EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 January 2022
EMA/95110/2022 – Rev.[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Paxlovid

Chemical name / International non-proprietary 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 (PF-07321332) / ritonavir

Procedure No. EMEA/H/C/005973/0000

Note

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

[1] The amendment concerns the editorial correction of a factual mistake in relation to an excipient contained in the product.

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List of abbreviations

3CL	3C-like
3CLpro	3C-like protease
5d	5-day
10d	10-day
19F	fluorine-19
Ω	inter-individual variance
%RSE	Percent relative standard error
ACE-2	angiotensin-converting enzyme 2
ADE	antibody-dependent enhancement
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
Ae	amount of unchanged drug excreted in urine
AESI	adverse events of special interest
Al	Aluminium
ALB	Albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
API	active pharmaceutical ingredient
APTT (aPTT)	activated partial thromboplastin time
AS	Active substance
ASMF	Active Substance Master File
AST	aspartate aminotransferase
AUC	area under concentration-time curve
AUC24	area under the concentration-time curve from time zero to 24 hours
AUCinf	area under the serum concentration-time profile from time zero extrapolated to infinite time
AUCinf (dn)	Dose normalised AUCinf
AUClast	area under the serum concentration-time profile from time zero to the time of the last quantifiable concentration
AUClast (dn)	area under the serum concentration-time profile from time zero to the time of the last quantifiable concentration, dose normalised
AUCtau/AUCt	area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval
ACE2	angiotensin converting enzyme 2 receptor
ADR	adverse drug reaction
BCRP	breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BID	twice daily
BiPAP	Bilevel positive airway pressure
BMI	body mass index
BP	blood pressure
BSA	Body surface area
BUN	blood urea nitrogen
C12	plasma concentration at 12 hours post dose
C24	plasma concentration at 24 hours post dose
Caco-2	human colonic adenocarcinoma cells
CC50	cytotoxicity concentration 50%
Cav	average free concentration
Cb/Cp	concentration in blood/concentration in plasma
Ceff	efficacious concentration
CHOL	Cholesterol
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
CL	clearance
CL/F	apparent clearance
Clbile	biliary intrinsic clearance of drug from eg, plasma
CLr	renal clearance
CMA	conditional marketing authorisation
CMC	Chemistry Manufacturing and Controls

Cmax	the observed maximum concentration
Cmax.ss	Cmax at steady-state
Cmin	minimal concentration (Ctrough)
CO	Clinical Overview
CoA	Certificate of analysis
CoV	Coronavirus
COVID-19	coronavirus disease 2019
CPE	cytopathic effect
C-QTc	concentration-QTc
QTc	corrected QT interval
CRP	C-reactive protein
CSR	clinical study report
CT	Connecticut; Computerised tomogram
CTA	clinical trials application
Ctrough	drug concentration observed at the last planned timepoint prior to dosing
CV	coefficient of variation; cardiovascular
CYP	cytochrome P450
CYP1A2	cytochrome P450 1A2
CYP3A4	cytochrome P450 3A4
CYP2B6	cytochrome P450 2B6
CYP2C9	cytochrome P450 2C9
DAIDS	Division of AIDS
DDI	drug-drug interaction
DBP	diastolic blood pressure
dNHBE	differentiated normal human bronchial epithelial cells
+dP/dT	cardiac contractility
EC50	drug concentration at which 50% inhibition of viral replication is observed; Concentration required for 50% effect
EC90	drug concentration at which 90% inhibition of viral replication is observed; Concentration required for 90% effect
ECG	Electrocardiogram
E-DMC	external data monitoring committee
ED	Emergency department
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EoT	end of therapy
EPIC-HR	evaluation of protease inhibition for COVID-19 high-risk
ER	Emergency room
EU	European Union
EUA	Emergency Use Authorisation
EV71	Enterovirus 71
F1	relative bioavailability
f2	similarity factor
FC	food consumption
FDA	Food and Drug Administration
FE	food effect
FIB	Fibrinogen
FIH	first-in-human
fm	fraction metabolised
FOB	functional observational battery
FRET	fluorescence resonance energy transfer
FTIR	Fourier transform infrared spectroscopy
fu	fraction unbound
GC(-MS)	Gas chromatography (tandem mass spectrometry)
GCP	Good Clinical Practice
GD	gestation days
GeoMean	geometric mean
GFR	Glomerular filtration rate
GFR CKD-EPI	Glomerular Filtration Rate Chronic Kidney Disease Epidemiology
Equat	Collaboration equation
GI	Gastrointestinal
GISAID	global initiative on sharing avian influenza data

GLOB	Globulin
GMP	Good Manufacturing Practice
HCl	hydrochloric acid
HCV	Hepatitis C virus
HCoV	human coronavirus
HDPE	High Density Polyethylene
HEK	human embryonic kidney
HHS	Department of Health and Human Services
HIV	human immunodeficiency virus
HRMS	High Resolution Mass Spectrometry
HPD	hours post-dose
HPLC(/MS)	high-performance liquid chromatography (tandem mass spectrometry)
HRV1B	Human rhinovirus 1B
HR	heart rate
IB	Investigator's Brochure
IC50	the drug concentration at which 50% inhibition of the 3CL protease enzyme is observed
ICH	International Council for Harmonisation
ICU	intensive care unit
IgG	Immunoglobulin G
IIV	inter-individual variability
IND	Investigational New Drug
INR	International normalised ratio
IOV	inter-occasion variability
IPPV	Intermittent positive pressure ventilation
IR	immediate release
IR	Infrared spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
IV	Intravenous
Ka	absorption rate constant
KF	Karl-Fischer titration
Ki	inhibition constant
KI	concentration at 50% kinact
Kiapp	apparent inhibition constant
Kinact	maximal rate of enzyme activation
kp,uu	unbound partition coefficient
LC-MS/MS	liquid chromatography tandem mass spectrometry
(L)LDPE	(Linear) Low Density Polyethylene
LLN	Lower limit of normal
LOQ	limit of quantification
LS	least-squares
LV +dP/dt max	maximum positive slope of the left ventricular pressure wave; an index of cardiac contractility
M	male; metabolite
M&E/ME	metabolism and excretion
MA	marketing authorisation
MAA	Marketing Authorisation Application
mAb	monoclonal antibody
MAD	multiple ascending dose
MATE	multidrug and toxic compound extrusion
MDCK	Madin-Darby canine kidney cell line
MDR1	multidrug resistance 1
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
Mfg	Manufacturing
MHV	mouse hepatitis virus
min	Minute
mITT	modified intent-to-treat
mITT1	modified intent-to-treat 1
mITT2	modified intent-to-treat 2
MO	Major Objection
Mpro	main protease
MRC-5	human lung epithelial cells-5
mRNA	messenger ribonucleic acid

msec	Milliseconds
MT	mid-turbinate
N	Number (N = Number of participants; n = Number in tables for sample; No. = Number, when adjective)
ND	not determined
NDA	New Drug Application
NF	US national formulary
NI	non-inferiority
NMR	nuclear magnetic resonance
NOAEL	no-observed-adverse-effect-level
NP	Nasopharyngeal
NR	not reported
NTCP	sodium taurocholate cotransporting polypeptide
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
OATP1B	organic anion-transporting polypeptide 1B
OCT	organic cation transporter
OPA	Oriented PolyAmide
PAH	Pulmonary arterial hypertension
Papp	apparent permeability coefficient
PBO	Placebo
PBPK	physiological based pharmacokinetic modelling and simulation
pcVPC	prediction corrected visual predictive check
PD	pharmacodynamic(s)
PDE	Phosphodiesterase
PE	polyethylene
PEPT	peptide transporter 1
P-gp	p-glycoprotein
Ph. Eur.	European Pharmacopoeia
PI	prediction interval
PK	pharmacokinetic(s)
PMAR	Population Modeling Analysis Report
PO	by mouth
POC	proof of concept
popPK	population pharmacokinetics
PR	time from the onset of the P wave to the start of the QRS complex in the electrocardiogram
PRO	patient reported outcomes
PSD	Particle size distribution
PT	Preferred Term; prothrombin time
PTR	peak to trough ratio
PVC	Polyvinylchloride
PXRD	Solid state X-Ray diffraction
q12h	every 12 hours
q24h	every 24 hours
QC'd	quality controlled
QD	once daily
QRS	Deflections in the tracing of the electrocardiogram comprising the Q, R, and S waves, representing the depolarisation of the ventricles
QSP	quantitative systems pharmacology
QT	time from the beginning of the QRS complex to the end of the T wave in the electrocardiogram
QTc	QT interval corrected for heart rate
QTcF	QTc corrected using Fridericia's formula
(Q)SAR	quantitative structure activity relationship
QTPP	quality target product profile
Rac	observed accumulation ratio for AUC_T
Rac,Cmax	observed accumulation ratio for Cmax
rBA	relative bioavailability
RdRp	RNA-dependent RNA polymerase
REC	Recommendation
RH	relative humidity
RNA	Ribonucleic acid
ROW	Rest of the World

rpm	rotations per minute
RT-PCR	reverse transcriptase–polymerase chain reaction
RTV	Ritonavir
RR	respiratory rate
SAD	single ascending dose
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SARS-CoV-2-MA10	Severe acute respiratory syndrome coronavirus 2 (mouse-adapted virus)
SBP	systolic blood pressure
SC	Subcutaneous
SD	standard deviation
SE	supratherapeutic exposure / standard error
SM	Starting material
SmPC	summary of product characteristics
SO	Specific obligation
SoA	schedule of activities
SoC	standard of care
SOC	System Organ Class
t½	terminal elimination half-life
TBD	To be determined
TDI	time-dependent inhibitor / inhibition
TEAE	treatment-emergent adverse event
TI	therapeutic index
T/R	test/reference ratio
Tmax	the time to reach Cmax
TMPRSS2	transmembrane serine protease 2
TSH	thyroid stimulating hormone
UFLC-MS	ultra-fast liquid chromatography tandem mass spectrometry
UGT	uridine diphosphate-glucuronosyltransferase
UHPLC-HRMS	ultra-high-performance liquid chromatography - high resolution mass spectrometry
UK	United Kingdom
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
UV(VIS)	Ultraviolet (visible) spectroscopy
VeroE6	monkey kidney cells E6
VOC	variant of concern
VOI	variant of interest
Vss	volume of distribution at steady state
v/v	volume per volume
V/F	apparent volume of distribution
WOCBP	woman of child-bearing potential
WHO	World Health Organization
WT	wild type
w/v	weight per volume
w/w	weight per weight
XRD	X-Ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 7 January 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Paxlovid, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 July 2021.

A combination pack request was submitted to the Agency on 31st May 2021. In accordance with Eudralex, Notice to Applicants, Volume 2A, Chapter 1, Section 5.5, "In very exceptional circumstances, which must be considered on a case by case basis, the marketing of distinct medicinal products in the same package may be indispensable for public health reasons. Such reasons cannot be related to convenience or commercial purposes". Further to consultation with ETF on 6th July 2021, the CHMP endorsed via written procedure the outcome of the review process that the proposed combination pack was considered indispensable for public health, in order to facilitate patient access to the medicinal product in the current pandemic situation. The European Commission has been informed of this outcome and endorsed the acceptance of the combination pack in the context of the Covid-19 emergency situation, stressing that the studies to support co-formulation shall be accelerated, and the progress of these ongoing studies must be reported to the EMA.

The applicant applied for the following indication:

"PAXLOVID is indicated for the treatment of mild-to-moderate Coronavirus Disease 2019 (COVID 19) in adult and adolescent patients (12 years of age and older weighing at least 40 kg) and who are at high risk for progression to severe COVID 19 (see section 5.1)".

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0566/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0566/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

1.5.2. New active substance status

The applicant requested the active substance (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 contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
9 July 2021	EMA/SA/0000061585	*EMA staff*

The scientific advice pertained to the following quality, non-clinical and clinical aspects:

a) *Justification for co-packaging PF-07321332 with RTV*
b) *Non-clinical safety strategy*
c) *Clinical pharmacology programme*
d) *Strategy regarding the investigation of human ADME*
e) *Dose regimen selection*
f) *Adequacy of the phase 3 outpatient study (C4671005) to support a conditional MAA for treatment of adult patients with symptomatic COVID-19*
g) *Acceptance of non-EU data to support a CMA*
h) *Options for EUA in the EU and appropriate communication channels to request additional guidance*

Scientific advice compliance

Overall, there is some degree of fulfilment to the CHMP advice given to the applicant's questions raised in the request of scientific advice.

However, some issues deserve to be underlined.

- It was clearly identified by the CHMP that it was difficult to predict whether the DDI potential of PF 07321332/ritonavir 300/100 mg BID would be similar to that of ritonavir 100 mg BID. As part of the response the CHMP underline the contributory value of PBPK simulations. However as a particular caveat, the applicant during the procedure was not able to provide a relevant PBPK model of simulation insofar that this model was only based on data from Healthy

volunteers and not from patients while PK data were collected in adult patient in the C467-1005 (EPIC-HR) study.

- Finally, the applicant's questions on the clinical development of the drugs were too broad to enable the Committee to elaborate an advice.

1.7. COVID-19 EMA pandemic Task Force (COVID-ETF)

In line with their mandate as per the EMA Emerging Health Threats Plan, the ETF undertook the following activities in the context of this conditional marketing authorisation application:

The ETF endorsed the Scientific Advice letter, confirmed eligibility to the rolling review procedure based on the information provided by the applicant and agreed the start of the rolling review procedure.

Furthermore, the ETF discussed the (Co-)Rapporteur's assessment reports overviews and provided their recommendation to the CHMP.

For the exact steps taken at ETF, please refer to section 1.8.

1.8. Steps taken for the assessment of the product

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

Rapporteur: Jean-Michel Race Co-Rapporteur: Fátima Ventura

The Rapporteur appointed by the PRAC was: PRAC Rapporteur: Martin Huber

ETF discussion on Scientific Advice on	6 July 2021
The CHMP confirmed eligibility to the centralised procedure on	22 July 2021
Agreement by ETF to start the rolling review procedure on	10 December 2021
The application was received by the EMA on	7 January 2022
The procedure started on	10 January 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	14 January 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 January 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 January 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	20 January 2022
ETF discussions took place on	21 January 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 January 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 January 2022

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Paxlovid on	27 January 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	27 January 2022

Paxlovid was evaluated as part of 'OPEN', an initiative started in December 2020 with the aim of increasing international collaboration in the EU review of COVID-19 vaccines and therapeutics. More information can be found on the EMA website.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

In December 2019, the World Health Organization (WHO) was informed about a cluster of cases of viral pneumonia of unknown cause in Wuhan, China. In mid-January 2020, the pathogen causing this atypical pneumonia was identified as a novel coronavirus, severe acute respiratory coronavirus 2 (SARS-CoV-2) and genome sequence data were published. Since then, the virus has spread globally, on 30 January 2020 the WHO declared the outbreak a Public Health Emergency of International Concern and on 11 March 2020 a pandemic. The pandemic is ongoing despite unprecedented efforts to control the outbreak.

According to European Centre for Disease Prevention and Control (ECDC), histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

2.1.2. Epidemiology and risk factors

As of 24 January 2022, there have been over 349 million confirmed cases of SARS-CoV-2 infection globally with approximately 5.59 million deaths resulting from infection and subsequent coronavirus disease (COVID-19) as registered by WHO (https://covid19.who.int/). The majority of infections result in asymptomatic or mild disease with full recovery.

Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Other risk factors include organ transplantation and chromosomal abnormalities. Increasing age is another risk factor for severe disease and death due to COVID-19.

2.1.3. Aetiology and pathogenesis

SARS-CoV-2 is a positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment. It is enveloped and the virions are 50–200 nanometres in diameter. Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins.

The spike protein contains a polybasic cleavage site, a characteristic known to increase pathogenicity and transmissibility in other viruses. The Spike is responsible for allowing the virus to attach to and fuse with the membrane of a host cell. The S1 subunit catalyses attachment to the angiotensin converting enzyme 2 (ACE-2) receptor present on cells of the respiratory tract, while the S2 subunit facilitates fusion with the cell membrane. The spike protein is considered a relevant antigen for vaccine development because it was shown that antibodies directed against it neutralise the virus and it elicits an immune response that prevents infection in animals.

It is believed that SARS-CoV-2 has zoonotic origins and it has close genetic similarity to bat coronaviruses. Its gene sequence was published mid-January 2020 and the virus belongs to the beta-coronaviruses.

Human-to-human transmission of SARS-CoV-2 was confirmed in January 2020. Transmission occurs primarily via respiratory droplets from coughs and sneezes and through aerosols. The median incubation period after infection to the development of symptoms is four to five days. Most symptomatic individuals experience symptoms within two to seven days after exposure, and almost all symptomatic individuals will experience one or more symptoms before day twelve. Common symptoms include fever, cough, fatigue, breathing difficulties, and loss of smell and taste and symptoms may change over time.

The major complication of severe COVID-19 is acute respiratory distress syndrome (ARDS) presenting with dyspnoea and acute respiratory failure that requires mechanical ventilation. In addition to respiratory sequelae, severe COVID-19 has been linked to cardiovascular sequelae, such as myocardial injury, arrhythmias, cardiomyopathy and heart failure, acute kidney injury often requiring renal replacement therapy, neurological complications such as encephalopathy, and acute ischemic stroke.

2.1.4. Clinical presentation, diagnosis

The severity of COVID-19 disease varies. The disease may take a mild course with few or no symptoms, resembling other common upper respiratory diseases such as the common cold. Mild cases typically recover within two weeks, while those with severe or critical disease may take three to six weeks to recover. Among those who have died, the time from symptom onset to death has ranged from two to eight weeks.

Studies among hospitalised patients have found that high SARS-CoV-2 viral load is associated with worse outcomes, including increased mortality rates (Magleby, 2020) (Westblade, 2020). Community-based studies in non-hospitalised patients show symptomatic patients have higher viral load across both adults and children compared to asymptomatic individuals (Chung, 2021).

The gold standard method of testing for presence of SARS-CoV-2 is the reverse transcription polymerase chain reaction (RT-PCR), which detects the presence of viral RNA fragments. As this test detects RNA but not infectious virus, its ability to determine duration of infectivity of patients is limited. The test is typically done on respiratory samples obtained by a nasopharyngeal swab, a nasal swab or sputum sample.

2.1.5. Management

The management of COVID-19 cases has developed during 2020 and 2021, and includes supportive care, which may include fluid therapy, oxygen support, and supporting other affected vital organs.

Treatment of hospitalised patients encompass anti-inflammatory agents such as dexamethasone, targeted immunomodulatory agents and anticoagulants as well as antiviral therapy which at this stage are only registered via IV administration (e.g. Veklury (EMEA/H/C/005622)).

Monoclonal antibodies and notably bi-therapies to overcome potential escape by VOC with mutations on spike are perceived as of potential value. This was particularly true for immunocompromised individuals especially where vaccines might not induce adequate immune response in those patients of particular medical need. Thurs, recently, three monoclonal antibodies Ronapreve (casirivimab/imdevimab, EMEA/H/C/005814), Regkirona (regdanvimab, EMEA/H/C/005854) and Xevudy (sotrovimab, EMEA/H/C/005676) have been authorised for the treatment of COVID-19 disease in adult. In the case of Ronapreve also adolescents (from 12 years of age and weighing at least 40 kilograms), who do not require supplemental oxygen and who are at increased risk of their disease becoming severe.

Ronapreve is also approved for prevention of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kilograms.

Other products have been repurposed to be used for the treatment of COVID-19, such as Kineret (anakinra, EMEA/H/C/000363) in adult patients with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure determined by plasma concentration of soluble urokinase plasminogen activator receptor (suPAR)≥6 ng/ml, and RoActmera (tocilizumab, EMEA/H/C/000955) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Additionally, there are 5 approved vaccines for active immunisation against SARS-CoV-2 aiming to prevent COVID-19 disease: Comirnaty (EMEA/H/C/005735), Spikevax (EMEA/H/C/005791), Vaxzevria (EMEA/H/C/005675), COVID-19 vaccine Janssen (EMEA/H/C/005737) and Nuvaxovid (EMEA/H/C/005808).

While care for individuals with COVID-19 has improved with clinical experience, there remains an urgent need for vaccines and therapeutics able to prevent, mitigate and treat COVID-19 infections during the ongoing pandemic. Especially protection of vulnerable groups and mitigating the effects of the pandemic on a population level are desired. In addition, some studies have shown that patients might experience potential sequelae, including chronic fatigue, thrombotic events post infection, non-reversible lung disease, etc; although these aspects have not been fully determined yet.

2.2. About the product

Paxlovid is a combination pack medicinal product containing two active substances in separate pharmaceutical forms: PF-07321332 and ritonavir. PF-07321332 is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro). Inhibition of the SARS-CoV-2 Mpro renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication. Ritonavir inhibits the CYP3A-mediated metabolism of PF-07321332, thereby providing increased plasma concentrations of PF-07321332.

The recommended dosage is 300 mg PF-07321332 (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) orally every 12 hours for 5 days.

The combination pack has been considered indispensable for public health by the CHMP and the European Commission, in order to facilitate patient access to the medicinal product in the current pandemic situation.

The applicant applied for the following indication: "PAXLOVID is indicated for the treatment of mild-to-moderate Coronavirus Disease 2019 (COVID-19) in adult and adolescent patients (12 years of age and older weighing at least 40 kg) and who are at high risk for progression to severe COVID-19 (see section 5.1)".

2.3. Type of application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide clinical comprehensive data.
- Unmet medical needs will be addressed, as in the framework of the ongoing COVID-19 pandemic there is an urgent need for safe and effective therapeutic interventions that can reduce viral

transmission, improve time to clinical recovery and prevent the progression of infection to more severe disease, hospitalisation and death. Such a therapeutic would also have the potential as an effective treatment for future coronavirus epidemics. Thus, development of pan-coronavirus treatments has a critical role in global health protection to prevent potential future pandemics.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. The applicant is providing data from their Phase 2/3 study C4671005 (EPIC-HR), which achieved overwhelming efficacy at the predefined interim analysis (based on 45% of the targeted sample size of around 3000 patients). Study C4671005 was conducted in the high-risk population. According to the applicant, the scheduled interim analysis showed an 89% reduction in risk of COVID-19-related hospitalisation or death from any cause compared to placebo in patients treated within three days of symptom onset (primary endpoint). In the overall study population through Day 28, no deaths were reported in patients who received PF-07321332/ritonavir compared to 10 (1.6%) deaths in patients who received placebo. Therefore, the benefits to public health of the immediate availability of the product outweigh the risks of further additional data requirement.

2.4. Quality aspects

2.4.1. Introduction

The finished product Paxlovid consists of two separately manufactured dosage forms both presented as film-coated tablets of pink and white colour, which are co-packaged together. Pink tablets contain the active substance (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, hereafter referred as PF-07321332; white tablets contain ritonavir.

The PF-07321332 immediate release film-coated tablet (pink) contains 150 mg of PF-07321332 as active substance. Other ingredients are:

Tablet core: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal silicon dioxide and sodium stearyl fumarate;

Film-coating: hydroxy propyl methylcellulose, titanium dioxide, polyethylene glycol and iron oxide red.

The ritonavir immediate release film-coated tablet (white) contains 100 mg of the active substance ritonavir. Other ingredients are:

Tablet core: copovidone, sorbitan laureate, anhydrous colloidal silica, calcium hydrogen phosphate, anhydrous and sodium stearyl fumarate;

Film-coating: hypromellose, titanium dioxide, macrogol, hydroxy propyl cellulose, talc, anhydrous colloidal silica and polysorbate 80.

The ritonavir 100 mg film-coated tablets co-packaged in Paxlovid have been approved in EU countries as a generic product since 2015. The reference product Norvir has been approved since 25/08/1996 via the centralised procedure EU/1/96/016/005.

The finished product Paxlovid is packaged into a composite "Oriented PolyAmide/Aluminum Foil/Polyvinylchloride foil blister" (OPA/Alu/PVC) with aluminium foil lidding; each tablet is placed into an individual blister cavity.

The blister packaging configuration provides the recommended dosage which is 300 mg PF-07321332 (two 150 mg tablets) and 100 mg ritonavir (one 100 mg tablet) to be taken together, orally, twice daily for 5 days. The blister configuration is depicted in Figure 1:

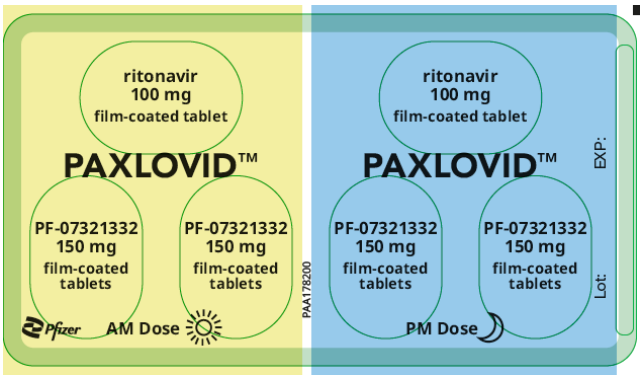


Figure 1. Blister configuration of Paxlovid

Five blister cards are packed in an outer carton, providing 5 days treatment.

2.4.2. Active Substance PF-07321332

2.4.2.1. General Information

The chemical name (IUPAC) of PF-07321332 is (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, corresponding to the molecular formula $C_{23}H_{32}F_3N_5O_4$. It has a molecular mass of 499.54 g/mol and the following structure (Figure 2):

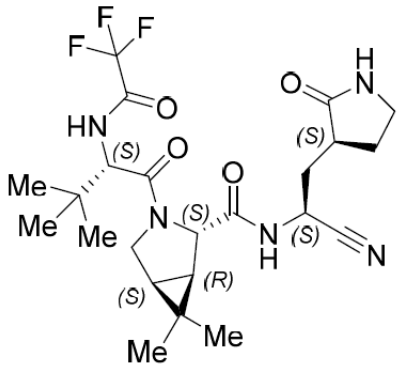


Figure 2. Chemical structure of PF-07321332 active substance

The structure of the active substance (AS) PF-07321332 was elucidated by a combination of analytical methods, including 1H-NMR, 13C-NMR, High Resolution Mass Spectrometry (HRMS), UV-VIS spectroscopy and attenuated total reflectance (ATR) FTIR spectroscopy. The molecular structure and absolute configuration of PF-07321332 was independently confirmed using single crystal X-ray diffraction technique.

PF-07321332 is a non hygroscopic, white to pale coloured crystalline powder. It has low solubility in (unbuffered) water and buffered aqueous media with pH from 1.97 to 6.96 ranging between 0.98 and 1.15 mg/mL.

PF-07321332 has 6 asymmetric centres, giving 32 possible stereoisomers (azabicyclo[3.1.0]hexane moiety can only exist in the syn configuration) as could be derived from Figure 2, which shows the absolute configuration.

As an additional element of the chiral control strategy, chiral identification assays have been developed for each of the starting materials (SMs) to ensure that the correct enantiomer of each is used in the active substance synthesis.

PF-07321332 manufactured by the manufacturing process is isolated as crystalline polymorphic form 1 (anhydrous form) as confirmed by powder X-ray diffraction (XRPD). Form 2 and Form 3 are further possible polymorphic forms. Form 1 is the thermodynamically most stable form at relevant temperatures and humidities. As the AS is poorly soluble, the polymorphic form could have an influence on the performance of the product, and thus it should be demonstrated that the polymorphic form does not change during storage of the AS **(REC3)**.

Overall, the provided general information on the active substance is sufficient.

2.4.2.1. Manufacture, characterisation and process controls

The manufacturing process consists of several chemical transformation steps. A brief description of the manufacturing process is given including reagents and solvents, some in-process controls, and batch scale sizes. The projected commercial manufacturing scale for PF-07321332.

The manufacturing process proposed for commercial supply has been described, however some further details of the manufacturing process and aspects of its control strategy should be provided; this was raised initially as a Major Objection (MO). Specifically, amounts or ratios for all compounds, reagents, catalysts, and solvents should be described; process conditions and parameters (like temperature, reaction time, pH, etc.) should be established and described; it should be clearly defined in which of the steps processing aids are used; conditions of reprocessing should be described and the effect on the impurity profile should be investigated. Since different process conditions may lead to a different impurity profile, it is requested that in order to improve the control strategy description and to confirm a consistent impurity profile, additional details should be included in the manufacturing process proposed for PF-07321332 commercial supply. In the context of a CMA this issue can be classified as a Specific Obligation (SO) and the data will be provided post-approval **(SO1)** at latest in June 2022 as committed by the applicant.

The proposed choice of starting materials (SMs) are considered acceptable. Adequate justification to support the definition of the SMs according to ICH Q11 guideline have been provided. All three SMs are significant structural fragments of the active substance and there are sufficient chemical steps, and a form conversion step, between them and the final active substance. The synthesis routes for each of the SMs used by each of the suppliers are sufficiently described. However, some of the synthesis routes of the SM are still being optimised which could result in changes in the synthesis routes. Therefore, the final synthesis routes for the starting materials should be provided as soon as possible, at latest in June 2022 **(REC2)**. Names and addresses for the SM manufacturers were provided in the responses but the dossier needs to be updated accordingly with this information **(REC2)**. Provisional SM specifications, analytical procedures and summary of validation data were provided. However, the provisional SM specifications are not yet completely finalised. The SM specifications should be clearly updated based on historical batch data and comparative data should be presented **(REC2)**. Appropriate acceptance limits for impurities, including chiral impurities, should be included in the starting material specifications. See discussion below concerning the control strategy for impurities **(SO2)**.

A list of the reagents, solvents and catalysts used in the manufacturing process with identification of ICH classification for solvents as well as the respective specifications has been submitted. The specifications for raw materials are acceptable.

Three intermediates are isolated. Provisional specifications have been established for the intermediates PF-07336591-01 and PF-07320267 in the manufacturing process of PF-07321332 active substance. The provisional intermediate specifications are not yet completely finalised, but the provided information submitted suffices in the context of the current emergency situation. However, in order ensure comprehensive control of impurities throughout the lifecycle of the product, for each of the isolated intermediates, intermediate specifications should be clearly established including at least the test parameters description, assay/purity, limits of identified, unidentified and total impurities. See discussion below concerning the control strategy for impurities **(SO2)**.

A short discussion on inorganic and organic impurities (including elemental, genotoxic and chiral impurities) was provided. The applicant stated that the active substance control strategy for the impurities has not yet been fully established. The control strategy for the impurities, including chiral impurities, in the AS should be clearly defined. The carry-over of impurities arising from the synthesis of the starting materials and the proposed manufacturing process of the AS for commercial supply should be investigated on three pilot-or production batches. More information about the potential formation of other chiral impurities and their control strategy should be provided. Based on these data appropriate methods for control and acceptance criteria for impurities, including chiral impurities, should be included in the SMs and intermediates specifications. If necessary, toxicological qualified limits for additional impurities should be included in the AS specification. The applicant has committed to continue to re-evaluate the specifications and limits as additional manufacturing experience becomes available and as part of validation, currently scheduled to complete in June 2022.
This issue of the control strategy for the impurities in the AS was raised initially as major objection. In the context of a CMA this issue can be classified as a Specific Obligation **(SO2)**. The data should be provided at latest in June 2022 as proposed by the applicant.
The residual solvents used in the final manufacturing step are specified in the active substance specifications with adequate limits according to ICH Q3C guideline. Purge factors for the residual solvents have been calculated. However, as the control strategy of the manufacturing process has not been completely finalised, the calculation of the purge factors cannot be concluded as final.
Therefore, the carry-over of residual solvents used in the manufacturing steps before the final step should be also investigated on three consecutive production batches **(REC3)**.

The provided risk assessment concerning the potential presence of nitrosamines in the active substance is sufficient. Potential sources of nitrosamine impurities currently listed in EMA guidance were addressed. No risks are identified.
A short description of the manufacturing process development is provided. The proposed and current manufacturing process is mainly similar to the earlier processes reported. Changes from process to process have been adequately described. The earlier routes were used to provide earlier development, pre-clinical and clinical batches. The applicant stated that at this stage of development Quality Risk Management is in-progress, an enhanced synthetic Route is being developed, and validation is ongoing consistent with ICH Q7 and ICH Q11 for active substance. A commitment has also been given to submit the enhanced control strategy for the current Route and the enhanced Route for Agency review and approval by variation as applicable **(REC2)**.

PF-07321332 is packaged in two sealed, low density polyethylene (LDPE) anti-static liners, which is then inserted in a high-density polyethylene (HDPE) drum or equivalent secondary container. A representative IR spectrum for the low-density polyethylene liner is provided as well as the corresponding specification. The provided information is acceptable.

2.4.2.2. Specification

The active substance specification includes tests for assay (HPLC), appearance, identification (IR, HPLC), impurities (HPLC), residual solvents (GC), water content (Ph. Eur.), solid state polymorphic form (PXRD), residue on ignition (Ph. Eur.), and particle size distribution (laser diffraction).

The active substance specification contains all relevant test parameters. The justifications for the specifications, including individual specified organic impurities, qualified at toxicological levels or in line with ICH Q3A (R2), are acceptable in the context of this procedure. However, this provisional active substance specification should be revised in line with CHMP recommendations (RECs) and a final specification should be established for commercial supply.

As the control strategy for the impurities will be finalised at the latest in 2Q 2022 (SOB2) if necessary, additional impurities should be specified in the AS specification. In addition, the structure of one of the impurities should be stated and it should be classified according to ICH M7 **(REC3)**. Acceptance criteria for particle size distribution (PSD) have been set but should be tightened taking into account clinical batches, unless it could be show on PK or bioavailability data that the set upper limits of the PSD have no impact on the performance of the finished product **(REC4)**. With regard to the omission of testing for microbial enumeration it is stated that microbiological quality will be evaluated for three primary stability lots at initial release and when stored under the proposed long-term storage conditions and results will be reported **(REC4)**.

The absence of elemental impurities of class 1 and class 2a has been shown on six batches of active substance for Class 1/2A and two batches for Class 3 Element. All of these elemental impurities were <30% of ICHQ3D option 1 limit. It is stated that the Class 1/2A elemental impurities, will continue to be monitored in the active substance and an appropriate control strategy will be established; this is acknowledged. The data should be provided at the latest in 2Q 2022 **(REC3).**

The descriptions of the analytical procedures are acceptable in the context of the present conditional marketing authorisation in an emergency situation. The results of methods validation studies have been conducted and some validation data for the in-house methods were provided. However, not all validation parameters required according to ICH Q2(R) guideline have been investigated and will be provided later. A MO was initially raised requesting complete validation data for the HPLC method for assay and impurity testing and for the residual solvent method to be provided in order ensure comprehensive control of impurities throughout the lifecycle of the product. In the context of a CMA this data can be provided post-approval by June 2022 as a specific obligation (**SO3).** In addition, section 3.2.S.4.2 should be updated with the description of the residual solvent methods and the description and validation of the XRPD method **(REC4).**

The quality of the reference standard for the active substance is sufficiently proven.

Satisfactory batch analysis data are given for active substance batches used for toxicological batch and clinical batches. The batch data covers all synthesis routes used in the manufacturing development. Batch analysis data for three production batches of the current process are within set specifications.

2.4.2.3. Stability

Stability data for two active substance batches produced by earlier manufacturing processes for up to 6 months under long term conditions at 25°C/60% and under accelerated conditions at 40°C/ 75% RH were given showing compliance with specifications. The stability batches were packaged in double LDPE bags which are placed in HDPE drums.

No significant changes were observed. The stability of the active substance batches produced by earlier synthetic routes are supportive for proposed synthetic route as all synthetic routes have the same polymorphic form, similar synthetic chemistry and same final solvents. Differences in purity profile at release are not expected to impact stability. However, the applicant should provide further stability data for batches of PF-07321322 AS manufactured by the current route and from previous routes **(REC5)**.

A photostability study was completed under ICH conditions using light source option 2 two batches from earlier routes. No changes were observed in the photostability studies. The applicant has demonstrated that the active substance is photostable.

Samples of PF-07321332 from earlier synthetic routes were subjected to forced degradation conditions to confirm the suitability of the assay and purity method and to identify potential primary degradation products. Forced degradation data on a batch of PF-07321332 AS manufactured by the commercial synthetic route should also be provided **(REC5).**

Taking into account the requirements of the ICH Q1E guideline the proposed re-test period and storage conditions can be accepted. A commitment was given that the first three batches from route F will be placed on stability under long-term conditions at 30°C/75% RH for 36 months and under accelerated conditions at 40°C/75% RH over 6 months **(REC5)**.

2.4.3. Active substance ritonavir

Ritonavir is an established active substance described in the Ph. Eur. The supplier of ritonavir used in the manufacture of Paxlovid is Hetero Drugs Limited. Ritonavir from Hetero is already approved for use in other medicinal products in the EU, using the AMSF procedure.

2.4.3.1. General information

The chemical name (Ph. Eur.) of ritonavir is Thiazol-5-ylmethyl[(1S,2S,4S)-1-benzyl-2-hydroxy-4-[[(2S)-3- methyl-2-[[methyl[[2-(1 metylethyl)thiazol-4-yl] methyl] carbamoyl] amino] butanoyl] amino]-5-phenylpentyl]carbamate, corresponding to the molecular formula C37H48N6O5S2. It has a molecular mass of 720.94 g/mol and the following structure (Figure 3):

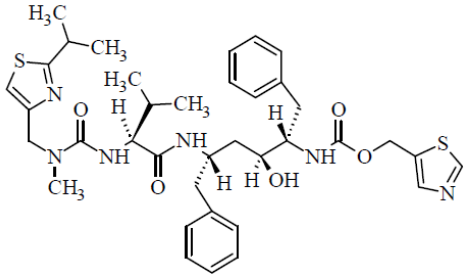


Figure 3. Chemical structure of ritonavir active substance

The molecular structure of ritonavir was investigated and confirmed by the 1H and 13C NMR spectroscopy, mass spectrometry, UV spectroscopy, and InfraRed spectroscopy.

Ritonavir is a white or almost-white, non-hygroscopic, crystalline powder, practically insoluble in water, freely soluble in methanol and sparingly soluble in acetonitrile.

Ritonavir exhibits isomerism. It contains 4 chiral centres which are introduced selectively in the synthetic process. Enantiopurity is determined by a chiral HPLC method in the active substance

specification. It also exhibits polymorphism; Hetero consistently produces polymorphic Form-I, characterised by a XRD pattern, and tested in the active substance specification.

2.4.3.1. Manufacture, process controls, characterisation and container closure

Ritonavir from Hetero is already approved in the EU using the AMSF procedure. A Letter of Access specifying the ASMF version (applicant's and Restricted Part of the ASMF) has been submitted.

The chemical synthesis and a brief description of manufacturing process of intermediate and final active substance were provided. The manufacturing process consists of four chemical reaction steps followed by a purification and drying step. The 4 starting materials are well defined, have been justified are controlled by acceptable specifications and are acceptable.

Information on possible impurities is provided covering Ph. Eur. impurities, additional non-Ph. Eur. impurities, residual solvents, genotoxic impurities, and elemental impurities.

Details of the impurity studies carried out considering all the above impurities and the residual solvents of ritonavir (Form-I) were enclosed. Studies have been carried out to check the presence of the other possible impurities from the manufacturing process of ritonavir and its starting materials.

A study has been conducted to check the possible presence of Class-I solvents in ritonavir with a validated method. From the study results it was concluded that all Class-I solvents are absent in the batches tested and therefore do not need to be controlled at the level of active substance.

Based on the evaluation of the process, three impurities were identified as potential genotoxic impurities. Studies have been carried out to check their presence in final AS with a validated method. From the studies it was clear that these compounds are below detection limit in all the batches being tested.

A risk assessment for the following Class 1, 2A, 2B and 3 elemental impurities as per ICH Q3D requirement was carried out for ritonavir production scale batches. Results from batch analysis obtained demonstrate that Class 1 and 2A along with intentionally added Class 2B and class 3 elemental impurities were found to be insignificant levels in ritonavir production scale batches. Considering the manufacturing process, the potential presence of Class 1 and 2A and intentionally added Class 2B and Class 3 elemental impurities in ritonavir are highly remote. It is concluded that the active substance complies with ICH Q3D and that no further controls are required.

The active substance is packaged in transparent polyethylene bag, tied with a plastic tag. This bag is placed in a black bag tied using another plastic tag. The polyethylene bags are made from LDPE (Low Density Polyethylene) and LLDPE (Linear Low-Density Polyethylene) respectively. The bags are placed in an HDPE drum. The packaging materials complies with relevant EU regulations and Ph. Eur. requirements.

Specifications and test procedures for packing materials, IR spectrums of the polythene bags, in-house and supplier certificates of analysis for packing material and compliance certificate of packing material have been provided.

2.4.3.2. Specification analytical procedures, reference standards, batch analysis

The proposed active substance specifications includes tests for appearance, solubility, identification (IR, HPLC), polymorphic form (XRD), related substances (HPLC), water content (Ph. Eur.), sulfated ash (Ph. Eur.), assay (HPLC), specific rotation (Ph. Eur.) and residual solvents (GC). 4-Nitrophenyl chloroformate and [(5-Thiazolyl)methyl]- (4-nitrophenyl)carbonate content (UFLC-MS) and 1,3-

Dichloroacetone (GC-MS) content are not part of the release specifications but are going to be monitored on the first batch of every year and multiple of every 10th batch.

The active substance specification contains all the requirements of the Ph. Eur. with additional requirements for polymorphic form, specific optical rotation, residual solvents, and additional non-Ph. Eur. impurities. The limits for impurities are in compliance with Ph. Eur., ICH Q3A, ICH Q3C, ICH Q3D, and ICH M7. The active substance complies with relevant EMA and ICH guidelines where appropriate.

The applicant provided an acceptable active substance specification as applied by the ASMF holder. It is also noted that the AS is converted to the *premix* and shipped to the ritonavir finished product manufacturer. The *ritonavir premix* specification applied by the finished product manufacturer has been provided in dossier section 3.2.P.3.4. This is acceptable, however the applicant's own specification for ritonavir AS should also be provided **(REC1).**

The analytical procedures are described, and their suitability was demonstrated by validation data. The reference standards are sufficiently characterised.

The provided batch data of three ritonavir batches demonstrate compliance with the active substance specification. No significant differences between the batches was observable.

2.4.3.3. Stability

Stability studies were initiated for the first three ritonavir AS validation batches, as per the ICH Q1A guideline at accelerated (40±2°C/ 75±5% RH), intermediate (30±2°C/ 65±5% RH), and long term conditions 25±2°C/ 60±5% RH. The batches were stored in the specified container closure system for 60, 12 and 6 months under long term, intermediate and accelerated conditions respectively. The methods adopted for conducting the stability studies are stability indicating which were established based on the degradation studies performed. The available stability data have been evaluated and no significant changes were observed in any of the stability batches. It has also been demonstrated that the active substance is photostable.

A forced degradation study has been performed under various stress conditions. The summary report on appearance, identification by IR and HPLC, P-XRD, related substances by HPLC, water and assay by HPLC is provided demonstrating that the methods adopted for conducting the stability studies are stability indicating.

Based on the evaluation of stability data, the claimed retest period and storage condition is endorsed.

2.4.4. Paxlovid finished medicinal product

The proposed medicinal product Paxlovid consists of PF-07321332 150 mg film-coated tablets and ritonavir 100 mg film-coated tablets, which are separately manufactured, but co-packaged on the same blister for ease of daily co-administration.

2.4.5. PF-07321332 film-coated tablets

2 . 4 . 5 . 1 . Description of the product and pharmaceutical development

Description of PF-07321332 film-coated tablets

The PF-07321332 tablets are described as an oval, pink, film-coated tablet, with the dimensions of approx. 8.5 x 17.5 mm, debossed with "PFE" on one tablet side and with "3CL" on the opposite side.

PF-07321332 finished product was designed as an immediate release (IR) dosage form, containing 150 mg PF-07321332 as active substance.

Excipients used for manufacturing the PF-07321332 tablet are listed in section 2.4.1 of this report and in section 6.1 of the SmPC. All excipients are confirmed to comply with Ph. Eur, with exception of the film coat Opadry Pink, though all of its components are compendial, Ph. Eur. and NF, respectively).

Pharmaceutical development

The objective of pharmaceutical development was to rapidly develop a physically and chemically stable solid oral dosage form with the appropriate biopharmaceutical properties and quality attributes according to the quality target product profile (QTPP).

A Quality Target Product Profile (QTPP), in accordance with ICH Q8 was established to guide formulation and process development activities. Oriented towards this QTPP, quality attributes were derived as basis for the prospective finished product specification. Through a combination of experimental studies, risk assessments, and manufacturing experience across a range of scales and equipment types, an accelerated understanding of the formulation and process conditions and their impact on the quality attributes of the finished product was obtained.

The active substance PF-07321332 is a non-hygroscopic and white to off-white crystalline compound with low aqueous solubility across the physiologically relevant pH range. The solubility is pH independent, as it is a non-ionisable compound. PF-07321332 is tentatively classified as BCS II/IV (low solubility with permeability to-be-determined) compound. A definite BCS classification for the active substance PF-07321332 on the basis of sound analytical data should be provided **(REC6).**

Different polymorphic forms have been identified for PF-07321332. The polymorphic Form claimed to be the thermodynamically most stable form under relevant manufacturing and storage conditions and has been used for all drug product development and clinical manufacture activities. In addition, it should be investigated, and data should be presented whether the polymorphic form selected for PF-07321332 finished product manufacture can remain stable under the proposed manufacturing conditions and during shelf life **(REC6)**.

For registration stability and clinical product batches manufactured to date the AS PSD had been stated. It is stated that particle size of all batches would continue to be monitored using a validated laser diffraction method with dry dispersion. As the data set in terms of PSD is premature, the stated PSD ranges used for producing clinical and registration stability batches is regarded as the provisional PSD specification, unless/until new PK data can justify wider PSD ranges. Considering that the active substance PSD, may impact the finished product characteristics and performance, an in-depth discussion with respect to potential PSD impact on manufacturability and bio-performance of the PF-07321332 IR film-coated tablets should be provided **(REC6)**.

All excipients and corresponding quantities chosen are typically used for oral solid dose products such as the film-coated tablets in question, thus acceptable. All excipients are confirmed to comply with Ph. Eur, with exception of the film coat Opadry Pink, though all of its components are compendial, Ph. Eur. and NF, respectively).Section 3.2.P.4 for the dossier for PF-07321332 tablets should be updated to include compendial and non-compendial excipients used for the manufacture of PF-07321332 150 mg film-coated tablets and their function. In addition, the same section should be updated with an adequately compiled specification for the film coat system Opadry Pink, with a confirmation of compliance with the EU regulation 231/2012 for red iron oxide and with exemplary CoAs for the non-compendial excipient Opadry **(REC8).**

Concerning compatibility, no experimental data of the PF-07321332 with each of the selected excipients are available. Instead, reference is made to the finished product stability study at ICH storage conditions. Based on stability data available to date, no active substance-excipient incompatibility has been observed.

During formulation development, some formulations were tested in terms of desired quality attributes and bio-performance. For the first-in-human study an oral suspension formulation was developed.

The different formulations used for different Phase of clinical development have been adequately described. The development core tablet formulations have very similar compositions with one difference (in the 150 mg formulation the disintegrant was replaced). Both formulations were manufactured with the same process, applying dry granulation, followed by tablet compression and film coating.

The dissolution performance of representative PF-07321332 150 mg immediate release film-coated tablet batches was investigated in dissolution media over the physiological range. The dissolution conditions were satisfactorily justified and were found to be most suitable and thus are proposed for the routine quality control (QC).

The discriminatory power of the dissolution method was studied by testing diverse "bad" batches and is considered appropriately addressed. Following a request during the rolling review, a revised dissolution specification has been provided for 150 mg PF-07321332 film-coated tablets and is accepted. Based on the dissolution results provided, the discriminating capability of the proposed dissolution method is considered demonstrated, with regard to the timepoint set for routine QC testing.

The manufacturing process development of PF-07321332 150 mg immediate release film-coated tablets comprises a conventional dry granulation process including the following steps: blending, screening, lubrication, dry granulation, milling, blending, followed by tablet compression and film coating.

A risk assessment considering requirements from the QTPP was conducted to identify the potential relationships between the process parameters and quality attributes. Based on this assessment, quality attributes including assay, content uniformity, dissolution, disintegration and tablet appearance were determined to be potentially impacted by the process parameters.

As next step, based on the outcome of this risk assessment, statistically designed experiments were conducted at laboratory scale, with additional learnings gained during manufacture of clinical, technical transfer and registration stability batches to collect more manufacturing process understanding and to recommend acceptable operating ranges for finished product manufacture. The operating ranges studied for the process parameters at laboratory and large manufacturing scales were shown to be robust for all quality attributes studied. It is stated that parameters would continue to be evaluated to further refine the control strategy of finished product manufacturing for commercial supplies. Impact on manufacturability and dissolution of the finished product of certain steps needs to be addressed in further detail **(REC6)**.

Overall, the manufacturing process development experiments have defined operating ranges for the proposed unit operations, which are considered appropriate for manufacturing PF-07321332 finished product of acceptable quality. However, the control strategy with respect to unit operations should be substantially amended (see below in *Manufacture of the product and process controls)*.

The container closure system including the microbiological attributes has been adequately justified. For further details refer below to *Co-packed medicinal product Paxlovid.*

2.4.5.1. Manufacture of the product and process controls

The respective manufacturing sites along with their corresponding responsibilities are clearly specified. Confirmations are available stating that the manufacturers operate under GMP.

A brief description is provided for the developed manufacturing process consisting of the following steps: initial blending, screening, lubrication, dry granulation followed by milling, blending and lubrication, followed by tablet compression and film coating.

The 150 mg film-coated tablets use compendial excipients and are manufactured using conventional processing equipment. The narrative description of the manufacturing process is presented with an acceptable level of detail in the context of this procedure, with regard to process parameters limits and hold times. However the following updates in the process description should be made: the individual process steps should be numerated in line with the corresponding numeration indicated in the flow chart; the term „Package" currently stated at Step 10 needs to be replaced with „Co-package" or similar to adequately reflect the co-packaging of PF-07321332 with ritonavir film-coated tablets in the same blister **(REC7)**.

In addition it has been clarified that there are no intermediates in the manufacturing process but more details on the process description, fully reflecting the information level required in the Guideline on Manufacture of the Finished Dosage Form (EMA/CHMP/QWP/245074/2015) (e.g. the operating ranges defined within the process development) should be sufficiently considered in the process narrative and will be added once validation is complete **(REC7)**. The applicant has noted that based on available batch data at the commercial site, including tech transfer, ICH registration stability, clinical, and commercial manufacture, there is no indication of criticality associated with any hold time between the manufacturing steps; all unit operations, have shown to be robust enough and in-process testing as well as enhanced analytical testing are in place to ensure appropriate quality of each released batch. However, it should be further clarified whether hold times are intended to be applied for the PF-07321332 finished product manufacture and, if so, relevant supportive stability data should be provided **(REC7)**. As manufacturing experience will be accumulated appropriate controls will be implemented, if needed, and critical process steps and parameters should be described **(REC7)**. Considering the presented information and commitments made, in the context of this procedure, the level of detail of the narrative description of the manufacturing process is acceptable. Batch formulae for batch sizes are provided.

With respect to process validation data, the applicant provided some batch data from recent commercial batches and responded that the requested validation scheme will be available in April 2022 and validation data be provided in June 2022. The few data provided suggest high reproducibility and may be regarded as supportive only, but they cannot adequately replace a full process validation data. Therefore, full process validation data, considering all requirements specified in the Guideline on Process Validation for Finished Products (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1), should be provided **(REC7)**.

2.4.5.2. Product specification analytical procedures, batch analysis, reference standards

PF-07321332 150 mg film-coated tablets specifications include appropriate tests for this kind of dosage form including for appearance, identity (HPLC and IR), assay (HPLC), degradation products (HPLC), dissolution (Ph. Eur., HPLC), content uniformity (Ph. Eur.) and microbial limits (Ph. Eur.). During stability, only appearance, assay, degradation products, dissolution and microbial purity are performed.

Sufficient information on specifications has been provided. However, some additional testing parameters like content uniformity, tablet thickness, and tablet weight should be included in the release specifications **(REC9)**.

The impurities and degradation products have been sufficiently discussed. There are no impurities in the finished product that are different from those present in the active substance. However, to complete the discussion on degradation products, the degradation pathway of the possible degradation products should be highlighted under the section 3.2.P.5.5 and linked sufficiently to 3.2.S.3.2 **(REC9)**. The finished product contains no Class 1 or Class 2 mutagenic impurities or degradation products.

The dissolution limit has been satisfactorily justified. An elemental impurities risk assessment was completed in line with ICH Q3D. The risk of the mentioned elemental impurities in each of the key sources, including the AS, excipients, container closure system, manufacturing equipment, and utilities were assessed. Batch data from testing representative lots of the in-going AS and film coating were considered in the risk assessment, as well as data from the Lhasa Elemental Impurities Excipients Database. The data showed that the risk of the Class 1, Class 2A elemental impurities exceeding the 30% Control Threshold of the Option 2 concentration limits and associated Oral PDEs were low to negligible. Testing by sufficiently validated Inductively Coupled Plasma- Mass Spectrometry (ICP-MS) on representative lots of the finished product confirmed the overall low - negligible risks for Class 1 and Class 2A elemental impurities and Li exceeding their PDEs in the finished product. Based on the risk assessment and on the discussion presented it can be concluded that no elemental impurities testing and no additional EI controls are needed for the PF-07321332 IR tablets.

A risk assessment on the potential presence and formation of nitrosamine in the finished product was completed, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The applicant states, that no vulnerable amines have been identified in AS or excipients, as well as no nitrosamine risk have been identified from the packaging material used. To support this risk assessment, the limit for any N-nitrosamine without specific toxicological information has been calculated as 30 ppb, using the acceptable lifetime intake of 18 ng/day recommended by EMA in "Nitrosamine impurities in human medicinal products" (09-Jul- 2020), in combination with the maximum daily dose of PF-07321332 of 600 mg and a conservative 10 year to lifetime treatment duration. The limit for DIPNA is 44 ppb, using the acceptable intake of 26.5 ng/day in combination with the maximum daily dose of PF-07321332 of 600 mg.

Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Overall, the specification limits have been sufficiently justified. In addition, justification has been provided concerning exclusion of tests on water content, nitrosamines, chiral purity, elemental impurities. Further information on justification of the limit for assay during shelf life should be provided **(REC9)**.

The descriptions of the analytical procedures and their validations provided are acceptable. Some additional information concerning some validation parameters for the three methods used for identity, assay degradation products and content uniformity should be provided **(REC9)**. Satisfactory information regarding the reference standards has been provided during the procedure.

Batch analysis data were provided for seven batches of PF-07321332 150 mg film-coated tablets. These batches were manufactured according to the details described in Section P.3.3 Description of Manufacturing Process and Process Controls and tested by the methods described in Section P.5.2 Analytical Procedures. Some of the data presented were evaluated against specifications that differ from those described in Section P.5.1. Specification(s) but all data were within the specifications at the time.

Adventitious agents

PF-07321332 150 mg film-coated tablets contain lactose monohydrate, which is the only excipient in PF-07321332 150 mg tablets that is of animal origin. It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.6. Ritonavir film-coated tablets

2.4.6.1. Description of the product and pharmaceutical development

Ritonavir 100 mg film-coated tablets are described as white to off white, capsule shaped, film-coated tablet, debossed with 'H' on one side and 'R9' on other side. Its approximate dimensions are 17.14 mm x 9.13 mm.

Pharmaceutical development

The finished product has been developed as a generic to the reference product Norvir, which is authorised in the EU by AbbVie Deutschland GmbH & Co. Its qualitative composition is essentially similar to the reference product.

Ritonavir active substance is a white to light tan powder. Due to its low solubility and permeability properties, it has been assigned to BCS Class IVa.

Excipients matching those of the EU reference product were chosen, all of which complying with Ph. Eur. monographs, including those contained in the non-compendial coating mixture. All excipients are common ingredients for this product type. Their compatibility with the ritonavir premix was confirmed by stability data. Minor amendments should be made to the composition table as to specify the active ingredient at the declared amount (100 mg) along with one total amount of each excipient used **(REC12)**.

Pharmaceutical development started with pre-formulation studies based on published information, physicochemical characterisation and *in-vitro* dissolution data of the US and EU reference products. Formulation development was driven by ritonavir's key physicochemical characteristics and reference product's *in-vitro* dissolution characteristics., additional information is required on the stability of the polymorph form during storage and manufacturing conditions **(REC13)**.

Following several trial formulations, a manufacturing process was chosen which resulted in tablets with acceptable *in vitro* dissolution data. The manufacturing process development was described. A process robustness study was conducted, identifying the possible variables during various stages of the

manufacturing process and their effect on the *in vitro* dissolution performance of the formulation. Optimisation studies of different steps of the process were conducted. Nevertheless, little information on the development of the manufacturing process is provided. Critical process parameters during manufacture are identified with specified set points. However, justification based on development data is awaited for CPPs during dry mixing, lubrication, compression, and film-coating **(REC13)**.

The proposed dissolution method for routine QC testing is paddles, 75 rpm 900 ml water with 60 mM Polyoxyethylene 10 Laurylether. As the requirements of Reflection Paper EMA/CHMP/CVMP/QWP/336031/2017 apply to ritonavir film-coated tablets as part of the CMA for Paxlovid, justification of the dissolution conditions are awaited, particularly the choice of media (water with surfactant at a specific concentration), and the agitation speed (75 rpm) **(REC13)**.

For commercial batches used in the bioequivalence study, *in vitro* dissolution studies were conducted and compared to the results obtained with the EU reference product. The dissolution profiles were found similar in all media when compared to the reference product, with acceptable f2 values.

Based on the development data, the biopharmaceutical performance of the test product is considered similar if not exceeding that of the reference product. Yet, the proposed limit for dissolution testing is not considered appropriate as it is located in the plateau and furthermore it does not allow for discrimination between batches. As a consequence an MO was raised initially; the applicant is required to tighten the *in-vitro* dissolution specification in 3.2.P.5.1 according to the results obtained for the biobatches as per the Reflection Paper EMA/CHMP/CVMP/QWP/336031/2017 e.g. to NMT 75 % (Q) in 45 min. In the context of a CMA this can be addressed as a specific obligation post-approval by June 2022 **(SO4)**.

In summary, the finished product has been shown to be comparable to the reference product if not superior, based on key parameters *in vitro* dissolution and related substances profile/levels. However, several aspects of pharmaceutical development, including discussion of the proposed control strategy for the manufacturing process including manufacture of the polymorph form, need to be addressed, and compliance with current ICH Q8 (R2) should be established as discussed above.

In the context of the CMA, the quality documentation provided for ritonavir film-coated tablets is considered acceptable from a risk-based perspective, as the product is currently registered in several European countries with the currently proposed specifications.

The choice of container closure system for the co-packaged medicinal product is based on PF-07321332 tablets and is justified and was confirmed by results of accelerated stability studies. As for the bulk tablets, the suitability of the primary container (HDPE, with polypropylene closure) was confirmed by results of accelerated stability studies for 3 months. No significant changes were observed for water content, assay, related compounds, and dissolution.

No risk of nitrosamine formation is identified originating from the packaging components. No overages are used during manufacture of ritonavir film-coated tablets. Microbiological attributes and compatibility are not applicable for the proposed finished product.

Detailed information on the container closure system (LDPE bag placed in triple laminated aluminium bag) for ritonavir bulk tablets was provided including specifications, analytical procedures and certificates of analysis issued by both the suppliers and the product manufacturer.

2.4.6.1. Manufacture of the product process controls and characterisation

All manufacturing sites and their operations were defined. The manufacturing process uses three stages for preparation of the premix: Stage-I (RPM-I: preparation of premix), Stage-II (RPM-II:

pulverisation), Stage-III (RPM-III: blending, sifting, packaging). Afterwards, the material is sifted/mixed and prepared for hot melt extrusion, milled/sifted, (pre)lubricated, before compression and coating take place. The process is considered as non-standard procedure due to the hot melt extrusion included. Process descriptions were provided along with flow charts. Batch formulae for production batch sizes were presented. Routine in-process controls were presented. For the intermediate a detailed specification including a description of analytical methods and certificates of analysis, packaging material and hold times were presented. However, stability data of the intermediate product are required and, the specifications for the packaging material for the intermediate product is awaited **(REC14)**. Overall, the process is well-described and controlled by in-process tests. Nevertheless, the applicant is expected to provide further details and justification for the control strategy employed based on development data **(REC14)**.
Process validation data were provided for commercial batches at both minimum and maximum batch size. Key parameter during dry mixing and lubrication was blend uniformity, monitored in individual samples taken at several locations to make sure that the active substance is evenly distributed throughout the blend. During compression and coating, it has been confirmed that the physical tablet parameters (mass variation, uniformity of dosage units, friability, hardness) comply with pre-defined requirements. The process has been shown to be reliable, robust and reproducible in order to obtain tablets that comply with the specifications and quality characteristics defined on the respective validation protocol.

Also, validation results of the manufacturing process of three batches of ritonavir premix were provided. The critical steps of the process were monitored. The critical steps of the process were monitored in order to ensure that the process is suitable and reproducible. The following critical steps were validated through additional or more frequent than routine in-process control testing: pulverising, sifting and packing. The results obtained demonstrate that the manufacture of ritonavir premix is acceptable and reproducible in order to obtain an intermediate complying with the specifications and quality characteristics defined in the respective validation protocol. Nevertheless, some additional validation data for the hot melt extrusion process should be provided, to justify time/temperature regimes in the context of chemical instability of the AS to ensure satisfactory quality specifications whilst the least temperature stress is applied. Furthermore, the process optimisation study results should be disclosed **(REC14)**.

2.4.6.2. Product specification analytical procedures, batch analysis, reference standards

The finished product release specifications include appropriate tests for this kind of dosage form including description, identification (HPLC and UV), average weight (mass), water content (KF), dissolution (Ph. Eur. - HPLC), uniformity of dosage units (content uniformity Ph. Eur.), related substances (HPLC), assay (HPLC) and microbial purity (Ph. Eur.).

During stability studies, tests for appearance, assay, degradation products, dissolution and microbial purity are performed. Different specifications limits are applied for shelf life concerning water content and degradation products. During shelf life, the following parameters are tested: Description, assay, related substances, water content, dissolution, microbial purity.

Sufficient information on specifications has been provided. The specifications for ritonavir 100 mg film-coated tablets are generally in line with the requirements of the relevant Ph. Eur. monographs, ICH guidelines and batch analysis data.

If not otherwise justified, the limit for dissolution testing should be revised as per the Reflection Paper EMA/CHMP/CVMP/QWP/336031/2017 (e.g. to NMT 75% (Q) in 45 min) (as discussed previously in Pharmaceutical Development (SO4)).

There are no impurities in the product that are different from those present in the active substance. If not otherwise justified, the limit for water content, which has been set to the shelf life specification with NMT 6.5% should be tightened according to the data obtained as the maximum amount found is 4 % **(REC15)**. In summary, satisfactory information or justification of specifications has been provided in the context of this CMA. Revision of specification limits for dissolution and water content is expected as discussed.

A risk assessment for elemental impurities as per ICH Q3D has been provided, which sufficiently justify absence of test for elemental impurities in the finished product. The component approach has been used. However, data of three consecutive batches or six pilot batches are awaited and the respective analytical methods validation data, should be provided **(REC15).**

A risk assessment for the presence of nitrosamines as per the requirements of EMA guidance on Information on nitrosamine for marketing authorisation holders (EMA/189634/2019 & CMDh/404/2019) and (EMA/428592/2019 & CMDh/405/2019) has been provided. For ritonavir premix and ritonavir 100 mg film-coated tablets no risk for presence of nitrosamine impurities was identified. However, for completeness of the assessment further information is awaited. Specifically, the analytical method validation data for the methods of analysis of nitrosamines impurities, should also be provided **(REC15).**

The analytical methods which are mentioned in the specifications have been sufficiently described. Validation design and appropriate validation data has been provided for almost all methods described under analytical procedures including the method used for the determination of blend assay, blend content uniformity. Validation data have been presented for the method used for determination of assay and dissolution testing as well as for identification by UV and microbial purity.

Information on reference standards used including certificates of analysis has been provided. Some information is still expected concerning the purpose of the reference standards used **(REC16)**.

Batch analysis data have been presented for four batches. All data were within the specifications. Certificates of analyses have been presented. However, clarifications concerning discrepancies of some of the specification parameters reported in the CoAs is awaited **(REC15)**.

Adventitious agents

There are no excipients of human or animal origin used in the manufacture ritonavir 100 mg Film-coated tablets.

2.4.7. Co-packed Paxlovid

2.4.7.1. Container closure system for the co-packaged finished product

The co-packed finished medicinal product Paxlovid consists of separately manufactured film-coated tablets (2 x PF-07321332 150 mg and 1 x ritonavir 100 mg), which are co-packaged into a blister.

The container closure system for PF-07321332 150 mg film-coated tablets and externally sourced ritonavir 100 mg film-coated tablets consists of a foil/foil blister system made from a composite Oriented PolyAmide/Aluminium Foil/Polyvinylchloride (OPA/Al/PVC) foil blister with aluminium foil lidding where each tablet is placed into an individual blister cavity. Illustrative drawings and representative IR spectra of the packaging components were provided. Some information concerning

declarations confirming regulatory compliance of material in contact with food should be provided **(REC10)**.

2.4.7.2. Stability for the co-packaged finished product

PF-07321332 150 mg film-coated tablets

Due to the accelerated pharmaceutical development, limited primary stability data is currently available for the PF-07321332 150 mg film-coated tablet.

In accordance with ICH guideline Q1A(R2), a primary stability study consisting of PF-07321332 150 mg film-coated tablets packaged in proposed commercial foil/foil blister packaging has been initiated. The primary stability batches were manufactured at 10% of the proposed commercial scale at Pfizer's Freiburg (Germany) site and packaged at the same facility.

Preliminary stability data for three primary batches of the 150 mg tablets were reported for three months at the long-term storage conditions of 30°C/ 75% RH and 25°C/60% RH and at the accelerated storage conditions of 40°C/ 75% RH. During stability, solely the stability indicating tests, appearance, assay, degradation products, water activity and dissolution were performed. Results met the specifications. However, the batch size of the primary stability batches should be detailed and the method used for determination of water activity should be described and validation data should be presented **(REC11).** In addition, photostability (in accordance with ICH guideline Q1B) of one batch was evaluated and data was provided. From the results it was concluded that PF-07321332 150 mg film-coated tablets are stable to light and no precautionary packaging or labelling is required.

Various supportive data of early development tablet formulations packaged in PCTFE/foil blisters, foil/foil blisters and (less protective) HDPE bottles were evaluated under different conditions. 3-month data at the long-term storage condition of 30°C/75% RH and at the accelerated storage condition of 40°C/75% RH for one batch of each formulation were reported. Additional supportive stability data from two developmental batches of the commercial formulation through 6 weeks storage at the long-term storage condition of 30°C/75% RH and at the accelerated storage condition of 40°C/75% RH were also presented.

Forced degradation studies on PF-07321332 150 mg film-coated tablets were performed, including thermal, thermal humidity and photolysis conditions, to establish the extent and nature of potential degradation pathways and to confirm the suitability of the assay and purity method. However, the stability indicating power for the method, which is used alternatively for the determination of assay, should be demonstrated **(REC9).**

Stress studies on film-coated tablets were performed. Total degradation products remained within specifications.

Based on the overall stability data from the primary stability studies, supportive studies, stress stability studies and forced degradation stability studies, the proposed shelf life and storage conditions are considered acceptable provided that the stability data will be monitored monthly **(REC11)**. In addition, the storage conditions will be reviewed and updated as necessary according to the stability data **(REC11)**.

Ritonavir film-coated tablets

Stability data for ritonavir 100 mg film coated tablets in the proposed co-packaged blister system is currently not available. Stability studies were carried out on three full batches of ritonavir 100 mg film-coated tablets packed in Alu-Alu blister and stored up to 36 months at 25ºC/60% RH and 6 months at

40°C/75% RH. No significant changes were observed in description, water content, resistance to crushing of tablets, dissolution, related compounds, assay, XRD and microbiological examination of ritonavir 100 mg Film-coated tablets and the results were found to be well-within the specification valid at that time. XRD test should be included in the regular tests of the post-approval stability protocol and stability commitment, while it should further be confirmed that microbiological tests will be performed annually **(REC17).**

A forced degradation study was carried out as a part of the analytical method validation in order to prove the specificity of the HPLC method for assay and related compounds of ritonavir premix and ritonavir 100 mg film-coated tablets.

Supporting stability data for batches of commercially available ritonavir 100 mg film-coated tablets packed in Alu-Alu blister are presented, for which a shelf life of 24 months has been approved. According to the data up to 36 months at 25ºC/60% RH and 6 months at 40ºC/75% RH, no significant changes were observed in description, water content, hardness, dissolution, related compounds, assay, XRD and microbiological quality. The results were found to be well within the shelf life specification.

Stability results of ritonavir bulk tablets were also presented. The studies were conducted with three commercial batches, stored up to 12 months at ICH long term conditions (25°C/60% RH). All test parameters remain within specifications.

For the bulk tablets, a shelf life of 12 months is confirmed when stored up to 25°C with excursions up to 14 days at 5 ± 3°C, -20 ± 5°C, 50 ± 2°C, but the proposed storage condition for the bulk tablets ("Do not store below 25°C") should be justified **(REC17)**. A statement is provided to confirm that the requirements of CPMP/QWP/072/96 are taken into account for setting the shelf life of ritonavir film-coated tablets.

In addition, the ritonavir bulk tablets component is considered as intermediate product for Paxlovid finished product, which is being introduced in the last steps of manufacture of Paxlovid. Therefore, the contents of Module 3.2.P ritonavir bulk tablets should be integrated as sub-chapter in Module 3.2.P.3 of Paxlovid in order to avoid confusion and repeating of documents **(REC18)**.

In conclusion, the presented stability data for ritonavir 100 mg film-coated tablets show that tablets are stable for 24 months without any special storage conditions. The commercially available Hetero Ritonavir 100 mg tablet in foil/foil blister container closure system has an approved shelf life of 24 months, which is considered appropriate for the Pfizer co-packaged presentation as well.

Co-packaged finished product

Stability data have been provided for the PF-07321332 tablet and ritonavir tablets packaged separately in the proposed packaging material (as discussed above). However, stability data for the co-packed Paxlovid finished product have not been provided and information concerning the final co-packed Paxlovid finished product to be marketed is reflected poorly in the dossier. The respective sections of 3.2.P PF-07321332 tablets should be updated to include the missing information for the co-packed Paxlovid finished product to be marketed **(REC18)**.

The applicant stated that stability studies for the co-packaged Paxlovid finished product are currently scheduled to start in January/February 2022, depending on packaging schedules.

The final shelf-life and storage condition for the co-packaged finished product Paxlovid is based on the more stringent shelf-life and storage condition for either of the two products, which is PF-07321332 150 mg film-coated tablets. Therefore, based on the overall available stability data presented for both components of the co-packaged product, the proposed shelf-life of 1 year with storage conditions "Do

not store above 25°C. Do not refrigerate or freeze", as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

The twelve months stability for the Paxlovid finished product is acceptable provided the applicant will monitor the stability data monthly and will immediately inform the authorities in the case of out of specification (OOS) results. Storage conditions "Do not store above 25°C", "Do not refrigerate or freeze" is accepted provided that these storage conditions will be updated as required when further stability data are available.

2.4.8. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The applicant has applied for conditional marketing authorisation (CMA). In the context of the current public health emergency situation due to COVID-19 pandemic and the pharmaceutical development of the proposed medicinal products, the submitted quality documentation is considered sufficient for CMA approval.

Paxlovid finished product comprises two separately manufactured dosage forms both presented as film-coated tablets. These two components of the finished product are film-coated tablets containing 150 mg PF-07321332 as active substance and film-coated tablets containing 100 mg ritonavir as active substance. For ease of daily co-administration, both components (PF-07321332 150 mg film-coated tablets and ritonavir film-coated tablets) are co-packaged in the same blister.

Active substance PF-07321332

The submitted information on development, manufacture, control and stability of the active substance indicate that currently manufactured batches are of appropriate quality and that is comparable to that of clinical development batches. Some issues, initially raised as MOs, in relation to the active substance should be addressed post-approval as Specific Obligations (SOs) in the context of the CMA. Two of these issues relate to the control strategy of the manufacturing process and the impurities in the active substance. A third issue that should be followed-up post approval as SO concerns the completion of the validation study of the method for assay and impurity testing, and of the method for the residual solvent.

Active substance ritonavir

Ritonavir is an established active substance described in the Ph. Eur. The supplier of ritonavir used in the manufacture of Paxlovid is Hetero Drugs Limited. Ritonavir from Hetero is already approved for use in other medicinal products in the EU, using the AMSF procedure; the ASMF is acceptable.

Finished product

PF-07321332 150 mg film-coated tablets are designed as an immediate release dosage form and are manufacture by a standard manufacturing process. Although relatively limited stability data were presented, they were adequate to establish an acceptable shelf life provided that the applicant will monitor the stability data monthly and will inform the authorities immediately in the case of out of specification results.

Ritonavir 100 mg film-coated tablets co-packaged in Paxlovid, are externally sourced and have been approved in EU countries since 2015 as a generic product of the reference product Norvir. Therefore, the quality of ritonavir film-coated tablets is considered acceptable in the context of the CMA. However, an issue concerning the acceptance criteria of the dissolution of ritonavir tablets, initially raised as MO should be addressed post-approval as a Specific Obligations (SO) in the context of the CMA.

Overall, the information on development, manufacture and control of the two components of the finished product (i.e. PF-07321332 150 mg film-coated tablets and ritonavir 100 mg film-coated tablets) has been presented in a satisfactory manner. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

At the time of the CHMP opinion, there were a number of minor quality issues having no impact on the benefit/risk ratio of the product, which pertain to supplementing various parts of the dossier module 3 with updated and new information relating to the PF-07321332 active substance attributes, manufacture, control strategy and stability of the finished product and to update the information relating to ritonavir tablet component in line with technical and scientific progress in compliance with Article 23 of Directive 2001/83/EC. These points are put forward as recommendations (RECs) for future quality development and were agreed by the applicant to be addressed within an acceptable timeframe.

The data presented to support consistent quality of the medicinal product Paxlovid is considered to be sufficient in the context of a conditional marketing authorisation in the current (COVID-19) pandemic emergency situation. To complete the quality documentation in the framework of the conditional marketing authorisation, the applicant should fulfil the mentioned specific obligations (SOBs) post-approval within an acceptable timeframe.

2.4.9. Conclusions on chemical, pharmaceutical and biological aspects

The quality of this medicinal product, submitted in the context of the current (COVID-19) pandemic, is considered to be consistent and acceptable in the context of a CMA in an emergency situation.

Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in an acceptable way. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform clinical performance.

The submitted information indicate that currently manufactured product batches are of appropriate quality that is comparable to that of clinical development batches. However, in order to confirm that the quality of future batches will also remain appropriate and comparable to that of clinical development batches over the life cycle of the medicinal product a number of issues are expected to be addressed though fulfilment of specific obligations (SOs) within the defined timeframe. The identified issues discussed in this report and listed in List 1 are compatible with the granting of a CMA.

The CHMP has identified the following specific obligations (SOs) to address the identified quality developments issues that may have a potential impact on the safe and effective use of the medicinal product, and which therefore are needed to achieve comprehensive pharmaceutical quality data and controls for the active substances and the finished product. In the List 2 of this report the specific points that need to be addressed in order to fulfil the imposed specific obligations are detailed.

List 1. The issues identified in quality documentation that require specific obligations (SOs).

Description	Due date
1. In order to improve the control strategy description and to confirm a consistent impurity profile, additional details should be included in the manufacturing process proposed for the active substance PF-07321332 for commercial supply.	June 2022
2. In order to ensure comprehensive control of impurities throughout the lifecycle	June 2022

Description	Due date
of the product, the control strategy for the active substance PF-07321332 for the impurities including chiral impurities and the active substance should be fully established.	
3. In order to ensure comprehensive control of impurities throughout the lifecycle of the product, full validation data for the HPLC method for assay and impurity testing, and for the residual solvent method used for the control of the active substance PF-07321332 should be provided.	June 2022
4. In order to improve the control strategy for the ritonavir film coated tablets, the limit for dissolution specification of ritonavir film coated tablets should be tightened according to the results obtained for the biobatches, e.g. to NMT 75 % (Q) in 45 min.	June 2022

List 2. Detailed List of Specific Obligations (SOs)

Post-authorisation measure(s)	Motivation
Proposed post-authorisation measure 1 with proposed classification category 2:	Motivation/Background information on measure, including due date:
1. In order to improve the control strategy description and to confirm a consistent impurity profile, additional details should be included in the manufacturing process proposed for the active substance PF-07321332 for commercial supply. The manufacturing process proposed for the active substance PF-07321332 for commercial supply and its control strategy should be clearly described and established: a) Therefore, amounts or ratios for all compounds, reagents, catalysts, and solvents should be documented. Process conditions and parameters like temperature, reaction time, pH, etc. should be established and described. It should be clearly defined in which of the steps carbon or filter aids will be used. b) If reprocessing is proposed the conditions should be described and the effect on the impurity profile should be investigated.	A clear description and definition of manufacturing process of the active substance and its control strategy is required as different process conditions may lead to a different impurity profile. The description of the process should be such that a consistent impurity profile is confirmed. Due date: June 2022
Proposed post-authorisation measure 2 with proposed classification category 2:	Motivation/Background information on measure, including due date:
2. In order to ensure comprehensive control of impurities throughout the lifecycle of the product, the control strategy for the active substance PF-07321332 for the	Due to safety reasons the active substance control strategy for the impurities of the active substance needs to be fully established as this

Post-authorisation measure(s)	Motivation
impurities including chiral impurities and the active substance should be fully established. The control strategy for the new active substance PF-07321332 for the impurities including chiral impurities and the API should be fully established: a) The carry-over of impurities arising from the synthesis of the starting materials and the proposed manufacturing process of the API for commercial supply should be investigated on three pilot-or production batches unless already specified in the API specification. b) More information about the potential formation of other chiral impurities and their control strategy should be provided. c) Appropriate acceptance criteria for unidentified and identified impurities including chiral impurities and total impurities should be included in the starting material and intermediate specifications taking into account batch analysis data for starting materials and intermediates and considering the purging capacity of the manufacturing process. The methods for control of these impurities should be described. d) As committed by the applicant the description of in-house methods for the intermediate specifications and the need for control of additional intermediate material attributes will be presented in the next variation. e) If necessary, toxicological qualified acceptance criteria for additional impurities including chiral impurities should be included in the API specification.	have an influence on the safety of the AS Due date: June 2022 (a), b), c), e)) Due date: February 2022 (d)
Proposed post-authorisation measure 3 with proposed classification category 2:	Motivation/Background information on measure, including due date:
3. In order to ensure comprehensive control of impurities throughout the lifecycle of the product, full validation data for the HPLC method for assay and impurity testing, and for the residual solvent method used for the control of the active substance PF-07321332 should be provided. Full validation data for the control of active substance PF-07321332 for the HPLC method for assay and impurity testing and for the residual solvent method should be provided.	In order to ensure the control of the active substance PF-07321332 and to demonstrate the suitability of the control methods for the active substance. Due date: June 2022

Post-authorisation measure(s)	Motivation
Proposed post-authorisation measure 4 with proposed classification category 2:	Motivation/Background information on measure, including due date:
4. In order to improve the control strategy for the ritonavir film coated tablets, the limit for dissolution specification of ritonavir film coated tablets should be tightened according to the results obtained for the biobatches. ritonavir dissolution specification: The current limit for dissolution testing is not meaningful as it is located in the plateau. Further it does not allow for discrimination between batches. As a consequence, the applicant is required to tighten the in-vitro dissolution specification in 3.2.P.5.1 according to the results obtained for the biobatches.	Compliance with EMA/CHMP/CVMP/QWP/336031/2017 Due date: June 2022

2.4.10. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Quality recommendations are covered in the list of recommendations in Annex I.

2.5. Non-clinical aspects

2.5.1. Introduction

Paxlovid contains two active substances: PF-07321332 and ritonavir. PF-07321332 is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro). Ritonavir inhibits the CYP3A-mediated metabolism of PF-07321332, thereby providing increased plasma concentrations of PF-07321332.

The non-clinical development programme was designed in accordance with ICH guideline M3. Ritonavir was originally developed as an antiretroviral agent used in HIV infection (at 600 mg BID dose); nowadays, it is exclusively used as a PK enhancer (mostly at 100 mg BID) for protease inhibitors in HIV and HCV infection; in the context of such PK enhancement use, ritonavir is often referred to as a 'booster'. As part of such boosted regimens ritonavir is of long-term use due to HIV being a chronic disease. Its non-clinical and clinical safety profile is well known and given that Paxlovid is intended for a 5 days treatment duration, no additional animal studies with ritonavir have been performed, which is acceptable. The following discussion on non-clinical aspects will therefore concentrate on PF-07321332.

2.5.2. Pharmacology

PF-07321332 is a potent and selective inhibitor of the SARS-CoV-2 3CLpro that exhibits a broad-spectrum activity across the Coronaviridae family of 3CL proteases demonstrating its potential for a "pancoronavirus" activity but of uncertain efficacy against notably MERS-CoV until adequate clinical efficacy demonstration. The critical amino acid residues involved in enzyme-inhibitor binding interactions are particularly well conserved within this family of viruses.

2.5.2.1. Primary pharmacodynamic studies

In vitro primary pharmacodynamic studies

In vitro primary pharmacodynamic data are included in the clinical pharmacology section of this assessment report.

In vivo pharmacodynamic studies

A total of two *in vivo* studies were presented evaluating the antiviral activity of PF-07321332. PF-07321332 showed antiviral activity in mouse models with mouse-adapted (MA) SARS-CoV-2 infection in BALB/c and 129 mouse strains (studies 105036 and 022652). Oral administration of PF-07321332 at 300 mg/kg or 1000 mg/kg twice daily initiated 4 hours post-inoculation or 1000 mg/kg twice daily initiated 12 hours post inoculation with SARS-CoV-2 MA10 (mouse-adapted virus) resulted in reduction of lung viral titres and ameliorated indicators of disease (weight loss and lung pathology) compared to placebo-treated animals.

The applicant has used a mouse-adapted virus which was modified from the original virus with several nucleotide changes. The relevance of its nucleotide changes is not clear to the intended extrapolation to the clinical setting. The applicant has discussed the choice of the mouse-adapted virus as *in vivo* model rather than a modified mice model such as K18-hACE2 mice which could have been used with the SARS-CoV-2 and its variant. SARS-CoV-2 MA exhibited more clinically relevant phenotypes than those seen in Hfh4-ACE2 transgenic mice, which expresses human ACE2, and thus SARS-CoV-2 MA is used by numerous investigators in the SARS-CoV-2 field.

No animal studies have been performed to evaluate the reduction of viral load in the upper respiratory tract and the impact of PF-07321332 treatment on viral transmission. The applicant rightly pointed out that analysis of SARS-CoV-2 transmission in hamsters by Abdelnabi *et al* (preprint) shows that the treatment of hamsters by PF-07321332 prevents transmission of SARS-CoV-2.

While ritonavir at booster dose does not exhibit an *in vitro* antiviral activity on SARS-CoV-2, there is an ongoing *in vivo* study with PF-07321332 in combination with ritonavir using a mouse-adapted model of SARS-CoV-2 infection (MA-SARS-CoV-2) in BALB/c mice. At the present stage, the lack of this study for the combination PF-07321332/ritonavir is acceptable given that ritonavir is used as a PK enhancer and the lack of antiviral effect by ritonavir. However, ritonavir affects both 07321332 metabolism and transport. This study, which should be provided post-approval, is considered essential for a better understanding of PF-07321332 distribution and efficacy following co-administration of PF-07321332 and ritonavir.

2.5.2.2. Secondary pharmacodynamic studies

In vitro studies were undertaken against a wide panel of receptors, transporters, ion channels and enzyme assays, and the results indicated no significant inhibition of functional or enzyme activity at human relevant concentrations (study 100054569). No off-target was identified up to 100 µM (39x the predicted human unbound Cmax at the intended clinical regimen).

PF-07321332 was also tested for inhibitory activity against 11 PDE subtypes (1 to 11) and the IC_{50} values were determined to be >200 µM (study 20LJ074), which represented 78x the predicted human unbound PF-07321332 Cmax at the intended clinical regimen.

2.5.2.3. Safety pharmacology programme

PF-07321332 was assessed in a series of safety pharmacology studies to assess potential pharmacodynamic effects on vital organ systems (central nervous, cardiovascular, and respiratory).

For the *in vivo* safety pharmacology studies, two studies covering the respiratory and central nervous system in Wistar Han rats, different groups (study 8455743) and the cardiovascular system in cynomolgus monkeys (study 20GR275) were assessed.

Relating to the effects on pulmonary system, administration of 1000 mg/kg of PF-07321332 (Cmax 51.5 µg/ml from rat 2-wk study) single dose resulted in test article related higher respiratory rate (up to +44%) and minute volume (up to +38%) compared with vehicle controls from 40 to 160 minutes post-dose. Relating to the effects on CNS, in the quantitative locomotor assessment, administration of 1000 mg/kg of PF-07321332 single dose resulted in test article-related lower number of mean vertical movement counts (-36%) during the first 5 minutes of the assessment period and higher number of mean horizontal (+298%) and vertical (+838%) movement counts during the last 30 minutes of the assessment period compared with vehicle controls. These effects were observed at exposures 12-fold higher than the anticipated clinical Cmax. A no observed effect level (NOEL) of 60 mg/kg is reported (Cmax 13.3 µg/ml from rat 2-wk study), associated with PF-07321332 exposures 3.2-fold higher than the anticipated clinical Cmax.

Relating to the cardiovascular safety pharmacology study, it was conducted in conscious telemetered male monkeys in a cross-over design. PF-07321332 administered at 150 (75 BID) mg/kg/day (Cmax = 14.7 µg/ml) produced HR decreases of down to -14 bpm from 0.75–16.00 HPD and increased systolic, diastolic and mean blood pressure (up to +5 mmHg) from 0.75–5.5 HPD (diastolic only) and 7.25-9.00 HPD. The RR-interval was increased by up to +52 msec 0.75–16.00 HPD, consistent with the decrease in HR during this same time. Increases in both the PR interval (+3 msec) and QT-interval (up to +13 msec) were observed during the 0.75-9.00 HPD period, which were considered secondary to the decrease in HR. When the QT interval was corrected for HR (QTc), there was a test article-related decrease (down to -7 msec) during the 7.25-16.00 HPD period. It was also noted a decrease in LV +dP/dt max (down to -364 mmHg/sec) during the 0.75-9.00 HPD period. All measures returned to vehicle control levels within 24 HPD. These cardiovascular effects were observed at exposures 3.5-fold higher than the anticipated clinical Cmax. A no observed effect level (NOEL) of 40 (20 BID) mg/kg is reported, associated with PF-07321332 exposures 0.33-fold higher than the anticipated clinical Cmax. From *in vitro* and ex vivo data (studies 200804.QHJ, 20LJ076 and 20J075), there was no clinically meaningful effect of PF-07321332 on hERG, isolated guinea pig heart or isolated rat aorta assays. The IC_{50} values for PF-07321332 inhibition of the Nav1.5 (peak) sodium and the Cav1.2 calcium channel currents were both determined to be >300 µM, (study 20LJ073), which represented 117x the predicted human unbound PF-07321332 Cmax at the intended clinical regimen.

In these studies, no toxicokinetic parameters were included (except one measure of plasma concentration at 150 mg/kg/day in cardiovascular monkey study 20GR275). PF-07321332 Cmax values were extrapolated from 2-week studies in rats. Exposure from 4-week toxicity study are available; since Cmax observed in rats after 4-week administration were lower than those observed after 2-week administration, exposure margins extrapolated from the 2-week study in rat is acceptable. Exposure margins are expressed based on predicted human total PF-07321332 where a BID dose of 300/100 mg PF-07321332/ritonavir resulted in a Cmax of 4.14 µg/ml.

No safety pharmacology studies have been conducted with the combination of PF-07321332 with ritonavir. Given that that ritonavir is used as a PK enhancer and safety pharmacology studies were conducted at concentrations (*in vitro*) and doses (*in vivo*) that yielded exposures significantly higher

than the predicted PK values of 300 mg/100 mg PF-07321332/ritonavir, the lack of safety pharmacology studies with the combination is acceptable.

2.5.2.4. Pharmacodynamic drug interactions

In vivo pharmacodynamic drug interaction studies with PF-07321332 have not been conducted. *In vitro* antiviral activity of PF-07321332 is discussed in the clinical pharmacology section.

2.5.3. Pharmacokinetics

The LC-MS/MS methods implemented were validated for the quantitation of PF-07321332 in plasma. No analytical methods were developed for quantitation of circulatory metabolites of PF-07321332 or quantitation of PF-07321332 in tissues in GLP toxicity studies given that no quantifiable metabolites of PF-07321332 in human plasma were observed when PF-07321332 is co-administered with ritonavir.

The absorption was evaluated in two single dose administration studies in rat and monkey to study the PK profile of PF-07321332 (studies 103131 and 111728). PF-07321332 was rapidly absorbed and exhibited a moderate CL, with a moderate to low Vss, resulting in t½ values of 5 hours in rats and <1 hour in monkeys. Following oral dosing, the overall bioavailability was moderate to high (29 to >100%) in rats but low (<10%) in monkeys. Repeat dose pharmacokinetics of PF-07321332 were evaluated following 14- or 15-day administration in the toxicity studies in rats and monkeys (studies 20GR276 and 20GR289) and in embryo-foetal development (EFD) studies in rats and rabbits (21GR132 and 21GR126). In rats, systemic exposures increased with dose and decreased with treatment duration. In monkeys, while systemic exposures also increased with dose, there was no decrease in exposure with treatment duration. On the contrary, in the 4-week study, at the two highest tested doses, exposures were higher at the end of treatment compared to Day 1. There were no consistent sex-related differences in systemic exposure. Systemic exposure increased with increasing doses in pregnant rats and rabbits.

The distribution study results showed that PF-07321332 was moderately bound to plasma proteins in rat, monkey and human and similar across these species (study 010657). Concentration-dependent protein binding was observed in rabbit plasma (YDP/067/394). PF-07321332 preferentially distributed into plasma relative to blood cells in rat, monkey and human (study 100444).

An *in vivo* distribution study (quantitative whole-body autoradiography, QWBA) is on-going. The results from that study should be provided as it will provide an understanding of the distribution of 14C-labelled drug-related material in tissues.

The metabolism of PF-07321332 was evaluated *in vitro* in liver microsomes, hepatocytes and *in vivo* in rats and monkeys (studies 084546, 072016, 082057, 021055, 090141). A total of six metabolites were detected arising from hydroxylation, dehydrogenation, and hydrolysis reactions. The major metabolite was M4 (PF-07329268). In plasma of rats and monkeys, unchanged parent drug was the most prevalent drug-related entity, with M4 as a major metabolite in monkeys. All oxidative metabolites were formed by CYP3A4/5, with other CYP enzymes contributing very minor amounts. Unchanged parent drug was also the most prevalent drug-related entity in rat urine and bile. In human plasma unchanged PF-07321332 was the main circulated compound, M4 and M5 were found at trace levels.

The urinary and/or biliary excretion was assessed in single-dose PK studies after IV or oral dosing of PF-07321332 to rats (study 103131) and monkeys (study 111728). The percentage of PF-07321332 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. The low percentage of PF-07321332 dose

excreted unchanged in urine, bile, and faeces along with the relatively low CLr suggests minor urinary and biliary contributions to the overall elimination of PF-07321332.

Mass balance excretory pathways and metabolic profile of unlabelled PF-07321332 was also assessed (studies 014401 and 021626). The primary excretion routes of orally administered PF-07321332 with ritonavir were urinary excretion of unchanged drug. In urine and faeces, unchanged PF-07321332 accounted for 82.5% of the drug material (55% in urine and 27.5% in faeces). M5 was present at 12.1% in faeces and urine, M8 (PF-07331782) at 4.2%, m/z 519 at 0.8% and M7 (acyl glucuronide of M5) at 0.3%of the dose. In rabbit and in monkey, M3, M4, M5 and m/z 498 were detected in plasma. All of these metabolites are below 10% the threshold specified in ICH M3 requested for toxicity assessment and no quantifiable metabolites of PF-07321332 in human plasma were observed when PF-07321332 is co-administered with ritonavir.

Animal data suggested minor urinary and biliary contributions to the overall elimination of PF-07321332 whereas clinical results suggested that the primary excretion routes of orally administered PF-07321332 with ritonavir were urinary excretion of unchanged drug.

2.5.4. Toxicology

The toxicology programme for PF-07321332 has been designed in line with the requirements of ICH M3 (R2) and taking into consideration the proposed treatment duration of 5-days.

2.5.4.1. Single dose toxicity

No single dose toxicity study was performed.

2.5.4.2. Repeat dose toxicity

The species used for the GLP compliant pivotal studies included rats and monkeys based on similar PK profile seen in these species compared to human. Furthermore, the pharmacological target of PF-07321332 is an exogenous entity (virus-specific protein) and therefore there are no pharmacologically relevant species. The oral route of administration was selected as it is the route of clinical administration.

The toxicity of PF-07321332 was evaluated in 4 GLP repeat-dose toxicity studies up to 1 month in duration in rats (studies 20GR276 and 21GR122) and cynomolgus monkeys (20GR289 and 20GR125). Two preliminary 4-days studies in rats (20GR250) and monkeys (20GR271) were also evaluated.

Rats were administered once daily and monkeys twice daily as in human. This administration twice daily in monkeys was not supported by $T_{1/2}$ which is <1h, however this regimen scheme was performed to mimic clinical regimen. Final reports have been submitted for the studies except for the 1-month study in rats and in monkeys (unaudited draft).

There were no adverse findings in any of the studies. The NOAELs were the highest doses administered 1000 mg/kg in rat and 600 mg/kg (300 BID) in monkeys and represented 11x/8.0x and 21x/14x for rats and monkeys (Cmax/AUC24), respectively, over the predicted human total PF-07321332 Cmax and AUC24 at a dose of 300/100 mg PF-07321332/ritonavir BID. Margins of exposure were calculated based on toxicokinetic data from the 2-week rat repeated dose toxicity study (20GR276) and predicted human total PF-07321332 Cmax of 4.14 µg/mL and AUC24 of 68.6 µg h/mL at a BID dose of 300/100 mg PF-07321332/ritonavir, therefore the margins of exposure are only indicative at this stage as the PopPK model is only based on PK data collected from healthy volunteers. All non-adverse test article related clinical findings observed in rats (salivation and soft faeces, increases in aPPT, prothrombin,

platelet count) or in monkeys (sporadic occurrence of emesis, increases in ALT, AST, fibrinogen) are monitorable in human. Test article related effects associated with the oral administration of PF-07321332 to rats up to 1000 mg/kg/day for 1-month were limited to non-adverse findings in the liver, thyroid and pituitary gland. The pattern of linked findings in the liver, thyroid and pituitary glands are consistent with a rat specific response to hepatic enzyme induction resulting in increased thyroxine catabolism, raised serum thyroid stimulating hormone and thyroid follicular cell hypertrophy and anterior pituitary vacuolation (Childs et al, 1982; Greaves, 2012; Rosol et al, 2013). This mechanism is usually considered to have little to no relevance to humans mostly because of the marked differences in plasma half-life of thyroid hormones and in binding to transport proteins between rodents and humans (Rosol et al, 2013). No such findings were observed in monkeys.

2.5.4.3. Genotoxicity

PF-07321332 was assessed in a series of genetic toxicity studies consisting of the microbial bacterial reverse mutation, *in vitro* cytogenetic (micronucleus in human lymphoblastoid TK6 cells), and *in vivo* rat micronucleus assay up to 1000 mg/kg/day (studies 20GR288, 20GR286 and 20GR276a). All *in vitro* tests were conducted with and without exogenous metabolic activation using concentrations up to applicable guideline limits or those limited by cytotoxicity or insolubility. PF-07321332 was not genotoxic in either *in vitro* or *in vivo* assays.

2.5.4.4. Carcinogenicity

No carcinogenicity studies have been performed. Considering that the duration of treatment is limited to 5 days, the absence of carcinogenicity studies is in-line with the recommendations of ICH S1A. There are no microscopic findings indicative of pre-neoplastic changes from the limited duration repeat dose toxicity studies.

2.5.4.5. Reproductive and developmental toxicity

Fertility and embryo-foetal development studies were evaluated in rats and rabbits with PF-07321332 (studies 21GR146, 21GR132 and 21GR126). Pre- and postnatal development was evaluated in rats (21GR149) based on the interim results.

In the fertility study, there was no adverse effect of PF-07321332 on parental endpoints and on the reproductive performance of male and female rats treated at doses up to 1000 mg/kg/day from 14 days premating. C-section data did not highlight any treatment-related adverse effect on early embryonic development in the treated vs. concurrent control group. At the NOAEL of 1000 mg/kg/day for parental toxicity and fertility, the AUC-based exposure ratio reached 4.3.

In the rat embryo-foetal development study, PF-07321332 was not shown to induce maternotoxicity, foetotoxicity or teratogenicity at doses up to 1000 mg/kg/day administered during the whole period of organogenesis. Foetal examination showed increased litter and foetal incidences of 27th presacral vertebrae (skeletal variation) at the high dose level compared to concurrent controls (litter: 6%, 0%, 5%, 21%; foetal: 0.93%, 0.00%, 0.56%, 4.29%) and outside historical control range (litter: 0-10.5%; foetal: 0-2.4%). Since there were no associated skeletal malformations or variations in associated structures, or any other adverse effect on embryo-foetal development, this finding could be considered as non-adverse. Overall, the maternal and developmental NOAEL was 1000 mg/kg/day in rats. At this dose level, the AUC-based exposure ratio was 7.8.

In the rabbit embryo-foetal development study, slight effects on maternal body weight gain and food consumption were noted during the treatment period at the high dose level of 1000 mg/kg/day, but

were not considered as adverse based on low magnitude of difference from control and lack of impact on absolute body weights. PF-07321332-related, adverse, lower foetal weight (0.91x control) was observed at 1000 mg/kg/day. At foetal examination, the foetal and/or litter incidences of a skeletal malformation (fused sternebrae) and visceral/skeletal variations (small gallbladder, misaligned sternebrae, bent hyoid arch) were increased compared to those in both concurrent and historical controls. As regards the increased incidence of small gallbladder, a paternally-mediated effect (see e.g. Stomp et al 2012) could not be excluded based on further analysis of sire records. Overall, the developmental NOAEL in rabbits was 300 mg/kg/day and corresponds to an AUC-based exposure ratio of 2.8.

In the ongoing pre- and postnatal development toxicity study conducted in rats, a significant decrease in preweaning pup body weight gain from PND 10-17 at 1000 mg/kg/day was observed and translated into a decrease in pup body weight on PND 17 and 21. This effect seems transient since there is no significant impact on F1 offspring body weight or body weight gain from PND 21-56. In comparison to the interim results, with the final results additional data on any potential treatment-related effects on F1 oestrous cycles, reproductive performance (incl. intrauterine survival of F2 embryos), neurobehavior (auditory startle response, motor activity, learning and memory), and macroscopic examination at necropsy will be reported.

As regards ritonavir, developmental toxicity was identified in rats and rabbits mainly at maternally toxic dose levels, whereas there was no effect on fertility in rats.

PF-07321332 does not present a phototoxicity potential. No combination studies with administration of PF-07321332 with ritonavir have been conducted. Ritonavir is an already marketed drug as a PK enhancer with well characterised nonclinical and clinical safety profiles. No PD activity of ritonavir at 100 mg (BID) dose is expected and no overlapping or additive toxicities between PF-07321332 and ritonavir are expected since no target organs have been identified after PF-07321332 administration in rats and monkeys up to 1-month duration. A combination toxicity study, therefore, will not provide any additional information beyond the known individual toxicity profiles of PF-07321332 and ritonavir.

2.5.4.6. Local tolerance

Local tolerance studies with PF-07321332 have not been conducted.

2.5.5. Ecotoxicity/environmental risk assessment

An ERA for Paxlovid was performed according to the current guideline, the phase II assessment is still ongoing. Results of OECD107 study indicated LogDow < 4.5 for PF-07321332, therefore there is no need to screen PBT potential of PF-07321332. The PECsw value for PF-07321332 with 5 days of treatment (0.041 µg/L) is still higher than the 0.01 µg/L action limit. For ritonavir, reference is made to literature for LogDow value (< 4.5). No study report or detailed description of the conditions of the performed test was provided. The Log Dow for ritonavir needs to be determined experimentally according to the current guideline and sufficient details of the test performance need to be provided to determine the acceptability of the study. The PECsw value for ritonavir with 5 days of treatment (0.014 µg/L) is also higher than the 0.01 µg/L action limit.

2.5.6. Discussion on non-clinical aspects

The non-clinical studies are submitted in accordance with legal requirements; available guidelines and scientific advice has been followed.

Pharmacology

In vitro primary pharmacodynamic data is discussed under the clinical pharmacology section of this assessment report.

The *in vivo* proof of concept studies consistently support the antiviral activity of PF-07321332, as demonstrated by reduced infectious lung titres and ameliorated indicators of disease (weight loss and lung pathology) compared to placebo-treated animals in mouse models with mouse-adapted SARS-CoV-2 infection in BALB/c and 129 mouse strains. While ritonavir at booster dose does not exhibit an *in vitro* antiviral activity on SARS-CoV-2, the applicant confirmed there is an ongoing *in vivo* study with PF-07321332 in combination with ritonavir using a mouse-adapted (MA) model of SARS-CoV-2 infection (MA-SARS-CoV-2) in BALB/c mice. The final study report should be provided (**REC**). At the present stage, the lack of this study for the combination PF-07321332/ritonavir is acceptable given that ritonavir is used as a PK enhancer and the lack of antiviral effect by ritonavir. However, ritonavir affects both 07321332 metabolism and transport. This study is considered essential for a better understanding of PF-07321332 distribution and efficacy following co-administration of PF-07321332 and ritonavir.

No off-target was identified in secondary PD studies up to 100 µM (39x the predicted human unbound Cmax at the intended clinical regimen).

All pivotal safety pharmacology study reports contain GLP compliance statements, indicating they have been conducted in accordance with the principles of GLP, in an OECD MAD adherent country. Both *in vitro* and *in vivo* studies were conducted to address the safety pharmacology core battery, in line with ICH S7A. A higher respiratory rate (up to +44%), a higher minute volume (up to +38%), a lower number of mean vertical movement counts during the first 5 minutes of the assessment period (up to 36%) and a higher number of mean horizontal (+298%) and vertical (+838%) movement counts during the last 30 minutes were observed in rats after a single administration of 1000 mg/kg of PF-07321332 (12-fold higher than the anticipated clinical Cmax). In telemetered male monkeys the highest tested dose (150 (75 BID) mg/kg/day, 3.5-fold higher than the anticipated clinical Cmax) produced HR decreases of down to -14 bpm from 0.75–16.00 HPD and increased systolic, diastolic and mean blood pressure (up to +5 mmHg) from 0.75–5.5 HPD (diastolic only) and 7.25-9.00 HPD. The RR-interval was increased by up to +52 msec 0.75–16.00 HPD, consistent with the decrease in HR during this same time. Increases in both the PR interval (+3 msec) and QT-interval (up to +13 msec) were observed during the 0.75-9.00 HPD period, which were considered secondary to the decrease in HR. When the QT interval was corrected for HR (QTc), there was a test article-related decrease (down to -7 msec) during the 7.25-16.00 HPD period. PF-07321332 at 150 (75 BID) mg/kg/day also produced decreases in LV +dP/dt max (down to -364 mmHg/sec) during the 0.75-9.00 HPD period. These effects on safety pharmacology parameters were monitored in clinical trials and no safety concerns were identified and will be followed with the PSUR.

Pharmacokinetics

A nonclinical pharmacokinetic programme was carried out to evaluate the ADME properties of PF-07321332. All studies are available except the ongoing *in vivo* QWBA study performed with PF-07321332 (alone) which study report is requested by 31/03/2022 together with the applicant's assessment (**LEG**).

Toxicology

The non-clinical toxicology package for PF-07321332 has been designed in line with the requirements of ICH M3 (R2) and taking into consideration the proposed treatment period of 5-days in duration. All pivotal safety pharmacology study reports contain GLP compliance statements, indicating they have been conducted in accordance with the principles of GLP, in an OECD MAD adherent country.

Repeated dose toxicity study final reports have been submitted except for 1-month in rats and in monkeys. These final study reports 21GR122 and 21GR125 are requested by 31/01/2022 (**LEG**). In relation to reproductive and developmental toxicity, a rat fertility study and two EFD studies in rats and rabbits are completed and submitted. The pre- and postnatal development study was ongoing; the interim report has been provided. The final study report for the PPND (21GR149) is requested by 30/04/2022 (**LEG**). The applicant's submission of new non-clinical data should be accompanied with an updated non-clinical overview and related updated tabulated and written summaries.

The toxicity of PF-07321332 was evaluated in 4 pivotal GLP repeat-dose toxicity studies up to 1 month in duration in rats and cynomolgus monkeys. There were no adverse findings in any of the studies. The NOAELs were the highest doses administered (1000 mg/kg in rat and 600 mg/kg (300 BID) in monkeys and represented 11x/8.0x and 21x/14x for rats and monkeys(Cmax/AUC24), respectively, over the predicted human total PF-07321332 Cmax and AUC24 at a dose of 300/100 mg PF-07321332/ritonavir BID. The margins of exposure are only indicative at this stage. All non-adverse test article related clinical findings observed in rats (salivation and soft faeces, increases in aPPT, PT, PLT count) or in monkeys (sporadic occurrence of emesis, increases in ALT, AST, fibrinogen) are monitorable in human.

The margins of exposure are therefore only indicative at this stage and it is expected to be further substantiated with the awaited provision of a relevant PopPK model including PK data collected from the patients enrolled in the EPIC-HR study with relevant covariables to be studied (notably age, weight, formulation). The PopPK model should be updated and provided once available (refer to clinical pharmacology LEG).

The standard genotoxicity battery was performed, and negative results are acceptable by CHMP.

No adverse effect of PF-07321332 on fertility parameters were observed up to 1000 mg/kg/day (AUC-based exposure ratio reached 4.3). No effect of PF-07321332 on embryo-foetal development were observed in rats up to 1000 mg/kg/day (AUC-based exposure ratio was 7.8). In the rabbit embryo-foetal development study, slight effects on maternal body weight gain and food consumption were noted during the treatment period at the high dose level of 1000 mg/kg/day, but were not considered as adverse based on low magnitude of difference from control and lack of impact on absolute body weights. PF-07321332-related, adverse, lower foetal weight (0.91x control) was observed at 1000 mg/kg/day. The developmental NOAEL in rabbits was 300 mg/kg/day and corresponds to an AUC-based exposure ratio of 2.8. This is adequately reflected in section 5.3 of the SmPC. In the ongoing pre- and postnatal development toxicity study conducted in rats, a significant decrease in preweaning pup body weight gain from PND 10-17 at 1000 mg/kg/day was observed and translated into a decrease in pup body weight on PND 17 and 21. This effect seems transient since there is no significant impact on F1 offspring body weight or body weight gain from PND 21-56.

PF-07321332 does not present a phototoxicity potential. No combination studies with administration of PF-07321332 with ritonavir have been conducted.

An ERA for Paxlovid was performed according to the current guideline, the phase II assessment is still ongoing. The PECsw value for PF-07321332 with 5 days of treatment (0.041 µg/L) is higher than the 0.01 µg/L action limit. Based on literature, for ritonavir there is a Log Dow value (< 4.5). The Log Dow for ritonavir needs to be determined experimentally according to the current guideline and sufficient details of the test performance need to be provided to determine the acceptability of the study. The applicant needs to clarify this point in the further ERA update. The PECsw value for ritonavir with 5 days of treatment (0.014 µg/L) is also higher than the 0.01 µg/L action limit. The ERA part II should be provided (**REC**).

2.5.7. Conclusion on the non-clinical aspects

The applicant sufficiently addressed concerns raised for the purpose of granting a CMA in an emergency situation.

The CHMP is of the view that non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

The CHMP considers the following measures necessary to address the non-clinical issues:

a) The ongoing whole body autoradiographic study in rats with PF-07321332 (alone) should be provided by 30 April 2022.

b) The final reports of the two on-going repeat-dose toxicity studies (21GR122 and 21GR125) should be provided by 31 January 2022.

c) The final report of the on-going pre- and post-natal development study (21GR149) should be provided by 30 April 2022.

Nonclinical recommendations and legally binding measures are covered in Annex I.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

No routine GCP inspection was conducted for this application and no issues and/or concerns that would warrant the need for a GCP inspection were identified during the assessment of the clinical data submitted in support of the application. This is in addition to the listing of any GCP inspections conducted, with the respective reports, the standard statement that the applicant claimed GCP compliance of all trials included in the application and the statement of compliance with Directive 2001/20/EC for trials conducted outside the EU.

Table 1. Tabular overview of clinical studies

Study ID	Study Title	Study Details/Primary Endpoints	Total Sample Size
Study 1001 (Completed)	A Phase 1, randomised, double-blind, sponsor-open, placebo controlled, single-	FIH study of PF-07321332 in healthy adult participants. Study 1001 is a 5-part study.	

Study ID	Study Title	Study Details/Primary Endpoints		Total Sample Size
	and multiple-dose escalation study to evaluate the safety, tolerability, and pharmacokinetics of PF-07321332 in healthy adult participants	PART-1 (SAD) PART-2 (MAD) PART-5 (supratherapeutic exposures for QTc assessment)	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 participants PART-2: 29 participants PART-5: 10 participants
		PART-3 (relative bioavailability):	Ratio of AUC_{last}, AUC_{inf} and C_{max} of tablet formulation and suspension	PART-3: 12 participants
		PART-4 (metabolism and excretion):	Percent recovery and cumulative recovery of drug-related material in urine and feces	PART-4: 6 participants
Study 1010 (Ongoing)	A Phase 1, non-randomised, open-label study to assess the pharmacokinetics, safety and tolerability of PF-07321332 boosted with ritonavir in adult participants with moderate hepatic impairment and healthy participants with normal hepatic function	Plasma PF-07321332 PK parameters: C_{max}, AUC_{last}, AUC_{inf} (if data permit)		8 participants without hepatic impairment and 8 participants with moderate hepatic impairment
Study 1011 (Completed)	A Phase 1, non-randomised, open-label study to assess the pharmacokinetics, safety and tolerability of PF-07321332 boosted with ritonavir in adult participants with renal impairment and in healthy participants with normal renal function	Plasma PF-07321332 PK parameters: Cmax, AUC_{inf} (or AUC_{last} if AUC_{inf} cannot be reliably estimated) Urine PF-07321332 PK parameters: A_e, CL_r, if applicable and as data permit		34 participants (8 each in mild, moderate, severe renal impairment, and 10 healthy participants)
Study 1012 (Ongoing)	A Phase 1, open-label, 3-treatment, 6-sequence, 3-period cross-over study to estimate the effect of PF-07321332/ritonavir and ritonavir on the pharmacokinetics of dabigatran in healthy participants	AUC_{inf} and C_{max} of dabigatran with PF-07321332/ritonavir (test) versus dabigatran alone (reference)		~ 24 healthy participants

Study ID	Study Title	Study Details/Primary Endpoints	Total Sample Size
Study 1013 (Ongoing)	A Phase 1, open-label, 3-treatment, 6-sequence, 3-period crossover study to estimate the effect of PF-07321332/ritonavir and ritonavir on the pharmacokinetics of midazolam in healthy participants	AUC_{inf} and C_{max} of midazolam with PF-07321332/ritonavir (test) versus midazolam alone (reference)	~12 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 PF-07321332 boosted with ritonavir in healthy participants	PF-07321332 C_{max} and AUC_{inf} with carbamazepine (test) versus without carbamazepine (reference)	12 healthy participants
Study 1015 (Completed)	A Phase 1, open-label, fixed sequence, 2-period crossover study to estimate the effect of itraconazole on the pharmacokinetics of PF-07321332/ritonavir in healthy participants	PF-07321332 C_{max} and AUC_{tau} with itraconazole (test) versus without itraconazole (reference)	12 healthy participants
Study 1005 (Completed)	An interventional efficacy and safety, Phase 2/3, double-blind, 2-arm study to investigate orally administered PF-07321332/Ritonavir compared with placebo in non-hospitalised symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness	Primary objective: • To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in non-hospitalised symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease. Primary endpoint: • Proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28.	Total ~3100

Study 1005 (EPIC-HR, C4671005) is the single pivotal study supporting this conditional marketing authorisation application. This Phase 2/3, randomised, double-blind, placebo-controlled study in non-hospitalised, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness will determine the efficacy, safety, and tolerability of PF-07321332/ritonavir compared with placebo in a 1:1 ratio.

Additionally, there are on-going studies 1002 and 1006 for the treatment of COVID-19 in patients who are at low risk of progressing to severe disease and in the preventing of symptomatic SARS CoV-2 infection in adult household contacts of individuals with symptomatic COVID-19, respectively.

2.6.2. Clinical pharmacology

Paxlovid (PF-07321332/ritonavir) is a combination therapy of PF-07321332, a new chemical entity, which is a potent and selective peptidomimetic inhibitor of the SARS-CoV-2 3CL, a viral encoded enzyme that is critical to SARS-CoV-2 replication cycle, and ritonavir.

In the current submission, the applicant is seeking an initial approval for Paxlovid for the treatment of adult and adolescent patients (12 years of age and older weighing at least 40 kg) with symptomatic, confirmed COVID-19 who are at high risk for progressing to severe disease, including hospitalisation and/or death.

The proposed recommended oral dose of PF-07321332/ritonavir is 300 mg/100 mg twice daily (BID). The drug product for registration is a tablet containing PF-07321332 at one strength 150 mg and a tablet containing ritonavir at one strength 100 mg.

The clinical pharmacology programme as presented in Table 1 consisted of 7 Phase 1 studies performed completed or ongoing in healthy volunteers. The following Phase 1 studies have been conducted:

- 1 SAD and MAD study in Caucasian and Japanese healthy subjects (Study 1001)
- Relative bioavailability, QTc analysis, food effect and mass balance study (Study 1001)
- 6 PK studies investigating intrinsic (Studies 1010 and 1011 for respectively hepatic and renal impairment) and extrinsic factors (Studies 1012, 1013, 1014, 1015).

Phase 1 studies 1012, 1013 and Phase 2/3 studies 1002 and 1006 are ongoing. PK data from these studies will be submitted as soon as they become available.

A population PK analysis was performed and comprised PK data from healthy volunteers only. In addition, a simulation exercise was performed (separated report) to evaluate the predictive performance of the developed Pop-PK model on the observed PK data in patients from Study 1005.

2.6.2.1. Pharmacokinetics

Methods

Analytical methods

Throughout the clinical development, two bioanalytical methods were developed to quantify, simultaneously, PF-07321332 and ritonavir, in human K2EDTA plasma (Report c4679002), and only PF-07321332 in urine (Report c4679003). Both methods were developed and validated by York Bioanalytical Solution (York, YO26 6QR, UK).

Generally, the used bioanalytical methods appear to be adequate and comply with acceptance criteria of the bioanalytical method validation EMA Guideline. Description and validation reports were provided with satisfactory results regarding specificity, sensitivity, precision, accuracy, dilution factor linearity, matrix effect. Short and long-term stability of the analytes in biological matrix were tested and shown to be satisfactory. ISR were provided for each study with satisfactory results (100%).

Pharmacokinetic data analysis

Standard non-compartmental (model-independent) PK methods were used to calculate PK parameters (C_{max}, C_{min}, T_{max}, AUCs, CL/F and Vz/) using the NCA approach.

The Population PK analysis (Report PMAR-EQDD-C467a-POC-1246) was performed using a nonlinear mixed effects modelling methodology as implemented in the nonlinear mixed effects modelling (NONMEM) software system, version 7.5.0, using first-order conditional estimation method with interaction (FOCEI) as the estimation method.

Perl-speaks-NONMEM (PsN) version 5.2.6 was used for prediction corrected visual predictive check (pcVPC), and sampling importance resampling (SIR) for generating the model parameter uncertainty.

R (version 4.0.3) and/or R libraries was/were used for data manipulations, exploratory graphical and numerical analyses, model diagnostics, post-processing of NONMEM output, creation of simulation data sets, as well as data summary.

Overall, the standard NCA and the population methodology are acceptable for PK data analyses.

Statistical analysis

Generally, standard summary statistics (e.g. mean, median, standard deviation [SD], and coefficient of variation [CV]) have been generated. For comparison, in most cases the 90 % confidence intervals (CI) were calculated in case of equivalence testing. In addition, in case significance levels were used, the significance level in most trials was 5%. This was considered acceptable.

Absorption

Following oral single administration, at the recommended dose of PF-07321332/ritonavir 300 mg/100 mg, median Tmax was 3 hours and ranged between 1 to 6 hours, indicating that absorption is rapid. For note, the observed geometric mean PF-07321332 (CV%) Cmax and AUCinf were 2.21 µg/mL (33) and 23.01 µg*hr/mL (23), respectively.

Absolute Bioavailability

The absolute bioavailability of PF-07321332 was not investigated.

Relative bioavailability / Bioequivalence

Several oral formulations of PF-07321332 were developed and evaluated during the development programme:

- An extemporaneously prepared oral suspension used in Studies **1001** and **1015**
- An uncoated 250 mg immediate release (IR) tablet used for Study **1001** (Part 3)
- A 100 mg IR film-coated tablet used for Study **1011** and in a few patients in the Phase 2/3 Study **1005**
- A 150 mg IR film-coated tablet used for Study **1005** and other Phase 2/3 studies (Studies **1002** and **1006**) as well as in a Phase 1 study **1014.**
-

The clinical study supplies for the 150 mg tablets used for the pivotal phase 3 study **1005** were manufactured at both the Pfizer Groton (Connecticut, USA) and Freiburg (Germany) using identical formulation and manufacturing process.

The proposed commercial formulation dosage form for PF-07321332 is two 150 mg IR film-coated tablets and one 100 mg tablet of ritonavir.

Comparison of uncoated tablet 250 mg versus suspension 250 mg

The relative bioavailability of PF-07321332 formulated as the 250 mg tablet vs 250 mg oral suspension was evaluated in Study **1001** (Part 3) in 12 healthy volunteers without ritonavir combination, as part of an open label, randomised, 3 period, 3 sequence cross-over design (food effect also investigated, please refer to the next section) with a wash-out period of 2 days.

The estimated ratio of geometric means for Cmax was 56.38% (90% CI of the ratio 43.42%-73.19%) and for AUClast was 81.21% (90% CI of the ratio 69.21%–95.28%). Cmax and AUClast of uncoated tablet was reduced by 44% and 19%, respectively compared to the suspension formulation.

Dissolution profiles of the tablet 100 mg vs 150 mg

The comparability of PF-07321332 film coated tablets from representative batches of 100 mg and 150 mg was investigated through dissolution profiles comparison at a clinical dose of 300 mg (3X 100 mg vs 2 x 150 mg) at three different pH. An f2 test was calculated to assess similarity of dissolution profiles between the two tablet formulations, and all values were ≥50 suggesting equivalence in dissolution performance of PF-07321332 3x100 mg versus 2x150 mg tablets.

Dissolution profiles of tablet 150 mg by site Manufacturing

The dissolution performance of representative batches of PF-07321332 150 mg film-coated tablets manufactured at Groton, CT, US and Freiburg; Germany sites was assessed in dissolution media over the physiological pH range. Similarly, to the preceding the estimated f2 were ≥50 suggests that *in vitro* dissolution performances are equivalent.

Influence of food

The effect of a high fat meal was investigated at two levels, following the administration of 250 mg PF-07321332 alone (Study **1001** –**Part 3**) or in combination with ritonavir (Study **1001 Part 1**) in a cross-over design.

Results, indicated that relative to fasted conditions and in combination with ritonavir, administration with high-fat meal causes only a slight increase on Cmax (geometric mean ratio of 1.15) and no evident effect on exposure AUCs (geometric mean ratios of 1.01 and 1.01, for AUC0-t, AUC0-inf respectively). Tmax was delayed by 1.25 h and half-life slightly increased by 1h in the fed state compared to fasted state (6.9 vs 6 h).

Overall, the applicant preconise that commercial tablet formulation could be administered without regards to food. The proposed dosing recommendation could be supported.

Table 2. Statistical summary of plasma PF-07321332 PK parameters when administered with ritonavir- Food effect (Part 1 SAD, Study 1001)

	Adjusted Geometric Means			
Parameter (Unit)	**PF-07321332 250 mg Suspension/ ritonavir 100 mg, Fed (Test)**	**PF-07321332 250 mg Suspension/ ritonavir 100 mg, Fasted (Reference)**	**Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]**	**90% CI (%) for Ratio[a]**
AUC_{inf} (ng.hr/mL)	28640	28220	101.52	(89.57, 115.07)
AUC_{last} (ng.hr/mL)	28020	27600	101.53	(90.18, 114.31)
C_{max} (ng/mL)	3323	2882	115.30	(99.36, 133.79)

Influence of gastric modifier

The influence of gastric modifier was not investigated.

Distribution

PF-07321332 was found to be weakly bound to plasma protein (69%). B/P ratio was approximately 0.6 indicating a limited penetration of PF-07321332 into red blood cells.

Following administration of PF-07321332/ritonavir supplied as tablet formulation at 300 mg/100 mg, the mean apparent volume of distribution (Vz/F) in healthy volunteers was 109.4 L. For note, results from the PopPK analysis (based on 20 healthy volunteers using the oral suspension) indicated a total apparent distribution volume of 111 L for a 300 mg/100 mg (theoretical dose).

Elimination

The excretion and biotransformation of a 300mg/100 mg PF-07321332/ritonavir oral dose as suspension was investigated in 6 healthy subjects using ^{19}F-NMR and HPLC-MS/MS methods.

By quantitative ^{19}F-NMR, mean ± SD (range) mass recovery was 84.9% ± 8.9% (70.7-95.5%) which consisted of PF-07321332 at 80.7± 8% and M8 metabolite at 4.2%± 1.3% (silent due to loss of trifluoroacetyl group). The excretion into urine and faeces was 48.6% and 35.3%, respectively, mainly as unchanged PF-07321332. Most material excreted in urine emerged in the first 24 h while in faeces in 5 days.

PF-07321332 was found to be predominantly metabolised by CYP3A enzymes. Metabolite profiling was performed in the three matrices (plasma, urine and faeces). In plasma unchanged PF-07321332 was the main circulated compound, M4 and M5 were found at trace levels. In urine and faeces after normalisation of the data to complete mass balance, unchanged PF-07321332 accounted for 82.5% of the drug material (55% in urine and 27.5% in faeces). M5 was present at 12.1% in faeces, M8 at 4.2% in plasma. The proposed metabolic scheme is presented in the following figure.

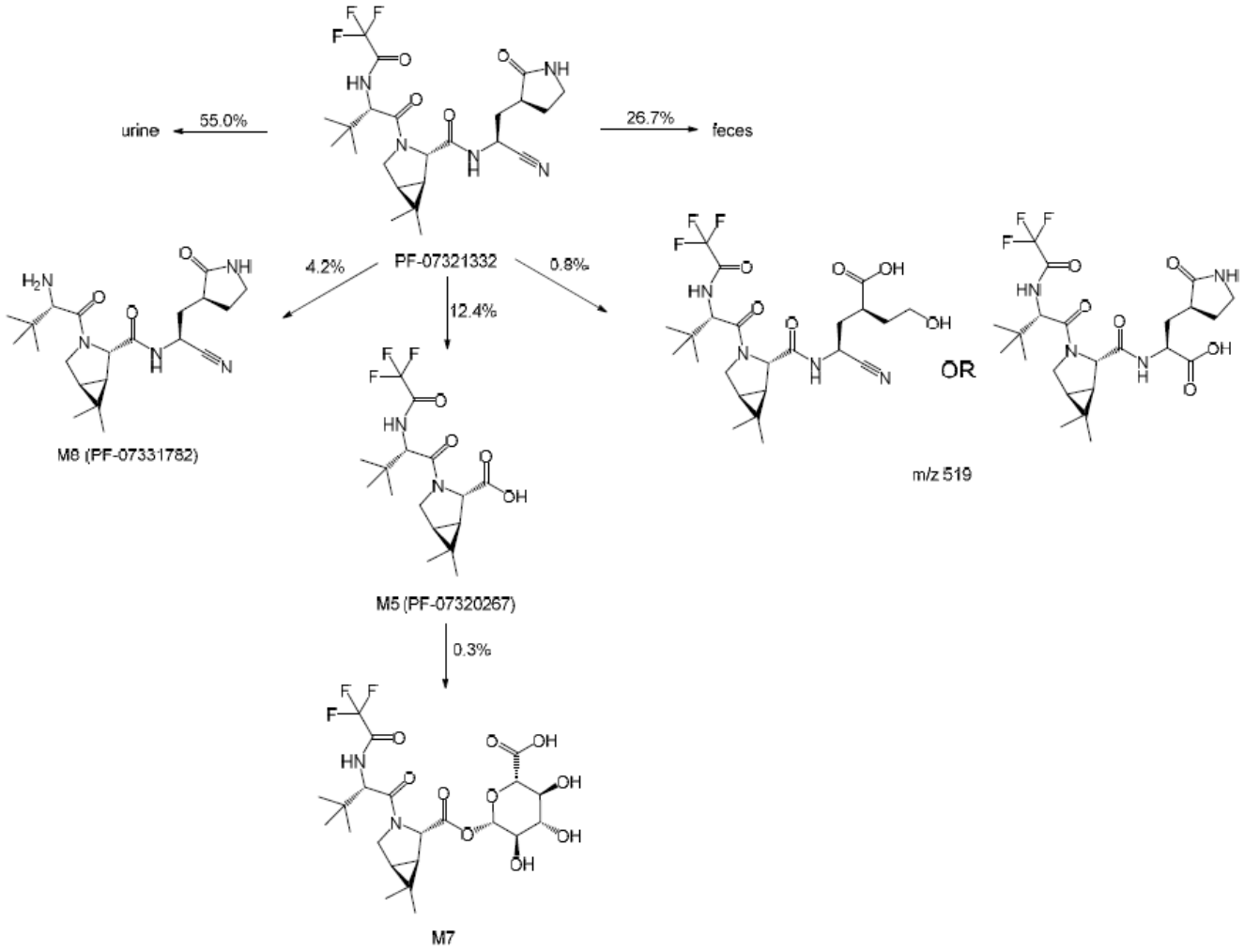


Figure 4 : Summary profile of PF-07321332 metabolism and disposition in healthy participant

Across clinical studies in healthy volunteers after single or multiple oral doses of PF-07321332/ritonavir as oral suspension half-life ranged from 6.8 to 9.5 h. After single oral dose PF-07321332/ritonavir as tablet formulation half-life ranged from 6.05 to 7.72 h. At the recommended 300/100 mg PF-07321332/ ritonavir dose in the fasted state, the arithmetic mean (+SD) terminal elimination half-life of PF-07321332, following single dose was 6.1 (1.8) hours.

Dose proportionality and time dependency

Dose proportionality

Dose proportionality of PF-07321332 (with or without ritonavir) was investigated following single and multiple escalating oral dose in healthy volunteers during Study 1001.

Part 1 (SAD) of Study 1001

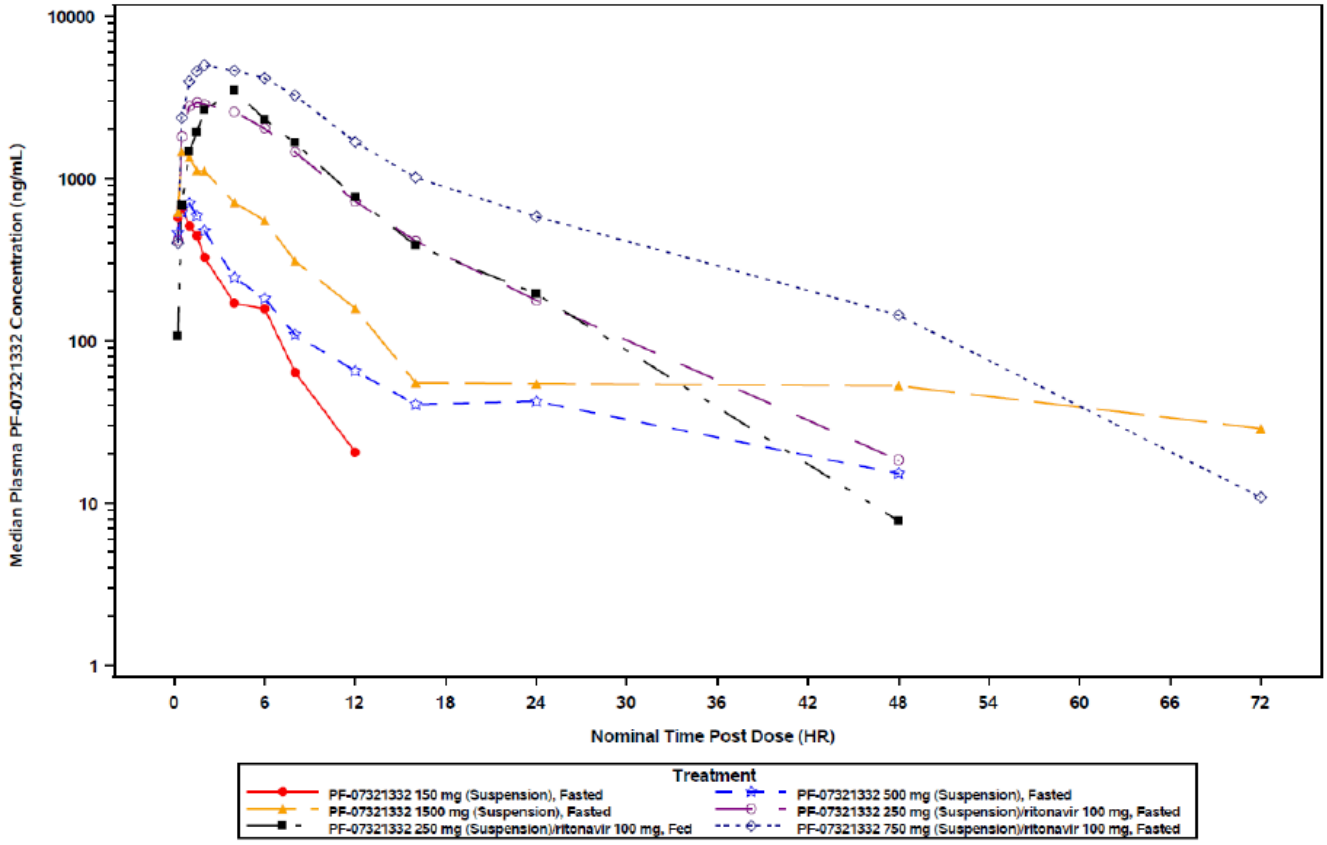
The interval of investigated doses ranged from 150 to 1500 mg for PF-07321332 (without ritonavir) and PF-07321332/ritonavir at two dose levels 250 and 750 mg. PK parameters following SAD of PF-07321332 (with or without ritonavir) as oral suspension are presented in Table 3 and associated median PK profiles in Figure 5.

Table 3. Descriptive summary of plasma PF-07321332 PK parameters (Part 1 –SAD, Study 1001)

Parameter (Unit)[a,b]	PF-07321332 150 mg (Suspension), Fasted (N=4)	PF-07321332 500 mg (Suspension), Fasted (N=4)	PF-07321332 1500 mg (Suspension), Fasted (N=4)	PF-07321332 250 mg (Suspension)/ ritonavir 100 mg, Fasted (N=4)	PF-07321332 250 mg (Suspension)/ ritonavir 100 mg, Fed (N=4)	PF-07321332 750 mg (Suspension)/ ritonavir 100 mg, Fasted (N=4)
N1, N2	4, 3	4, 2	4, 0	4, 4	4, 4	4, 4
AUC_{inf} (ng.hr/mL)	2247 (42)	5480, 5450	NR	28220 (14)	28640 (17)	66760 (45)
AUC_{inf}(dn) (ng.hr/mL/mg)	14.97 (42)	11, 10.9	NR	112.8 (14)	114.2 (17)	89.14 (45)
AUC_{last} (ng.hr/mL)	2125 (34)	3753 (29)	10870 (47)	27600 (13)	28020 (16)	64230 (39)
AUC_{last}(dn) (ng.hr/mL/mg)	14.15 (34)	7.507 (29)	7.247 (47)	110.4 (13)	112.0 (16)	85.77 (40)
CL/F (L/hr)	66.83 (43)	91.2, 91.8	NR	8.865 (14)	8.735 (17)	11.22 (45)
C_{max} (ng/mL)	667.7 (28)	674.4 (38)	1538 (32)	2882 (25)	3323 (13)	5086 (25)
C_{max}(dn) (ng/mL/mg)	4.450 (28)	1.349 (38)	1.025 (32)	11.53 (25)	13.32 (13)	6.782 (25)
$t_{1/2}$ (hr)	2.023 ± 0.54556	18.5, 25.6	NR	6.935 ± 1.0794	6.005 ± 1.6502	12.86 ± 8.4196
T_{max} (hr)	0.634 (0.550 - 1.50)	1.00 (0.517 - 1.00)	1.00 (0.533 - 2.00)	2.75 (1.50 - 4.00)	4.00 (4.00 - 4.00)	2.00 (1.50 - 4.00)
V_z/F (L)	190.6 (36)	2440, 3390	NR	87.98 (28)	73.48 (47)	181.9 (35)

Ritonavir dosed at -12h, 0h and 12h post-dose.
Source: Table 14.4.5.1.1 and 16.2.5.5.1.1
N = Total number of participants in the treatment group
N1 = Number of participants contributing to the summary statistics
N2 = Number of participants where $t_{1/2}$, AUC_{inf}, AUC_{inf}(dn), CL/F and V_z/F were determined
NR = Not Reported
a. Geometric Mean (Geometric %CV) for all except: Median (Range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$
b. Individual values were listed when there were less than 3 evaluable measurements
Summary statistics were not presented if fewer than 3 participants had reportable parameter values.

Figure 5: Median plasma PF-07321332 concentration time profiles following single oral doses of PF-07321332 with or without ritonavir (Part 1-SAD-Study 1001)



Part 2 (MAD) of Study 1001

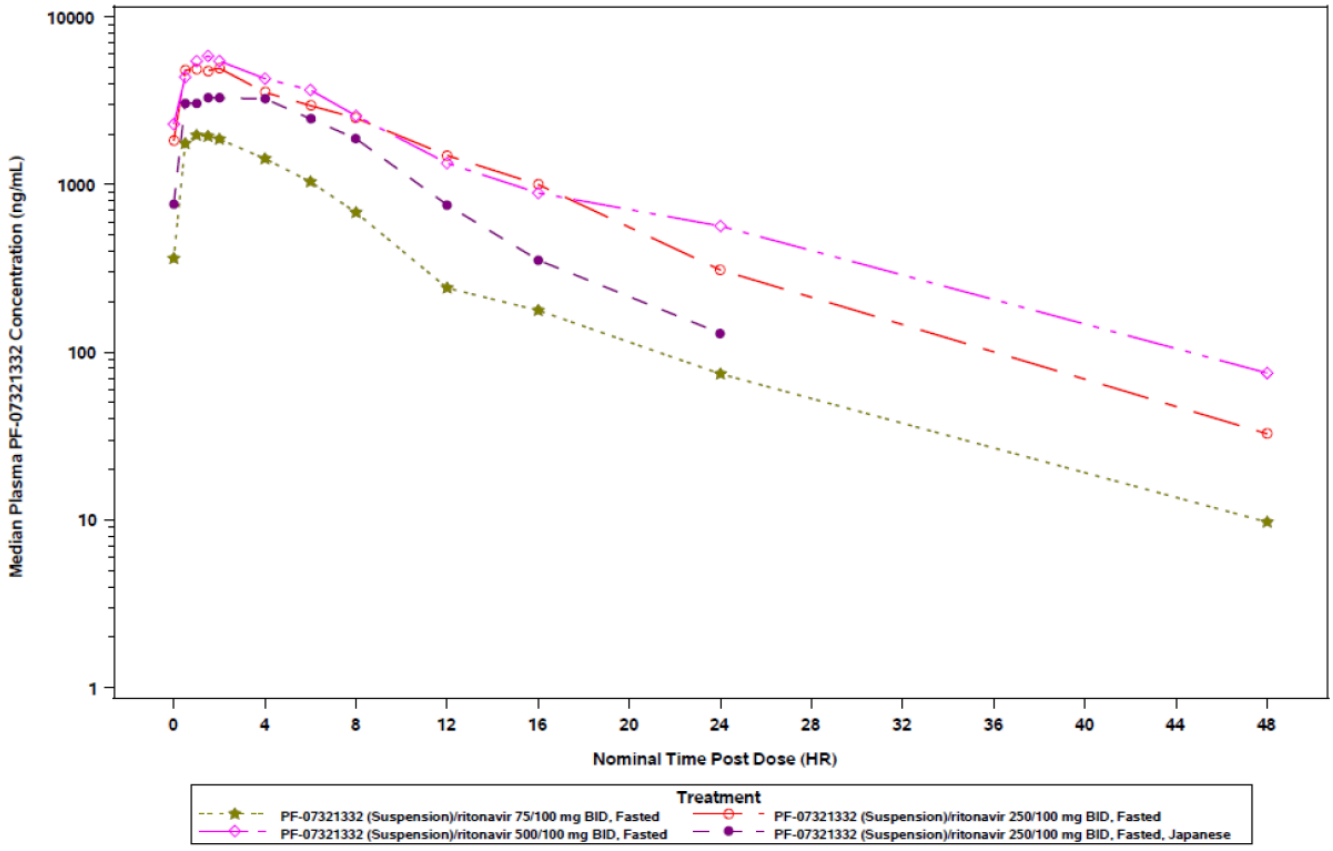
Part 2 (MAD) used PF-07321332/ritonavir from 75 mg/100 mg to 500 mg /100 mg. PK parameters following MAD of PF-07321332 enhanced by ritonavir as oral suspension are presented in **Table 4** and associated median PK profiles at Day 10 in Figure 6.

Table 4. Descriptive summary of plasma PF-07321332 PK parameters (Part 2 –MAD, Study 1001)

Parameter (Unit)[a]	PF-07321332 (Suspension)/ritonavir 75/100 mg BID, Fasted (N=4)	PF-07321332 (Suspension)/ritonavir 250/100 mg BID, Fasted (N=4)	PF-07321332 (Suspension)/ritonavir 500/100 mg BID, Fasted (N=7)	PF-07321332 (Suspension)/ritonavir 250/100 mg BID, Fasted, Japanese (N=4)
Day 1				
N1	4	4	7	4
AUC_{tau} (ng.hr/mL)	6017 (33)	18700 (43)	22610 (37)	13130 (26)
AUC_{tau} (dn) (ng.hr/mL/mg)	80.19 (33)	74.76 (43)	45.23 (37)	52.60 (26)
C_{max} (ng/mL)	1042 (28)	2435 (36)	3051 (32)	1925 (25)
C_{max}(dn) (ng/mL/mg)	13.89 (28)	9.755 (36)	6.103 (32)	7.698 (25)
T_{max} (hr)	1.75 (1.00 - 2.00)	1.50 (1.00 - 4.00)	2.00 (1.50 - 2.17)	2.75 (1.00 - 4.02)
Day 5				
N1	4	4	7	4
AUC_{tau} (ng.hr/mL)	12570 (17)	35560 (26)	38150 (23)	25480 (26)
AUC_{tau} (dn) (ng.hr/mL/mg)	167.7 (17)	141.9 (26)	76.32 (23)	102.0 (26)
C_{av} (ng/mL)	1049 (17)	2963 (26)	3181 (23)	2124 (26)
CL/F (L/hr)	5.966 (17)	7.032 (26)	13.11 (23)	9.814 (26)
C_{max} (ng/mL)	2224 (27)	4774 (21)	5296 (21)	3674 (28)
C_{max}(dn) (ng/mL/mg)	29.66 (27)	19.10 (21)	10.59 (21)	14.70 (28)
C_{min} (ng/mL)	251.0 (11)	1315 (37)	1195 (29)	707.3 (35)
PTR	8.857 (27)	3.635 (21)	4.430 (14)	5.194 (19)
R_{ac}	2.091 (24)	1.901 (22)	1.685 (29)	1.937 (18)
$R_{ac, Cmax}$	2.133 (25)	1.959 (16)	1.733 (24)	1.909 (26)
T_{max} (hr)	1.00 (1.00 - 1.50)	0.750 (0.500 - 1.50)	1.50 (1.00 - 2.02)	1.26 (1.00 - 2.02)
Day 10				
N1,N2	4, 4	4, 4	7, 7	4, 4
AUC_{tau} (ng.hr/mL)	12650 (16)	37780 (27)	39780 (20)	26930 (15)
AUC_{tau} (dn) (ng.hr/mL/mg)	168.3 (16)	151.1 (26)	79.56 (20)	107.7 (15)
C_{av} (ng/mL)	1053 (16)	3147 (27)	3314 (20)	2245 (14)
CL/F (L/hr)	5.933 (16)	6.617 (27)	12.57 (20)	9.278 (15)
C_{max} (ng/mL)	2055 (14)	5123 (24)	5607 (17)	3772 (21)
C_{max}(dn) (ng/mL/mg)	27.40 (14)	20.49 (25)	11.22 (17)	15.08 (21)
C_{min} (ng/mL)	245.3 (27)	1480 (27)	1279 (31)	12.50 (2.0814162E15)
PTR	8.383 (16)	3.462 (5)	4.385 (17)	6.270 (32)
R_{ac}	2.104 (30)	2.022 (16)	1.757 (26)	2.047 (16)
$R_{ac, Cmax}$	1.971 (34)	2.101 (16)	1.840 (29)	1.962 (14)
$t_{1/2}$ (hr)	7.955 ± 2.0401	6.795 ± 1.7072	8.047 ± 1.7871	5.163 ± 2.0915
T_{max} (hr)	1.00 (1.00 - 2.00)	1.00 (1.00 - 2.00)	1.50 (1.00 - 2.00)	1.50 (0.500 - 2.02)
V_z/F (L)	66.43 (24)	63.40 (13)	142.4 (37)	65.04 (31)
Ae_{tau} (mg)	47.83 (12)	129.9 (4)	116.5 (122)	135.4 (5)
Ae_{tau} %	63.79 (12)	51.81 (4)	23.35 (121)	54.20 (5)
CL_r (L/hr)	3.782 (20)	3.433 (23)	2.934 (128)	5.028 (11)

Source: Table 14.4.5.1.2.1 and 14.4.5.1.2.2
N = Total number of participants in the treatment group
N1 = Number of participants contributing to the summary statistics
N2 = Number of participants where $t_{1/2}$ and V_z/F were determined
a. Geometric Mean (Geometric %CV) for all except: Median (Range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$
For the parameters analyzed on the log scale, zero values had been substituted with 0.0001 prior to log transformation.
Summary statistics were not presented if fewer than 3 participants had reportable parameter values.

Figure 6. Median plasma PF-07321332 concentration time profiles following multiple oral doses of PF-07321332/ritonavir (Part 2-mAD-Study 1001)

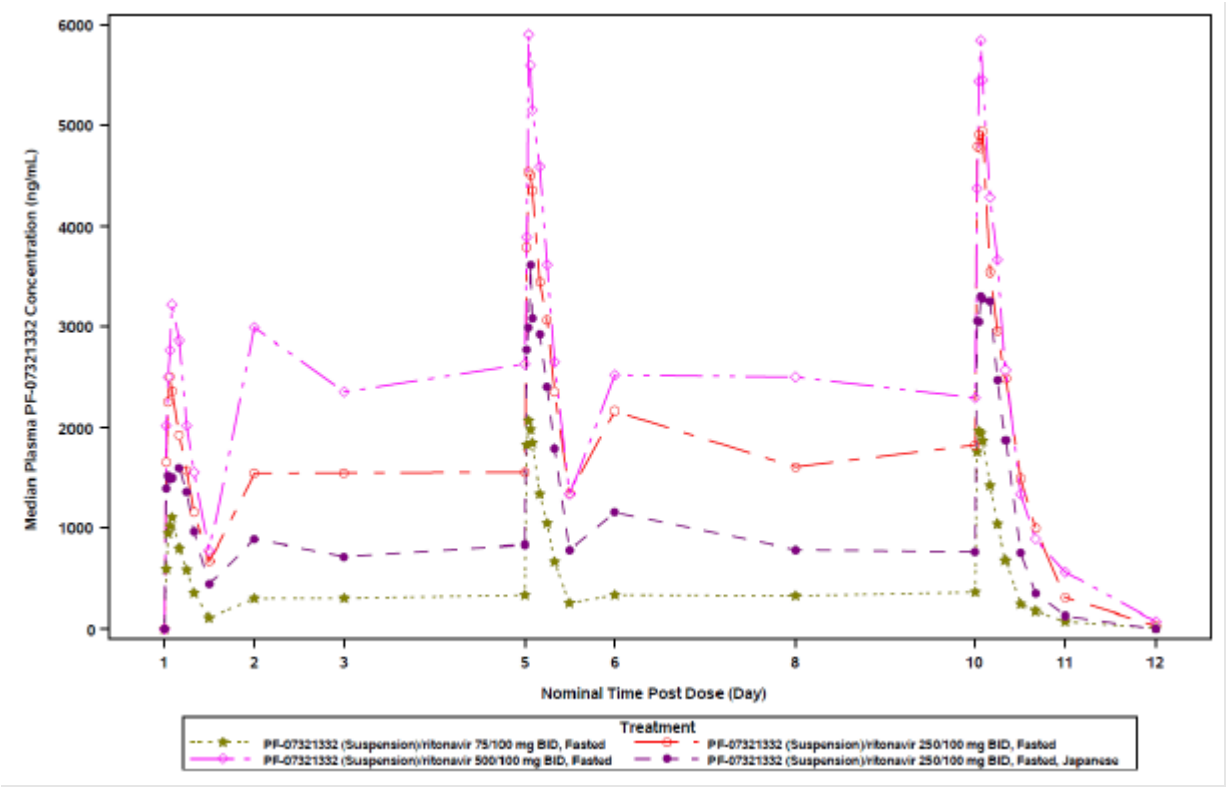


Overall, based on phase 1 dose-escalation data (Study **1001**) in healthy volunteers, the systemic exposures (Cmax, AUCs) of PF-07321332 boosted by 100 mg of ritonavir appeared to exhibit less than dose proportional increase over the dose range of 75 mg to 500 mg after single and multiple oral administration.

Time dependency

Median plasma PF-07321332 concentration time profiles including Ctrough concentrations are presented in **Figure 7** below and associated PK parameters in Table 4. Overall, after repeated administration, steady-state plasma concentrations appeared to have been achieved by Day 2 with minimal accumulation (~2) after BID dosing.

Figure 7. Median plasma PF-07321332 concentration -time profiles across all dosing days following MAD of PF-07321332/ritonavir (Part 2, MAD, Study 1001)



Population PK modelling

A preliminary population PK model of PF-07321332 was developed using plasma concentration data collected in healthy adult data from Study C4671001 (data cutoff date 30 June 2021). The analysis PK dataset included 536 evaluable plasma concentrations from 20 subjects who received 250 and 750 mg single dose and 75, 250 and 500 BID administration of PF-07321332 (suspension formulation) in combination with 100 mg ritonavir (RTV). Modelling used NONMEM, version 7.5. The first-order conditional estimation method with interaction was used during model development.

The final model was a linear 2-compartment model with first-order absorption, a dose-dependent absorption implemented by separate power functions for ka and relative bioavailability (F1) and a linear elimination. Standard allometric scaling of body weight with exponents fixed to 0.75 and 1 was applied on clearance (CL/F) and volumes of distribution, respectively. Residual random effects were described with a combined proportional and additive model in the log domain. IIV were included on all parameters, with a full variance and covariance of the Ω matrix. IOV was included to ka.

Parameter estimates for the final model are presented below.

Table 5. Parameter estimates for the final population PK model based on preliminary data from Study C4671001

	Final Run (CP1:ST-21050660)			1000 SIR[a] Run Statistics				
Parameter	Estimate	%RSE	Shrinkage (%)	Mean	%RSE	Median	Lower 2.5%	Upper 97.5%
CL (θ_1) [L/h]	1.02	18.9		1.02	10.7	1.02	0.800	1.24
V2 (θ_2) [L]	8.20	20.8		8.21	13.0	8.21	6.03	10.2
Q (θ_3) [L/h]	0.444	8.91		0.446	5.58	0.447	0.395	0.493
V3 (θ_4) [L]	5.65	20.2		5.84	17.5	5.90	3.68	7.64
k_{a1mg} (θ_5) [1/h]	22.7	4.15		22.6	2.67	22.6	21.5	23.9
k_{apower} (θ_6)	-0.533	6.25		-0.537	5.30	-0.536	-0.592	-0.481
$F1_{1mg}$ (θ_7)	1.06	30.5		1.05	23.1	1.05	0.591	1.56
$F1_{power}$ (θ_8)	-0.375	16.7		-0.376	10.4	-0.378	-0.455	-0.305
Proportional Error (θ_9) [%]	3.36	111		3.73	57.6	3.50	0.506	7.82
Additive Error (θ_{10}) [ng/mL]	399	11.5		405	30.2	375	250	671
$\omega^2_{1,1}$ IIV_{CL} [%CV]	26.4	29.2	1e-10	26.0	19.6	25.9	20.4	31.0
$\Omega_{2,1}$ COV_{CL-V2}	0.0684	36.0		0.0646	22.1	0.0637	0.0377	0.0962
$\omega^2_{2,2}$ IIV_{V2} [%CV]	30.7	41.9	5.73	31.6	29.3	31.4	22.1	39.7
$\Omega_{3,1}$ COV_{CL-k_a}	0.0582	73.2		0.0602	51.2	0.0599	0.00709	0.122
$\Omega_{3,2}$ COV_{V2-k_a}	0.138	41.4		0.133	33.5	0.129	0.0489	0.227
$\omega^2_{3,3}$ IIV_{k_a} [%CV]	54.3	33.6	15.5	55.3	32.7	54.2	39.3	72.8
$\Omega_{4,1}$ COV_{CL-V3}	0.125	58.6		0.104	43.8	0.0987	0.0157	0.229
$\Omega_{4,2}$ COV_{V2-V3}	0.0393	152		0.0279	116	0.0262	-0.0589	0.121
$\Omega_{4,3}$ COV_{k_a-V3}	-0.151	90.5		-0.148	62.5	-0.149	-0.347	0.0269
$\omega^2_{4,4}$ IIV_{V3} [%CV]	69.9	73.0	7.89	69.1	49.1	66.4	38.2	101
$\omega^2_{6,6}$ IOV_{k_a} [%CV]	60.7	15.6	38.1;51.6;5.23[b]	60.8	15.3	61.2	50.7	68.6
$\sigma^2_{1,1res}$	1 Fixed		5.58	1 Fixed				

In general, structural parameters were precisely estimated (low %RSE <20%), except for F1 at 1 mg dose (%RSE = 30.5%). However, proportional error, variance and covariance of the Ω block were poorly estimated (%RSE >30%). This is specifically problematic for the proportional residual error estimated to be low 3.36% but with an RSE% of 111%. These high %RSE and the high condition number (>1000) suggested that the final model is over-parameterised, which is expected given the inclusion of a full variance-covariance block for IIV and the available limited data. Sampling importance resampling were performed and overall were in line the model parameters estimates. All η and ε shrinkage were <20% except for IOV in ka. No major deficiencies were noted GOF plots. The pcVPCs indicated that the final model described the data reasonably well; even clear under-prediction of the low 5th quantile at 250 mg dose with RTV fed and fasted regimens (Please refer to the respective figures) and tendency to over-predict the terminal elimination phase are noted.

The additive error was estimated at 339 ng/L (more than 33 times the LLOQ of 10 ng/mL and even larger than the target IC90% value of 292 ng/mL). Such finding, with the poor precision of the proportional error portion compromise the validity of the model. To handle this point during simulations, the large residual errors was excluded. This approach is not endorsed as it would imply estimation of PK parameters and associated variabilities necessary different from that in the final model and used for simulation. Therefore, model-based PK predictions should be considered with caution.

The parameter estimates after adjustment by F1 at a dose of 300 mg are CL 8.2 L/h, volume of distribution 111 L, and ka 1.1 h-1. This gives a population mean half-live T1/2 of 15 hours, which is not consistent with that obtained from NCA calculations (mean T1/2 =7 hours). No clear estimate of the bioavailability 300 mg dose is provided / could be found. Importantly, given the observed 44% lower Cmax in tablets compared to the suspension formulation (relative bioavailability part in study

1001), the adequacy of using the current model (based only on tablet formulation data) to simulate PK data for the tablet formulation is not deemed adequate.

The covariate (age, body weight, BMI, ethnicity, renal and hepatic impairment) effects could not be considered adequately explored given the very limited data and the demographic characteristics of subjects included in the dataset (ranges of age, BW and renal clearance were [21-56y], [58-99 kg] and [70 -141 ml/min], respectively and no information on BMI, ethnicity and hepatic impairment could be found). For note, a high-fat meal reduced ka by approximately 50%. However, considering its minimal impact on Cmin, and the inclusion of IIV and IOV on ka, the applicant did not retain the food effect in the final model for subsequent simulation.

Using the final Pop-PK model and doses from 100 to 500 mg/100mg RTV BID for 5 days, the predicted PK exposures (Table 6) showed that, for a typical 70 kg subject, a dose of PF-07321332/ritonavir 300/100 mg BID would result in median Day 1 and steady state Ctrough (=C12h) concentrations ~3-4 x IC90 and ~6 x IC90, respectively. With this dose, it is projected to have >90% of subjects would achieve Ctrough ≥IC90 even after the first dose and with IIV in CL inflated to 60%.

Table 6. Predicted C12h and Percentage of Simulated Subjects Achieving C12h above IC90 of 292 ng/mL (IIV in CL Inflated to 60%)

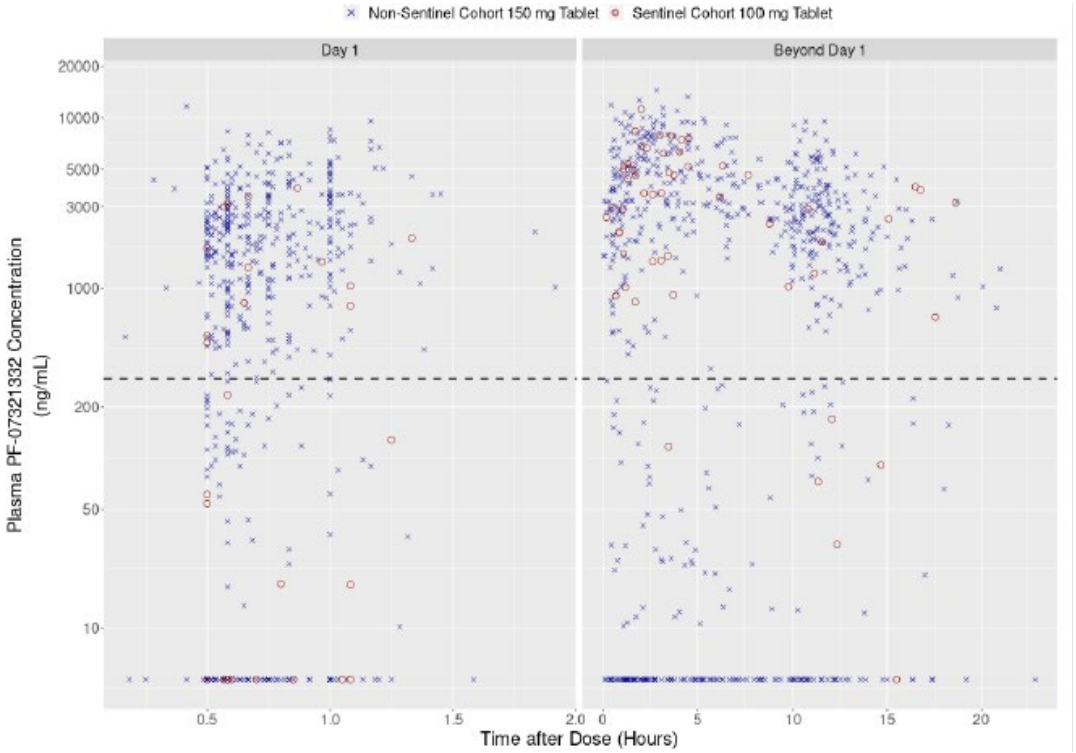
Dose (mg) + RTV[a]	Dose Number	C_{12h} (ng/mL) Median	10^{th} percentile	90^{th} percentile	% Subjects Achieved $C_{12h} \geq IC_{90}$
100	1st (Day 1)	458	141	1018	71.5
	2nd (Day 1)	631	175	1546	79.2
	9th (Day 5)	852	238	2276	85.3
200	1st (Day 1)	743	228	1608	85.0
	2nd (Day 1)	1012	281	2443	89.2
	9th (Day 5)	1361	383	3575	93.4
300	1st (Day 1)	987	307	2124	90.7
	2nd (Day 1)	1347	378	3202	93.6
	9th (Day 5)	1800	498	4670	95.7
400	1st (Day 1)	1209	378	2565	94.0
	2nd (Day 1)	1657	468	3879	95.3
	9th (Day 5)	2197	605	5679	97.4
500	1st (Day 1)	1417	449	2979	95.5
	2nd (Day 1)	1952	552	4516	96.5
	9th (Day 5)	2563	704	6640	97.8

Pharmacokinetics in target population

Preliminary PK data were collected from the ongoing pivotal efficacy and safety Phase 2/3 study (**C4671005**) in patients with confirmed diagnosis of SARS-CoV-2 infection who were at increased risk of progressing to severe illness. Patients received PF-07321332/ritonavir or placebo orally q12h for 5 days (10 doses total). Sparse PK sampling was collected on Day 1 (0.5 to 1.5 hr post dose), on Day 5 (up to 2 hours pre-dose) and optionally on Days 2, 3, or 4. At cutoff date (28 October 2021), a total of 1298 plasma PF-07321332 concentrations, including 1068 evaluable samples and 230 (17.7%) BLQ samples from 601 patients were available for analysis. There were 46 participants who did not have any evaluable samples (all observations were BLQs).

The observed plasma PF-07321332 concentrations in patients are shown in **Figure 8**.

Figure 8. Observed Plasma PF-07321332 Concentration versus Time after Dose for Participants with COVID-19 on PF-07321332/ritonavir 300 mg/100 mg q12h in Study C4671005 Stratified by Day



PK data at Day 5 (Table *7*) indicated that 140 out of 173 (>80%) patients achieved a Cmin≥ IC90. When excluding the BLQ samples during Day 5 visit, 140 out of 153 (>90%) patients achieved the target Cmin. Overall, the observed concentrations from patients appears to be consistent with those (dose-normalised to 300 mg) in the healthy participants. However, it is worth noting that a high number of BLQ (17.7% of the dataset) was observed after and beyond the first dose. Such finding requires further investigation. Of these BLQ, 95 samples (41.3%) were collected at Day 1, while no BLQ samples at or beyond 30 min post-dose was observed in healthy volunteers after of PF-07321332/ritonavir dosing.

Table 7. Summary of Cmin at the Planned Day 5 Visit and Percentage of Participants in Study C4671005 Achieving C_{min} ≥EC90

Scenario	Number of Participants	Observed C_{min}[a] (ng/mL)			BLQ[b] Samples		Participants with $C_{min} \geq EC_{90}$	
		Median	10th percentile	90th percentile	Number	Percentage	Number	Percentage
All Participants	173	2180	0	5600	20	11.6	140	80.9
Excluded Participants with only BLQ Samples	167	2290	57.2	5698	14	8.38	140	83.8
Excluded All Participants with BLQ Samples on Day 5	153	2440	701	5808	0	0	140	91.5

Repository artifact ID FI-26856380. Lines 1–2 substituted.
BLQ = below limit of quantification; C_{min} = minimum concentration; EC_{90} = concentration required for 90% of maximum effect.
[a]Samples collected between 10 and 14 hours post-dose at the planned Day 5 visit.
[b]BLQ defined as <10 ng/mL and was set to 0.

A predictive check (simulation) approach was performed to assess the adequacy of the preliminary Pop-PK model in describing the patient data from Study 1005 (PF-07321332/ritonavir 300 mg/100 mg BID).

Overall, a fair agreement was observed. The majority of the PF-07321332 concentrations in COVID-19 patients fall within the 90% prediction interval generated from simulation. The median observed data

at Day 1 (Figure 9) and at steady state (**Figure 10**) appears to be consistent with the model predictions generated Pop-PK model. However, as noted above, a high number of unexpected BLQ concentrations after the first dose and at steady was observed.

Figure 9. Median and 90% Prediction Intervals (5th and 95th percentile) for PF-07321332 concentrations after first dose based on 1000 Simulations (PF-07321332/ritonavir 300 mg/100 mg q12h) overlaid with observed Data from Study C4671005

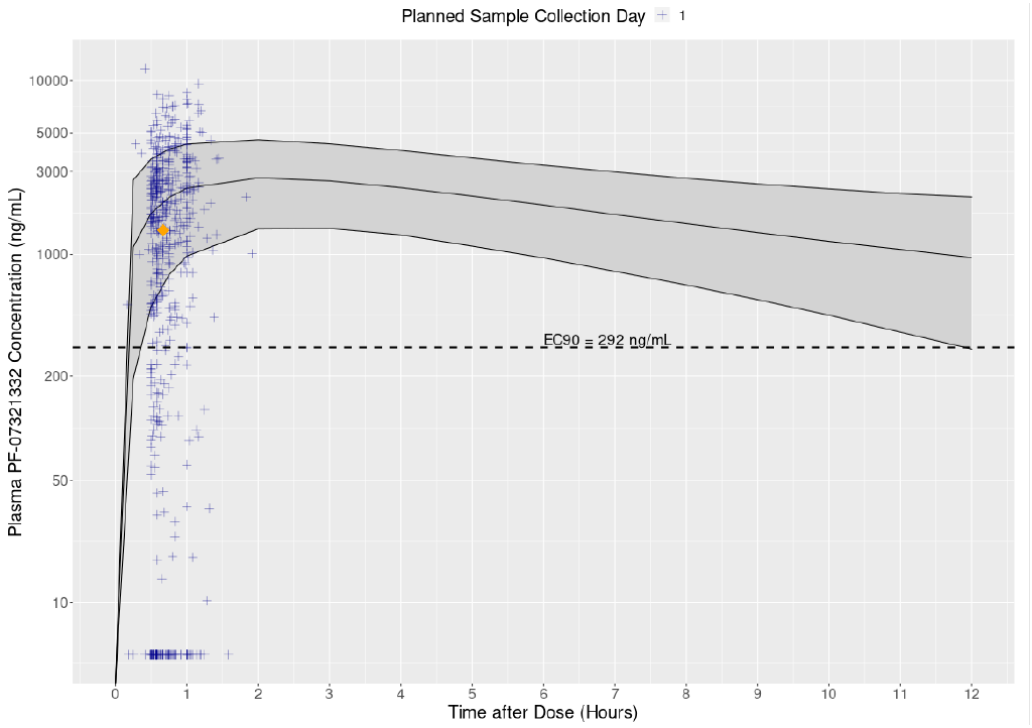
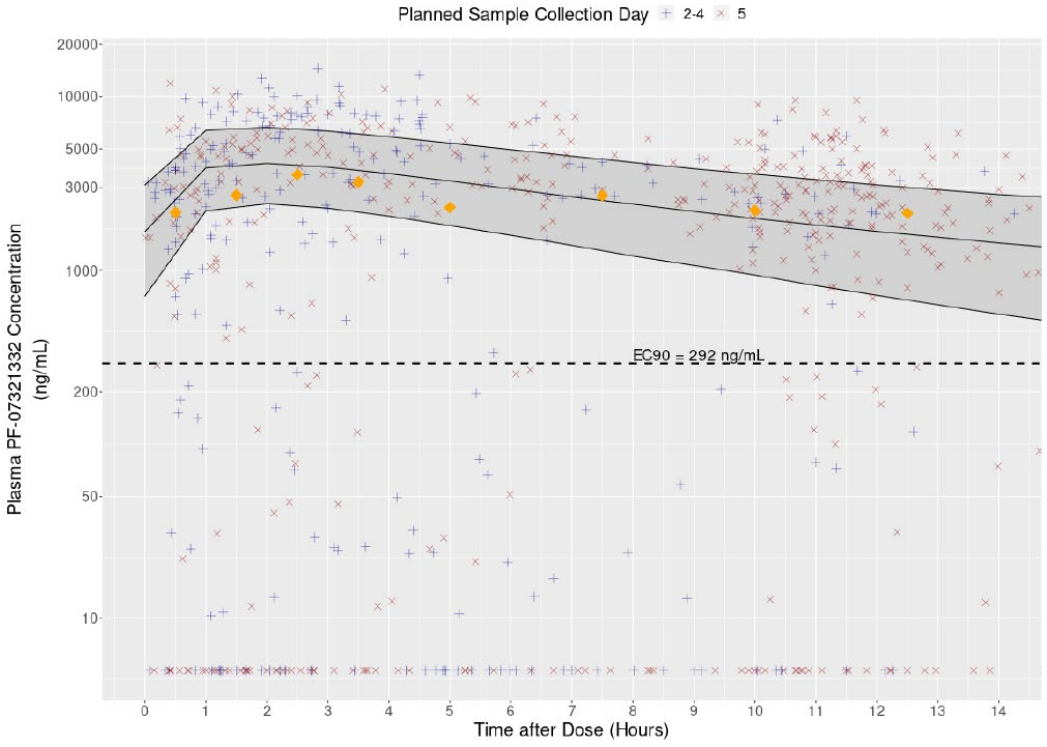


Figure 10. Median and 90% Prediction Intervals (5th and 95th percentile) for PF-07321332 concentrations at steady-state based on 1000 Simulations (PF-07321332/ritonavir 300 mg/100 mg q12h) overlaid with observed Data from Study C4671005



Special populations

Renal impairment

A formal study (**C4671011**) investigated the effect of mild, moderate and severe impairment on the PK of PF-07321332. Subjects were administered a single oral 100 mg dose of PF-07321332 in combination with the PK enhancer ritonavir administered as a 100 mg dose at -12, 0, 12, and 24 hours relative to PF-07321332 dosing. The number of subjects per category of renal impairment was n=8 versus 10 subjects for the normal healthy controls. The estimated eGFR calculated using CKD-EPI equation was used a measure of renal function.

PK data indicated that PF-07321332 systemic exposure increased with increasing severity of renal impairment, specifically in the moderate and severe impaired subjects Figure 11,

Table **8**). The geometric mean (90% CI) ratios for Cmax and AUCinf relative to subjects with normal renal function were:

- For the mild impaired group: 129.78% (101.93%, 165.25%) and 123.84 % (99.64%, 153.91%), respectively
- For the moderate impaired group: 138.12% (113.18%, 168.55%) and 187.40% (148.52%, 236.46%), respectively
- For the severe impaired group: 148.02% (111.40%, 196.68%) and 304.49 % (237.60%, 390.21%), respectively

Consistent with the increase on PF-07321332 systemic exposures, the apparent CL/F and CLr decreased with increased renal impairment severity. Mean CL/F in the moderate and severe group

decreased 47% and 67% and mean renal clearance decreased 47% and 80% respectively compared to the normal renal functional group.

Figure 11. Median Plasma PF-07321332 Concentration-Time Plot, Following a Single Oral Dose of PF-07321332/Ritonavir, Protocol C4671011

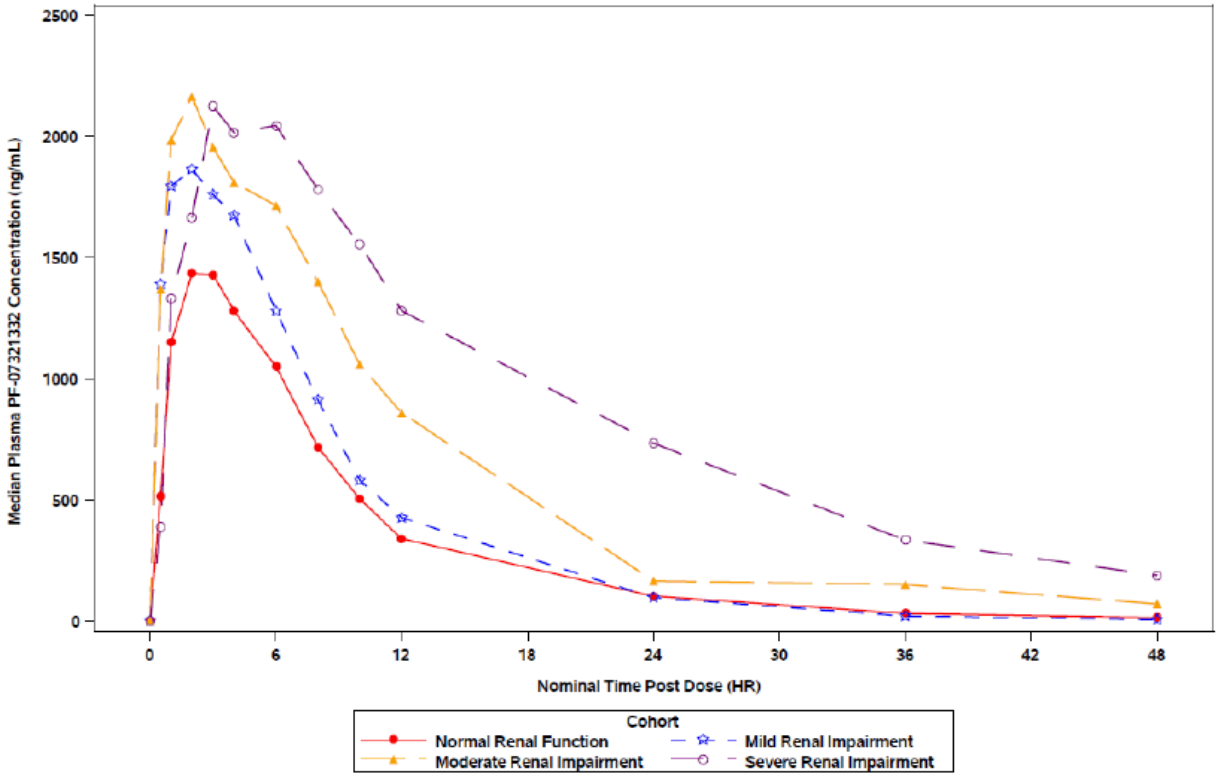


Table 8: Descriptive Summary of Plasma and Urine PF-07321332 PK Parameters. Protocol C4671011

Parameter (Unit)[a]	Normal Renal Function (N=10)	Mild Renal Impairment (N=8)	Moderate Renal Impairment (N=8)	Severe Renal Impairment (N=8)
N1, n	10, 10	8, 8	8, 6	8, 7
AUC_{inf} (ng.hr/mL)	14460 (20)	17910 (30)	27110 (27)	44040 (33)
AUC_{last} (ng.hr/mL)	14270 (20)	17770 (30)	26660 (21)	39420 (28)
C_{12} (ng/mL)	341.9 (35)	438.0 (30)	785.6 (33)	1213 (33)
C_{24} (ng/mL)	99.10 (35)	112.8 (55)	179.1 (108)	694.2 (42)
CL/F (L/hr)	6.913 (20)	5.581 (30)	3.689 (27)	2.270 (33)
C_{max} (ng/mL)	1600 (31)	2077 (29)	2210 (17)	2369 (38)
$t_{1/2}$ (hr)	7.725 ± 1.8234	6.606 ± 1.5344	9.948 ± 3.4171	13.37 ± 3.3225
T_{max} (hr)	2.000 (1.00 - 4.00)	2.000 (1.00 - 3.00)	2.500 (1.00 - 6.00)	3.000 (1.00 - 6.05)
V_Z/F (L)	74.95 (35)	51.95 (32)	50.34 (27)	42.73 (26)
Ae (mg)	31.20 (45)	42.65 (23)	30.83 (56)	18.46 (50)
Ae %	31.20 (45)	42.65 (23)	30.83 (56)	18.46 (50)
CL_r (L/hr)	2.180 (50)	2.395 (33)	1.154 (71)	0.4398 (73)

Hepatic impairment

A formal study (**C4671010**) investigated the effect of moderate hepatic impairment on the PK of PF-07321332, in comparison to matched healthy subjects with normal hepatic function. Subjects were administered a single oral 100 mg dose of PF-07321332 in combination with the PK enhancer ritonavir administered as a 100 mg dose at -12, 0, 12, and 24 hours relative to PF-07321332 dosing. The number of subjects was n=8 in each cohort. Categorisation of participants into normal hepatic function or hepatic impairment group was based on Child-Pugh scores.

The study is still ongoing and only a preliminary PK report (22 November 2021) is provided.

Preliminary median PK profiles and PK data by hepatic function are shown in Figure 12 and summarised in Table 9. Overall, data suggest that PK exposure following single dose administration of PF-07321332 enhanced with ritonavir in subjects with moderate hepatic impairment (AUCinf = 15.07 µg*h/mL and Cmax 1.92 µg/mL) were comparable to those in participants with normal hepatic function AUCinf = 15.28 µg*h/mL and Cmax = 1.89 µg/mL).

Figure 12. Median Plasma PF-07321332 Concentration-Time Profiles Following a Single Oral Dose of PF-07321332 Enhanced with Ritonavir

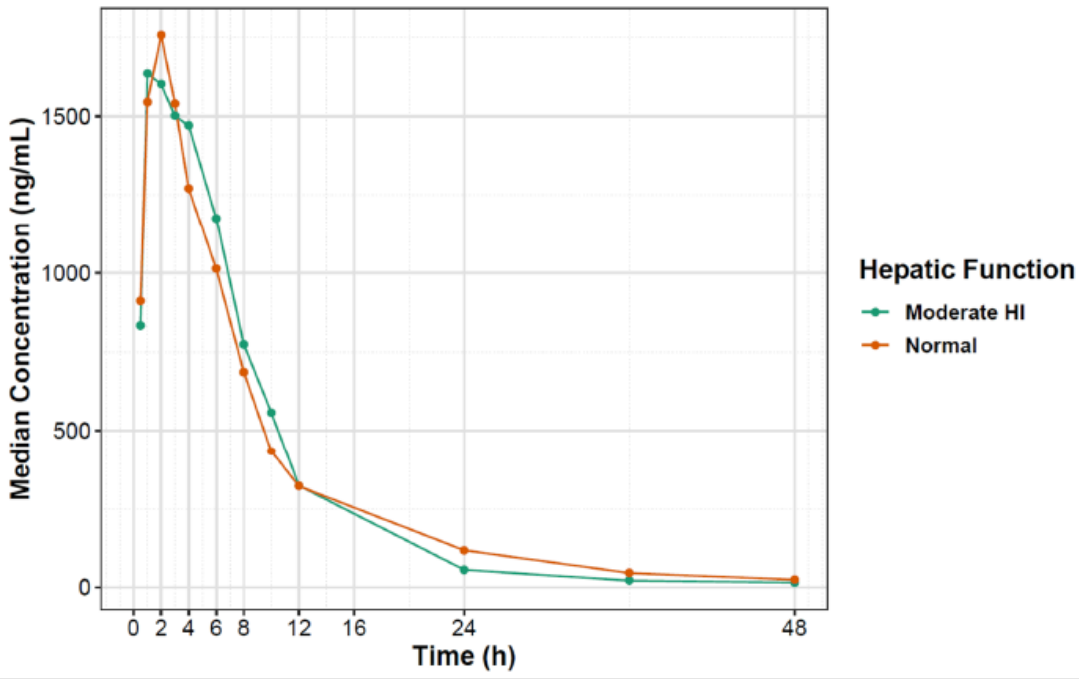


Table 9. Descriptive Summary of Preliminary (Unaudited) Plasma PK Parameters of PF-07321332 by Hepatic Function in Study C4671010

Hepatic Function	PK Parameters[a]				
	N,n[b]	T_{max} (hr)	C_{max} (µg/mL)	AUC_{inf} (µg.hr/mL)	$t_{½}$ (hr)
Normal Hepatic Function	8,8	2 (0.5-2)	1.89 (20)	15.28 (36)	7 (29)
Moderate Hepatic Impairment	8,8	1.5 (1-2)	1.92 (48)	15.07 (43)	5.5 (32)

Abbreviations: %CV = percent coefficient of variation; AUC_{last}= Area under the concentration-time curve from time zero to last measurable concentration; C_{max}= Peak plasma concentration; T_{max}=Time to achieve C_{max}; $t_{½}$=Half-life

a. Geometric mean (geometric % CV) except $t_{½}$ and T_{max}. Arithmetic mean and %CV for $t_{½}$ and median (range) for T_{max}.
b. N is total number of subjects, n=number of subjects with estimates of half-life

Gender

No formal dedicated PK study was performed to investigate the potential effect of gender on the PKs of PF-07321332.

Among the 20 subjects included in the dataset for PF-07321332, both sexes were represented with less female (n= 4; 20 %) than male (n = 16; 80 %). Sex was not identified as a significant covariate on the PK parameters of PF-07321332. However, such conclusion should be sought cautiously as the validity of the population-PK analysis is still to be proven.

Race / Ethnicity

No formal dedicated PK study was performed to investigate the potential effect of gender on the PKs of PF-07321332.

Race effect on PF-07321332/ritonavir PK has been explored as part of Study 1001 in only 4 Japanese healthy volunteers. AUCtau and Cmax values were approximately 30% and 21-26%, respectively, lower in Japanese participants compared to Caucasian subjects. Drug accumulation was similar in Japanese compared to Caucasian subjects (~2).

Body weight

No formal dedicated PK study was performed to investigate the potential effect of body weight on the PKs of PF-07321332.

The Population model included an allometric relationship of baseline body weight on apparent clearance (CL/F) and apparent volume of distribution (V/F) with exponents fixed to 0.75 and 1, respectively. However, the impact of this covariate on the systemic exposure of PF-07321332 was not clearly shown / explored (no results could be found).

Elderly

Preliminary PK data provided in patients (study C4671005) indicates an age between 18 and 86 years. However, the number of elderly patients included in the following subgroups of age: [65 to 74 years], [75 to 84 years] and >85 years is not detailed.

No subject older than 65 years was included in Population dataset.

Children and adolescents

No PK data are available. The safety and efficacy of PF-07321332/ritonavir in children and adolescents below the age of 18 years have not yet been established.

The applicant claimed an indication covering the adolescents aged 12 years of age and above and weighing > 40 kg with the same dosing regimen as adults, 300/100 mg PF-07321332/ritonavir BID. According to the applicant, the proposed dose is justified based on Population PK simulations.

The preliminary Population PK model was used to simulate exposures in adolescent patients >40 kg. These model-based simulations suggest that a PF-07321332/ritonavir 300 mg/100 mg BID dose in adolescents (i.e., ≥12 to < 18 years of age) provides reasonably comparable exposures in adults receiving the same dose and maintained PF-07321332 plasma concentration above EC90 over the entire dosing interval suggestive of pharmacodynamic activity of PF-07321332/ritonavir and thus the therapeutic response.

The distribution of simulated C_{min} on Day 5 by dose of either PF-07321332/ritonavir 150 mg/100 mg BID or 300 mg/100 mg BID regimen in adolescent subjects are depicted in ***Figure 13***. The distribution of simulated Cmin on Day 5 based on adults from the Study 1005 is provided for reference. Summary statistics for simulations results for all exposure parameters are presented in Table 10.

Figure 13 : Distribution of Cmin on Day 5 by Treatment in Simulated Adolescent Subjects

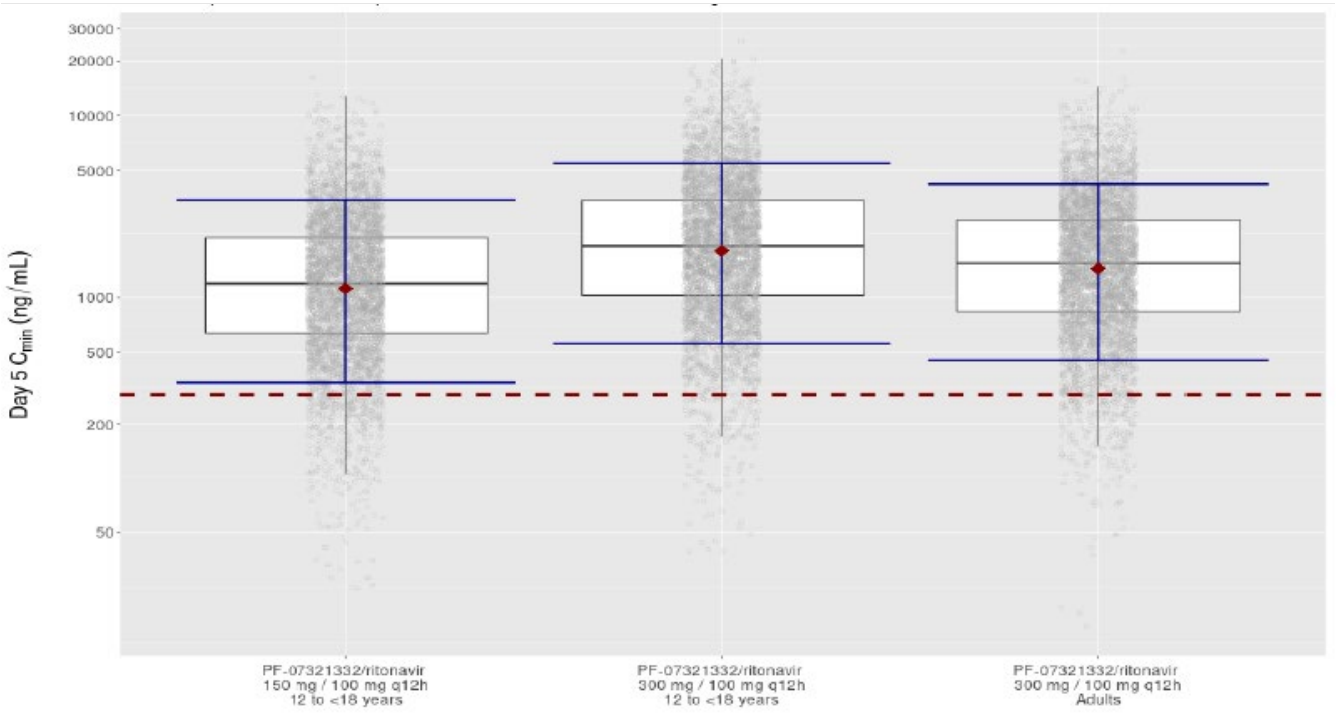


Table 10. Statistical Summary (Geometric Mean and Percentiles) of the Output of the Modelling and Simulation Evaluation

Age Group	Dose (mg) + Ritonavir 100 mg q12h (BID)	N	$AUC_{0\text{-}12h}$ (ng·h/mL)			C_{max} (ng/mL)			C_{min} (ng/mL)		
			Geo Mean	Percentile		Geo Mean	Percentile		Geo mean	Percentile	
				10^{th}	90^{th}		10^{th}	90^{th}		10^{th}	90^{th}
12 to <18 years	150	5000	27602	12302	61731	3825	2077	7114	1122	340	3435
	300	5000	42797	19099	95375	5592	2996	10501	1807	556	5476
Adults	300	5000	32239	14404	71154	4079	2160	7786	1440	453	4214

Based on these simulations, a considerable overlap in C_{min} values of PF-07321332 between the PF-07321332/ritonavir 150 mg/100 mg BID and PF-07321332/ritonavir 300 mg/100 mg BID administrations in adolescents as compared to reference C_{min} values in adults (300 mg/100 mg BID). As that could be expected, a dose of PF-07321332/ritonavir 300 mg/100 mg BID in adolescents achieved a larger distribution of subjects above the *in vitro* EC90 of 292 ng/mL as compared to those receiving the 150 mg/100 mg BID regimen, but detailed difference and statistical comparison was not provided.

Pharmacokinetic interaction studies

Paxlovid interaction profile, as a co-packed combination of PF-0713321332, and ritonavir, has been investigated mainly by assessing PF-0713321332 interaction potency in studies 102559 (CYP inducer via AhR, CAR and PXR), 103243 (UGT and CYP inhibitors), 113907 and 12202 (CYP inhibitions), 020944 (transporter inhibition), 124535 and 095737 (substrate of efflux transporters, P-gp and BCRP),

and studies -013448, -110227, -114514, -124557 and - 013448 (hepatobiliary/renal uptake transporters). Interaction studies was also studied as part of clinical trials in studies -1014 and 1015, to characterise the effects of carbamazepine on the single dose PK of PF-07321332 300 mg/ritonavir 100 mg in healthy participants and to estimate the effect of multiple doses of itraconazole on the PK of PF-07321332 following multiple doses of PF-07321332/ritonavir respectively.

Paxlovid as perpetrator

The Appraisal of PF-07321332 interaction profile was based on *in vitro* studies. Its induction potential, inhibition of UGTs, inhibition of CYPs isoforms, as well as inhibition of transporters were performed in line with EMA drug-drug interaction guideline (CPMP/EWP/560/95/Rev. 1).

PF-07321332 was found to be an inducer of CYP3A4, CYP2B6, CYP2C8 and CYP2C9. It was identified as time-dependent inhibitor of CYP3A4 with estimated KI of 15.5 µM and 13.9 µM, and estimated Kinact to 0.0142 min-1, and 0.0165 min-1, using respectively midazolam and testosterone as substrate. PF-07321332 was also an inhibitor of P-gp (IC50 70.6 µM), OATP1B1 (IC50 44.4 µM), and OCT1 (IC50 138.1 µM). Based on *in vitro* results, PF-07321332 may *in vivo* inhibit OCT1. For renal transporters, MATE1 Rr=0.023, slightly above the cut-off criteria (Rr≥0.002). However, since metformin is also substrate of OCT1, significant interactions with metformin could not be excluded. With respect to OATP1B1 inhibition potential, PF-07321332 shows an Rh of 0.110, which is above the EMA cut-off criteria of 0.04. Given the large drug-drug interaction spectrum of Paxlovid, clinical interaction study to assess the magnitude of interaction with these transporters or thorough justification of the lack of such investigation based on scientific evidence and rationale should continue.

Ritonavir (RTV) interaction profile was based on Norvir SmPC. RTV is an inducer of CYP1A2, CYP2C8, CYP2C9, and CYP2C19, as well as inducer of UGTs. Ritonavir has also shown to be a time-dependent inhibitor of CYP3A4, an inhibitor of CYP2D6, and a P-gp inhibitor.

Overall, based on *in vitro* studies, Paxlovid, as co-packed combination of PF-07321332 with ritonavir, is considered inhibitor of CYP2D6, P-gp, BCRP, OATP1B1, OATP1B3, and OCT1. It induces UGTs, CYP3A4, CY2B6, CYP2C8, CYP2C9, CYP1A2, and CYP2C19.

There is a possibility of additive effect in the induction of CYP enzymes. However, taking in consideration the low dose of ritonavir used for a short duration and its predicted induction of less than 30%, it can be agreed that this magnitude of induction unlikely to necessitate dose adjustments and that it is appropriate to give guidance within the Paxlovid label based on Norvir (ritonavir) label which already states the risk of induction that was observed for higher doses.

Paxlovid net effect on CYP3A4 and P-gp substrates *in vivo* is not yet established given Paxlovid is substrate, inhibitor, and inducer of CYP3A4, and also substrate and inhibitor of P-gp. This is currently being assessed in the following on-going studies, DDI study 1013 with midazolam, and DDI study 1012 with dabigatran. Preliminary PK data from the midazolam DDI study was provided. The study consists of 3 treatments: single oral dose of midazolam 2 mg (Treatment A); PF-07321332/ ritonavir 300/100 mg q12h (total 9 doses) + single oral dose of midazolam 2 mg on the Day 5 morning (Treatment B); ritonavir 100 mg q12h (total 9 doses) + single oral dose of midazolam 2 mg on the Day 5 morning (Treatment C). The test/reference ratios of the adjusted geometric means (90% CI) for midazolam AUCinf and Cmax were 1430.02 % (1204.54%, 1697.71%) and 368.33% (318.91%, 425.41%), respectively, when midazolam was co-administered with PF-07321332/ritonavir (Test) compared of midazolam administered alone (Reference). Midazolam CL/F was decreased by 93% and t½ was increased by 2-fold, when midazolam was co-administered with PF-07321332/ritonavir compared of midazolam administered alone. The test/reference ratios of the adjusted geometric means (90% CI) for midazolam AUCinf and Cmax were 1645.15 % (1385.75%, 1953.11%) and 387.20% (335.25%, 447.21%), respectively, when midazolam was co-administered with ritonavir (Test) compared of

midazolam administered alone (Reference). Midazolam CL/F was decreased by 94% and t½ was increased by 2.3-fold, when midazolam was co-administered with ritonavir compared of midazolam administered alone. Midazolam systemic exposure increased several-fold when co-administered with the strong CYP3A inhibitor ritonavir. However, coadministration of midazolam with PF-07321332/ritonavir did not result in any further increase in midazolam exposure compared to ritonavir alone. This information was included in the SmPC.

As a precautionary measure, other potential victim drugs were added in 4.3 and 4.5 sections of Paxlovid SmPC.

Concomitant therapy with ritonavir- or cobicistat-containing regimen, it is indicated that no dose adjustment is needed and that Patients diagnosed with human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection who are receiving ritonavir- or cobicistat-containing regimen should continue their treatment as indicated. Although it is acceptable to conclude that it may be essential to administer ritonavir together with PF-07321332 to get the PK enhancement of PF-07321332, doses of ritonavir higher than 100 mg twice-a-day may increase incidence of adverse reactions. The benefit of Paxlovid in HIV and HCV patients who are receiving a PK booster, and subsequently are also infected with SARS-CoV-2 and need Paxlovid, is considered outweighing the risk of adverse events associated with an additional booster dose of ritonavir or cobicistat. Staggering of dose or skipping the ritonavir administration if PF-07321332 administered at the same time as other ritonavir-regimen would be confusing to patients and prone to error because some HIV treatments are QD and other BID. Therefore, keeping the PK booster together with associated protease inhibitor as indicated is considered acceptable.

It is noteworthy that given the high-risk targeted population (including notably old patients, patients with cardiovascular disease), additional DDI studies with amiodarone and clozapine notably as victim drugs should have been performed by the applicant, since critical in this population. These studies could allow these patients, for whom treatment cessation could not be clinically easily handled, to benefit from Paxlovid treatments.

Paxlovid as victim

Administered with ritonavir, PF-07321332 is mainly excreted unchanged. Notably, 55.0% and 27.5% of the dose is excreted as parent compound in urine and faeces, respectively. Regarding the fraction of PF-07321332 metabolised, CYP3A4 was identified as the major contributor (fm = 0.99) of the oxidative metabolism, based on *in vitro* studies.

PF-07321332-transporter interaction profile was studied based on *in vitro* inhibition studies. PF-07321332 was found to be a substrate of the human MDR1 P-gp.

In vivo PF-07321332 interaction profile was assessed in clinical studies with a potent inhibitor and an inducer of CYP3A4 enzyme. After co-administration of PF-07321332/ritonavir (300/100 mg SD) and carbamazepine (dose escalation design: 100mg BID from day 1 to 3, 200mg BID from day 4 to 7, 300 mg BID from day 8 to 15), the AUC0-∞ and Cmax of PF-07321332 were decreased by 55% and 43%, respectively, as compared to administration of PF-07321332/ritonavir alone.

Based on *in vivo* results, the SmPC specified a contraindication for the coadministration of Paxlovid with potent CYP3A inducers regarding the significant clinical impacts on both PF-07321332 and ritonavir PK.

After co-administration of PF-07321332/ritonavir (5 oral doses 300/100 mg q12h) and itraconazole (200 mg orally q24h for 8 days), the AUCtau and Cmax of PF-07321332 were increased by 38% and 19%, respectively, as compared to administration of PF-07321332/ritonavir alone. PF-07321332 exposure increases observed in the itraconazole study are not expected to be clinically relevant.

Therefore, no dosing adjustment of PF-07321332/ritonavir is necessary when a CYP3A4 inhibitor is co-administrated with Paxlovid.

Overall, the applicant has proposed to integrate the long list of DDI related to ritonavir, including contraindications. The CHMP has considered that this conservative measure should indeed apply at this stage. However, the CHMP has judged necessary to explain the reasoning in a dedicated introductory statement to the physicians before the table of DDI in the SmPC *"**As a conservative measure,** the drug-drug interactions pertaining to ritonavir used in chronic HIV infection (600 mg BID when originally used as an antiretroviral agent and 100 mg BID as currently used as a pharmacokinetic enhancer with antiretroviral agents), should apply for Paxlovid. Future investigations may enable to adjust the recommendations related to drug-drug interactions to the 5 days treatment duration of Paxlovid"*

The CHMP is committed to revisit for adjustment the ritonavir driven DDI in relation to the use of Paxlovid as soon as the requested data in pharmacokinetics would be available (including PopPK), to better guide healthcare professionals especially in the outpatients setting less familiar with those ritonavir driven DDI than HIV specialists at hospital. The CHMP has alerted healthcare professionals organisations on the complexity of the interaction profile of this treatment.

The applicant is expected to particularly review the contraindication with drugs expected to be used in the targeted population at high risk of progression to severe COVID-19 including drugs for which treatment cessation cannot be foreseen even for a short period, such as amiodarone, clozapine.

2.6.2.2. Pharmacodynamics

Mechanism of action

PF-07321332 is a peptidomimetic inhibitor of the coronavirus type 3C protease (3CLpro), including the SARS-CoV-2, 3CL protease. Inhibition of the 3CL protease renders the protein incapable of processing polyprotein precursors, leading to inhibition of viral replication.

From the co-crystal structure of PF-07321332 bound to SARS-CoV-2 3CLpro, 6 contact residues (Cys145, Gly143, Glu166, His163, Phe140, His164) were identified in the active site of 3CLpro to form either covalent or hydrogen bonds between 3CLpro and PF-07321332. Examination of residues within 4 Å from PF-07321332 binding sites identified 7 additional potentially critical residues. The conservation of these contact residues was assessed by aligning SARS-CoV-2 genomes with complete and high coverage sequences (N = 3,163,857; GISAID; last accessed 11-08-2021). The 13 residues explored (presented in **Table 11**) were highly conserved, with frequency of mutation <0.024%.

Table 11. Mutations at Key PF-07321332 Contact Residues on SARS-CoV-2 3CLpro

Residue Position	Reference AA	Mutation(s)	Number of Subjects	Interaction with PF-07321332
41	His (H)	H41Y, H41L	3	Catalytic site, hydrophobic contact
49	Met (M)	M49I, M49T, M49V, M49L, M49K	745	Side chain Hydrophobic contact
54	Tyr (Y)	Y54*	1	No direct contact
140	Phe (F)	None	0	Backbone Hydrogen bond
143	Gly (G)	G143S, G143C	5	Backbone Hydrogen bond
145	Cys (C)	C145I, C145F, C145Y	4	Catalytic site (covalent bond)
163	His (H)	None	0	Side chain Hydrogen bond
164	His (H)	H164N	2	Backbone Hydrogen Bond
165	Met (M)	M165I, M165K, M165V, M165L, M165T	42	Side Chain Hydrophobic contact
166	Glu (E)	E166G	3	Backbone and side chain contact
167	Leu (L)	L167*, L167I, L167S	38	Side Chain Hydrophobic contact
168	Pro (P)	P168S, P168R, P168A, P168T	122	Side Chain Hydrophobic contact
189	Gln (Q)	Q189K, Q189*, Q189H, Q189L	15	No direct contact

PF-07321332 has also demonstrated selectivity for coronavirus 3CLpro, showing little or no activity against a panel of human proteases, as well as HIV protease. IC50 against human chymotrypsin was >10 μM and against all other tested proteases was >100 μM.

Primary and Secondary pharmacology

Antiviral activity

PF-07321332 exhibited antiviral activity against SARS-CoV-2 infection of dNHBE cells, a primary human lung alveolar epithelial cell line (EC_{50} value of 61.8 nM and EC_{90} value of 181 nM) after 3 days of drug exposure (**Table 12**).

It is considered as a pancoronavirus antiviral against other alpha and betacoronaviruses (SARS-CoV-1, HCoV-229E, MERS-CoV, HCoV-OC43, HCoV-HKU1, and HCoV-NL63). But the clinical relevance uncertain since only based on *in vitro* data with no clinical data available except against SARS-Cov-2.

PF-07321332 activity is selective to the coronavirus family and PF-07321332 did not inhibit enterovirus 71 (EV71) or human rhinovirus 1B (HRV1B) viral-induced CPE, (EC50 >100 μM), nor did it demonstrate cytotoxicity in noninfected rhabdomyosarcoma cells or Hela cells (CC50 of >100 μM).

The *in vitro* antiviral activity was demonstrated in VeroE6 ACE-2 cells with an EC50 of 0.0745 μM in the presence of P-gp inhibitor to better represent physiological cells, A549-ACE2 cells with EC50/EC90 values of 0.0779 μM / 0.215 μM, and physiologically relevant dNHBE (differentiated normal human bronchial epithelial) cells with EC50 of 0.0618 μM and 0.0326 μM, at Day 3 and Day 5 post-infection respectively. The metabolite, PF-07329268 inhibited SARS-CoV-2 CPE in VeroE6 ACE-2 cells with an EC50 value of 0.690 μM, in the presence of P-gp inhibitor. The antiviral activity of PF-07321332 was specific and not due to cellular toxicity (no cytotoxicity was observed up to >100 μM in VeroE6 ACE-2 cells) resulting in a TI of >21.5 in the absence of P-gp inhibitor.

Table 12. EC50 for PF-07321332 and Remdesivir in dNHBE Cells at 3 and 5 Days Post Inoculum

Virus Collection Day	PF-07321332							
	[ab] EC_{50} (μM)			GeoMean (95% CI)	[ab] EC_{90} (μM)			GeoMean (95% CI)
	N=1	N=2	N=3		N=1	N=2	N=3	
3	0.0757	0.0678	0.0461	0.0618 (0.0324 to 0.118)	0.157	0.141	0.2676	0.181 (0.0769 to 0.425)
5	0.0555	0.0231	0.0271	0.0326 (0.0102 to 0.104)	0.0924	0.0436	0.0440	0.0561 (0.0192 to 0.164)
Virus Collection Day	Remdesivir							
	[ab] EC_{50} (μM)			GeoMean (95% CI)	[ab] EC_{90} (μM)			GeoMean (95% CI)
	N=1	N=2	N=3		N=1	N=2	N=3	
3	0.0019	0.0053	0.0026	0.00297 (0.000805 to 0.0109)	0.0043	0.0099	0.0322	0.0111 (0.000901 to 0.137)
5	0.0024	0.0069	0.0098	0.00545 (0.000885 to 0.0336)	0.008	0.0136	0.0349	0.0156 (0.0024 to 0.0993)

a. EC_{50} curves were fit to a Hill slope of 3 when >3 and defined by top dose only which was ≥50%.
b. Data generated at Utah State University: (2020). SARS-CoV-2 (USA_WA1/2020; Washington strain). Study Report PF-07321332_23Oct20_010204.

Systemic exposure of PF-07321332 in humans is likely limited by CYP3A4 mediated metabolism. As such, ritonavir, a strong CYP3A4 inhibitor is co-administered with PF-07321332 in clinical trials in order to boost exposure. Ritonavir exhibited no inhibition of SARS-CoV-2 viral replication in A549-ACE2 cells up to 3 μM. No host cell cytotoxicity was observed for PF-07321332 or ritonavir up to 3 μM in non-infected A549-ACE2 cells.

Efficacy in major SARS-CoV-2 Variants of Concern (VOC)

The antiviral activity of PF-07321332 against SARS-CoV-2 variants B.1.1.7 (Alpha), B.1351 (Beta), P.1 (Gamma) and B.1.1.1.37 (Lambda, λ) and B.1.621 (Mu, μ) was demonstrated using a cytopathic effect protection assay in Vero E6 P-gp Knockout cells, with reported EC50 values of 75.3 nM, 171 nM, 87.7 nM, 59.5nM and 65.1 nM respectively, compared with 96.3 nM for WA1 (USA-WA1/2020). Due to the inability of the SARS-CoV-2 delta variant to exhibit CPE in the Vero E6 P-gp knockout cell line, the variants were also evaluated in Vero E6 TMPRSS2 with P-gp inhibitor. Mean EC50 values were 92.8 nM, 170 nM, 217 nM, 204 nM, 93 nM, and 82.2 nM and 138 nM in the USA-WA1/2020 SARS-CoV-2 strain and alpha, beta, gamma, lamda, and delta and Mu variants, respectively (remdesivir assay control EC50 range: 79.8 – 169 nM). Vero E6-TMPRSS2 is a relevant model for SARS-CoV-2 and close to "physiological" conditions. SARS-CoV-2 target cells are respiratory epithelial cells expressing ACE2 and TMPRSS2 (with absence of PGP efflux system).

The impact of PF-07321332 on viral loads was also measured using a qPCR-based method, showing inhibition of the VeroE6 Pgp knockout cells with mean EC50 values of 32.2 nM, 41.0 nM, 127.2 nM, 24.9 nM, 21.2 nM, 15.9 nM and 25.7 nM in the USA-WA1/2020 SARS-CoV-2 strain and the alpha, beta, gamma, delta, lambda and Mu variants, respectively (remdesivir EC50 1.9 - 14.8 nM). The activity *in vitro* on beta variant was of lesser extent.

The Delta variant represented the most prevalent VOC circulating notably in Europe when the phase 2/3 clinical study C4671005 was performed. Therefore, the population has quasi exclusively consisted in patients infected by this VOC (98%, in vast majority 21J sublineage). Four isolates that are representative of the sub lineages of Delta (21A, 21I and 21) were tested and demonstrated susceptibility to PF-07321332 across the different clades. The Delta variants tested all had Mpro sequences that were identical to the reference strain. From a large genomic surveillance of ~2.2 million Delta isolates in GISAID, ~92% are identical to reference strain Mpro sequence. There are a small percentage of Delta subvariants that contain mutations at K88R, K90R, V73I and A260V (Table below). Three mutations (K88R, K90R, A260V) have been tested with no significant drop in potency by biochemical assay. The applicant plans to also test the V731I change and has been requested by the CHMP to shortly test activity of emerging VOC.

Table 13. Mutation and Global Frequency Analysis for Delta Variant from GISAID (B.1.617.2 and AY.X; n=2,218,609)

Mutation	Frequency
K90R	1.13%
K88R	0.35%
A260V	0.31%
V73I	0.23%
~92% of Delta isolates share the same 3CLpro sequences with the reference sequence (Wuhan-1)	

All patients with treatment failure TF (7 events) from study C4671005, were infected by a 21J isolate compared to 37 events of TF in the placebo participants (27 infected with 21J-Delta). The applicant clarified that Mpro retrieved from consensus genome sequence for these 7 events are all identical to reference sequence. The allele frequency of minor variants found are less than 5.05%, with a median value of 2.04%. There is therefore a low probability that these breakthrough cases are due to a lack of effectiveness against Delta clades 21J. The applicant is planning on isolating the viruses from the breakthrough cases and testing them in an antiviral assay against PF-07321332 for confirmatory purposes. The applicant was requested to substantiate the resistance data through the analysis of treatment failure in all applicant's clinical studies, since at this stage the resistance pattern of Paxlovid remains to be determined. Even *in vitro*, only the model of MHV-3CL was used and not the relevant SARS-CoV-2.

Upon CHMP request to obtain data on the predominant circulating Omicron VOC, the applicant provided dedicated results**:** PF-07321332 showed antiviral activity against the Omicron variant with EC50 values of 70 nM and 23 nM in the HeLa-ACE2 and Vero-TMPRSS cells compared to the SARS-CoV-2 USA-WA1/2020 strain which had EC50 values of 207 nM and 38 nM in the same cell lines, respectively (**Table 14**). No PGP inhibitor was used in Vero-TMPRSS cells contrary to other variants tested in this cell line. Out of 166 omicron isolates retrieved from GISAID, two mutations have been found in the 3CLpro. The P132H mutation has been found in all omicron isolates thus far and A70S has been found in one omicron isolate, both are located greater than 18 angstroms from the inhibitor. In a biochemical assay with recombinant Mpro expressing P132H, the activity was not reduced compared to the USAWA1/2020 Mpro (ki=0.635 Ki fold change <1).

Table 14. PF-07321332 activity against SARS-CoV-2 variants in HeLa-ACE2 cells and Vero-TMPRSS Cells

SARS-CoV-2	Drug	HeLa-ACE2 Geomean IC_{50} (nM) N=2	Vero -TMPRSS2 Geomean IC_{50} (nM) N=1
USA-WA1/2020	PF-07321332	207	38
	Remdesivir	1596	47
	EIDD-1931	NC	1117
(mouse-adapted) MA-SARS-CoV-2/WA1	PF-07321332	128	17
	Remdesivir	498	16
	EIDD-1931	NC	762
Alpha variant (B.1.1.7)	PF-07321332	118	22
	Remdesivir	612	38
	EIDD-1931	NC	597
Beta variant (B.1.351)	PF-07321332	225	121
	Remdesivir	594	25
	EIDD-1931	NC	2348
Delta variant (B.1.617.2)	PF-07321332	169	73
	Remdesivir	693	14
	EIDD-1931	NC	1810
Omicron variant (B.1.1.529)	PF-07321332	70	23
	Remdesivir	759	19
	EIDD-1931	NC	253

EIDD-1931 is the active metabolite of molnupiravir. NC= Mean not calculated as first experiment did not determine an IC_{50}.
1. Arithmetic means calculated for the HeLa-ACE2 only as Vero-TMPRSS is only N=1.

Viral resistance

PF-07321332 was only evaluated in resistance selection assay against murine hepatitis virus (MHV) infected L929 cells (10 passages). This led to the emergence of P55L and S144A mutations in 3CLpro as well as two lower frequency mutations (Thr129Met, Thr50Lys) in 3CLpro gene (frequency <4.6%).The presence of the substitutions P55L and S144A, was associated with a decrease in PF-07321332 susceptibility with 4.4 to 5-fold increase in mean EC50 values (ranging from 2.65-2.93 µM compared to 0.6 µM for parent MHV in murine L929 cells), **Table 15**. These preliminary results indicate a possible likelihood of resistance development to PF-07321332, however the clinical relevance of these results remains unclear. S144A reduced PF-07321332 susceptibility by 90-fold (based on Ki value) in a biochemical assay.

The applicant confirmed that *In vitro* selection of PF-07321332 resistant SARS-CoV-2 is being evaluated to further substantiate the genetic barrier, which appears limited at this stage. Mutants that can replicate at each passage should be monitored for reduction viral fitness or decrease in susceptibility to the treatment.

Table 15. Antiviral Activity of PF-07321332 against Mutant MHV

MHV Virus and mutants	Mutations	Titer at 48h post-infection (PFU/mL)	Log reduction at 48h post-infection (PFU/mL)	EC_{50} Geomean µM (Range)	EC_{50} Fold-change
Parent Virus	N/A	1.5e+06	N/A	0.60 (0.4-1.0)	1
30XEC50-13	Pro55Leu, Ser144 Ala Thr129Met, Thr50Lys	12500	2 logs	2.93 (2.0-4.5)	4.9
40XEC50-11	Pro55Leu, Ser144 Ala Pro15Ala	25000	2 logs	2.80 (1.6-4.4)	4.7
30XEC50-1	Pro55Leu, Ser144 Ala	125000	1 log	2.63 (1.4-3.9)	4.4
40XEC50-1	Pro55Leu, Ser144 Ala	72500	2 logs	2.65 (1.6-3.8)	4.4

N/A = not applicable

Potency against mutated SARS-COV-2 3CL protease enzymes

The potency of PF-07321332 to inhibits the proteolytic activity of mutant SARS-CoV-2 3CL protease was evaluated using a biochemical assay.

The tested mutants were:

a) The low frequency mutations at key contact residues on SARS-CoV- 2 3CL-Protease. Those with drop in potency are six: E166A (33-fold change), F140A (39-fold change), H164N (6.4-fold change), H172Y (233-fold change), Q189K (65.4- fold change), and Y54A (23.6-fold change).

b) Emerging naturally occurring mutations found in the population; those with drop in potency were A234V, D248E, P108S, T135I, T45I, G15S and the Ki change is less than 5-fold.

c) Mutations emerging from the resistance experiment using MHV surrogate for SARS-CoV-2. Those with drop in potency are S144A and the double mutation S144A and E55L.

The table below summarises results for the 14 mutants that showed a statistically significant drop in potency, with GeoMean Ki values of 1.84 - 217 nM and with a fold change to wild type potency SARS-CoV-2 3CLpro ranging from 2.0 to 233-fold change.

Table 16. Potency of PF-073211332 Against 3CL-Protease Mutations with Significance (P-Value) Compared to Wild Type

Mutant	Potency Shift	Fold Shift in Potency	Ki (nM) GeoMean	Ki (nM) lower 95% CI	Ki (nM) upper 95%	n	p-value[b] to wild type Ki
A70T	More	2.75	<0.339	0.241	0.476	5	0.00721
A234V	Less	2.52	2.35	0.821	6.73	5	0.0286
D248E	Less	3.66	3.41	0.896	13.0	4	0.0158
E166A	Less	33.4	31.2	15.1	64.3	6	2.71E-07
F140A	Less	39.0	36.4	22.4	59.2	6	1.72E-08
G15S	Less	4.36	4.07	2.62	6.32	4	0.000179
H164N	Less	6.41	<5.98	1.95	18.3	8	0.00183
H172Y	Less	233	217	78.0	604	3	1.51E-07
P108S	Less	2.77	2.59	1.76	3.81	4	0.00193
Q189K	Less	65.4	61.0	50.1	74.4	6	2.12E-08
S144A	Less	91.9	85.7	36.9	199	3	6.80E-08
S144A & E55L	Less	101	94.2	23.5	377	3	2.49E-05
T135I	Less	3.46	3.23	0.350	29.7	3	0.0482
T45I	Less	1.97	1.84	1.09	3.10	4	0.0176
Y54A	Less	23.6	22.0	14.2	34.3	4	1.70E-07
Wild Type	N/A	N/A	0.933	0.471	1.85	9[a]	N/A

a. The n values represent the number of Ki values used to determine the geomean and CI which is lower than the experiment count due to censoring, ie experimental values that are < or > are excluded from GeoMean calculation.
b. p-value calculated as a t-test statistic for log Ki values compared to wild type

To evaluate the impact of the above-mentioned mutations i.e G15S, S144A, H164N, E166A, H172Y, Q189K on virus replication fitness as well as on PF-07321332 activity, each mutation was engineered into recombinant SARS-CoV-2. L89F and K90R, were introduced into recombinant viruses as controls, as they had no significant impact on 3CLpro inhibition of PF-07321332 in the enzymatic assay. Generation of recombinant viruses containing Y54A or F140A was not successful, consistent with the possible lethality of these mutations to virus replication.

Of the recombinant mutant viruses tested, Q189K showed reduced virus RNA replication (4-fold than those of the wildtype at 72 hours post-infection), while K90R had increased levels (4-fold than those of the wildtype at 48 and 96 hours post-infection). Recombinants containing L89F, S144A or E166A had similar replicated virus RNA levels to those of the wildtype virus (**Table 17**). Testing is ongoing to evaluate replication fitness of other mutant viruses.

Table 17. Comparison of Virus RNA Levels vs Wild Type at Different Time Points

Time	Mutant Virus	RNA Ratio [a]	95% Lower CI	95% Upper CI	Dunnett p-value [b]
24	L89F	1.09	0.55	2.18	0.9945
	K90R	1.27	0.64	2.54	0.7639
	S144A	0.6	0.3	1.21	0.1877
	E166A	1.24	0.62	2.47	0.8338
	Q189K	1.37	0.69	2.73	0.5664
48	L89F	2.19	0.73	6.55	0.1989
	K90R	4.04	1.35	12.1	0.0121
	S144A	1.16	0.39	3.45	0.9937
	E166A	1.23	0.41	3.66	0.9726
	Q189K	0.55	0.18	1.65	0.4155
72	L89F	1.6	0.45	5.67	0.7314
	K90R	1.23	0.35	4.38	0.9837
	S144A	0.33	0.09	1.17	0.0921
	E166A	0.3	0.08	1.06	0.0622
	Q189 K	0.25	0.07	0.89	0.0314
96	L89F	3.04	0.97	9.53	0.0577
	K90R	4.3	1.37	13.5	0.0121
	S144A	1.32	0.42	4.14	0.9255
	E166A	1.01	0.32	3.18	1
	Q189 K	0.71	0.23	2.22	0.8474

[a] Ratio of Virus RNA over USA-WA1 RNA
[b] Testing of Virus RNA vs Wild-type SARS-CoV-2 (USA-WA1) RNA

Virological data from study C4671005

Viral titres measured via RT-PCR in nasal swabs over time

Participants with samples collected using unvalidated (local) swabs or collected at non-NP sites were excluded from this POC 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, ie, using 1.69 Log10 (copies/mL) for Log10 (viral load) values below 2 Log10 (copies/mL).

Results in the mITT analysis set were also examined by serology status and baseline viral load (**Table 18**). As expected, the additional viral load reduction from PF-07321332/ritonavir treatment relative to placebo were more apparent in participants who were seronegative than participants who were seropositive (-1.230 versus -0.473 log10 copies/mL, p=0.0022), and more apparent in participants with higher versus lower ((≥4 log10 copies/mL versus < 4 log10 copies/mL) viral load at baseline -1.020 versus -0.475 log10 copies/mL, p=0.0109). Compared to results in the overall mITT population, similar findings were observed when viral load over time was analysed by serology status and by baseline viral load. Viral load results at Day 1 and Day 5 (and over time) for the mITT1 and mITT2 analysis set were consistent with the mITT analyses (**Table 19**).

Results should be interpreted with particular caution in terms of magnitude given the descriptive analysis.

Viral load results over time for the mITT2 analysis set were consistent with the mITT analyses.

Table 18. Statistical Analysis of Observed and Change From Baseline in Log10 Transformed Viral Load (copies/mL) Data Over Time - mITT Analysis Set (Protocol C4671005)

		Observed			Change from baseline					Versus Placebo		
Visit	Treatment	n	Mean (SD)	Median (range)	n	Mean (SD)	Median (range)	n1	LS Mean (SE)	95% CI	LS Mean Diff (SE)	95% CI of Diff	p-value
Baseline	PF-07321332 300 mg + Ritonavir 100 mg (N=697)	552	5.984 (2.075)	6.395 (1.700, 9.160)									
	Placebo (N=682)	553	5.868 (2.102)	6.310 (1.700, 9.150)									
Day 3	PF-07321332 300 mg + Ritonavir 100 mg (N=697)	529	4.164 (2.245)	4.490 (0.000, 8.570)	529	-1.821 (1.832)	-1.710 (-7.990, 4.130)	526	-1.880 (0.098)	(-2.072, -1.688)	-0.553 (0.114)	(-0.776, -0.330)	<.0001
	Placebo (N=682)	525	4.668 (2.410)	5.120 (0.000, 9.540)	525	-1.201 (1.755)	-1.230 (-7.920, 5.590)	517	-1.327 (0.100)	(-1.523, -1.132)			
Day 5	PF-07321332 300 mg + Ritonavir 100 mg (N=697)	508	2.804 (1.900)	2.775 (0.000, 7.820)	508	-3.202 (1.752)	-3.115 (-8.420, 3.450)	505	-3.271 (0.096)	(-3.458, -3.083)	-0.868 (0.105)	(-1.074, -0.661)	<.0001
	Placebo (N=682)	507	3.602 (2.330)	3.770 (0.000, 8.700)	507	-2.252 (1.809)	-2.170 (-8.190, 5.100)	499	-2.403 (0.096)	(-2.592, -2.213)			
Day 10	PF-07321332 300 mg + Ritonavir 100 mg (N=697)	502	1.499 (1.638)	1.700 (0.000, 7.340)	502	-4.535 (2.102)	-4.920 (-8.660, 1.360)	499	-4.575 (0.086)	(-4.744, -4.407)	-0.439 (0.099)	(-0.633, -0.245)	<.0001
	Placebo (N=682)	475	1.867 (1.810)	1.700 (0.000, 7.630)	475	-3.978 (2.108)	-4.090 (-8.680, 4.830)	467	-4.136 (0.089)	(-4.310, -3.962)			
Day 14	PF-07321332 300 mg + Ritonavir 100 mg (N=697)	507	0.914 (1.299)	0.000 (0.000, 8.090)	507	-5.098 (2.129)	-5.460 (-8.980, 3.990)	504	-5.141 (0.080)	(-5.298, -4.984)	-0.162 (0.084)	(-0.326, 0.003)	0.0541
	Placebo (N=682)	500	0.990 (1.318)	0.000 (0.000, 6.540)	500	-4.833 (2.106)	-5.135 (-8.730, 3.970)	492	-4.980 (0.081)	(-5.138, -4.821)			

N = number of participants in the analysis set.
n = Number of participants with non-missing data in the analysis set.
n1 = Number of participants with non-missing data in the analysis set and the covariates in the statistical model.
Participants are excluded from the analysis for reasons of Not Detected or Missing baseline viral load result. Results from local swab use are also excluded.
Results are obtained from a Mixed Effects Repeated Measures (MMRM) Analysis of Covariance Model: Treatment, Visit, Visit by Treatment interaction as fixed effects, geographic region, baseline SARS-CoV-2 serology status, baseline viral load score and nasopharyngeal sample site (Y/N) as covariates along with participant as a random effect.

Table 19. Statistical Analysis of Observed and Change From Baseline in Log10 Transformed Viral Load (copies/mL) Data Over Time - mITT1 Analysis Set (Protocol C4671005)

		Observed			Change from baseline						Versus Placebo		
Visit	Treatment	n	Mean (SD)	Median (range)	n	Mean (SD)	Median (range)	n1	LS Mean (SE)	95% CI	LS Mean Diff (SE)	95% CI of Diff	p-value
Baseline	PF-07321332 300 mg + Ritonavir 100 mg (N=1039)	814	5.673 (2.103)	5.980 (1.700, 9.160)									
	Placebo (N=1046)	831	5.529 (2.157)	5.910 (1.700, 9.150)									
Day 3	PF-07321332 300 mg + Ritonavir 100 mg (N=1039)	767	3.910 (2.179)	4.040 (0.000, 8.570)	767	-1.756 (1.743)	-1.700 (-7.990, 4.130)	760	-1.782 (0.077)	(-1.934, -1.631)	-0.468 (0.091)	(-0.647, -0.290)	<.0001
	Placebo (N=1046)	779	4.324 (2.392)	4.670 (0.000, 9.540)	779	-1.193 (1.734)	-1.190 (-8.030, 5.590)	769	-1.314 (0.077)	(-1.466, -1.162)			
Day 5	PF-07321332 300 mg + Ritonavir 100 mg (N=1039)	736	2.703 (1.834)	2.705 (0.000, 7.820)	736	-2.977 (1.778)	-2.935 (-8.420, 3.560)	729	-3.012 (0.076)	(-3.161, -2.863)	-0.695 (0.085)	(-0.861, -0.530)	<.0001
	Placebo (N=1046)	741	3.340 (2.271)	3.160 (0.000, 8.700)	741	-2.166 (1.785)	-2.130 (-8.190, 5.100)	731	-2.317 (0.076)	(-2.465, -2.168)			
Day 10	PF-07321332 300 mg + Ritonavir 100 mg (N=1039)	730	1.436 (1.585)	1.700 (0.000, 7.340)	730	-4.275 (2.104)	-4.440 (-8.660, 1.980)	722	-4.281 (0.067)	(-4.414, -4.149)	-0.351 (0.078)	(-0.503, -0.198)	<.0001
	Placebo (N=1046)	709	1.714 (1.763)	1.700 (0.000, 7.630)	709	-3.768 (2.046)	-3.750 (-8.680, 4.830)	699	-3.931 (0.068)	(-4.064, -3.797)			
Day 14	PF-07321332 300 mg + Ritonavir 100 mg (N=1039)	740	0.871 (1.231)	0.000 (0.000, 8.090)	740	-4.813 (2.144)	-5.130 (-8.980, 3.990)	732	-4.829 (0.063)	(-4.952, -4.706)	-0.168 (0.067)	(-0.299, -0.037)	0.0122
	Placebo (N=1046)	744	0.963 (1.306)	0.000 (0.000, 6.540)	744	-4.515 (2.130)	-4.680 (-9.150, 3.970)	735	-4.661 (0.063)	(-4.784, -4.538)			

N = number of participants in the analysis set.
n = Number of participants with non-missing data in the analysis set.
n1 = Number of participants with non-missing data in the analysis set and the covariates in the statistical model.
Participants are excluded from the analysis for reasons of Not Detected or Missing baseline viral load result. Results from local swab use are also excluded.
Results are obtained from a Mixed Effects Repeated Measures (MMRM) Analysis of Covariance Model: Treatment, Visit, Visit by Treatment interaction as fixed effects, geographic region, symptom onset duration (<=3, >3), baseline SARS-CoV-2 serology status, baseline viral load score and nasopharyngeal sample site (Y/N) as covariates along with participant as a random effect.

Resistance analysis

The applicant submitted viral NGS analysis data from 878 subjects treated in study 005, of whom 371 participants had a matched D1 and D5 sample analysed for TEMs (***Table 20***).

Table 20. Distribution of VOC by Treatment and Treatment Failure

CLADE	PF-07321332 300 mg + Ritonavir 100 mg		Placebo		ALL
	No Treatment Failure	Treatment Failure	No Treatment Failure	Treatment Failure	
20A	0(0%)	0(0%)	0(0%)	1 (0.11%)	1 (0.11%)
20C	1 (0.11%)	0(0%)	2 (0.23%)	0(0%)	3 (0.34%)
20G	1 (0.11%)	0(0%)	0(0%)	0(0%)	1 (0.11%)
20I (Alpha, V1)	1 (0.11%)	0(0%)	0(0%)	0(0%)	1 (0.11%)
20J (Gamma, V3)	2 (0.23%)	0(0%)	1 (0.11%)	0(0%)	3 (0.34%)
21A (Delta)	45 (5.13%)	0(0%)	29 (3.3%)	0(0%)	74 (8.43%)
21G (Lambda)	2 (0.23%)	0(0%)	0(0%)	0(0%)	2 (0.23%)
21H (Mu)	2 (0.23%)	0(0%)	0(0%)	0(0%)	2 (0.23%)
21I (Delta)	70 (7.97%)	0(0%)	61 (6.95%)	9 (1.03%)	140 (15.95%)
21J (Delta)	301 (34.28%)	7 (0.8%)	316 (35.99%)	27 (3.08%)	651 (74.15%)

Note:
880 subjects has Day 1 and/or Day 5 sequencing data available, out of those subjects, only 878 received either placebo or PF-07321332/Ritonavir. Percentages in parentheses were calcualted using a total of 878 subjects. For each subject, CLADE is determined from Day 1 Sample, if Day 1 sample is not available, Day 5 Sample will be used.

Table 21 examines the association between baseline Mpro/3CLpro gene mutations versus those without Mpro/3CLpro mutations.

Table 21. Summary of Association Between Baseline (Day 1) 3CLpro Mutations and Treatment Failure

	PF-07321332 300 mg + Ritonavir 100 mg (N=384)	Placebo (N=385)
3CL^{pro} mutation at baseline, N1 (%)	43 (11.2%)	44 (11.4%)
Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28	0 (0.0%)	2 (4.5%)
No 3CL^{pro} mutation at baseline, N2 (%)	333 (86.7%)	326 (84.7%)
Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28	5 (1.5%)	33 (10.1%)
Comparing Mutation versus No Mutation		
Odds Ratio (95% CI)	NE	0.45 (0.10, 1.96)
p-value	NE	0.2868

N is participants with sequencing data and baseline viral load ≥4 log10 copies/mL.

Odds ratio, 95% CI and p-value are produced by a logistic regression. These actions occur at the various event levels: Events < 10, logistic regression not performed; 10 ≤ events < 30, performed with no covariates; 30 ≤ events < 40, also adj. by baseline viral load and by serology status; 40 ≤ events < 50, also adj. by age; 50 ≤ events < 60, also adj. by gender; 60 ≤ events < 70, also adj. by symptom onset (≤ 3 days, > 3 days); 70 ≤ events < 110, also adj. by received/expected to receive mAbs; Events ≥ 110, also adj. by geographic regions.
Baseline visit is set up according to study days of Day -2 to Day 1. For day 1 records, only results that are within 1 hour post start of dosing will be treated as baseline data.
3CL^{pro} mutations are within the defined regions of 3CL ^{pro} gene, 3CL cleavage or PF-07321332 contact sites.
Mutations identified with a frequency ≥5%.
NE = Not evaluable due to a logistic regression not performed if the number of events < 10 or if there are 0 observations in any outcome category.

Individual mutations within the Mpro/3CLpro gene region and in Mpro/3CLpro target cleavage regions were also monitored. Table 22 shows Mpro/3CLpro gene or cleavage mutations that occurred in more than 2 Paxlovid treated participants by treatment and TF in the 371 participants with Day 1 and Day 5 matched samples.

Table 22. Mpro/3CLpro Contact and Cleavage Treatment Emergent Mutations by Treatment and Treatment Failure in >2 Participants.

Genome Region	NSPPOS	AAREF	AASUB	3CLpro TYPE	PF-07321332 + Ritonavir Treatment Failure (n=3)	Placebo Treatment Failure (n=14)	PF-07321332 + Ritonavir (n=168)	Placebo (n=203)
Mpro/3CLpro	46	S	F		0	0	1	0
			P		0	0	1	0
	107	Q	X		0	0	2	0
	153	D	Y		0	0	2	0
	189	Q	H	Contact	0	0	1	0
			K		1	0	6	7
	190	T	I	Contact	0	0	2	0
			A		0	0	0	1
	222	R	X		0	0	2	0
	260	A	T		0	0	1	0
			V		0	0	3	0
	269	K	I		0	0	1	0
			N		0	0	1	0
			X		0	0	1	0
	270	E	D		0	0	1	0
			V		0	0	1	0
			X		0	0	1	0

Protein	AAPOS	AAREF	AASUB	3CLpro TYPE	PF-07321332 + Ritonavir Treatment Failure (n=3)	Placebo Treatment Failure (n=14)	PF-07321332 + Ritonavir (n=168)	Placebo (n=203)
helicase	5328	A	S	Cleavage	0	0	2	0
3'-to-5'_exonuclease	6449	T	I	Cleavage	0	0	2	0
			P		0	0	1	0
	6451	L	F	Cleavage	0	0	1	0
			H		0	0	1	0
			I		0	0	1	0

Baseline visit is set up according to study days of Day -2 to Day 1. For day 1 records, only results that are within 1 hour post-start of dosing will be treated as baseline data. TEM in this table is defined as a mutation identified at Day 5 among participants with both Baseline and D5 valid sequencing data (samples with viral load ≥2.7 Log10 copies/mL were submitted for sequencing). Mutations identified with a frequency ≥5%.

Associations between TEMs in Mpro/3CLpro gene regions and treatment were also examined statistically (***Table 23***).

The prevalence of TEMs were higher in placebo compared to PF-07321332 /ritonavir-treated participants and additional analysis is ongoing.

Table 23. Summary of Association between Treatment Emergent Mutations with Log10 Viral Load ≥4 and Treatment

	PF-07321332 300 mg + Ritonavir 100 mg (N=168)	Placebo (N=215)
Participants with Any Treatment Emergent Mutation	89 (53.0%)	145 (67.4%)
Odds ratio (95% CI) vs Placebo	0.51 (0.33, 0.79)	
p-value vs Placebo	0.0029	
3CL^{pro} (Nsp5) whole gene region, n (%)	8 (4.8%)	13 (6.0%)
Odds ratio (95% CI) vs Placebo	0.78 (0.31, 1.92)	
p-value vs Placebo	0.5846	
PF-07321332 contact sites within 3CL ^{pro} gene, n (%)	3 (1.8%)	2 (0.9%)
Odds ratio (95% CI) vs Placebo	NE	
p-value vs Placebo	NE	
3CL^{pro} protein cleavage sites within genes that express SARS-CoV-2 proteins, n (%)	4 (2.4%)	4 (1.9%)
Odds ratio (95% CI) vs Placebo	NE	
p-value vs Placebo	NE	
Other regions in the SARS-CoV-2 genome, n (%)	89 (53.0%)	145 (67.4%)
Odds ratio (95% CI) vs Placebo	0.51 (0.33, 0.79)	
p-value vs Placebo	0.0029	

N is participants with sequencing data and baseline viral load ≥4 log10 copies/mL and a valid viral load measurement at Day 5.

Treatment Emergent Mutation in this table is defined as mutation identified at Day 5 among participants with VL ≥4 log10 copies/mL.

Odds ratio, 95% CI and p-value are produced by a logistic regression. These actions occur at the various event levels: Events < 10, logistic regression not performed; 10 ≤ events < 30, performed with no covariates; 30 ≤ events < 40, also adj. by baseline viral load and by serology status; 40 ≤ events < 50, also adj. by age; 50 ≤ events < 60, also adj. by gender; 60 ≤ events < 70, also adj. by symptom onset (≤ 3 days, > 3 days); 70 ≤ events < 110, also adj. by received/expected to receive mAbs; Events ≥ 110, also adj. by geographic regions.

Baseline visit is set up according to study days of Day -2 to Day 1. For day 1 records, only results that are within 1 hour post start of dosing will be treated as baseline data.

3CL^{pro} mutations are within the defined regions of 3CL ^{pro} gene, 3CL cleavage or PF-07321332 contact sites.

Mutations identified with a frequency ≥5%.

NE = Not evaluable due to a logistic regression not performed if the number of events < 10 or if there are 0 observations in any outcome category.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Several oral formulations of PF-07321332 were developed and evaluated during the development programme (oral suspension, uncoated tablet at 250 mg, film coated tablet of 100 mg and 150 mg). Presently only one relative bioavailability study was performed comparing performance of the oral suspension to the uncoated tablet at 250 mg and based on the results from Study 1001 Part 3, the biocomparison between these two formulations clearly indicated that they were different with a 44% decrease on Cmax and 19% decrease on AUClast. However, such results should be interpreted with caution since ritonavir boosted formulations were not compared (for example 250mg/100 mg oral suspension vs 250 mg/100 mg uncoated tablet).

Between uncoated tablet dosed at 250 mg and film coated tablet dosed at 100 (or 150 mg), minor changes are observed in terms of drug loading and presence/absence of coated ingredients. Only dissolution tests were performed 1) between the film-coated tablets dosed at 100 mg and 150 mg, and 2) between site manufacturing of the 150 mg film-coated tablet with for both satisfactory results based on f2. Therefore, at least, an *in vitro* dissolution test comparing the 250 mg uncoated tablet with the film coated tablets should be performed (**REC**).

The applicant proposed to test the formulation effect as a covariate in the future PopPK model development, this is acceptable provided the PK dataset will include all the formulations used during the clinical development programme (oral suspension, 250 mg uncoated tablet, 100 mg and 150 mg film-coated tablets and 150 mg film-coated tablet by manufacturing process). This analysis should be provided as part of the updated PK Pop model.

Following administration of PF-07321332/ritonavir supplied as tablet formulation at 300 mg/100 mg, the mean apparent volume of distribution (Vz/F) in healthy volunteers was 109.4 L. However, in patients the Vz/F was not explored / provided.

Overall, in healthy participants in the fasted state, the arithmetic mean (+SD) terminal elimination half-life ($t_{1/2}$) of PF-07321332, following single dose of 300/100 mg PF-07321332/ ritonavir, was 6.1 (1.8) hours. However, no information regarding $t_{1/2}$ of PF-07321332 in patients could be found. This should be further investigated / confirmed in patients.

Population PK modelling

A preliminary population PK modelling report (PMAR-EQDD-C467a-Proof of Concept-1246) based only on n= 20 healthy adult and the suspension formulation data (study C4671001, cutoff date 30 June 2021) was provided.

In summary, the preliminary Population PK model and model-based simulations (PMAR-EQDD-C467a-Proof of Concept-1246) was not considered valid / reliable. Several issues are raised:

a) The residual error model appears to be mis-specified. In one hand, the additive term, estimated to 339 ng/L, is considered too high (30-fold) compared to lower limit of quantification (10 ng/mL). In the other hand, the proportional error (even low =3.36%) was estimated with very poor precision (RSE% =111%). This questions the validity of the model.

b) To minimise the large additive error (higher than the target IC90% value of 292 ng/mL), the residual errors was excluded in the simulations. This approach is not endorsed as it would imply estimation of PK parameters and associated variabilities necessary different from that in the final model. Therefore, model-based PK predictions should be considered with caution (as issued from a model whose adequacy to the observed data has not been demonstrated).

c) Large discrepancy (more than 2-fold) for the estimation of the terminal half-live T1/2 between the population approach (15h) and the NCA calculations (7h) was observed. This should be justified and its impact on model-based predictions should be further discussed.

d) The model-based PK predictions projected with the tablet formulation are not deemed reliable. In one hand, the Pop-PK model was developed using only the suspension formulation and on the other hand, Cmax of the tablet formulation appears 44% lower than that of the suspension formulation (Please refer to the relative bioavailability part in study 1001).

Only very limited data in healthy volunteers (n=20) are part of the analysed dataset. The lack of PopPK model with all completed data from healthy volunteers and especially more full data from patients in pivotal phase 2/3 studies (very sparse data essentially steady state Ctrough are actually available) was consider critical caveat by the CHMP; it is deemed to better inform the model. Therefore, the applicant should update the model by inclusion of these data. The covariate effects (age, body weight, BMI, ethnicity, renal and hepatic impairment, pharmaceutical formulation, disease) should be explored as part of the work required to update the model. This is important to formally demonstrate the similarity of the PK features of PF-07321332 in patients compared to healthy volunteers and to address clear dosing recommendations for the specific subgroups that currently are not clearly informed (renal impairment, hepatic impairment, elderly, obese and underweighted patients). The update Population PK model should be submitted by 31 March 2022 (**LEG**).

Pharmacokinetics in target population

Preliminary PK data were collected from the ongoing pivotal efficacy and safety Phase 2/3 study (C4671005) in patients with confirmed diagnosis of SARS-CoV-2 infection. Patients received PF-07321332/ritonavir or placebo orally q12h for 5 days (10 doses total). Sparse PK sampling was

performed: A total of 1298 plasma PF-07321332 concentrations, including 1068 evaluable samples and 230 (17.7%) BLQ samples from 601 patients were available for analysis.

The available PK data at day 5 indicated that 140 out of 173 (>80%) patients achieved a Cmin≥ IC90. When excluding the BLQ samples, 140 out of 153 (>90%) patients achieved the target Cmin. Even the observed concentrations from patients appears to be consistent with those in healthy participants (dose-normalised to 300 mg), more rich data in patients are required to allow reliable estimation of the PK parameters of PF-07321332 in the target population. In addition, it is worth noting that a high number of BLQ (17.7% of the dataset) was observed after and beyond the first dose. Such findings are expected to be revisited in the elaboration of the updated popPK model with inclusion of the PK data.

Special populations

Renal and hepatic impairment:

A formal dedicated PK study (C4671011) was performed to investigate the effect renal impairment on the PK of PF-07321332. Participants were graded using the recommended metric creatinine clearance CLCR (absolute GFR expressed as mL/min). Overall, the applicant propose that no dose adjustment is needed in mild renal impairment. Besides, the dose of PF-07321332 should be reduced by one-half: PF-07321332/ritonavir 150 mg/100 mg BID. These dosing recommendations in these two subgroups are agreed.

In severe renal impaired subjects, an increase of AUC by 204% was observed compared to the normal renal group. In addition, no appropriate dosing recommendations in this subgroup are currently proposed. Thus, based on the significant 3-fold increase on the systemic exposure of PF-07321332 in patients with severe renal impairment (eGFR <30 mL/min), including ERSD (end-stage renal disease) haemodialysis patients, it is recommended, from a PK perspective, to not use the drug product in this subgroup of patients. This is reflected accordingly in the SmPC, as an explicit warning, to discourage the use at this stage, pending further investigations notably based on update of popPK model.

A formal study (1010) investigating the effect of moderate hepatic impairment on the PK of PF-07321332, in comparison to matched healthy subjects with normal hepatic function, was performed.

The study is still ongoing and only a preliminary PK report is provided.

No dose adjustment for patients with mild or moderate hepatic impairment is proposed by the applicant. Provided that PK data/conclusion is confirmed in, the proposed dosing recommendations in patients with mild and moderate hepatic impairment could be agreed. The final clinical study report for C4671010 should be provided (**REC**).

At this time, no clinical / PK data are available for patients with severe hepatic impairment. Pending availability of clinical (efficacy/safety) data and an appropriate dosing recommendation with PF-07321332 in this subgroup of patients, it is recommended, from a PK perspective, to not use the drug product in patients with severe hepatic impairment. This is reflected accordingly in the SmPC, as an explicit warning, to discourage the use at this stage, pending further investigations notably based on the update of PopPK model.

It is noteworthy that during the Art 5.3 (December 2021), the CHMP recommended as a very conservative measure a contraindication for the severe hepatic impairment and for the severe renal impairment. However, given that a larger safety database from the final analysis of the unique C4671005 clinical study (around 1000 patients treated) with no major safety concern identified (which is in line with the lack of the target organs identified from the non-clinical data) and given that rather than evidence of harm, there is a lack of data to inform on a posology in patients with severe renal impairment and severe hepatic impairment, the CHMP concluded to remove the contraindication while including warnings. The CHMP has elaborated explicit warnings to alert healthcare professionals that no

dose recommendation could be established and that further investigations were ongoing (having in mind the forthcoming update of PKPD).

Gender:

The provided investigations regarding a potential gender effect on the PKs of PF-07321332 are not considered conclusive or informative as the validity of the Population model is not proven. The effect will be investigated as part of the update PopPK model.

Race / Ethnicity:

Race effect on PF-07321332/ritonavir PK has been investigated as part of Study 1001 in only 4 Japanese healthy volunteers. AUCtau and Cmax values were approximately 30% and 21-26%, respectively, lower in Japanese participants compared to Caucasian subjects. Drug accumulation was similar in Japanese compared to Caucasian subjects (~2).

PTR (Peak to through ratio) was 6.27 therefore with an observed geometric mean Cmax of 3772 ng/mL which consequently leads to a geometric mean Cmin of 601 ng/mL (only twice the EC90 target). Importantly, cautions should be taken with this result since only 4 subjects were included in the analysis. These preliminary results will be confirmed by using the awaited update PopPK analysis.

Body weight:

Overall, the provided investigations regarding a potential body weight effect on the PKs of PF-07321332 are not considered conclusive or informative. Therefore, the PKs of PF-07321332 in the obese and underweighted patients is not considered as clearly elucidated and the updated popPK model is expected to this purpose.

Elderly:

Overall, the PKs of PF-07321332 in elderly patients could not be considered elucidated yet and additional analyses are requested to allow a better understanding of the age effect in this subgroup. Again, the update PopPK model is expected to this purpose.

Children and adolescents

The safety and efficacy of PF-07321332 in children and adolescents below the age of 18 years have not yet been established.

No PK data are available. Thus, the PKs of PF-07321332 in adolescent patients <18 years is not considered elucidated yet.

For the current CMA under assessment, the applicant claimed that adolescent patients > 40 kg could be treated with Paxlovid with the same dose as adults, 300/100 mg PF-07321332/ritonavir BID.

According to the applicant, this dose is justified based on Population PK simulations; however, this extrapolation is based on PK data in healthy volunteers, which the CHMP considered as not adequate. As per the simulated data, it is expected that a PF-07321332/ritonavir 300 mg/100 mg BID dose in adolescents (i.e., ≥12 to < 18 years of age) will provide comparable exposures in adults receiving the same dose and maintained PF-07321332 plasma concentration above EC90 over the entire dosing interval suggestive of a therapeutic response. However, such conclusion is not endorsed from a PK perspective. The preliminary Population PK model used to simulate exposures in adolescent patients is not considered valid/ reliable; and therefore, no valid conclusion could be drawn the model-based simulations. Together with the lack of PK data (PK of PF-07321332 not characterised in adolescents) and clinical data (efficacy and safety) in the target adolescent population, this issue regarding dose selection is considered of a major concern. Consequently, the applicant withdrew the adolescent patient population from the indication.

Interactions

Based on *in vitro* studies, and given the calculated R values being below or just above the 2012 EMA guidance cut-off criteria for MATE1 respectively, the potential for PF-07321332 to cause clinically significant DDI based on inhibition of MATE1 only would be low, but interactions with OCT1, and OATP1B1 *in vivo* could not be excluded. The applicant has committed to perform a PBPK model exercise with commercial software (SimCYP) utilising compound files for metformin and rosuvastatin. The PBPK modelling robustness should be demonstrated and high level of qualification of the model should be provided (multiple substrates, multiple perpetrators, based on *in vivo* results), to waive the need for a clinical DDI study. Otherwise clinical studies to document the magnitude of interactions of these widely prescribed drugs are needed, especially for metformin. If possible, careful attention to patient co-medicated with metformin should be brought in the on-going studies. (**REC**).

Due to both inhibition, and induction effect of Paxlovid, as co-packed combination of PF-07321332 and ritonavir, on CYP3A4 and P-gp, the net effect of Paxlovid on CYP3A4 and P-gp drug substrates needs to be assessed *in vivo*.

Given the high-risk targeted population (including notably old patients, patients with cardiovascular disease), additional DDI studies with amiodarone and clozapine notably as victim drugs and critical in this population, should have been performed. These studies could allow these patients, for whom treatment cessation could not be clinically easily handled, to benefit from Paxlovid treatments. The applicant should improve the characterisation of the DDI profile post-authorisation.

Drug-drug interactions are being assessed in studies 1013 with midazolam, and study 1012 with dabigatran. According to preliminary study results of the DDI study conducted with midazolam, midazolam exposure (AUCinf) was increased by 14.3-fold and Cmax increased by 3.86 fold in co-administration with PF-07321332/ ritonavir 300/100 mg. The full CSR for 1013 and the clinical DDI study with dabigatran should be provided (**REC**).

Taking the relatively short duration of treatment with Paxlovid into account (5 days), it is acknowledged that the current proposal for section 4.5 of the SmPC based on the interactions derived from ritonavir use in HIV treatment may be too restrictive. Nevertheless, in the absence of dedicated studies, more refined and therefore relevant recommendations can currently not be provided. The applicant should improve the characterisation of the DDI profile post-authorisation with the objective of enlarging patient population eligible to Paxlovid. Having in mind this issue, the CHMP has addressed a letter to several Healthcare Professionals organisation to raise awareness about the DDI with Paxlovid.

Pharmacodynamics

PF-PF-07321332 is an orally bioavailable 3CLpro (3C-like protease) peptidomimetic inhibitor shown to be active against SARS-CoV-2 3CLpro (EC50=61.8 nM, in dNHBE cells). The *in vitro* data supports the selectivity of PF-07321332 for SARS-CoV-2 3CLpro with low or no measurable cytotoxicity in mammalian cells.

PF-07321332 demonstrated antiviral activity against the alpha, beta, lambda, gamma, delta, mu and omicron variants with EC50 values ranging between 59.5-171 nM in a cell-based assay similar to EC50 values of the control agent remdesivir with however a moderate decrease in PF-07321332 susceptibility against the beta variant (4-fold increase in EC50 $p<0.05$). PF-07321332 showed *in vitro* antiviral activity against the Omicron variant with EC50 values of 70 nM and 23 nM in the HeLa-ACE2 and Vero-TMPRSS cells, compared to the SARS-CoV-2 USA-WA1/2020 strain which had EC50 values of 207 nM and 38 nM in the same cell lines, respectively.

PF-07321332 was only evaluated in resistance selection assay against MHV infected L929 cells (10 passages). *In vitro* selection of PF-07321332 resistant SARS-CoV-2 should be provided. It is

recommended as well to conduct the assay against variants currently circulating (mainly Omicron and Delta) (**REC**).

In phenotypic assessments for naturally occurring (based on public data) Mpro/3CLpro mutations, reduced PF-07321332 activity (≥3-fold higher Ki values) was identified for the following substitutions: G15S (4.4-fold), T135I (3.5-fold), S144A (91.9-fold), H164N (6.4-fold), H172Y (233-fold), Q189K (65.4-fold), and D248E (3.7-fold). The clinical impact of these polymorphisms is unknown. Additional biochemical analysis in non-naturally occurring mutations showed higher Ki values for the following: Y54A (23.6-fold), F140A (39.0-fold), and E166A (33.4-fold). Cell based PF-07321332 antiviral activity against all the mutant viruses should be performed (**REC**).

It is agreed that there is a low probability that events of TF in the Paxlovid arm of study C46710053CL which all occurred in patients infected with the Delta (21J) subvariant are due to a lack of effectiveness against this clade. The applicant clarified that Mpro retrieved from consensus genome sequence for these 7 events are all identical to reference sequence and the allele frequency of minor variants found on Mpro are less than 5.05%. Phenotypic analysis to determine the impact of these specific mutations on potency and cell based antiviral activity are to be performed (**REC**).

Individual mutations within the Mpro/3CLpro gene region and target cleavage regions were also monitored among participants who had a matched D1 and D5 sample analysed for TEMs in study C4671005. A260T substitution emerged in one Paxlovid subject and the A260V substitution emerged in 3 other subjects; neither emerged in any placebo subjects. A260T/V could be a possible Paxlovid TEM. Nevertheless, the potential impact of either substitution on resistance is unclear as no TF occurred in any of these patients. In a biochemical assay with recombinant Mpro expressing A260V, no reduction in PF-07321332 susceptibility was observed. This is also the case for the Mpro D153Y, Q107X and cleavage site T6449I substitutions that emerged in 2 Paxlovid treated subjects each and TF occurred in any of these patients. Mutations should continue to be monitored for possible clinical evidence of treatment resistance and the full planned genotyping and phenotyping analyses at baseline and in treatment failure from the pivotal study 1005 should be provided (**REC**).

The Mpro Q189K substitution emerged in 5 Paxlovid and 7 placebo treated subjects. It is thus unclear if Q189K could be considered a TEM. In addition, genomic position 189 is located in an AT rich region and probability of sequencing artefacts are high; nevertheless, this position should also continue to be monitored closely for possible clinical evidence of Paxlovid resistance. One case of TF was observed in Paxlovid treated subjects and the mutation has shown a drop in potency by biochemical assay (65-fold change).

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics and pharmacodynamics of Paxlovid have been described in support of the use in the target population in the context of a conditional marketing authorisation to be used under emergency situations and a particular medical need. The CHMP considers the following measures necessary to address the clinical pharmacology issues:

a) The PopPK model results including PK data collected from the patients enrolled in the EPIC-HR study with relevant covariables and relevant update to the exposure margins should be provided by 31 March 2022

Clinical pharmacology recommendations and legally binding measures are covered in the list of post-authorisation measures in Annex I.

2.6.5. Clinical efficacy

The clinical development is based on the single pivotal Phase 2/3 C4671005 study conducted in non-hospitalised, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illnesses.

Of note, two other Phase 2/3 clinical studies are conducted, but are not part of this procedure: (i) in non-hospitalised symptomatic adult participants with COVID 19 who are at standard risk of progressing to severe illness (Study C4671002), and (ii) the second as a post-exposure prophylaxis regimen (i.e., close contacts of patients with positive COVID-19) (Study C4671006).

Table 24. Overview of key efficacy data submitted

Study id and design / reference	**Key objectives / endpoints**	**Population**	**Inclusion/ exclusion criteria**	**Treatment**	**Main efficacy results**
Therapeutic indication					
Study 1005	Primary objective: • To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in non-hospitalised symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease. Primary endpoint: • Proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28.	Non-hospitalised, symptomatic adult participants with COVID-19, who were at increased risk of progressing to severe illness (including n = 1361)	Main inclusion criteria: • Confirmed SARS-CoV-2 infection as determined by RT-PCR (other molecular or antigen tests) within 5 days prior randomisation • Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior randomisation • Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 : diabetes, overweight (BMI > 25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease,	• 300/100 mg PF-07321332/ritonavir administered orally q12h for 5 days • placebo administered orally q12h for 5 days	• mITT: A 6.32% (95% CI: -9.041% to -3.593%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 7.093% to 0.776%, with PF-07321332/ritonavir in comparison with placebo treatment. • mITT-1: A 5.765% (95% CI: -7.917% to -3.613%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 6.764% to 0.999%, with PF-07321332/ritonavir in comparison with placebo treatment.

			hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically related technological dependence, or were 60 years of age and older regardless of comorbidities Main exclusion criteria: • History of hospitalisation for the medical treatment of COVID-19 • Current need for hospitalisation or anticipated need for hospitalisation within 48 hours after randomisation • Prior to current disease episode, any confirmed SARS-CoV-2 infection • Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit. • Oxygen saturation of <92%		

2.6.5.1. Dose response study

No dose response study was conducted. The dose selection for the pivotal study was based on relevant available preclinical and clinical data, including repeat-dose toxicology studies, clinical safety, and PK data from the Phase 1 study (C4671001), and *in vitro* pharmacology studies with PF-07321332 (refer PK and pharmacology sections).

2.6.5.2. Main study

A single pivotal trial (C4671005 or EPIC-HR) provides data for the evaluation of efficacy. This is a phase 2/3, randomised, double-blind, placebo-controlled study.

In December 2021, the EMA issued advice on use of Paxlovid for treating COVID-19 based on the interim analysis in an Article 5(3) procedure. The results of a planned interim analysis that was conducted after approximately 45% of participants in the mITT analysis set completed Day 28 assessments and included participants randomised through 29 September 2021 (data cut-off 26 October 2021).

While the Art 5.3 was based on the primary interim analysis on the basis of which the DSMB recommended to stop the enrolment of the patient, the assessment of the marketing authorisation application is also based on the supportive final analysis; it presents the results of the primary analysis of all enrolled participants who completed the Day 34 visit.

The planned 24-weeks follow-up has not been completed yet. Those data will be provided when the 24-weeks follow-up will be completed.

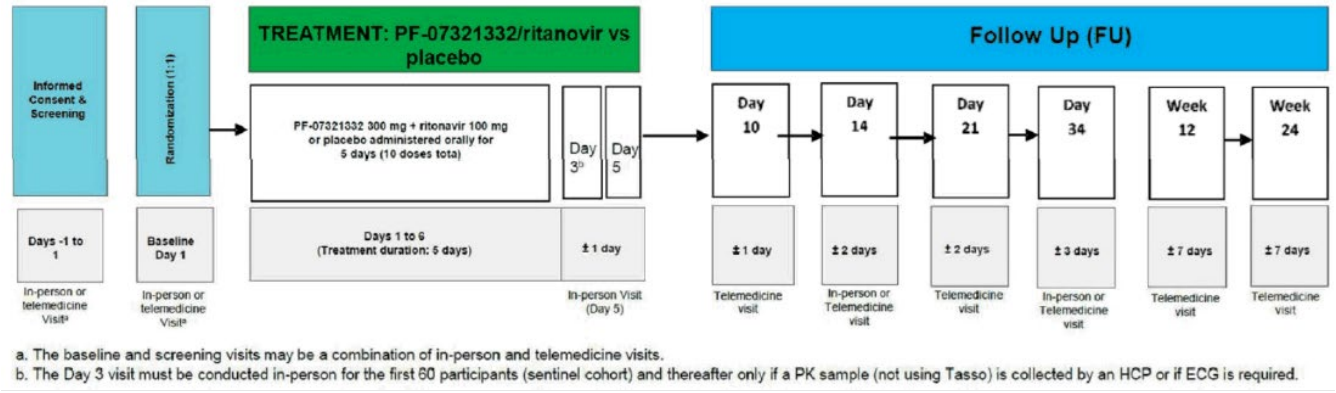
Study C4671005

Methods

This Phase 2/3, randomised, double-blind, placebo-controlled study in non-hospitalised, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness will determine the efficacy, safety, and tolerability of PF-07321332/ritonavir compared with placebo in a 1:1 ratio.

Participants were screened within 48 hours of randomisation. Eligible participants have received PF-07321332 plus ritonavir or placebo orally q12h for 5 days (10 doses total). The total study duration is up to 24 weeks, study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow-up at Weeks 12 and 24.

Figure 14. Schema of the study



a. The baseline and screening visits may be a combination of in-person and telemedicine visits.
b. The Day 3 visit must be conducted in-person for the first 60 participants (sentinel cohort) and thereafter only if a PK sample (not using Tasso) is collected by an HCP or if ECG is required.

- **Study Participants**

Key inclusion Criteria

Participants are eligible to be included in the study were male and female aged ≥18 years with:

Type of Participant and Disease Characteristics

- Confirmed SARS-CoV-2 infection as determined by RT-PCR in any specimen collected within 5 days prior to randomisation. RT-PCR was the preferred method; however, with evolving approaches to confirmation of SARS-CoV-2 infection, other molecular or antigen tests that detect viral RNA or protein were allowed. Participants may be enrolled based on positive results of a rapid SARSCoV-2 antigen test performed at screening.

- Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of randomisation and at least 1 of the specified signs/symptoms attributable to COVID-19 present on the day of randomisation:

  Cough, Shortness of breath or difficulty breathing, Fever (>38°C), Chills or shivering, Fatigue, Muscle or body aches, Diarrhoea, Nausea, Vomiting, Headache, Sore throat, Stuffy or runny nose.

- Has at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 including:
  - ≥60 years of age;
  - BMI >25;
  - Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes;
  - Immunosuppressive disease (e.g., bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications:
    - Has received corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days within 30 days prior to study entry.
    - Has received treatment with biologics (e.g., infliximab, ustekinumab), immunomodulators (e.g., methotrexate, 6MP, azathioprine) or cancer chemotherapy within 90 days prior to study entry.
    - HIV infection with CD4 cell count <200 mm3 and a viral load less than400 copies/mL
  - Chronic lung disease (if asthma, requires daily prescribed therapy);
  - Known diagnosis of hypertension;
  - CVD, defined as history of any of the following: myocardial infarction, stroke, TIA, HF, angina with prescribed nitroglycerin, CABG, PCI, carotid endarterectomy, and aortic bypass;
  - Type 1 or Type 2 diabetes mellitus;
  - CKD provided the participant does not meet Exclusion Criterion 5;
  - Sickle cell disease;
  - Neurodevelopmental disorders (e.g., cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies);
  - Active cancer, other than localised skin cancer, including those requiring treatment as long as the treatment is not among the prohibited medications that must be administered/continued during the trial period;
  - Medical-related technological dependence (e.g., CPAP [not related to COVID-19]).

Key exclusion Criteria

Main exclusion criteria were:

Medical Conditions

- History of hospitalisation for the medical treatment of COVID-19.

- Current need for hospitalisation or anticipated need for hospitalisation within 48 hours after randomisation in the clinical opinion of the site investigator.
- Prior to current disease episode, any confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any specimen collection.
- Known medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child-Pugh Class B or C, or acute liver failure.
- Receiving dialysis or have known moderate to severe renal impairment.
- Known HIV infection with a viral load greater than 400 copies/mL or taking prohibited medications for HIV treatment (from known medical history within past 6 months of the screening visit).
- Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere with the evaluation of response to the study intervention.
- Any comorbidity requiring hospitalisation and/or surgery within 7 days prior to study entry, or that is considered life threatening within 30 days prior to study entry, as determined by the investigator.

Diagnostic Assessments

- Oxygen saturation of <92% on room air obtained at rest within 24 hours prior to randomisation.

Prior/Concomitant Therapy

- Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment and for 4 days after the last dose of PF-07321332/ritonavir.
- Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of PF-07321332/ritonavir and during study treatment.
- Has received or is expected to receive convalescent COVID-19 plasma.
- Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit.

As a note, throughout the study period, provision was made to allow study visits to be conducted at a participant's home or at another non-clinic location approved by the investigator where possible when participants are unwilling or unable to attend a clinic visit.

- **Treatments**

The dosing instruction were:

- 2 tablets of PF-07321332 150 mg (or 3 tablets of 100 mg for some participants in the sentinel cohort) or placebo for PF-07321332 q12h
- 1 capsule of ritonavir 100 mg or placebo for ritonavir q12h.

The treatment was administered for 5 days (10 doses in total).

- **Objectives and outcomes/endpoints**

The primary objective and endpoint were:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	The difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease, who did not receive COVID-19 therapeutic mAb treatment and were treated ≤3 days after COVID-19 symptom onset. This will be estimated without regard to adherence to randomized treatment.

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

Hospitalisation was defined as >24 hours of acute care, in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic. This included specialised acute medical care unit within an assisted living facility or nursing home. This did not include hospitalisation for the purposes of public health and/or clinical trial execution.

The analysis was conducted in the modified intent-to-treat (mITT) analysis set [all treated subjects with onset of symptoms ≤3 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody (mAb) treatment], the mITT1 analysis set (all treated subjects with onset of symptoms ≤ 5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), and the complementary population of analysis represented in mITT2 comprised all treated subjects with onset of symptoms ≤5 days).

Of note the CHMP has considered that the mITT1 was of particular relevance since in line with the SmPC recommendation of posology. Consequently, the results of this population of analysis were to be highlighted in a dedicated table in the section 5.1 of the SmPC while the results from the primary population of analysis (mITT) and the complementary one (mITT2) were to be covered through corresponding statements.

The secondary objectives and endpoints were as follows:

Secondary:	**Secondary:**	**Secondary:**
• To describe the safety and tolerability of PF-07321332/ritonavir relative to placebo in the treatment of nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Incidence of TEAEs. • Incidence of SAEs and AEs leading to discontinuations.	Not applicable.
• To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28	The difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with symptomatic COVID-19 who are at increased risk of progression to severe
		disease and who did not receive COVID-19 therapeutic mAb treatment. This will be estimated without regard to adherence to randomized treatment.
• To compare PF-07321332/ritonavir to placebo for the duration and severity of signs and symptoms in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Time (days) to sustained alleviation of all targeted signs/symptoms through Day 28. • Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28. • Time (days) to sustained resolution of all targeted signs/symptoms through Day 28. • Duration of each targeted COVID-19 sign/symptom. • Progression to a worsening status in 1 or more self-reported COVID-19-associated symptoms through Day 28. • Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.	The absolute difference in median time to sustained alleviation or resolution of symptoms for all nonhospitalized adult patients with COVID-19 who are at increased risk of progression to severe disease. This will be estimated irrespective of adherence to randomized treatment.
• To compare PF-07321332/ritonavir to placebo for all-cause mortality in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with death (all cause) through Week 24.	• Not applicable.
• To determine the PK of PF-07321332 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• PF-07321332 PK in plasma and whole blood (if feasible).	• Not applicable
• To describe the viral load in nasal samples over time in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Viral titers measured via RT-PCR in nasal swabs over time.	• Not applicable.
• To compare PF-07321332/ritonavir to placebo for COVID-19-related medical visits in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Number of COVID-19 related medical visits through Day 28.	• Not applicable
• To compare PF-07321332/ritonavir to placebo for COVID-19-related hospitalizations in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Number of days in hospital and ICU stay in participants with COVID-19 related hospitalization.	• Not applicable.

In terms of efficacy, only the Proportion of participants with COVID-19-related hospitalisation or death from any cause through Day 28, with the different estimands, and the Viral titres measured via RT-PCR in nasal swabs over time have been analysed at the interim analysis, as planned in the protocol.

- **Sample size**

This study was designed to have 90% statistical power to show a difference of 3.5% in the proportion of participants hospitalised/dying who did not receive COVID-19 therapeutic mAb between the treatment arms (PF07321332/ritonavir versus placebo) and were treated ≤3 days after COVID-19 symptom onset, using a 2-sided Type I error rate of 5%. The proportion of hospitalisation/death in the placebo arm was assumed to be 7%.

The sample size needed to detect a 3.5% difference with 90% power at a 2-sided significance level of 5% was determined to be 1717 randomised participants. Enrolment of participants who at baseline had received or were expected to receive COVID-19 therapeutic mAb treatment was estimated to be approximately 20% of participants and limited/capped to 25% enrolment. Enrolment of participants that had COVID-19 symptom onset >3 days prior to randomisation was expected to be approximately 25% and was to be limited to approximately 1000 participants. Assuming a 5% dropout rate, the total sample size for this study was to be approximately 3100 participants.

To allow for a 5% dropout rate, enrolment was to be stopped after approximately 1870 participants had been enrolled to ensure at least 1779 participants were available for the primary analysis.

- **Randomisation and blinding (masking)**

Eligible participants with a confirmed diagnosis of SARS-CoV-2 infection were randomised (1:1) to receive PF-07321332 and ritonavir or placebo orally q12h for 5 days (10 doses total).

Randomisation was stratified by geographic region and by whether participants had received/were expected to receive treatment with COVID-19 therapeutic mAbs (yes/no) based on the site investigator's assessment at time of randomisation.

Randomisation for the strata where participants had received or were expected to receive COVID-19 therapeutic mAb treatment was to be capped at a maximum of 25% enrolment.

This is a double-blind study. The majority of sponsor staff were blinded to study intervention allocation. There was an unblinded team supporting the interactions with, and the analyses for, the E-DMC while the study was on-going. The team consisted of medical monitor/clinicians, reporting statistician and reporting programmer(s) and was separate from the direct members of the study team. After all participants completed the Day 34 visit (or Early Termination (ET) prior to Day 34 visit), the study was to be unblinded and analyses through Day 34, including the primary efficacy endpoint analyses, was to be conducted. However, a blinded study team is to manage the completion of the study until all participants had completed the Week 24 visit (or ET prior to the Week 24 visit). The blinded team was to be separate from the unblinded team.

- **Statistical methods**

<u>Interim analysis</u>

A planned IA for efficacy and futility with a potential sample size-re-estimation was conducted and reviewed by an independent E-DMC after approximately 45% overall participants had completed the Day 28 assessments in the mITT analysis set (i.e., 28 days after randomisation).

A second IA for efficacy and futility was planned after approximately 70% of participants in the mITT analysis set completed the Day 28 assessments (i.e., 28 days after randomisation).

Subsequent to the planned interim analyses, there were 2 analyses planned for reporting the results of this study. The primary analysis was to be performed after all participants had completed the Day 34 visit. The follow-up analysis was to be performed after all participants had completed the Week 24 visit.

The nominal significance level for the 2 planned interim and final proportion of hospitalisation/death analyses was determined by means of the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary. Further details are provided in the statistical methods section under multiplicity adjustment procedures.

Changes after interim analysis results

Following the availability of the first interim analysis results, the protocol was amended (Amendment 4, 20 November 2021) to remove the second interim analysis as the planned interim analysis objective was achieved. The sample size was also updated from 3100 to approximately 3000 participants due to the removal of the second interim analysis.

Analysis populations for the interim analysis

The efficacy analysis sets are described in the table below.

Analysis set	**Description**
Modified Intent-To-Treat (mITT)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28 visit, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 onset. Participants will be analysed according to the study intervention to which they were randomised.
Modified Intent-To-Treat 1 (mITT1)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28 visit and who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment. Participants will be analysed according to the study intervention to which they were randomised.
Modified Intent-To-Treat 2 (mITT2)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, and with at least 1 post-baseline visit through Day 28. Participants will be analysed according to the study intervention to which they were randomised.

Other analysis sets were used for disposition, baseline or safety summaries.

Full Analysis Set (FAS): All participants randomly assigned to study intervention regardless of whether or not study intervention was administered.

Safety Analysis Set (SAS): All participants who receive at least 1 dose of study intervention. Participants were analysed according to the intervention they actually received.

Analysis populations for the final analysis

The mITT, mITT1 and mITT2 populations were updated as part of SAP version 1.4 for the final analysis (no longer requiring at least 1 post-baseline visit through Day 28 visit), following an FDA request.

Analysis set	Description
Modified Intent-To-Treat (mITT)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 onset. Participants will be analysed according to the study intervention to which they were randomised.
Modified Intent-To-Treat 1 (mITT1)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, and who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment. Participants will be analysed according to the study intervention to which they were randomised.
Modified Intent-To-Treat 2 (mITT2)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention. Participants will be analysed according to the study intervention to which they were randomised.

The definitions for the FAS and the SAS remained the same.

A **Per Protocol** set was also defined for the final analysis: All participants in the mITT set without important protocol deviations considered to impact the interpretation of the primary efficacy endpoint.

Hypothesis testing and multiplicity adjustment

The primary hypothesis to be tested was whether or not there is a difference in proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28 between PF-7321332/ ritonavir and placebo. The statistical hypothesis was as follows:

$$\text{Ho: } \pi_{\text{PF-7321332}} - \pi_{\text{placebo}} = 0$$

versus

$$\text{Ha: } \pi_{\text{PF-7321332}} - \pi_{\text{placebo}} \neq 0$$

Where $p_{PF\text{-}7321332}$ and $p_{placebo}$ are the proportions of participants with hospitalisation or death through Day 28. The hypotheses will be tested at an overall significant level of 5% (2-sided).

Following the positive test of the primary endpoint, sequential testing was to be performed for the following 2 secondary endpoints:

1. Proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28 who did not receive COVID-19 therapeutic mAb treatment, regardless of their onset of COVID-19 related signs and symptoms.
2. Time (days) to sustained alleviation of all targeted signs/symptoms through Day 28.

Other secondary endpoints listed below were to be subsequently tested following the Hochberg procedure:

a) Time (days) to sustained resolution of all targeted signs/symptoms through Day 28.

b) Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.

c) Number of COVID-19 related medical visits through Day 28.

The nominal significance level for the 2 planned interim and final proportion of hospitalisation/death analyses was determined by means of the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary, with an overall 2-sided type I error rate of 5%. For the first IA (45%), O'Brien-Fleming

approach was used for decision making, i.e., reject H0 with 2-sided p-value ≤0.002, or reject H1 with 2-sided p-value >0.9184. The actual stopping boundaries depended on the exact timing of the IA.

For the second IA (70%), O'Brien-Fleming approach was to be used for decision making, ie, reject H0 with 2-sided p-value ≤0.014, or reject H1 with 2-sided p-value >0.337. The actual stopping boundaries were to depend on the available percentage of information.

A sample size re-estimation was to be conducted during the first interim analysis based on conditional power. The sample size could have been adjusted one time and the increase was to be capped at 30%. The Cui, Hung, and Wang (1999) method would be used to control the Type I error probability.

Primary endpoint

The cumulative proportion of participants who experienced a COVID-19-related hospitalisation or death due to any cause during the first 28 days of the study was estimated for each treatment group of the mITT analysis set using the Kaplan-Meier method to consider losses to follow-up and patients who discontinued early.

The estimand was the difference of the proportions in the 2 treatment groups and its 95% confidence interval was presented, as well as, the associated two-sample proportion test. For the 95% CI, the corresponding estimate of the standard error was computed using Greenwood's formula (Kalbfleisch and Prentice; 1980). The Greenwood's formula to estimate the variance of the difference of proportions at Day 28 is sqrt[Var(S_{PF}(28))+Var($S_{Placebo}$(28))]. Instead of dealing with S(t_i) the log-log approach to CI was used. The 95% CI was computed for the estimate of L(t)= log(-log(S(t))), the hazard function.

$$Var(\hat{L}(t)) = Var\left[log\left(-log\left(\hat{S}(t)\right)\right)\right]$$

The CI will be in right range when transforming back to S(t) = exp (-exp (L(t)). Antilogging this confidence interval gives a 95% confidence interval for the difference itself.

The above primary analysis was to be conducted for the 2 planned interim analyses as well. Two-sided 95% CI (adjusted for the 2 planned interim analyses) and associated p-value (two-sample proportion test) for the null hypothesis of no difference between treatment groups were to be presented. Significance level was to be determined using the O'Brien-Fleming approach at the interim analysis and the final analysis. The overall significance level was set at 5% (2 sided).

For participants who completed Day 28 efficacy assessment (Day 34 visit), they were censored at their last visits. For participants who discontinued before Day 28 assessment or are lost to follow-up, they were censored at the last known date in the study.

Participants were analysed under the mAb stratum assigned at randomisation/baseline.

The proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28 were summarised.

Sensitivity analyses of the primary endpoint

A sensitivity analysis of the primary endpoint was performed using the mITT2 analysis set.

Two additional sensitivity analyses were performed: 1) excluding all data from Indian sites and additional participants from a non-compliant US site. 2) excluding participants from the sentinel cohort of the study treated with active treatment (3 doses of 100 mg).

A post-hoc sensitivity analysis was performed using the mITT analysis set whereby participants that did not have follow-up data through Day 21 were hypothetically assumed to experience both COVID-19-related hospitalisation and death in a worst-case scenario.

Secondary endpoints

Proportion of participants with COVID-19 related hospitalisation or death due to any cause through Day 28 in the mITT1 analysis set

The analysis of the proportion of participants with COVID-19 related hospitalisation or death due to any cause through Day 28 in the mITT1 analysis set was similar to the primary endpoint analysis.

Time (days) to Sustained Alleviation and Time to Resolution of Targeted COVID-19 Sign/Symptoms through Day 28

The time (days) to sustained alleviation and time to resolution were defined for all targeted COVID-19 associated symptoms based on self-assessment.

Sustained alleviation of all targeted COVID-19 signs/symptoms was defined as the event occurring on the first of 4 consecutive days when all symptoms scored as moderate or severe at study entry are scored as mild or absent AND all symptoms scored mild or absent at study entry are scored as absent. The first day of the 4 consecutive-day period is considered the First Event Date.

Sustained resolution is defined as when all targeted symptoms are scored as absent for 4 consecutive days. The first day of the 4 consecutive-day period is considered the First Event Date.

For symptoms with no reported severity in baseline, the symptom was to be absent in order to be counted as sustained alleviated/resolved (missing severity at baseline were treated as mild).

Day 25 is the last possible day the symptom alleviation and resolution endpoints can be achieved (definition includes data from the subsequent three days) and Day 28 is the last day participants report their daily signs and symptoms.

The time to sustained symptom alleviation/resolution for the purpose of this study is defined as:

- For a participant with sustained symptom alleviation/resolution (event), time to event is calculated as (First Event Date) – (First Dose Date) +1.
- For a participant that either completes Day 28 of the study or discontinues from the study before Day 28 without sustained symptom alleviation/resolution (censored), censoring date is at the last date on which symptom alleviation/resolution is assessed, and time is calculated as (Censoring Date) – (First Dose Date) +1 or Day 25 whichever occurs first.

The decision to require 4 consecutive days with all targeted symptoms absent was based on exploratory analyses of data from the ACTIV-2/A5401 study, which suggested that this choice (rather than requiring fewer consecutive days) better captured sustained symptom resolution with low probability of subsequent relapse.

Participants who are hospitalised for the treatment of COVID-19 or death from any cause during the 28-day period were classified as not achieving sustained symptom alleviation/resolution and were censored at day 25.

Cox proportional hazard model analyses were used for time to sustained symptom alleviation/resolution. Cox proportional hazard model included treatment and region effect as independent variables. In addition, the stratification variables were added to the model analyses depending of the analysis population.

Number of COVID-19 Related Medical Visits Through Day 28

The number of COVID-19 related medical visits through Day 28 were analysed with a negative-binomial regression model, using the log-total number of days of data collection as the participant

offset variable. The resulting analysis shows the difference in estimated rate of medical visits between treatment groups. The analyses were done using mITT, mITT1, and mITT2 populations.

Subgroup analyses

Pre-specified 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).

Changes to planned analyses

Several important changes were made to the planned analyses as part of protocol amendments 2, 3 and 4. Most relevant modifications are briefly described in the table below.

Protocol amendment	Change in planned analyses
Amendment 2 02 August 2021	The primary analysis set (mITT) has been refined to include just those participants who were treated ≤3 days after COVID-19 symptom onset (symptom onset window reduced from <5 days to ≤3 days). Other impacts include: 1. Key secondary endpoint added as a consequence on mITT1 population, i.e. regardless of COVID-19 symptom onset 2. Sample size increased from 2260 to approximately 3000 (adjusted for updated primary efficacy analysis) 3. Enrolment of participants that had COVID-19 symptom onset > 3 days prior to randomisation expected to be approximately 25% and limited to 1000 participants
Amendment 3 26 October 2021	Additional planned interim analysis for efficacy and futility to be done after approximately 70% of participants in the mITT analysis set complete the Day 28 assessments (i.e., 28 days after randomisation). Other impacts include: 4. Modification of first interim analysis to be planned for efficacy and futility (rather than efficacy and safety) 5. Sample size increased from 3000 to 3100 participants due to addition of second interim analysis
Amendment 4 20 November 2021	Second interim analysis removed because the planned interim objective was achieved, and sample size reduced from 3100 to 3000 as a result.

Several changes were also implemented by SAP amendments. Key changes were:

- A sensitivity analysis of the primary endpoint based on mITT2 in the SAP (v1.1; 12 October 2021) was initially described as a secondary analysis of the primary endpoint (in protocol amendment 2, 2 August 2021)
- The POC analysis of viral load was specified in the SAP.

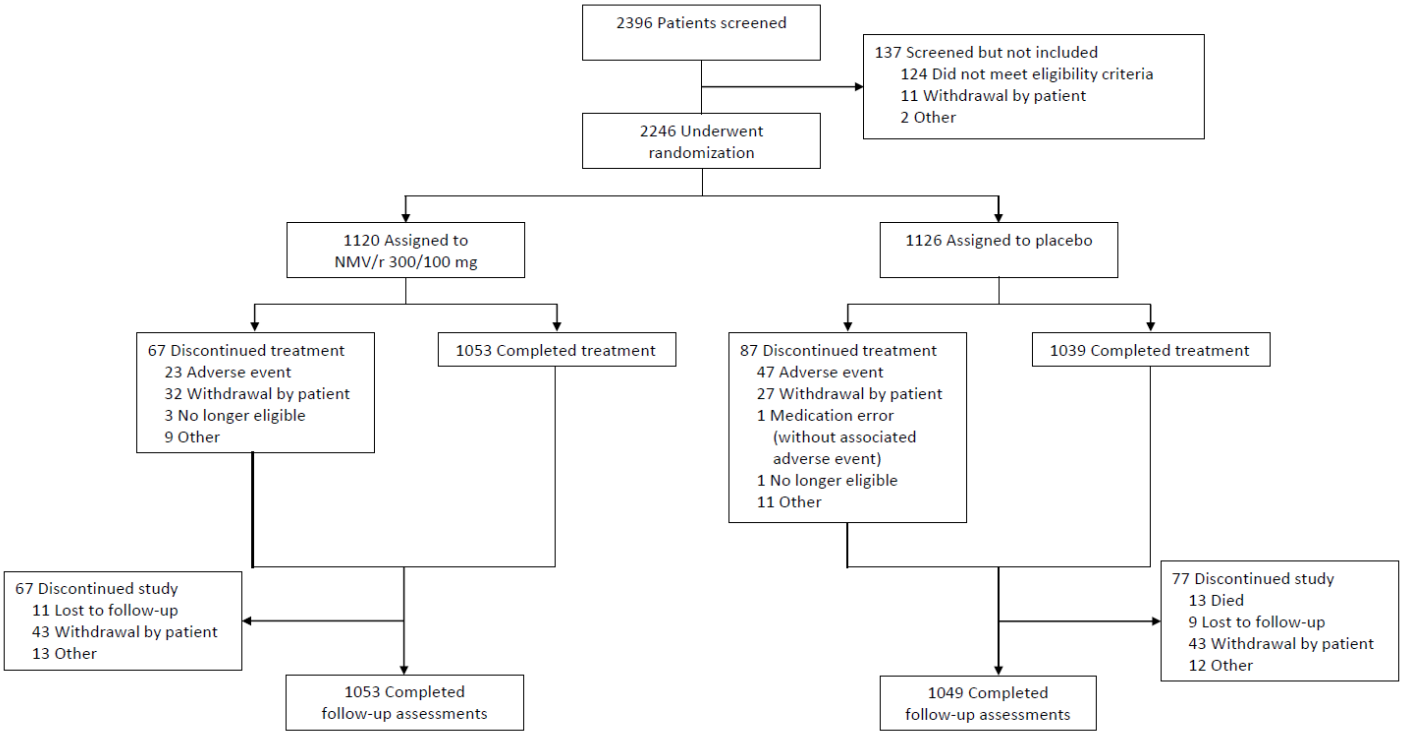
- mITT, mITT1 and mITT2 populations updated for the final analysis as requested by the FDA. They are no longer required to provide at least one post-baseline measurement through Day 28 visit.

Results

- **Participant flow**

Of the 2396 participants screened for entry into the study, 2246 participants were randomised and 137 participants did not fulfil all eligibility criteria at screening. The most common reason for screen failure was not having a confirmed SARS-CoV-2 infection as determined by RT-PCR collected within 5 days of randomisation.

Figure 15. Participant flow



- **Recruitment**

The study was conducted in 343 sites in Argentina, Brazil, Bulgaria, Colombia, Czech Republic, Hungary, India, Japan, Republic of Korea, Malaysia, Mexico, Poland, Puerto Rico, Russian Federation, South Africa, Spain, Taiwan, Thailand, Turkey, Ukraine, United States. The trial began on 16 July 2021 and the and the primary completion date was 09 December 2021.

Halt of centre's recruitment

The applicant made a data driven decision to halt recruitment (22 September 2021, total of 193 participants randomised) in India due to observations in a blinded data review of a >90% rate of serology positive participants at baseline (92% versus 45% in patients from India versus ROW, respectively), with corresponding low levels of viral load measured at baseline from a blinded assessment (mean baseline viral load [Log10 copies/mL] = 2.36 versus 5.25 copies/mL in patients from India versus ROW, respectively), and the high frequency of participants experiencing mild COVID-19 symptoms at baseline (73% versus 15% of participants with only mild symptoms at baseline, India versus ROW, respectively).

- **Conduct of the study**

Protocol Amendments

The applicant indicates that the permitted window in the inclusion criteria for a positive RT-PCR test prior to randomisation was updated from 3 days to 5 days (Protocol Amendment 1, 02 July 2021) (For other mains protocol amendment, please see Statistical methods' section).

Deviation

Overall, the most frequently reported important protocol deviations occurred within the Procedures/Tests, Investigational Product, and Laboratory categories. All other categories occurred in ≤2.5% of participants.

- In the Procedures/Test category, most deviations (18.3% participants) were due to the participant missing more than 25% of their COVID-19-related symptoms diary entries.
- In the Investigational Product category, most deviations (≥1% participants) were: PF 07321332/placebo and ritonavir/placebo were taken > 5 minutes apart (9.5%), dose window more than +/- 4 hours (4.2 %), and compliance >115% (1.0%).
- In the Laboratory category, most deviations (5.0% participants) were NP/nasal swab not done.

The applicant considers that protocol deviations were comparable between both treatment groups.

GCP noncompliance

A US site, terminated for GCP noncompliance, reported a total of 12 important protocol deviations in 12 of 37 enrolled participants at the site: 8 participants in PF-07321332/ritonavir arm and 4 participants in placebo arm. Important protocol deviations by category include:

- Inclusion/Exclusion criteria (PF-07321332/ritonavir: 3 participants; placebo: 0 participants)
- Investigational Product (PF-07321332/ritonavir: 3 participants; placebo: 1 participant)
- Procedures/Tests (PF-07321332/ritonavir: 2 participants; placebo: 3 participants).

Stop of the study

On 03 November 2021, the E-DMC reviewed data from the 45% interim analysis and determined that the pre-specified criteria for stopping the trial due to overwhelming efficacy had been achieved (PF-07321332/ritonavir is superior to placebo in the mITT analysis set for reduction in hospitalisation/death; p<0.0001, the pre-specified p-value per protocol to stop the trial for efficacy was p<0.002). Further enrolment in the study was stopped.

- **Baseline data**

The baseline demographics characteristics were overall equally distributed across treatment arms (**Table 25**).

Table 25. Demographic and Baseline Characteristics - Full Analysis Set

	PF-07321332 300 mg + Ritonavir 100 mg (N=1120)	Placebo (N=1126)	Total (N=2246)
Age (Years), n (%)			
< 18	0	0	0
18 - 44	556 (49.6)	517 (45.9)	1073 (47.8)

	PF-07321332 300 mg + Ritonavir 100 mg (N=1120)	Placebo (N=1126)	Total (N=2246)
45 - 59	338 (30.2)	349 (31.0)	687 (30.6)
60 - 64	86 (7.7)	112 (9.9)	198 (8.8)
65 - 74	104 (9.3)	117 (10.4)	221 (9.8)
≥ 75	36 (3.2)	31 (2.8)	67 (3.0)
Mean (SD)	45.33 (15.40)	46.34 (15.51)	45.84 (15.46)
Median (range)	45.00 (18.00, 86.00)	46.50 (18.00, 88.00)	46.00 (18.00, 88.00)
Gender, n (%)			
Male	566 (50.5)	582 (51.7)	1148 (51.1)
Female	554 (49.5)	544 (48.3)	1098 (48.9)
Race, n (%)			
White	800 (71.4)	807 (71.7)	1607 (71.5)
Black or African American	60 (5.4)	50 (4.4)	110 (4.9)
Asian	154 (13.8)	161 (14.3)	315 (14.0)
American Indian or Alaska Native	96 (8.6)	95 (8.4)	191 (8.5)
Native Hawaiian or other Pacific Islander	0	0	0
Multiracial	1 (<0.1)	2 (0.2)	3 (0.1)
Other	0	0	0
Not reported	8 (0.7)	9 (0.8)	17 (0.8)
Unknown	1 (<0.1)	2 (0.2)	3 (0.1)
Ethnicity, n (%)			
Hispanic or Latino	499 (44.6)	505 (44.8)	1004 (44.7)
Not Hispanic or Latino	616 (55.0)	614 (54.5)	1230 (54.8)
Not reported	5 (0.4)	7 (0.6)	12 (0.5)
Unknown	0	0	0
Weight (kg)			
Mean (SD)	81.39 (17.51)	82.28 (18.85)	81.84 (18.19)
Median (range)	80.00 (42.00, 158.3)	80.00 (42.00, 173.0)	80.00 (42.00, 173.0)
Height (cm)			
Mean (SD)	167.1 (9.64)	167.5 (10.24)	167.3 (9.94)
Median (range)	167.0 (136.9, 196.0)	167.6 (125.2, 207.3)	167.6 (125.2, 207.3)
BMI (kg/m^2), n (%)			
< 25	220 (19.6)	217 (19.3)	437 (19.5)
25 - < 30	492 (43.9)	489 (43.4)	981 (43.7)
30 - < 35	276 (24.6)	268 (23.8)	544 (24.2)
35 - < 40	78 (7.0)	88 (7.8)	166 (7.4)
≥ 40	53 (4.7)	63 (5.6)	116 (5.2)
Mean (SD)	29.09 (5.50)	29.25 (5.74)	29.17 (5.62)
Median (range)	28.20 (16.58, 58.07)	28.34 (16.05, 59.07)	28.30 (16.05, 59.07)
Duration since first diagnosis (Days), n (%)			
≤ 3	1044 (93.2)	1072 (95.2)	2116 (94.2)

	PF-07321332 300 mg + Ritonavir 100 mg (N=1120)	Placebo (N=1126)	Total (N=2246)
> 3	76 (6.8)	54 (4.8)	130 (5.8)
Mean (SD)	1.30 (1.29)	1.31 (1.23)	1.30 (1.26)
Median (range)	1.00 (0.00, 5.00)	1.00 (0.00, 9.00)	1.00 (0.00, 9.00)
Duration since first symptom (Days), n (%)			
≤ 3	754 (67.3)	735 (65.3)	1489 (66.3)
> 3	366 (32.7)	391 (34.7)	757 (33.7)
Mean (SD)	2.93 (1.12)	2.99 (1.09)	2.96 (1.10)
Median (range)	3.00 (0.00, 7.00)	3.00 (0.00, 9.00)	3.00 (0.00, 9.00)
Number of risk factors of interest, n (%)			
0	2 (0.2)	0	2 (<0.1)
1	449 (40.1)	425 (37.7)	874 (38.9)
2	393 (35.1)	408 (36.2)	801 (35.7)
3	183 (16.3)	192 (17.1)	375 (16.7)
4	77 (6.9)	75 (6.7)	152 (6.8)
> 4	16 (1.4)	26 (2.3)	42 (1.9)
Comorbidities, n (%)			
Cardiovascular disorder	42 (3.8)	50 (4.4)	92 (4.1)
Chronic kidney disease	6 (0.5)	8 (0.7)	14 (0.6)
Chronic lung disease	62 (5.5)	41 (3.6)	103 (4.6)
Cigarette smoker	428 (38.2)	448 (39.8)	876 (39.0)
Diabetes mellitus	135 (12.1)	138 (12.3)	273 (12.2)
Hypertension	359 (32.1)	380 (33.7)	739 (32.9)
Immunosuppression	6 (0.5)	7 (0.6)	13 (0.6)
Cancer	5 (0.4)	6 (0.5)	11 (0.5)
Neurodevelopmental disorder	2 (0.2)	1 (<0.1)	3 (0.1)
Sickle cell disease	0	0	0
HIV infection	0	1 (<0.1)	1 (<0.1)
Device dependence	4 (0.4)	3 (0.3)	7 (0.3)
COVID-19 mAb treatment, n (%)			
Received/expected to receive	70 (6.3)	70 (6.2)	140 (6.2)
Not received/not expected to receive	1050 (93.8)	1056 (93.8)	2106 (93.8)
Geographic region, n (%)			
United States	463 (41.3)	465 (41.3)	928 (41.3)
Europe	334 (29.8)	335 (29.8)	669 (29.8)
India	95 (8.5)	98 (8.7)	193 (8.6)
Rest of World	228 (20.4)	228 (20.2)	456 (20.3)
Serology status, n (%)			
Negative	518 (46.3)	537 (47.7)	1055 (47.0)
Positive	581 (51.9)	568 (50.4)	1149 (51.2)
Unknown	21 (1.9)	21 (1.9)	42 (1.9)
Viral load (Log_{10} copies/mL), n (%)			
0	191 (17.1)	184 (16.3)	375 (16.7)
< 2.7	300 (26.8)	332 (29.5)	632 (28.1)

	PF-07321332 300 mg + Ritonavir 100 mg (N=1120)	Placebo (N=1126)	Total (N=2246)
< 4	406 (36.3)	413 (36.7)	819 (36.5)
≥ 4	677 (60.4)	676 (60.0)	1353 (60.2)
≥ 5	583 (52.1)	582 (51.7)	1165 (51.9)
≥ 6	442 (39.5)	441 (39.2)	883 (39.3)
< 7	783 (69.9)	814 (72.3)	1597 (71.1)
≥ 7	300 (26.8)	275 (24.4)	575 (25.6)
≥ 8	118 (10.5)	113 (10.0)	231 (10.3)
≥ 9	4 (0.4)	5 (0.4)	9 (0.4)
≥ 10	0	0	0
Mean (SD)	4.67 (2.88)	4.59 (2.86)	4.63 (2.87)
Median (range)	5.41 (0.00, 9.16)	5.30 (0.00, 9.15)	5.35 (0.00, 9.16)

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

A total of 2,246 participants were randomised to receive either Paxlovid or placebo in the supportive final analysis.

All participants had a laboratory confirmed SARS-CoV-2 diagnosis, with 94.2% of participants having a qualifying SARS CoV-2 positive test collected within 3 days of first dose of study intervention.

Across treatment groups:

- 93.8% participants did not receive or were not planning to receive mAbs for the disease under study at the time of randomisation.
- 53.0% of participants were serological positive at baseline.
- 60.2% participants had baseline viral load ≥4.0 Log10 copies/mL and 25.6% of participants had a very high baseline viral load (≥7.0 log10 copies/mL)

The most common risks factor at baseline were across treatment groups:

- BMI >25 kg/m^2: 80.5% (BMI >30 kg/m2: 36.8%)
- Cigarettes smokers: 39.0%
- Hypertension: 32.9%

Across treatment groups, 38.9% and 35.7% had respectively 1 and 2 risk factors.

As a significant caveat, immunosuppressed patients were poorly represented in the clinical study (<1%). This is notably specified in the description of the study population in section 5.1. The mean age of the whole population was 46 years with 13% of participants 65 years of age and consequently the population of patients older than 75 was very limited (3%) with an expected scarce number of patients 75 years of age and older; 66% of participants had onset of symptoms ≤3 days from initiation of study treatment; 37% were obese, which is limited since the inclusion criteria was also compatible for the inclusion of overweight patients (BMI > 25 kg/m2), this has unfortunately somewhat diluted the obese

patients (BMI > 30 kg/m2); 12% had diabetes mellitus. It is noteworthy that a high proportion (51%) were serological positive while not expected to be vaccinated neither to have prior COVID-19 and only a limited proportion of participants (6.2%) either received or were expected to receive COVID-19 therapeutic mAb treatment at the time of randomisation and were excluded from the mITT and mITT1 analyses.

Overall, the demographic and baseline characteristics are consistent across the interim and the final analysis.

Variants of concern

An analysis was conducted to examine the prevalence of VOCs by treatment and by treatment failure. The primary variant across both treatment arms was Delta (98.53%) and was distributed in high prevalence as subvariants Delta/21J (74.15%), Delta/21I (15.95%) and Delta/21A (8.43%). In the group receiving PF-07321332/ritonavir, 7 participants experienced TF, and all were infected with the Delta (21J) subvariant.

Concomitant medication

During the study treatment and follow-up periods (through Day 34), concomitant medications reported by participants included the following:

- 38 (1.7%) participants received mAb for COVID-19 treatment (bamlanivimab, etesevimab, casirivimab, imdevimab, and regdanvimab), which is lower than what was reported in the 6.2% of participants who were expected to receive mAb at the time of randomisation (baseline). Of the participants who received mAb for COVID-19 treatment, 12 (1.1%) participants were in the PF-07321332/ritonavir group and 26 (2.3%) participants were in the placebo group (Table 14.4.2.1).
- 61 (2.7%) participants received favipiravir: (27 [2.4%] participants for PF-07321332/ritonavir and 34 [3.0%] for placebo).
- 19 (0.9%) participants received remdesivir (2 [0.2%] for PF-07321332/ritonavir and 17 [1.5%] for placebo).
- 186 (8.4%) participants received corticosteroids with ATC2 classification of "Corticosteroids for systemic use" (69 [6.2%] for PF-07321332/ritonavir and 117 [10.5%] for placebo). Corticosteroids were administered for any reason, such as underlying conditions (e.g., rheumatoid arthritis, asthma) and COVID-19

The proportion of participants who took a prohibited concomitant medication/vaccine was higher in the placebo group compared with the PF-07321332/ritonavir group (1.5% and 0.6%, respectively).

Supplemental Oxygen

Participants who required oxygen supplementation for COVID-19 during the C4671005 study were able to continue study treatment. During the study, 9 participants were administered supplemental oxygen for COVID-19 in the PF-07321332 group; of these, 5 (55.6%) participants had an event (hospitalisation). Within the placebo group, 55 participants were administered supplemental oxygen for COVID-19; of these, 47 participants (85.5%) had an event of hospitalisation or death.

Serostatus

Patients were considered seropositive at baseline if they had evidence of antibodies to either the S or the N antigen. Serology testing did not discriminate between IgG or IgM. Given the current turnaround time, serology testing was not part of the screening process prior to enrolment. Participants may have been unaware of prior (potentially asymptomatic) SARS-CoV-2 infection and tested seropositive at baseline. Additional exploratory testing is planned to further characterize the immune response to

SARS-CoV-2 at baseline and over time (including cytokine, immune cell markers and neutralising antibody responses).

Additionally, the population enrolled in Study C4671005 was limited to unvaccinated patients at high risk of progression to severe COVID-19. However, study C4671002 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, an additional reduction in viral load of ~1.0 log10 copies/mL relative to placebo at Day 5 was observed, similar to what has been characterised in unvaccinated/high risk patients from Study C4671005. These results suggest that the antiviral activity of PF-07321332/ritonavir is consistent across vaccinated and unvaccinated patients, as would be anticipated with an antiviral with an intracellular target. Some further insights might be obtained from the smaller sample sized study in patients at standard risk of developing severe COVID-19 including patients vaccinated or non-vaccinated against SARS-CoV-2. However, the added value of this additional C4671002 or EPIC-SR study performed in patients at standard risk is uncertain given that study of lower sample size failed on its primary endpoint. As immunity to SARS-CoV-2 wanes and/or is compromised by emerging variants of concern, risk of hospitalisation/death in vaccinated patients may increase and become more reflective of the C4671005 unvaccinated patient population. Therefore, data from both C4671002 and C4671005 will inform the anticipated efficacy of treatment in both vaccination and unvaccinated patients.

Moreover, the CHMP requested to investigate the high proportion of patients with seropositive status having in mind that those patients were not expected to receive vaccine against SARS-CoV-2 nor had prior episode of COVID-19. The applicant specified that investigations were ongoing to this purpose.

- **Numbers analysed**

The analysis of efficacy was performed using the mITT, mITT1, and mITT2 sets as follow.

Table 26. Participant Evaluation Groups - All Screened Participants (Protocol C4671005)

	PF-07321332 300 mg + Ritonavir 100 mg (N=1120) n (%)	Placebo (N=1126) n (%)	Total (N=2246) n (%)
Screened: 2396			
Screened failure: 137			
Not screen failure but not randomized: 13			
Assigned to treatment	1120 (100.0)	1126 (100.0)	2246 (100.0)
Treated	1109 (99.0)	1115 (99.0)	2224 (99.0)
Not treated	11 (1.0)	11 (1.0)	22 (1.0)
Safety analysis set	1109 (99.0)	1115 (99.0)	2224 (99.0)
Full analysis set	1120 (100.0)	1126 (100.0)	2246 (100.0)
mITT analysis set	697 (62.2)	682 (60.6)	1379 (61.4)
mITT1 analysis set	1039 (92.8)	1046 (92.9)	2085 (92.8)
mITT2 analysis set	1109 (99.0)	1115 (99.0)	2224 (99.0)
Per-protocol analysis set	680 (60.7)	658 (58.4)	1338 (59.6)

PFIZER CONFIDENTIAL SDTM Creation: 11DEC2021 (22:19) Source Data: adsl Table Generation: 12DEC2021 (11:42)
(Data cutoff date : 11DEC2021 Database snapshot date : 11DEC2021) Output File: ./nda/C4671005 EUA/adsl s002
Table 14.1.1.1 PF-07321332 is for Pfizer internal use.

A total of 13 participants who were not screen failures were not randomised. Further examination of those 13 participants showed all but 2 withdrew consent. One participant did not come to the Day 1 visit within 48 hours after screening and the other participant decided not to complete the baseline. Generally, the treatment duration was compliant with what is required in the Protocol.

- **Outcomes and estimation**

Primary analysis

COVID-19-Related Hospitalisation or Death from Any Cause (mITT)

This analysis was conducted in patients who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 onset. Through Day 28, there were 9 deaths in the placebo group and none in the PF-07321332/ritonavir group.

Table 27. Primary Analysis of Proportion of Participants 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	697	682
Participants with event, n (%)	5 (0.717)	44 (6.452)
Participants with COVID-19 hospitalisation	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
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 hospitalised for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time 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.

Interim analysis - COVID-19-Related Hospitalisation or Death from Any Cause (mITT)

The primary analysis from the interim report is presented below.

Table 28. Primary Analysis of Proportion of Participants 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.

Sensitivity Analyses

At the request of FDA, a post-hoc sensitivity analysis of the mITT analysis set was performed whereby participants who did not have follow-up data through Day 21 were hypothetically assumed to have experience both COVID-19-related hospitalisation and death in a worst-case scenario:

- 2 participants in the PF-07321332/ritonavir group and 1 participant in the placebo group were assumed to have had a primary endpoint event.
- A 5.66% (95% CI: -7.69% to -3.63%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 6.68% to 1.02%, with PF-07321332/ritonavir in comparison with placebo treatment.

Additionally, to evaluate whether the results in the primary analysis were affected by data from India and a non-compliant US site, the analysis was repeated while excluding data from these sites.

- 5 participants in the PF-07321332/ritonavir group and 44 participants in the placebo group were assumed to have had a primary endpoint event.
- A 5.87% (95% CI: 7.86% to -3.88%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 6.60% to 0.73%, with PF-07321332/ritonavir in comparison with placebo treatment.
- It is to note that, of 193 participants from India randomised, none progressed to hospitalisation or death.

The results of an additional sensitivity analysis that excluded participants from the sentinel cohort of the study treated with active treatment (3 x 100 mg PF-07321332 tablets) were consistent with those observed in the primary analysis.

Sensitivity Analyses using mITT2

This analysis aimed to assess the treatment effect in a population including participants who received mAb treatment or planned to receive mAb treatment (as a note, one participant in each treatment

group had received mAb treatment). The population includes patients regardless they received treatment within 3 days and after 3 days since onset of symptom.

Table 29. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28 - mITT2, Kaplan-Meier Method

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
N	1109	1115
Participants with event, n (%)	9 (0.812)	68 (6.099)
Participants with COVID-19 hospitalisation	9 (0.812)	67 (6.009)
Participants with death	0	12 (1.076)
Average time at risk for event (Days)[a]	27.057	26.040
Average study follow-up (Days)[b]	27.216	27.083
Estimated proportion (95% CI), %	0.822 (0.429, 1.574)	6.185 (4.909, 7.779)
Difference from Placebo (SE)	-5.363 (0.776)	
95% CI of difference	-6.884, -3.842	
p-value	<.0001	

N = number of participants in the analysis set.
The cumulative proportion of participants hospitalised for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time 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_mitt2

The results of the analyses were consistent with the mITT primary analysis and conclusions remain unchanged:

- when participants who received a therapeutic COVID-19 mAb treatment postbaseline were considered to have experienced a primary endpoint event, treatment with PF-07321332/ritonavir reduced the primary event rate from 6.678 to 0.867%, showing a 5.811% absolute reduction relative to placebo (p<.0001). Two participants in the PF-07321332/ritonavir group and 3 participants in the placebo group received mAb treatment postbaseline.

Secondary Efficacy Analysis

1) Proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28 (mITT-1)

This secondary analysis assessed the treatment effect in a population including participants who have received treatment within 3 days of symptom onset and those who have received treatment after 3 days. Through Day 28, there were 12 deaths in the placebo group and none in the PF-07321332/ritonavir group.

Table 30. Proportion of Participants 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	1039	1046
Participants with event, n (%)	8 (0.770)	66 (6.310)
Participants with COVID-19 hospitalisation	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	

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

Interim analysis - Proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28 (mITT-1)

The first secondary analysis from the interim report is presented below.

Table 31. Proportion of Participants 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.

2) Time to Sustained Alleviation of All Targeted Signs/Symptoms Through Day 28 (mITT)

Because statistical significance was achieved in the analyses of both the primary and first secondary endpoints, the time to sustained alleviation in all targeted signs/symptoms through Day 28 was analysed with an alpha level of 5% in the sequential testing procedure. The median time to sustained alleviation in the placebo group was 15 days and was reduced to 13 days in the PF-07321332/ritonavir group.

Table 32. Time to Sustained Alleviation of All Targeted Signs and Symptoms Through Day 28 - mITT Analysis Set (Protocol C4671005)

		PF-07321332 300 mg + Ritonavir 100 mg (N=697)	Placebo (N=682)
Parameter			
Time to sustained alleviation (Days)	N1	686	674
	Participants with event, n (%)	526 (76.676)	463 (68.694)
	Median (95% CI)	12.000 (12.000, 13.000)	15.000 (13.000, 16.000)
	Q1, Q3	8.000, 21.000	9.000, -
	Hazard ratio (95% CI) versus Placebo	1.269 (1.117, 1.442)	
	p-value	0.0002	
	Proportional hazard assumption p-value	0.5252	

3) Time to Sustained Resolution of All Targeted Signs/Symptoms Through Day 28 (mITT)

The median time to sustained resolution in the placebo group was 19 days and was reduced to 16 days in the PF-07321332/ritonavir group.

Table 33. Time to Sustained Resolution of All Targeted Signs and Symptoms Through Day 28 - mITT Analysis Set (Protocol C4671005)

		PF-07321332 300 mg + Ritonavir 100 mg (N=697)	Placebo (N=682)
Parameter			
Time to sustained resolution (Days)	N1	686	674
	Participants with event, n (%)	464 (67.638)	414 (61.424)
	Median (95% CI)	16.000 (15.000, 17.000)	18.000 (17.000, 20.000)
	Q1, Q3	10.000, -	11.000, -
	Hazard ratio (95% CI) versus Placebo	1.201 (1.049, 1.375)	
	p-value	0.0080	
	Proportional hazard assumption p-value	0.5137	

3) Proportion of Participants with a Resting Peripheral Oxygen Saturation ≥95% at Days 1 and 5 (mITT)

Participants who had a resting peripheral oxygen saturation ≥95% at baseline (Day 1) were more likely to maintain those levels at Day 5 than those with a resting peripheral oxygen saturation <95% at baseline but the treatment difference was not significant (p=0.2331).

Table 34. Proportion of Participants With Resting Peripheral Oxygen Saturation >= 95% at Days 1 and 5 - mITT1 Analysis Set, Breslow-Day Test (Protocol C4671005)

	PF-07321332 300 mg + Ritonavir 100 mg (N=697)	Placebo (N=682)
Participants with Day 1 < 95%, n (%)	45 (6.456)	52 (7.625)
< 95% at Day 5	11 (24.444)	13 (25.000)
≥ 95% at Day 5	31 (68.889)	35 (67.308)
Participants with Day 1 ≥ 95%, n (%)	652 (93.544)	630 (92.375)
< 95% at Day 5	11 (1.687)	22 (3.492)
≥ 95% at Day 5	607 (93.098)	565 (89.683)
Odds ratio for Day 5 vs Day 1 (95% CI)	19.581 (7.879, 48.661)	9.539 (4.435, 20.518)
p-value from Breslow-Day test: homogeneity of odds ratios across treatment groups	0.2331	

N = number of participants in the analysis set.
Breslow-Day test was applied for testing homogeneity of odds ratio.

4) Number of COVID-19 related medical visits (mITT)

Compared with the PF-07321332/ritonavir group, there were approximately 5 times as many participants in the placebo group who had COVID-19 related medical visits (52 vs 10). The total number of visits was approximately 4 times as high in the placebo group (81 vs 22).

Table 35. Analysis of COVID-19 Related Medical Visits - mITT Analysis Set (Protocol C4671005)

	PF-07321332 300 mg + Ritonavir 100 mg (N=697)	Placebo (N=682)
Proportion of participants with COVID-19 related medical visits, n (%)[a]	10 (1.435)	52 (7.625)
Total number of medical visits across all participants	22	81
Analysis of number of medical visits		
Mean (SD)	0.032 (0.342)	0.119 (0.541)
Median (range)	0.000 (0.000, 7.000)	0.000 (0.000, 9.000)
Number of medical visits per day[b]		
Mean (SD)	0.0009 (0.0094)	0.0054 (0.0290)
Median (range)	0.0000 (0.0000, 0.1892)	0.0000 (0.0000, 0.5000)
LS mean	0.0008	0.0029
95% CI	(0.0004,0.0014)	(0.0017,0.0049)
Versus Placebo		
LS mean ratio	0.263	
95% CI for LS mean ratio	(0.130,0.532)	
p-value	0.0002	

N = number of participants in the analysis set.
a. Medical Visits include emergency room, practitioner's office, home healthcare services, urgent care, telephone consultation, outpatient infusion center, other, COVID-19-Related-Hospitalization (ICU and non-ICU stays). The Medical Visits and Hospitalization events are limited through Day 34 visit.
b. Number of medical visits per day = Number of medical visits/Number of days follow up limited to Day 37
Negative binomial regression model includes main effects of treatment, geographic region, baseline SARS-CoV-2 serology status and baseline viral load (< 4 log10 copies/mL, >= 4 log10 copies/mL) , and the log number of days follow up as the participant offset variable.

- **Ancillary analyses**

Subgroup analysis

1) Serological status

Subgroup analysis by serology status performed in mITT-1 are presented below.

Table 36. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28, by Subgroup of Serology Status - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Negative	N	487	505
	Participants with event, n (%)	7 (1.437)	58 (11.485)
	Participants with COVID-19 hospitalization	7 (1.437)	57 (11.287)
	Participants with death	0	11 (2.178)
	Average time at risk for event (Days) [a]	26.760	24.691
	Average study follow-up (Days) [b]	27.076	26.584
	Estimated proportion (95% CI), %	1.466 (0.702, 3.051)	11.713 (9.179, 14.887)
	Difference from Placebo (SE)	-10.247 (1.547)	
	95% CI of difference	-13.279, -7.214	
	p-value	<.0001	
Positive	N	540	528
	Participants with event, n (%)	1 (0.185)	8 (1.515)
	Participants with COVID-19 hospitalization	1 (0.185)	8 (1.515)
	Participants with death	0	1 (0.189)
	Average time at risk for event (Days) [a]	27.289	27.199
	Average study follow-up (Days) [b]	27.302	27.515
	Estimated proportion (95% CI), %	0.185 (0.026, 1.307)	1.522 (0.764, 3.021)
	Difference from Placebo (SE)	-1.337 (0.565)	
	95% CI of difference	-2.445, -0.229	
	p-value	0.0180	

2) Number of baseline comorbidities

Subgroup analysis by number of baseline comorbidities performed in mITT-1 are presented below.

Table 37. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28, by Subgroup of number of baseline comorbidities - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
0-1	N	829	832
	Participants with event, n (%)	4 (0.483)	43 (5.168)
	Participants with COVID-19 hospitalization	4 (0.483)	42 (5.048)
	Participants with death	0	5 (0.601)
	Average time at risk for event (Days) [a]	27.191	26.067
	Average study follow-up (Days) [b]	27.268	26.983
	Estimated proportion (95% CI), %	0.491 (0.185, 1.303)	5.254 (3.923, 7.019)
	Difference from Placebo (SE)	-4.763 (0.818)	
	95% CI of difference	-6.365, -3.160	
	p-value	<.0001	
2-3	N	206	211
	Participants with event, n (%)	4 (1.942)	23 (10.900)
	Participants with COVID-19 hospitalization	4 (1.942)	23 (10.900)
	Participants with death	0	7 (3.318)
	Average time at risk for event (Days) [a]	26.456	25.569
	Average study follow-up (Days) [b]	26.927	27.280
	Estimated proportion (95% CI), %	1.978 (0.747, 5.185)	10.936 (7.405, 15.997)
	Difference from Placebo (SE)	-8.958 (2.364)	
	95% CI of difference	-13.592, -4.323	
	p-value	0.0002	
≥ 4	N	4	3
	Participants with event, n (%)	0	0
	Participants with COVID-19 hospitalization	0	0
	Participants with death	0	0
	Average time at risk for event (Days) [a]	28.000	28.000
	Average study follow-up (Days) [b]	28.000	28.000
	Estimated proportion (95% CI), %	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)
	Difference from Placebo (SE)	0.000 (0.000)	
	95% CI of difference	0.000, 0.000	
	p-value	-	

3) Age

Subgroup analysis by age performed in mITT-1 are presented below.

Table 38. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28, by Subgroup of Age - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Age < 65 years	N	908	909
	Participants with event, n (%)	7 (0.771)	46 (5.061)
	Participants with COVID-19 hospitalization	7 (0.771)	46 (5.061)
	Participants with death	0	4 (0.440)
	Average time at risk for event (Days) [a]	27.100	26.160
	Average study follow-up (Days) [b]	27.249	27.121
	Estimated proportion (95% CI), %	0.782 (0.374, 1.634)	5.133 (3.870, 6.794)
	Difference from Placebo (SE)	-4.351 (0.794)	
	95% CI of difference	-5.907, -2.795	
	p-value	<.0001	
Age ≥ 65 years	N	131	137
	Participants with event, n (%)	1 (0.763)	20 (14.599)
	Participants with COVID-19 hospitalization	1 (0.763)	19 (13.869)
	Participants with death	0	8 (5.839)
	Average time at risk for event (Days) [a]	26.687	24.730
	Average study follow-up (Days) [b]	26.885	26.547
	Estimated proportion (95% CI), %	0.763 (0.108, 5.295)	14.697 (9.742, 21.847)
	Difference from Placebo (SE)	-13.933 (3.129)	
	95% CI of difference	-20.066, -7.800	
	p-value	<.0001	

4) Gender

Subgroup analysis by gender performed in mITT-1 are presented below.

Table 39. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28, by Subgroup of Gender - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Male	N	520	540
	Participants with event, n (%)	4 (0.769)	41 (7.593)
	Participants with COVID-19 hospitalization	4 (0.769)	41 (7.593)
	Participants with death	0	8 (1.481)
	Average time at risk for event (Days) [a]	27.133	25.746
	Average study follow-up (Days) [b]	27.302	27.028
	Estimated proportion (95% CI), %	0.781 (0.294, 2.066)	7.706 (5.733, 10.321)
	Difference from Placebo (SE)	-6.926 (1.220)	
	95% CI of difference	-9.317, -4.534	
	p-value	<.0001	
Female	N	519	506
	Participants with event, n (%)	4 (0.771)	25 (4.941)
	Participants with COVID-19 hospitalization	4 (0.771)	24 (4.743)
	Participants with death	0	4 (0.791)
	Average time at risk for event (Days) [a]	26.963	26.213
	Average study follow-up (Days) [b]	27.104	27.065
	Estimated proportion (95% CI), %	0.781 (0.294, 2.067)	5.007 (3.411, 7.321)
	Difference from Placebo (SE)	-4.226 (1.051)	
	95% CI of difference	-6.286, -2.167	
	p-value	<.0001	

5) BMI

Subgroup analysis by BMI performed in mITT-1 are presented below.

Table 40. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28, by Subgroup of BMI - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
< 25 kg/m [2]	N	209	207
	Participants with event, n (%)	1 (0.478)	9 (4.348)
	Participants with COVID-19 hospitalization	1 (0.478)	9 (4.348)
	Participants with death	0	1 (0.483)
	Average time at risk for event (Days) [a]	26.459	26.923
	Average study follow-up (Days) [b]	26.579	27.493
	Estimated proportion (95% CI), %	0.483 (0.068, 3.379)	4.365 (2.295, 8.221)
	Difference from Placebo (SE)	-3.882 (1.502)	
	95% CI of difference	-6.826, -0.937	
	p-value	0.0098	
25 - < 30 kg/m [2]	N	458	466
	Participants with event, n (%)	3 (0.655)	28 (6.009)
	Participants with COVID-19 hospitalization	3 (0.655)	28 (6.009)
	Participants with death	0	4 (0.858)
	Average time at risk for event (Days) [a]	27.378	26.039
	Average study follow-up (Days) [b]	27.537	27.157
	Estimated proportion (95% CI), %	0.658 (0.213, 2.027)	6.095 (4.248, 8.706)
	Difference from Placebo (SE)	-5.436 (1.179)	
	95% CI of difference	-7.747, -3.126	
	p-value	<.0001	

6) Hypertension

Subgroup analysis by hypertension status performed in mITT-1 are presented below.

Table 41. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28, by Subgroup of hypertension status - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Hypertension = Yes	N	338	351
	Participants with event, n (%)	5 (1.479)	42 (11.966)
	Participants with COVID-19 hospitalization	5 (1.479)	41 (11.681)
	Participants with death	0	11 (3.134)
	Average time at risk for event (Days) [a]	26.601	24.863
	Average study follow-up (Days) [b]	26.932	26.769
	Estimated proportion (95% CI), %	1.508 (0.630, 3.586)	12.123 (9.106, 16.047)
	Difference from Placebo (SE)	-10.614 (1.877)	
	95% CI of difference	-14.294, -6.935	
	p-value	<.0001	
Hypertension = No	N	700	695
	Participants with event, n (%)	3 (0.429)	24 (3.453)
	Participants with COVID-19 hospitalization	3 (0.429)	24 (3.453)
	Participants with death	0	1 (0.144)
	Average time at risk for event (Days) [a]	27.263	26.532
	Average study follow-up (Days) [b]	27.333	27.186
	Estimated proportion (95% CI), %	0.434 (0.140, 1.340)	3.500 (2.359, 5.177)
	Difference from Placebo (SE)	-3.066 (0.745)	
	95% CI of difference	-4.526, -1.605	
	p-value	<.0001	

7) Diabetes mellitus

Subgroup analysis by diabetes mellitus status performed in mITT-1 are presented below.

Table 42. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28, by Subgroup of diabetes mellitus status - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Diabetes mellitus = Yes	N	125	127
	Participants with event, n (%)	2 (1.600)	9 (7.087)
	Participants with COVID-19 hospitalization	2 (1.600)	9 (7.087)
	Participants with death	0	4 (3.150)
	Average time at risk for event (Days) [a]	26.800	26.197
	Average study follow-up (Days) [b]	27.024	27.189
	Estimated proportion (95% CI), %	1.607 (0.404, 6.271)	7.119 (3.769, 13.235)
	Difference from Placebo (SE)	-5.512 (2.550)	
	95% CI of difference	-10.510, -0.515	
	p-value	0.0306	
Diabetes mellitus = No	N	913	919
	Participants with event, n (%)	6 (0.657)	57 (6.202)
	Participants with COVID-19 hospitalization	6 (0.657)	56 (6.094)
	Participants with death	0	8 (0.871)
	Average time at risk for event (Days) [a]	27.081	25.941
	Average study follow-up (Days) [b]	27.227	27.026
	Estimated proportion (95% CI), %	0.668 (0.300, 1.480)	6.301 (4.896, 8.092)
	Difference from Placebo (SE)	-5.634 (0.853)	
	95% CI of difference	-7.305, -3.963	
	p-value	<.0001	

8) Cigarette smoker

Subgroup analysis by cigarette smoker performed in mITT-1 are presented below.

Table 43. Proportion of Participants with COVID-19-Related-Hospitalisation or Death From any Cause Through Day 28, by Subgroup of cigarette smoker - mITT1, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Cigarette smoker = Yes	N	405	424
	Participants with event, n (%)	4 (0.988)	17 (4.009)
	Participants with COVID-19 hospitalization	4 (0.988)	17 (4.009)
	Participants with death	0	2 (0.472)
	Average time at risk for event (Days) [a]	27.081	26.752
	Average study follow-up (Days) [b]	27.323	27.486
	Estimated proportion (95% CI), %	0.998 (0.376, 2.636)	4.043 (2.533, 6.423)
	Difference from Placebo (SE)	-3.045 (1.081)	
	95% CI of difference	-5.164, -0.926	
	p-value	0.0049	
Cigarette smoker = No	N	632	622
	Participants with event, n (%)	4 (0.633)	49 (7.878)
	Participants with COVID-19 hospitalization	4 (0.633)	48 (7.717)
	Participants with death	0	10 (1.608)
	Average time at risk for event (Days) [a]	27.024	25.441
	Average study follow-up (Days) [b]	27.123	26.746
	Estimated proportion (95% CI), %	0.646 (0.243, 1.711)	8.026 (6.126, 10.481)
	Difference from Placebo (SE)	-7.380 (1.146)	
	95% CI of difference	-9.627, -5.134	
	p-value	<.0001	

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 44. Summary of efficacy for trial C4671005

Title: An Interventional Efficacy and Safety, Phase 2/3, Double-Blind, 2-Arm Study to Investigate Orally Administered PF-07321332/Ritonavir Compared With Placebo in Non-hospitalised Symptomatic Adult Participants With COVID-19 Who are at Increased Risk of Progressing to Severe Illness				
Study identifier	C4671005			
Design	This Phase 2/3, randomised, double-blind, placebo-controlled study in non-hospitalised, symptomatic adult participants with COVID-19 at increased risk of progressing to severe illness determined the efficacy, safety, and tolerability of PF-07321332/ritonavir compared with placebo. Eligible participants with a confirmed diagnosis of SARS-CoV-2 infection were randomised (1:1) to receive PF-07321332/ritonavir or placebo orally q12h for 5 days (10 doses total). Randomisation was stratified by geographic region and whether participants had received/were expected to receive COVID-19 therapeutic mAb treatment (yes/no) based on the site investigator's assessment at the time of randomisation.			
	Duration of main phase:		24 weeks	
	Duration of Run-in phase:		not applicable	
	Duration of Extension phase:		not applicable	
Hypothesis	Superiority			
Treatments groups	Intervention group		PF-07321332/ritonavir. 5 days, 1120 participants randomised	
	Control group		Placebo. 5 days, 1126 participants randomised	
Endpoints and definitions	Primary endpoint	Proportion of participants With COVID-19 related hospitalisation or death from any cause through Day 28.	The difference in proportions of patients experiencing COVID-19-related hospitalisation or death from any cause through Day 28 in non-hospitalised adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease, who did not receive COVID-19 therapeutic mAb treatment and were treated ≤3 days after COVID-19 symptom onset. This will be estimated without regard to adherence	
	First secondary endpoint	Proportion of participants With COVID-19 related hospitalisation or death from any cause through Day 28.	The difference in proportions of patients experiencing COVID-19-related hospitalisation or death from any cause through Day 28 in non-hospitalised adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease and who did not receive COVID-19 therapeutic mAb treatment. This will be estimated without regard to adherence to randomised treatment.	
Database lock	09 December 2021			
Results and Analysis				
Analysis description	**Primary Analysis (interim analysis)**			
Analysis population and time point description	Modified Intent to treat (patients treated ≤3 days after COVID-19 symptom onset) Day 28			
Descriptive statistics and estimate variability	Treatment group	PF-07321332 300 mg + Ritonavir 100 mg	Placebo	
	Number of subjects	697	682	

Title: An Interventional Efficacy and Safety, Phase 2/3, Double-Blind, 2-Arm Study to Investigate Orally Administered PF-07321332/Ritonavir Compared With Placebo in Non-hospitalised Symptomatic Adult Participants With COVID-19 Who are at Increased Risk of Progressing to Severe Illness				
Study identifier	C4671005			
	Participants with event, n (%)	5 (0.717)	44 (6.452)	
	Estimated proportion of Participants With COVID-19-Related-Hospitalisation or Death From Any Cause, %	0.723	6.531	
	95% CI	0.302, 1.729	4.901, 8.676	

Effect estimate per comparison	Primary endpoint	Comparison groups	PF-07321332 300 mg + Ritonavir 100 mg vs Placebo
		Difference from Placebo (SE)	-5.807 (1.005)
		95% CI of difference	-7.777, -3.837
		P-value	<.0001
Notes	Sensitivity and supplemental analysis are consistent with the primary analysis. Through Day 28, there were 9 deaths in the placebo group and none in the PF-07321332/ritonavir group.		
Analysis description	**First secondary analysis (supportive final analysis)**		
Analysis population and time point description	Modified Intent to treat 1 (patients treated ≤3 and > 3 days after COVID-19 symptom onset) Day 28		

Descriptive statistics and estimate variability	Treatment group	PF-07321332 300 mg + Ritonavir 100 mg	Placebo	
	Number of subjects	1039	1046	
	Participants with event, n (%)	8 (0.770)	66 (6.310)	
	Estimated proportion of Participants With COVID-19-Related-Hospitalisation or Death From Any Cause, %	0.781	6.400	
	95% CI	0.391, 1.556	5.063, 8.075	

Effect estimate per comparison	Primary endpoint	Comparison groups	PF-07321332 300 mg + Ritonavir 100 mg vs Placebo
		Difference from Placebo (SE)	-5.619 (0.810)
		95% CI of difference	-7.207, -4.031
		P-value	<.0001
Notes	Through Day 28, there were 12 deaths in the placebo group and none in the PF-07321332/ritonavir group.		

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical study in support of this procedure was a phase 2/3, randomised, double-blind, placebo-controlled study (C4671005 or EPIC-HR study) to compare the efficacy, safety, and tolerability of PF-07321332/ritonavir versus placebo in non-hospitalised, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness. The total study duration was up to 24 weeks, study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow-up at Weeks 12 and 24.

The general design of this phase 2/3 clinical trial appears appropriate. Additionally, considering the pandemic context and the need of curative treatments for the COVID-19, supporting the MAA with a single pivotal study is deemed acceptable.

The selection criteria are globally consistent with the target population. To be enrolled, positive RT-PCR, or other molecular or antigen tests, and initial onset signs/symptoms attributable to COVID-19 were needed, both within 5 days prior randomisation. This seems reasonable to define symptomatic patients with COVID-19, as well as the list of the specified signs/symptoms.

Risk factors of progressing to severe illness were predefined. Some inclusion criteria were not sufficiently stringent and thus have somewhat diluted the population at the highest risk of progressing to severe disease. Patients were to be enrolled on the basis of being overweight (BMI >25 kg/$m^{2,}$), likely referring to CDC, and not necessarily requiring obesity (BMI >30 kg/m^2) based on WHO's criteria and ECDC. Additionally, the lower bound for age regardless of comorbidities was >60 y/o, and not > 65 y/o, hence not enriching the population with very old patients.

In absence or further stratification factors, it is not fully clear in which extent both subpopulations, patients with mild-illness and patients with moderate illness, are sufficiently represented and well balanced across the treatment groups. Additionally, the selection criteria allowed to enrol patients with oxygen saturation of ≥92% on room air, while SpO2 <94% is one of the criteria to define severe illness. Nonetheless, current need for hospitalisation or anticipated need for hospitalisation within 48 hours after randomisation was an exclusion criterion, as such it might be unlikely that patients with severe illness were recruited at screening.

Considering that the applicant has not provided a definition of 'mild to moderate disease patients' and also considering that non-severe patients are best defined as not requiring O2, the CHMP requested that the indication be updated to not state 'mild to moderate' but rather 'not requiring O2', when describing the target population. The indication was updated accordingly.

Regarding prior and concomitant medication, drug-drug interactions related to CYP3A4, due to the administration of ritonavir, was taken into account.

It should also be highlighted that subjects were not vaccinated (allowed only from Day 34, while primary timepoint is at Day 28) but could receive mAb.

Regarding the study treatment, patients were instructed to take 2 tablets of PF-07321332 150 mg (or 3 tablets of 100 mg for some participants in the sentinel cohort) plus 1 capsule of ritonavir 100 mg q12h. Taking into consideration the assessment of pharmacodynamics and Scientific Advice provided by CHMP, the rationale for dose selection, based on reaching unbound Ctrough values above EC90 and assuming an inflated intrasubject variability, can be agreed, all the more in view of the clinical results with this selected dose. Further scrutiny will apply once the results of the updated PopPK model will be submitted.

The treatment duration, 5 days (10 doses), was defined by the company based on other antiviral agents used in the treatment of acute respiratory infections, such as remdesivir for SARS-CoV-2 and oseltamivir for influenza. This is agreed, based on the results of the clinical study with this tested treatment duration. This should be further explored in immunodeficient patients characterised by a prolonged clearance of the virus (potentially resulting in emergence of resistance). Even though the CHMP considered it was not feasible to proceed with a clinical study in immunocompromised patients, this issue should be monitored post-authorisation.

The choice of placebo as comparator is considered appropriate. The study designed allowed the use of mAb as considered standard of care for COVID-19 patients requiring oxygen and at increased risk of progressing to severe COVID-19. Enrolment of participants that had received or were expected to receive COVID-19 therapeutic mAb treatment was to be limited to approximately 25% of participants.

The primary objective and the primary endpoint of percentage of increased risk patients with COVID-19 related hospitalisation or death all causes within 28 days is of particular clinical relevance. There are no objections with the proposed secondary endpoints. The time to alleviation or resolution of symptoms as part of the secondary endpoints is of limited value to substantiate the clinical benefit.

The sample size calculations appear to be in line with corresponding protocol assumptions. The assumed proportion of hospitalisation/death in the placebo arm (7%) is consistent with the observed rate at interim and final analyses.

Following the availability of the first interim analysis results, the protocol was amended to remove the second interim analysis as the planned interim analysis objective was achieved.

Randomisation was stratified by geographic region and by whether participants had received/were expected to receive treatment with COVID-19 therapeutic mAbs (yes/no) based on the site investigator's assessment at time of randomisation. First, it is unclear to which extent this latter factor is appropriate to define patients most at risk of progressing to severe illness. Secondly, as the study primary analysis is restricted to patients who were treated ≤3 days after COVID-19 symptom onset, time since COVID-19 symptom onset at randomisation (≤3 vs >3 days) would have been expected as an additional stratification factor of the randomisation. The lack of stratification for the time since symptom onset could raise a concern about the preservation of the randomisation in the primary analysis population (mITT). Nevertheless, given the observed balance of treatment arms and other stratification factors in the primary analysis set, this issue is not thought to have affected the results.

Based on the SAP, all efficacy populations (mITT, mITT1 and mITT2) excluded subjects who were not treated (both interim and final analyses) or without at least 1 post-baseline visit through Day 28 (IA only). Efficacy analysis sets would be generally expected to include all randomised subjects regardless of treatment with study drug and regardless of post-baseline visit attendance. Similarly, it would be expected for the COVID-19 symptom onset criteria ≤3 days to be defined using the randomisation date, rather than using the treatment start date. The applicant did not provide additional analyses of the primary endpoint using alternative efficacy analysis sets. Nevertheless, considering the mITT, mITT1, mITT2 in the supportive final analysis to include subjects without post-baseline measurements and the relatively small frequency of untreated patients, this concern is not thought to impact the study conclusions.

The primary analysis method (proportions derived from Kaplan-Meier method with 95% CIs based on Greenwood's formula of the variance estimate) appears overall acceptable. The Lan-DeMets procedure with O'Brien-Fleming boundaries for the testing of the primary endpoint across interim and final analyses is expected to provide an appropriate control of the study type I error.

Some discrepancies were noted in the statistical analysis plan, such as the definition of analysis populations and the sequential testing of the secondary endpoints, which were clarified.

Although the primary analysis method seems acceptable, the censoring of subjects who discontinued before their Day 28 assessment or were lost to follow up could be questioned. Data from subjects who withdrew early could lead to biased estimates. As part of the assessment, the applicant provided a post-hoc sensitivity analysis with the assumption that subjects not providing follow-up data through Day 21 hypothetically experienced both COVID-19-related hospitalisation and death. This may have provided an alternative treatment effect estimate under more conservative assumptions, which was consistent with the supportive final analysis.

There were several important changes to the planned analyses that were implemented while the study was ongoing. A change in the primary analysis population and the addition of a key secondary endpoint are two key updates to the study design which could potentially raise concerns about the trial integrity. Nevertheless, these modifications were performed before unblinding the study. More importantly, the primary analysis has been repeated on all mITT, mITT1 and mITT2 populations. These alternative populations may be used to assess the robustness and consistency of the primary analysis results on wider analysis sets.

Efficacy data and additional analyses

The enrolment in the study was stopped upon recommendation by the E-DMC following the review of data from the 45% interim analysis and determined that the pre-specified criteria for stopping the trial due to efficacy had been achieved. This is acceptable.

This report included as part of this marketing authorisation includes the results from 2426 randomised participants, while 1361 participants only (n=678 for PF-07321332/ritonavir, n=683 for placebo) were included in the 45% interim analysis.

The proportion of discontinuation remained limited, with 93.1% of the randomised participants who completed the treatment phase and 93.6 % who completed the follow-up period until day 34, with well-balanced proportions across the treatment groups.

Overall, the number of important protocol deviations was comparable between the treatment groups.

Overall, demographic and baseline characteristics are balanced across the treatment groups. It should be noted that a high percentage of patients with positive serology status at baseline was observed (51.2% vs 47.0%), while the exclusion criteria included any confirmed SARS-CoV-2 infection prior the study and, participants who have received or are expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit. According to the applicant, serology testing did not discriminate between IgG or IgM. This did not allow to explore if the positive status was due to unaware of prior (potentially asymptomatic) SARS-CoV-2 infection or to immune response related to the current COVID-19 episode (at the time of the enrolment). However, the applicant is committed to provide the results of the exploratory testing planned to further characterise the immune response to SARS-CoV-2 at baseline and over time (**REC**).

Across treatment groups, 38.9% and 35.7% had respectively 1 and 2 risk factors. Main risk factors observed in the participants were overweight (80.5% with a BMI >25 kg/m2, 36.8% with a BMI >30 kg/m2), hypertension (32.9%) and diabetes mellitus (12.2%). 21.67% were older than 60 years of ages and 12.8% older than 65 years of age. Patients with immunodeficiency were poorly represented with less than 1% of the study population. There are concerns on the maintenance of the benefit in patient with immunodeficiency for which a prolonged period of viral shedding could occur. This is of importance as viral clearance might be lower in those patients with a potential risk of treatment failure and emergence of resistance with the recommended 5 days treatment. Therefore, the applicant needs to particularly monitor treatment failure in this subset of patients post approval (**REC**).

Additionally, it is noteworthy that cigarettes smokers are largely represented (39%). Cigarette smoking is not per se considered a risk factor. Thus, the applicant is committed to further elaborate in which extent participants with "cigarettes smoke" at baseline presented this solely factor or other comorbidities, and its potential impact of the results (**REC**).

60.4% participants had baseline viral load ≥4.0 Log10 copies/mL.

The population enrolled was mainly from US (41.3%) and Europe (29.8%). This appears sufficient to generalise the results of the study results to the European population.

Given the period the study was conducted, the primary variant across both treatment arms was Delta (98.53%) and was distributed in high prevalence as subvariants Delta/21J (74.15%), Delta/21I (15.95%) and Delta/21A (8.43%). As the vast majority of the participants were infected with the Delta variant, the clinical efficacy of Paxlovid is only demonstrated in this VOC. However, *in vitro* data are supportive of activity of Paxlovid against other major VOCs including the currently circulating omicron variant.

Sequencing data are available from 878 participants, completed genotyping and phenotyping analyses from the pivotal C4671005 study should be provided (refer to clinical pharmacology recommendation).

While 6.2% of the participants were expected to receive mAb at the time of randomisation, only 1.7% participants received mAb for COVID-19 treatment, 12 participants (1.1%) in the PF-07321332/ritonavir group and 26 participants (2.3%) in the placebo group, remaining a limited proportion. Additionally, 186 (8.4%) participants received corticosteroids with ATC2 classification of "Corticosteroids for systemic use" during the study period (through Day 34); 69 (6.2%) for PF-07321332/ritonavir and 117 (10.5%) for placebo which seems consistent with the observed efficacy of the study treatment.

The determination of primary efficacy was based on a planned interim analysis of 774 subjects in mITT population. The estimated risk reduction was -6.3% with unadjusted 95% CI of (9.0%, 3.6%) and a 95% CI of (-10.61%, -2.02%) when adjusting for multiplicity. The 2-sided p-value was < 0.0001 with 2-sided significance level of 0.002.

In the supporting final analysis, the primary endpoint of the study was met with a 5.807% (95% CI: -7.777% to - 3.837%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 6.531% to 0.723% at Day-28, with PF-07321332/ritonavir in comparison with placebo treatment. No patient died in the Paxlovid treatment group whereas 9 deaths occurred in the placebo group according to the mITT and 12 deaths according to the mITT1. The results are consistent with the outcomes of the interim analysis. Sensitivity analyses were also generally consistent with primary results; remove data from Indian participants and the site terminated for GCP noncompliance did not change the conclusions.

Likewise, the primary results are consistent with the analysis conducted in mITT1 and mITT2 (respectively - 5.619% [95% CI: -7.207% to -4.031%; p<0.0001] and - 5.363% [95% CI: -6.884% to -3.842; p<0.0001]).

These finding were also supported by the results in the secondary endpoint reduction in the number of COVID-19 related medical visits. While statistically significant, a limited effect was observed in the median time to sustained alleviation of all targeted signs/symptoms through day 28 and the median time to sustained resolution of all targeted signs/symptoms through day 28.

Long-term data (i.e. at Week 34) are planned to be collected in the clinical study EPIC-HR but not yet available. The applicant has committed to provide the follow-up data as soon as available to ensure no further events onset which could potentially impact the main outcomes (**REC**).

A large proportion of participants started treatment beyond 3 days after COVID-19 onset (i.e. 38.6%) and are excluded of the mITT. If such proportion of patients failed to start the treatment within 3 days while clinical trials offer generally optimal conditions and follow-up, it is unlikely that the proportion will be better in clinical practice. Results in mITT1 may thus appear more appropriate for generalisation and more representative of the population of interest (notably encompassing patients treated within 5 days since symptoms onset). This is adequately reflected in the SmPC.

Given above considerations regarding the population of interest, together with the much larger number of subjects available in mITT1 than in mITT, subgroup analyses are assessed with mITT1 outcomes.

Overall, results were consistent in subgroup analyses for the risk factors mainly represented. It can be observed an absolute reduction of: 6.847% (95% CI: -9.823% to -3.871%; p<0.0001) in patients with a BMI >30 kg/m2, 10.614% (95% CI: -14.294% to -6.935%; p<0.0001) in patients with hypertension, 13.933% (95% CI: -20.066% to -7.800%; p<0.0001) in patients older than 65, and 5.512% (95% CI: -10.510% to -0.515%; p=0.0306) in patients with diabetes mellitus. The absolute reduction, 3.045% (95% CI: -5.164% to -0.926%; p=0.0049) in patients who are cigarettes smoker, was smaller while statistically significant.

In patients with positive serology status at baseline (55.6%), a limited, but statistically significant, absolute reduction of 1.337% (95% CI: -2.445% to -0.229%; p=0.0180) was observed. This makes it difficult to conclude on a relevant clinical efficacy. It has to be underlined that the number of events was low in the placebo group (8 hospitalisation and 1 death). As expected, the effect size is lower than the one observed in patients with seronegative status. However, given the lack of correlates of protection, the variable protection against circulating VOC, the fact that serostatus determination cannot be a prerequisite of treatment in a context of a pandemic and given the need to administer the antiviral treatment as early as possible, it is acknowledged that in practice those patients will be treated and some of them could retrieve a significant benefit. More broadly, the question therefore arises of the generalisability of the results to vaccinated patients with high risk for progression to severe COVID-19. The applicant noted that results of the study C4671002, in which vaccinated participants were enrolled, could provide supportive data. During the procedure, the applicant communicated on the failure to meet the primary endpoint of this study, preventing from formally interpreting the subgroup analyses. The applicant is committed to provide C4671002 study results as soon as available (**REC**).

Additionally, the applicant did not want to limit the indication to participants who do not require supplemental oxygen. However, oxygen supplementation for COVID-19 was an exclusion criterion and only started after randomisation in case of patient's need. Therefore, participants who required oxygen supplementation for COVID-19 were not randomised across groups and no conclusion can be drawn on the available data. Additionally, there is no reason to deviate from the harmonised wording to qualify the patients with non-severe type of COVID-19 i.e. not requiring O2. This was in fact the position adopted by the CHMP as part of the Article 5(3) procedure with the similar clinical study in support. The applicant adjusted the indication accordingly.

Finally, upon submission of the CMAA, the applicant covered in the indication the use of Paxlovid in the adolescents, on the basis of extrapolation from adults PK based on PK simulation from PopPK model only including PK data from healthy subjects (N=20) and not PK data in patients. Therefore, the applicant withdrew this age group from the indication as a response to the major objection by the CHMP due the lack of appropriate PK/PD data in high risk adolescent patients.

2.6.7. Conclusions on the clinical efficacy

The efficacy data submitted are considered sufficient to support the use of Paxlovid for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

While the clinical data are comprehensive, some further investigations are worth being undertaken, such as patients with seropositive status at baseline, the need to further elaborate in which extent participants with "cigarettes smoke" at baseline presented other comorbidities, further scrutiny through ongoing studies in immunocompromised patients (including chronic kidney disease, immunosuppression, cancer, or HIV infection) and the planned long-term data (i.e. at Week 34) from study C4671005.

Clinical efficacy recommendations are covered in Annex I.

2.6.8. Clinical safety

The safety data is primary based on the supportive final analysis (of the larger sample size than primary interim analysis) of the pivotal Study C4671005 (treatment in patients COVID-19 positive at High Risk, EPIC-HR) at the data cut-off date of 11 Dec 2021. Safety data from supportive Phase 1 studies 1001, 1011, 1014 and 1015 were also submitted.

As of the data cut-off (11 Dec 2021), 2246 (100.0%) participants were randomised into Study 1005, 2224 participants were included in the safety analysis set and 2102 (93.6%) participants had completed the safety follow-up (Day 34).

2.6.8.1. Patient exposure

The duration of treatment in the safety analysis set was similar across the two treatment arms (median duration of treatment of 5.00 days in both arms). A total of 94.1% in PF-07321332/ritonavir arm and 93.1% in placebo had a treatment compliance with study intervention from ≥80% to ≤115% reflecting a high adherence to treatment.

Table 45. Duration of treatment (actual dosing day) – safety analysis set (Protocol C4671005)

Table 9. Duration of Treatment (Actual Dosing Day) - Safety Analysis Set (Protocol C4671005)

	PF-07321332 300 mg + Ritonavir 100 mg (N=1109)	Placebo (N=1115)	Total (N=2224)
Duration of treatment (Days)[a]			
n	1109	1115	2224
Mean (SD)	5.05 (0.72)	5.03 (0.78)	5.04 (0.75)
Median (range)	5.00 (1.00, 6.00)	5.00 (1.00, 7.00)	5.00 (1.00, 7.00)
Category (Days)[a]			
1	15 (1.4)	11 (1.0)	26 (1.2)
2	8 (0.7)	22 (2.0)	30 (1.3)
3	17 (1.5)	24 (2.2)	41 (1.8)
4	10 (0.9)	9 (0.8)	19 (0.9)
5	871 (78.5)	856 (76.8)	1727 (77.7)
> 5	188 (17.0)	193 (17.3)	381 (17.1)

a. The Total Number of Dosing Days on which study drug was actually administered
PFIZER CONFIDENTIAL SDTM Creation: 12DEC2021 (10:10) Source Data: adex Table Generation: 12DEC2021 (12:09)
(Data cutoff date : 11DEC2021 Database snapshot date : 11DEC2021) Output File: ./nda/C4671005_EUA/adex_s001
Table 14.4.1.1 PF-07321332 is for Pfizer internal use.

Study intervention compliance was assessed by site personnel by reviewing the electronic study intervention diary, discussion with the participant, and through accounting of unused study

intervention returned by the participant at the study visits. Overall, treatment compliance with study intervention (≥80% to ≤115%) was 93.6% and adherence was similar for both PF-07321332/ritonavir and placebo treatment groups. The most frequently reported important protocol deviation related to investigational product was PF-07321332/placebo and ritonavir/placebo were taken > 5 minutes apart (9.5%) which was not expected to impact the safety profile.

Overall demographic and baseline characteristics in the safety analysis set (SAS) were comparable between the two arms of study C4671005. The median age is 46.00 yrs (range 18.00 – 88.00) with a greater proportion of 18-44 (47.7%); subjects ≥65 years of age represented 12.9% of total safety database. The repartition of male and female is comparable (50.9% of male, 49.1% female). As described above, there was 36.8% of subjects with obesity (BMI ≥30) and 43% of subjects with overweight (BMI 25≤30). Patients with most reported comorbidities patients with hypertension (33.0%), with diabetes mellitus (12.2%), with chronic lung disease (4.5%) and with cardiovascular disease (4.1%). There was a significant proportion of cigarettes smokers which is disputable as being per se a risk factor unless associated with comorbidities. The other comorbidities defining the high risk of developing severe illness from COVID-19 were reported in <1% of SAS. The large majority of subjects in the SAS did not receive/not expected to receive COVID-19 mAb treatment (93.8%).

Participants with known medical history of active liver disease or acute liver failure and participants receiving dialysis or have known moderate to severe renal impairment were excluded from the pivotal study C4671005; no safety data in these populations was gained in Study C4671005.

2.6.8.2. Adverse events

- Treatment-emergent adverse events (TEAEs), All causalities

The occurrence of TEAEs in PF-07321332/Ritonavir and placebo arms was comparable, i.e. 22.6% and 23.9% respectively. Serious AEs were less reported in PF-07321332/ritonavir arm than placebo arm, i.e. 1.6% and 6.6% respectively. There were 3 additional deaths reported in the final report compared to the 45% interim analysis (none in PF-07321332/ritonavir arm and 13 in placebo arm). The majority of reported AEs in the study were low grade. Grade ≥3 TEAEs were also less reported in PF-07321332/ritonavir arm than placebo arm, i.e. 4.1% and 8.3% respectively. No AE leading to study discontinuation occurred in PF-07321332/ritonavir arm and occurred at 1.2% subjects in placebo arm. AEs leading to drug discontinuation were more reported in placebo arm than PF-1332/ritonavir arm, 4.2% and 2.1% respectively. There were no data on the AEs leading to treatment modifications.

Table 46. Treatment-Emergent Adverse Events (All Causalities) - DAIDS Grade - Safety Analysis Set (Protocol C4671005)

Number (%) of Participants	PF-07321332 300 mg + Ritonavir 100 mg n (%)	Placebo n (%)
Participants evaluable for adverse events	1109	1115
Number of adverse events	476	525
Participants with adverse events	251 (22.6)	266 (23.9)
Participants with serious adverse events	18 (1.6)	74 (6.6)
Participants with Maximum Grade 3 or 4 adverse events	45 (4.1)	93 (8.3)
Participants with Maximum Grade 5 adverse events	0	13 (1.2)
Participants discontinued from study due to adverse events[a]	0	13 (1.2)
Participants discontinued study drug due to AE and continue study[b]	23 (2.1)	47 (4.2)
Participants with dose reduced or temporary discontinuation due to adverse events	4 (0.4)	4 (0.4)

Includes AEs that started on or prior to Day 34 visit.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study.
b. Participants who have an AE record that indicates that action taken with study treatment was drug withdrawn but AE did not cause the participants to be discontinued from study.
MedDRA v24.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 12DEC2021 (10:10) Source Data: adae Table Generation: 12DEC2021 (12:02)
(Data cutoff date : 11DEC2021 Database snapshot date : 11DEC2021) Output File: ./nda/C4671005 EUA/adae s020 Table 14.3.1.2.1 PF-07321332 is for Pfizer internal use.

All-causality TEAEs were most common (reported in ≥3% of participants in PF-07321332/ritonavir group) in the SOCs of Gastrointestinal disorders (6.0% in PF-07321332/ritonavir and 4.8% in placebo), Infections and Infestations (2.1% in PF-07321332/ritonavir and 6.8% in placebo), Investigations (8.0% in PF-07321332/ritonavir and 9.3% in placebo), Nervous system disorders (7.2% in PF-07321332/ritonavir and 2.3% in placebo), and Respiratory, thoracic and mediastinal disorders (2.1% in PF-07321332/ritonavir and 3.0% in placebo).

The most frequently reported TEAEs in the PF-07321332/ritonavir group (≥1%) were Dysgeusia (5.6%), Diarrhoea (3.1%), Fibrin D-dimer increased (1.9%), Alanine aminotransferase increased (1.5%), Creatinine renal clearance decreased (1.4%), Nausea (1.4%), Headache (1.4%) and Vomiting (1.1%).

The reported TEAEs (≥0.5%) that occurred at a greater frequency in the PF-07321332/ritonavir group compared with the placebo group were Dysgeusia (5.6% vs 0.3%), Diarrhoea (3.1% vs 1.6%), Vomiting (1.1% vs 0.8%), Headache (1.4% vs 1.3%), Pyrexia (0.7% vs 0.6%), Myalgia (0.6% vs 0.2%), Hypertension (0.6% vs 0.2%), Chills (0.5% vs 0), Dyspepsia (0.5% vs 0.4%); these TEAEs were mostly Grade 1-2. In PF-07321332/ritonavir arm, a total of 34 (3.1%) subjects experienced a Grade 3 AE and 11 (1.0%) had a Grade 4 events. The majority of the Grade 3-4 events were reported in the SOC Investigations (Creatinine renal clearance decreased, Fibrin D dimer increased) and Infections and infestations (COVID-19, COVID-19 pneumonia, abscess, pyelonephritis chronic, sepsis/viral sepsis).

- Treatment-related TEAEs

Treatment-related TEAEs were highly reported in PF-1335/ritonavir arm compared to placebo, i.e. 7.8% and 3.8% respectively. Despite the higher incidence of treatment-related TEAEs with PF-1335/ritonavir, only 1 (0.1%) treatment-related TEAE was considered as serious and 5 (0.4%) were Grade ≥3.

Table 47. Treatment-Emergent Adverse Events (Treatment Related) - DAIDS Grade - Safety Analysis Set (Protocol C4671005)

Number (%) of Participants	PF-07321332 300 mg + Ritonavir 100 mg (N=1109) n (%)	Placebo (N=1115) n (%)
Participants evaluable for adverse events	1109	1115
Number of adverse events	123	52
Participants with adverse events	86 (7.8)	42 (3.8)
Participants with serious adverse events	1 (<0.1)	0
Participants with Maximum Grade 3 or 4 adverse events	5 (0.5)	5 (0.4)
Participants with Maximum Grade 5 adverse events	0	0
Participants discontinued from study due to adverse events[a]	0	0
Participants discontinued study drug due to AE and continue study[b]	9 (0.8)	7 (0.6)
Participants with dose reduced or temporary discontinuation due to adverse events	2 (0.2)	3 (0.3)

Includes AEs that started on or prior to Day 34 visit.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study.
b. Participants who have an AE record that indicates that action taken with study treatment was drug withdrawn but AE did not cause the participants to be discontinued from study.
MedDRA v24.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 12DEC2021 (10:10) Source Data: adae Table Generation: 12DEC2021 (12:02)
(Data cutoff date : 11DEC2021 Database snapshot date : 11DEC2021) Output File: ./nda/C4671005_EUA/adae_s021
Table 14.3.1.3.1 PF-07321332 is for Pfizer internal use.

The most frequently reported treatment-related TEAEs in the PF-07321332/ritonavir group (≥1%) were Dysgeusia (3.7%), and Diarrhoea (1.9%).

Most of the TEAEs and treatment-related TEAEs experienced by participants in both treatment groups were mild to moderate (Grade 1-2) in severity. No Grade 4 or 5 treatment-related AEs occurred with PF-07321332/ritonavir. There was 5 (0.4%) cases of Grade 3 treatment-related TEAEs in the PF-07321332/ritonavir group: one case of palpitations (reported as serious AE, event resolved), two cases of ALAT increase, one case of ASAT increase, one case of dysgeusia and one case of rash maculo-papular. In the placebo arm, one participant had a potentially life-threatening (Grade 4) event (Blood glucose increased) that was considered related to treatment and 4 patients experienced Grade 3 treatment-related AEs (2 cases of nausea, one case of hepatic enzyme increased and one case of rash). No participant in either treatment group had an event of death related to an AE (Grade 5).

Hypertension

The proportion of hypertension events was higher in PF-07321332/ritonavir arm compared to placebo arm but reported at a low frequency (0.6% vs 0.25%). As regards this apparent imbalance, there was no case of hypertension considered as related to PF-07321332/ritonavir. Of the 7 cases of hypertension reported with PF-07321332/ritonavir, 6 were low grade (four Grade 1 events, two Grade 2 events) and resolved. Nevertheless, although not considered related, one patient not treated for hypertension, has experienced a Grade 3 hypertension on Day 5 that did not resolve, see narrative below.

A participant received study intervention from Days 1 to 3. The participant had the following risk factors: BMI >25 kg/m2, and history of Diabetes mellitus. He experienced 2 SAEs (Abscess [Grade 3] and Sepsis [Grade 4]) on Day 4. On Day 5, he had an event of Grade 3 Hypertension and Grade 3 pneumonia. On Day 6, he experienced Grade 2 Insomnia. All of the events were assessed as not related to study intervention by the investigator. All events resolved except severe Hypertension and

severe Pneumonia, which were reported as not recovered/not resolved. The participant was permanently discontinued from study intervention and did not complete the study due to withdrawal of consent on Day 11.

It is outlined that hypertension events mostly occurred during the Paxlovid treatment schedule based on the listing of AEs within PF-07321332/ritonavir, i.e. 6 of the 7 patients experiencing hypertension had an event onset between Day 2 and Day 5 and one patient had hypertension at Day 25. Based on the provided listings of AEs and on risk factors, it is observed that the majority of patients experiencing hypertension with PF-07321332/ritonavir had no history of hypertension (4 of 7 patients). Taking into account these data and the known risk of hypertension with ritonavir at a upper dosage and a long-term treatment duration (see section 4.8 of the SmPC of Ritonavir 100mg) making unclear the contributory effect of PF-07321332, it is considered necessary to further evaluate the risk of hypertension in the routine PV and follow-up questionnaires. Ongoing clinical studies notably study in standard risk population (C-4671002) of patients without having risk factor patients. Due to this sensitive issue in a population where hypertension is already a risk factor, the CHMP has asked the company to complete the preliminary safety review covering safety data from ongoing early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March by April 2022 (**LEG**) awaiting for a global safety review planned to be made by the applicant on the 3 applicant's sponsored clinical studies performed (EPIC-HR, EPIC-SR and study in PEP) planned to be provided in June 2022.

Myalgia

A similar apparent imbalance (0.6 vs 0.2% for Paxlovid vs Placebo respectively) was observed for myalgia events. Given the known risk of myalgia with ritonavir at a upper dosage and a long-term treatment duration (see section 4.8 of the SmPC of Ritonavir 100mg) the contributory effect of PF-07321332 and more globally of Paxlovid 5 days treatment duration, the CHMP has also requested a safety review (**REC**).

Hepatotoxicity

Detailed narratives on all participants included in the safety population from the final analysis with hepatotoxicity in study 1005 were provided.

Hepatotoxicity cases occurred at similar rate in both arms and were reported in 11 (1.0%) subjects in PF-07321332/ritonavir arm and 16 (1.4%) subjects in placebo arm. The majority of hepatotoxicity cases reported in the safety population were hepatic transaminase elevation > 5xULN. Indeed a risk of hepatotoxicity is associated with ritonavir and mentioned in the section 4.8 of the SmPC of Ritonavir 100 mg, i.e. Hepatic transaminase elevations exceeding five times the upper limit or normal, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir alone or in combination with other antiretrovirals. Hepatotoxicity is addressed in section 4.4 of the proposed SmPC of Paxlovid considering the known risk with ritonavir which is endorsed.

Adverse drug reactions

The proposed list of adverse reactions in section 4.8 of the SmPC is as follows:

Table 48. adverse reactions with Paxlovid

System organ class	Frequency category	Adverse reactions
Nervous system disorders	Common	Dysgeusia, headache
Gastrointestinal disorders	Common	Diarrhoea, vomiting

Dysgeusia and diarrhoea were known risks with ritonavir mentioned in section 4.8 of SmPC of Ritonavir 100 mg at very common frequency and based on the safety data in study 1005 their inclusion as ADR for Paxlovid is agreed. Vomiting and headache were listed as ADR in the proposed SmPC which is supported based on their frequencies, see all causality AEs section above.

Adverse event of special interest (AESI)

1) Hemodynamic events

Vital signs measurements did not suggest clinically meaningful changes relative to hemodynamic events across treatment groups.

Table 49. Summary of Treatment-Emergent Hemodynamic Adverse Events by Decreasing Frequency (All Causalities) - Safety Analysis Set (Protocol C4671005)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=1109)	Placebo (N=1115)
Number (%) of Participants: by Preferred Term	n (%)	n (%)
Hypertension	7 (0.6)	2 (0.2)
Hypotension	1 (0.1)	4 (0.4)

2) Inflammatory events

Table 50. Summary of Treatment-Emergent Inflammatory Adverse Events by Decreasing Frequency (All Causalities) - Safety Analysis Set (Protocol C4671005)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=1109)	Placebo (N=1115)
Number (%) of Participants: by Preferred Term	n (%)	n (%)
Fibrin D dimer increased	21 (1.9)	31 (2.8)
Activated partial thromboplastin time prolonged	9 (0.8)	12 (1.1)
C-reactive protein increased	9 (0.8)	13 (1.2)
Haptoglobin increased	3 (0.3)	3 (0.3)
Prothrombin time prolonged	3 (0.3)	5 (0.4)
Leukocytosis	2 (0.2)	0
Platelet count increased	2 (0.2)	1 (0.1)
White blood cell count increased	2 (0.2)	0

3) Thyroid-related events

Table 51. Summary of Treatment-Emergent Thyroid-related Adverse Events by Decreasing Frequency (All Causalities) - Safety Analysis Set (Protocol C4671005)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=1109)	Placebo (N=1115)
Number (%) of Participants: by Preferred Term	n (%)	n (%)
Blood thyroid stimulating hormone increased	6 (0.5)	7 (0.6)
Thyroxine increased	1 (0.1)	0
Thyroxine free increased	0	1 (0.1)

No difference was observed in the incidence rates of AESI between the two treatment arms except the hypertension events for hemodynamic events reported at a greater frequency in PF-07321332/ritonavir than placebo and Fibrin D dimer increased for the inflammatory events reported at

a greater frequency in placebo compared to PF-07321332/ritonavir (2.8% vs 1.9%) likely in relation to disease progression in the placebo arm.

2.6.8.3. Serious adverse events, deaths, and other significant events

The overall incidence of participants with all-causality treatment-emergent SAEs was lower in the PF-07321332/ritonavir treatment group (1.6%) compared with placebo (6.6%).

Table 52. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) - Safety Analysis Set (Protocol C4671005)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=1109)	Placebo (N=1115)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)
With any adverse event	18 (1.6)	74 (6.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	1 (0.1)
Anaemia	0	1 (0.1)
CARDIAC DISORDERS	1 (0.1)	0
Palpitations	1 (0.1)	0
GASTROINTESTINAL DISORDERS	0	1 (0.1)
Rectal haemorrhage	0	1 (0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1)	0
Chest discomfort	1 (0.1)	0
INFECTIONS AND INFESTATIONS	10 (0.9)	56 (5.0)
Abscess	1 (0.1)	0
Atypical pneumonia	0	1 (0.1)
COVID-19	2 (0.2)	8 (0.7)
COVID-19 pneumonia	6 (0.5)	37 (3.3)
Pneumonia	1 (0.1)	11 (1.0)
Sepsis	1 (0.1)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (0.1)
Craniocerebral injury	0	1 (0.1)
Eye injury	0	1 (0.1)
Hand fracture	0	1 (0.1)
Road traffic accident	0	1 (0.1)
Wrist fracture	0	1 (0.1)
INVESTIGATIONS	4 (0.4)	4 (0.4)
Alanine aminotransferase increased	0	1 (0.1)
Creatinine renal clearance decreased	2 (0.2)	3 (0.3)
Fibrin D dimer increased	0	1 (0.1)
Haemoglobin decreased	1 (0.1)	0
Oxygen saturation decreased	1 (0.1)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	1 (0.1)
Colon adenoma	0	1 (0.1)
NERVOUS SYSTEM DISORDERS	2 (0.2)	0
Brain stem stroke	1 (0.1)	0
Facial paralysis	1 (0.1)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1)	18 (1.6)
Acute respiratory failure	0	5 (0.4)
Dyspnoea	1 (0.1)	3 (0.3)
Hypoxia	0	2 (0.2)
Interstitial lung disease	0	2 (0.2)
Pneumonitis	0	5 (0.4)
Pulmonary embolism	0	2 (0.2)
Respiratory failure	0	1 (0.1)
VASCULAR DISORDERS	1 (0.1)	0
Hypertensive crisis	1 (0.1)	0

The most frequently reported treatment emergent SAEs in the PF-07321332/ritonavir group (≥2 participants) were COVID-19 (2 participants, 0.3% [compared with 7 participants, 1% in the placebo group]), and COVID-19 pneumonia (4 participants, 0.6% [compared with 21 participants, 3.1% in the placebo group]). All of these SAEs were considered related to the disease under study.

Regarded the non-COVID-19 related SAEs occurring with PF-07321332/ritonavir, it was reported one case of Chest discomfort, Dyspnoea, Palpitations (resolved at Day 5), one case of Facial paralysis (recovered with sequelae at Day 37), one case of Abscess, Sepsis (resolved at Day 9), one case of Haemoglobin decreased (resolved at Day 7) and one case of Creatinine renal clearance decreased (Low creatinine was a pre-existing condition that the participant was unaware of, SAE ongoing at the time of the last available report).

Among the non-related COVID-19 SAEs reported, one case was considered as treatment related, see the narrative below.

Participant experiencing SAEs of Chest discomfort, Dyspnoea, and Palpitations resulting in permanent discontinuation from study intervention:

The participant received study intervention from Days 1 to 2. The participant had the following risk factors: BMI >25 kg/m2.

The participant started experiencing COVID-19 signs and symptoms from Day -3 and had a confirmed positive test result for SARS-CoV-2 on the same day. Further on Day 2, the participant was hospitalised due to the SAEs of Grade 2 Chest discomfort, Grade 2 Dyspnoea, and Grade 3 Palpitations. On the same day (Day 2), a chest X-ray showed left sinus infarction in lower lobe, which was related to COVID-19. The participant's ECG was normal. The participant received oxygen therapy and was treated with enoxaparin, acetylsalicylic acid, famotidine, potassium phosphate and multivitamin supplement as prophylaxis. Study intervention was permanently discontinued on Day 2 in response to the events of Chest discomfort, Dyspnoea, and Palpitations. The events of Chest discomfort, Dyspnoea, Palpitations, and Pyrexia were reported as resolved on Day 5.

In the opinion of the investigator, there was a reasonable possibility that the events of Chest discomfort, Dyspnoea, and Palpitations were related to the study intervention (ritonavir); there was not a reasonable possibility that the events were related to the study intervention (PF-07321332), concomitant drug or clinical trial procedure.

There were **no deaths in the PF-07321332 + Ritonavir arm** according to the provided data on study 1005. A total of 13 deaths were reported in the placebo arm, all related to COVID-19 and respiratory event (hypoxia, acute respiratory distress/failure).

2.6.8.4. Laboratory findings

The clinical safety laboratory tests were to be performed at baseline, Day 5 then Days 14 and 34 required only if clinically relevant abnormal laboratory values were present from a sample drawn at the previous study visit.

The overall incidence of laboratory test abnormalities occurring within 34 days of first dose was comparable between both treatment groups. No major haematological and clinical chemistry abnormalities were detected in both PF-07321332/ritonavir and placebo arms. The most frequently occurring laboratory test abnormalities (occurring in ≥5% participants in any treatment group) were fibrinogen (<0.75 x baseline; >1.25 x baseline), aPTT (>1.1 x ULN), D-Dimer (>1.5 x ULN), PT (>1.1 x ULN), bicarbonate (<0.9 x LLN), thyrotropin (>1.2 x ULN), glucose (>1.5 x ULN), creatine kinase (>2.0 x ULN), and neutrophils (>1.2 x ULN).

Elevations of hepatic transaminases >3xULN were reported at comparable rates in both PF-07321332/ritonavir and placebo arms, i.e ASAT at 1.4% in each arm; ALAT at 3.6% and 4.2% respectively.

Vital signs

Baseline values for systolic and diastolic blood pressure, heart rate, oxygen saturation (%), body temperature, and respiratory rate, were similar across both treatment groups, and there were no clinically meaningful differences between treatment groups in the mean changes from baseline in vital signs assessments.

- The mean maximum change from baseline in vital signs were comparable for participants in the PF-07321332/ritonavir treatment group compared with the placebo group.
- The incidence of participants with diastolic blood >90 mmHg, pule rate >120 bpm or systolic blood pressure >140 mmHg was comparable across treatment groups.

ECGs

Overall, few (≤5%) participants in either treatment group had clinically significant findings in Study 1005. Mean baseline values and mean changes from baseline were similar between treatment groups for all ECG parameters.

The Study 1001 Part 5 aimed to evaluate QTc of PF-07321332/ritonavir at supratherapeutic dose. The upper bounds of 90% CI for ΔΔQTcF estimates across the entire concentration range (supratherapeutic, 2 x therapeutic exposure and therapeutic exposure) were all less than 10 ms suggesting no clinically relevant effect of PF-07321332/ritonavir on QTcF interval.

2.6.8.5. Safety in special populations

At the time of the data cutoff in Study 1005 (final CSR), there was 2 reported pregnancy in the safety database. Both participants were in the placebo group and will continue to be followed for pregnancy outcomes. Please refer to nonclinical part.

2.6.8.6. Safety related to drug-drug interactions and other interactions

Refer to drug-drug interaction in the pharmacokinetic section

2.6.8.7. Discontinuation due to adverse events

- AEs leading to treatment discontinuation

The AEs leading to treatment discontinuation were more reported in placebo arm than PF-07321332/ritonavir arm, i.e. 4.2% and 2.1% respectively. The most frequently reported AEs leading to discontinuation with PF-07321332/ritonavir treatment were Nausea (0.5%), Vomiting (0.4%) and Creatinine renal clearance decreased (0.3%).

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=1109)	Placebo (N=1115)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**
INVESTIGATIONS	9 (0.8)	9 (0.8)
Creatinine renal clearance decreased	3 (0.3)	4 (0.4)
Glomerular filtration rate decreased	2 (0.2)	2 (0.2)
White blood cell count decreased	2 (0.2)	0
Alanine aminotransferase increased	1 (0.1)	0
Aspartate aminotransferase increased	1 (0.1)	1 (0.1)
Differential white blood cell count abnormal	1 (0.1)	0
Haemoglobin decreased	1 (0.1)	0
Oxygen saturation decreased	1 (0.1)	0
Blood glucose increased	0	1 (0.1)
Glomerular filtration rate abnormal	0	1 (0.1)
GASTROINTESTINAL DISORDERS	7 (0.6)	8 (0.7)
Nausea	5 (0.5)	5 (0.4)
Vomiting	4 (0.4)	2 (0.2)
Abdominal pain lower	1 (0.1)	0
Colitis	1 (0.1)	0
Diarrhoea	1 (0.1)	1 (0.1)
Gastritis	0	1 (0.1)
NERVOUS SYSTEM DISORDERS	4 (0.4)	2 (0.2)
Dysgeusia	2 (0.2)	0
Dizziness	1 (0.1)	1 (0.1)
Headache	1 (0.1)	0
Restless legs syndrome	0	1 (0.1)
INFECTIONS AND INFESTATIONS	2 (0.2)	20 (1.8)
COVID-19	1 (0.1)	4 (0.4)
COVID-19 pneumonia	1 (0.1)	13 (1.2)
Pneumonia	0	3 (0.3)
VASCULAR DISORDERS	2 (0.2)	0
Hypertension	1 (0.1)	0
Hypertensive crisis	1 (0.1)	0
CARDIAC DISORDERS	1 (0.1)	0
Palpitations	1 (0.1)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1)	2 (0.2)
Chest discomfort	1 (0.1)	0
Asthenia	0	1 (0.1)
Peripheral swelling	0	1 (0.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.1)	0
Myalgia	1 (0.1)	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.1)	0
Vaginal haemorrhage	1 (0.1)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1)	9 (0.8)
Dyspnoea	1 (0.1)	1 (0.1)
Acute respiratory failure	0	1 (0.1)
Cough	0	1 (0.1)
Hypoxia	0	1 (0.1)
Interstitial lung disease	0	1 (0.1)
Pneumonitis	0	3 (0.3)
Respiratory failure	0	1 (0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.1)	1 (0.1)
Rash maculo-papular	1 (0.1)	0
Rash	0	1 (0.1)
PSYCHIATRIC DISORDERS	0	1 (0.1)
Insomnia	0	1 (0.1)
RENAL AND URINARY DISORDERS	0	1 (0.1)
Renal impairment	0	1 (0.1)

- AEs leading to study discontinuation

No participant in the PF-07321332/ritonavir group discontinued the study due to TEAEs (all causalities) compared with 13 participants (1.2%) in the placebo group.

2.6.8.8. Supportive studies

- Study 1001 – Phase 1 study
    - Part 1 – SAD (n=13): Out of 12 TEAEs, 7 were observed in placebo (alone or enhanced with ritonavir) treatment groups, and 5 were observed in the PF-07321332 500 mg, 1500 mg and 250 mg/ritonavir treatment groups. The SOCs with participants reporting all-causality TEAEs across all treatment groups, including placebo, were Nervous system disorders (4 events; 2 placebo and 2 treated), Gastrointestinal disorders (3 events; all placebo), General disorders and administration site conditions (2 events; 1 placebo and 1 treated), Psychiatric disorders (2 events; 1 placebo and 1 treated) and Investigations (1 event; treated). None of the TEAEs in PART-1 were treatment-related. No participant had an SAE, severe AE, or dose reduced or temporary discontinuation due to AEs.
    - Part 2 – MAD (n=29): TEAEs were reported at similar rate across the 6 treatment arms in PART-2. The SOCs with the greatest number of participants reporting all-causality TEAEs were Gastrointestinal disorders (13 events; 1 placebo and 12 treated), followed by General disorder and administration site conditions (8 events; 2 placebo and 6 treated), Nervous system disorders (6 events; all treated) and Investigations (5 events; 2 placebo and 3 treated). The numbers of treatment-related TEAEs were also similar between the 6 treatment arms in PART-2. No participant had an SAE, severe AE, discontinuation from study due to AEs, or dose reduced or temporary discontinuation due to AEs in PART-2.
    - Part 3 – RBA/FE (n=12): TEAEs were reported at similar rate in PF- 07321332 250 mg (suspension), fasted and PF- 07321332 250 mg (tablet), fasted group (3/12, 25.0% in each group) and in 1/12 (8.3%) subjects included in the PF- 07321332 250 mg (tablet), fed group. The SOCs with participants reporting all-causality or treatment-related TEAEs were General disorders and administration site conditions (5 events, 1 treatment-related), and Nervous system disorders (3 events, all treatment-related). Of note the case of Chest discomfort reported with PF- 07321332 was considered as treatment-related similarly to the SAE case reported in Study 1005.
    - Part 4 – M&E (n=6): Only 1 all-causality TEAE (Nasopharyngitis) was reported in PART-4. This AE was not treatment related.
    - Part 5 – SE (n=10): The incidences of all-causality and treatment-related TEAEs were the same between the 2 groups, treated and placebo in PART-5. The most frequently reported SOC of TEAE was Gastrointestinal disorders (6 events, 2 treatment-related).
- Study 1011 (Renal impairment):

A total of 35 participants were assigned to treatment and 34 of them were treated, 8 each in mild, moderate, and severe renal impairment group and 10 in healthy control group. There was an imbalance in AEs with a higher incidence of AEs in severe renal impairment compared to patients with normal renal function and mild/moderate renal impairment. All-causality AEs were reported by 2 participants in the normal renal function group and by 1, 1 and 5 participants in the mild, moderate,

and severe renal impairment groups, respectively. Most of the all-causality AEs (17 out of 22) were reported by participants in the severe renal impairment group. One participant in the severe renal impairment had 3 SAEs, including 1 severe SAE (Pulmonary oedema), and 2 moderate SAEs (1 Acute kidney injury, 1 Pneumonia), and all 3 were considered not treatment related. This participant discontinued study due to the SAE of Acute kidney injury. There were no deaths in this study. All-causality AEs were most frequently reported under the SOCs of Gastrointestinal disorders, General disorders and administration site conditions, and Nervous system disorders.

- Study 1014

All 12 participants took at least 1 dose of study intervention and were included in the safety analysis.

In Period 1 (PF-07321332 300 mg/ritonavir 100 mg as a single oral dose), 4 AEs were reported in 4 (33.3%) participants, and 1 AE was considered treatment related. The TEAEs reported by PT were Vessel puncture site haematoma, Dysgeusia, Sciatica and Polyuria (1 participant each, 8.3%). All 4 TEAEs were mild in severity.

In Period 2 (Carbamazepine on a titration schedule for 15 days + PF-07321332 300 mg/ritonavir 100 mg as single dose at Day 14), 18 AEs were reported in 9 (75.0%) participants, and 8 AEs reported in 6 (50%) participants were considered treatment related. One participant discontinued from study due to treatment related AE. The most frequently reported all-causality TEAEs by PT, regardless of SOC, were Transaminases increased (5 participants, 41.7%). The majority of the TEAEs (17/18) were mild in severity. There was 1 moderate TEAE of Inappropriate antidiuretic hormone secretion (Hyponatremia/SIADH) leading to study discontinuation and considered treatment-related.

- Study 1015

Twelve participants received at least 1 study treatment and were thus included in the safety analysis.

All-causality 26 and 48 AEs were reported by 7 and 10 participants in Periods 1 and 2, respectively. None of the AEs were considered serious or severe by the investigator. No participants discontinued from the study or study treatment or had dose reductions due to AEs. Among the all-causality TEAEs, 24 out of 26 AEs in Period 1 and 43 out of 48 AEs in Period 2 were considered treatment related.

In Period 1, 1 participant reported Vomiting and Headache (both related to study treatment); 1 participant reported Dizziness (not related to study treatment) and Headache (related to study treatment).

In Period 2, 1 participant reported Constipation (related to study treatment); and 1 participant reported Anorectal discomfort, Constipation, Diarrhoea, and Gastrointestinal motility disorder (all related to study treatment).

One participant experienced the event of Atrioventricular block first degree on Study Day 3 in Period 1, which continued through Period 2. The event resolved on Study Day 13.

2.6.8.9. Post marketing experience

No data has been provided. Data will be presented for authorities as part of routine pharmacovigilance.

2.6.9. Discussion on clinical safety

The safety data provided by the applicant is primarily based on the final analysis of the pivotal study C4671005/EPIC-HR at the data cut-off date of 11 Dec 2021. The treatment was intended at the posology of PF-07321332 300mg and ritonavir 100mg every 12h for 5 days. As of the data cut-off, 2246 (100.0%) participants were randomised into study C4671005, 2224 participants were included in the safety analysis set and 2102 (93.6%) participants had completed the safety follow-up (Day 34).

Overall demographic and baseline characteristics in the safety analysis set (SAS) were comparable between the two arms. Participants with known medical history of active liver disease or acute liver failure, and participants receiving dialysis or have known moderate to severe renal impairment were excluded from the pivotal study C4671005; thus, no safety data in these populations was generated.

The duration of treatment in the safety analysis set was similar across the two treatment arms (median duration of treatment of 5.00 days in both arms). A total of 94.1% in PF-07321332/ritonavir arm and 93.1% in placebo had treatment compliance with study intervention from ≥80% to ≤115% reflecting a high adherence to treatment.

The incidence of TEAEs was slightly lower in PF-07321332/ritonavir compared to placebo, i.e. 22.6% and 23.9% respectively. It should be noted that the majority of the adverse events occurring in the study may be confounded with COVID-19 symptoms. The majority of reported AEs in the study were low grade. Grade ≥3 TEAEs were less reported in PF-07321332/ritonavir arm than placebo arm, i.e. 4.1% and 8.3% respectively. In PF-07321332/ritonavir arm, a total of 34 (3.1%) subjects experienced a Grade 3 AE and 11 (1.0%) had a Grade 4 events. The majority of the Grade 3-4 events were reported in the SOCs Investigations (Creatinine renal clearance decreased, Fibrin D dimer increased) and Infections and infestations (COVID-19, COVID-19 pneumonia, abscess, pyelonephritis chronic, sepsis/viral sepsis). Treatment-related TEAEs were however more reported in PF-07321332/ritonavir arm compared to placebo, i.e. 7.8% and 3.8% respectively.

The most frequently reported TEAEs in the PF-07321332/ritonavir group (≥1%) were Dysgeusia (5.6%), Diarrhoea (3.1%), Fibrin D-dimer increased (1.9%), Alanine aminotransferase increased (1.5%), Creatinine renal clearance decreased (1.4%), Nausea (1.4%), Headache (1.4%) and Vomiting (1.1%). Dysgeusia and Diarrhoea were the most frequently reported treatment-related TEAEs in the PF-07321332/ritonavir group (3.7% and 1.9% respectively). The reported TEAEs (≥0.5%) that occurred at a greater frequency in the PF-07321332/ritonavir group compared with the placebo group were Dysgeusia (5.6% vs 0.3%), Diarrhoea (3.1% vs 1.6%), Vomiting (1.1% vs 0.8%), Headache (1.4% vs 1.3%), Pyrexia (0.7% vs 0.6%), Myalgia (0.6% vs 0.2%), Hypertension (0.6% vs 0.2%), Chills (0.5% vs 0), Dyspepsia (0.5% vs 0.4%); these TEAEs were mostly Grade 1-2. There was 5 (0.4%) cases of Grade 3 treatment-related TEAEs in the PF-07321332/ritonavir group: one case of palpitations (reported as serious AE, event resolved), two cases of ALAT increase, one case of ASAT increase, one case of dysgeusia and one case of rash maculo-papular.

Hypertension occurred at a low frequency overall but with an apparent imbalance (0.6% and 0.2%, in the PF 07321332/ritonavir and placebo group, respectively). There was no case of hypertension considered as related to PF-07321332/ritonavir. Of the 7 cases of hypertension reported with PF-07321332/ritonavir, 6 were low grade (four Grade 1 events, two Grade 2 events) and resolved. Although not considered related, one patient, not treated for hypertension, experienced a Grade 3 hypertension on Day 5 that did not resolve. It is noted that hypertension events mostly occurred during the Paxlovid treatment schedule based on the listing of AEs within PF-07321332/ritonavir, i.e. 6 of the 7 patients experiencing hypertension had an event onset between Day 2 and Day 5 and one patient had hypertension at Day 25. Based on the provided listings of AEs and on risk factors, it is observed that the majority of patients experiencing hypertension with PF-07321332/ritonavir had no

history of hypertension (4 of 7 patients). Narratives of the hypertension cases occurring in PF-07321332/ritonavir were provided. Based on these observations and due to the limited number of cases, a causality with Paxlovid cannot be concluded at this stage. Additionally, the possible contributory effect of DDI with ritonavir cannot be excluded for the serious case of hypertensive crisis. Due to this sensitive issue in a population where hypertension is already a risk factor, the CHMP has asked the company to complete the preliminary safety review covering safety data from ongoing early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March by April 2022, awaiting for a global safety review planned to be made by the applicant on the 3 applicant's sponsored clinical studies performed (EPIC-HR, EPIC-SR and study in PEP) planned to be provided in June 2022 **(LEG**). Additionally, this issue will be further followed-up through routine PV and follow-up questionnaires, together with the review of the upcoming safety data. The CHMP has considered that it would be premature to conclude on causality, therefore it is not reflected in section 4.8 of the SmPC.

There was also an apparent imbalance for myalgia, more reported in PF-07321332/ritonavir arm than the placebo arm (7 [0.6%] vs 2 [0.2%]). The narratives for all the myalgia cases occurring in the PF-07321332/ritonavir arm were provided. Two cases were considered related to treatment and four were considered due to COVID-19. The limited number preclude any conclusion on a correlation between myalgia and Paxlovid at this stage. Ongoing studies are expected to provide more data regarding this issue. Taking into account the imbalance of myalgia events across the treatment arms, the two PF-07321332/ritonavir related cases of myalgia reported in study C4671005 and the known risk of myalgia with ritonavir (when used for the treatment of HIV infection at a higher dosage and for a long-term treatment duration), it was agreed to further evaluate the issue of myalgia through routine PV and to review the upcoming requested safety data as part of Post Authorisation Measure based on early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March by April 2022, awaiting for a global safety review planned to be made by the applicant on the 3 applicant's sponsored clinical studies performed (EPIC-HR, EPIC-SR and study in PEP) planned to be provided in June 2022 (**REC**).

There were pre-specified adverse event of special interest (AESI) including hemodynamic events, inflammatory events, and thyroid-related events. No difference was observed on the incidence rates of AESI between the two treatment arms except the hypertension events for hemodynamic events, which were reported at a greater frequency in PF-07321332/ritonavir than placebo and Fibrin D dimer increased for the inflammatory events reported at a greater frequency in placebo compared to PF-07321332/ritonavir (2.8% vs 1.9%).

Serious AEs were less reported in PF-07321332/ritonavir arm than placebo arm, i.e. 1.6% and 6.6% respectively. The SAEs were mostly related to COVID-19. The most frequently reported SAEs with PF-07321332/ritonavir were COVID-19 pneumonia, COVID-19, and creatinine renal clearance decreased and occurred less frequently compared to placebo group (0.5% vs 3.3%, 0.2% vs 0.7% and 0.2% vs 0.3% respectively). Among the non-related COVID-19 SAEs reported, one case of chest discomfort, dyspnoea and palpitations was considered by the investigator as reasonably possible to be related to the treatment. The treatment was permanently discontinued on Day 2 and the events were reported as resolved on Day 5. The SAEs occurring with PF-07321332/ritonavir treatment were manageable. The majority of the reported SAEs with PF-07321332/ritonavir were considered as resolved/recovered and 2 cases were ongoing at the time of the report (creatinine renal clearance decreased and oxygen saturation decreased).

No death occurred in the PF-07321332/ritonavir group while a total of 13 deaths (12 in the 28-day period and 1 in the safety follow-up period) were reported in the placebo arm, all related to COVID-19.

The overall incidence of laboratory test abnormalities occurring within 34 days of first dose was comparable between both treatment groups. No major haematological and clinical chemistry abnormalities were detected in both PF-07321332/ritonavir and placebo arms.

No in-depth QT study was performed. Based on ECG data collected, the applicant did not identify any clinically relevant difference between treatment groups. In addition, the study 1001 Part 5 aimed to evaluate QTc of PF-07321332/ritonavir at supratherapeutic dose and the ΔΔQTcF estimates suggested no clinically relevant effect of PF-07321332/ritonavir on QTcF interval.

In light of the nonclinical findings, it is appropriate that Paxlovid is not recommended during pregnancy and in women of childbearing potential not using contraception.

No summary of AEs by age group was provided by the applicant. Data on safety profile of PF-07321332/ritonavir with regard to children ≥12 to <18 years of age included initially in the claimed indication was lacking. Additionally, data was also missing in patients with severe renal impairment, with severe hepatic impairment and in pregnant women and WOBPC. These issues are addressed as safety concerns in the RMP (missing information).

The AEs leading to treatment discontinuation were more reported in placebo arm than PF-07321332/ritonavir arm, i.e. 4.2% and 2.1% respectively. The most frequently reported AEs leading to discontinuation with PF-07321332/ritonavir treatment were Nausea (0.5%), Vomiting (0.4%) and Creatinine renal clearance decreased (0.3%). There was no study discontinuation due to AE with PF-07321332/ritonavir and 13 in placebo arm (subjects who died).

No notable safety signal was detected with PF- 07321332/ritonavir in the supportive studies except study 1011. An imbalance in AEs was observed in study 1011 (renal impairment) with a higher incidence of AEs in severe renal impairment compared to patients with normal renal function and mild/moderate renal impairment, which can be expected in view of the significant over-exposure observed in this study (approx. 90% in patients with moderate impairment and approx. 200% in patients with severe impairment). 5 of the 8 patients with severe renal impairment (RI) reported an AE, of which one participant who had 3 SAEs and discontinued study due to a SAE of Acute kidney injury that may be related to the severe renal impairment condition. Two participants in the normal renal function, one participant in mild renal impairment and one participant in moderate renal impairment groups experienced an AE. As expected, in view of the large increase of PK exposure in patients with severe renal impairment (+204%), an increase of AEs is observed in those patients.

One case of Atrioventricular block was reported with PF-07321332/ritonavir in study 1015 and one case of Chest discomfort was reported with PF- 07321332 in study 1001 and considered as treatment-related. Taking into account the SAE of Palpitations, Chest discomfort and dyspnoea that occurred with Paxlovid in Study 1005, a risk of cardiovascular events cannot be ruled out but the limited cases reported prevent any conclusion at this stage.

Two clinical studies sponsored by the applicant are still on-going that will provide additional information regarding the safety profile and possible rare adverse reactions of Paxlovid.

2.6.10. Conclusions on the clinical safety

Based on the provided safety data, no major concern was identified in the safety profile of Paxlovid. The most frequent adverse reactions were dysgeusia, diarrhoea, vomiting and headache which are described in section 4.8 of the SmPC. The safety profile is expected to be further substantiated with the on-going studies in treatment of patients with standard risk of COVID-19 and post exposure prophylaxis. Given that in these two studies patients are less likely to have comorbidities, the causality assessment might be facilitated.

The CHMP considers the following measures necessary to address the clinical issues:

a) A safety review for hypertension covering safety data from ongoing early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March should be provided by April 2022, awaiting for a global safety review planned to be submitted covering the 3 applicant's sponsored clinical studies (EPIC-HR, EPIC-SR and study in PEP) in June 2022.

Risk of medication errors related to the co-packaged blister (including in relation to the dose adjustment in patients with moderate renal impairment), the handling of the numerous drug drug interactions by healthcare professionals in the outpatient setting less familiar than infectious diseases specialists at hospital used to handle the ritonavir driven interactions in the field of HIV infection, will be a source of particular scrutiny in post-marketing safety data as part of routine pharmacovigilance.

Clinical safety recommendations and legally binding measures are covered in Annex I.

2.7. Risk Management Plan

2.7.1. Safety concerns

The applicant has submitted an RMP including the following summary of safety concerns:

Table 53. Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Safety in patients with hepatic impairment Safety in patients with renal impairment Safety during use in pregnancy and lactation

Risks considered important for the inclusion in the summary of safety concerns

Missing information

Safety in patients with hepatic impairment: Since participants with known medical history of active liver disease or acute liver failure were excluded from the pivotal study C467-1005 (EPIC-HR), safety in patients with hepatic impairment should be considered as missing information. Of note in the PK study in patients with hepatic impairment, the category of patients with severe hepatic impairment was not covered. In moderate hepatic impairment, the PK data did not significantly differ from the control.

Safety in patients with renal impairment: There is a lack of data in the moderate to severe renal impairment population in study C467-1005 since this population was excluded. The results of the completed PK study C4671011 showed a PF-07321332 systemic exposure (AUC and C_{max}) increase with a magnitude depending on the severity of the renal impairment: in severe renal impairment, increase of AUC by 204% leading the CHMP to propose a contraindication in this sub-population at the time of Art 5(3) prior procedure and a dose reduction by one-half is proposed in population with moderate renal impairment. However, efficacy and safety data of Paxlovid at this reduced posology is

lacking. In addition, a higher incidence of AEs in severe renal impairment compared to patients with normal renal function and mild/moderate renal impairment was observed in study C4671011. It is therefore considered that the safety profile of PF-07321332/ritonavir in this population cannot be established yet and that the use in patients with renal impairment should be added as missing information. As per the routine risk minimisation measures, it has been considered that the inclusion in the SmPC of a warning and precaution for use of PF-07321332/ritonavir was more appropriate than a formal contra-indication, given that there is a lack of data to inform on a posology, rather than evidence of harm.

Safety during use in pregnancy and lactation: Considering that the current epidemiology data raise concerns on the SARS-CoV-2 infection for both the pregnant women and their newborns, the loss of foetal weight observed as part of the Paxlovid non-clinical findings and that clinical experience of Paxlovid is currently missing in pregnant women, it is agreed that safety during use in pregnancy and lactation is included as missing information.

Risks not considered important for inclusion in the summary of safety concerns

Hypertension: based on the final analysis of the pivotal Study C467-1005/EPIC-HR (cut-off date of 11 Dec 2021), hypertension occurred at a low frequency overall (0.6% and 0.2%, in the PF-07321332/ritonavir and placebo group, respectively) but was more frequent in the PF-07321332/ritonavir group. Most of events were low grade and none was considered treatment-related in the PF- 07321332/ritonavir group. Nevertheless, considering that the hypertension events mostly occurred with a short time to onset, the majority of patients experiencing hypertension had no history of hypertension and that hypertension is a known risk with ritonavir, it remains uncertain the causality of hypertension with Paxlovid.

This risk will be further evaluated through routine pharmacovigilance and relevant updates should be provided within the upcoming PSUR. A targeted follow-up questionnaire is to be implemented.

Myalgia: based on the final analysis of the pivotal Study C467-1005/EPIC-HR (cut-off date of 11 Dec 2021), myalgia was reported at a low frequency (0.6% and 0.2%, in the PF- 07321332/ritonavir and placebo group, respectively) but was more frequent in the PF- 07321332/ritonavir group. Since two of the seven cases reported with PF- 07321332/ritonavir were considered treatment-related and considering myalgia is a known risk of ritonavir, it remained questionable whether there is a causal relationship between myalgia and PF-07321332/ritonavir. Myalgia will be monitored through routine pharmacovigilance, including PSUR.

The applicant clarified that hypertension is monitored as an event of special interest (under 'hemodynamic events') in the ongoing development programme and both events are evaluated during safety reviews of interval and cumulative data from the clinical studies. Hypertension and myalgia will be reviewed via routine pharmacovigilance activities. Furthermore, the applicant will provide a cumulative safety review of all available data on hypertension and myalgia from available sources, including spontaneous data, compassionate use and literature (cut off-date 31sth March) by 30th April 2022 awaiting for a global safety review planned to be made by the applicant on the 3 applicant's sponsored clinical studies performed (EPIC-HR, EPIC-SR and study in PEP) planned to be provided in June 2022.

Drug-drug interactions (DDI) (with CYP3A substrates and CYP3A inducers): Paxlovid contains ritonavir, a well-known inhibitor of cytochrome P450 CYP3A (and PgP inhibitor), which may interact with other medicines leading to clinically significant reactions, including potentially life-threatening or fatal reactions, loss of therapeutic effect of Paxlovid and possible development of viral resistance. The applicant will closely monitor cases potentially indicative of drug-drug interactions via routine pharmacovigilance and present relevant data within the upcoming PSURs.

The applicant considers that the list of contraindicated medicinal products in Section 4.3, in addition to the comprehensive list of drug interactions included in Section 4.5 are sufficient to mitigate the risk of drug interactions by appropriately informing prescribers of the potential medicinal products which may interact with Paxlovid. In addition, the applicant included a QR code and website link on the PL and outer carton, which link to the MAH product website (COVID19oralRx.com) that includes a drug interaction tool. This tool will provide another mechanism to communicate the drug interactions listed in the SmPC.

Furthermore, an additional communication regarding this DDI is proposed by the EMA and will be circulated to all relevant professional societies on the day of the CHMP opinion, which is the same day that the product information is published on EMA website.

2.7.2. Pharmacovigilance plan

Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: the applicant will implement the following:

- Pregnancy follow-up questionnaires (Exposure During Pregnancy Follow-up Questionnaire for non-study cases and Exposure During Pregnancy Supplemental Form for study cases) are also utilised to collect further data on pregnancy outcome and reproductive and developmental toxicity.
- A Data Capture Aid has been created to gather data about the safety during use in lactation.
- Two further DCAs, for lack of efficacy (including fields to request information on the COVID-19 variant) and for hypertension are provided.

Monitoring of data on treatment failure due to emerging variants:

As part of the enhanced signal detection activities for the duration of the COVID-19 pandemic, monitoring of data on treatment failure due to emerging variants from all available data sources, will include (not limited to):

- Spontaneous cases (using a targeted follow-up questionnaire for lack of efficacy as stated above)
- Clinical trial data
- Literature
- Studies conducted by public health authorities

If the review of the data leads to an impact on the benefit risk of the product, a benefit-risk discussion and any warranted product information updates will be submitted within 1 month from assessment via appropriate variation procedure. Additionally, the interval and cumulative data will be summarised in a dedicated section in the PSUR.

Additional pharmacovigilance activities

The applicant proposes the following 5 studies to further evaluate safety and to address missing information in the post marketing setting.

The following table outlines proposed additional pharmacovigilance activities in RMP version 1.2.

Summary of additional Pharmacovigilance activities

Table 54. Ongoing and Planned Additional Pharmacovigilance Activities

Study (short name and title) Status	Summary of objectives	Safety concerns addressed	Milestones	*Due dates*
Category 3 - *- Required additional pharmacovigilance activities*				
Study C4671010 A Phase 1, Non-Randomised, Open-Label Study to Assess the Pharmacokinetics, Safety and Tolerability of PF-07321332 Boosted With Ritonavir in Adult Participants with Moderate Hepatic Impairment and Healthy Participants With Normal Hepatic Function. *Ongoing*	To estimate the effect of moderate hepatic impairment on the plasma PK of PF-07321332/ritonavir. To evaluate the safety and tolerability of PF-07321332 and ritonavir, following a single oral dose administration of PF-07321332 pharmacokinetically boosted with ritonavir, in participants with moderate hepatic impairment and in healthy participants with normal hepatic function.	Safety in patients with hepatic impairment	*Final report submission*	*31 March 2022*
PASS in pregnant and breastfeeding women A post-authorisation safety study of PF-07321332/ritonavir use in pregnant and breastfeeding women *Planned*	A cohort/prevalence study using secondary data from electronic health records and/or claims in European countries to assess use of PF-07321332/ritonavir during pregnancy and if feasible lactation. The study will also evaluate pregnancy outcomes (major congenital malformations, spontaneous abortions, stillbirths, small-for-gestational-age births) as feasible in data sources, and other safety events of interest in women exposed to PF-07321332/ritonavir versus not exposed to PF-07321332/ritonavir or another appropriate comparator. As feasible, maternal, and infant outcomes will be assessed in lactating women.	Safety during use in pregnancy and lactation	*Protocol submission*	*30 April 2022*
			Estimate study start	*EMA approval of protocol and PF-07321332/ritonavir commercially available*
			Progress report submission	*30 November 2022*
			Interim report 1 submission	*30 November 2023*
			Interim report 2 submission	*29 November 2024*
			Final report submission	*28 November 2025*
PK and safety study in lactating adult women A multiple dose, pharmacokinetic and	To assess penetration of PF-07321332 in human breast milk and to measure the concentration of PF-	Safety during use in pregnancy and lactation	*Estimate study start*	*EMA approval of protocol and PF-07321332/ritonavir commercially available*

Study (short name and title) **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	***Due dates***
safety study in healthy lactating adult women. *Planned*	07321332 in breastmilk in healthy women.		*Final study results submission*	*15 September 2023*
PASS in moderate and severe renal impairment A post-authorisation safety study of PF-07321332/ritonavir use in moderate and severe renal impairment. *Planned*	To assess the safety of PF-07321332/ritonavir in patients with moderate and severe renal impairment.	Safety in patients with renal impairment	*Study feasibility assessment*	*28 February 2022*
			Protocol submission	*30 April 2022*
			Estimate study start	*EMA approval of protocol and PF-07321332/ritonavir commercially available*
			Progress report submission	*30 November 2022*
			Interim report 1 submission	*30 November 2023*
			Interim report 2 submission	*29 November 2024*
			Final report submission	*30 November 2025*
PASS in moderate and severe hepatic impairment A post-authorisation safety study of PF-07321332/ritonavir use in moderate and severe hepatic impairment. *Planned*	To assess the safety of PF-07321332/ritonavir in patients with moderate and severe hepatic impairment.	Safety in patients with hepatic impairment	*Study feasibility assessment*	*28 February 2022*
			Protocol submission	*30 April 2022*
			Estimate study start	*EMA approval of protocol and PF-07321332/ritonavir commercially available*
			Progress report submission	*30 November 2022*
			Interim report 1 submission	*30 November 2023*
			Interim report 2 submission	*29 November 2024*
			Final report submission	*30 November 2025*

2.7.3. Risk minimisation measures

Routine risk minimisation activities are proposed to manage the safety concerns of the medicinal product.

Table 55. Summary Table of Risk Minimisation Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Safety in patients with hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 *Posology and method of administration*, Section 4.4 *Special warnings and precautions for use*, and Section 5.2 *Pharmacokinetic properties*. Pack size. Medicine's legal status. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Study C4671010 (Final CSR Due date: 31 March 2022). PASS in moderate and severe hepatic impairment (Final report submission by 30 November 2025).
Safety in patients with renal impairment	Routine risk minimisation measures: SmPC Section 4.2 *Posology and method of administration*, Section 4.4 *Special warnings and precautions for use* and Section 5.2 *Pharmacokinetic properties*. Pack size. Medicine's legal status. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS in moderate and severe renal impairment (Final report submission by 30 November 2025).
Safety during use in pregnancy and lactation	Routine risk minimisation measures: SmPC Section 4.6 *Fertility, pregnancy and lactation*. Pack size. Medicine's legal status. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Pregnancy follow-up questionnaires and DCA for lactation to collect relevant information during follow-up activities. Additional pharmacovigilance activities: PASS in pregnant and breastfeeding women (Final study results submission by 28 November 2025). PK and safety study in lactating adult women (Final study results submission by 15 September 2023)

2.7.4. Conclusion

The CHMP and PRAC considers that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 31.12.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons for the approval of the conditional marketing authorisation under emergency use.

The applicant has endeavoured to ensure that the package leaflet is comprehensive and supports patient adherence and understanding, especially for patients that may have limited direct access to healthcare professionals. Further adjustments have been made to the language in the PIL to support this.

The applicant commits to complete user testing and provide it as soon as possible.

2.9.2. Labelling exemptions

The following exemptions from labelling requirements have been granted on the basis of article 63.3 of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the flexibilities described in the Labelling flexibilities for COVID-19 therapeutics (EMA/35618/2021, from 12 March 2021) document which aims at facilitating the preparedness work of COVID-19 therapeutics' developers and the associated logistics of early printing packaging activities. The ultimate goal is to facilitate the large scale and rapid deployment of COVID-19 therapeutics for EU citizens within the existing legal framework.

Considering the self-administration context and the need for the information to be readily available and understood by the users in their national language, The QRD Group agreed to a maximum of 2 months length of deviation for all of the below requests, in particular:

a) Agreed to market an outer and immediate packaging in English only for all EU markets for a maximum period of 2 months following the EC decision;

b) An English only Package Leaflet was not agreed. The applicant shall liaise with the respective national competent authorities (NCAs) and discuss the provision of a paper PL alongside the pack in the national language(s). As noted above this has to be seen in the context of self-administration. It is crucial that the user has from the start the information in their national

language.

c) Agreed to provide national translations of the package leaflet via a Quick Response (QR) code, but as a supplement to the paper package leaflet, as indicated above.

d) Agreed to use one Global GTIN within the unique identifier for all EU markets;

e) Agreed to omit the NHRN (national code) to be encoded in the Datamatrix for some countries;

f) Agreed to omit the Blue Box information and to provide it via a QR code instead;

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

2.9.3. Quick Response (QR) code

A request to include a QR code in the labelling for the purpose of ensuring easy access to the most recent versions of the product information to patients and HCPs has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code:

Based on whether they select the patient or the HCP area, the user will be sent through to the most appropriate local website which will provide them with the following:

a) The most up to date 'Package Leaflet; Information for the Patient' (formatted as a PDF)

b) The most up to date Summary of Product Characteristics (formatted as a PDF)

c) Information about how to ensure that the HCP has obtained an authentic version of the medicine, manufactured by Pfizer.

In addition, a so-called "Drug Interaction Finder." will be included which will replicate the two drug interactions tables ('Contraindicated for concomitant use' and 'Potentially significant interactions with other medicinal products') in a searchable format. This would support patient safety by allowing HCPs to more easily identify a medicine which may interact with PF-07321332 and ritonavir.

2.9.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Paxlovid ((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 /ritonavir) is included in the additional monitoring list as it contains a new active substance and the product is approved under a conditional marketing authorisation..

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COVID-19 manifests as a wide range of illness, from asymptomatic infection to severe pneumonia, ARDS, and death. Although approximately 80% cases are asymptomatic or mild, patients who are hospitalised with COVID-19 may have significant morbidity and mortality, and are at increased risk of developing complications such as severe inflammation associated with elevations in proinflammatory cytokines, ARDS, acute cardiac injury, thromboembolic events, hypercoagulability, and/or kidney injury. Moreover, other comorbidities, such as hypertension, obesity, and diabetes, as well as older age increase the risk for worse outcomes.

3.1.2. Available therapies and unmet medical need

The therapeutic armamentarium is limited for patients infected with SARS-CoV-2, who are at increased risk of progression to severe disease and not O2 requiring, as targeted in the C4671005 patients.

While some anti-spike monoclonal antibodies have been a valuable tool, the emerging VOC with mutations in the spike protein are constantly threatening their activity. Currently, sotrovimab is almost the unique mAb that maintains activity against the currently circulating omicron variant.

Remdesivir is also indicated for the same patient population as Paxlovid. However, remdesivir is only available via intravenous administration. There is a need to have an oral antiviral effective against COVID-19 disease.

3.1.3. Main clinical studies

The clinical development is based on the single pivotal phase 2/3 C4671005/EPIC-HR study conducted in non-hospitalised, symptomatic adult patients with COVID-19 who are at increased risk of progressing to severe illnesses. It was a double-blinded, placebo-controlled trial, in a 1:1 ratio and conducted in a superiority setting.

Eligible patients have received PF-07321332 plus ritonavir or placebo orally q12h for 5 days (10 doses total). The total study duration is up to 24 weeks, study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34.

3.2. Favourable effects

The determination of primary efficacy was based on a planned interim analysis of 774 subjects in mITT population. The estimated risk reduction was -6.3% with unadjusted 95% CI of (9.0%, 3.6%) and a 95% CI of (-10.61%, -2.02%) when adjusting for multiplicity. The 2-sided p-value was < 0.0001 with 2-sided significance level of 0.002.

In the supporting final analysis, the primary endpoint of the study was met with a 5.807% (95% CI: -7.777% to - 3.837%; p<0.0001) absolute reduction in proportion of COVID-19-related hospitalisation or death from any cause at Day 28, reducing the primary endpoint event rate from 6.531% to 0.723% at Day-28, with PF-07321332/ritonavir in comparison with placebo treatment, in patients who did not

receive or were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days after COVID-19 symptom onset (mITT). No patient died in the Paxlovid treatment group whereas 9 deaths occurred in the placebo group. Sensitivity analyses were also generally consistent with the primary results.

Similar benefit was observed in the mITT1 population of analysis with an absolute reduction of 5.619% (95% CI: -7.207% to -4.031%; p<0.0001). mITT1 includes patients treated within 5 days since symptoms onset in line with the posology recommendation. Again, no patients died in the Paxlovid treatment group whereas 12 deaths occurred in the placebo group.

In line with the study period, the primary variant across both treatment arms was Delta (98.53%) and was distributed in high prevalence as subvariants Delta/21J (74.15%). As the vast majority of the participants were infected with the Delta variant, the clinical efficacy of Paxlovid is only demonstrated in this VOC. However, *in vitro* data are supportive of activity of Paxlovid against other major VOCs including the currently circulating omicron variant.

3.3. Uncertainties and limitations about favourable effects

The identified quality issues concerning the active substance PF-07321332 manufacture and finished product control strategy, to be addressed through fulfilment of specific obligations, pose some uncertainties with regard to the batch to batch consistency between the product batches studied in pharmaceutical, preclinical and clinical development, and future commercial batches.

A high rate of patients with positive serological status at baseline was observed, which needs to be better understood. According to the applicant, serology testing at baseline did not discriminate between IgG or IgM. This did not allow to differentiate whether the positive status was due to unawareness of prior (potentially asymptomatic) SARS-CoV-2 infection or to immune response related to the current COVID-19 episode (at the time of the enrolment). The applicant indicated that exploratory testing is planned to further characterise the immune response to SARS-CoV-2 at baseline and over time.

As rather expected, a much more limited effect could be observed in patients with positive serology status at baseline. Therefore, uncertainties remain on the magnitude of the benefit in this subpopulation. More broadly, the question therefore arises of the generalisability of the results to vaccinated patients with increased risk for progression to severe COVID-19. The benefit of the treatment in the vaccinated subpopulation needs to be further substantiated.

Patients with immunodeficiency were poorly represented with less than 1% of the study population. There are concerns on the maintenance of the benefit in patients with immunodeficiency for which a prolonged period of viral shedding could occur. This could lead to potential risk of treatment failure and emergence of resistance with the recommended 5 days treatment duration. The applicant will have to particularly monitor treatment failure in this subset of patients in post-approval.

3.4. Unfavourable effects

The incidence of TEAEs was slightly lower in PF-07321332/ritonavir compared to placebo, i.e. 22.6% and 23.9% respectively. The majority of reported AEs in the study were low grade and non-serious, and no death occurred with PF-07321332/ritonavir. Grade ≥3 TEAEs were also less reported in PF-07321332/ritonavir arm than placebo arm (4.1% vs 8.3%). The most frequently reported TEAEs in the PF-07321332/ritonavir group (≥1%) were Dysgeusia (5.6%), Diarrhoea (3.1%), Fibrin D-dimer increased (1.9%), Alanine aminotransferase increased (1.5%), Creatinine renal clearance decreased (1.4%), Nausea (1.4%), Headache (1.4%) and Vomiting (1.1%). The reported TEAEs (≥0.5%) that

occurred at a greater frequency in the PF-07321332/ritonavir group compared with the placebo group were Dysgeusia, Diarrhoea, Vomiting, Headache, Pyrexia, Myalgia, Hypertension, Chills, Dyspepsia. The most frequently reported treatment-related TEAEs in the PF-07321332/ritonavir group (≥1%) were Dysgeusia (3.7%), and Diarrhoea (1.9%).

Serious AEs were less reported in PF-07321332/ritonavir arm than placebo arm (1.6% vs 6.6%). The most frequently reported SAEs with PF-07321332/ritonavir were COVID-19 pneumonia, COVID-19, and Creatinine renal clearance decreased. Among the non-related COVID-19 SAEs reported, one case of Chest discomfort, dyspnoea and palpitations was considered by the investigator as reasonably possible to be related to the treatment (ritonavir). The majority of the reported SAEs with PF-07321332/ritonavir were considered as resolved/recovered and 2 cases were ongoing at the time of the report (creatinine renal clearance decreased and oxygen saturation decreased).

Finally, the complexity of the interaction profile driven by the ritonavir booster dose co-packaged with the antiviral PF-07321332 in Paxlovid is of importance, all the more for outpatients population, having in mind that general practitioners might be less familiar with the handling DDI derived from ritonavir than healthcare professionals at hospital in the field of HIV infection. Nevertheless, it can also be acknowledged that the short 5 days treatment duration could mitigate the burden.

At this stage the CHMP has adopted to apply the list of DDI in the SmPC of ritonavir into that of Paxlovid as indicated in the SmPC as a conservative measure. In order to highlight and mitigate this issue, the CHMP has addressed a letter to several Healthcare professionals' organisations to raise awareness about the DDI with Paxlovid.

3.5. Uncertainties and limitations about unfavourable effects

There are uncertainties on the impact of hepatic impairment on the safety profile of Paxlovid. Participants with known medical history of active liver disease or acute liver failure were excluded from the pivotal study C4671005 (EPIC-HR). In the PK study in patients with hepatic impairment, the interim analysis data in moderate HI did not significantly differ from the control, nevertheless the category of patients with severe HI was not covered.

In addition, the safety profile of PF-07321332/ritonavir in patients with moderate and severe renal impairment cannot be established yet. There is a lack of data in the moderate to severe renal impairment population in study C4671005 (exclusion of this population) and the results of the completed Phase 1 study C4671011 showed a PF-07321332 systemic exposure (AUC and Cmax) increase with a magnitude depending on the severity of the renal impairment and a higher proportion of AEs in the severe renal impairment compared to the other groups.

In severe renal impairment, there was an increase of AUC by 204%. No recommendation in terms of dose adjustment could be elaborated at this stage.

For both patients with severe renal impairment and severe hepatic impairment, given that there is a lack of data to inform on a posology, rather than evidence of harm, an explicit warning has been introduced in the SmPC at this stage pending dedicated investigations (notably through an updated PopPK model).

In moderate renal impairment, a dose reduction by one-half of PF-07321332 has been proposed by the company but was not tested in clinic. The adequacy of this dose adjustment in patients and the risk of medical errors will be particularly scrutinised in post approval.

Hypertension occurred at a low frequency overall but with an apparent imbalance (0.6% and 0.2%, in the PF- 07321332/ritonavir and placebo group, respectively). Most of events were low grade and none

was considered treatment-related in the PF- 07321332/ritonavir group. Nevertheless considering that the hypertension events mostly occurred with a short time to onset (mainly between Day 2 and Day 5), the majority of patients experiencing hypertension had no history of hypertension (4 of 7 patients) and that hypertension is a known risk with ritonavir, it remains uncertain whether there is a causal relationship between of hypertension with Paxlovid. Given this sensitive issue in a population where hypertension is already a risk factor, the CHMP requested a safety review for hypertension covering safety data from ongoing early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March 2022, by April 2022 followed by the integrated safety report with its three sponsored studies (C4671005/EPIC-HR, C4671002/EPIC-SR and C467PEP) in June 2022.

Myalgia occurred at a low frequency with also an apparent imbalance (0.6% and 0.2%, in the PF-07321332/ritonavir and placebo group, respectively). Since two cases of the 7 reported with PF-07321332/ritonavir were considered treatment-related and considering myalgia is a known risk of ritonavir, again it remains uncertain whether there is a causal relationship between myalgia and Paxlovid. A safety review for myalgia was also requested covering safety data from ongoing early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March 2022, by April 2022 followed by the integrated safety report with its three sponsored studies (C4671005/EPIC-HR, C4671002/EPIC-SR and C467PEP) in June 2022.

3.6. Effects Table

Table 56. Effects Table for Paxlovid in the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19 (data cut-off: 09 December 2021).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Proportion of participants With COVID-19 related hospitalisation or death from any cause through Day 28.	Primary endpoint (95% CI) mITT: in who did not receive COVID-19 therapeutic mAb treatment and were treated ≤3 days after COVID-19 symptom onset.	% of event	0.723 (0.302, 1.729)	6.531 (4.901, 8.676)	- Consistency across mITT and mITT1 - Consistent with sensitivity and supplemental analysis - Supported by the secondary endpoint reduction in the number of COVID-19 related medical visits But: - Need of further data to ensure the generalisation of the results to the following subpopulation: vaccinated patients, patients with risk factors which are poorly represented in the C4671005 study and smokers. - Need to further explore the serologic status at baseline. - Efficacy analysis sets would be expected to consistently include all randomised subjects regardless of treatment with study drug or post-baseline visit attendance.	C4671005 Phase 2/3 study
	First key secondary endpoint (95% CI) mITT1: in who did not receive COVID-19 therapeutic mAb treatment and were treated ≤3 days and > 3 days after COVID-19 symptom onset.	% of event	0.781 (0.391, 1.556)	6.400 (5.063, 8.075)		
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
TEAEs	All causalities	%	22.6	23.9	Mainly low grade	C4671005 Phase 2/3 study
Grade ≥3 TEAEs	All causalities	%	4.1	8.3	Mostly reported in the SOCs Investigations and Infections and infestations	
Dysgeusia	All causalities	%	5.6	0.3	Identified AE with ritonavir	
Vomiting	All causalities	%	1.1	0.8	Identified AE with ritonavir	
Diarrhoea	All causalities	%	3.1	1.6	Identified AE with ritonavir	
Headache	All causalities	%	1.4	1.3	Identified AE with ritonavir	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The identified quality issues discussed in this report and to be addressed through fulfilment of specific obligations, raise some uncertainties with regard to the batch to batch consistency between the product batches studied in pharmaceutical, preclinical and clinical development and future commercial batches. However, the submitted data indicate that batches to date are of appropriate quality that is comparable to that of clinical development batches. Considering the emergency context of this application the above identified quality issues do not preclude granting of a CMA. However, in order to confirm that the quality of future batches will also remain appropriate and comparable to that of clinical development batches over the life cycle of the medicinal product, these issues are expected to be addressed though fulfilment of specific obligations, within the defined due dates.

The primary endpoint of the study, proportion of COVID-19-related hospitalisation or death from any cause at Day 28, was met with consistency and further supported by the results of sensitivity analyses and in the first secondary analysis in mITT1, while, based on the provided safety data, no major concern was identified in the safety profile of PF-07321332/ritonavir combination, which appears comparable to placebo at the intended dosage of 300mg/100mg Q12h for 5 days. However, the complexity of the interaction profile driven by the ritonavir booster dose could be a limiting factor for its use.

3.7.2. Balance of benefits and risks

The submitted quality data is currently not fully comprehensive, but this is considered acceptable in the emergency context and the quality package will be completed though fulfilment of specific obligations by defined due dates.

Overall, there is a clinical benefit of Paxlovid by reducing the risk of hospitalisation or death in the target population of adults with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19.

Based on the provided safety data, no major concern was identified in the safety profile of PF-07321332/ritonavir combination. The most frequent adverse reactions were dysgeusia, diarrhoea, vomiting and headache which are described in section 4.8 of the SmPC.

The demonstrated benefits of Paxlovid outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive quality data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment life-threatening disease. In addition, the COVID-19 pandemic constitutes an emergency situation. It is a public health threat duly recognised by the World Health Organisation as well as the EU.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data. The CHMP has identified specific obligations concerning pharmaceutical (quality) data, which are expected to provide comprehensive data for this product. No concerns have been identified with the ability to complete these specific obligations, as the applicant has indicated that they consider respective due dates as feasible.
- Unmet medical needs will be addressed, as in the framework of the ongoing COVID-19 pandemic there is an urgent need for safe and effective therapeutic interventions that can reduce viral transmission, improve time to clinical recovery and prevent the progression of infection to more severe disease, hospitalisation and death. Paxlovid has demonstrated efficacy on patient at increased risk of severe COVID-19, it is also for oral use that can be taken outside the hospital setting.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. COVID-19 inarguably represents the most significant public health emergency of our time. In this context it is considered that the benefits to public health of the immediate availability of Paxlovid outweigh the risks inherent in the fact that additional quality data are still required.

3.8. Conclusions

The overall benefit/risk balance of Paxlovid is positive, subject to the conditions stated in section 'Recommendations'

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus

that the benefit-risk balance of Paxlovid is favourable in the following indication(s):

Paxlovid is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID 19 (see section 5.1).

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order improve the control strategy description and to confirm a consistent impurity profile, additional details should be included in the manufacturing process proposed for the active substance PF-07321332 for commercial supply.	30 June 2022
In order ensure comprehensive control of impurities throughout the lifecycle of the product, the control strategy for the active substance PF-07321332 for the impurities including chiral impurities and the active substance should be fully established.	30 June 2022
In order ensure comprehensive control of impurities throughout the lifecycle of the product, full validation data for the HPLC method for assay and impurity testing, and	30 June 2022

Description	Due date
for the residual solvent method used for the control of the active substance PF-07321332 should be provided.	
In order to improve the control strategy for the ritonavir film coated tablets, the limit for dissolution specification of ritonavir film coated tablets should be tightened according to the results obtained for the biobatches, e.g. to NMT 75 % (Q) in 45 min.	30 June 2022

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that the active substance (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 is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Annex I - List of recommendations (RECs) and Legally binding measures (LEGs)

Area	Number	Description	Classification
Quality	1	To update the quality dossier. By removing references to emergency supply product; by replacing the provisional specifications with final specifications for starting materials, intermediates, both active substances and finished product. The applicant committed to provide the updated information as soon as possible at latest in 2Q 2022.	REC
Quality	2	In order to improve the quality dossier for the Active substance PF-07321332 it is recommended to update the section "2.3 Control of materials" and "2.4 Control of critical steps and intermediates" as follows: a) It is stated that some of the synthesis routes of the starting materials are still under development and being optimised which could result in changes of the synthesis routes. Therefore, the final synthesis routes for the starting materials should be provided as soon as possible at latest in 2Q 2022 as committed by the applicant. b) Section S.2.3 should be updated with information on the several suppliers for starting materials together with the update on batch genealogy. The applicant committed to provide the data by July 2022. c) Starting materials specifications should be updated based on a complete and robust batch history as soon as available preferably before commercial application as committed by the applicant. d) Comparative data will be expected by July 2022 as committed by the applicant once definitive specifications for PF-07321332 active substance are set. e) The assay limits in the starting material specifications should be raised based on batch analysis data for the starting material suppliers and taking into account the impurity limits. Accordingly revised starting material specifications should be provided as soon as possible at latest in 2Q 2022 as committed by the applicant. f) The applicant is required to submit variation for the addition of any sites and the modified active substance synthesis route prior to implementing these changes after CMA approval.	REC

Quality	3	It is recommended to update the section "3. Characterisation" of the Active substance PF-07321332 as follows: a) As the active substance is badly soluble, the polymorphic form can have an influence on the bio performance of the drug product. Therefore, it should be demonstrated that the polymorphic form does not change during storage of the active substance. The applicant committed to provide the updated information as soon as possible at latest in 2Q 2022. b) The structure of an identified impurity should be stated, and it should be classified according to ICH M7. The applicant committed to provide the updated information as soon as possible at latest in 2Q 2022. c) It is stated that the concentrations of the solvents used will be investigated on 3 consecutive production batches of the AS. The data should be submitted. This investigation should be also performed concerning potential residues of the solvent which is used in step 1. The applicant committed to provide the updated information as soon as possible at latest in 2Q 2022. d) The applicant states that the Class 1/2A elemental impurities, will be monitored in PF-07321332 active substance and an appropriate control strategy will be established at the time of registration. The applicant committed to provide the updated information as soon as possible at latest in 2Q 2022.	REC
Quality	4	The section '4. Control of drug substance' for the Active substance PF-07321332 is recommended to update as follows: a) An updated section 3.2.S.4.2 including description of the residual solvent method and the XRD method should be provided as soon as possible. Validation data which show that the XRPD method is suitable to distinguish polymorphic forms should be provided. The applicant committed to submit the data as soon as possible at latest in 2Q 2022. b) Based on the PSD of AS batches used in drug product batches used in the pivotal clinical studies the set acceptance criteria for PSD in the active substance specification cannot be accepted. Therefore, the PSD limits should be tightened unless it could be show on PK or bioavailability data that the set upper limits of the PSD have no impact on the bio performance of the drug product.	REC

		An accordingly revised active substance specification should be provided as soon as possible at latest in 2Q 2022 as committed by the applicant. c) It is stated that microbiological quality will be evaluated for three primary stability lots at initial release and when stored under the proposed long-term storage conditions. Data will be reported at the time of registration filing. The applicant committed to submit the data as soon as possible at latest in 2Q 2022.	
Quality	5	The section '7. Stability' for the Active substance PF-07321332 should be updated as follows: a) The applicant commits to include batches of PF-07321322 active substance manufactured by earlier and current synthetic routes on stability studies. Stability data from batches manufactured by the current synthetic route and from previous routes should be provided as soon as possible at latest in 2Q 2022 as committed by the applicant. b) Forced degradation data on a batch of PF-07321332 active substance manufactured by the commercial synthetic route should be provided as soon as available at latest in 2Q 2022 as committed by the applicant.	REC
Quality	6	The section 3.2.P.2 Pharmaceutical Development for the Drug Product PF-07321332 should address the following issues: a) With respect to BCS classification, a BCS class should be definitely determined for PF-07321332 on the basis of sound analytical data. b) The particle size distribution (PSD) set for the active substance is considered premature. A discussion in depth with respect to potential PSD impact on manufacturability and bio-performance of the PF-07321332 IR film-coated tablets should be provided. Additionally, the PSD should encompass three percentile values D10, D50 and D90, unless otherwise justified. c) Data should be presented, investigating whether the polymorphic form selected for PF-07321332 drug product can remain stable under the proposed drug product manufacturing conditions and during shelf life.	REC

		d) A certain manufacturing process step needs to be addressed in detail rather than just shortly mentioned in the blend homogeneity experiments. The applicant has provided a commitment to update the above information as soon as possible at latest in 2Q 2022.	
Quality	7	The section 3.2.P.3 for the Drug Product PF-07321332 should be updated in terms of the following aspects a) The numeration of the individual process steps in the manufacturing process narrative should be brought in line with the corresponding numeration indicated in the flow chart. Further, the term 'Package' needs to be replaced with 'Co-package' or similar to adequately reflect the co-packaging of PF-07321332 with ritonavir film-coated tablets in the same blister. b) The manufacturing process description should be amended to contain more details e.g. the operating ranges worked out within the process development, fully reflecting the information level required in the Guideline on Manufacture of the Finished Dosage Form (EMA/CHMP/QWP/245074/2015). c) Critical steps are not mentioned at all but should be specified, among others the co-packaging step, which is regarded as critical, since this packaging involves the placing of two different bulk drug products into the same blister. d) Please clarify, whether hold times are intended to be applied for the PF-07321332 drug product manufacture. If any, suitable stability data as respective justification needs to be provided. e) Process validation data to full extent, considering all requirements as specified in the Guideline on Process Validation for Finished Products (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1), should be provided. In this context, it should also be shown that the four recently available emergency supply batches have been manufactured achieving acceptably reproducible results between and within batches for the respective stages of the process. The applicant has provided a commitment to update the above information as soon as possible at latest in 2Q 2022.	REC
Quality	8	The section 3.2.P.4 for the Drug Product PF-07321332 should be revised to include the details as follows	REC

		a) All excipients (compendial and non-compendial) used for manufacture of PF-07321332 150 mg film-coated tablets should be included in this section, each with a concise description including respective function. b) An adequately compiled specification considering identity etc. for the film coat system Opadry Pink should be provided, along with an analytical procedure. If non-compendial, sound validation needs to be addressed for the non-compendial test method. c) Compliance with the EU regulation 231/2012 should be confirmed for red iron oxide. d) Exemplary CoAs should be provided for the non-compendial excipient Opadry Pink. The applicant has provided a commitment to update the above information as soon as possible at the latest in 2Q 2022.	
Quality	9	The section P.5 Control of the Drug Product PF-07321332 should be updated as follows a) Additional parameters should be included in the release specification. b) Validation data should be presented concerning intermediate precision and robustness for the three methods used for identity, assay degradation products and content uniformity. c) For the method, which is used alternatively for determination of assay, the stability indicating power should be demonstrated by using appropriate stress tests with the finished product. d) For completeness of the validation data additional validation information should be submitted. e) The degradation pathway of 4 possible degradation products should be highlighted under the section 3.2.P.5.5, the link to 3.2.S.3.2 is not considered sufficient. f) The limit for assay in the shelf life specification should be tightened. Even if limited stability data are available, a widening of the limit for assay is not considered acceptable, as no degradation is observed during stability studies including stress tests performed. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	REC

Quality	10	The section P.7 Container closure system for the Drug Product PF-07321332 should be updated as follows: For the container closure system used appropriate food declarations should be provided. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	REC
Quality	11	The section P.8 Stability for the Drug Product PF-07321332 should be updated as follows a) The batch size of the Primary batches used for the stability studies should be detailed. b) The method used for determination of water activity should be described and validation data should be presented. c) It should be confirmed that the precaution advice "Do not store above 25 °C" and "Do not refrigerate or freeze" will be deleted when it has been demonstrated by stability data, that these precaution advices are not necessary. d) Based on 3 months stability data submitted for the primary stability batches of the PF-07321332 tablets including the supportive stability data, a shelf life of 12 months with the precaution advice "Do not store above 25°C. Do not refrigerate or freeze" is considered acceptable provided, the stability samples will be monitored monthly, and any Out Of Specification results (OOS results) will be provided immediately to the Authorities. The applicant has provided a commitment to update the information as soon as possible at latest in 2Q 2022.	REC
Quality	12	Ritonavir Module 3.2.P.1 of should be updated as follows: The active ingredient should be included at the declared amount (100 mg). For each individual excipient, one total amount should be given. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	REC
Quality	13	Ritonavir Module 3.2.P.2 should be updated as follows. In the context of the CMAA, the quality documentation for ritonavir film-coated tablets is considered acceptable from a risk-based perspective as the product is currently registered in several European countries with the proposed specifications. However, the requirements of EMA/CHMP/CVMP/QWP/336031/2017 apply to ritonavir film-	REC

		coated tablets as part of the CMA for Paxlovid, as this is a new drug product: a) Only fragmented information is provided in the development section, which is to be completed in line with the requirements of ICH Q8 (R2). The underlying QTPP should be disclosed, taking into account properties of the active substance ritonavir as well as published information on the reference product. The active substance's material attributes should be defined, including the potential presence of other polymorph forms or potential conversion between forms as well as their clinical relevance (physiological properties), and their impact on the CQA of the drug product. Also, the proposed particle size distribution specification should be addressed and justified and its impact on the CQA of the drug product (e.g. the dissolution specification) be evaluated. Sections 3.2.P.2.1 and 3.2.P.2.2.3 should be updated accordingly. b) Critical process parameters during manufacture are identified with specified set points. However, justification based on development data is awaited particularly for a certain step of this non-standard procedure. Particularly, the impact of different settings on the chemical purity of the drug product and on potential conversion of the polymorph form should be discussed and supported by development results. c) Justification of the dissolution conditions are awaited, particularly the choice of media and the agitation speed. Section 3.2.P.2.2.1 should be updated. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	
Quality	14	Ritonavir Module 3.2.P.3 of should be updated as follows: a) The process descriptions should be updated to include amounts of and reaction conditions for the given batch size of both the intermediate and the film-coated tablets, as well as the in-process controls. b) Specifications for packaging material for the intermediate are awaited, along with stability data of the intermediate. c) The specification for the intermediates should be provided and /or updated. Section 3.2.P.3.4 should be updated.	REC

		d) Validation data for the non-standard process step should be provided. Furthermore, the process optimisation study results should be disclosed. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	
Quality	15	Ritonavir Module 3.2.P.5 should be updated as follows: a) It should be highlighted why different specification limits are outlined for dissolution testing and impurity limits under the Certificates of Analysis for some batches. Both specification limits for dissolution testing differ from that outlined under 3.2.P.5.1. Levels of impurities found for one impurity exceed the limit detailed under P.5.1. These discrepancies should be clarified. b) The applicant states that the analysis of elemental impurities is ongoing. Data of three production batches and analytical method validation will be submitted in January 2022. The applicant should commit that these data including validation report will be implemented as soon as possible and will be send to the competent Authorities when available. c) The applicant states that method validation for three batches of ritonavir active substance which have been tested for nitrosamine impurities are in progress and will be submitted in January 2022. The applicant should commit that the validation report including calculation of allowable limits of nitrosamine impurities will be implemented in the documentation and will be send to the competent Authorities when available. d) If not otherwise justified, the limit for water content, which has been set to the shelf life specification should be tightened according to the data obtained. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	REC
Quality	16	Ritonavir Module 3.2.P.6 should be updated as follows: The purpose of the reference standard used should be highlighted. The statement that the reference standards are used for the analysis of the film coated tablets is not sufficient. Especially the purpose of the intermediate primary reference standard should be detailed. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	REC

Quality	17	Ritonavir Module 3.2.P.8 should be updated as follows: a) Please clarify on the proposed storage declaration for the bulk tablets ("Do not store below 25 °C") and update section 3.2.P.8.1. b) As for the post-approval stability protocol and stability commitment for the co-packaged product, XRD should be included in the regular tests. It should further be confirmed that microbiological tests will be performed annually. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	REC
Quality	18	Drug product co-packed Paxlovid: Information and data on the bulk products PF-07321332 and ritonavir film coated tablets have been provided. However, information and data concerning the final co-packed drug product Paxlovid to be marketed is reflected poorly in the dossier. The drug product ritonavir (bulk tablets), as documented in current separate Module 3.2.P, is considered as Intermediate product, which is being introduced in the last steps of manufacture of PF-07321332 tablets. Therefore, The contents of Module 3.2.P ritonavir bulk tablets should be integrated as sub-chapter in Module 3.2.P.3 of PF-07321332 tablets in order to avoid confusion and repeating of documents. The respective sections of 3.2.P PF-07321332 tablets should be updated to include the missing information for the co-packed drug product Paxlovid to be marketed. A separate Module for the co-packaged drug product would not be required. The applicant has provided a commitment to update the information as soon as possible at the latest in 2Q 2022.	REC
NC	19	The on-going whole body autoradiographic study report in rats with PF-07321332 (alone) should be provided by 31 March 2022, together with the applicant's assessment need to be submitted as soon as available.	LEG
NC	20	The final study reports of the two 1-month repeat-dose toxicity studies (21GR122 and 21GR125) should be provided by 31 January 2022.	LEG
NC	21	The final study report for the pre- and postnatal development (21GR149) should be provided by 30 April 2022. Meanwhile, in case of any new safety concern identified during the	LEG

		ongoing analysis of these data, the applicant should inform the EMA.	
NC	22	The Environmental Risk Assessment should be completed and provided by 31 December 2024	REC
NC	23	The study report for the on-going *in vivo* study with PF-07321332 in combination with ritonavir using a mouse-adapted (MA) model of SARS-CoV-2 infection (MA-SARS-CoV-2) in BALB/c mice should be provided by 28 February 2022.	REC
C (PK)	24	*In vitro* dissolution test comparing the 250 mg uncoated tablet with the film coated tablets should be provided to substantiate the bridge.	REC
C (PK)	25	The updated PopPK model results including PK data collected from the patients enrolled in the EPIC-HR study with relevant covariables and relevant update to the exposure margins should be provided by 31 March 2022	LEG
C (PK)	26	The final clinical study report for C46711010 investigating the effect of moderate hepatic impairment on the PK of PF-07321332 should be provided.	REC
C (PK)	27	The PBPK model exercise with commercial software (SimCYP) utilising compound files for metformin and rosuvastatin should be provided. The PBPK modelling robustness should be demonstrated and high level of qualification of the model should be provided (multiple substrates, multiple perpetrators, based on *in vivo* results).	REC
C (PK)	28	Two studies are currently being performed to assess the effect of PF-07321332/ritonavir on midazolam as a CYP3A4 substrate (Study 1013) and dabigatran as a P-gp substrate (Study 1012). The study results should be provided.	REC
C (PD)	29	Evaluation of *in vitro* selected resistant SARS-CoV-2 (WA) against PF-07321332 should be provided. It is also recommended to additionally conduct the resistance assay with the current circulated variants (delta and omicron).	REC
C (PD)	30	The final report of *In vitro* Virus RNA Replication Efficiency of the Recombinant SARS-CoV-2 Containing Engineered Mutations in 3CL Protease PF-07321332 should be provided.	REC
C (PD)	31	*In vitro* cell-based efficacy data of PF-07321332 against mutant viruses that showed a drop in PF-07321332 potency as measured by biochemical assay and viruses from the breakthrough cases in study C46710053CL should be provided.	REC
C (PD)	32	The full planned genotyping and phenotyping analyses at baseline and in treatment failure from the pivotal 1005 study.	REC

		It is highly recommended to examine the impact of mutations outside of the 3CLpro gene and 3CLpro cleavage regions.	
C	33	Patients with immunodeficiency were poorly represented with less than 1% of the study population. The applicant should monitor treatment failure in this subset of patients in post-approval.	REC
C	34	Cigarettes smokers are largely represented while, in the state of art, uncertainties remain on the increase risk related to this factors. The applicant should elaborate in which extent participants with "cigarettes smoke" at baseline presented this solely risk factors or other comorbidities, and a potential impact of the results.	REC
C	35	Long-term data from study C4671005 (i.e. at Week 34) should be provided to ensure that no further events onset potentially impacting the main outcomes.	REC
C	36	The applicant is committed to provide the results of the exploratory testing planned to further characterize the immune response to SARS-CoV-2 at baseline, including serology status.	REC
C	37	The applicant is committed to provide C4671002 study results as soon as available. Additionally, the applicant is committed to elaborate on collecting post-approval data especially in patients who still remain at risk of severe disease after vaccination.	REC
C (safety)	38	A safety review for hypertension covering safety data from ongoing early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March should be provided by April 2022, awaiting for a global safety review planned to be submitted covering the 3 applicant's sponsored clinical studies (EPIC-HR, EPIC-SR and study in PEP) in June 2022	LEG
C (safety)	39	A safety review for myalgia covering safety data from ongoing early access worldwide and notably from US (Emergency Use Authorisation) and literature data with cut-off date 31st March should be provided by April 2022, awaiting for a global safety review planned to be submitted covering the 3 applicant's sponsored clinical studies (EPIC-HR, EPIC-SR and study in PEP) in June 2022	REC
C	40	The user consultation with target patient groups should be carried out and the results provided.	REC