



Medicines & Healthcare products
Regulatory Agency



Public Assessment Report

National Procedure

Paxlovid 150 mg/100 mg film-coated tablets

(nirmatrelvir and ritonavir)

PLGB 00057/1710

The Public Assessment Report summarises the initial assessment at the time of approval in December 2021. The text in the original report remains unchanged.

Our advice is regularly updated on the basis of significant new data and our latest advice can be found in the [Summary of Product Characteristics](#).

Pfizer Limited

LAY SUMMARY

Paxlovid 150 mg/100 mg film-coated tablets (nirmatrelvir and ritonavir)

This is a summary of the Public Assessment Report (PAR) for Paxlovid 150 mg/100 mg film-coated tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Paxlovid in this lay summary for ease of reading.

For practical information about using Paxlovid, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Paxlovid and what is it used for?

This application is a full-dossier application. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indication.

Paxlovid is used for the treatment of COVID-19 in adults who do not require supplemental oxygen. It is only used in patients who are at increased risk for progression to severe COVID-19, including hospitalisation or death.

Patients must talk to their doctor if they do not feel better or if they feel worse while on treatment with Paxlovid.

How does Paxlovid work?

Paxlovid stops SARS-CoV-2, the virus that causes COVID-19 from multiplying. This can help the body to overcome the virus infection and may help the patient get better faster.

Paxlovid contains the active ingredients nirmatrelvir (formerly, PF 07321332) and ritonavir. Nirmatrelvir works by blocking the activity of an enzyme needed by the virus to multiply. Ritonavir (a protease inhibitor), slows the breakdown of nirmatrelvir, enabling nirmatrelvir to remain in the body for longer at levels that can stop the virus multiplying.

How is Paxlovid used?

Paxlovid consists of two different film-coated tablets: nirmatrelvir tablets and ritonavir tablets that are co-packaged together. The route of administration is by mouth.

The recommended dose is 2 tablets of nirmatrelvir with 1 tablet of ritonavir twice daily (a dose in the morning and a dose in the evening).

The blister foil (direct packaging of the tablets) for each day of treatment is divided into two different coloured sections to indicate which tablets need to be taken at each time of day - one side for the dose in the morning (AM dose) and the other side for the dose in the evening (PM dose).

A course of treatment lasts 5 days. For each dose, the patient should take all 3 tablets together at the same time. For patients with poor kidney function the advice is to take two tablets for 5 days. The treating doctor's advice should be followed. The tablets should be swallowed

whole and should not be chewed, broken or crushed. Paxlovid can be taken with or without meals.

Paxlovid is used for treating mild-to-moderate COVID-19.

Paxlovid is licenced for use in adults.

For further information on how Paxlovid is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Paxlovid have been shown in studies?

Paxlovid has been studied in non-hospitalised symptomatic adult patients with COVID-19 who have at least one prespecified risk factor of progressing to severe COVID-19. Paxlovid significantly reduced the proportion of participants with COVID-19 related hospitalisation or death by 89.1%, compared with placebo.

What are the possible side effects of Paxlovid?

For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at <https://coronavirus-yellowcard.mhra.gov.uk> or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with Paxlovid (which may affect more than 1 in 100 but less than 1 in 10 people) are

- Diarrhoea
- Vomiting
- Altered sense of taste

Why was Paxlovid approved?

It was concluded that Paxlovid has been shown to be effective in the treatment of COVID-19 (caused by SARS-CoV-2) in adults who are at risk for developing severe illness.

Furthermore, the side effects observed with use of this product are considered to be acceptable for this type of treatment. Therefore, the MHRA and CHM concluded that the benefits are greater than the risks and recommended that this medicine can be approved for use.

Paxlovid has been granted a Conditional Marketing Authorisation (CMA). CMAs are intended for medicinal products that address an unmet medical need, such as a lack of alternative therapy for a serious and life-threatening disease. CMAs may be granted where

comprehensive clinical data is not yet available, but it is judged that such data will become available soon.

What measures are being taken to ensure the safe and effective use of Paxlovid?

As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed for Paxlovid. The RMP details the important risks of Paxlovid, how these risks can be minimised, any uncertainties about Paxlovid (missing information), and how more information will be obtained about the known risks and uncertainties.

‘Drug interactions with CYP3A4 substrates and CYP3A4 inhibitors’ is included in the RMP as an important identified risk of Paxlovid. Areas of missing information include safety of Paxlovid in patients with active liver impairment; use during pregnancy and pregnancy outcomes; use during breastfeeding and whether there are any adverse effects on the breastfed child; and the possible emergence of viral variants that are resistant to treatment and effectiveness against viral variants of concern.

All suspected side effects reported by patients and healthcare professionals will be continuously monitored. Any new safety signals identified will be reviewed, and if necessary, appropriate action will be taken to minimise the risk to patients.

Routine pharmacovigilance activities include the monitoring and assessment of adverse drug reaction reports (ADRs) and signal detection. The company will compile and submit to MHRA monthly summary safety reports for Paxlovid. If there are any reports of exposures to Paxlovid during pregnancy, the company has in place a detailed follow-up questionnaire to ensure that all relevant information about the exposure, the pregnancy and the outcome is captured for full assessment of the case.

In addition to routine pharmacovigilance activities, the Company has committed to carry out further studies including a study to assess the safety and tolerability of the product in patients with moderately impaired liver function and in patients with normal liver function; and a post-authorisation safety study in pregnant and breastfeeding women. The Company has committed to implementing an antiviral surveillance programme and will also assess the feasibility and usefulness of conducting a study to provide information on the emergence of viral variants in patients treated with Paxlovid.

Information about a medicine, including the known side effects and how to manage them is provided in the product information for healthcare professionals (the Summary of Product Characteristics or ‘SmPC’) and patients (the Patient Information Leaflet or ‘PIL’). The SmPC and PIL are routine risk minimisation measures. No additional risk minimisation measures are necessary for Paxlovid.

Other information about Paxlovid

A Conditional Marketing Authorisation for Paxlovid was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 31 December 2021.

The full PAR for Paxlovid follows this summary.

This summary was last updated in October 2022.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Paxlovid 150 mg/100 mg film-coated tablets (PLGB 00057/1710) could be approved.

The product is indicated for the treatment of COVID 19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID 19.

The names of the active substances are nirmatrelvir and ritonavir. Nirmatrelvir was formerly known as PF 07321332.

Nirmatrelvir is a peptidomimetic inhibitor of the coronavirus 3C-like (3CL) protease, including the SARS-CoV-2 3CL protease. Inhibition of the 3CL protease renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication. Nirmatrelvir was shown to be a potent inhibitor of SARS-CoV-2 3CL protease ($K_i=0.00311 \mu\text{M}$ or $\text{IC}_{50}=0.0192 \mu\text{M}$) in a biochemical enzymatic assay.

Ritonavir is included as a metabolic booster and is not active against SARS-CoV-2 3CL protease. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir. The cytochrome P450 (CYP) superfamily are a group of enzymes involved in drug metabolism. The CYP3A subfamily is the most abundant group of CYP enzymes in the liver. By inhibiting the CYP3A metabolism of nirmatrelvir, ritonavir increases plasma concentrations of nirmatrelvir.

This application was approved under Regulation 50 of The Human Medicines Regulations 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), as a full-dossier application. All non-clinical data submitted were from studies conducted in accordance with Good Laboratory Practice (GLP). All clinical data submitted were from studies conducted in accordance with Good Clinical Practice (GCP). The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

This product has been authorised as a Conditional Marketing Authorisation (CMA). A CMA is granted in the interest of public health and is intended for medicinal products that fulfil an unmet medical need and the benefit of immediate availability outweighs the risk posed from less comprehensive data than normally required. Unmet medical needs include, for example, treatment or diagnosis of serious and life-threatening diseases where no satisfactory treatment methods are available. CMA may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon. Adequate evidence of safety and efficacy to enable the MHRA to conclude that the benefits are greater than the risks is required, and has been provided for Paxlovid 150 mg/100 mg film-coated tablets. The CMA for Paxlovid 150 mg/100 mg film-coated tablets, including the provision of any new information, will be reviewed every year until the full MA is granted and this report will be updated as necessary.

In line with the legal requirements for development of medicines in children, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) MHRA-100164-PIP01-21. At the time of the submission of the application the PIP was not yet completed as some measures were deferred.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 30 December 2021 to consider the wording of the SmPC, in particular, aspects of the therapeutic indication and details of potential interactions with other medicines. The CHM also discussed how best to monitor and mitigate against risks of SARS-CoV-2 resistance. The CHM agreed, on the evidence before them, that the application could be granted, albeit with conditions.

A CMA was granted for this product in Great Britain (GB, consisting of England, Scotland and Wales) on 31 December 2021.

II QUALITY ASPECTS

II.1 Introduction

Each pink nirmatrelvir film-coated tablet contains 150 mg of nirmatrelvir. Each white ritonavir film-coated tablet contains 100 mg of ritonavir.

In addition to nirmatrelvir and ritonavir, this product also contains the excipients, as follows:

Nirmatrelvir (pink colour) tablet

Tablet core: Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal silicon dioxide, sodium stearyl fumarate.

Film-coat: Hypromellose (E464), titanium dioxide (E171), macrogol (E1521), iron oxide red (E172).

Ritonavir (white colour) tablet

Tablet core: Copovidone, sorbitan laurate, silica colloidal anhydrous (E551), calcium hydrogen phosphate anhydrous, and sodium stearyl fumarate.

Film-coat: Hypromellose (E464), titanium dioxide (E171), macrogol (E1521), hydroxypropyl cellulose (E463), talc (E553b), silica colloidal anhydrous (E551), and polysorbate 80 (E433).

The finished product is packaged in cartons containing 5 daily-dose OPA/Al/PVC foil blister cards of 30 tablets. Each daily blister card contains 4 nirmatrelvir tablets and 2 ritonavir tablets. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCES

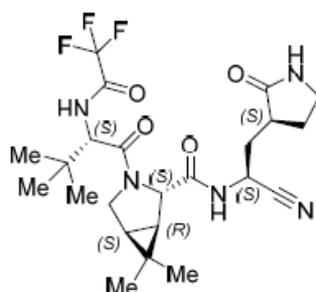
rINN: Nirmatrelvir

Chemical Name: a. CAS Style Name: 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[(1S)-1 cyano-2-[(3S)-2-oxo-3-pyrrolidinyl]ethyl]-3-[(2S)-3,3-dimethyl-1-oxo-2-[(2,2,2-trifluoroacetyl)amino] butyl]-6,6-dimethyl-, (1R,2S,5S)-

b. IUPAC Style Name: (1R,2S,5S)-N-((1S)-1-Cyano-2-((3S)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide

Molecular Formula: C₂₃H₃₂F₃N₅O₄

Chemical Structure:



Molecular Mass: 499.54 g/mol

Appearance: White to pale coloured powder

Solubility: Low solubility in aqueous media under physiologically relevant pH;

soluble in methyl isobutyl ketone (MIBK), 1-butanol and isopropyl acetate, sparingly soluble in anisole, n-propyl acetate, n-butyl acetate, insoluble in heptane.

Nirmatrelvir is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

rINN: Ritonavir

Chemical Names:

USP:

i) 2, 4, 7, 12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-5-thiazolymethyl ester [5S-(5R*,8R*,10R*,11R*)]

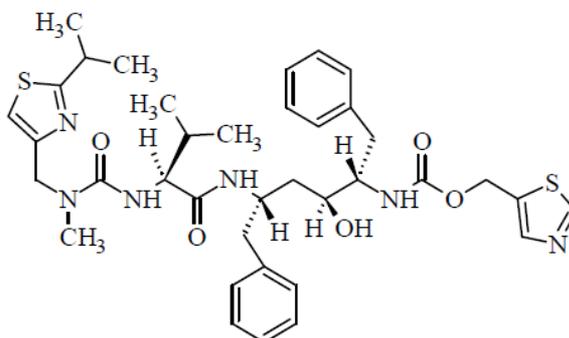
ii) 5-Thiazolymethyl [(αS)- α-[(1S,3S)-1-hydroxy-3-[(2S)-2-[3-[(2-isopropyl-4-thiazolyl)methyl]-3-methylureido]-3-methylbutyramido]-4-phenylbutyl]phenethyl]carbamate

EP:

Thiazol-5-ylmethyl[(1S,2S,4S)-1-benzyl-2-hydroxy-4-[[[(2S)-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl] methyl] carbamoyl] amino] butanoyl]amino]-5-phenylpentyl]carbamate

Molecular Formula: $C_{37}H_{48}N_6O_5S_2$

Chemical Structure:



Molecular Mass: 720.94

Appearance: white or almost-white powder
Solubility: practically insoluble in water, freely soluble in methanol, In methylene chloride, sparingly soluble in acetonitrile

Ritonavir is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products. The supplier has certified that this material is manufactured in compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, EMA/410/01 Rev. 3. Bovine milk used in production is sourced from healthy animals that meet milk quality standards for human consumption. No other ruminant materials are used during the process. This is accepted.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 1 year, with the storage conditions “Store below 25°C”, and “Do not refrigerate or freeze” is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a conditional marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

Nirmatrelvir is a peptidomimetic inhibitor of the coronavirus 3C-like (3CL) protease, including the SARS CoV 2 3CL protease (3CLpro). Inhibition of the 3CL protease renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication. Nirmatrelvir was shown to be a potent inhibitor of SARS CoV-2 3C-like protease (the dissociation constant describing the binding affinity between the inhibitor and the enzyme, $K_i = 0.00311 \mu\text{M}$ or the concentration required to produce half maximum inhibition, $IC_{50} = 0.0192 \mu\text{M}$) in a biochemical enzymatic assay.

Ritonavir is not active against SARS-CoV-2 3CLpro. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.

The primary pharmacodynamic properties of nirmatrelvir were evaluated in a series of *in vitro* enzymatic, and viral cell culture assays to determine the potency and specificity against SARS-CoV-2. *In vivo* studies were conducted in a mouse model using a mouse-adapted SARS coronavirus, SARS-CoV-2-MA10, able to infect mice. The absorption, distribution, metabolism and excretion (ADME) properties of nirmatrelvir have been studied in rats and monkeys and a full range of drug-drug interaction studies. The toxicology studies were conducted in metabolically similar species to humans, the rat and monkey, studies have been completed up to 1-month of repeated dosing. The embryo-fetal toxicity potential of nirmatrelvir was evaluated in GLP definitive rat and rabbit studies, and nirmatrelvir's effects on fertility was evaluated in a GLP rat study. Evaluation of effects of nirmatrelvir on pre and postnatal development is currently ongoing in a dedicated study in rats and the applicant has committed to provide the final draft report. The genotoxicity potential of nirmatrelvir was evaluated in a battery of genotoxicity studies.

All studies were conducted in accordance with current Good Laboratory Practice (GLP), unless otherwise specified.

III.2 Pharmacology

The mechanism of action of nirmatrelvir has been demonstrated by biochemical, crystallographic, and cell-based methods.

Data on binding and inhibition

The applicant presents inhibition data of nirmatrelvir against the SARS-CoV-2 3CLpro enzyme, which performs a critical role in viral replication of SARS-CoV-2. An IC_{50} of 0.0192 μ M and a K_i of 0.00311 μ M were measured in an enzymatic assay.

The oxidative human metabolite of nirmatrelvir, PF-07329268, is also a potent inhibitor of the SARS-CoV-2 3CLpro with an IC_{50} of 0.0175 μ M and a K_i of 0.00315 μ M.

Nirmatrelvir has also been shown to potently bind and inhibit SARS-CoV-2 3CLpro from all types of coronaviruses (alpha and beta), such as SAR-CoV-2, SARS-CoV-1, HKU1, OC43, MERS, 229E and NL63.

Molecular structure

Using x-ray crystallography the applicant has demonstrated the covalent binding characteristics of nirmatrelvir to the viral protease. In total there are 13 contact points on the SARS-CoV-2 3CLpro by nirmatrelvir, across the S1, S2 and S3 regions.

Selectivity of nirmatrelvir for SARS-CoV-2 3CLpro was confirmed in a screen of similar human and viral protease enzymes. nirmatrelvir was more than 500-fold more selective for the 3CL protease than for other proteases.

Antiviral Activity of nirmatrelvir

To evaluate its *in vitro* anti-viral activity, nirmatrelvir, was evaluated in two representative cell systems. In the physiologically relevant lung epithelial dNHBE cells, and human adenocarcinoma derived alveolar basal epithelial A549-ACE2 cells expressing ACE2.

- 1) A549 cells – these cells express ACE2, SARS-CoV-2 replication was inhibited successfully in a nanoluciferase assay. The concentration effective in producing 50% of the maximal response, EC_{50} was 77.9 nM and the concentration effective in producing 90% of the maximal response, EC_{90} was 215 nM.
- 2) dNHBE cells were incubated for 3 days with nirmatrelvir, SARS-CoV-2 replication was inhibited significantly: EC_{50} was 61.8 nM and EC_{90} was 181 nM.
- 3) dNHBE cells were incubated for 5 days with nirmatrelvir, SARS-CoV-2 replication was inhibited even more significantly: EC_{50} was 32.6 nM and EC_{90} was 56.1 nM.

Nirmatrelvir antiviral activity was also evaluated against other coronaviruses, including SARS-CoV-1, MERS-CoV, and human CoV-229E, in VeroE6, Vero81, and MRC-5 cells, respectively. For all coronaviruses evaluated, nirmatrelvir demonstrated significant inhibitory activity.

In addition, the lack of anti-viral activity of nirmatrelvir was demonstrated in two other respiratory viruses, the enterovirus 71 in human rhabdomyosarcoma cells and the human rhinovirus 1B in H1 HeLa cells.

Tests Against Major SARS-CoV-2 Variants

The applicant presents data on the potential anti-viral effects of nirmatrelvir. This was performed in a cell-based assay using the VeroE6 TMPRSS2 and VeroE6 P-gp Knockout cell lines. As nirmatrelvir and remdesivir are P-gp substrates, a P-gp inhibitor was used to suppress P-gp, which is highly expressed in the VeroE6 cells. Two cell lines were used as

nirmatrelvir activity was not measurable in the VeroE6 P-gp Knockout cell line using the CPE CellTiter-Glo Luminescent Cell-based Assay but were measurable in the TMPRSS2 cells.

Nirmatrelvir was shown to have anti-viral activity in a range of SARS-CoV-2 variants of concern (VOCs), and these include the original Wuhan strain, the alpha, beta, gamma, lambda, and delta variants with EC₅₀s ranging from 71.2 to 217 nM in VeroE6 TMPRSS2 cells, and 15.9 to 127.2 nM in VeroE6 P-gp Knockout cells. These figures compare well to that for remdesivir which was tested in parallel.

These data were reviewed in early December 2021, at the time of the emergence of the B.1.1.529 variant of concern, named as omicron, first reported by the WHO on 26 November 2021. Omicron has a large number of mutations including more than 30 genetic mutations of the spike protein of SARS-CoV-2. The spike protein of SARS-CoV-2 is targeted by some of the currently approved COVID-19 vaccines and may present a potential risk of variant escape for nirmatrelvir. The key binding sites of nirmatrelvir are on the S1, S2 and S3 regions of the SARS-CoV-2 main protease (3CLpro). The reported regions with the majority of mutations found in the omicron variant are different, localised mainly on the spike protein. The Company has committed to provide data from cell-based antiviral assays to evaluate the effect of the Omicron variant (B.1.1.529) on the inhibitory activity of nirmatrelvir.

Tests Against Various Protein Enzyme Mutations

There is emerging evidence that mutations on SARS-CoV-2 3CLpro enzymes would have negative impacts on the potency of nirmatrelvir inhibition. The applicant has explored 38 mutants of SARS-CoV-2 3CLpro, 15 of these are located at key contact residues for nirmatrelvir. Inhibitory activity of nirmatrelvir was reduced in 6/15 of these mutants, and the applicant has indicated further evaluation is ongoing. It is anticipated these studies will be completed at the time of submission of the full Marketing Authorisation application. This is acknowledged and acceptable.

Evaluation of *In Vitro* Selected Resistant MHV Against nirmatrelvir

Virus resistant development has initially been evaluated using the murine hepatitis virus (MHV) and the applicant is currently exploring the effect of multiple passages on SARS-CoV-2 activity.

Results against 4 mutant murine hepatitis virus confirms the lowering of inhibitory activity of nirmatrelvir. The potential for further mutations to SARS-CoV-2 resulting in increased anti-viral resistance will be explored by the applicant and the data provided once available.

The Company has committed to provide updated anti-viral activity results regarding newly circulating variants of concern on a regular monthly basis.

The Company has also committed to provide regular monthly data to evaluate the potential of mutations to SARS-CoV-2 resulting in increased anti-viral resistance.

***In Vivo* studies**

Nirmatrelvir was evaluated in a mouse adapted SARS-CoV-2 model (SARS-CoV-2 MA10). BALB/c mice were infected intranasally with SAR-CoV-2, leading to infection-related weight-loss. Following infection 2 groups of mice were treated with nirmatrelvir twice daily (300 mg/kg and 1000 mg/kg), and weight loss was improved versus vehicle-treated mice. The lungs of infected mice were also examined for viral titres. Nirmatrelvir treated mice had significantly reduced virus levels compared to the untreated controls. Histopathological

analysis of the lungs of the infected mice also confirm limited cellular integration, and reduced virus replication in nirmatrelvir treated mice. Results from 2 independent laboratories were provided to ensure reproducibility.

The animal model appears suitable and the findings were similar in 129 mice also infected with the SARS-CoV-2-MA10 virus, where reduced body weight loss and reduced lung viral titres occurred in nirmatrelvir- treated mice over untreated controls. The *in vivo* evidence of effectiveness of nirmatrelvir in the treatment of SARS-CoV-2 is adequate for the purposes of this application.

Ritonavir

The pharmacology is well-established for ritonavir. It has been identified as a potent Human Immunodeficiency Virus (HIV)-1 protease inhibitor. Its pharmacodynamic role as a direct antiviral agent in the treatment of SARS-CoV-2 infection is not established, however its role in increasing the *in vivo* concentration of the co-administered 3CLpro inhibitor, nirmatrelvir, is understood and is a well-established approach in treating HIV.

Secondary pharmacodynamics

Nirmatrelvir demonstrated a limited off-target selectivity profile in a broad panel of G protein-coupled receptors, kinases, transporters and phosphodiesterase enzyme inhibitor screens, and was devoid of activity against the cardiac ion channels Cav1.2, and Nav1.5 at clinically relevant exposures.

Safety pharmacology

The standard battery of safety pharmacology studies in line with ICH S7A was conducted to assess potential effects on vital organ systems (central nervous, cardiovascular, and respiratory).

Central nervous and respiratory systems:

Doses of up to 1000 mg/kg of nirmatrelvir to male Wistar Han rats produced no test article-related effects on functional observational battery (FOB) parameters. At the highest dose of 1000 mg/kg there were some treatment related changes in mean horizontal and vertical movement counts. Also, at this dose there were observations of higher respiratory rates and minute volume compared with the vehicle control. Overall, it is agreed that these effects are minimal and are of limited clinical significance.

Cardiovascular:

The *in vitro* studies consisted of hERG, isolated guinea pig heart or isolated rat aorta assays. Following exposure to nirmatrelvir there were no significant findings to indicate adverse effects on cardiac parameters.

Nirmatrelvir was administered at doses up to 150 (75 BID) mg/kg/day to cynomolgus monkeys, the highest dose produced minor and transient effects such as increased systolic, diastolic and mean BP, HR decreases, and associated RR, PR, and QT interval increases. There was a treatment-related decrease in QTc although no arrhythmias were noted. In addition, there were no correlating clinical signs or histopathological findings in the repeat-dose GLP toxicity studies up to 1 month in duration in rats or monkeys. The monkey studies also included ECG data and there were no nirmatrelvir -related changes in ECG parameters (HR, RR-, PR-, QRS-, QT-, QTc-intervals) or ECG in these studies.

Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interactions study has been conducted to date. Please refer to Section IV.2 Clinical pharmacology.

III.3 Pharmacokinetics

Methods of analysis

The lower limit of quantification (LLOQ) and upper limit of quantification (ULOQ) determined for each of the analysis methods is generally acceptable for nirmatrelvir. These studies are not performed in compliance with GLP, although are considered to have been performed according to principles of GLP. There is provision for this situation in the Guideline on bioanalytical method validation (EMA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**). There are no concerns with the information related to analytical methods provided.

None of the non-clinical studies were administered ritonavir, hence no analytical methods have been developed to measure this. The absence of this data is accepted.

Absorption

Single intravenous or oral doses of nirmatrelvir (MTBE solvate) were administered to rats. In addition, single oral doses of the crystalline anhydrous free base form of nirmatrelvir were also administered to rats. Following oral dosing, the bioavailability was very good (29-100%). Plasma clearance (CL) was moderate with a $t_{1/2}$ value of ~5 hours.

Single intravenous or oral doses of nirmatrelvir (MTBE solvate) were administered to monkeys. Following oral dosing, the bioavailability was low (<10%). Plasma CL was low with a $t_{1/2}$ value of <1 hour.

In rats following repeat administration, a decrease in nirmatrelvir AUC₂₄ was observed across dose groups on Day 14 compared with Day 1, with accumulation ratios ranging from 0.18 to 0.74.

Multiple dose toxicokinetic studies were performed in monkeys. In monkeys, a decrease in nirmatrelvir AUC₂₄ was observed primarily in the females in the mid dose group (100 mg/kg/day) with an accumulation ratio of 0.56. For the high dose group (600 mg/kg/day), AUC₂₄ of nirmatrelvir increased on Day 14 compared to Day 1 with accumulation ratios up to 1.7.

Systemic exposure increased with increasing dose in both pregnant rats and rabbits.

Distribution

The binding of nirmatrelvir to plasma proteins in rat, monkey, and human at concentrations ranging from 0.3 to 10 μ M was moderate and similar across these species and there was no concentration-dependency in this concentration range. Protein plasma binding was also evaluated in rabbits and concentration-dependent binding was observed.

The mean (\pm SD) red blood cell partition coefficient (K_p) and whole blood to plasma concentration ratios (C_b/C_p) of nirmatrelvir at a concentration of 1 μ M in human blood was 0.17 ± 0.11 and 0.60 ± 0.024 , respectively.

Metabolism

In vitro metabolism

The metabolism of nirmatrelvir was evaluated *in vitro* in liver microsomes (mouse, rat, hamster, rabbit, monkey, and human), hepatocytes (rat, monkey, and human), and *in vivo* in rat and monkey. A total of six metabolites were detected arising from hydroxylation, dehydrogenation, and hydrolysis reactions. The major metabolite was M4 (PF-07329268), an oxidative metabolite arising from hydroxylation at the 5-position of the pyrrolidinone ring, resulting in a pair of interconverting diastereomers. Other hydroxylation reactions occurred are considered to result in minor metabolites.

Besides oxidative biotransformation pathways, a metabolite M5 (PF-07320267) obtained through a hydrolytic cleavage across an amide bond in nirmatrelvir, was also detected as a minor metabolite in circulation and excreta from animals. The formation of M5 (PF-07320267) was observed in incubations of nirmatrelvir in human gut microbiota, alongside the destrifluoroacetyl metabolite M8 (PF-07331782). Approximately, 3.1% and 1.4% of nirmatrelvir was converted to M5 and M8 over the course of a 24-hour incubation with gut microbiota.

Experiments were conducted in human liver microsomes to determine the cytochrome P450 (CYP) isoforms involved in the *in vitro* metabolism of nirmatrelvir to four major metabolites, PF-07329265 (M1), PF-07329266 (M2), PF-07329267 (M3), and PF-07329268 (M4) for which standards were available.

Metabolite formation rates derived from incubations in human liver microsomes were used to calculate fractional pathways of clearance (fCL).

Percent inhibition with selective CYP inhibitors was determined in human liver microsome incubations by monitoring metabolite formation of nirmatrelvir. The clearance fractions and percent inhibition data were used to calculate the fraction metabolised (fm) for each CYP isoform pathway. Recombinant CYP results were used as qualitative support of the human liver microsomes fm estimations. Based on the collective results obtained, CYP3A4 was predicted to be the major contributor (fm= 0.99) to the *in vitro* metabolism of nirmatrelvir. No significant CYP3A5 contribution to the metabolism of nirmatrelvir is expected.

In vivo metabolism

In plasma of rats and monkeys, unchanged parent drug was by far the most prevalent drug-related entity, with M4 as a major metabolite in monkey; all other metabolites, including the hydrolysis product, were minor. The same was true for the profile of drug-related entities detected in rat urine and bile. Across a panel of human cytochrome P450 enzymes, oxidative metabolites were generated by CYP3A4 and CYP3A5, and any other reactions observed in other enzymes were trace. There were no human-unique metabolites observed.

Excretion

Urinary and/or biliary excretion of nirmatrelvir was assessed in single-dose pharmacokinetic studies after intravenous or oral dosing of nirmatrelvir to rats and monkeys. The percentage of nirmatrelvir dose excreted unchanged was 17% in the urine, 9% in the bile, and up to 11% in the faeces in rats, and 7% in the urine and 4% in the faeces in monkeys.

III.4 Toxicology

Rats and monkeys were selected as the toxicology species based on ADME results demonstrating similarities in metabolism and plasma protein binding of nirmatrelvir in rat, monkey and human. In addition, there is no pharmacologically relevant species since the target for nirmatrelvir is a virus-specific protein, and nirmatrelvir possesses a low off-target potential based on secondary pharmacology assessments conducted.

General Toxicology

Single dose toxicity studies were omitted. Repeat-dose toxicity studies up to 1-month duration of nirmatrelvir in rats and monkeys resulted in no adverse findings.

Repeat-dose toxicity studies of ritonavir in animals identified major target organs as the liver, retina, thyroid gland and kidney. Hepatic changes involved hepatocellular, biliary and phagocytic elements and were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium and retinal degeneration have been seen in all of the rodent studies conducted with ritonavir, but have not been seen in dogs. Ultrastructural evidence suggests that these retinal changes may be secondary to phospholipidosis. However, clinical trials revealed no evidence of medicinal product-induced ocular changes in humans. All thyroid changes were reversible upon discontinuation of ritonavir. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests.

Renal changes including tubular degeneration, chronic inflammation and proteinuria were noted in rats and are felt to be attributable to species-specific spontaneous disease. Furthermore, no clinically significant renal abnormalities were noted in clinical trials.

Genotoxicity

Paxlovid has not been evaluated for the potential to cause mutagenicity.

The standard battery of genotoxicity studies has been conducted, and these were negative. It is concluded that nirmatrelvir is non-genotoxic.

Ritonavir is confirmed to be non-genotoxic.

Carcinogenesis

Paxlovid, as a combination, has not been evaluated for the potential to cause carcinogenicity.

Due to the short treatment period, nirmatrelvir has not been evaluated for the potential to cause carcinogenicity.

Long-term carcinogenicity studies of ritonavir in mice and rats revealed tumorigenic potential specific for these species, but are regarded as of no relevance for humans.

Reproductive toxicity

In a fertility and early embryonic development study, nirmatrelvir was administered to male and female rats by oral gavage at doses of 60, 200, or 1,000 mg/kg/day once daily beginning 14 days prior to mating, throughout the mating phase, and continued through Gestation Day (GD) 6 for females and for a total of 32 doses for males. There were no effects on fertility, reproductive performance, or early embryonic development at doses up to 1,000 mg/kg/day representing 12x/4.3x based on the predicted human C_{max}/AUC₂₄ at a twice-daily dose of 300 mg/100 mg nirmatrelvir/ritonavir.

Developmental studies were completed in both pregnant rats and rabbits. The relevance of rabbit findings should be considered in line with the lower activity of nirmatrelvir in this species.

In rats there were limited adverse findings in maternal measurements, no mortality is noted, although one animal in the 100 mg/kg/day group was euthanised on GD 21 after it delivered

its litter prior to the scheduled caesarean section. This was not considered to be treatment related as this was the only incident and also the early delivery at GD21. Regarding fetal effects, there were no signs of reduction in weight gain or evidence of variations or malformations. The NOAEL is agreed to be 1000 mg/kg/day, representing a 16x/7.8x based on the predicted human total C_{max}/AUC₂₄ at a BID dose of 300/100 mg nirmatrelvir/ritonavir.

In rabbits there were no significant findings in terms of mortality, there were signs of dose dependent reduction in maternal weight and preimplantation loss. There was a significant decrease in fetal body weight at the highest dose tested, 1000 mg/kg/day, although this was not translated into any other adverse effects, including absence of variations or malformations. The applicant suggests the maternal NOAEL as the highest dose of 1000 mg/kg/day factoring the lack of significant findings, this is agreed. Due to the decreases in fetal weight the developmental NOAEL is also agreed as 300 mg/kg/day. The clinical safety margin at 300 mg/kg/day represents a 2.8-fold margin from the predicted human exposure (AUC) and 10-fold from the predicted human C_{max}.

Ritonavir produced no effects on fertility in rats.

Ritonavir was administered orally to pregnant rats (at 0, 15, 35, and 75 mg/kg/day) and rabbits (at 0, 25, 50, and 110 mg/kg/day) during organogenesis (on GD 6 through 17 and 6 through 19, respectively). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits. Increased incidences of early resorptions, ossification delays and developmental variations, as well as decreased foetal body weights were observed in the rat in the presence of maternal toxicity. A slight increase in the incidence of cryptorchidism was also noted in rats (at a maternally toxic dose). In the rabbit, resorptions, decreased litter size and decreased foetal weights were observed in the presence of maternal toxicity. In pre- and post-natal development study in rats, administration 0, 15, 35, and 60 mg/kg/day ritonavir from GD 6 through Post-natal Day 20 resulted in no developmental toxicity.

III.5 Ecotoxicity/Environmental Risk Assessment

Due to the urgent unmet clinical need for the product, a post approval commitment has been made to submit a full Environmental Risk Assessment (ERA).

III.6 Discussion on the non-clinical aspects

The grant of a conditional marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The following completed clinical studies were submitted with this application. From the ongoing studies, the interim study report from study 1005, topline results from the overall enrolled cohort of patients in study 1005 and the topline results from study 1010 were provided

Ritonavir Bioequivalence study

The source of Ritonavir was supported by a bioequivalence study which is not discussed further.

Clinical pharmacology studies

Study ID	Study Title	Study details/Primary Endpoints	Total
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				Sample Size
Study 1001 (completed)	A Phase 1, randomised, double-blind, sponsor-open, placebo-controlled, single- and multiple-dose escalation study to evaluate the safety, tolerability and pharmacokinetics of nirmatrelvir in healthy adult participants	First in human (FIH) study of nirmatrelvir in healthy adult participants. Study 1001 is a 5-part study.	Frequency, severity and causal relationship of TEAEs and withdrawals due to TEAEs. Frequency and magnitude of abnormal laboratory findings. Changes from baseline in vital sign measurements and 12-lead ECG parameters	Part-1: 13 Part-2: 29 Part-5: 10
		Part-1 (SAD) Part-2 (MAD) Part-5 (supratherapeutic exposures for QTc assessment)		
		Part-3 (relative bioavailability)	Ratio of AUC _{last} , AUC _{inf} and C _{max} of tablet formulation and suspension	Part-3: 12
		Part-4 (metabolism and excretion)	Percent recovery and cumulative recovery of drug-related material in urine and faeces	Part-4: 6
Study 1011 (completed)	A Phase 1, non-randomised, open-label study to assess the pharmacokinetics, safety and tolerability of nirmatrelvirboosted with ritonavir in adult participants with renal impairment and healthy participants with normal renal function	Plasma nirmatrelvir PK parameters: C _{max} , AUC _{inf} (or AUC _{last} if AUC _{inf} cannot be reliably estimated) Urine nirmatrelvir PK parameters: A _e , CL _r , if applicable and as data permit		34 (8 each in mild, moderate, severe renal impairment and 10 healthy participants).
Study 1014 (completed)	A phase 1, open-label, fixed sequence, 2 period crossover study to estimate the effect of carbamazepine on the pharmacokinetics of nirmatrelvir boosted with ritonavir in healthy participants	Nirmatrelvir C _{max} and AUC _{inf} with carbamazepine (test) versus without carbamazepine (reference)		12
Study 1015 (completed)	A phase 1, open-label, fixed sequence, 2 period crossover study to estimate the effect of itraconazole on the pharmacokinetics of nirmatrelvir/ ritonavir in healthy participants	Nirmatrelvir C _{max} and AUC _{tau} with itraconazole (test) versus without itraconazole (reference)		12

Pivotal Clinical Studies to Support the Safety and Efficacy Assessments

Study ID	Study Title	Dose and Duration of Study	Comparator	Total Planned Sample Size
Study 1005 (completed) – Only interim study report and topline results of	An interventional efficacy and safety, Phase 2/3, double-blind, 2-arm study to investigate orally administered	300/100 mg nirmatrelvir/Ritonavir administered orally q12h for 5 days	Placebo	3100

the overall participating cohort was submitted to support the CMA.	nirmatrelvir/Ritonavir compared with the placebo in non-hospitalised symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness.			
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Ongoing clinical pharmacology studies

Study ID	Study Title	Study details/Primary Endpoints	Total Sample Size
Study 1010 (ongoing)	A Phase 1, non-randomised, open-label study to assess the pharmacokinetics, safety and tolerability of nirmatrelvir boosted with ritonavir in adult participants with moderate hepatic impairment and healthy participants with normal hepatic function	Plasma nirmatrelvir PK parameters: C_{max} , AUC_{last} , AUC_{inf} (if data permit)	8 without hepatic impairment and 8 with moderate hepatic impairment
Study 1012 (ongoing)	A phase 1, open-label, 3 treatment, 6 sequence, 3 period crossover study to estimate the effect of nirmatrelvir/ritonavir and ritonavir on the pharmacokinetics of dabigatran in healthy participants	AUC_{inf} and C_{max} of dabigatran with nirmatrelvir/ritonavir (test) versus dabigatran alone (reference)	Approx. 24
Study 1013 (ongoing)	A phase 1, open-label, 3 treatment, 6 sequence, 3 period crossover study to estimate the effect of nirmatrelvir/ritonavir and ritonavir on the pharmacokinetics of midazolam in healthy participants	AUC_{inf} and C_{max} of midazolam with nirmatrelvir/ritonavir (test) versus midazolam alone (reference)	Approx. 12

Ongoing Phase 2/3 clinical studies

Study ID	Study Title	Dose and Duration of Study	Comparator	Total Planned Sample Size
Study 1002 (On-going) Will be submitted as a variation to the future CMA when data are available	An interventional efficacy and safety, phase 2/3, double-blind, 2-arm study to investigate orally administered nirmatrelvir/Ritonavir compared with placebo in non-hospitalised symptomatic adult participants with COVID-19	300/100 mg nirmatrelvir ritonavir administered orally q12h for 5 days	Placebo	1140

	who are at low risk of progressing to severe illness			
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IV. 2 Clinical Pharmacology

The clinical pharmacology of nirmatrelvir (with and without coadministration with ritonavir) has been studied in 4 completed studies, including a 5-part Phase 1 study (Study 1001). Hepatic impairment, dabigatran- and midazolam-interaction studies are ongoing.

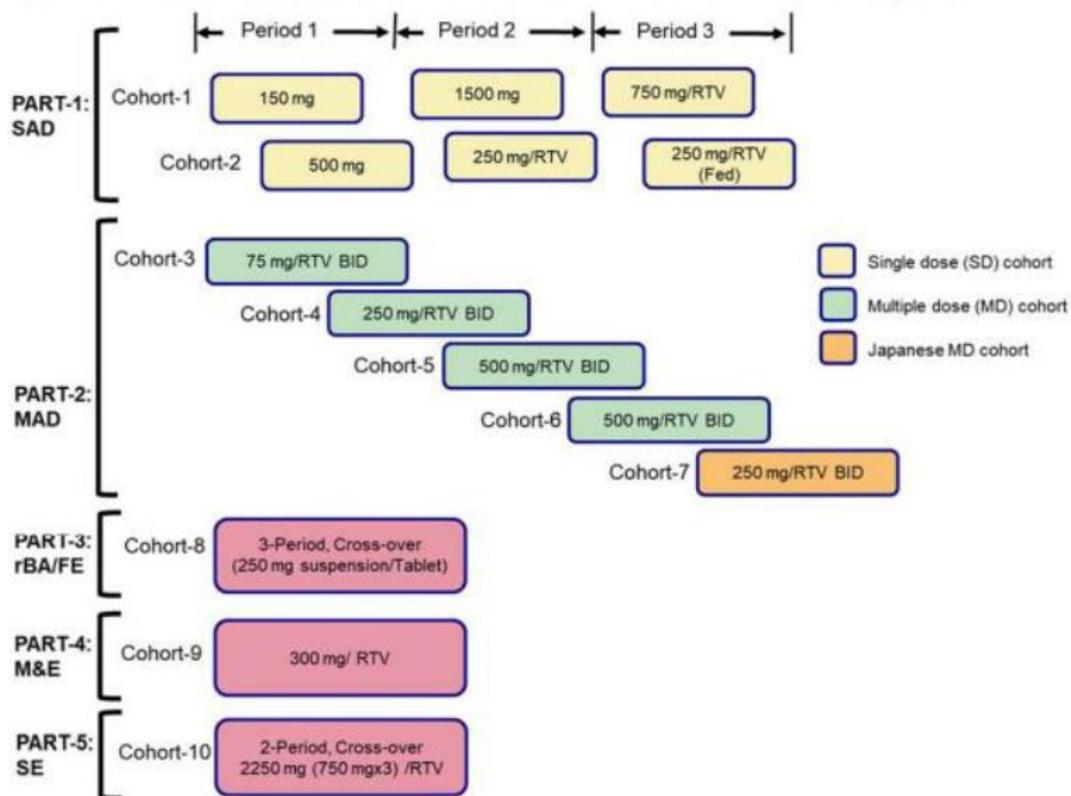
Study 1001

This was a Phase 1, randomised, double-blind, sponsor-open, placebo-controlled, single- and multiple-dose escalation study to evaluate the safety, tolerability and pharmacokinetics of nirmatrelvir in healthy adult participants.

The study was composed of 5 parts; Part 1 was a single-ascending dose (SAD) study, Part 2 was a multiple ascending dose (MAD) study, Part 3 was a relative bioavailability study, Part 4 was a metabolism and excretion study and Part 5 was a suprathapeutic exposure study (figure 1).

An extemporaneously prepared oral suspension and an uncoated 250 mg immediate release tablet were developed to support clinical Study 1001.

Figure 1. Study design Schema of Study 1001 in healthy Adult Participants



Part 1- SAD study

Less than dose proportional increases in nirmatrelvir exposure was observed following single dose administration of nirmatrelvir as an oral suspension at doses of 150 mg, 500 mg, and

1500 mg without ritonavir under fasted conditions. The median T_{max} was observed at 0.634 to 1-hour post-dose across all doses tested without ritonavir. Of the doses administered without ritonavir, mean t_{1/2} could only be reported for the 150 mg dose, which was 2.02 hours. Use of ritonavir as PK enhancer appeared to considerably increase nirmatrelvir2 exposure.

Use of ritonavir as PK enhancer increased nirmatrelvir exposure with dose-normalised C_{max} and AUC values increasing up to 10-15-fold. The geometric mean AUC_{inf}, AUC_{last} and C_{max} following a single dose of nirmatrelvir 250 mg in the fasted state enhanced with ritonavir was 28.22 µg·h/mL, 27.6 µg·h/mL and 2.882 µg/mL, respectively. Comparatively, the geometric mean AUC_{inf}, AUC_{last} and C_{max} following a single dose of nirmatrelvir 250mg in fasted state (without ritonavir) in Part-3 was 3.513 µg·h/mL, 3.318 µg·h/mL and 0.883 µg/mL, respectively.

A (tertiary) objective of this study was to evaluate the effect of food (high fat meal) on the exposure of nirmatrelvir following a single oral dose of nirmatrelvir tablet formulation, if evaluated. The Part 1 food interaction study used the suspension formulation and not the final tablet formulation. This arm of the study ritonavir was co-administered with nirmatrelvir.

Part 2- MAD study

Following multiple dose administration of nirmatrelvir/ritonavir at doses of 75/100 mg, 250/100 mg, and 500/100 mg BID under fasted conditions, a median T_{max} of 0.750 to 2.75 hours post-dose was observed across all treatments on Days 1, 5, and 10. nirmatrelvir exposure on Days 1, 5, and 10 appeared to increase in a less than dose proportional manner across the doses studied with dose normalized AUC_{tau} and C_{max} values decreasing as the dose increased.

Steady-state plasma concentrations appeared to have been achieved by Day 2 for all doses and treatments. Plasma nirmatrelvir accumulation was approximately 2-fold following multiple dosing and values were similar on Day 5 and Day 10. Geometric mean accumulation ratios ranged from 1.8 to 2.1 for AUC_{tau} (Rac) and C_{max} (Rac, C_{max}), on Day 10, across all treatments.

Following multiple dosing of nirmatrelvir/ritonavir, nirmatrelvir mean t_{1/2} values on Day 10 ranged from 6.8 to 8.0 hours across all treatments in non-Japanese participants.

Urinary recovery (%A_{tau}) of unchanged nirmatrelvir decreased with an increase in nirmatrelvir dose, with 64%, 52% and 23% of the dose recovered in urine for the 75 mg, 250 mg, and 500 mg nirmatrelvir doses enhanced with 100 mg ritonavir, respectively. However, renal clearance (CL_r) was similar across all doses with 3.782, 3.433 and 2.934 L/hr at 75 mg, 250 mg and 500 mg nirmatrelvir doses enhanced with 100 mg ritonavir, respectively.

Part 3- Bioavailability study

This study compared the tablet and suspension formulations. A total of 12 participants were treated in Part-3 and completed the study. All the 12 participants were between the age of 20-48 years and were male.

Nirmatrelvir plasma exposure for the tablet was lower compared to the suspension following a single 250 mg oral dose of nirmatrelvir, with approximately 19% and 44% lower geometric mean AUC_{last} and C_{max} values, respectively. The test/reference ratios of the adjusted geometric means (90% CI) for nirmatrelvir AUC_{last} and C_{max} were 81.21% (69.21%, 95.28%) and 56.38% (43.42%, 73.19%) respectively, for the tablet treatment (Test) compared to the suspension treatment (Reference). Following a single 250 mg oral dose of

nirmatrelvir administered as tablet or oral suspension, median T_{max} of 1.0 hour post-dose was observed. Plasma concentrations for the tablet formulation were lower than those observed for the suspension and appeared to decline more slowly over time, with mean t_{1/2} values of 9.09 hours for the tablet compared to 5.63 hours for the suspension.

Influence of food

The (secondary) objective of this study was to evaluate the effect of food (high-fat high-calorie meal) on the exposure of nirmatrelvir following a single oral dose of nirmatrelvir tablet formulation.

Plasma nirmatrelvir exposure was higher for the fed treatment following administration of a single oral 250 mg nirmatrelvir tablet with a high-fat, high-calorie meal, with approximately 1.5 and 2.4-fold higher geometric mean AUC_{last} and C_{max} values for fed treatment compared to the fasted treatment, respectively. The test/reference ratios of the adjusted geometric means (90% CI) for nirmatrelvir AUC_{last} and C_{max} were 148.91% (126.92%, 174.72%) and 244.84% (188.58%, 317.87%), respectively, for the fed treatment (Test) compared to the fasted treatment (Reference). Following administration of a 250 mg nirmatrelvir tablet with a high-fat, high-calorie meal, a median T_{max} of 1.75 hours post-dose was observed compared to 1.0 hour post-dose for the fasted treatment. Plasma concentrations for the fed treatment were higher than those observed for the fasted treatment and appeared to decline more rapidly over time, with mean t_{1/2} values of 1.85 hours for the fed treatment compared to 9.09 hours for the fasted treatment.

In Part 1, dosing with a high fat meal modestly increased the exposure of nirmatrelvir (approximately 15% increase in mean C_{max} and 1.6% increase in mean AUC_{last}) relative to fasting conditions following administration of a suspension formulation of nirmatrelvir co-administered with ritonavir tablets .

Part 4 – Metabolism and excretion study

This was an open-label, non-randomised, single period study to evaluate the metabolism and excretion of nirmatrelvir. Urine and faeces were collected for determination of total drug-related material and metabolite profiling.

Overall mean ± SD (range) mass recovery of nirmatrelvir-related material in excreta (urine and faeces) was calculated at 84.9% ± 8.9% (70.7%, 95.5%) which included 80.7% ± 8.0% by quantitative 19F- NMR and 4.2% ± 1.3% excreted as metabolite M8 (19F- NMR silent due to loss of trifluoroacetyl group) quantified by UHPLC-HRMS. The excretion into urine and faeces was 49.6% and 35.3% of dose, respectively. Almost all the excretion of drug-related material occurred over the first 5 days following the dose, and most of the drug-related material that was excreted in the urine appeared in within the first day following the dose.

In plasma, the only drug-related entity quantifiable by 19F- NMR was unchanged nirmatrelvir. In excreta, nirmatrelvir was the predominant drug-related entity. After normalization of the data to 100% mass balance, unmetabolized nirmatrelvir represented 82.5% of the drug-related material, with 55.0% in urine and 27.5% in faeces. Metabolite M5, arising via hydrolysis, was present at 12.1% of dose with almost all in the faeces. All other fluorine-containing metabolites were minor (<1% of dose), and M8 was 4.2% of dose.

Part 5 - Supratherapeutic exposures

This was a double-blind, sponsor-open, randomised, cross-over cohort to evaluate safety and tolerability at supratherapeutic exposures.

A total of 10 participants were treated in Part-5. All the 10 participants were between the age of 20-57 years and the majority were male (7/10 participants).

The total dose planned for nirmatrelvir was 2250 mg administered as 3 split doses of 750 mg at 0, 2h and 4h, pharmacokinetically enhanced with ritonavir (3 doses of 100 mg at -12, 0 and 12 hours relative to nirmatrelvir). Nirmatrelvir was administered approximately 2h after breakfast.

Triplicate electrocardiogram (ECG) measurements, vital signs, and pharmacokinetic samples were collected in fasted state (approximately 4h after the food) at nominal times of 0, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12, 24, 48, 72 and 96 hours after the first dose.

Nirmatrelvir mean C_{max} was observed in a median T_{max} of 5.0 hours after the first split dose. Nirmatrelvir mean t_{1/2} was 7.5 hours. Nirmatrelvir mean AUClast and C_{max} values were 188.2 µg·hr/mL and 15.94 µg/mL, respectively. Inter-individual variability for nirmatrelvir exposure based on geometric %CV was 35% for both AUClast and AUC_{inf} and 27% for C_{max}.

Following suprathereapeutic 2250 mg oral suspension nirmatrelvir enhanced with 100 mg ritonavir, nirmatrelvir mean AUClast and C_{max} values were 188.2 µg·hr/mL and 15.94 µg/mL, respectively.

Study 1011 – Impaired renal function study

This was A Phase 1, non-randomised, open-label study to assess the pharmacokinetics, safety and tolerability of nirmatrelvir, boosted with Ritonavir, in adult participants with renal impairment and in healthy participants with normal renal function.

On Day -1, 12 hours prior to dosing of nirmatrelvir, participants received a 100 mg ritonavir tablet. On Day 1, following an overnight fast of at least 10 hours, participants received 100 mg nirmatrelvir and 100 mg ritonavir at 0800 hours. Participants received 2 additional doses of 100 mg ritonavir at 12 and 24 hours after receiving nirmatrelvir.

Participants were selected and categorised into normal renal function or renal impairment groups based on their estimated glomerular filtration rate (eGFR).

nirmatrelvir systemic exposure increased with increasing severity of renal impairment. Results of the statistical comparisons for nirmatrelvir adjusted geometric mean(90%CI) AUC_{inf} test/reference ratios comparing the varying degrees of renal impairment (test) to normal renal function (reference) were 123.84% (99.64%, 153.91%) for participants with mild renal impairment, 187.40% (148.52%, 236.46%) for participants with moderate renal impairment, and 304.49% (237.60%, 390.21%) for participants with severe renal impairment. Adjusted geometric mean (90% CI) C_{max} test/reference ratios were 129.78% (101.93%, 165.25%) for participants with mild renal impairment, 138.12% (113.18%, 168.55%) for participants with moderate renal impairment, and 148.02% (111.40%, 196.68%) for participants with severe renal impairment.

Results of the regression analysis using estimated glomerular filtration rate (eGFR) showed a decrease in CL/F for nirmatrelvir with an increase in severity of renal impairment. Renal clearance also decreased especially for the moderate and severe renal impairment groups with an approximately 47% and 80% decrease in geometric mean CL_r values, respectively, compared to the normal renal functional group.

Urinary recovery of unchanged nirmatrelvir was 31.2%, 42.7%, 30.8%, and 18.5% for the normal functional group, mild, moderate, and severe renal impairment groups, respectively.

The systemic exposure of nirmatrelvir increased with increasing severity of renal impairment. It is known that ritonavir is primarily metabolised by the liver and its renal clearance is negligible.

Study 1014 - Effect of carbamazepine

This was a Phase 1, fixed sequence, 2-period study to estimate the effect of a strong cytochrome P450 3A4 (CYP3A4) inducer, carbamazepine, on the pharmacokinetics of nirmatrelvir and ritonavir in healthy participants. This study consisted of 2 periods. Period 1 included nirmatrelvir/ritonavir 300 mg/100mg as a single oral dose and Period 2 included carbamazepine on a titration schedule as follows: Days 1, 2, and 3 at 100 mg twice daily (BID), Days 4-7 at 200 mg BID, and Days 8-15 at 300 mg BID.

Twelve participants were enrolled into the study. All 12 participants were treated and 10 completed the study.

The test/reference ratios of the adjusted geometric means for nirmatrelvir AUC_{inf} and C_{max}(90% CIs) were 44.50% (33.77%, 58.65%) and 56.82% (47.04%, 68.62%), respectively, following nirmatrelvir/ritonavir 300 mg/100 mg co-administration with multiple oral doses of carbamazepine (Test) compared to nirmatrelvir/ritonavir administered alone (Reference).

The test/reference ratios of the adjusted geometric means for ritonavir AUC_{inf} and C_{max}(90% CIs) were 16.57% (13.32%, 20.60%) and 25.59% (18.76%, 34.91%), respectively, following nirmatrelvir/ritonavir 300 mg/100 mg co-administration with multiple oral doses of carbamazepine (Test) compared to administration of nirmatrelvir/ritonavir alone (Reference).

The effect of co-administration of carbamazepine, a strong CYP3A4 inducer, on the pharmacokinetics of nirmatrelvir and ritonavir in healthy participants decreased the exposure (AUC and C_{max}) of both nirmatrelvir and ritonavir. This is in line with the expectation that both nirmatrelvir and ritonavir are CYP3A substrates.

Study 1015 – Effect of itraconazole

This was a Phase 1, open-label, 2-period, fixed sequence crossover study to estimate the effect of the strong CYP3A4 inhibitor, itraconazole, on the PK of nirmatrelvir in healthy participants. In Period 1, participants received nirmatrelvir/ritonavir 300/100mg orally every 12 hours for a total of 5 doses, with the last dose administered on the morning of Day 3. In Period 2, participants received itraconazole 200 mg orally once a day (QD) for 8 days. On Days 4 through 6 of Period 2, participants received nirmatrelvir/ritonavir 300/100mg orally every 12 hours for a total of 5 doses.

A total of 12 participants were assigned to treatment and received treatment with nirmatrelvir/ritonavir 300/100 mg in Period 1. One participant discontinued due to withdrawal. The remaining 11 participants completed Period 1 and continued to receive itraconazole 200mg + nirmatrelvir/ritonavir 300/100mg in Period 2 and all completed Period 2.

Co-administration of multiple oral doses of itraconazole 200 mg increased nirmatrelvir

exposure. The ratios of the adjusted geometric means (90% CIs) for nirmatrelvir AUC_{tau} and C_{max} were 138.82% (129.25%, 149.11%) and 118.57% (112.50%, 124.97%), respectively, when nirmatrelvir/ritonavir was co-administered with multiple doses of itraconazole (Test) as compared to nirmatrelvir/ritonavir administered alone (Reference).

Co-administration of multiple oral 200 mg doses of itraconazole increased ritonavir exposure with approximately 21% and 15% increases in ritonavir geometric mean AUC_{tau} and C_{max}, respectively, compared to nirmatrelvir/ritonavir administered alone.

The effect of co-administration of itraconazole, a strong CYP3A4 inhibitor, on the PK of nirmatrelvir and ritonavir in healthy participants increased the exposure (AUC and C_{max}) of both nirmatrelvir and ritonavir. This is in line with the expectation that both nirmatrelvir and ritonavir are CYP3A substrates.

IV.3 Clinical efficacy

The application for use of Paxlovid in non-hospitalised adult patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19, was supported by the interim analysis of study 1005.

Study 1005 - Phase 2/3 study in high risk Covid-19

This was an interventional efficacy and safety, Phase 2/3, double-blind, 2-arm study to investigate orally administered nirmatrelvir/ritonavir compared with placebo in non-hospitalised symptomatic adult participants with Covid-19 who are at increased risk of progressing to severe illness.

Methods

Eligible participants with a confirmed diagnosis of SARS-CoV-2 infection were randomised (1:1) to receive nirmatrelvir/ritonavir or placebo orally every 12 hours for 5 days (10 doses total). Randomisation was stratified by geographic region and whether participants received/were expected to receive COVID-19 therapeutic monoclonal antibody (mAb) treatment based on the site investigator's assessment at the time of randomisation. Approximately 3100 participants were planned to be randomly assigned to study intervention.

Enrolment of participants who received/were expected to receive mAb treatment for COVID-19 was limited to approximately 25% of participants. Enrolment of participants who had COVID-19 symptom onset >3 days prior to randomisation was limited to a total of approximately 1000 patients.

Participants were screened within 48 hours of randomisation. The treatment duration was 5 days, efficacy assessments were conducted through Day 28, a safety follow-up through Day 34, and long-term follow-up at weeks 12 and 24.

Participants were provided an electronic handheld device or used their own device to record daily COVID-19 signs and symptoms, study intervention administration, and patient reported outcome (PRO) assessments in the study diary.

Details of participants' COVID-19 related medical visits including hospitalisation were collected during study visits.

A nasopharyngeal/nasal swab was collected to measure SARS-CoV-2 RNA by RT-PCR.

Safety assessments included targeted physical examinations, vital signs, ECG, laboratory assessments, pregnancy testing, Adverse Events (AEs), Serious Adverse Events (SAEs) and other safety reporting.

Additionally, blood samples were collected for pharmacokinetic analysis.

An independent external – data monitoring committee reviewed unblinded data to ensure safety of participants throughout the study. In addition to safety review, they reviewed

- Sentinel cohort safety review – After first 60 patients completed day 10
- Proof of concept assessment – viral load data of approximately 200 participants in the primary analysis set with evaluable data of day 5 assessments.
- Interim analyses: A planned interim analysis for efficacy and futility with sample size re-estimation was done after approximately 45% of participants in the mITT analysis set complete Day 28 assessments. A second interim analysis for efficacy and futility was also planned to be performed after approximately 70% of participants in the mITT analysis set complete Day 28 assessments.

Treatments

Eligible patients were randomized in a 1:1 ratio to:

- Nirmatrelvir 150mg tablet/ritonavir 100 mg capsule
- Placebo for nirmatrelvir/placebo for ritonavir

Nirmatrelvir 150 mg or its placebo was dispensed in a blister wallet, while ritonavir 100 mg capsules or its placebo was dispensed in HDPE bottles. Participants were instructed to take

- 2 tablets of nirmatrelvir 150 mg or placebo for nirmatrelvir every 12 hours and
- 1 capsule of ritonavir 100 mg or placebo for ritonavir every 12 hours

Primary endpoint

The primary endpoint of the study was the proportion of participants with Covid-19 related hospitalisation or death from any cause through day 28.

Results

As of the data cutoff (26 October 2021) 1361 (100.0%) participants in the interim analysis had entered the treatment phase, 1086 (79.8%) participants had completed the safety follow-up (Day 34) and no participants had completed the long-term safety follow-up.

At the 45% interim analysis, the event rate of a COVID-19-related hospitalisation or death from any cause through Day 28 in the mITT population of patients treated within 3 days of symptom onset and who were not going to receive mAbs is provided in the table below:

Primary analysis of proportion of patients with Covid-19 related hospitalisation or death from any cause through Day 28 – mITT, Kaplan-Meier method

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
N	389	385
Participants with event, n (%)	3 (0.8)	27 (7.0)
Participants with COVID-19 hospitalization	3 (0.8)	27 (7.0)
Participants with death	0	7 (1.8)
Average time at risk for event (Days) ^a	27.2	25.9
Average study follow-up (Days) ^b	27.3	26.9
Estimated proportion (95% CI), %	0.776 (0.251, 2.386)	7.093 (4.919, 10.174)
Difference from Placebo (SE)	-6.317 (1.390)	
95% CI of difference	-9.041, -3.593	
p-value	<.0001	

N – number of participants in the analysis set.

The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.

a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.

b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.

The study met its primary endpoint at the interim analysis which showed a significant ($p < 0.0001$) reduction in the proportion of patients with COVID-19 related hospitalisation or death from any cause through Day 28 by 89.1% in the treatment arm as compared to placebo.

This is highly clinically relevant, although the total number of events of interest for the primary endpoint was only 30 and the total number of patients enrolled in the study was lower than the planned number of around 3000 patients.

Based on the convincing evidence of benefit at the interim analyses, further recruitment in to the study was stopped based on the recommendations of the independent data monitoring committee. The topline results after completion of day 28 from the total recruited population (Primary completion date – PCD) in the mITT population is presented below:

Table 1. Primary Analysis of Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 - mITT, Kaplan-Meier Method

	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo
N	697	682
Participants with event, n (%)	5 (0.717)	44 (6.452)
Participants with COVID-19 hospitalization	5 (0.717)	44 (6.452)
Participants with death	0	9 (1.320)
Average time at risk for event (Days) ^a	27.288	26.188
Average study follow-up (Days) ^b	27.448	27.245

	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo
Estimated proportion (95% CI), %	0.723 (0.302, 1.729)	6.531 (4.901, 8.676)
Difference from Placebo (SE)	-5.807 (1.005)	
95% CI of difference	-7.777, -3.837	
p-value	<.0001	

N = number of participants in the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.
PFIZER CONFIDENTIAL SDTM Creation: 12DEC2021 (10:10) Source Data: adtte Table Generation: 12DEC2021 (11:37)
(Data cutoff date : 11DEC2021 Database snapshot date : 11DEC2021) Output File: ./nda/C4671005_EUA/adtteh_s001_mitt

The analysis of COVID-19 related hospitalisation or death in patients treated within 5 days of symptom onset regardless of mAb usage (mITT2) from the interim analyses is provided in the table below.

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
N	661	669
Participants with event, n (%)	7 (1.1)	43 (6.4)
Participants with COVID-19 hospitalization	7 (1.1)	43 (6.4)
Participants with death	0	10 (1.5)
Average time at risk for event (Days) ^a	27.0	25.9
Average study follow-up (Days) ^b	27.2	26.9
Estimated proportion (95% CI), %	1.067 (0.510, 2.226)	6.492 (4.856, 8.655)
Difference from Placebo (SE)	-5.425 (1.038)	
95% CI of difference	-7.460, -3.390	
p-value	<.0001	

The results in the mITT2 population supports the inference of a clinically significant efficacy seen in the primary endpoint. The treatment significantly reduced the proportion of patients hospitalised/death through day 28 by 83.6% compared to placebo, which although relatively smaller than the 89.1% in the mITT population, suggests the treatment is beneficial if started within 5 days of symptom onset regardless of whether patients received mAbs.

The analysis of COVID-19 related hospitalisation or death in patients when treated within 5 days of symptom onset and who were not going to receive mAbs (mITT1 population) from the interim analyses is provided in the table below:

Secondary analysis of proportion of patients with Covid-19 related hospitalisation or death from any cause through Day 28 – mITT1, Kaplan-Meier method

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
N	607	612
Participants with event, n (%)	6 (1.0)	41 (6.7)
Participants with COVID-19 hospitalization	6 (1.0)	41 (6.7)
Participants with death	0	10 (1.6)
Average time at risk for event (Days) ^a	27.0	25.9
Average study follow-up (Days) ^b	27.2	26.8
Estimated proportion (95% CI), %	0.999 (0.450, 2.209)	6.764 (5.025, 9.074)
Difference from Placebo (SE)	-5.765 (1.098)	
95% CI of difference	-7.917, -3.613	
p-value	<.0001	

N – number of participants in the analysis set.

The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.

a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.

b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.

The results from the mITT1 is supportive of the inference made from the primary endpoint. These results and the results from the mITT2 populations taken together shows that a beneficial treatment effect can be anticipated even if the treatment is started within 5 days of first symptom onset. The topline results from the PCD in the mITT1 population is presented below and was also supportive of this inference of a highly clinically relevant benefit.

Table 2. Secondary Analysis of Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 - mITT1, Kaplan-Meier Method

	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo
N	1039	1046
Participants with event, n (%)	8 (0.770)	66 (6.310)
Participants with COVID-19 hospitalization	8 (0.770)	65 (6.214)
Participants with death	0	12 (1.147)
Average time at risk for event (Days) ^a	27.048	25.972
Average study follow-up (Days) ^b	27.203	27.046
Estimated proportion (95% CI), %	0.781 (0.391, 1.556)	6.400 (5.063, 8.075)
Difference from Placebo (SE)	-5.619 (0.810)	
95% CI of difference	-7.207, -4.031	
p-value	<.0001	

Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo
<p>N = number of participants in the analysis set. The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.</p> <p>a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.</p> <p>b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.</p> <p>PFIZER CONFIDENTIAL SDTM Creation: 12DEC2021 (10:10) Source Data: adtte Table Generation: 12DEC2021 (11:37) (Data cutoff date : 11DEC2021 Database snapshot date : 11DEC2021) Output File: ./nda/C4671005_EUA/adtteh_s001_mitt1</p>	

Secondary Endpoint: Change from baseline in Viral load

Change from baseline in viral load was a secondary endpoint to support the proof of concept and the statistical analysis first occurred when a sufficient number (approx. 200 patients) in the mITT analysis set completed the viral load assessment at Day 5 and had valid viral load assessments at both day 1 and day 5.

A validated quantitative SARS-CoV-2 RT-PCR assay was used to measure viral load (copies/mL). Participants with samples collected using unvalidated (local) swabs or collected at non-nasopharyngeal sites were excluded from this assessment, as were participants with no virus detected at baseline (0 copies/mL). Viral load below the detection limit of 100 copies/mL was imputed as approximately 50 copies/mL, i.e., using 1.69 Log₁₀ (copies/mL) for Log₁₀ (viral load) values below 2 Log₁₀ (copies/mL).

The change in viral load after treatment in the mITT, mITT1 and mITT2 populations are presented in the table on the next page.

Statistical analysis of change from baseline in Log₁₀ transformed viral load (copies/ml) data – mITT, mITT1 and mITT2

Analysis Population		Analysis Visit		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
mITT	Day 5	n		144	159
		LS mean (SE)		-2.99 (0.12)	-1.96 (0.12)
		Versus placebo			
		LS mean difference (SE)		-1.03 (0.16)	
		1-sided 80% CI for LS mean difference		(-Infy, -0.89)	
mITT1	Day 5	n		211	240
		LS mean (SE)		-2.69 (0.10)	-1.75 (0.09)
		Versus placebo			
		LS mean difference (SE)		-0.93 (0.13)	
		1-sided 80% CI for LS mean difference		(-Infy, -0.83)	
mITT2	Day 5	n		233	266
		LS mean (SE)		-2.81 (0.14)	-1.85 (0.13)
		Versus placebo			
		LS mean difference (SE)		-0.96 (0.12)	
		1-sided 80% CI for LS mean difference		(-Infy, -0.86)	

n=Number of participants with non-missing data in the analysis population and the covariates in the statistical model. Infy=Infinity. Only Upper Limit for 80% CI is presented.

Participants are excluded from the analysis for reasons of Not Detected or Missing baseline viral load result, and local swabs use. Results from samples collected at non-nasopharyngeal site are also excluded.

Change from baseline modeled using ANCOVA

For mITT analysis set Model = Treatment + Baseline viral load + geographic region + serology status.

For mITT1 analysis set Model = Treatment + Baseline viral load + geographic region + serology status + symptom onset.

For mITT2 analysis set Model = Treatment + Baseline viral load + COVID-19 mAb treatment + geographic region + serology status + symptom onset.

The antiviral efficacy of Paxlovid was consistently demonstrated to be greater than placebo in all three analyses populations of mITT, mITT1 and mITT2. The magnitude of change as compared to placebo was around 1log₁₀ greater reduction in viral assay count change at day 5 as compared to the baseline and this effect size was comparable across the three analyses populations. This provides some proof of concept to link the observed clinically relevant effects on hospitalization/death to these antiviral effects.

Special populations

No specific clinical studies in special populations were conducted. However, phase 2/3 pivotal study data was analysed in subgroups. Prespecified subgroup analyses of the primary and first key secondary endpoints using the mITT and mITT1 analysis sets, respectively, were conducted by age (<65, ≥65 years), gender, race, BMI (<25, 25-29, ≥30 kg/m²), baseline serology status (antibody negative, antibody positive), baseline viral load ([<104, ≥104 copies/mL] and [<107, ≥107 copies/mL]), baseline comorbidities and number of baseline comorbidities present (0-1, 2-3, ≥4).

Generally, the subgroup analyses in the data presented at the interim analyses produced comparable results as in the overall mITT population except in the following cases where few events occurred, and the overall size of the subgroup was small:

- Few participants (0 for nirmatrelvir/ritonavir; 3 for placebo) in the subgroup of Asian (p=0.0772) and Others (p=0.0732) had events. No participants in the subgroup of Black or African American had an event; therefore, no statistical test could be performed
- Few participants (0 for nirmatrelvir/ritonavir; 3 for placebo) in the subgroups of BMI <25 kg/m² (p=0.0778)
- No participant had an event in the subgroup of ≥ 4 baseline comorbidities and a statistical test could not be performed

Some salient observations in the subgroup results at interim analyses are presented below.

- In the subgroup of seropositive cases, though the number of participants were reasonable, the number of events were few and a significant effect could not be demonstrated
- In the subgroup of smokers, although the number of participants were reasonable, a significant effect could not be demonstrated
- In the subgroup of participants with a baseline viral load <4, a significant effect could not be demonstrated despite reasonable number of participants, as the event rate was low
- The total number of participants aged >65 years were few, but nevertheless, a significant effect could be demonstrated. Similarly a significant effect could be demonstrated for the risk factor of diabetes mellitus although the number of participants were comparable to that of age >65 years.

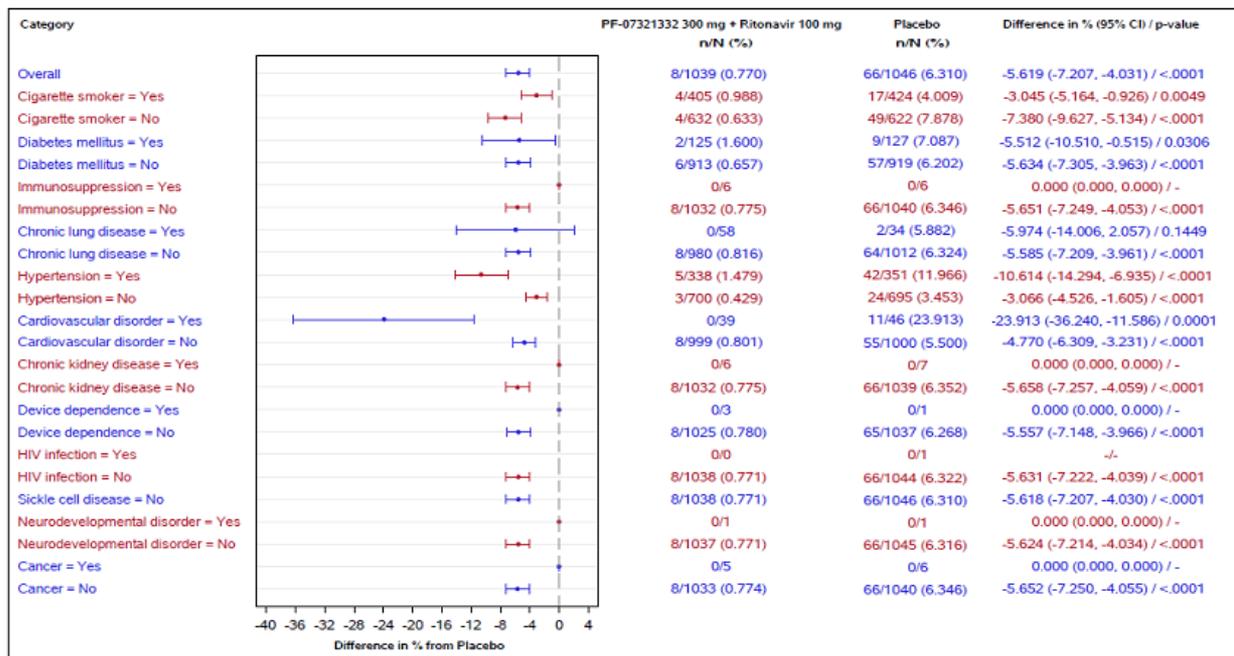
It is noted that the effect of treatment may be variable in different subgroups and a greater effect is observed in subgroups with higher risk (e.g. elderly, diabetes) and a benefit could be conclusively demonstrated with fewer participants as compared to the subgroups with relatively lower risk (e.g. smokers, seropositive patients and baseline viral load <4) as the event rates of hospitalisation/death in such high risk subgroups are high.

In this context the number needed to treat (NNT) to prevent one hospitalisation/death is a more informative/appropriate parameter than the percentage reduction in hospitalisation/death.

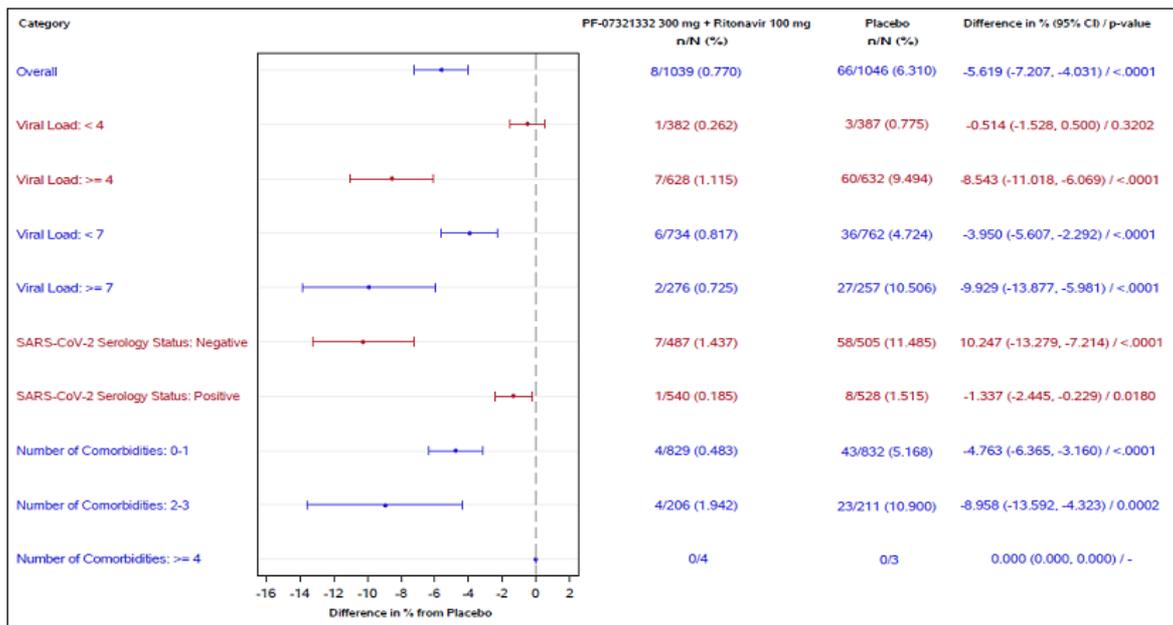
Additional analyses of primary endpoint by subgroups, including by age, BMI, viral load, and baseline comorbidities/risk factor in the mITT1 population from the topline results of the primary completion date (PCD) was conducted and is presented below (see table on following page):

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo	RRR	NNT
PCD mITT1 subgroup				
Age <65	0.67	4.861	86.22	23.9
Age >65	1.064	16.327	93.48	6.6
BMI<25	0.69	3.777	81.73	32.4
BMI 25 - < 30	0.667	7.114	90.62	15.5
BMI >= 30	0.811	7.33	88.94	15.3
VL < 4	0	0.459	100.00	217.9
VL >= 4	1.132	9.141	87.62	12.5
VL < 7	0.664	4.613	85.61	25.3
VL >=7	0.917	9.964	90.80	11.1
Smokers	1.06	4.534	76.62	28.8
Non-smokers	0.493	8.009	93.84	13.3
Diabetics	0	8.333	100.00	12.0
Non-diabetics	0.818	6.277	86.97	18.3
Hypertensives	1.77	12.278	85.58	9.5
Non-hypertensives	0.217	3.423	93.66	31.2
CVD	0	26.471	100.00	3.8
Non-CVD	0.751	5.471	86.27	21.2

Smoking as a risk factor was included in the Study 1005 protocol as it is identified by the Center for Disease Control and Prevention (CDC) as an underlying condition associated with higher risk for severe COVID-19. At the time of interim analysis, the number of participants with risk factor was limited. Results of smokers in the final analysis from the topline results in the PCD dataset, which includes a larger sample size are presented in the Forest plot below (mITT1).



Data described below are analyses of the primary endpoint by subgroups, including baseline serology status and low baseline viral load, in the mITT1 population at the primary completion date (PCD).



The two subgroups highlighted above (seropositive at baseline and low baseline viral load) are at lower risk for progression to severe COVID-19, with rates of hospitalisation/death of 1.5 and 0.78%, respectively in the placebo arm of study 1005. While this low event rate in the placebo arm results in a lower absolute risk reduction relative to patients in higher risk groups (1.3 and 0.51%, respectively), the relative risk reduction for the two subgroups is 88% and 66%, respectively, suggesting that these groups also benefit from treatment. As viral load and serology status information are unavailable at time of treatment initiation, the available data support initiation of treatment regardless of the viral count or serology status

As expected, the absolute benefits in seropositive and low baseline viral load subgroup is low due to the risk for these subgroups being low. However, it is acknowledged that a treatment effect is discernable in all subgroups and in an adequately large subgroups, the effects could be demonstrated conclusively in subgroups.

Overall conclusions on clinical efficacy

The efficacy of Paxlovid in reducing hospitalisation/death in adult patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease has been conclusively demonstrated in the interim analyses of the study 1005 from 45% of the initially intended target population.

In a clinical trial in high-risk adults with symptomatic COVID-19 infection, a five day treatment course of Paxlovid reduced the risk of COVID-19 related hospitalisation and death within 28 days by 89% when compared to a placebo group when treatment was started within 3 days of the onset of COVID-19 symptoms. The number of hospitalisations and deaths were 0.8% (3 out of 389) in the Paxlovid group compared with 7% (27 out of 385) in the placebo group. Similar favourable results were seen in patients when treatment was started within 5 days of the start of symptoms.

There is no clinical data with use of Paxlovid on the Omicron variant till date. The applicant commits to provide a report on the sequencing and phenotypic analysis of the remaining samples from clinical study 1005. In addition, the applicant has made a commitment to submit further updates on activity of variants of concern and mutational viral resistance.

There are no plans to generate clinical data on the effects of Paxlovid on the Omicron variant, but a post marketing surveillance on the genetic mutations in any future VoC will be monitored to evaluate potential impact on efficacy of Paxlovid. This is consistent with the approaches of other products currently authorised in this rapidly evolving clinical setting and a careful review of emerging data is necessary.

Study 1002 is running in parallel and is recruiting both unvaccinated patients without risk factors for severe COVID-19, as well as fully vaccinated patients with risk factors for severe COVID-19. In a pre-planned interim analysis of data from this trial, a reduction in viral load of ~1.0 log₁₀ copies/mL was observed, similar to what has been characterised in unvaccinated/high risk patients from Study 1005. These results suggest that the antiviral activity of nirmatrelvir/ritonavir is consistent across vaccinated and unvaccinated patients, as would be anticipated with an antiviral with an intracellular target.

The Company has committed to providing the full study report of the phase 2/3 study 1002 for efficacy and safety in vaccinated individuals as a condition of the CMA.

Both the constituents of Paxlovid are CYP3A4 inhibitors and there is a huge potential for drug interactions. Consequently, the study had an extensive list of concomitant medications which was excluded and in clinical practice this is unlikely to be adhered to or needed particularly for a short five-day duration of therapy. However, the clinical experience with a broad spectrum of concomitant medications is currently not available.

Currently only data from the primary endpoint of hospitalisation/deaths and the secondary endpoint of viral clearance which provides support to the proof of concept for the observed efficacy has been presented. No data on the other secondary endpoints of time to resolution of symptoms have been presented. In addition, as the magnitude of beneficial effect was large it was possible to demonstrate it conclusively in fewer patients which means the clinical experience with the use of this treatment from a representative sample of a full spectrum of patients that are likely to be prioritised for this treatment in clinical deployment is less than satisfactory particularly in the elderly patients with multiple co-morbidities.

In terms of using the clinical data available, to inform on effectiveness in a real-world pandemic situation, there are a number of important limitations to consider, including but not limited to uncertainty in relation to circulating SARS-CoV-2 variants, and the generalisability of the treatment benefit to a largely vaccinated public. These gaps will be addressed in the future when i) full study reports will be submitted and ii) additional supportive data expected to be supplied from other ongoing studies. These will need to be reviewed and monitored in the post marketing setting.

In conclusion, and with recognition of the aforementioned caveats that accompany the COVID-19 pandemic situation, the data to support the application demonstrated a highly clinically relevant and statistically significant benefit.

IV.5 Clinical safety

The safety profile of Paxlovid to support the current CMA comes mainly from the 45% interim analysis of study 1005 which includes 1349 participants (safety analysis set) (database cutoff on 26 October 2021). In addition, safety data from the completed 4 phase I studies are also available.

In the 45% interim analysis of study 1005, a total of 678 patients (full analysis set) entered the study in the nirmatrelvir/ritonavir arm. Parallel group, comparative safety data from 683 patients who received placebo are available to provide context to the observed safety profile.

Adverse Drug Reactions (Treatment related TEAEs)

The overall incidence of treatment-related TEAEs was higher in the nirmatrelvir/ritonavir group (7.3%) compared with the placebo group (4.3%).

This higher incidence is mainly due to gastrointestinal side effects of diarrhoea and vomiting and nervous system side effect of dysgeusia. All the events of vomiting and diarrhoea were mild (grade 1-2) and out of 25 events of dysgeusia, 24 was grade 1-2 and only 1 event was grade 3, which is reassuring.

Serious Adverse Events (SAEs)

The overall incidence of participants with all causality SAEs was lower in the nirmatrelvir/ritonavir treatment group (1.9%) compared with placebo (6.8%). The higher incidence of SAEs in placebo was mainly attributable to the more frequent reports of complications/worsening of COVID-19 in the placebo group

All SAEs were considered not related to treatment except for events of chest discomfort, dyspnoea and palpitations in one participant which was considered treatment related to ritonavir by the investigator. The participant discontinued the study due to these events.

There were 10 deaths reported in placebo group and none in the treatment group. All deaths were considered related to COVID-19 and not related to study treatment.

Laboratory findings and vital signs

No clinically meaningful differences were observed between the nirmatrelvir/ritonavir and placebo groups with respect to haematology, and clinical chemistry laboratory test results.

Thyroid stimulating hormone (TSH) changes were observed with the administration of nirmatrelvir/ritonavir during the Phase 1 Study 1001. Low-level inflammation (increase in fibrinogen) in the 15-day non-human primate toxicology study and changes in platelets, globulin and albumin/globulin ratio and coagulation system (increase in prothrombin time and activated partial thromboplastin time) in the 14-day rat toxicology study were reported. Based on these observations, TSH and thyroxine (free) in addition to AEs, fibrinogen, platelets, D-dimer, prothrombin time and activated partial thromboplastin time, albumin, and total protein were monitored in Study 1005 and the incidence of participants shifting from out of range value to a within range value for these parameters was similar across treatment groups.

No clinically meaningful findings in vital sign measurements (heart rate, systolic and diastolic blood pressure, oxygen saturation, body temperature and respiratory rate) were observed in this study. The assessments and observations were comparable across treatment groups.

The mean maximum change from baseline in vital signs were comparable in both treatment groups. Likewise, the incidence of participants with increased diastolic or increased systolic blood pressure was comparable across treatment groups.

Safety in special populations

Elderly patients, pregnant women, vulnerable race/ethnic groups, immunosuppressed or immunocompromised individuals, cancer patients and a wide range of comorbidities on multiple concomitant treatments are most vulnerable and are likely to be the priority group for whom antiviral treatment with Paxlovid is likely to be considered. The safety data in these groups are limited and so it will need to be monitored in the post-marketing setting.

Safety related to drug-drug interactions

Two pharmacokinetic drug interaction studies have been conducted and two more are ongoing (see section IV.2)

The study 1005 excluded patients who were on concomitant medicines that may potentially interact with Paxlovid and as such there is no reliable clinical data from study 1005 to support positive recommendations on the concomitant use of medicines that could potentially interact with Paxlovid based on the knowledge of its effects on the drug metabolism pathways. In the absence of such data, it is agreed that the SmPC should be based on the extensive experience with ritonavir 100 mg which is mainly based on long-term use, although it is acknowledged that this is a conservative approach based on the short duration of treatment with Paxlovid and the safety profile of Paxlovid as ascertained in the study 1005.

It is acknowledged that the use of Paxlovid is for a short duration of 5 days as compared to the chronic treatment with ritonavir in HIV. However, as there is a lack of wide clinical experience with Paxlovid and as the potential for drug interactions are not yet fully understood, the SmPC reflects a conservative approach and uses the evidence base of ritonavir 100 mg to inform the warnings and precautions for use.

Discontinuation due to AEs

Fewer participants in the nirmatrelvir/ritonavir group (2.4%) than in the placebo group (4.3%) discontinued study intervention due to an AE.

The imbalance can be explained fully by the additional events in infection and respiratory disorders due to worsening of COVID that was seen in the placebo arm which is unrelated to study treatment. The events that led to discontinuation in the treatment arm to a greater degree than in placebo arm was nausea and vomiting, that were all mild to moderate (grade 1-2).

Overall conclusions on clinical safety

The safety profile of Paxlovid (co-administration of nirmatrelvir and ritonavir) as characterised in study 1005 is acceptable and there were no major concerns raised based on the safety data emerging from this study. The common adverse reactions characterised in this study are diarrhoea, vomiting and dysgeusia. However, given the large potential for Paxlovid to have adverse drug interactions, it is remarkable that no AEs attributable to drug interaction were detected. This is likely to be due to the carefully selected study population with a conservatively pre-specified long list of medications that were excluded from concomitant use in the study.

The characterisation of safety in a carefully selected study population which was terminated early due to compelling efficacy at interim analysis leaves gaps in the characterisation of the safety profile which should be addressed based on the data from the ongoing studies to some extent. However the most vulnerable patients to COVID in whom the treatment should ideally be deployed first are the elderly with number of co-morbidities, pregnant women, immunodeficient or immunocompromised individuals and these are unlikely to be included

in the ongoing studies in the low risk population or in the post-exposure prophylactic study. In this context, the safety profile needs to be adequately monitored in the post-marketing setting. Overall, the characterised safety profile of Paxlovid is acceptable.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulations 2012, as amended. The following table summarises the safety concerns listed in the RMP and the pharmacovigilance activities and risk minimisation measures proposed to address each of these concerns, and these are acceptable:

Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important identified risks		
Drug-drug interactions with CYP3A4 substrates and CYP3A4 inhibitors	Routine risk minimisation measures only	<u>Routine activities beyond ADR reporting and signal detection:</u> Monthly summary safety reports. <u>Additional pharmacovigilance activities:</u> None
Missing information		
Use in patients with active hepatic impairment	Routine risk minimisation measures only	<u>Routine activities beyond ADR reporting and signal detection:</u> Monthly summary safety reports. <u>Additional pharmacovigilance activities:</u> Study C4671010 to assess safety and tolerability of Paxlovid in patients with moderate impaired liver function and in patients with normal liver function
Use in pregnancy	Routine risk minimisation measures only	<u>Routine activities beyond ADR reporting and signal detection:</u> Monthly summary safety reports and Pregnancy follow-up questionnaires to collect relevant information during follow-up activities. <u>Additional pharmacovigilance activities:</u> Post authorisation safety study (PASS) to monitor and assess pregnancy outcomes following use of Paxlovid during pregnancy.
Use in breast feeding	Routine risk minimisation measures only	<u>Routine activities beyond ADR reporting and signal detection:</u> Monthly summary safety reports. <u>Additional pharmacovigilance activities:</u> PASS to monitor and assess the safety of use of Paxlovid while breast feeding.
Emergence of resistant viral variants and variants of concern	Routine risk minimisation measures only	<u>Routine activities beyond ADR reporting and signal detection:</u> Monthly summary safety reports. <u>Additional pharmacovigilance activities:</u> The company will assess the feasibility and utility of conducting a study. Antiviral surveillance programme.

IV.7 Discussion on the clinical aspects

The grant of a conditional marketing authorisation is recommended.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

Due to the urgent unmet need for the product, a commitment has been made that the PIL will be evaluated via a user consultation study in accordance with legal requirements.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product in the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19.

Paxlovid has been authorised with a Conditional Marketing Authorisation (CMA). The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

Description	Due date
1. Full user testing of the leaflet will need to be carried out prior to the medicine being widely deployed	
2. The Company will evaluate the limits for assay and related substances in the specifications of the starting materials, intermediates and final nirmatrelvir drug substance in line with batch analysis data as more batches become available	Estimated date by Q2 2022
3. The Company will provide additional stability data of drug substance batches as further data are generated.	Estimated date by Q4 2022
4. The dossier will be updated with the latest ASMF version of ritonavir.	Estimated date by Q1 2022
5. The Company will inform the Licensing Authority of any changes in the manufacturing process of the finished product and to report immediately any out of specification result that may occur during routine manufacture or stability studies with a course of action.	
6. The Company will provide the full study report of the phase 2/3 study 1005	Estimated date Jan 2022
7. The Company will provide the final viral sequencing report from study 1005 (including the analytical reports) to identify treatment emergent mutations and any co-relation to treatment failure.	Estimated date Apr 2022
8. The Company will provide the full study report of the phase 2/3 study 1002 for efficacy and safety in vaccinated individuals	Estimated date by Q3 2022
9. The Company will provide the full study report of the ongoing Phase I study 1010 characterising the PK in hepatic impairment patients.	Estimated date by Q1 2022
10. The Company will provide the full study report of the ongoing Phase I study 1012 characterising the potential for drug interaction with dabigatran which is a P-gp substrate.	Estimated date by Q1 2022
11. The Company will provide the full study report of the ongoing Phase I study 1013 characterising the potential for drug interaction with midazolam which is a CYP 3A substrate.	Estimated date by Q1 2022
12. The Company will provide the population PK report taking into account all the available PK data from phase I studies and study 1005	Estimated date by Q1 2022
13. The Company will provide data from cell-based antiviral assays to evaluate the effect of the Omicron variant (B.1.1.529) on the inhibitory activity of nirmatrelvir	Estimated date of submission, end of January 2022
14. The Company will provide updated anti-viral activity results against Paxlovid regarding newly circulating variants of concern on a regular monthly basis.	Ongoing until time of full MAA submission.
15. The Company will provide regular monthly data to evaluate the potential of mutations to SARS-CoV-2 resulting in increased anti-viral resistance.	Ongoing until time of full MAA

	submission
16. The Company has committed to provide the final draft report for the rat pre- and post-natal development study.	Draft report is planned for the end April 2022, and final report is expected in June 2022
17. The Company has committed to provide completed Phase I and Phase II environmental risk assessment studies and an updated environment risk assessment for nirmatrelvir and ritonavir	These should be completed Q2 2023
18. The MHRA is to be informed of the outcome of the pending FDA inspection	
19. The company will add 'Drug interactions' to the RMP as an important identified risk.	
20. The company will add 'Emergence of viral variants' to the RMP as missing information along with proposals for monitoring further data on this topic	
21. The company will provide a protocol for a post authorisation safety study to collect information on pregnancy outcomes in women exposed to Paxlovid within 6 months of approval of the conditional marketing authorisation. A high-level summary of the study should be provided within 3 months of approval of the conditional marketing authorisation.	
22. The company will perform weekly signal detection.	
23. The company will submit monthly summary safety reports to MHRA that will include the following information: - interval and cumulative number of reports overall and by age groups, and special populations - estimated exposure - any changes to reference safety information - details of any signals under review or closed - review of special topics of interest including reports with a fatal outcome, reports concerning patients <18 years, patients >75 years, pregnant women, drug interactions, off-label use and medication errors.	
24. Should the UK deployment strategy for Paxlovid change after approval of the conditional marketing authorisation (for example Paxlovid is prescribed outside of a clinical trial or outside of the relatively controlled environment of the COVID Medicines Delivery Unit), the company will: - promptly and urgently review the need for additional risk minimisation measures in relation to drug interactions - submit to MHRA proposals for a drug utilisation study to characterise the use of Paxlovid in clinical practice in the UK, including whether the SmPC contraindications and warnings regarding drug interactions are adhered to in clinical practice.	

The Summary of Product Characteristics (SmPC), PIL and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved GB versions of the SmPC and PIL for this product is available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.

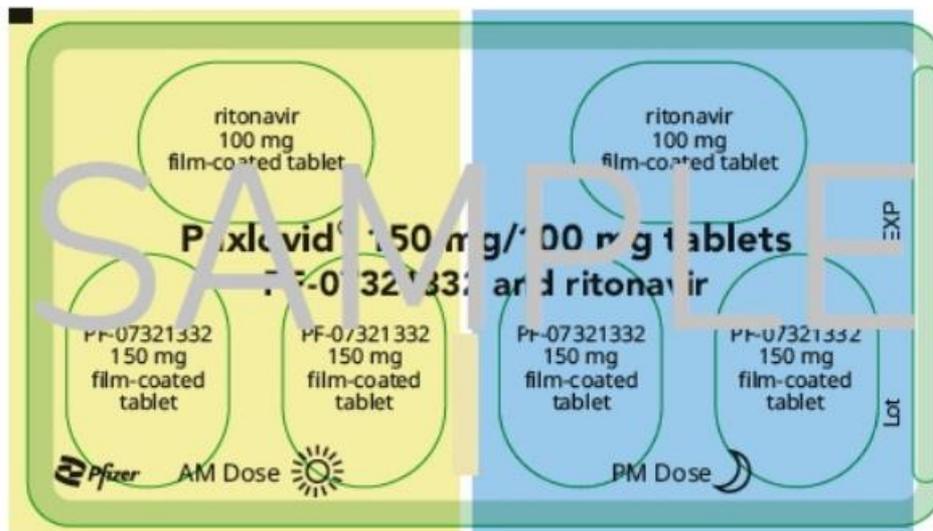


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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N