frequency	Dose Number	C_{min} (ng/mL) Median	10^{th} percentile	90^{th} percentile	Ratio of Median to Adult	% Subjects Achieved $C_{min} \geq EC_{90}$
Normal	Adult	300 mg BID	1st (Day 1)	797	228	1545	-	86.4
			10th (Day 5)	1726	282	5290	-	89.5
Normal	6 to <12 years	300 mg BID	1st (Day 1)	1110	358	1991	1.39	92.0
			10th (Day 5)	2581	465	7446	1.49	94.1
	12 to <18 years	300 mg BID	1st (Day 1)	949	302	1785	1.19	90.4
			10th (Day 5)	2085	396	6447	1.21	92.9
Mild	6 to <12 years	300 mg BID	1st (Day 1)	1158	392	2080	1.45	93.7
			10th (Day 5)	2881	522	8042	1.67	94.6
	12 to <18 years	300 mg BID	1st (Day 1)	1033	364	1915	1.30	92.5
			10th (Day 5)	2510	493	7052	1.45	94.0
Moderate	6 to <12 years	150 mg BID	1st (Day 1)	952	426	1597	1.19	94.5
			10th (Day 5)	2830	720	6923	1.64	96.2
	12 to <18 years	150 mg BID	1st (Day 1)	849	367	1443	1.07	93.1
			10th (Day 5)	2495	595	6121	1.45	95.7
Severe	6 to <12 years	300 mg on Day 1 follow by 150 mg QD on Days 2-5	1st (Day 1)	1261	496	2135	1.58	95.3
			5th (Day 5)	2056	499	4481	1.19	94.6
	12 to <18 years	300 mg on Day 1 follow by 150 mg QD on Days 2-5	1st (Day 1)	1112	445	1944	1.39	94.4
			5th (Day 5)	1841	443	3953	1.07	93.4

Renal Function	Age Group	Nirmatrelvir Dose[a] & Frequency	Dose Number	C_{min} (ng/mL) Median	10^{th} percentile	90^{th} percentile	Ratio of Median to Adult	% Subjects Achieved $C_{min} \geq EC_{90}$
Normal	Adult	300 mg BID	1st (Day 1)	797	228	1545	-	86.4
			10th (Day 5)	1726	282	5290	-	89.5
Normal	6 to <18 years	300 mg BID	1st (Day 1)	1027	328	1897	1.29	91.2
			10th (Day 5)	2326	429	6976	1.35	93.5
Mild	6 to <18 years	300 mg BID	1st (Day 1)	1095	377	2002	1.37	93.1
			10th (Day 5)	2699	509	7480	1.56	94.3
Moderate	6 to <18 years	150 mg BID	1st (Day 1)	896	391	1525	1.12	93.8
			10th (Day 5)	2666	652	6542	1.54	96.0
Severe	6 to <18 years	300 mg on Day 1 follow by 150 mg QD on Days 2-5	1st (Day 1)	1182	474	2044	1.48	94.8
			5th (Day 5)	1946	462	4245	1.13	94.0

2.4.4. Conclusions on clinical pharmacology

The PK of nirmatrelvir could not be considered as characterised in children aged 6-<18 years and weighing ≥ 20 kg. From the initial PIP, more than 90% of the planned PK data had been removed due to a bio analysis issue and approximately half of the children planned to be enrolled had been recruited. This was considered as a major concern. To address the paucity of the PK data in children, the MAH was reported to have used a model-based approach to support the selected dose in children. However, the approach was not considered acceptable. These concerns were both resolved by developing and validating new PopPK models with the available data, and by committing to collect additional paediatric PK data for full CHMP acceptance.

Furthermore, it was highlighted that without a clear definition of the observed adult reference target and the absence of reliable PK parameter exposures that matched the adult target in children aged 6 to < 18 years and weighing ≥ 20 kg, for future type II variation, any dosing recommendations in subjects

aged < 6 years appeared to be compromised.

From a pharmacodynamic point of view, the MAH supported the antiviral effect of nirmatrelvir/ritonavir in paediatric participants (≥ 6 to <18 years of age and weighing at least 20 kg) with COVID-19 who were at risk of progression to severe disease with results from Study 1026 regarding secondary and exploratory efficacy endpoints. Comparison of efficacy results for secondary and tertiary efficacy endpoints from pivotal Study 1026 (paediatric participants) and relevant efficacy endpoints from Studies 1005 and 1002 (adult participants) were provided and established a correlation on reduction of viral RNA concentration observed from baseline through end of treatment (Day 5).

From a PK/PD standpoint, there is no direct data to establish this correlation, instead PK simulations were performed and the MAH argued that the proposed regimens would achieve similar exposure to adults taking 300 mg nirmatrelvir with 100 mg ritonavir twice daily for 5 days, ensuring >90% of paediatric patients reach a C_{min} ≥ EC90 of 292 ng/mL after the first dose and throughout the 5-day period. However, the PK similarity at the selected dose in the paediatric, needed to be demonstrated. The issue was resolved for children ≥6 years and ≥20 kg by developing and validating new PopPK models, and committing to collect more paediatric PK data. For children <6 years, dosing recommendations are still not supported until further data are generated.

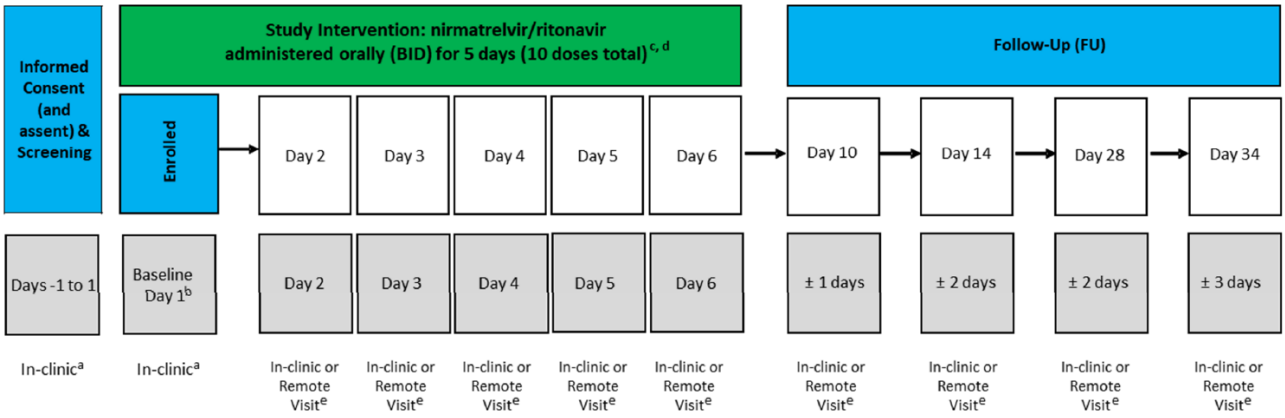
2.5. Clinical efficacy

2.5.1. Main study

Study C4671026: A Phase 2/3, Interventional Safety, Pharmacokinetics, and Efficacy, Open-Label, Multi-Center, Single-Arm Study to Investigate Orally Administered PF-07321332 (Nirmatrelvir)/Ritonavir in Nonhospitalized Symptomatic Paediatric Participants With COVID-19 Who Are at Risk of Progression to Severe Disease

Methods

Study design



a. The Screening (up to 48 hours) and Baseline Visits should be conducted at the site.
b. At the Baseline/Day 1 Visit, Tasso device will be provided to participant/parent and training will be given, as appropriate, for PK sample collection.
c. Nirmatrelvir/ritonavir dosage will be assigned based on age and weight.
d. Study intervention is a total of 10 doses. If only 1 dose was administered on Day 1, study intervention administration should end on Day 6.
e. For participants in Bulgaria and South Africa, all study visits must be conducted at the site location.

Study 1026 is a Phase 2/3, interventional, open-label, multi-center, single-arm study designed to investigate safety, pharmacokinetics and efficacy of orally administered nirmatrelvir/ritonavir in nonhospitalised symptomatic paediatric participants with COVID-19 who are at risk of progression to severe disease. Participants are being enrolled into 5 cohorts in a tiered scheme based on age and/or weight.

- Cohort 1: Weight ≥40 kg, (a) ≥12 to < 18 years or (b) ≥6 to <12 years

- Cohort 2: Weight ≥20 to <40 kg, ≥6 to 18 years

- Cohort 3: ≥2 to <6 years

- Cohort 4: ≥1 month (≥28 days) to <2 years

- Cohort 5: <1 month (<28 days) old

Results in this paediatric extension procedure are for 75 participants in Cohort 1 and Cohort 2 who were enrolled in the study and received treatment (data cutoff 07 Jun 2024). Enrolment into Cohorts 3 through 5 has not yet been initiated.

Study participants

Eligible participants were children:

- with a confirmed SARS-CoV-2 infection as determined by RT-PCR or another method of diagnosis approved by a health authority in any specimen collected within 72 hours prior to enrolment and initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of enrolment and at least 1 of the specified signs/symptoms attributable to COVID-19 present on the day of enrolment;

- having at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 including:

    - Overweight or Obese (BMI [kg/m2] ≥85th percentile for age and gender based on CDC growth charts, see Appendix 8)
        - For children <2 years of age, sex specific weight-for-length;
    - Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes;
    - Immunosuppressive disease (eg, bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications:
        - Has received corticosteroids at a dose known to cause immune suppression, based on the clinical judgement of the investigator, for at least 14 days, within 30 days prior to study entry
        - Has received treatment with biologics (eg, infliximab, ustekinumab), immunomodulators (eg, methotrexate, 6MP, azathioprine) or cancer chemotherapy within 90 days prior to study entry
        - HIV infection with CD4 cell count <200 mm3 and a viral load lower than 400 copies/mL;
    - Chronic lung disease
        - If asthma, requires daily prescribed therapy;
    - Known diagnosis of hypertension;

- Cardiovascular disease;
- Type 1 or Type 2 diabetes mellitus;
- Chronic kidney disease defined as eGFR between 45 to 89 mL/min/1.73m2 or eCrCl between 45 to 89 mL/min;
- Sickle cell disease;
- Neurodevelopmental disorders (eg, cerebral palsy, Down's syndrome, ADHD, intellectual and developmental disabilities, learning disabilities, limitations with self-care of activities of daily living) or other conditions that confer medical complexity (eg, genetic or metabolic syndromes and severe congenital anomalies, congenital malformations);
- Active cancer, other than localised skin cancer, including those requiring treatment as long as the treatment is not among the prohibited medications that must be administered/continued during the trial period;
- Infants (<1 year of age);
- Spinal cord injury

- with ability to swallow tablets confirmed by participants' parent(s)/legal guardian(s) for Cohorts 1 and 2 using the presentation of nirmatrelvir/ritonavir supplied in the study.

Participants are excluded from the study notably in case of:

- History of hospitalisation for the medical treatment of current COVID-19 infection;

- Current need for hospitalisation or anticipated need for hospitalisation for the treatment of COVID-19 within 48 hours after enrolment in the clinical opinion of the site investigator;

- Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere with the evaluation of response to the study intervention;

- Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behaviour or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study;

- Known medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child Pugh Class B or C or acute liver failure;

- Current or expected use of any prohibited medication, including notably monoclonal antibody treatment, antiviral treatment (eg, molnupiravir) or convalescent COVID-19 plasma for treatment of COVID-19;

- Total bilirubin ≥2 X ULN (except for Gilbert's syndrome) within past 6 months of the screening visit;

- Dialysis or known moderate to severe renal impairment ie, eGFR <45 mL/min/1.73 m2 or eCrCl <45 mL/min) within 6 months of the screening visit;

- Pregnancy or breastfeeding.

Treatments

Based on PK modelling and simulation, participants receive initially nirmatrelvir/ritonavir orally q12h for 5 days (10 doses total) at a dose defined by age and weight range:

- Cohort 1 (6 to less than 18 years of age and weighing at least 40 kg): nirmatrelvir/ritonavir 300 mg/100 mg q12h. Of note, after a complementary PK analysis, additional subjects from Cohort 1 had received nirmatrelvir/ritonavir 150 mg/100 mg q12h.

- Cohort 2 (6 to less than 18 years of age and weighing 20 to less than 40 kg): nirmatrelvir/ritonavir 150 mg/100 mg q12h.

Participants may take nirmatrelvir/ritonavir with or without food.

Objectives

Primary objectives are:

- To determine the PK of nirmatrelvir/ritonavir in paediatric participants from birth to <18 years of age, using modelling and simulation approaches, in order to identify the appropriate dose for each paediatric age group that achieved systemic exposures comparable to adults.

- To describe the safety and tolerability of nirmatrelvir/ritonavir in the treatment of nonhospitalised symptomatic paediatric participants with COVID-19 who were at risk of progression to severe disease.

Efficacy assessments are secondary and tertiary objectives.

Outcomes/endpoints

Endpoint	Analysis Type	Analysis Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Primary:				
PK parameters including C_{max} and $AUC_{0\text{-}tau}$ (and if the data permitted $t_{1/2}$, C_{trough}) of nirmatrelvir and ritonavir. In adolescents (≥12 years to <18 years of age), robust PK sampling was performed. A sparser approach was incorporated for younger participants as PK samples were more difficult to obtain.	Primary analysis	PK concentration population and PK parameters population	All data collected were included regardless of intercurrent events. Missing data were not imputed.	Descriptive statistics

Endpoint	Analysis Type	Analysis Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Incidence of TEAEs, SAEs, AEs leading to discontinuations, and vital sign measurements	Primary analysis	Safety population	All data were included regardless of intercurrent events. Missing and partial data were handled according to Pfizer standards.	Summary
Secondary:				
SARS-CoV-2 viral RNA measured via RT-PCR in nasopharyngeal or nasal swabs over time (change from Baseline to Day 5).	Secondary analysis	Safety population	All data collected were included regardless of intercurrent events. Used cohort dose groups, baseline viral RNA concentration (continuous) and nasopharyngeal (yes, no).	ANCOVA analysis
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	Secondary analysis	Safety population	All data were included regardless of intercurrent events. Kaplan-Meier method to take account of losses to follow-up.	Kaplan-Meier method
Exploratory:				
Post-treatment increases in SARS-CoV-2 RNA shedding levels (ie, viral RNA rebound) in nasopharyngeal or nasal.	Exploratory analysis	Safety population	All data collected were included regardless of intercurrent events. Missing data were not imputed.	Descriptive statistics
SARS-CoV-2 viral RNA measured via RT-PCR in nasopharyngeal or nasal swabs over time (change from Baseline to Day 6).	Exploratory analysis	Safety population	All data collected were included regardless of intercurrent events. Used cohort dose groups, baseline viral RNA concentration (continuous) and nasopharyngeal (yes, no).	ANCOVA analysis
Duration of all targeted COVID-19 signs/symptoms through Day 28.	Exploratory analysis	Safety population	All data collected were included regardless of intercurrent events. Missing data were not imputed.	Kaplan-Meier method
Duration of each targeted COVID-19 sign/symptom through Day 28.	Exploratory analysis	Safety population	All data collected were included regardless of intercurrent events. Missing data were not imputed.	Kaplan-Meier method
Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28.	Exploratory analysis	Safety population	All data collected were included regardless of intercurrent events. Missing data were not imputed.	Descriptive statistics

Sample size

The study sample size was determined to comply with requests from Health Authorities, and to obtain point estimates (with variability measure) for the levels of PK parameters, safety data, and viral load level in children from birth to <18 years of age. For viral load, since the variability as well as the

clinical relevance of change in viral load are not well understood in the paediatric population, data from adult population in study C4671005 are utilised. In study C4671005, the standard deviation of change from baseline in viral load is approximately 1.8 log10 (copies/mL). Assuming the standard deviation in viral load among the paediatric participants is also 1.8 log10 (copies/mL), in an age group with 50 participants or more, the half-length of the 2-sided 95% CI for the group is expected to be 0.5 log10 (copies/mL) or less. A total of 100 participants in Cohort 1 and 2 will limit the half-length of the 2-sided 95% CI for the group mean to approximately 0.35 log10 (copies/mL). To support dosing in children younger than 6 years of age, 42 participants as young as less than 1 month old will also be included. All endpoints will be summarised using descriptive statistics.

Planned sample size by age cohort:

- Cohort 1: Weight ≥40 kg, 70 participants*
    a. ≥12 to <18 years
    b. ≥6 to <12 years
- Cohort 2: Weight ≥20 to <40 kg, 6 to <18 years, 50 participants*
- Cohort 3: ≥2 to <6 years, 20 participants
- Cohort 4: ≥1 month (≥28 days) to <2 years, 20 participants
- Cohort 5: <1 month (<28 days) old no minimum, approximately 2 participants

**Minimum of 5 paediatric participants per 2-year age groups (ie, 6 to 7 years, 8 to 9 years, 10 to 11 years, 12 to 13 years, 14 to 15 years, and 16 to <18 years) for Cohorts 1 and 2 combined.*

Cohort 1 planned enrolment was increased from 50 to 70 participants to enrol approximately 20 additional participants (approximately 10 participants in each Cohort 1a and Cohort 1b) to evaluate nirmatrelvir/ritonavir 150 mg/100 mg dose q12h for 5 days in Cohort 1 participants (≥6 to <18 years of age and weighing ≥40 kg).

Statistical methods

There was no statistical hypotheses tested. Two-sided 95% CI of relevant endpoints was provided.

Estimand PK1: The primary PK estimand will be the geometric mean of the derived and/or population predicted PK parameters C_{max} and $AUC_{0\text{-}tau}$ (and if the data permit, $t_{1/2}$, C_{trough}) for nirmatrelvir/ritonavir in paediatric participants from birth to <18 years of age.

Estimand S1: A treatment-policy estimand strategy will be used in non-hospitalised, symptomatic, paediatric participants with COVID-19 who are at risk of progression to severe disease to estimate the safety of nirmatrelvir/ritonavir in terms of the proportion of participants with TEAEs. Estimand S1 will be the estimand for other AE endpoints (SAE and AEs leading to discontinuation).

Results

Participant flow

As of the data cutoff (07 Jun 2024), 82 participants were screened for entry into the study (Cohort 1 and Cohort 2). A total of 77 participants were assigned to study intervention and were included in the FAS. Of these, 75 participants (61 participants in Cohort 1 and 14 participants in Cohort 2) received at

least 1 dose of study intervention and comprised the SAS. In total, 4/77 (5.2%) participants in the FAS did not complete the treatment phase of the study:

- Two of the participants did not receive study intervention: 1 participant was withdrawn by parent/guardian and 1 participant was randomised in error.

- Two of the participants received study intervention but discontinued study intervention early: 1 participant due to a non-serious AE (Viral infection) and 1 participant (on Day 3) due to inability to swallow tablets.

Table 6. Participant Evaluation Groups - All Screened Participants (Protocol C4671026)

	Cohort 1a 150mg (N=9) n (%)	Cohort 1a 300mg (N=39) n (%)	Cohort 1b 300mg (N=13) n (%)	Cohort 1 (N=61) n (%)	Cohort 2 150mg (N=16) n (%)	Total (N=77) n (%)
Screened: 82 Screened Failure: 5 Not Screen Failure but not Randomized: 0						
Assigned to Treatment	9 (100.0)	39 (100.0)	13 (100.0)	61 (100.0)	16 (100.0)	77 (100.0)
Treated	9 (100.0)	39 (100.0)	13 (100.0)	61 (100.0)	14 (87.5)	75 (97.4)
Not Treated	0	0	0	0	2 (12.5)	2 (2.6)
Safety analysis set	9 (100.0)	39 (100.0)	13 (100.0)	61 (100.0)	14 (87.5)	75 (97.4)
Full analysis set	9 (100.0)	39 (100.0)	13 (100.0)	61 (100.0)	16 (100.0)	77 (100.0)
PK concentration analysis set	9 (100.0)	38 (97.4)	13 (100.0)	60 (98.4)	13 (81.3)	73 (94.8)
PK parameter analysis set	8 (88.9)	37 (94.9)	12 (92.3)	57 (93.4)	11 (68.8)	68 (88.3)

Cohort 1a: ≥ 40 kg, ≥ 12 to < 18 years, Cohort 1b: ≥ 40 kg, ≥ 6 to < 12 years, Cohort 2: ≥ 20 to < 40 kg, ≥ 6 to < 18 years.
PFIZER CONFIDENTIAL SDTM Creation: 11JUN2024 (16:29) Source Data: adsl Table Generation: 18JUN2024 (09:03)
(Database snapshot date : 07JUN2024) Output File: ./nda_ph23/C4671026_sNDA/adsl_s002
Table 14.1.1.1 Nirmatrelvir/ritonavir is for Pfizer internal use.

Table 5. Disposition Events Summary - Full Analysis Set (Protocol C4671026)

Number (%) of Participants	Cohort 1a 150mg (N=9) n (%)	Cohort 1a 300mg (N=39) n (%)	Cohort 1b 300mg (N=13) n (%)	Cohort 1 (N=61) n (%)	Cohort 2 150mg (N=16) n (%)	Total (N=77) n (%)
Disposition phase: Treatment						
Participants Entered:	9 (100.0)	39 (100.0)	13 (100.0)	61 (100.0)	16 (100.0)	77 (100.0)
Discontinued	0	0	0	0	4 (25.0)	4 (5.2)
Reason for discontinuation						
Adverse event	0	0	0	0	1 (6.3)	1 (1.3)
Death	0	0	0	0	0	0
Lack of efficacy	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0
Non-compliance with study drug	0	0	0	0	0	0
Pregnancy	0	0	0	0	0	0
Protocol deviation	0	0	0	0	0	0
Study terminated by sponsor	0	0	0	0	0	0
Withdrawal by participant	0	0	0	0	0	0
Medication error without associated adverse event	0	0	0	0	0	0
No longer meets eligibility criteria	0	0	0	0	0	0
Withdrawal by parent/guardian	0	0	0	0	1 (6.3)	1 (1.3)
Other	0	0	0	0	2 (12.5)	2 (2.6)
Completed	9 (100.0)	39 (100.0)	13 (100.0)	61 (100.0)	12 (75.0)	73 (94.8)
Ongoing	0	0	0	0	0	0
Disposition phase: Follow-up						
Participants Entered:	9 (100.0)	39 (100.0)	13 (100.0)	61 (100.0)	16 (100.0)	77 (100.0)
Discontinued	0	0	0	0	2 (12.5)	2 (2.6)
Reason for discontinuation						
Adverse event	0	0	0	0	0	0
Death	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0
Study terminated by sponsor	0	0	0	0	0	0
Withdrawal by participant	0	0	0	0	0	0
Withdrawal by parent/guardian	0	0	0	0	1 (6.3)	1 (1.3)
Other	0	0	0	0	1 (6.3)	1 (1.3)
Completed	9 (100.0)	39 (100.0)	13 (100.0)	61 (100.0)	14 (87.5)	75 (97.4)
Ongoing	0	0	0	0	0	0

Disposition phase: Treatment reflects status (discontinued, completed, ongoing) of study intervention and reasons for discontinuation of study intervention.
Cohort 1a: ≥ 40 kg, ≥ 12 to < 18 years, Cohort 1b: ≥ 40 kg, ≥ 6 to < 12 years, Cohort 2: ≥ 20 to < 40 kg, ≥ 6 to < 18 years.
PFIZER CONFIDENTIAL SDTM Creation: 11JUN2024 (16:29) Source Data: adds Table Generation: 18JUN2024 (09:03) (Database snapshot date : 07JUN2024) Output File: ./nda ph23/C4671026 sNDA/adds s001
Table 14.1.1.2 Nirmatrelvir/ritonavir is for Pfizer internal use.

Conduct of the study

Important Protocol Deviations (IPD)

There were 72 (93.5%) participants with IPDs.

Table 7. Summary of Important Protocol Deviations - Full Analysis Set (Protocol C4671026)

Protocol Deviation Category/Subcategory	Cohort 1a 150mg (N=9) n (%)	Cohort 1a 300mg (N=39) n (%)	Cohort 1b 300mg (N=13) n (%)	Cohort 1 (N=61) n (%)	Cohort 2 150mg (N=16) n (%)	Total (N=77) n (%)
Participants with any protocol deviation	9(100.0)	36(92.3)	11(84.6)	56(91.8)	16(100.0)	72(93.5)
Concomitant Medications	0	0	1 (7.7)	1 (1.6)	1 (6.3)	2 (2.6)
Took prohibited concomitant medication/vaccine	0	0	1 (7.7)	1 (1.6)	1 (6.3)	2 (2.6)
Inclusion/Exclusion	0	0	0	0	1 (6.3)	1 (1.3)
Inc #1: Participant who is not the weight required per protocol for Cohorts 1 and 2.	0	0	0	0	1 (6.3)	1 (1.3)
Informed Consent	0	1 (2.6)	0	1 (1.6)	0	1 (1.3)
Participant/LAR did not sign the ICD but gave verbal consent	0	1 (2.6)	0	1 (1.6)	0	1 (1.3)
Investigational Product	2 (22.2)	6 (15.4)	1 (7.7)	9 (14.8)	4 (25.0)	13 (16.9)
Dosing/Administration error: Dose window was >+/-4 hours	2 (22.2)	3 (7.7)	1 (7.7)	6 (9.8)	0	6 (7.8)
Dosing/Administration error: Doses 1 and 2 were given < 4 hours apart	1 (11.1)	0	0	1 (1.6)	1 (6.3)	2 (2.6)
Dosing/Administration error: First dose not administered on day of randomization	0	2 (5.1)	0	2 (3.3)	2 (12.5)	4 (5.2)
Dosing/Administration error: compliance is <80%	0	1 (2.6)	0	1 (1.6)	0	1 (1.3)
Dosing/Administration error: compliance is >115%	0	2 (5.1)	0	2 (3.3)	1 (6.3)	3 (3.9)
Nirmatrelvir and ritonavir tablets were taken more than 15 minutes apart	0	0	0	0	1 (6.3)	1 (1.3)
Laboratory	9 (100.0)	34 (87.2)	11 (84.6)	54 (88.5)	15 (93.8)	69 (89.6)
Lab not Properly collected, stored or handled	3 (33.3)	28 (71.8)	8 (61.5)	39 (63.9)	8 (50.0)	47 (61.0)
Lab not done	0	0	2 (15.4)	2 (3.3)	4 (25.0)	6 (7.8)
NP/nasal swab not done	1 (11.1)	1 (2.6)	0	2 (3.3)	3 (18.8)	5 (6.5)
NP/nasal swab not properly collected, stored or handled	0	1 (2.6)	0	1 (1.6)	0	1 (1.3)
PK samples collected outside protocol defined window	2 (22.2)	18 (46.2)	9 (69.2)	29 (47.5)	7 (43.8)	36 (46.8)
PK samples not done	7 (77.8)	4 (10.3)	1 (7.7)	12 (19.7)	8 (50.0)	20 (26.0)
PK samples not properly collected, stored or handled	2 (22.2)	6 (15.4)	0	8 (13.1)	4 (25.0)	12 (15.6)
Procedures/Tests	2 (22.2)	3 (7.7)	1 (7.7)	6 (9.8)	2 (12.5)	8 (10.4)
Acceptability and palatability questionnaire not done	0	1 (2.6)	0	1 (1.6)	1 (6.3)	2 (2.6)
Pregnancy test not done	1 (11.1)	0	0	1 (1.6)	0	1 (1.3)
Targeted physical exam not done	1 (11.1)	1 (2.6)	1 (7.7)	3 (4.9)	1 (6.3)	4 (5.2)
Vital signs not done	1 (11.1)	1 (2.6)	1 (7.7)	3 (4.9)	1 (6.3)	4 (5.2)
Visit Schedule	1 (11.1)	1 (2.6)	0	2 (3.3)	1 (6.3)	3 (3.9)
Visit not done	1 (11.1)	0	0	1 (1.6)	1 (6.3)	2 (2.6)
Visit not performed per protocol	0	1 (2.6)	0	1 (1.6)	0	1 (1.3)

The most frequently reported IPDs occurred within the Laboratory category (69 [89.6%]), with the most frequently reported sub-categories being Lab not properly collected, stored or handled (47 [61.0%]) and PK samples collected outside protocol defined window (36 [46.8%]):

- IPDs reported with the "Lab not properly collected stored or handled" subcategory are related to Day 1 and Day 5 safety labs. Most IPDs in this subcategory represent laboratory samples that were collected by the site but were unable to be analysed by the central laboratory. Of the 47 participants with IPDs in this subcategory, 25 and 21 participants were enrolled at sites in the US and Mexico, respectively, and 1 participant was enrolled in South Africa. All the affected sites were retrained for sample collection, storage and handling instructions as per the study laboratory manual. Additionally, to mitigate future IPDs, all sites in Mexico were instructed to use a local laboratory for haematology samples after samples collected at a number of sites in Mexico were severely haemolysed and unable to be analysed by PPD.

- The majority of PK-related IPDs in the "PK samples collected outside protocol defined window" subcategory was for Tasso M20 or blood to plasma ratio samples, which were not included in the PK analysis. Plasma PK for all participants was analysed using actual time post-dose rather than nominal time post-dose so that there is no significant impact of having PK collections outside of window.

Within the Concomitant Medications category and "Took prohibited concomitant medication/vaccine" subcategory, 1 participant in Cohort 1b 300 mg and 1 participant in Cohort 2 received Tozinameran vaccination prior to Day 34, which is a prohibited concomitant medication/COVID-19 vaccine per protocol.

One participant in Cohort 2 had an IPD in the Inclusion/Exclusion category due to the participant's weight being outside of the eligibility criteria for Cohorts 1 and 2; this participant was randomised in error and was not dosed.

One participant in Cohort 1 did not sign Assent and the participant's LAR did not sign the ICD at Screening, however, they provided a verbal consent and later signed both the Assent and the ICD.

Protocol amendments

There were 3 protocol amendments:

Table 1. Global Substantial Modifications

Date of Protocol Amendment	Amendment
17 February 2022	Protocol Amendment 1 was created primarily to address comments received from the US FDA, offer protocol clarifications, and correct identified non-intended errors.
21 November 2022	Protocol Amendment 2 was created primarily to provide details for oral formulation and dosing in younger cohorts, incorporate changes from prior PACLs, provide clarifications, and correct errors.
06 April 2023	Protocol Amendment 3 was created primarily to enroll additional participants into Cohort 1 to evaluate nirmatrelvir/ritonavir at a lower dose. For Cohort 1 participants, 3 venous plasma PK samples time matched to Tasso PK sampling were added at the following timepoints: Day 5 pre-morning dose and 1- and 2-hours post-dose. Two of these venous samples were aliquoted into separate plasma and blood tubes to calculate blood-to-plasma ratio.

Two recruitment pauses occurred since the start of the study.

- The first pause occurred on 13 Jan 2023. Study enrolment was paused in order to conduct PK analysis. Based on Tasso M20 PK data available at the time, which has since been excluded based on discordance, observed exposures (AUC, C_{max}, and C_{trough}) in Cohort 1 (300 mg/100 mg dose) were approximately 2-fold higher than adult exposures predicted by a PopPK model. Thus, the study reopened on 06 Apr 2023 under Protocol Amendment 3 to enrol approximately 20 additional participants in Cohort 1 (10 participants in Cohort 1a and 10 participants in Cohort 1b) who were planned to be administered a lower nirmatrelvir/ritonavir dose of 150 mg/100 mg.

- The second pause occurred on 12 Jan 2024, and the study is still paused as of the data cutoff of 07 Jun 2024. Study enrolment was paused to conduct PK analysis and modelling of available data of Cohort 1a (150 mg/100 mg dose) participants and to evaluate the PK data collected from the Tasso M20 device. In this evaluation, Tasso M20 PK samples collected from Cohort 1a participants were not concordant with venous plasma PK samples collected at approximately the same time. As a result of this Tasso M20 discordance, all Tasso M20 PK samples collected in this study were excluded from PK analysis.

Inspections

No inspection was performed.

Baseline data

A total of 77 participants were randomised. Of these, 75 participants received at least 1 dose of nirmatrelvir/ritonavir: 61 participants in Cohort 1 (6 to less than 18 years of age and weighing at least 40 kg) and 14 participants in Cohort 2 (6 to less than 18 years of age and weighing 20 to less than 40 kg).

At baseline, mean (SD) age was 12.39 (3.40) years; 53.2% were female; 57.1% were White, 20.8% were Black or African American, and 11.7% were American Indian or Alaska Native; 61% were Hispanic or Latino. Median (range) weight (kg) was 54.65 (20.3, 200). 54.5% participants were not vaccinated. The most frequently reported conditions in at least 25% of participants in either cohort present at the start of the study were obesity (37 [49.3%] participants overall) and chronic respiratory disease (30 [40.0%] participants overall). The mean (SD) baseline viral load across all cohorts was 5.52 (2.36) log10 copies/mL.

Table 8. Demographic and Baseline Characteristics - Full Analysis Set (Protocol C4671026)

	Cohort 1a 150mg (N=9)	Cohort 1a 300mg (N=39)	Cohort 1b 300mg (N=13)	Cohort 1 (N=61)	Cohort 2 150mg (N=16)	Total (N=77)
Age, n (%)						
≥ 6 to < 12 years	0	0	13 (100.0)	13 (21.3)	14 (87.5)	27 (35.1)
≥ 12 to < 18 years	9 (100.0)	39 (100.0)	0	48 (78.7)	2 (12.5)	50 (64.9)
Mean (SD)	15.67 (1.22)	14.26 (1.98)	9.85 (1.21)	13.52 (2.64)	8.06 (2.35)	12.39 (3.40)
Median (range)	16.00 (14.0, 17.0)	14.00 (12.0, 17.0)	10.00 (8.0, 11.0)	13.00 (8.0, 17.0)	7.00 (6.0, 14.0)	13.00 (6.0, 17.0)
Gender, n (%)						
Male	5 (55.6)	17 (43.6)	7 (53.8)	29 (47.5)	7 (43.8)	36 (46.8)
Female	4 (44.4)	22 (56.4)	6 (46.2)	32 (52.5)	9 (56.3)	41 (53.2)
Race, n (%)						
White	5 (55.6)	19 (48.7)	9 (69.2)	33 (54.1)	11 (68.8)	44 (57.1)
Black or African American	2 (22.2)	10 (25.6)	1 (7.7)	13 (21.3)	3 (18.8)	16 (20.8)
Asian	1 (11.1)	1 (2.6)	0	2 (3.3)	1 (6.3)	3 (3.9)
American Indian or Alaska Native	0	7 (17.9)	2 (15.4)	9 (14.8)	0	9 (11.7)
Not reported	1 (11.1)	2 (5.1)	0	3 (4.9)	0	3 (3.9)
Unknown	0	0	1 (7.7)	1 (1.6)	1 (6.3)	2 (2.6)
Ethnicity, n (%)						
Hispanic or Latino	5 (55.6)	24 (61.5)	9 (69.2)	38 (62.3)	9 (56.3)	47 (61.0)
Not Hispanic or Latino	3 (33.3)	15 (38.5)	4 (30.8)	22 (36.1)	7 (43.8)	29 (37.7)
Not reported	1 (11.1)	0	0	1 (1.6)	0	1 (1.3)
Weight (kg)						
Mean (SD)	76.39 (23.37)	69.65 (28.30)	48.12 (6.98)	66.06 (26.15)	29.03 (5.59)	58.75 (27.80)
Median (range)	75.00 (45.5, 113.0)	68.30 (40.4, 200.0)	46.70 (40.0, 63.3)	62.50 (40.0, 200.0)	28.70 (20.3, 39.4)	54.65 (20.3, 200.0)

	Cohort 1a 150mg (N=9)	Cohort 1a 300mg (N=39)	Cohort 1b 300mg (N=13)	Cohort 1 (N=61)	Cohort 2 150mg (N=16)	Total (N=77)
Height (cm)						
Mean (SD)	169.4 (12.02)	161.1 (7.89)	143.6 (9.34)	158.6 (12.11)	128.3 (9.53)	152.6 (16.78)
Median (range)	168.0 (152.4, 188.0)	160.2 (147.5, 177.0)	140.0 (130.8, 157.0)	158.0 (130.8, 188.0)	129.0 (109.0, 143.0)	154.7 (109.0, 188.0)
BMI (kg/m^2)						
Mean (SD)	26.37 (6.84)	26.70 (10.35)	23.32 (2.40)	25.93 (8.78)	17.59 (2.57)	24.28 (8.61)
Median (range)	25.10 (17.1, 38.1)	24.60 (16.2, 76.2)	22.80 (19.8, 27.4)	24.50 (16.2, 76.2)	17.50 (13.6, 23.7)	22.65 (13.6, 76.2)
Vaccination status, n (%)						
Complete	4 (44.4)	13 (33.3)	4 (30.8)	21 (34.4)	6 (37.5)	27 (35.1)
Partial	2 (22.2)	5 (12.8)	0	7 (11.5)	1 (6.3)	8 (10.4)
Not vaccinated	3 (33.3)	21 (53.8)	9 (69.2)	33 (54.1)	9 (56.3)	42 (54.5)
Duration since first diagnosis (Days)						
Mean (SD)	1.56 (1.01)	1.31 (1.15)	1.23 (0.93)	1.33 (1.08)	0.67 (0.90)	1.20 (1.07)
Median (range)	1.00 (0.0, 3.0)	1.00 (0.0, 4.0)	2.00 (0.0, 2.0)	1.00 (0.0, 4.0)	0.00 (0.0, 3.0)	1.00 (0.0, 4.0)
Number of risk factors of interest, n (%)						
0	0	0	0	0	1 (6.3)	1 (1.3)
1	7 (77.8)	32 (82.1)	12 (92.3)	51 (83.6)	11 (68.8)	62 (80.5)
2	2 (22.2)	4 (10.3)	1 (7.7)	7 (11.5)	3 (18.8)	10 (13.0)
3	0	3 (7.7)	0	3 (4.9)	1 (6.3)	4 (5.2)
Comorbidities, n (%)						
Cancer	1 (11.1)	2 (5.1)	0	3 (4.9)	1 (6.3)	4 (5.2)
Cardiovascular disorder	0	1 (2.6)	0	1 (1.6)	1 (6.3)	2 (2.6)
Chronic kidney disease	0	1 (2.6)	0	1 (1.6)	0	1 (1.3)
Chronic lung disease	2 (22.2)	16 (41.0)	5 (38.5)	23 (37.7)	8 (50.0)	31 (40.3)
Cigarette smoker	1 (11.1)	0	0	1 (1.6)	1 (6.3)	2 (2.6)
Diabetes mellitus	0	3 (7.7)	0	3 (4.9)	0	3 (3.9)
Hypertension	1 (11.1)	1 (2.6)	0	2 (3.3)	0	2 (2.6)
Immunosuppression	1 (11.1)	2 (5.1)	1 (7.7)	4 (6.6)	1 (6.3)	5 (6.5)
Neurodevelopmental disorder	0	2 (5.1)	0	2 (3.3)	2 (12.5)	4 (5.2)
Obesity	5 (55.6)	20 (51.3)	8 (61.5)	33 (54.1)	4 (25.0)	37 (48.1)
Sickle cell disease	0	1 (2.6)	0	1 (1.6)	2 (12.5)	3 (3.9)
Geographic region, n (%)						
United States	8 (88.9)	21 (53.8)	6 (46.2)	35 (57.4)	9 (56.3)	44 (57.1)
Europe	0	1 (2.6)	0	1 (1.6)	1 (6.3)	2 (2.6)
Rest of World	1 (11.1)	17 (43.6)	7 (53.8)	25 (41.0)	6 (37.5)	31 (40.3)
Viral load (Log_{10} copies/mL)						
Mean (SD)	5.39 (1.85)	5.76 (2.41)	5.84 (1.92)	5.72 (2.21)	4.66 (2.85)	5.52 (2.36)
Median (range)	4.88 (1.7, 8.1)	6.55 (0.0, 8.6)	6.32 (0.0, 7.7)	6.32 (0.0, 8.6)	5.45 (0.0, 7.5)	6.28 (0.0, 8.6)

Prior medications were reported for 54 (88.5%) participants in Cohort 1 and 10 (71.4%) participants in Cohort 2. The most commonly reported (≥20% participants overall) prior medications were:

- Tozinameran (COVID-19 vaccine) (26 [42.6%] participants in Cohort 1 and 5 [35.7%] participants in Cohort 2)

- Ibuprofen (22 [36.1%] participants in Cohort 1 and 6 [42.9%] participants in Cohort 2)

- Paracetamol (16 [26.2%] participants in Cohort 1 and 4 [28.6%] participants in Cohort 2)

- Salbutamol (15 [24.6%] participants in Cohort 1 and 4 [28.6%] participants in Cohort 2)

Concomitant medications during the study were reported for 50 (82.0%) participants in Cohort 1 and 11 (78.6%) participants in Cohort 2. The most commonly reported concomitant medications (≥20% participants overall) were:

- Ibuprofen (22 [36.1%] participants in Cohort 1 and 4 [28.6%] participants in Cohort 2)

- Salbutamol (15 [24.6%] participants in Cohort 1 and 4 [28.6%] participants in Cohort 2)

- Paracetamol (15 [24.6%] participants in Cohort 1 and 2 [14.3%] participants in Cohort 2)

Numbers analysed

A total of 77 participants were assigned to study intervention. Of these, 75 participants (61 participants in Cohort 1 and 14 participants in Cohort 2) received at least 1 dose of study intervention and comprised the SAS. Two of the participants did not receive study intervention (1 participant was withdrawn by parent/guardian and 1 participant was randomised in error).

Table 9. Duration of Treatment (Study) - Safety Analysis Set (Protocol C4671026)

	Cohort 1a 150mg (N=9)	Cohort 1a 300mg (N=39)	Cohort 1b 300mg (N=13)	Cohort 1 (N=61)	Cohort 2 150mg (N=14)	Total (N=75)
Duration of Treatment (Days)[a]						
n	9	39	13	61	14	75
Mean (SD)	5.33 (0.50)	5.21 (0.41)	5.31 (0.48)	5.25 (0.43)	5.07 (0.73)	5.21 (0.50)
Median (range)	5.00 (5.00, 6.00)	5.00 (5.00, 6.00)	5.00 (5.00, 6.00)	5.00 (5.00, 6.00)	5.00 (3.00, 6.00)	5.00 (3.00, 6.00)
Category (Days)[a]						
1	0	0	0	0	0	0
2	0	0	0	0	0	0
3	0	0	0	0	1 (7.1)	1 (1.3)
4	0	0	0	0	0	0
5	6 (66.7)	31 (79.5)	9 (69.2)	46 (75.4)	10 (71.4)	56 (74.7)
> 5	3 (33.3)	8 (20.5)	4 (30.8)	15 (24.6)	3 (21.4)	18 (24.0)

a. The total number of days from first to and including last day of each study treatment (ADSL.TRTEDT - ADSL.TRTSDT + 1).
Cohort 1a: ≥ 40 kg, ≥ 12 to < 18 years, Cohort 1b: ≥ 40 kg, ≥ 6 to < 12 years, Cohort 2: ≥ 20 to < 40 kg, ≥ 6 to < 18 years.

Participants self-administered or parents/guardians assisted with administration of study intervention at home and compliance was assessed at each visit. Compliance was also assessed by site personnel upon return of study intervention through counting returned tablets and direct questioning, if applicable.

In total, 93.3% participants received ≥80% to ≤115% of the expected nirmatrelvir dosing regimen (Table 10). Two participants were in the <80% compliance category: one took 6 doses of nirmatrelvir instead of 10 doses (1 dose of study treatment respectively on Days 1, 2, 3 and 5) which was considered a Dosing/Medication error and reported as IPD; another participant took 5 doses of nirmatrelvir instead of 10 doses as this participant discontinued from study intervention after Day 3 because of inability to swallow tablets; the participant was compliant with treatment dosing until discontinuation of treatment on Day 3. Three participants who were in the >115% compliance category

took 12 doses of nirmatrelvir instead of 10 doses which was considered a Dosing/Medication error and reported as IPDs.

Table 10. Summary of Compliance of Nirmatrelvir - Safety Analysis Set (Protocol C4671026)

	Cohort 1a 150mg (N=9)	Cohort 1a 300mg (N=39)	Cohort 1b 300mg (N=13)	Cohort 1 (N=61)	Cohort 2 150mg (N=14)	Total (N=75)
Category, n (%)						
< 80%	0	1 (2.6)	0	1 (1.6)	1 (7.1)	2 (2.7)
>= 80% - <= 115%	9 (100.0)	36 (92.3)	13 (100.0)	58 (95.1)	12 (85.7)	70 (93.3)
> 115%	0	2 (5.1)	0	2 (3.3)	1 (7.1)	3 (4.0)

Outcomes and estimation

The main endpoints – PK and safety – are described in their respective sections.

As regards efficacy, the following endpoints were assessed:

Viral RNA Measured Via RT-PCR in Nasopharyngeal or Nasal Swabs Over Time (Change From Baseline to Day 5):

The adjusted mean (SE) change in SARS-CoV-2 viral RNA concentrations from baseline through Day 5 ranged from -3.395 (0.449) log10 copies/mL to -4.763 (0.567) log10 copies/mL across cohorts and dose subgroups.

Table 5. Statistical Analysis of Observed and Change From Baseline in Log10 Transformed Viral Load (copies/mL) Data Over Time - Safety Analysis Set (Protocol C4671026)

		Observed			Change from Baseline				
Visit	Cohort Group	n	Mean (SD)	Median (Range)	n	Mean (SD)	Median (Range)	LS Mean (SE)	95% CI
Baseline	Cohort 1a 150 mg (N=9)	9	5.389 (1.854)	4.880 (1.700, 8.080)					
	Cohort 1a 300 mg (N=39)	35	6.416 (1.457)	6.750 (1.700, 8.620)					
	Cohort 1b 300 mg (N=13)	12	6.329 (0.821)	6.415 (5.030, 7.680)					
	Cohort 2 150 mg (N=14)	11	5.934 (1.498)	6.380 (3.330, 7.520)					
Day 4	Cohort 1a 150 mg (N=9)	8	1.579 (1.792)	1.095 (0.000, 4.030)	8	-3.904 (1.039)	-4.095 (-4.880, -1.700)	-4.404 (0.524)	(-5.453, -3.356)
	Cohort 1a 300 mg (N=39)	34	3.178 (1.617)	3.420 (0.000, 5.830)	34	-3.242 (1.519)	-3.170 (-7.260, 0.720)	-3.235 (0.251)	(-3.738, -2.732)
	Cohort 1b 300 mg (N=13)	12	2.820 (1.296)	2.975 (0.000, 4.910)	12	-3.509 (1.291)	-3.560 (-5.400, -1.110)	-3.578 (0.412)	(-4.402, -2.754)
	Cohort 2 150 mg (N=14)	11	3.269 (1.460)	2.810 (1.700, 6.540)	11	-2.665 (1.764)	-3.590 (-4.930, 0.950)	-2.834 (0.411)	(-3.655, -2.012)
Day 5	Cohort 1a 150 mg (N=9)	8	1.225 (1.106)	1.700 (0.000, 3.000)	8	-3.951 (1.953)	-4.730 (-6.330, 0.000)	-4.763 (0.567)	(-5.897, -3.629)
	Cohort 1a 300 mg (N=39)	35	2.001 (1.593)	2.290 (0.000, 4.540)	35	-4.414 (1.584)	-4.160 (-7.690, 0.320)	-4.369 (0.257)	(-4.882, -3.856)
	Cohort 1b 300 mg (N=13)	12	1.839 (1.288)	1.905 (0.000, 3.740)	12	-4.490 (1.340)	-4.765 (-6.320, -2.280)	-4.589 (0.443)	(-5.475, -3.703)
	Cohort 2 150 mg (N=14)	11	2.792 (2.061)	2.620 (0.000, 6.570)	11	-3.142 (1.900)	-3.470 (-6.380, 0.400)	-3.395 (0.449)	(-4.292, -2.498)
Day 6	Cohort 1a 150 mg (N=9)	9	1.550 (1.575)	1.700 (0.000, 3.740)	9	-3.839 (1.521)	-4.620 (-5.250, -0.900)	-4.452 (0.495)	(-5.441, -3.463)
	Cohort 1a 300 mg (N=39)	35	1.521 (1.581)	1.700 (0.000, 5.880)	35	-4.895 (1.750)	-5.530 (-7.330, 0.480)	-4.784 (0.248)	(-5.280, -4.287)
	Cohort 1b 300mg (N=13)	12	1.669 (1.206)	1.700 (0.000, 3.690)	12	-4.660 (1.434)	-4.815 (-7.680, -2.330)	-4.673 (0.432)	(-5.537, -3.808)
	Cohort 2 150 mg (N=14)	11	2.325 (1.359)	1.700 (1.700, 6.330)	11	-3.609 (1.955)	-4.470 (-5.350, 0.740)	-3.847 (0.439)	(-4.725, -2.969)

Supportive Secondary Efficacy Endpoint - Proportion of Participants With COVID-19 Related Hospitalisation or Death From Any Cause Through Day 28:

There were no COVID-19 hospitalisations or deaths from any cause through Day 28 reported in any participants enrolled in Cohort 1 and Cohort 2.

Post-treatment Increases in SARS-CoV-2 RNA Shedding Levels (ie, Viral RNA Rebound) in NP or Nasal Swabs:

A total of 10 participants had an increase in viral RNA concentration of 0.5 log10 copies/mL from EOT at either Day 10 or Day 14: 9 (12.0%) participants at Day 10 and 4 (5.5%) participants at Day 14, respectively. Of the 10 total participants, 3 participants had 0.5 log10 copies/mL increases in viral RNA concentration above the LLOQ of 2.0 log10 copies/mL (imputed as 1.70 log10 copies/mL).

Table 6. Analysis of Proportion of Participants With Viral Load Rebound at Day 10 or Day 14 - Safety Analysis Set (Protocol C4671026)

	Cohort 1a 150mg		Cohort 1a 300mg		Cohort 1b 300mg		Cohort 1		Cohort 2 150mg		Total	
Participants With Viral Load Rebound	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Day 10	9	3 (33.3)	39	4 (10.3)	13	2 (15.4)	61	9 (14.8)	14	0	75	9 (12.0)
Day 14	9	2 (22.2)	38	1 (2.6)	13	0	60	3 (5.0)	13	1 (7.7)	73	4 (5.5)
Day 10/14	9	1 (11.1)	39	0	13	1 (7.7)	61	2 (3.3)	13	0	74	2 (2.7)

N = number of participants with non-missing data at the end of treatment and the given time point.
Viral load rebound at Day 10/14: (a) Value < 2.0 at end of treatment followed by ≥ 3.0 at Day 10 or Day 14, or (b) Value ≥ 2.0 at end of treatment followed by Day 10 or Day 14 value ≥ 0.5 increase relative to end of treatment and at least ≥ 3.0.
Cohort 1a: ≥ 40 kg, ≥ 12 to < 18 years, Cohort 1b: ≥ 40 kg, ≥ 6 to < 12 years, Cohort 2: ≥ 20 to < 40 kg, ≥ 6 to < 18 years.

One participant in Cohort 1a 150 mg met the definition of SARS-CoV-2 RNA rebound at Day 10 and Day 14. The SARS-CoV-2 RNA rebound was associated with new or worsening COVID-19 signs and symptoms on Day 14 (severe cough on Day 14); all COVID-19 signs and symptoms were resolved on Day 28. This same participant experienced 2 SAEs (Haemoglobin decreased and Platelet count decreased).

One participant in Cohort 1b met the definition of SARS-CoV-2 viral RNA rebound at Day 10. The SARS-CoV-2 RNA rebound was not associated with new or worsening COVID-19 signs and symptoms.

Viral RNA Measured Via RT-PCR in Nasopharyngeal or Nasal Swabs Over Time (Change From Baseline to Day 6):

The adjusted mean (SE) of change in SARS-CoV-2 RNA concentrations from Baseline to Day 6 ranged from -3.847 (0.439) log10 copies/mL in Cohort 2 to -4.784 (0.248) log10 copies/mL in Cohort 1a 300 mg.

By Day 6, observed mean of SARS-CoV-2 RNA concentrations were largely at undetectable levels — <1.7 log10 copies/mL across all Cohort 1 subgroups and 2.325 log10 copies/mL for Cohort 2.

Time to Alleviation and Resolution of All Targeted COVID-19 Signs/Symptoms:

Most participants achieved resolution of all targeted COVID-19 signs and symptoms by Day 28. Median time to resolution of all targeted COVID-19 signs and symptoms was 10.0 days for Cohort 1a 150 mg, 6.0 days for Cohort 1a 300 mg and Cohort 1b, and 5.0 days for Cohort 2.

Table 15. Analysis of Time to Alleviation of All Targeted Signs and Symptoms Through Day 28 - Safety Analysis Set (Protocol C4671026)

Parameter		Cohort 1a 150mg (N=9)	Cohort 1a 300mg (N=39)	Cohort 1b 300mg (N=13)	Cohort 2 150mg (N=14)
Time to alleviation (Days)	N1	9	39	13	14
	Participants with event, n (%)	9 (100.000)	37 (94.872)	13 (100.000)	13 (92.857)
	Median (95% CI)	10.000 (4.000, 16.000)	5.000 (4.000, 6.000)	5.000 (4.000, 6.000)	5.000 (4.000, 6.000)
	Q1, Q3	4.000, 15.000	4.000, 6.000	5.000, 6.000	4.000, 6.000

N = number of participants in the analysis set.
N1 = number of participants with non-missing data in the analysis set.
Q1, Median and Q3 are obtained from Kaplan Meier (KM) method.
Targeted signs and symptoms are only collected at Baseline, Day 4, Day 5, Day 6, Day 10, Day 14 and Day 28.
Cohort 1a: ≥ 40 kg, ≥ 12 to < 18 years, Cohort 1b: ≥ 40 kg, ≥ 6 to < 12 years, Cohort 2: ≥ 20 to < 40 kg, ≥ 6 to < 18 years.

Table 16. Analysis of Time to Resolution of All Targeted Signs and Symptoms Through Day 28 - Safety Analysis Set (Protocol C4671026)

Parameter		Cohort 1a 150mg (N=9)	Cohort 1a 300mg (N=39)	Cohort 1b 300mg (N=13)	Cohort 2 150mg (N=14)
Time to resolution (Days)	N1	9	39	13	14
	Participants with event, n (%)	9 (100.000)	36 (92.308)	12 (92.308)	13 (92.857)
	Median (95% CI)	10.000 (4.000, 16.000)	6.000 (5.000, 9.000)	6.000 (5.000, 10.000)	5.000 (4.000, 9.000)
	Q1, Q3	4.000, 15.000	4.000, 10.000	5.000, 10.000	5.000, 9.000

N = number of participants in the analysis set.
N1 = number of participants with non-missing data in the analysis set.
Q1, Median and Q3 are obtained from Kaplan Meier (KM) method.
Targeted signs and symptoms are only collected at Baseline, Day 4, Day 5, Day 6, Day 10, Day 14 and Day 28.
Cohort 1a: ≥ 40 kg, ≥ 12 to < 18 years, Cohort 1b: ≥ 40 kg, ≥ 6 to < 12 years, Cohort 2: ≥ 20 to < 40 kg, ≥ 6 to < 18 years.

Proportion of Participants with Severe Signs/Symptoms Attributed to COVID-19 Through Day 28:

Overall, 14 (18.7%) of participants reported at least 1 severe pre-specified targeted sign or symptom attributable to COVID-19 at Baseline. A higher proportion of participants in Cohort 1a 150 mg (3 [33.3%]) and Cohort 2 (5 [35.7%]) reported severe symptoms compared to Cohort 1a 300 mg (4 [10.3%]) and Cohort 1b (2 [15.4%]). The most frequently reported severe symptoms at Baseline overall were Rhinorrhoea (5 [6.7%]), Fever (4 [5.3%]), and Sore throat (4 [5.3%]).

Few participants reported a severe COVID-19 sign or symptom at assessments after the Baseline visit:

- By Day 6, when participants are expected to have completed a full course of treatment, 1 participant reported severe symptoms (chills or shivering, fever, muscle pain and nausea); this participant discontinued treatment due to an AE of Viral infection.

- At the Day 14 visit, 1 participant reported a severe COVID-19 sign or symptom (cough); an increase in SARS-CoV-2 viral RNA concentration (6.53 log10 copies/mL) was observed on the same day.

At the Day 28 visit, no participants reported a severe COVID-19 sign or symptom.

Table 17. Analysis of Proportion of Participants With Any Severe Targeted Signs and Symptoms Attributed to COVID-19 Over Time - Safety Analysis Set (Protocol C4671026)

	Cohort 1a 150mg		Cohort 1a 300mg		Cohort 1b 300mg		Cohort 1		Cohort 2 150mg		Total	
Participants With Event	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Baseline	9	3 (33.3)	39	4 (10.3)	13	2 (15.4)	61	9 (14.8)	14	5 (35.7)	75	14 (18.7)
Day 4	9	2 (22.2)	39	1 (2.6)	12	0	60	3 (5.0)	14	1 (7.1)	74	4 (5.4)
Day 5	8	1 (12.5)	39	0	13	0	60	1 (1.7)	14	1 (7.1)	74	2 (2.7)
Day 6	9	0	39	0	13	0	61	0	14	1 (7.1)	75	1 (1.3)
Day 10	9	0	39	0	13	0	61	0	13	0	74	0
Day 14	9	1 (11.1)	38	0	13	0	60	1 (1.7)	14	0	74	1 (1.4)
Day 28	9	0	39	0	13	0	61	0	14	0	75	0

Ancillary analyses

Viral sequencing data

The current report provides the second cumulative interim analysis of viral sequencing data for 131 samples/66 participants with available data from Study C4671026.

Viral variant data was available for the 66 nirmatrelvir/ritonavir treated participants in the study at the time of this interim analysis 2. Omicron was the only variant observed in the study, with 22B (54.5%) and 21L (12.1%) the major Omicron subvariants observed.

Among the 62 participants with viral sequencing data at baseline, 7 Mpro (T24I, I78M, P96S, P108S, P132S, V148A, P184L) and 1 cleavage region mutations (V3855I) were observed at baseline. All baseline Mpro and cleavage mutations were observed in 1 participant each.

No emergent Mpro and cleavage mutations were observed in ≥2 participants. No persistent mutation or emergent mutation with increasing amino acid frequency (AAFREQ) in Mpro and cleavage region was observed.

Individual mutations were observed to emerge in 2 participants (1 participant with cleavage mutation A3939T at Day 10 during viral RNA rebound and 1 participant with Mpro mutation P252L [5.9 EC50 shift] at Day 4). These mutations were observed at a low AAFREQ (<20%) and were transient in nature. Both participants achieved viral control by Day 14 and did not experience COVID-19-related hospitalisation or death from any cause through Day 28. Thus, these mutations were not clinically significant.

Summary of main study

Table 1. Summary of Efficacy for trial C4671026

Title: A Phase 2/3, Interventional Safety, Pharmacokinetics, and Efficacy, Open-Label, Multi-Center, Single-Arm Study to Investigate Orally Administered PF-07321332 (Nirmatrelvir)/Ritonavir in Nonhospitalised Symptomatic Paediatric Participants With COVID-19 Who Are at Risk of Progression to Severe Disease	
Study identifier	C4671026

Design	Phase 2/3, open-label, multi-center, single-arm study. 5 cohorts: - Cohort 1: Weight ≥40 kg a. ≥12 to <18 years b. ≥6 to <12 years - Cohort 2: Weight ≥20 to <40 kg, ≥6 to <18 years - Cohort 3: ≥2 to <6 years - Cohort 4: ≥1 month (>28 days) to <2 years - Cohort 5: <1 month (<28 days) **Only results from Cohorts 1 and 2 are available.**		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	34 days not applicable not applicable	
Hypothesis	Exploratory: To determine the PK and safety of nirmatrelvir/ritonavir in paediatric participants		
Treatments cohorts	Cohort 1a (weight ≥40 kg, ≥12 to <18 years)		Nirmatrelvir/ritonavir 300/100 mg BID during 5 days (n=39) (+9 subjects treated with a lower dose nirmatrelvir/ritonavir 150/100 mg BID)
	Cohort 1b (weight ≥40 kg, ≥6 to <12 years)		Nirmatrelvir/ritonavir 300/100 mg BID during 5 days (n=13)
	Cohort 2 (weight ≥20 to <40 kg, ≥6 to <18 years)		Nirmatrelvir/ritonavir 150/100 mg BID during 5 days (n=16)
Endpoints and definitions	Co-Primary endpoint	PK	PK parameters including C_{max} and $AUC_{0\text{-}tau}$ (and if the data permitted $t_{1/2}$, C_{trough}) of nirmatrelvir and ritonavir. In adolescents (≥12 years to <18 years of age), robust PK sampling was performed. A sparser approach was incorporated for younger participants as PK samples were more difficult to obtain
	Co-Primary endpoint	Safety	Incidence of TEAEs, SAEs, AEs leading to discontinuations, and vital sign measurements.
	Secondary endpoint	Efficacy	SARS-CoV-2 viral RNA measured via RT-PCR in nasopharyngeal or nasal swabs over time (change from Baseline to Day 5)
	Secondary endpoint	Efficacy	Proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28
	Secondary endpoint	Efficacy	Acceptability and palatability assessments of nirmatrelvir/ritonavir
	Tertiary endpoint	Efficacy	Duration of all and each targeted COVID-19 Signs/Symptoms
Database lock	07 June 2024		

Results and Analysis

Analysis description	**Secondary Analysis**
Analysis population and time point description	Safety Analysis Set: All participants enrolled in the study, who take at least 1 dose of study intervention.

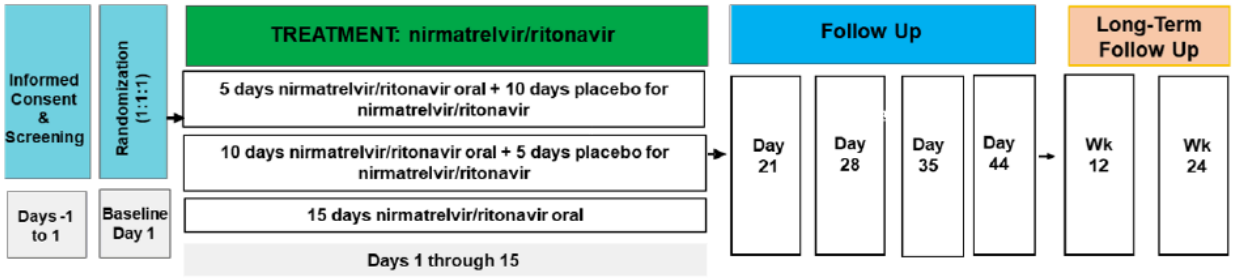
Descriptive statistics and estimate variability	Treatment group	Cohort 1a 150/100 mg	Cohort 1a 300/100 mg	Cohort 1b 300/100 mg	Cohort 2 150/100 mg
	Number of subject	9	39	13	14
	Viral load (adjusted mean of change from Baseline to Day 5, log10 copies/mL)	-4.763	-4.369	-4.589	-.395
	95% CI	-5.897, -3.629	-4.882, -3.856	-5.475, -3.703	-4.292, -2.498
	Time to resolution (median, days)	10	6	6	5
	95% CI	4-16	5-9	5-10	4-9

Supportive studies

Study C4671034

This is a Phase 2, randomised, 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-hospitalised 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.

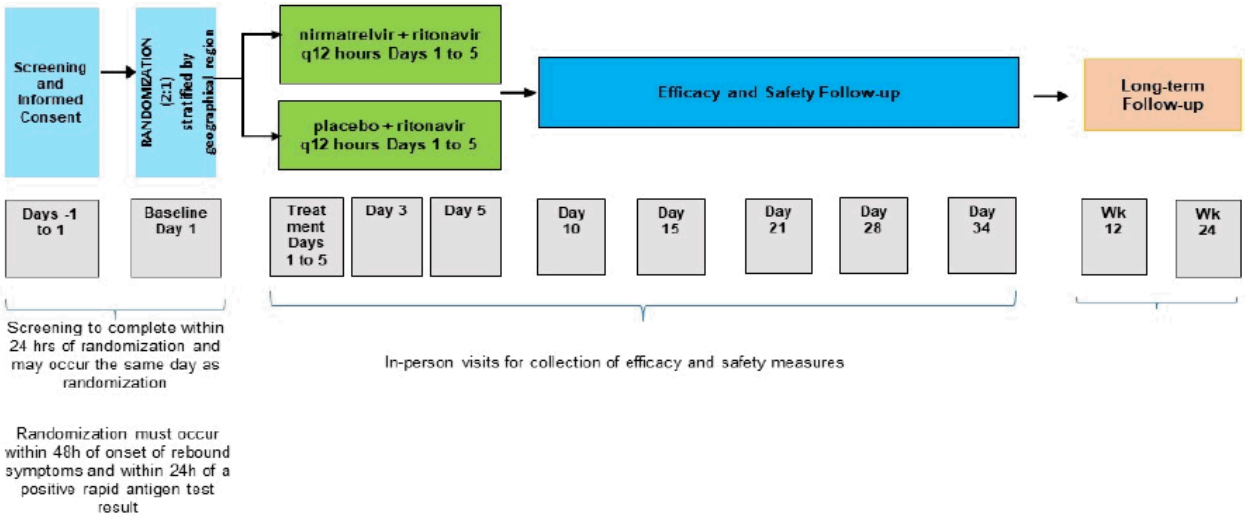
The study will enrol approximately 150 participants + 50 participants with COVID-19 rebound. Non-hospitalised, symptomatic, immunocompromised participants ≥12 years of age and weighing ≥40 kg with COVID-19 were enrolled in this study. Participants included in the trial had a confirmed SARS-CoV-2 infection within 5 days of randomisation and were experiencing at least 1 symptom of COVID-19. To adequately capture a representative range of participants who were immunocompromised, enrolment was stratified and capped for participants with corticosteroid or TNF blocker use as the sole form of immunosuppression.

A total of 156 participants were randomised and 155 treated. Due to GCP quality issues in a study site, data from 5 subjects were excluded from efficacy analyses. 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 the site where GCP quality issues were observed. This paediatric patient 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. No moderate/severe symptoms were reported, nor any increased of symptoms after the end of treatment.

Study C4671042

This is a Phase 2, randomised, 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.



Participants were ≥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.

A total of 436 participants were included and assigned to treatment. Only one paediatric patient was included. At baseline (Day 1), the paediatric 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. This paediatric patient had no COVID-19 related medical visit or hospitalisation and had sustained resolution of all targeted signs and symptoms observed at baseline (i.e. moderate cough, headache, low energy or tiredness, and mild muscle or body aches) by Day 8.

Literature data

As of data cut-off, 17 Oct 2024, the MAH has reviewed published literature and identified 9 published literature articles that evaluated the efficacy of nirmatrelvir/ritonavir in paediatric patients with COVID-19 who are at risk of progression to severe disease:

Effectiveness of Paxlovid in the treatment of the SARS-CoV-2 Omicron variant infection in children with hematologic malignancies: a retrospective cohort study (Deng X et al, 2024)

Summary: Deng X et al. describes a retrospective, non-randomised study on paediatric patients with hematologic malignancies (HMs) infected with the SARS-CoV-2 Omicron variant who had been

admitted to the Shanghai Children's Medical Center, Shanghai, China from December 1, 2022, to March 1, 2023. The Paxlovid-treated group (Group P) comprised 21 patients, and the non-Paxlovid-treated group (Group N) comprised 21 patients. Children aged 12–14 years who weighed >40 kg were given Paxlovid (nirmatrelvir/ritonavir) 300 mg/100 mg orally twice a day, those aged 6–12 years who weighed 20–40 kg were given 150 mg/100 mg twice a day, and those aged less than 6 years who weighed <20 kg were given 150 mg/50 mg twice a day. The patients treated with Paxlovid within 5 days of diagnosis had a median viral clearance time of 5 days [interquartile range (IQR), 4–8 days], which was significantly shorter than that of the patients who were not treated with Paxlovid (P=0.03). The clinical course of the SARS-CoV-2 Omicron variant infection for most of the children with HMs was non-severe (97.6%), and only one child progressed to severe disease (2.4%). There were no significant differences in the clinical outcomes between the two groups after the propensity score matching (PSM) analyses. Eight patients, 5 with Paxlovid and 3 non-Paxlovid, (19%) had repeat-positive (re-positive) test results. No factor was found to be statistically significant in predicting re-positive test results based on the binary logistic regression analysis.

Authors' Conclusions: Administering Paxlovid within 5 days of the diagnosis of the SARSCoV-2 Omicron variant infection in children 6-14 years who weighed <20 kg to >40 kg may effectively shorten the clearance time of the virus. The clinical symptoms related to COVID-19 were all alleviated in the children who used Paxlovid in this study. Specifically, the children with fever improved within 1–6 days of medication initiation. At the follow up, eight of the 12 children (66.7%) with pneumonia had their lung imaging evaluated, and the results showed remarkable recovery. There is still the possibility the patients may have repositive test results.

Safety and efficacy of Paxlovid in paediatric intensive care unit patients with COVID-19 (Fan P et al, 2024)

Summary: Fan P et al. describes a retrospective analysis that was performed on children with COVID-19. This study included 31 patients with newly diagnosed COVID-19, including 19 boys and 12 girls aged 1 month to 15 years and weighing 5-85 kg. Among these children, 22 (71%) had co-morbidities. Twelve and 19 participants were assigned to the Paxlovid and control groups, respectively. Approximately 35% had received vaccination against the novel coronavirus. The control group exhibited a significantly lower mean age in comparison to the Paxlovid group ($p<0.001$). However, no significant differences were observed between the groups in terms of other baseline data and biochemical indexes at admission. On Day 5 of drug administration, the Paxlovid group exhibited a statistically significant decrease in temperature compared to the control group ($p<0.05$). Additionally, the Paxlovid group exhibited a significantly shorter conversion time to negativity for novel coronary genes in the respiratory tract (9.5 days) compared to the control group (16 days, $p < 0.05$). The administration of Paxlovid did not result in any observed adverse reactions; two patients exhibited a transient elevation in liver enzyme levels.

Authors' Conclusions: The application of Paxlovid in critically ill paediatric patients with COVID-19 can effectively control symptoms and promote virus clearance, demonstrating efficacy and a relatively low-risk profile.

The feasibility, safety, and efficacy of Paxlovid treatment in SARS-CoV-2-infected children aged 6-14 years: a cohort study (Yan et al, 2022)

Summary: Yan et al. describe in this prospective cohort study of 5 paediatric participants aged 6 to 14 years (15–44 kilograms), with underlying diseases and confirmed COVID-19. Underlying diseases included congenital heart defects, cerebral palsy, Down syndrome, and leukaemia. Participants were treated with nirmatrelvir/ritonavir for 5 days, within 5 days of symptom onset as follows:

- aged 6-14 years with bodyweight < 20 kg: 150 mg/100 mg once daily

- aged 6-14 years with bodyweight 20-40 kg: 150 mg/100 mg twice daily
- aged 12-14 years with bodyweight > 40 kg: 300 mg/100 mg twice daily.

An age-matched control group of 30 participants with underlying diseases who were not treated with Paxlovid was used to compare AEs and viral shedding times. Compared with age-matched controls, the viral shedding times were not significantly different between groups. All patients recovered and were discharged home within 2 weeks.

Authors' Conclusions: The authors concluded that Paxlovid is a feasible and safe option for treating SARS-CoV-2-infected children aged 6–14 years with underlying diseases. They noted that the efficacy was inconclusive, based on this study.

Case Report: Application of nirmatrelvir/ritonavir to treat COVID-19 in a severe aplastic anemia child after allogeneic hematopoietic stem cell transplantation (Huan et al, 2022)

Summary: Huang et al. presented the case of a 5-year-old boy with mild COVID-19 who was admitted to hospital, 103 days after receiving a stem cell transplant, with low-grade fever, nasal congestion, fatigue, and abdominal pain. On Day 4 after SARS-CoV-2 positive test, the patient developed thrombocytopenia, neutropenia, and lymphocytopenia, and nirmatrelvir/ritonavir tablets regimen (150 mg of nirmatrelvir + 50 mg of ritonavir twice daily for 5 days) was implemented. On day 5, WBC and N counts continued to decrease, and a single dose of granulocyte-colony stimulating factor was given. The WBC and N counts decreased again on Day 8 and stabilised after the complete course of nirmatrelvir/ritonavir treatment, accompanied by the relief of clinical symptoms. No significant adverse events were reported, the patient only experienced mild increase of serum creatinine and urea nitrogen, which returned to normal by Day 5. On Day 25, the SARS-CoV-2 test was negative.

Authors' Conclusions: Nirmatrelvir/ritonavir can effectively inhibit the replication of SARS-CoV-2 without any significant adverse effects. Nirmatrelvir/ritonavir could be a potential therapy choice for children with COVID-19 and underlying diseases.

Monoclonal antibody and antiviral therapy for mild-to-moderate COVID-19 in paediatric patients (Vora et al, 2023)

Summary: Vora et al. analysed 66 high-risk paediatric patients, who received approval for early therapy for mild-to-moderate COVID-19 (nirmatrelvir/ritonavir [12 patients; median age 14.5 years], sotrovimab, and remdesivir). A total of 9 children received nirmatrelvir/ ritonavir, while 11 were treated with sotrovimab and 27 with remdesivir. The median time from the onset of infection to the first dose of nirmatrelvir tablets; ritonavir tablets was 3 days (range: 1-6). One patient who received nirmatrelvir/ritonavir visited the Emergency Department (ED) for an episode of shortness of breath but was discharged in good/stable condition. None of the patients who received nirmatrelvir/ritonavir required hospitalisation within 7 days following the treatment request.

Authors' Conclusions: It was concluded that these therapies were generally well-tolerated and subsequent COVID-19-related ED visits or hospitalisations were uncommon.

Hospitalisation and ED encounters for COVID-19 after Paxlovid treatment - California, December 2021-May 2022 (Malden et al, 2022)

Summary: Malden et al. reviewed 5,287 patients (aged ≥12 years; 73% with ≥3 doses of COVID-19 vaccine; 8% unvaccinated) treated with a 5-day treatment course of nirmatrelvir/ritonavir and analysed the number of COVID-19-related hospitalisations or ED visits during the 5-15 days post-treatment. A total of 36 (0.7%) patients who received nirmatrelvir/ritonavir were children and adolescents (aged 12-17 years), none of them required hospital admission or ED visit.

Authors' Conclusions: When administered as an early-stage treatment, Paxlovid might prevent COVID-19–related hospitalisation among persons with mild to moderate COVID-19 cases who are at risk for progression to severe disease.

Effectiveness of nirmatrelvir/ritonavir in children and adolescents aged 12–17 years following SARS-CoV-2 Omicron infection: A target trial emulation (Wong et al, 2024)

Summary: Wong et al. performed a retrospective cohort study aiming to emulate a hypothetical randomised controlled trial by using data cloning, to evaluate the effectiveness of nirmatrelvir/ritonavir in non-hospitalised paediatric patients aged 12-17 years with SARS-CoV-2 Omicron variant infection. Nirmatrelvir/ritonavir treatment was associated with a reduced 28-day all-cause hospitalisation/hospitalisation (absolute risk reduction = 0.23, 95% CI = 0.19–0.31; relative risk = 0.66, 95% CI = 0.56–0.71).

Author's Conclusion: Authors reported that nirmatrelvir/ritonavir treatment was effective in reducing the 28-day all-cause hospitalisation risk among non-hospitalised paediatric patients aged 12-17 years with SARS-CoV-2 Omicron variant infection. The authors also noted that no events of mortality, in-hospital disease progression, or adverse clinical outcomes were observed among nirmatrelvir/ritonavir users.

Clinical effectiveness of nirmatrelvir plus ritonavir on the short- and long-term outcome in high-risk children with COVID-19 (Wu et al, 2024)

Summary: Wu J.Y et al. describes this retrospective cohort study that investigated the clinical effectiveness of nirmatrelvir/ritonavir on short-term outcome and the risk of post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (PASC) among paediatric patients with COVID-2019. Two cohorts comprising 633 patients each (nirmatrelvir/ritonavir and control groups), with balanced baseline characteristics, were identified using the propensity score matching (PSM) method. During the initial 30 days, the nirmatrelvir/ritonavir group showed a lower incidence all-cause hospitalisations, deaths, or ED visits (HR = 0.546, 95% CI: 0.372–0.799, p = 0.002) and a lower risk of hospitalisation compared with the control group (HR = 0.463, 95% CI: 0.269–0.798), with no deaths in either group. Between days 30–180, the nirmatrelvir/ritonavir group showed a non-significant reduction in PASC symptoms like fatigue, cardiopulmonary issues, pain, cognitive problems, headaches, dizziness, sleep disorders, anxiety, and depression compared to the control group.

Authors' Conclusions: This study underscores the potential effectiveness of nirmatrelvir/ritonavir in treating high-risk paediatric patients with COVID-19, demonstrating significant reductions in short-term adverse outcomes such as ED visits, hospitalisation, or mortality within the initial 30-day period. Nirmatrelvir/ritonavir shows promise in potentially preventing the development of PASC.

Clinical efficacy analysis of paxlovid in children with haematological diseases infected with the omicron SARS-CoV-2 new variant (Li et al, 2023)

Summary: Li et al. describes this retrospective comparison study of 20 children with haematological diseases infected with the SARS-CoV-2 Omicron variant. Participants were divided into 2 groups, as follows:

- Group A: 7 males and 2 females, aged 4–14 years, mean (7.67 ± 3.162) years, weight range 18–60 kg with hematologic neoplastic diseases and 2 high-risk factors for the development of severe and critical illnesses. Group A participants were treated with Paxlovid (n = 9).
- Group B: 7 males and 4 females, aged 2–11 years, mean (5.73 ± 3.165) years, weight range 10.5–32 kg. Participants with haematological malignancies and 1 risk factor for haematological

malignancies and no other risk factors for severe or critical illness. Group B participants did not receive Paxlovid treatment (n = 11).

The authors reported that Paxlovid treatment in children with haematological diseases infected with SARS-CoV-2 resulted in a faster viral clearance compared to those who did not receive Paxlovid.

Authors' Conclusions: Authors reported no apparent adverse reactions in children 12 years old and younger with underlying haematological diseases Paxlovid treatment shortens virus clearance time and reduces the risk of developing severe disease. The authors noted that it is necessary to pay attention to whether there are signs of secondary bacterial infection, and it may be necessary to combine antibiotics in time for treatment.

2.5.2. Discussion on clinical efficacy

Study C47671026 was the pivotal study for this paediatric extension, in accordance to Paxlovid PIP. Additionally, there were two Phase 2 clinical trials within the development program allowed for enrolment of adolescent participants (12 years of age and older): C4671034 (in immunocompromised participants) and C4671042 (in participants with COVID-19 rebound). However, only 2 paediatric subjects were included in these additional studies, making them not relevant for this application.

Study C47671026 is an ongoing Phase 2/3, interventional, open-label, multi-center, single-arm study designed to investigate safety, pharmacokinetics and efficacy of orally administered nirmatrelvir/ritonavir in nonhospitalised symptomatic paediatric participants with COVID-19 who are at risk of progression to severe disease. The study design, endpoints, statistical methods and population of the study were in accordance to the nirmatrelvir/ritonavir PIP and usual for a paediatric study designed for an extension of indication.

Participants are being enrolled into 5 cohorts in a tiered scheme based on age and/or weight. At this stage, only patients from Cohort 1 (Weight ≥40 kg, (a) ≥12 to < 18 years or (b) ≥6 to <12 years) and Cohort 2 (Weight ≥20 to <40 kg, ≥6 to 18 years) were included. Based on PK modelling and simulation, participants receive initially nirmatrelvir/ritonavir 300 mg/100 mg (Cohort 1) or 150 mg/100 mg (Cohort 2) q12h for 5 days. However, after a complementary PK analysis during study, additional subjects from Cohort 1 had received a lower dose of nirmatrelvir/ritonavir at 150 mg/100 mg q12h. Indeed, concentration-time data (from whole blood PK samples collected with Tasso M20 device) for 39 paediatric participants enrolled in Cohort 1a and 13 participants in Cohort 1b was used in a subsequent assessment of 300 mg/100 mg nirmatrelvir/ritonavir dosing in Cohort 1. These PK parameters calculated using blood concentrations were converted to corresponding plasma PK parameters using the nirmatrelvir blood-to-plasma ratio of 0.713, which was obtained from previous studies. Therefore, this update of PK analysis has provided a 2.3-fold, 1.6-fold, and 1.5-fold increase in geometric mean C_{max}, AUC_{tau}, and C_{min}, respectively, in paediatric participants compared to adults. Based on these new data, a reduced dose of 150 mg/100 mg nirmatrelvir/ritonavir BID was proposed for an additional n = 20 participants in Cohort 1. However, a second PK analysis performed during study has highlighted concerns about the concordance between Tasso M20 PK samples collected and venous plasma PK samples collected at approximately the same time. As a result of this Tasso M20 discordance, all Tasso M20 PK samples collected in this study were excluded from PK analysis. The inclusions were stopped, and a total of 9 additional subjects were included in Cohort 1a and treated with nirmatrelvir/ritonavir 150 mg/100 mg q12h. As the study was still paused as of the data cutoff of 07 Jun 2024, a clarification was requested on whether randomisation continues and regarding the participants of cohort 1, what was the dose administered since 07 June 2024. The MAH clarified that no further randomisation or dosing took place in Cohort 1 after June 7, 2024; the study remained paused, and the data set for regulatory review was locked as of that date.

As of the data cutoff (07 Jun 2024), a total of 77 participants were assigned to study intervention. Of these, 75 participants (61 participants in Cohort 1 and 14 participants in Cohort 2) received at least 1 dose of study intervention. While the initially agreed Paediatric Investigation Plan stipulated cohort sizes of 70 participants in cohort 1 and 50 participants in cohort 2, this was revised in the most recent PIP modification procedure (EMA/PE/0000225184). The MAH argued that the totality of plasma PK and safety data to date would likely be sufficient to inform dosing recommendations in paediatric patients from 6 years of age and 20 kg weight. The PDCO agreed that a minimum of 57 PK-evaluable participants in cohort 1 and 17 (specifically, 11 with sparse sampling completed to date and an additional 6 participants with multiple samples) in cohort 2 would be acceptable. It was noted by PDCO that the decision did not affect the MAH's prerogative to determine at what point they would submit the cumulative data to date to CHMP to seek a paediatric indication, because a compliance check of the ongoing paediatric clinical study is not required for validation of this extension. In the end, it would appear that the submission has been made before recruiting any of the additional 6 PK-evaluable participants requested for cohort 2.

An important rate of important protocol deviations (IPDs) is noted, with 93.5% of subjects concerned. Most of these IPDs (89.6%) concern laboratory data: biological samples (blood samples and nasal swab) for safety analyses and PK samples that have not been performed, were collected outside protocol defined window, or not properly collected, stored or handled. These PK samples impacted by IPDs correspond to the Tasso M20 samples ruled out and the plasma samples not initially planned to be used for PK analysis but finally taken into account for the final PK analysis. For the safety analyses impacted by IPDs, the MAH is requested to detail the number of subjects and, for each subject, the number and the nature of the safety analyses not carried out. The MAH should also discuss whether some laboratory safety data could be missing in subjects experiencing laboratory abnormalities (e.g. transaminases elevation or neutrophils diminution). Some other IPDs concern missing protocol-defined assessments (e.g. pregnancy test, physical examination, vital signs). Therefore, the MAH is also requested to detail, for each subject concerned, the number and the nature of the missing protocol-defined assessments (physical examination and vital signs), and whether some data could be missing in subjects experiencing abnormalities. The issues were solved by providing subject-level details and demonstrating that missing data did not lead to missed detection of clinically relevant safety issues. This CHMP considered this acceptable.

At baseline, mean (SD) age was 12.39 (3.40) years; 53.2% were female; 57.1% were White, 20.8% were Black or African American, and 11.7% were American Indian or Alaska Native; 61% were Hispanic or Latino. Median (range) weight (kg) was 54.65 (20.3, 200). Age and weight ranges (i.e. 20-40 kg and >40 kg) are well represented in each cohorts (subjects weighing 40 to 200 kg in Cohort 1, and 20.3 to 39.4 kg in Cohort 2). The most frequently reported conditions were obesity (37 [49.3%] participants overall) and chronic respiratory disease (30 [40.0%] participants overall). Of note, the rate of subjects with immunodeficiency and therefore a high risk of severe COVID-19 is quite low – 6.5% of subjects with immunosuppression. The mean (SD) baseline viral load across all cohorts was 5.52 (2.36) log10 copies/mL.

The compliance for Paxlovid treatment was adequate, with only one subject who had interrupted the treatment due to difficulties to swallow the tablets. This seems low, given the tablet (17.6 mm x 8.6 mm) could be difficult to be administered to children from 6 years of age, but screening procedure has theoretically ruled out children for whom difficulty in swallowing such a tablet is expected. The oral powder formulation currently being developed could be a preferable option for many children.

Efficacy data and additional analyses

Efficacy results are only supportive given the non-comparative design and low number of subjects of this study. It could be highlighted:

- from Baseline to Day 5, a reduction of viral load (adjusted mean change: -3.395 log10 copies/mL to -4.763 log10 copies/mL across all cohorts) non-inferior to the reduction observed in adults in the studies 1005 (adjusted mean change: -3.087 log10 copies/mL) and 1002 (adjusted mean change: -3.419 log10 copies/mL);

- the lack of hospitalisations or death due to COVID-19;

- only 1 subject had reported persistence of severe COVID-19 symptoms after the end of treatment;

- most participants achieved alleviation and resolution of all targeted COVID-19 signs and symptoms by Day 28, with median times to alleviation and resolution of all targeted COVID-19 signs and symptoms ranging from 5.0 to 10.0 days across cohorts and dose subgroups;

- a tendency for a longer time to resolution of symptoms and a higher rate of viral load rebound at Day 10 for subjects in Cohort 1 who have been treated with the low posology of nirmatrelvir/ritonavir (150/100 mg BID). However, the reduction of viral load in these patients is similar to those observed in the other patients from Cohort 1.

As regards the rate of viral load rebound, data are unclear. The MAH was asked to detail for all participants who have experienced an increase in viral RNA after the end of treatment (n=10?): the cohort and posology; the viral load at the end of treatment, Day 10 and Day 14 (and the value of the increase in viral load to Day 10 and Day 14); the symptoms at the end of treatment, Day 10 and Day 14. The issue was resolved by providing comprehensive, participant-level data on viral load and symptoms by the MAH, which was considered satisfactory by the CHMP.

Viral variant data was available for the 66 nirmatrelvir/ritonavir treated participants. Omicron was the only variant observed in the study, with 22B (54.5%) and 21L (12.1%) the major Omicron subvariants observed. No emergent Mpro and cleavage mutations were observed in ≥2 participants. No persistent mutation or emergent mutation with increasing amino acid frequency in Mpro and cleavage region was observed.

In addition to the study C4671026, the summaries of 9 published literature articles evaluating the efficacy of nirmatrelvir/ritonavir in paediatric patients with COVID-19 who are at risk of progression to severe disease did not highlight any specific concern for the efficacy and use of Paxlovid in children.

2.5.3. Conclusions on the clinical efficacy

Efficacy results from study C4671026 are only supportive. However, these data did not highlight any efficacy concern with the selected posology of nirmatrelvir/ritonavir (i.e 300/100 mg BID for children ≥40 kg, 150/100 mg BID for children between 20 kg to <40 kg).

The MAH committed to provide PK data from 6 additional patients from cohort 2 as a **PAM**, and clarified that the data will be available by end of 2026.

2.6. Clinical safety

Introduction

Paxlovid is currently indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

The safety profile of Paxlovid is mainly characterised by non-serious events of dysgeusia, headache and gastrointestinal disorders such as diarrhoea and vomiting.

Skin rashes, pruritus and hypersensitivity reactions including anaphylaxis have also been reported and are listed in section 4.8 of the SmPC.

The main limiting factor for the use of Paxlovid in clinical practice is the important risk of interactions with other medicinal products, nirmatrelvir and ritonavir being notably both substrates and strong inhibitor of CYP3A4. Numerous drug-drug interactions are included in the SmPC, with the recommendations of consulting a multidisciplinary group to handle the complexity of some DDIs, in particular immunosuppressive drugs. Specific warnings have been included in section 4.4 with regard to this issue.

The MAH is now submitting a type II variation to extend the indication to paediatric patients 6 years of age and older weighing at least 20kg with the following doses:

- ≥ 6 years of age weighing ≥ 40 kg: 300mg nirmatrelvir /100mg ritonavir twice daily for 5 days
- ≥ 6 years of age weighing ≥ 20kg to <40kg: 150mg nirmatrelvir /100mg ritonavir twice daily for 5 days

This extension application is based on the interim results of the study C4671026, a Phase 2/3 interventional open-label, multi-center, single arm study designed to investigate safety, pharmacokinetics and efficacy of orally administered nirmatrelvir/ritonavir in nonhospitalised symptomatic paediatric participants with COVID-19 who are at risk of progression to severe disease. Only the results of the two first cohorts Cohort 1 and Cohort 2 (among the 5 planned cohorts) are available for the time being and have been submitted in the dossier:

Cohort 1 included participants weighing ≥ 40kg

- Cohort 1a: ≥ 12 to <18 years of age
- Cohort 1b: ≥ 6 to < 12 years of age

Cohort 2 included participants weighing ≥ 20kg to <40kg, children were aged ≥ 6 to < 18 years

Participants in cohort 1 received either the standard dose nirmatrelvir/ritonavir 300mg/100mg twice daily or nirmatrelvir/ritonavir 150mg/100mg twice daily.

Participants in cohort 2 received nirmatrelvir/ritonavir 150mg/100mg twice daily.

Additional supportive safety data are only derived from two paediatric participants enrolled in Phase 2 completed studies:

- One paediatric participant was enrolled in Study 1034 evaluating the safety and tolerability of nirmatrelvir/ritonavir for the treatment of COVID-19 in nonhospitalised, symptomatic, immunocompromised participants ≥12 years of age and weighing ≥40 kg with COVID-19. The participant was enrolled in the NMV/r 300/100mg 10-day treatment group and completed the study. This patient did not experience any TEAE or SAEs.
- One paediatric participant was enrolled in Study 1042 evaluating the safety and tolerability of nirmatrelvir/ritonavir in 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. This participant was treated with nirmatrelvir/ritonavir 300 mg/100 mg during 5 days and completed the study. No TEAEs or SAEs were observed.

Patient exposure

As of 7 June 2024, a total of 75 patients received at least 1 dose of NMV/r in study 1026:

- 61 patients weighing ≥40 kg were exposed to NMV/r in Cohort 1:
  - 52 subjects at a dose of 300mg/100mg (39 subjects aged ≥12 to <18 years and 13 subjects aged ≥6 to <12 years of age)
  - 9 participants aged ≥12 to <18 years at a dose of 150mg/100mg
- 14 patients weighing ≥20kg to <40 kg received NMV/r in Cohort 2 at the 150mg/100mg dose

Treatment duration was 5 days in this study. All subjects received the full dose except one patient in Cohort 2 who received NMV/r during 3 days.

At baseline, the mean age was 12.39 years and 53.2% were female. The most frequently reported comorbidities were obesity (49.3% of participants overall) and chronic respiratory disease (40.0% of participants overall).

Adverse events

An overview of treatment-emergent adverse events (TEAEs) (all causality and drug-related) reported in the study are displayed in the table below:

Treatment-Emergent Adverse Events (All Causalities and Treatment Related) – DAIDS Grade - Safety Analysis Set (Protocol C4671026)

	Cohort 1a 150mg (N=9) n (%)	Cohort 1a 300mg (N=39) n (%)	Cohort 1b 300mg (N=13) n (%)	Cohort 1 (N=61) n (%)	Cohort 2 150mg (N=14) n (%)	Total (N=75) n (%)
All Causality TEAEs						
Number of TEAEs	4	21	0	25	16	41
Participants with:						
TEAEs	2 (22.2)	12 (30.8)	0	14 (23.0)	6 (42.9)	20 (26.7)
Treatment-emergent SAEs	1 (11.1)	0	0	1 (1.6)	0	1 (1.3)
Non-Serious TEAEs	1 (11.1)	12 (30.8)	0	13 (21.3)	6 (42.9)	19 (25.3)
Maximum Grade 3 or 4 TEAEs	1 (11.1)	0	0	1 (1.6)	0	1 (1.3)
Maximum Grade 5 TEAEs	0	0	0	0	0	0
Discontinuations from study due to TEAEs[a]	0	0	0	0	0	0

Treatment-Emergent Adverse Events (All Causalities and Treatment Related) – DAIDS Grade - Safety Analysis Set (Protocol C4671026)

	Cohort 1a 150mg (N=9) n (%)	Cohort 1a 300mg (N=39) n (%)	Cohort 1b 300mg (N=13) n (%)	Cohort 1 (N=61) n (%)	Cohort 2 150mg (N=14) n (%)	Total (N=75) n (%)
Permanent discontinuations from any study intervention due to TEAEs and continue study[b]	0	0	0	0	1 (7.1)	1 (1.3)
Dosing interruptions of any study intervention due to TEAEs	0	0	0	0	0	0
Treatment-related TEAEs						
Number of TEAEs	0	4	0	4	3	7
Participants with:						
TEAEs	0	4 (10.3)	0	4 (6.6)	2 (14.3)	6 (8.0)
Treatment-emergent SAEs	0	0	0	0	0	0
Maximum Grade 3 or 4 TEAEs	0	0	0	0	0	0
Maximum Grade 5 TEAEs	0	0	0	0	0	0
Discontinuations from study due to TEAEs[a]	0	0	0	0	0	0
Permanent discontinuations from any study intervention due to TEAEs and continue study[b]	0	0	0	0	0	0
Dosing interruptions of any study intervention due to TEAEs	0	0	0	0	0	0

Most common TEAE (all causality)

Overall, 20 (26.7%) participants reported a total of 41 TEAEs (all drug causality). All but one reported non serious TEAEs. They were all mild to moderate in severity, except two Grade 4 SAEs (haemoglobin decreased and platelet count decreased) reported in a single patient, considered as not related to study drug and further described thereafter in the paragraph on SAEs.

The most frequently reported TEAEs were diarrhoea and headache, which were reported in 3 (4.0%) participants each. Vomiting, dizziness and cough were reported in 2 (2.7%) participants each.

A numerically higher proportion of participants (6 [42.9%] participants) in Cohort 2 reported all-causality TEAEs compared to Cohort 1 subgroups (14 [23.%] participants); Diarrhoea was the only AE reported in more than 1 participant in Cohort 2.

Treatment–related TEAEs:

Seven treatment-related TEAEs were reported in 6 (8.0%) participants: 4 (6.6%) participants in Cohort 1 and 2 (14.3%) participants in Cohort 2, including Diarrhoea (n = 2), Coating in mouth, Vomiting, Dysgeusia, Rash, and Rash pruritic (n = 1 for each).

All the treatment-related TEAEs were mild (Grade 1) in severity, except for 1 moderate (Grade 2) TEAE of Rash. None of the treatment-related TEAEs led to discontinuation from study or study intervention

Serious adverse event/deaths/other significant events

Death:

No deaths were reported in the study

SAEs:

One (1.3%) participant in Cohort 1a 150 mg experienced 2 Grade 4 all-causality SAEs (Haemoglobin decreased and platelet count decreased) on Day 10. Both the investigator and the Sponsor considered the events as not related to study drug. The events were considered likely due to the participant's medical history diagnosis. The patient was also receiving concomitant medications which confound the causality assessment.

Hypersensitivity

Hypersensitivity is an ADR which has been identified during post-marketing surveillance of nirmatrelvir/ritonavir.

During review for hypersensitivity events (MedDRA Hypersensitivity SMQ [narrow scope]), 2 participants (both from Cohort 1a) were identified with relevant treatment-related AEs:

- One patient experienced at Day 5 of treatment Grade 2 Rash on arm and chest that was reported as recovering/resolving at the time of the last available report
- One patient developed Grade 1 rash pruritic at day 3 of treatment which was reported as resolved on day 11.

Laboratory findings

The incidence of laboratory test abnormalities (without regard to baseline abnormality) is displayed in the table below:

Table 20. Incidence of Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) - Safety Analysis Set (Protocol C4671026)

Laboratory Abnormalities:			Cohort 1a 150mg		Cohort 1a 300mg		Cohort 1b 300mg		Cohort 1 61		Cohort 2 150mg		Total 75	
Number of Participants Evaluable for Laboratory Abnormalities:			9		39		13		28 (45.9%)		14		36 (48.0%)	
Number (%) of Participants with Laboratory Abnormalities:			5 (55.6%)		18 (46.2%)		5 (38.5%)				8 (57.1%)			
Group	Parameter (Units)	Primary Criteria	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
HEMATOLOGY	Hemoglobin (g/dL)	< 0.8x LLN	9	1 (11.1)	34	0	12	0	55	1 (1.8)	14	1 (7.1)	69	2 (2.9)
	Hematocrit (%)	< 0.8x LLN	9	1 (11.1)	34	1 (2.9)	12	0	55	2 (3.6)	14	2 (14.3)	69	4 (5.8)
	Erythrocytes (10^12/L)	< 0.8x LLN	8	0	33	2 (6.1)	12	0	53	2 (3.8)	14	3 (21.4)	67	5 (7.5)
	Platelets (10^9/L)	< 0.5x LLN	9	1 (11.1)	34	1 (2.9)	12	1 (8.3)	55	3 (5.5)	14	0	69	3 (4.3)
		> 1.75x ULN	9	0	34	0	12	0	55	0	14	1 (7.1)	69	1 (1.4)
	Leukocytes (10^9/L)	< 0.6x LLN	8	0	34	2 (5.9)	12	2 (16.7)	54	4 (7.4)	14	1 (7.1)	68	5 (7.4)
	Lymphocytes (10^9/L)	< 0.8x LLN	9	2 (22.2)	34	4 (11.8)	12	3 (25.0)	55	9 (16.4)	14	1 (7.1)	69	10 (14.5)
	Neutrophils (10^9/L)	< 0.8x LLN	9	3 (33.3)	34	3 (8.8)	12	4 (33.3)	55	10 (18.2)	14	2 (14.3)	69	12 (17.4)
		> 1.2x ULN	9	0	34	1 (2.9)	12	0	55	1 (1.8)	14	0	69	1 (1.4)
	Basophils (10^9/L)	> 1.2x ULN	9	0	34	0	12	0	55	0	14	2 (14.3)	69	2 (2.9)
	Eosinophils (10^9/L)	> 1.2x ULN	9	0	34	4 (11.8)	12	0	55	4 (7.3)	14	3 (21.4)	69	7 (10.1)
	Monocytes (10^9/L)	> 1.2x ULN	9	0	34	1 (2.9)	12	0	55	1 (1.8)	14	1 (7.1)	69	2 (2.9)
CLINICAL CHEMISTRY	Bilirubin (mg/dL)	> 1.5x ULN	9	0	39	0	12	0	60	0	14	1 (7.1)	74	1 (1.4)
	Alanine Aminotransferase (U/L)	> 3.0x ULN	9	0	38	0	12	0	59	0	14	1 (7.1)	73	1 (1.4)
	Protein (g/dL)	< 0.8x LLN	9	0	39	0	12	1 (8.3)	60	1 (1.7)	14	0	74	1 (1.4)
	Albumin (g/dL)	< 0.8x LLN	9	1 (11.1)	39	0	12	0	60	1 (1.7)	14	0	74	1 (1.4)
		> 1.2x ULN	9	1 (11.1)	39	3 (7.7)	12	2 (16.7)	60	6 (10.0)	14	2 (14.3)	74	8 (10.8)
	Sodium (mEq/L)	< 0.95x LLN	9	0	39	1 (2.6)	12	0	60	1 (1.7)	14	0	74	1 (1.4)
	Potassium (mEq/L)	> 1.1x ULN	9	0	38	2 (5.3)	12	1 (8.3)	59	3 (5.1)	14	0	73	3 (4.1)
	Chloride (mEq/L)	< 0.9x LLN	9	0	39	1 (2.6)	12	0	60	1 (1.7)	14	0	74	1 (1.4)
	Calcium (mg/dL)	< 0.9x LLN	9	0	39	1 (2.6)	12	0	60	1 (1.7)	13	0	73	1 (1.4)
	Bicarbonate (mEq/L)	< 0.9x LLN	8	0	39	0	12	0	59	0	13	1 (7.7)	72	1 (1.4)
		> 1.1x ULN	8	0	39	0	12	0	59	0	13	1 (7.7)	72	1 (1.4)
	Glucose (mg/dL)	> 1.5x ULN	9	0	39	1 (2.6)	12	0	60	1 (1.7)	14	0	74	1 (1.4)

N = total number of participants with at least one observation of the given laboratory test while on study treatment or during lag time.
n = number of participants with a laboratory abnormality meeting specified criteria while on study treatment or during lag time.
Percentages are displayed for the laboratory tests having a category with ≥ 1 evaluable participants.
Cohort 1a: ≥ 40 kg, ≥ 12 to < 18 years, Cohort 1b: ≥ 40 kg, ≥ 6 to < 12 years, Cohort 2: ≥ 20 to < 40 kg, ≥ 6 to < 18 years.
PFIZER CONFIDENTIAL SDTM Creation: 11JUN2024 (16:29) Source Data: adlb Table Generation: 19JUN2024 (10:58)
(Database snapshot date : 07JUN2024) Output File: ./nda_ph23/C4671026_sNDA/adlb_s301
Table 14.3.4.1.1 Nirmatrelvir/ritonavir is for Pfizer internal use.

No potential Hy's Law cases (i.e ALT or AST > 3xULN and Total Bilirubin > 2xULN and ALP < 2xULN) were identified.

One case of Temple's Corollary (i.e subjects with ALT or AST ≥ 3x ULN and Total Bilirubin < 2xULN) was identified at Day 34 in a Cohort 2 participant with Baseline AST, ALT, and total bilirubin values within the normal range.

No new safety signal was identified with regard to vital signs parameters.

Discontinuation due to adverse events

In Cohort 1, no participants discontinued study intervention due to any AE

In Cohort 2, one participant discontinued study intervention due to a non-serious (Grade 2) AE of Viral Infection on Day 5. The event was reported as resolved the day after. The investigator assessed the causality of the event as not related to the study intervention and noted relatedness to "rebound COVID or possible acute viral syndrome"

Post-marketing experience

Exposure:

it has been estimated that 23,122,499 patients have been exposed to nirmatrelvir/ritonavir cumulatively, from the first EUA up to the end of June 2024.

Paediatric data:

Post-marketing safety data regarding the use of nirmatrelvir/ritonavir in the paediatric population has been assessed through 31 August 2024. There has been a total of 262 post-marketing cases reported in paediatric patients (aged ≤17 years), which is equivalent to 0.45% of the total nirmatrelvir/ritonavir post-marketing dataset of 57,686 cases. Most reports were from US (62.6%) and involved patients in the age range of 12 to ≤17 years (123 cases) with a similar proportion of cases in the ≤6 years group (19 cases) and the 7 to 11 years group (21 cases). One patient was reported to be "in his 10's", and 98 cases did not report the patient's age.

There was a total of 24 serious cases (9.2%); none of these resulted in death. The most frequently reported AEs (≥5%) were Off-label use (56.5%), Dysgeusia (8.0%), COVID-19 (6.9%), Disease recurrence and Product use issue (both 5.7%) and Drug interaction (5.0%). The AEs reported in the paediatric population are considered consistent with those reported in the adult population and the known safety profile of nirmatrelvir/ritonavir as presented in the product labelling. No new or unexpected safety issues have been identified with the use of nirmatrelvir/ritonavir in the paediatric population.

Literature

The MAH conducted a cumulative literature search through 31 August 2024 to retrieve published literature for the evaluation of safety and tolerability of nirmatrelvir/ritonavir in paediatric patients with COVID-19. This search identified 4 full publications and 3 conference abstracts which are summarised below:

Author/Year	Study Description	Findings Reported by Authors	Author's Conclusions
Yan et al. Ann Transl Med. 2022;10(11):619.	Prospective cohort study of 5 paediatric participants aged 6 to 14 years (15–44 kg), with underlying diseases and confirmed COVID-19. Underlying diseases included congenital heart defects, cerebral palsy, Down syndrome, and leukemia. Participants were treated with nirmatrelvir/ritonavir for 5 days, within 5 days of symptom onset as follows: • aged 6-14 years with bodyweight <20 kg: 150 mg/100 mg once daily • aged 6-14 years with bodyweight 20-40 kg: 150 mg/100 mg twice daily • aged 12-14 years with bodyweight >40 kg: 300 mg/100 mg twice daily. An age-matched control group of 30 participants with underlying diseases who were not treated with Paxlovid was used to compare AEs and viral shedding times.	• One patient developed transient diarrhea, and 1 patient had transiently elevated liver enzymes. No other AEs were reported. • There were no significant differences in incidences of diarrhea and elevated liver enzymes between the Paxlovid-treated cases and the age-matched controls. • All 5 Paxlovid-treated cases recovered, with viral shedding times ranging from 4 to 11 days. • Compared with age-matched controls, the viral shedding times were not significantly different between groups. • All patients recovered and were discharged home within 2 weeks.	Authors concluded that Paxlovid is a feasible and safe option for treating SARS-CoV-2-infected children aged 6–14 years with underlying diseases. They noted that the efficacy was inconclusive, based on this study.
Fan et al. Curr Med Chem. 2024;10.2174/0109298673313885240621110518	A retrospective comparison study of 31 paediatric patients admitted to the Paediatric Intensive Care Unit due to SARS-CoV-2 infection who received (n = 12) or did not receive (control group, n = 19) Paxlovid.	• On the fifth day of drug administration, the Paxlovid group exhibited a statistically significant decrease in temperature compared to the control group ($p < 0.05$). • The administration of Paxlovid did not result in any observed AEs. Only 2 patients exhibited a transient elevation in liver enzyme levels; one was a patient with underlying condition. ALT and AST levels were 72 and 48 U/L, respectively, on admission, they increased to 113 and 54 U/L, respectively, on the 5th day of treatment, but continued to improve after the end of treatment and returned to normal 2 weeks after cessation of treatment. The second patient had no underlying condition but was subsequently diagnosed with Mycoplasma pneumoniae, their ALT and AST levels which were normal	The authors concluded that the use of Paxlovid in critically ill paediatric patients with COVID-19 can effectively control symptoms and promote virus clearance, demonstrating efficacy and a relatively low-risk profile.

Author/Year	Study Description	Findings Reported by Authors	Author's Conclusions
		upon admission increased to 105 and 120 U/L, respectively, on the 3rd day of treatment but then had returned to normal by the 5th day of treatment. • The Paxlovid group also exhibited a significantly shorter conversion time to negativity for novel coronavirus genes in the respiratory tract (9.5 days) compared to the control group (16 days, p <0.05). • No instances of renal impairment were reported in the Paxlovid-treated group. • No drug-related adverse effects, such as hypersensitivity reactions, diarrhea, or vomiting, were observed in Paxlovid-treated patients.	
Li et al. Front Pediatr. 2023;11:1160929.	A retrospective comparison study of 20 children with hematological diseases infected with the SARS-CoV-2 Omicron variant. Participants were divided into 2 groups, as follows: Group A: children with hematologic neoplastic diseases and 2 high-risk factors for the development of severe and critical illnesses. Group A participants were treated with Paxlovid (n = 9). Group B: participants with hematological malignancies and 1 risk factor for hematological malignancies and no other risk factors for severe or critical illness. Group B participants did not receive Paxlovid treatment (n = 11).	Adverse reactions during Paxlovid treatment were 2 cases (22.2%) with bitter taste and 1 case (11.1%) with diarrhea after administration. There were no cases of symptoms of elevated liver enzymes and creatinine. The authors reported that Paxlovid treatment in children with hematological diseases infected with SARS-CoV-2 resulted in faster viral clearance compared to those who did not receive Paxlovid.	The authors reported no apparent adverse reactions in children 12 years old and younger with underlying hematological diseases.
Wong et al. Nat Commun. 2024;15(1):4917	A retrospective cohort study aiming to emulate a hypothetical randomised controlled trial by using data cloning, to evaluate the effectiveness of nirmatrelvir/ritonavir in nonhospitalised	• Nirmatrelvir/ritonavir treatment was associated with a reduced 28-day all-cause hospitalisation (absolute risk reduction = 0.23%, 95% CI = 0.19%–0.31%; relative risk = 0.66, 95% CI = 0.56–0.71).	The authors reported that nirmatrelvir/ritonavir treatment was effective in reducing the 28-day all-cause hospitalisation risk among nonhospitalised

Author/Year	Study Description	Findings Reported by Authors	Author's Conclusions
	paediatric patients aged 12-17 years with SARS-CoV-2 Omicron variant infection.	• No events of mortality, in-hospital disease progression, or adverse clinical outcomes were observed among nirmatrelvir/ritonavir users.	paediatric patients aged 12-17 years with SARS-CoV-2 Omicron variant infection. They also noted that no events of mortality, in-hospital disease progression, or adverse clinical outcomes were observed among nirmatrelvir/ritonavir users.

2.6.1. Discussion on clinical safety

The main safety data of Paxlovid in paediatric population aged ≥ 6 to < 18 years of age are derived from the 75 patients enrolled in the pivotal PK study 1026.

Two additional paediatric participants >12 years of age were exposed to NMV/r in the Phase 2 completed studies 1034 and 1042; both patients did not experience any adverse events during treatment.

In study 1026, a total of 41 treatment-emergent adverse events (regardless of drug causality) were reported in 20 participants (26.7%) including 14 participants (23%) in cohort 1 (patients weighing ≥ 40kg) and 6 participants (42.9%) in Cohort 2 (patients weighing ≥ 20kg to <40kg).

The most commonly reported TEAEs were diarrhoea and headache (4% each) and vomiting, dizziness and cough (2.7% each). These events are non-serious, mild to moderate in severity and the majority of them was not considered related to study drug. Among the 41 TEAEs reported, only seven TEAEs in 6 participants (8%) were considered as treatment related: diarrhoea in 2 participants, coating in mouth, vomiting, dysgeusia, rash and rash pruritic in 1 participant each. All except a Grade 2 rash were mild in severity. None of them led to study treatment discontinuation. Both Rash (grade 2) and Rash pruritic (grade 1) occurred in cohort 1a (nirmatrelvir/ritonavir, at a dose of 300 mg/100 mg). The MAH should discuss the drug causality in each case separately and discuss whether the frequency of this ADR (classified as uncommon in adult population) should be reconsidered for paediatric population. The issue was resolved by providing case-level causality assessment, referencing broader safety data, and committing to update the frequency classification if warranted when more paediatric data become available.

Diarrhoea, vomiting, dysgeusia, rash and prurit are already listed adverse reactions in section 4.8 of Paxlovid SmPC with the frequency common. Coating and mouth (reported as white film around inside of mouth) was not listed but was reported as Grade 1 in only one participant. No SmPC update is necessary on the basis of these cases.

No death was reported during the study. Two SAEs of haemoglobin decreased and platelet count decreased were reported in single participant in cohort 1a receiving the lowest dose. These events were not considered as related to study drug but more likely due to the patient's underlying disease and concomitant medications taken.

One participant in cohort 2 discontinued study intervention due to a grade 2 event of viral infection, not judged as drug-related by the investigator.

According to the MAH, no clinically significant laboratory abnormalities or vital signs parameters were detected in the study. Notably, no potential Hy's Law case was identified. However, several participants experienced decreased neutrophils (17.4%) or decreased lymphocytes (14.5%) during the study. The MAH should discuss these findings, taking also into the high number of protocol deviations that might have potentially underestimated laboratory safety data. One incidence of Temple's Corollary was identified in a Cohort 2 participant with baseline alanine aminotransferase, aspartate aminotransferase, and total bilirubin values within the normal range. There is also a case of total bilirubin increase not discussed. The MAH should present the narrative of these participants, discuss the cases in relation to potential hepatotoxicity and the inclusion of these observations as an ADRs in Table 4.8 of the SmPC. The MAH resolved the concerns by providing detailed subject-level data, demonstrating that observed lab abnormalities were not clinically meaningful or drug-related, and that protocol deviations did not compromise safety assessment.

As stated by the MAH, specific analyses of AEs for intrinsic factors (such as age, sex, and race), extrinsic factors (such as food) and other special situations were not carried out due to small sample sizes, which is

supported. However, the MAH should discuss the results based on the limitations resulting from the lack of specific analyses, particularly for weight and comorbidities. The issue was resolved by transparently acknowledging the limitation, providing available descriptive data. Eventually, no meaningful subgroup analysis could be performed due to the small sample size.

Cumulatively, it is estimated that approximately 23,122,499 patients have been exposed to nirmatrelvir/ritonavir. The review of the post-marketing data focused on paediatric population and the published articles identified by the MAH did not identify any significant new information with regard to nirmatrelvir/ritonavir and use in paediatric population. A transient elevation in liver enzyme levels is evoked in two articles, but the causality of Paxlovid cannot be established based on the available data. Moreover, transaminases elevations have been observed in patients with COVID-19. As a reminder, section 4.4 already mentions that hepatic transaminase elevations have occurred in patients receiving ritonavir and hepatobiliary disorders are still under close monitoring in forthcoming PSURs.

2.6.2. Conclusions on clinical safety

Overall, no new or unexpected major safety finding emerged from the data submitted in this application. However, it is acknowledged that the available safety data rely only on a small sample size. Moreover, further information was requested on haematology test abnormalities, hepatotoxicity and rashes. The MAH resolved the concerns by providing detailed subject-level data, demonstrating that observed lab abnormalities were not clinically meaningful or drug-related, and that protocol deviations did not compromise safety assessment. Overall, it is important that the safety profile of Paxlovid in paediatric population should continue to be closely monitored in future PSURs.

In addition, the CHMP requested the MAH to submit the following safety data:

Monitor medication errors via upcoming PSURs (next DLP: Dec 2025) and discuss the effectiveness of risk minimisation measures and need of further measures accordingly.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.2 is acceptable.

2.8. Update of the Product information

Please refer to the attached Product Information.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable, as:

- there have been no significant changes to the package leaflet to warrant a readability test to be included with this submission.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

While most children are at lower risk for COVID-19 progression to severe outcomes, children with some underlying medical conditions and comorbidities remain at increased risk for hospitalisation, death, and morbidity.

3.1.2. Available therapies and unmet medical need

Although there are symptomatic and/or supportive treatments for COVID-19, few antiviral drugs are available to treat COVID-19 in children. Remdesivir is approved in the EU for the treatment of COVID-19 in adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia who require supplemental oxygen, as well as adults and paediatric patients who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. Some monoclonal antibodies are approved in EU in paediatric populations for the treatment of COVID-19, but they have lost their neutralising activity against the current circulating SARS-CoV-2 variants.

Therefore, there is an unmet need for oral antiviral agents that could be used for the treatment of non-hospitalised paediatric patients who are at increased risk for severe COVID-19. Nirmatrelvir/ritonavir is the only oral antiviral currently approved in EU for the treatment of COVID-19.

3.1.3. Main clinical studies

The paediatric development program for nirmatrelvir/ritonavir includes the pivotal Phase 2/3 open-label, interventional study C4671026 conducted in participants from birth through < 18 years of age. Dose selection in paediatric patients with mild-to-moderate COVID-19 is primarily based on matching exposure to adult COVID-19 patients (ie, extrapolation from adults to paediatrics). Participants were enrolled into 2 cohorts: cohort 1 (weight ≥40 kg, ≥12 to < 18 years (1a) or ≥6 to <12 years (1b)) and cohort 2 (weight ≥20 to <40 kg, ≥6 to 18 years). A total of 77 participants were assigned to study intervention, 75 of them received at least 1 dose of treatment (61 participants in Cohort 1 and 14 participants in Cohort 2).

3.2. Favourable effects

There was a reduction of viral load (adjusted mean change: -3.395 log10 copies/mL to -4.763 log10 copies/mL across all cohorts) numerically non-inferior to the reduction observed in adults in the studies 1005 (adjusted mean change: -3.087 log10 copies/mL) and 1002 (adjusted mean change: -3.419 log10 copies/mL).

There was no hospitalisation or death due to COVID-19.

Only 1 subject (1.3%) had reported persistence of severe COVID-19 symptoms after the end of treatment.

3.3. Uncertainties and limitations about favourable effects

This study was not designed to assess the clinical efficacy of nirmatrelvir/ritonavir (vs placebo or comparator) in children. Therefore, the efficacy data are only supportive to the pivotal PK data.

3.4. Unfavourable effects

The most commonly reported TEAEs were diarrhoea and headache (4% each) and vomiting, dizziness and cough (2.7% each). These events are non-serious, mild to moderate in severity and the majority of them was not considered related to study drug. Among the 41 TEAEs reported, only seven TEAEs in 6 participants (8%) were considered as treatment related: diarrhoea in 2 participants, coating in mouth, vomiting, dysgeusia, rash and rash pruritic in 1 participant each. All except a Grade 2 rash were mild in severity. None of them led to study treatment discontinuation.

No death was reported during the study. Two SAEs of haemoglobin decreased and platelet count decreased were reported in single participant in cohort 1a receiving the lowest dose. These events were not considered as related to study drug but more likely due to the patient's underlying disease and concomitant medications taken.

No clinically significant laboratory abnormalities or vital signs parameters were detected in the study.

The association of nirmatrelvir with the PK booster ritonavir may make it difficult to use in high-risk patients treated with other drugs (particularly in case of cancer, organ transplantation or immunosuppressive therapies).

3.5. Uncertainties and limitations about unfavourable effects

This study was not designed to assess the clinical safety of nirmatrelvir/ritonavir (vs placebo or comparator) in children. Safety data are available for only 75 patients.

As stated above, the PK of nirmatrelvir cannot be considered to be characterised in children aged 6-<18 years and weighing ≥ 20 kg, due to an insufficient number of interpretable PK samples and a non-acceptable PPK model. Based on MAH's data, exposure of nirmatrelvir (AUC and C_{max}) are higher (x30-40%) in children <18 years old than in adults.

3.6. Effects Table

Table 1. Effects Table for Paxlovid in children from 6 years to <18 years of age (data cut-off: 07 Jun 2024)

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
Favourable Effects					

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
Virologic response	Reduction of viral load from baseline to Day 5	adjusted mean change (log10 copies/ml)	Cohort 1a (150 mg): -4.763 Cohort 1a (300 mg): -4.369 Cohort 1b (300 mg): -4.589 Cohort 2 (150 mg): -3.395	Low number of subject (n=75); no comparator	C4671026
Clinical efficacy	Time to resolution of symptoms	median, days (95% CI)	Cohort 1a (150 mg): 10 (4-16) Cohort 1a (300 mg): 6 (5-9) Cohort 1b (300 mg): 6 (5-10) Cohort 2 (150 mg): 5 (4-9)		
	Rate of hospitalisation or death due to COVID-19	N (%)	0 subject		
Unfavourable Effects					
Clinical safety	Treatment-emergent AEs	N (%)	Cohort 1a (150 mg): 2 (22.2%) Cohort 1a (300 mg): 12 (30.8%) Cohort 1b (300 mg): 0 Cohort 2 (150 mg): 6 (42.9%) Most common TEAEs: diarrhoea and headache (4% each) and vomiting, dizziness and cough (2.7% each)	Low number of subject (n=75); no comparator	C4671026
	Treatment-related TEAEs	N (%)	Cohort 1a (150 mg): 0 Cohort 1a (300 mg): 4 (10.3%) Cohort 1b (300 mg): 0 Cohort 2 (150 mg): 2 (14.3%) 7 treatment-related TEAEs in 6 participants (8%): diarrhoea in 2 participants, coating in mouth, vomiting, dysgueusia, rash and rash pruritic in 1 participant each. All except a Grade 2 rash were mild in severity.		
	Discontinuations from study	N (%)	1 (Grade 2 viral infection, not related to treatment)		
	SAEs and deaths	N (%)	1 subject with 2 SAEs (haemoglobin and platelet count decreased) not related to treatment. No death.		
Laboratory safety	neutrophils count <0.8 X LLN	N (%)	12 (17.4%)		
	lymphocyte count <0.8 X LLN	N (%)	12 (17.4%)		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

There is a medical need for an effective treatment of COVID-19 in paediatric patients who are at risk to severe disease. Currently, remdesivir is the only effective antiviral alternative available in EU (since monoclonal antibodies are no longer used as they are not effective against the SARS-CoV-2 variants currently circulating in EU), notably indicated for the treatment of paediatric patients who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. However, remdesivir is an IV therapy requiring administration in a setting where severe hypersensitivity reactions can be managed, limiting its use for non-hospitalised subjects. Therefore, if an efficacy similar to that observed in adults can be extrapolated to children, Paxlovid brings an improved mode of administration for the treatment of COVID-19 in children ≥6 years of age and ≥20 kg who do not require supplemental oxygen and who are at increased risk for progressing to severe disease.

In the new targeted population, a safety profile of Paxlovid similar to that of adults is expected. Overall, Paxlovid is well tolerated, with mainly mild to moderate gastrointestinal disorders, dysgeusia and headache reported. No new or unexpected major safety finding emerged from the data submitted in this paediatric extension application.

3.7.2. Balance of benefits and risks

Overall, as in adults, a positive benefits/risks ratio could be assumed in children ≥6 years of age and ≥20 kg, considering that nirmatrelvir exposure is similar between this targeted population and adults.

3.8. Conclusions

The overall benefit-risk of Paxlovid is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	I, IIIA, IIIB and A
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

A grouped application comprised of a Type II Variation and a Type IB Variation, as follows:

Type II (C.I.6.a): Extension of indication to include treatment of coronavirus disease 2019 (COVID-19) in paediatric patients 6 years of age and older weighing at least 20 kg for PAXLOVID, based on the final analysis of Cohorts 1 and 2 from pivotal Study C4671026; this is a Phase 2/3, Interventional Safety, Pharmacokinetics, and Efficacy, Open-Label, Multi-Center, Single-Arm Study to Investigate Orally Administered PF 07321332 (Nirmatrelvir)/Ritonavir in Nonhospitalised Symptomatic Paediatric Participants With COVID-19 Who Are at Risk of Progression to Severe Disease. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.5 of the SmPC are updated. The Package Leaflet is updated in accordance. A revised RMP Version 4.2 has also been approved. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor changes to the PI, and the PI is brought in line with the latest QRD template version 10.4. As part of the application, the MAH is requesting a 1-year extension of the market protection.

Type IB (B.II.e.5.a.2): To add a new pack-size of 10 film-coated tablets (5 nirmatrelvir tablets + 5 ritonavir tablets) specific to paediatric patients 6 years and older weighing 20 kg to less than 40 kg and moderate renal impaired patients (EU/1/22/1625/003); the Package Leaflet and Labelling are updated accordingly.

The group of variations leads to amendments to the Summary of Product Characteristics, Labelling, Package Leaflet and Annex A and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I, IIIA, IIIB and A and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMA/PE/0000225184 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).