16 December 2021
EMA/783153/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 5(3) of Regulation (EC) No 726/2004

Invented name: Paxlovid

INN/active substance: PF-07321332/ritonavir

Procedure number: EMEA/H/A-5(3)/1513

Note:

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

ACE2	Angiotensin-converting enzyme 2
ALT	Alanine aminotransferase
ASMF	Active Substance Master File
AST	Aspartate aminotransferase
ATR	Attenuated total reflectance
BCS	Biopharmaceutics classification system
BID	Twice (two times) a day
BMI	Body Mass Index
CAS	Chemical Abstracts Service
CHMP	Committee for Medicinal Products Human Use
CMC	Chemistry, Manufacturing and Controls
COVID-19	Coronavirus disease 2019
CPP	Critical Process Parameter
DDI	Drug-Drug Interactions
EC	European Commission
E-DMC	External data monitoring committee
EMA	European Medicines Agency
EPIC-HR	Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients
EUA	Emergency use authorization
FDA	Food Drug Administration
FTIR	Fourier transform infrared
GC	Gas Chromatography
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
HDPE	High-density polyethylene
hERG	human Ether-à-go-go-Related Gene
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
IC50	Half maximal inhibitory concentration
ICH	International Conference of Harmonization
ICP-MS	Inductively Coupled Plasma- Mass Spectrometry
IMPD	Investigational Medicinal Product Dossier

IPC	In-process Controls
IR	InfraRed
IUPAC	International Union of Pure and Applied Chemistry
Ki	Inhibition constant
LC	Liquid Chromatography
LDPE	Low density polyethylene
LoQ	List of Questions
MAA	Marketing Authorisation Application
mITT	modified Intention-to-Treat
MS	Mass Spectrometry
MTBE	t-butyl methyl ether
NMR	Nuclear Magnetic Ressonance
NMT	Not more than
NPC	4-nitrophenyl chloroformate
OC	Other concern
OPA/Al/PVC	Oriented PolyAmide/Aluminum Foil/Polyvinylchloride
OSD	Oral Solid Dose/Dosage
Ph.Eur./EP	European Pharmacopea
PK	Pharmacokinetics
QOS	Quality Overall Summary
QP	Qualified Person
QTPP	Quality Target Product Profile
RT-PCR	Reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SM	Starting Materials
TNC	5-Thiazolyl) methyl)-(4-nitrophenyl) carbonate
TSE/BSE	Transmissible spongiform encephalopathies/Bovine spongiform encephalopathies
UFLC	Ultra-Fast Liquid Chromatography
USP	United States Pharmacopea
UV	Ultraviolet
XRPD	X-ray powder diffraction

This list is not exhaustive

1. Information on the procedure

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus, is the causative agent of coronavirus disease 2019 (COVID-19). Early treatment of patients with confirmed COVID-19 presenting only mild symptoms could reduce the number of patients that progress to more severe disease and require hospitalisation or admittance to intensive care unit (ICU).

The European Medicines Agency (EMA) is aware of several therapeutic candidates with putative antiviral action which are currently in development for the treatment of these patients.

Amongst those treatments is Paxlovid (PF-07321332 150 mg film-coated tablets and ritonavir 100 mg film-coated tablets), an investigational SARS-CoV-2 protease inhibitor antiviral therapy, specifically designed to be administered orally so that it can be prescribed at the first sign of infection or at first awareness of an exposure, potentially helping patients avoid severe illness which can lead to hospitalization and death. PF-07321332 is designed to block the activity of the SARS-CoV-2-3CL protease, an enzyme that the coronavirus needs to replicate. Co-administration with a low dose of ritonavir as a pharmacokinetic booster helps to optimize the pharmacokinetics of this anti-protease against SARS-Cov-2 as originally considered in the therapeutic management in the field of HIV chronic infection.

PF-07321332 inhibits viral replication at a stage known as proteolysis, which occurs before viral RNA replication. In preclinical studies, PF-07321332 did not demonstrate evidence of mutagenic DNA interactions.

Paxlovid showed a significant diminution of the percentage of patients with COVID-19-related hospitalization or death from any cause in high risk patients with at least 1 post-baseline visit through Day 28, who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment, and were treated ≤ 3 days after COVID-19 symptom onset (primary endpoint) in Paxlovid arm compared to placebo arm -6.32 with a 95% unadjusted for multiplicity CI (-9.04, -3.59) $p<0.0001$ an in Interim Analysis of Phase 2/3 EPIC-HR study.

These results are of particular relevance and their application in the clinical setting before a formal marketing authorisation is considered important in view of the current pandemic situation. In that respect, there is public health interest to seek a harmonised scientific opinion at EU level on currently available information on Paxlovid and on potential conditions of use with a view to supporting national decisions.

On 19 November 2021 the Executive Director therefore triggered a procedure under Article 5(3) of Regulation (EC) No 726/2004, and requested the CHMP to give a scientific opinion on the currently available quality, preclinical and clinical data on the potential use of Paxlovid for the treatment of confirmed COVID-19 in adult patients.

2. Scientific discussion

2.1. Introduction

The causative agent of the coronavirus disease 2019 (COVID-19) pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a member of the coronavirus family. SARS-CoV-2 infects cells through the angiotensin-converting enzyme 2 (ACE2) receptor with the lung and bronchial epithelial cells as the primary sites of infection. Like other coronaviruses, SARS-CoV-2 encodes a main protease (mPro): $3CL^{pro}$.

PF-07321332 is a selective inhibitor of the SARS-CoV-2 protease, $3CL^{pro}$, to be administered as an oral agent for the treatment of patients with COVID-19, in combination with ritonavir. Inhibition of the 3CL protease renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication. Ritonavir is not active against SARS-CoV-2 $3CL^{pro}$ but inhibits the CYP3A-mediated metabolism of PF-07321332, thereby providing increased plasma concentrations of PF-07321332.

2.2. Quality aspects

The finished product Paxlovid consists of two separately manufactured medicinal products (PF-07321332 150 mg film-coated tablets and ritonavir 100 mg film-coated tablets), which are co-packaged together. 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 a centralized procedure EU/1/96/016/005.

The PF-07321332 immediate release film-coated tablet 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 product is an immediate release film-coated tablet containing 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 finished product Paxlovid is packaged into a composite "Oriented PolyAmide/Aluminum Foil/Polyvinylchloride foil blister" with aluminium foil lidding; each tablet is placed into an individual blister cavity.

The packaging provides the recommended dosage which is 300 mg PF-07321332 (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days as depicted below in Figure 1:

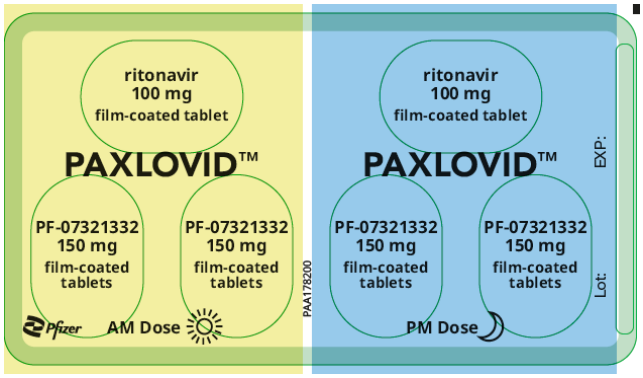


Figure 1. Paxlovid packaging configuration

Five of the blister cards are packed in a carton for 5 days treatment.

2.2.1. Active Substance (PF-07321332)

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):

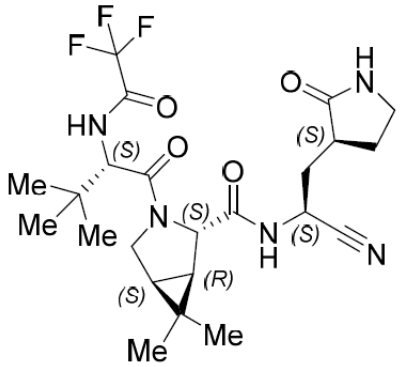


Figure 2. chemical structure of PF-07321332

The structure of 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. Its 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 (methyl tertiary butyl ether solvate) and Form 3 (an n-butyl acetate solvate) are further possible polymorphic forms. Form 1 is the thermodynamically most stable form at relevant temperatures and humidities.

Manufacture, process controls, characterisation and container closure

The manufacturing process consists of several chemical transformation steps. The description is acceptable in the context of this procedure, but further information and definitions are expected at the time of marketing authorisation application (MAA).

A brief description of the manufacturing process was given including reagents and solvents, some in-process controls, and yields. Appropriate in-process controls (IPC) have been established for each step. The projected commercial manufacturing scale range for PF-07321332 was defined. The company states that due to accelerated development of PF-07321332, scientific understanding of the synthesis

and a comprehensive control strategy are not completed yet. These will be completed at time of MAA which may implicate further changes to the synthetic process, though anticipated to be minor. In the context of an Art. 5(3) submission this level of information is acceptable, but further detailed information on the manufacturing process are expected at the time of MAA.

The starting materials are structural fragments of the active substance. The provisional SM specifications, analytical procedures and summary of validation data given are acceptable for this procedure. Names and addresses for the SM manufacturers are stated. Further data and information on starting materials (justification of starting materials according to ICH Q11, confirmation of structure, description of synthesis, some tightening of specifications) will be expected at the time of MAA. Comparative data will also be expected from each proposed SM supplier.

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 in the context of this procedure.

Provisional specifications have been established not for all isolated intermediates in the manufacturing process of PF-07321332 active substance. Detailed specifications for intermediates will be expected at the time of MAA, which should include discussion of impurity carry-over supported by batch analysis data.

A short description of the manufacturing process development is provided.

A discussion on inorganic and organic impurities (including elemental, genotoxic and chiral impurities), their carryover and control strategy has been provided and is acceptable in the context of this procedure. The residual solvents used in the final manufacturing step are specified in the active substance specifications with adequate limits according to ICH Q3C guideline.

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. Further data on impurities and their control strategy are expected at the time of the MAA.

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 in the context of this procedure, but more information and specifications are expected at the time of MAA.

Specification, analytical procedures, reference standards, batch analysis

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).

In principle, 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), as well as the rationale for omitting chiral purity, elemental impurities and microbial enumeration, are acceptable in the context of this procedure. However, additional batch analysis data to support the impurities, specifications limits and setting of acceptance criteria are expected at time of MAA.

The descriptions of the analytical procedures and the validation data provided are acceptable in the context of this procedure, but more data are expected at the time of MAA. The quality of the reference standard for the active substance is sufficiently proven for this procedure.

Satisfactory batch analysis data are given for active substance batches used for toxicological batch and clinical batches. Additional batch analysis data for batches which support the product specification are expected at the time of MAA.

Stability

Stability data for two active substance batches produced by earlier manufacturing processes 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 batches are supportive for the proposed manufacturing process as they have the same polymorphic form, similar synthetic chemistry and same final solvents. Differences in purity profile at release are not expected to impact stability. The company has demonstrated that the active substance is photostable.

Taking into account the requirements of the ICH Q1E guideline a re-test period of 12 months at 15-30°C can be accepted. Further available data should be provided at the time of the MAA.
A commitment was given that the first three batches 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.

2.2.2. 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 Active Substance Master File (ASMF) procedure.

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):

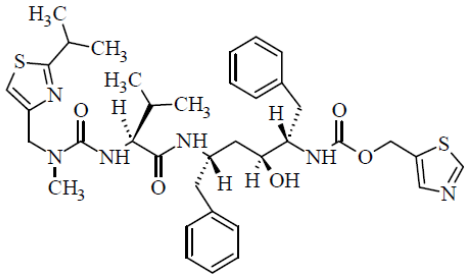


Figure 3. chemical structure of ritonavir

The molecular structure of ritonavir was investigated and confirmed by the ^{1}H and ^{13}C 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 an XRD pattern, and tested in the active substance specification.

Manufacture, process controls, characterisation and container closure

Ritonavir from Hetero is already approved in the EU using the AMSF procedure. However, a Letter of Access specifying the ASMF version (Applicant's and Restricted Part of the ASMF) has not been submitted and is required at the time of MAA to give permission to the National Competent Authorities/EMA to assess the data in the ASMF in relation to the MAA for Paxlovid. Pfizer commits to prove a Letter of Access issued by Hetero by 17-Dec-2021. In the context of this procedure, only the information presented by the company (Pfizer) were assessed.

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.

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.

Genotoxic studies: Based on the evaluation of the process, impurities were identified as potential genotoxic impurities. Studies have been carried out to check their presence in final API 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 (Form-I) 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.

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 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.

Stability

Stability studies were initiated for the first three Ritonavir API 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 of 60 months at 25ºC without any recommendations for storage is endorsed.

2.2.3. 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.

2.2.3.1 PF-07321332 150 mg film-coated tablet

Description of PF-07321332 film-coated tablets

The PF-07321332 tablets are described as oval, pink, film-coated tablets and debossed with "PFE" on one tablet side and with "3CL" on the opposite side.
The missing tablet dimensions are expected to be added to section 3.2.P.1 at time of MAA.

PF-07321332 film-coated tablet is an immediate release (IR) dosage form, containing 150 mg PF-07321332 as active substance.

Pharmaceutical Development

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 has low aqueous solubility across the physiologically relevant pH range. The solubility is pH independent, as it is a non-ionisable compound. Classification of permeability (low/high) will continue to evolve as additional data becomes available. It is tentatively classified as BCS II/IV (low solubility with permeability to-be-determined) compound. A clear BCS classification for the active PF-07321332 is expected at time of MAA.

Polymorphic forms have been identified for PF-07321332. The anhydrous crystalline form 1 is the thermodynamically most stable form under relevant manufacturing and storage conditions, and is used for all finished product development and clinical manufacture activities.

As the data set in terms of particle size distribution (PSD) is premature, a discussion in depth with respect to potential PSD impact on manufacturability and bio-performance of the PF-07321332 IR film-coated tablets is awaited at time of MAA.

Based on stability data available to date, no active substance-excipient incompatibility has been observed.

Excipients and corresponding quantities chosen are typically used for oral solid dose (OSD) products such as the film-coated tablets in question. The selected excipients are of compendial grade and comply with the requirements of the relevant Ph. Eur. monographs, with the exception of the colorant, which however comprises of compendial components.

The dissolution performance of representative PF-07321332 150 mg immediate release film-coated tablet batches was investigated in dissolution media over the physiological range. Following

experimentation the final test conditions were found to be suitable and thus are proposed for the routine quality control (QC).

The discriminatory power of the proposed dissolution method was studied. In light of emergency supply, the aspect *in-vitro dissolution* is considered appropriately addressed.

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, enhanced development studies were conducted to investigate the effects of process parameters on the aforementioned quality attributes. The operating ranges studied for the process parameters at laboratory and large manufacturing scales were shown to be robust for all quality attributes studied.

As summary and conclusion, the formulation development as well as manufacturing process development have been suitably worked out in the context of emergency supply and taking into account the selected dosage form „film-coated tablet". However, at time of MAA, a number of issues need to be further addressed, and importantly an appropriate control strategy. The criticality of the proposed quality attributes and process parameters needs to be specified. Furthermore, the robustness of the proposed manufacturing process needs to be demonstrated covering the whole commercial batch size range.

Microbiological attributes for PF-07321332 150 mg film-coated have been assessed during development and complied with the harmonised USP/EP requirements for non-aqueous preparations for oral use.

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/Aluminum Foil/Polyvinylchloride (OPA/Al/PVC) foil blister with aluminum foil lidding where each tablet is placed into an individual blister cavity. Illustrative drawings and representative IR spectra of the packaging components are provided. More detailed information on the packaging components (specifications, analytical procedures, certificates of analysis, quality declarations) are expected to be provided at the time of the MAA.

Manufacture of the finished product and process controls

The respective manufacturing sites along with their corresponding responsibilities are clearly specified.

For the all proposed finished product manufacturing sites located in the EU, the GMP certificates are available in EudraGMDP. For the Pfizer site in USA, a written confirmation is available stating that this site had been inspected by the FDA.

The manufacturing process comprises the following steps: initial blending, screening, intra-granular lubrication, dry granulation, milling, extra-granular blending and lubrication, followed by tablet compression and film coating.

Batch formulae for batch sizes ranges were provided.

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, by indicating the set limit of the different blending stages as well as the acceptance criteria of the in-process controls for compression. The level of detail provided on the manufacturing process is acceptable for this procedure. However, for the forthcoming MAA submission, the finished product manufacturing process needs to be described in

greater detail, specifying all crucial aspects such as critical process parameters (CPP) and in-process controls (IPC) and holding times of intermediates.

No process validation data were presented. This is acceptable considering the fact that conventional techniques and equipment are used and also the context of this procedure. It is stated that the manufacturing & packaging process validation will be completed and provided within the MAA when final process and controls will have been identified and appropriate process understanding has been developed.

Product specification, analytical procedures, batch analysis, reference standards

The finished product specifications include appropriate tests for this kind of dosage form including appearance, identity (HPLC and IR), assay (HPLC), degradation products (HPLC), dissolution (Ph. Eur., HPLC), content uniformity (Ph. Eur.) and microbial limits (Ph. Eur.).

In principle sufficient information on specifications has been provided. However, some additional testing parameters should be included in the specifications at time of MAA. Additionally, some amendments on the acceptance criteria and a clear distinction between release and shelf-life specifications are expected to occur at the time of MAA. Revision of the limit concerning dissolution testing is awaited at time of MAA.

The impurities and degradation products have been sufficiently discussed. The finished product contains no Class 1 or Class 2 mutagenic impurities or degradation products.

An elemental impurities risk assessment is in progress. Based on the discussion presented in relation to the active substance and in view of usage of compendial, well-precedented excipients, the contributions of elemental impurities from the active substance and the excipients into the finished product should be negligible. Complete information concerning the elemental impurities risk assessment is awaited at time of MAA.

A risk assessment on the potential presence and formation of nitrosamine in the finished product was completed. The Company states, that no vulnerable amines have been identified in active substance or excipients, as well as no nitrosamine risk have been identified from the packaging material used.

Overall, the specification limits have been sufficiently justified. In addition, justification has been provided concerning exclusion of tests. Further information on justification is awaited at time of MAA.

The descriptions of the analytical procedures and their validations provided are acceptable. Some additional information is awaited at time of MAA concerning some validation parameters. Information regarding the reference standards has been provided. Further information concerning the suitability of the reference standards used for the determination of assay of the finished product is awaited at time of MAA.

Batch analysis data were provided for batches of PF-07321332 150 mg film-coated tablets 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. All data found were within the specifications at the time. Some clarification concerning the use of different specifications is awaited at time of MAA.

Adventitious agents

Lactose monohydrate is the only excipient of animal origin. Relevant TSE safety confirmation is available and accepted.

2.2.3.2 Ritonavir 100 mg film-coated tablet

Description of Ritonavir 100 mg film-coated tablets

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. At time of MAA, 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.

The manufacturing process is described.

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.

In summary, the finished product has been shown to be comparable to the reference product with respect to key parameters *in vitro* dissolution and related substances profile/levels. However, several aspects of pharmaceutical development will need to be addressed at time of MAA, and compliance with current ICH Q8 (R2) should be established.

The choice of container closure system for the co-packaged medicinal product is based on PF-07321332 tablets and is justified. 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 aluminum bag) for Ritonavir bulk tablets was provided including specifications, analytical procedures and certificates of analysis issued by both the suppliers and the product manufacturer.

Manufacture, 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: pulverization), 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.

Overall, the process is well-described and controlled by in-process controls. Nevertheless, the applicant is expected to provide further details and justification for the control strategy employed based on development data. Besides, flow charts and in-process controls may need to be updated at time of MAA submission.

Process validation data were provided for commerical 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 blend intermediate were provided. The results obtained demonstrate that the manufacture of Ritonavir premix is acceptable and reproducible in order to obtain mixture that comply with the specifications and quality characteristics defined on the respective validation protocol.

Product specification, analytical procedures, batch analysis, reference standards

The finished product release and shelf life specifications**Error! Reference source not found.**, 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.).

In principle sufficient information on specifications has been provided. The specifications for Ritonavir 100 mg film-coated tablets are in line with the requirements of the relevant Ph. Eur. monographs, ICH guidelines and batch analysis data. However, some additional information is awaited at time of MAA.

There are no impurities in the product that are different from those present in the active substance. However, further information concerning impurity qualification is awaited at time of MAA.

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 at the time of MAA with details on the method used including LOD, LOQ of the analytical method.

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 will be requested at the time of MAA.

If not otherwise justified, the limit for dissolution testing should be revised at time of MAA. Preferably, more than one time point should be included in the specification on *in vitro* dissolution.

The analytical methods (Ph Eur 2.2.29 & in-house analytical methods) have been sufficiently described. Method validation has been provided for almost all methods described under analytical procedures including the method used for the determination of blend assay, blend content uniformity. Further information on validation data is awaited. 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. For completeness of demonstration of suitability of the methods used, validation data concerning Karl Fischer method are requested at time of MAA.

Information on reference standards used including certificates of analysis has been provided. Some information is expected at time of MAA concerning the purpose of the reference standards used as well as on demonstration of suitability for the finished product.

Batch analysis data have been presented. All data were within the specifications. However, clarification concerning specification parameters is awaited at time of MAA.

Adventitious agents

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

Stability conclusion 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.

Preliminary stability data for three primary batches of the 150 mg tablets were reported for 6 weeks 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 and dissolution were performed.

In addition, photostability (in accordance with ICH guideline Q1B) of one batch was evaluated and data was provided.

Various supportive data of early development formulations manufactured as different strength tablets packaged in several container closure systems were evaluated under different conditions. 3 months data at the long-term storage condition of 30ºC/75% RH and at the accelerated storage condition of 40ºC/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 30ºC/75% RH and at the accelerated storage condition of 40ºC/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.

Stress studies on film-coated tablets stored in an open container, placed in an oven were performed. Total degradation products remained within specifications.

The overall stability data from the primary stability studies, supportive studies, stress stability studies and forced degradation stability studies, reveal that no significant changes have been observed for appearance, assay, degradation products, dissolution or water content. The levels of degradations under different conditions of temperature, humidity, light remained low.

A shelf life of 12 months was proposed for the PF-07321332 150 mg film coated tablets. According to ICH Q1E the provided stability data would support shelf-life of 6 months. However based on EMA/CHMP/QWP/545525/2017 for Investigational medicinal products in clinical trials and considering the purpose of this application (between clinical and commercial stages in the product lifecycle) it is accepted that a greater flexibility can be applied; a shelf life of 12 months is thus considered acceptable in the context of this application (see also Co-packaged Finished Product below).

The proposed storage conditions and labeling for PF-07321332 150 mg film-coated tablets are "Do not store above 25°C"; "Do not refrigerate or freeze".

Ritonavir Film-coated Tablets

Stability data for Ritonavir 100 mg tablets in the Pfizer co-packaged foil/foil 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 40ºC/ 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.

A forced degradation study (acid, base, peroxide, thermal, photolytic and humidity) 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.

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 has been confirmed when stored under these conditions.

The proposed shelf-life for Ritonavir 100 mg film-coated tablets is 24 months. This medicinal product does not require 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

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 overall available stability data presented for both components of the co-packaged product, the proposed shelf-life of 12 months with storage conditions "Do not store above 25°C. Do not refrigerate or freeze", as stated in the CoU (sections 5.8 and 5.9).

The twelve months stability for the drug 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

results. Storage conditions "Do not store above 25°C", "Do not refrigerate or freeze" is accepted provided that this storage conditions will be updated as required when further stability data are available.

2.2.4 Discussion and conclusions on chemical and pharmaceutical aspects

This procedure, triggered under Article 5(3) of Regulation (EC) No 726/2004, intends to provide a harmonised scientific opinion at EU level on currently available information on Paxlovid and on potential conditions of use with a view to supporting national decisions before a formal marketing authorisation based on the currently available quality, preclinical and clinical data on the potential use of Paxlovid for the treatment of confirmed COVID-19 in adult patients. This is particularly relevance in the clinical setting in view of the current pandemic situation and the public health interest.

The proposed medicinal product Paxlovid consists of PF-07321332 150 mg film-coated tablets and ritonavir 100 mg film-coated tablets. For ease of daily co-administration, both products (PF-07321332 150 mg film-coated tablets and Ritonavir film-coated tablets) are co-packaged on the same blister.

Information on development, manufacture and control of the active substances and 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. A number of issues as detailed in the report above have been identified that require more comprehensive data for the future MAA.

The quality of this product is considered to be acceptable in the context of the present procedure, when used in accordance with the conditions defined in the Conditions of Use.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that, in the context of the present procedure, the product should have a satisfactory and uniform performance in clinical use.

The twelve months stability for the drug 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 results.

Storage conditions "Do not store above 25°C", "Do not refrigerate or freeze" is accepted provided that this storage conditions will be updated as required when further stability data are available.

2.3. Non-clinical aspects

2.3.1 Pharmacology

PF-07321332 is a selective inhibitor of the SARS-CoV-2 $3CL^{pro}$. The activity of the $3CL^{pro}$ is essential for viral replication; $3CL^{pro}$ digests the virus p1a and p1ab polyproteins at multiple junctions to generate a series of proteins critical for virus replication and transcription. No close human analogues of the coronavirus $3CL^{pro}$ are known. The essential functional importance in virus replication together with the absence of closely related homologues in humans, identify the $3CL^{pro}$ as an antiviral drug target.

Primary Pharmacodynamics

In vitro

In vitro pharmacodynamic (PD) studies are reported in the clinical part of this assessment report (AR) (please see below).

In vivo

Two *in vivo* models were conducted to evaluate the anti-viral efficacy of PF-07321332 against SARS-CoV-2 using a mouse-adapted virus, SARS-CoV-2-MA10. SARS-CoV-2-MA10 is a recombinant mouse adapted strain of SARS-CoV-2 (SARS-CoV-2 MA) capable of utilizing mACE2 for viral entry by remodelling the spike and receptor binding interface via reverse genetics. In addition to the spike Q498Y/P499T substitutions engineered into the parental SARS-CoV-2 MA, SARS-CoV-2 MA10 included 5 additional nucleotide changes, all resulting in non-synonymous coding change. Disease was reflected by body weight and lung pathology.

In study 105036, SARS-CoV-2-MA10 (dose of 1 x 10^5 $CCID_{50}$) was administrated by intranasal route in BLB/c mice. Six animals/group were treated twice daily beginning four hours post infection by *per os* (PO) administration at dose levels 0, 300, 1000 mg/kg in two separate experiments. Mice were weighed prior to infection and then everyday thereafter to evaluate infection-associated weight loss. Animal were euthanized on study day 4 and lung lobes were collected for histopathology analysis and for evaluating lung virus titers. Due to the similarity of both study results, data was combined (n=12/group) and assessed. Treatment with PF-07321332 at both 300 or 1000 mg/kg oral twice (two times) a day (BID) doses significantly protected mice from weight loss and reduced virus lung titers by approximately 1.39 log or 1.91 log, respectively, compared to placebo treated group. Pharmacokinetics (PK) results (5 animal/group) revealed that the overall unbound Cmin of PF-07321332 in the BALB/c mouse was approximately 0.9x EC_{90} and 4x EC_{90} at the 300 mg/kg and 1000 mg/kg BID doses of PF-07321332. Therefore, PF-07321332 has antiviral efficacy in the mouse-adapted model of SARS-CoV-2, maintaining ~1× EC90 at Cmin. Histopathological analysis of lungs from the treated mice showed that most of the infected mice exhibited multifocal pulmonary lesions, however, this was significantly reduced in the 300 and 1000 mg/kg BID groups, respectively in the PF-07321332 treated mice compared to the untreated mice.

In study 022652, SARS-CoV-2-MA10 (dose of 2.5 x 10^4 PFU) was administrated by intranasal route in the 129-mouse strain. Six animals/group were treated twice daily beginning four hours post infection by PO administration at dose levels 0, 300, 1000 mg/kg. An additional 6 animals were treated orally with 1000 mg/kg PF-07321332 twice daily beginning twelve hours post infection. Mice were weighed prior to infection and then everyday thereafter to evaluate infection-associated weight loss. Animal were euthanized on study day 3 and lung lobes were collected for histopathology analysis and for evaluating lung virus titers. Treatment with PF-07321332 at 300, 1000 mg/kg (dosed 4h post infection), 1000 mg/kg (dosed 12h post infection) oral BID doses significantly protected mice from weight loss and reduced virus lung titers by approximately 1.1 log, 4.3 log and 4.2 log respectively, compared to placebo treated group. PK results (6 animal/group) revealed that the overall unbound Cmin of PF-07321332 was approximately 1.5x EC_{90} and 7x EC_{90} at the 300 mg/kg and 1000 mg/kg BID doses of PF-07321332. Treatment with PF-07321332 at a dose of 1000 mg/kg BID dosed 4h post infection or 1000 mg/kg BID dosed 12 h post infection significantly reduced histopathology scores (around 80% and 50%, respectively) when compared to vehicle control group. No significant reduction was observed at 300 mg/kg dosed at 4h post infection (around 16%).

Overall, only animal data with SARS-CoV-2 mouse adapted are available. No studies have been performed to evaluate effect of PF-07321332 treatment in infected animal model with the variants of SARS-CoV-2. Translability in clinic of impact on viral replication in lung in animal model warrants particular caution.

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. This could be of value for the ongoing development in prevention.

Secondary Pharmacodynamics

In study 100054569, PF-07321332 was tested for potential secondary pharmacodynamic activity *in vitro* against a panel of enzymes, receptors and ion channels, with ≥ 50% inhibitory activity considered significant. No activity was observed when PF-07321332 was tested at 100 µM ((78x the predicted human unbound PF-07321332 Cmax at a BID dose of 300/100 mg PF-07321332/ritonavir, predicted Cmax unbound 2.56 µM).

In study 20LJ074, PF-07321332 was tested for inhibitory activity against 11 phosphodiesterase (PDE) subtypes (PDEs 1 to 11). The IC_{50} values were determined to be >200 µM for all PDE subtypes tested (78x the predicted human unbound PF-07321332 Cmax at a BID dose of 300/100 mg PF-07321332/ritonavir).

Safety Pharmacology

Five studies were conducted to address the safety pharmacology core battery, in line with the International Conference of Harmonization (ICH) guideline S7A requirements. 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.

- *In vitro*

Table 1 - human Ether-à-go-go-Related Gene (hERG) studies with PF-07321332

Type of study, GLP, Study no	Species, Gender and no/grp	Method of Admin, Duration of dosing	Concentrations	Safety pharmacology findings
hERG assay GLP 20LJ091 22/01/2021	*In vitro*	Human embryonic kidney cells (HEK293)	30, 300 µM Lot # PF-07321332-00-0018	Control: 2.0 ± 0.4% PF-07321332 30 µM : 2.5 ± 0.4% PF-07321332 300 µM : 5.9 ± 0.3% (statistically significant) Terfenadine 60 µM : 78.5± 2.7% IC_{50} value: > 300 µmol/L
Activity at Nav1.5 and Cav1.2 ion channels	*In vitro*	Nav1.5 and Cav1.2 ion channel expressed in CHO cells	0.003, 0.03, 0.3, 3, 30, 300 µM	IC_{50} value: > 300 µmol/L T+ Nav1.5 tetracaine : IC_{50} = 1.7 µM T+ Cav1.2 verapamil : IC_{50} = 2.9 µM

In the human ether-à-go-go-Related Gene (hERG) inhibition assay, administration of PF-07321332 at 300 µM resulted in statistically significant ($p < 0.05$) inhibition of hERG (5.9 ± 0.3%) when compared to the vehicle control (2.0 ± 0.4%),The IC_{50} for the inhibitory effect of PF-07321332 on hERG potassium current was not calculated but was estimated to be greater than 300 µM (>117x the predicted human unbound PF-07321332 Cmax at a BID dose of 300/100 mg PF-07321332/ritonavir).

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, the highest dose tested (>117x the predicted human unbound PF-07321332 Cmax at a BID dose of 300/100 mg PF-07321332/ritonavir).

- *Ex vivo*

Table 2 – *Ex vivo* studies

Type of study, GLP, Study no	Species, Gender and no/grp	Method of Admin, Duration of dosing	Concentrations	Safety pharmacology findings
Cardiovascular Assessment (Heart) Non-GLP 20LJ075 03/11/2020	*Ex vivo*	Guinea pig isolated Langendorff-perfused heart	0.03, 0.1, 0.3, 1, 3, 10, 30 and 100 µM Lot # PF-07321332-00-0007	No effect on cardiac contractility, left ventricular pressure, coronary perfusion pressure, PR, QRS or QT intervals
Cardiovascular Assessment (Aorta) Non-GLP 20LJ076 21/10/202O	*Ex vivo*	Rat isolated ascending aorta tissue	2 pM - 100 µM Lot # PF-07321332-00-0007	Vasoconstrictive Activity: no effect PF-07321332: IC_{50} > 100 µM Phenylephrine: IC_{50} =22.5 µM Vasorelaxant Activity: a statistically significant concentration-dependent vasorelaxation, IC_{50} = 50.3 µM

In the guinea pig isolated Langendorff-perfused heart model, PF-07321332 did not produce a statistically significant change in cardiac function or cardiac conduction at any of the concentrations tested (up to 100 µM, which is 39x the predicted human unbound PF-07321332 Cmax at a BID dose of 300/100 mg PF-07321332/ritonavir). In the rat isolated aorta tissue bath preparation, PF-07321332 produced a statistically significant concentration- dependent vasorelaxation when compared with the control. The IC_{50} was determined to be 50.3 µM, representing 20x the predicted human unbound PF-07321332 Cmax at a BID dose of 300/100 mg PF-07321332/ritonavir.

- *In vivo*

Table 3 - Safety pharmacology studies with PF-07321332

Type of study, GLP, Study no	Species, Gender and no/grp	Method of Admin, Duration of dosing	Doses (mg/kg)	Safety pharmacology findings
Pulmonary system (RR, TV, MV)	Rat/Wistar Han 6M/group	Oral gavage, Single dose 10 mL/kg (2% Polysorbate 80 in 0.5% [w/v] methylcellulose in purified water)	0, 0 (15% MTBE = 150 MTBE), 60, 1000	1000 mg/kg: ↑ RR (up to +44%), ↑ MV (+38%) (from 40-160 min)
Central nervous System (FOB, BT, LA) GLP 20GR274 26/01/2021	6M/group	Lot # PF-07321332-00-0018		FOB parameters: no effect quantitative locomotor assessment: 1000 mg/kg ↓ vertical movements (-36%) (first 5 min) ↑ horizontal (+298%) and vertical (+838%) movement (last 30 min)
Cardiovascular system (blood pressure, heart rate, ECG) GLP	Cynomolgus Monkey (telemetry) 2M/group	Oral gavage, BID 5 mL/kg (2% (v/v) Polysorbate 80 in 0.5% (w/v) methylcellulose in purified water) Lot # PF-07321332-00-0018	0, 0 (22.5 [11.5 BID] MTBE) 40 (20 BID) 150 (75 BID)	No clinical signs 0, 0 (MTBE), 40: none <u>150 mg/kg:</u> ↓ HR (-8 to -14 bpm) ↑ SBP (+4 mmHg),

20GR275 25/08/2021 (report amendment 1) Full report (12/02/2021)	Prior CV phase : at D1, all animal received one single dose of 150 (75 BID) to determine PK profile Cross over design: each animal will receive all 4 dose level at D9, D12, D16, D19	↑ DBP (+3-5 mmHg) ↑ MBP (+5 mmHg) Secondary to ↓ HR ↑ RR-I (+37-52 msec), ↑ PR-I(+3 msec), ↑ QT-I (+11-13 msec), ↓ QTc (-5 to -7 msec), ↓ LV+dP/dt max (-306 to -364 mmHg/sec) TK PK phase: 150 (75 BID) Cmax = 14.7 ± 9.24 µg/mL AUC24 = 131± 100 µg.h/ml

For the *in vivo* safety pharmacology studies, no toxicokinetics (TK) 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 a 4-week toxicity study is 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.

The central nervous system (CNS) and respiratory safety pharmacology studies were conducted in male Wistar Han rats in the same study but in different groups. 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 on CNS and respiratory system 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.

One dedicated cardiovascular safety pharmacology study 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 heart rate (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. 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.

2.3.2 Pharmacokinetics

The pharmacokinetics of PF-07321332 were determined in rats, dogs, monkeys and rabbits**.**

Absorption

Two single dose administration studies have been performed (studies 103131 in rat and 111728 in monkeys). 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. In the repeat dose toxicity studies, mean systemic exposures increased with increasing dose and there were no consistent sex-related differences in rats and monkeys.

Repeated dose PK parameters have been collected in repeated dose toxicity GLP-studies (up to 1-month). There were no consistent sex-related differences in systemic exposure, and mean exposure of PF-07321332 increased with increasing dose in rats and monkeys. In rats following repeat administration, a decrease in PF-07321332 AUC_{24} was observed across dose groups on Day14 or D25 compared with Day 1 (D14/D1: 0.18 to 0.74, D25/D1 0.38 to 0.56). In monkeys, AUC_{24} of PF-07321332 increased on D14 or D25 compared to Day 1 with accumulation ratios up to 1.7 (D14/D1: 0.83-1.7, D25/D1: 1.12-1.55). Systemic exposure increased with increasing doses in pregnant rats and rabbits.

Distribution

PF-07321332 was moderately bound to plasma proteins in rat, monkey and human and similar across these species. Concentration-dependent protein binding was observed in rabbit plasma (2 to 200 µM, 1% to 80%) but not in rat, monkey and human (0.3 to 10 µM, 31-48%) (study 010657). PF-07321332 preferentially distributed into plasma relative to blood cells in rat (0.83), monkey (0.68) and human (0.60) (study 100444). No *in vivo* distribution study (QWBA) was performed at this time.

Metabolism

The metabolism of PF-07321332 was evaluated *in vitro* in liver microsomes (mouse, rat, hamster, rabbit, monkey, and human), hepatocytes (rat, monkey, and human), and *in vivo* in rat and monkey. A total of six metabolites were detected arising from hydroxylation, dehydrogenation, and hydrolysis reactions. The major metabolite was M4 (PF-07329268), an oxidative metabolite arising from hydroxylation at the 5-position of the pyrrolidinone ring, resulting in a pair of interconverting diastereomers. In plasma of rats and monkeys, unchanged parent drug was by far the most prevalent drug-related entity, with M4 as a major metabolite in monkey. All oxidative metabolites were formed by CYP3A4/5, with other CYP enzymes contributing very minor amounts. Unchanged parent drug was the most prevalent drug-related entity in rat and monkey plasma and in rat urine and bile, with M4 as the most prevalent metabolite in monkey plasma (study 084546). CYP3A4 is predicted to be the major contributor (fm = 0.99) to the *in vitro* metabolism of PF-07321332; no significant CYP3A5 contribution is expected to the metabolism of PF-07321332 (study 072016). Besides oxidative biotransformation pathways, a metabolite M5 (PF-07320267) obtained through a hydrolytic cleavage across an amide bond in PF-07321332, was also detected as a minor metabolite in circulation and excreta from animals (study 082057). M7 (PF-07852082), the acyl-glucuronide conjugate of M5 (by UGT2B4 and 2B7), was identified in human urine in trace amounts. The remaining 13.5% of metabolism through the UGT pathway was unassigned (study 021055). Unchanged PF-07321332 was the predominant drug-related

entity in circulation in plasma from healthy adults administered with a single oral dose of 300 mg PF-07321332 in the presence of ritonavir (study 090141).

Excretion

Urinary and/or biliary excretion of PF-07321332 was assessed in single-dose PK studies after intra-venous (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 feces in rats, and 7% in the urine and 4% in the feces in monkeys. Based on the results of clinical study 021626 (mass balance study in healthy volunteers), the primary excretion routes of orally administered PF-07321332 with ritonavir were urinary excretion of unchanged drug.

Pharmacokinetic Drug Interactions

Drug-Drug Interactions (DDI) studies are reported in the clinical part of this report (please see below).

2.3.3. Toxicology

The nonclinical 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. The species used for the GLP compliant pivotal studies included rats and monkeys and are considered appropriate by CHMP, based on the similar PK profile seen in these species compared to humans (*in vitro* comparison data only at this stage). 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. Rats were administrated once daily and monkeys twice daily (no supportive $T_{1/2}$ in monkey) as it is recommended in humans. Six toxicity studies have been performed: two preliminary studies (4-day) and four pivotal studies (two 2-week and two 1-month repeated-dose studies). Final reports have been submitted except for the 1-month study in rats and in monkeys (unaudited draft). A rat fertility study (unaudited draft submitted), and two EFD studies in rats and rabbits are completed, with a rat PPND study currently ongoing. A standard battery for assessing genotoxicity potential is complete and final reports have been submitted. Margins of exposure were calculated on total Cmax and AUC_{24} (more conservative approach than the one with unbound Cmax and AUC_{24}). The calculation of these margins of exposure are based on predicted human Cmax/AUC_{24} which could not be validated given that the PKPOP available at this stage has particular limitations, notably only based on PK data from healthy volunteers (see clinical PK part of this AR). The margins of exposure are therefore only indicative at this stage and it is expected to be further substantiated at the time of the MAA with the awaited provision of a relevant PKPOP model including PK data collected from the patients enrolled in the EPIC-HR study with relevant covariables to be studied (notably age, weight, formulation,…).

Single dose toxicity studies

No dedicated studies with PF-07321332 have been conducted. This is considered acceptable by CHMP, given the availability of the more relevant repeat dose toxicity studies.

Repeat dose toxicity studies

The toxicity program includes six studies: two 4-d preliminary studies and four pivotal studies in rats and in monkeys up to 1-month duration. Except for the 2-week study in monkeys, all pivotal studies included a 2-week recovery period. As outlined in ICH M3 (R2) for a therapeutic indicated for up to 2-weeks duration of administration, a 1 month study is expected in both rodent and non-rodent species and therefore the duration of the provided studies is in-line with the expectations for the proposed posology of 5-days treatment. PF-07321332 was administered as a methyl tert-butyl ether (MTBE)

solvate, in the 2-week studies, and as a 50% PF-07321332: 50% HPMCAS-MG (hydroxypropyl methylcellulose acetate succinate-medium granular) spray dried dispersion suspension, in the 4-week studies. The 2-week studies included two control groups, one with administration of vehicle and the other with administration of vehicle spiked with 15% MTBE at an amount equivalent to that associated with the PF-07321332 high dose. Similarly, in the 4-week studies, vehicle control animals were administered an amount of HPMCAS-MF (medium fine) equivalent to the amount of HPMCAS administered to the PF-07321332 high dose group. The company has briefly addressed how the PF-07321332 forms used in the pivotal studies - PF-07321332 as methyl tert-butyl ether (MTBE) solvate or 50% PF-07321332: 50% HPMCAS-MG (hydroxypropyl methylcellulose acetate succinate-medium granular) spray dried dispersion suspension - compare with the PF-07321332 present in the medicine Paxlovid, indicating that the tested forms improved systemic exposures. This issue will be further discussed during the MAA procedure. As applicable, the company is also expected to discuss the impact of any identified differences on safety evaluation.

Regarding data on repeated dose toxicity in the CONDITIONS OF USE, information in section 6. "OTHER INFORMATION" is in accordance with the data provided for PF-07321332 and with the contents of the SmPC for the medicinal product Norvir (with ritonavir), as approved in the EU.

Non pivotal studies

Table 4 - Summary of non-pivotal repeat-dose toxicity studies

<table>
<tr><th>Study ID/ GLP</th><th>Species/ Sex/Number/ Group</th><th>Dose (mg/kg) /Route/</th><th>MTD (mg/kg/day)</th><th>Noteworthy findings</th></tr>
<tr><td>4 days

20GR250

Non-GLP

19/11/2020</td><td>Rat/ Wistar Han

3M+3F/group</td><td>Oral gavage, QD,

0, 30, 100, 1000

10 mL/kg (2% [v/v] polysorbate 80 in 0.5% [w/v] methylcellulose in purified water/Suspension)
Lot PF-07321332-00-0009</td><td>Not reported</td><td>None

NOAEL: Not determined due to non-reversible tox in testes at 1.5

TK
Cmax/AUC: F>M, dose-dependent increase, no accumulation (exposure even lower at D4)
<table>
<tr><th rowspan="2">Dose (mg/kg/day)</th><th rowspan="2">Study Day</th><th rowspan="2">Sex</th><th colspan="3">C_{max} (ng/mL)</th><th colspan="3">T_{max} (h)</th><th colspan="3">AUC_{24} (ng·h/mL)</th></tr>
<tr><th>Mean</th><th>S.D.</th><th>n</th><th>Mean</th><th>S.D.</th><th>n</th><th>Mean</th><th>S.D.</th><th>n</th></tr>
<tr><td rowspan="8">30</td><td rowspan="4">1</td><td>Male</td><td>9690</td><td>3600</td><td>3</td><td>0.50</td><td>0.0</td><td>3</td><td>11400</td><td>3520</td><td>3</td></tr>
<tr><td>Female</td><td>8350</td><td>3680</td><td>3</td><td>0.67</td><td>0.29</td><td>3</td><td>14000</td><td>2980</td><td>3</td></tr>
<tr><td rowspan="2">4</td><td>Male</td><td>3810</td><td>1630</td><td>3</td><td>0.67</td><td>0.29</td><td>3</td><td>4590</td><td>1220</td><td>3</td></tr>
<tr><td>Female</td><td>6600</td><td>2280</td><td>3</td><td>0.50</td><td>0.0</td><td>3</td><td>9610</td><td>1390</td><td>3</td></tr>
<tr><td rowspan="8">100</td><td rowspan="4">1</td><td>Male</td><td>20000</td><td>917</td><td>3</td><td>0.50</td><td>0.0</td><td>3</td><td>37600</td><td>2150</td><td>3</td></tr>
<tr><td>Female</td><td>23100</td><td>9450</td><td>3</td><td>0.83</td><td>0.29</td><td>3</td><td>71400</td><td>10300</td><td>3</td></tr>
<tr><td rowspan="2">4</td><td>Male</td><td>12900</td><td>2610</td><td>3</td><td>0.83</td><td>0.29</td><td>3</td><td>23800</td><td>2170</td><td>3</td></tr>
<tr><td>Female</td><td>16200</td><td>5350</td><td>3</td><td>0.83</td><td>0.29</td><td>3</td><td>41300</td><td>19500</td><td>3</td></tr>
<tr><td rowspan="8">1000</td><td rowspan="4">1</td><td>Male</td><td>62200</td><td>8100</td><td>3</td><td>1.7</td><td>2.0</td><td>3</td><td>685000</td><td>129000</td><td>3</td></tr>
<tr><td>Female</td><td>64900</td><td>22100</td><td>3</td><td>0.83</td><td>0.29</td><td>3</td><td>660000</td><td>51200</td><td>3</td></tr>
<tr><td rowspan="2">4</td><td>Male</td><td>21300</td><td>17300</td><td>3</td><td>4.0</td><td>0.0</td><td>3</td><td>268000</td><td>223000</td><td>3</td></tr>
<tr><td>Female</td><td>50900</td><td>26400</td><td>3</td><td>2.0</td><td>1.7</td><td>3</td><td>562000</td><td>449000</td><td>3</td></tr>
</table>
D4 1000 mg/kg/d:
Cmax = 21,300 ng/mL (M) 50,900 ng/mL (F)
AUC24 = 268,000 ng·h/mL (M) 562,000 ng·h/mL (F)</td></tr>
<tr><td>4 days

20GR271

Non-GLP

20/11/2020</td><td>Monkeys/ cynomolgus

1M+1F/group</td><td>Oral gavage, BID (6h apart)

0, 30 (15 BID), 300 (150 BID), or 1000 (500 BID)

5 mL/kg (2% [v/v] polysorbate 80 in 0.5% [w/v] methylcellulose in purified water/Suspension)
Lot</td><td>300<MTD<1000</td><td>≥300: emesis resulting in fluid loss, slight body weight loss, and clinical pathology changes indicative of an acute phase/inflammatory response and hemoconcentration/dehydration as the only test article-related effects

TK
dose-dependent increase, no accumulation, no sex differences (only 1/sex/group)
<table>
<tr><th>Dose[a] (mg/kg/day)</th><th>Study Day</th><th>Sex</th><th colspan="2">C_{max} (ng/mL)</th><th colspan="2">T_{max} (Hours)</th><th colspan="2">AUC_{24} (ng•Hours/mL)</th></tr>
<tr><th></th><th></th><th></th><th>Mean</th><th>n</th><th>Mean</th><th>n</th><th>Mean</th><th>n</th></tr>
<tr><td rowspan="6">30 (15 BID)</td><td rowspan="3">1</td><td>Male</td><td>620</td><td>1</td><td>7.0</td><td>1</td><td>6840</td><td>1</td></tr>
<tr><td>Female</td><td>504</td><td>1</td><td>7.0</td><td>1</td><td>5820</td><td>1</td></tr>
<tr><td>Overall</td><td>562</td><td>2</td><td>7.0</td><td>2</td><td>6330</td><td>2</td></tr>
<tr><td rowspan="3">4</td><td>Male</td><td>1100</td><td>1</td><td>0.50</td><td>1</td><td>4900</td><td>1</td></tr>
<tr><td>Female</td><td>2870</td><td>1</td><td>0.50</td><td>1</td><td>7350</td><td>1</td></tr>
<tr><td>Overall</td><td>1990</td><td>2</td><td>0.50</td><td>2</td><td>6130</td><td>2</td></tr>
<tr><td rowspan="6">300 (150 BID)</td><td rowspan="3">1</td><td>Male[b]</td><td>53600</td><td>1</td><td>1.0</td><td>1</td><td>169000</td><td>1</td></tr>
<tr><td>Female</td><td>41900</td><td>1</td><td>2.0</td><td>1</td><td>380000</td><td>1</td></tr>
<tr><td>Overall</td><td>47800</td><td>2</td><td>1.5</td><td>2</td><td>275000</td><td>2</td></tr>
<tr><td rowspan="3">4</td><td>Male</td><td>50100</td><td>1</td><td>1.0</td><td>1</td><td>443000</td><td>1</td></tr>
<tr><td>Female[c]</td><td>38900</td><td>1</td><td>7.0</td><td>1</td><td>459000</td><td>1</td></tr>
<tr><td>Overall</td><td>44500</td><td>2</td><td>4.0</td><td>2</td><td>451000</td><td>2</td></tr>
<tr><td rowspan="6">1000 (500 BID)</td><td rowspan="3">1</td><td>Male[d]</td><td>101000</td><td>1</td><td>4.0</td><td>1</td><td>1170000</td><td>1</td></tr>
<tr><td>Female[e]</td><td>116000</td><td>1</td><td>2.0</td><td>1</td><td>852000</td><td>1</td></tr>
<tr><td>Overall</td><td>109000</td><td>2</td><td>3.0</td><td>2</td><td>1010000</td><td>2</td></tr>
<tr><td rowspan="3">4</td><td>Male</td><td>133000</td><td>1</td><td>6.0</td><td>1</td><td>1660000</td><td>1</td></tr>
<tr><td>Female[e]</td><td>155000</td><td>1</td><td>7.0</td><td>1</td><td>1870000</td><td>1</td></tr>
<tr><td>Overall</td><td>144000</td><td>2</td><td>6.5</td><td>2</td><td>1770000</td><td>2</td></tr>
</table>
D4 1000 mg/kg/d:
Cmax = 144,000 ng/mL
AUC24 = 1,770,000 ng.h/mL</td></tr>
</table>

Pivotal studies

- *2-week toxicity study in rats plus a 2-week recovery period*

Table 5 - 2-week toxicity study in rats plus a 2-week recovery period

Study ID/GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg/week)/ Route	NOAEL /MTD (mg/kg/day)
2 wk with 2-wk recovery (+genotox assessment) 20GR276 GLP 15/04/2021 (Amendment 1)	Rat/ Wistar Han 10/sex/group (main) + 5/sex/group (rec)	0, 60, 200, 1000 Administrated as a MTBE solvate (1:1) Once dialy Oral gavage Lot # PF-07321332-00-0018	1000 mg/kg/day D14: Cmax = 51.5 µg/mL AUC24 = 292 µg•h/mL

Mortality: none

Clinical signs: none

Body weight, food consumption: none

Ophthalmic observations: None

Haematology/coagulation:
↑ PT ≥ 60 (M, 1.16x-2.50x), 1000 (F, 1.4x)
↑ APTT ≥ 200 (M, 1.09x-1.19x), 1000 (F, 1.11x), is unclear but
indicates alterations in the coagulation pathway.
↑ PLT 1000 (both sexes, 1.22x-1.25x),
↓ RBC mass parameters (HGB 0.95x, HCT , RBC) and ↑ FIB (F, 1.10x) 1000 mg/kg/day
(completely recovered)

Clinical chemistry:
↑ GLOB 1000 (both sexes 1.07x), ↓ A:G (F, 0.90x), ALP (F, 0.66x) and ↑ CHOL (F, 1.33x)
(completely recovered)

Urinalysis
↓ pH 1000 (M, 0.90x)
(completely recovered)

Organ weights:
↑ liver (both sexes) 1000, correlating microscopic finding of periportal hepatocyte hypertrophy
↓ heart (F) 1000
(completely recovered)

Histopathology:
LIVER: minimal to mild periportal hepatocellular hypertrophy (M 1000 and F ≥ 200) with increased incidence and severity of periportal hepatocyte vacuolation F,
(fully reversible), consistent with microsomal enzyme induction (considered non adverse)

THYROID: minimal to mild follicular cell hypertrophy (M+F 1000
(fully reversible), consistent with microsomal enzyme induction (considered non adverse)

KIDNEY: MTBE-related hyaline droplet in the renal tubule (M all dose or vehicle MTBE) (partially reversible), considered to be male rat specific

TK analysis
No sex differences, dose-dependent increases, no accumulation (systemic exposure lower at D14 in comparison to D1, 0.18 to 0.74)

Dose (mg/kg/day)[a, b]	Day	Sex	C_{max} (µg/mL)	T_{max} (h)	AUC_{24} (µg•hours/mL)	AUC_{24}/Dose (µg•hours/mL/mg/kg)
60	1	Male	11.0	0.50	25.0	0.417
		Female	14.8	0.50	29.8	0.497
		Overall	12.9	0.50	27.3	0.455
	14	Male	8.31	0.50	12.1	0.202
		Female	18.3	0.50	22.2	0.370
		Overall	13.3	0.50	17.2	0.287
200	1	Male	33.0	0.50	294	1.47
		Female	41.0	0.50	286	1.43
		Overall	37.0	0.50	291	1.46
	14	Male	23.8	0.50	53.2	0.266
		Female	30.4	0.50	108	0.540
		Overall	27.1	0.50	80.5	0.403
1000	1	Male	72.4	4.0	961	0.961
		Female	70.8	1.0	630	0.630
		Overall	62.1	2.0	796	0.796
	14	Male	50.6	2.0	283	0.283
		Female	52.3	2.0	299	0.299
		Overall	51.5	2.0	292	0.292

Interspecies comparison

Key Response(s)	Dose (mg/kg/day)	C_{max}[a] [µg/mL] (Total)	AUC_{24}[a] [µg•h/mL] (Total)	Exposure Margin[b] C_{max} (Total)	Exposure Margin[b] AUC_{24} (Total)
14-Day Oral Gavage GLP Toxicity Study in Rats (15 sex/group) (20GR276)					
↑ PT (M)	60	13.3	17.2	3.2	0.25
All of the above plus: ↑ APTT (M); periportal hepatocyte hypertrophy (F)	200	27.1	80.5	6.5	1.2
All of the above plus: ↑ PT (F); ↑ APTT (F); ↑ PLT; ↓ RBC mass (F); ↓ FIB (F); ↑ GLOB; ↑ CHOL (F); ↓ ALP (F); ↓ A/G (F); ↓ urine pH (M); ↓ heart weight (F); ↑ liver weight; periportal hepatocyte hypertrophy (M); periportal hepatocyte vacuolation (F); thyroid follicular cell hypertrophy	1000 (NOAEL)	51.5	292	12	4.3

- *2-week toxicity study in monkeys*

Table 6 - 2-week toxicity study in monkeys

Study ID/GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg/week)/ Route	NOAEL /MTD (mg/kg/day)
2 wk with 2-wk recovery 20GR289 GLP 10/03/2021	Monkey/cynomolgus 3/sex/group	0, 40 (20 BID), 100 (50 BID), or 600 (300 BID) Administrated as a MTBE solvate (1:1) Twice daily (6h apart) Oral gavage Lot # PF-07321332-00-0018	600 mg/kg/day D15: Cmax = 106 µg/mL AUC24 = 1220 µg.h/mL

Mortality: none

Clinical signs: emesis (M 600, F ≥ 100)

Body weight:

↓ bw (1M D15, 0.91x)

Food consumption: none

Ophthalmic observations: None

ECG/heart rate: none

Haematology/coagulation:
↑ fibrinogen (2M+1F, 600, 1.72x-2.09x),
↓ sodium (0.96x) chloride (0.93x) (1M, 600)

Urinalysis
↓ pH 1000 (M+F, 600, 0.73x-0.80x)

Organ weights: none

Histopathology: none

TK analysis
No sex differences, dose-dependent increases, no accumulation (M 0.83 to 1.7x, F 0.56 to 1.6x)

Dose (mg/kg/day)[a, b]	Day	Sex	C_{max} (µg/mL)	AUC_{24} (µg•h/mL)
40 (20 BID)	1	Male	1.72	6.14
		Female	1.86	14.7
		Overall	1.79	10.4
	15	Male	2.65	8.79
		Female	2.18	10.4
		Overall	2.42	9.61
100 (50 BID)	1	Male	6.80	39.7
		Female	15.8	129
		Overall	11.3	84.2
	15	Male	7.91	33.1
		Female	15.6	72.1
		Overall	11.8	52.6
600 (300 BID)	1	Male	65.6	795
		Female	53.5	651
		Overall	59.6	723
	15	Male	121	1390
		Female	90.4	1060
		Overall	106	1220

a. Animals were dosed orally twice daily for 15 days.
b. 3 animals/sex/dose group.

Interspecies comparison

Key Response(s)	Dose (mg/kg/day)	C_{max}[a] [µg/mL] (Total)	AUC_{24}[a] [µg•h/mL] (Total)	Exposure Margin[b] C_{max} (Total)	Exposure Margin[b] AUC_{24} (Total)
15-Day BID Oral Gavage GLP Toxicity Study in Cynomolgus Monkeys (3 sex/group) (20GR289)					
No findings	40 (20 BID)	2.42	9.61	0.58	0.14
↑ Emesis	100 (50 BID)	11.8	52.6	2.9	0.77
All of the above plus: ↓ BW	600	106	1220	26	18

- *4-week toxicity study in rats plus a 2-week recovery period*

Table 7 - 4-week toxicity study in rats plus a 2-week recovery period

Study ID/GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg/week)/ Route	NOAEL /MTD (mg/kg/day)
4 wk with 2-wk recovery 21GR122 GLP 22/11/2021 (unaudited draft)	Rat/ Wistar Han 15/sex/group (main) including 5/sex/group (rec Group vehicle and HD)	0, 60, 200, 1000 Administrated as a 50% spray dried dispersion formulation Once dialy Oral gavage Lot # BREC-2212-122	1000 mg/kg/day D25: Cmax = 44.5 µg/mL AUC_{24} = 548 µg.h/mL

Mortality: no test article related death (1F 60 found in the restrainer after TK blood collection)

Clinical signs: sporadic reports of salivation (all doses), soft feces (200 (single animal) and 1000 mg/kg/day)

Body weight, food consumption: none
Ophthalmic observations: none

Haematology/coagulation:
↑ PLT ≥ 200 (both sexes, 1.12x-1.28x),
↑ PT ≥ 200 M and 1000 F (1.06x-1.15x)
(fully reversible), considered non adverse

Clinical chemistry: none
Urinalysis: none

Organ weights:
↑ liver ≥ 60 (both sexes, 1.07x-1.83x), correlating microscopic finding of minimal to mild periportal hepatocyte hypertrophy ≥ 200 (both sexes) (completely recovered except for M 1000 partially reversible)

Histopathology:
LIVER: ≥ 200 periportal hepatocellular hypertrophy (both sexes) with increased incidence and severity of periportal hepatocyte vacuolation F 1000,
THYROID: ≥ 60 (M) and ≥ 200 (F) thyroid follicular cell hypertrophy
PITUITARY GLAND: ≥ 60 (M) vacuolation of endocrine cells in the pars anterior (distalis)
(fully reversible at 60 and 200, partially at M1000)
consistent with microsomal enzyme induction (considered non adverse)

TK analysis
No sex differences, dose-dependent increases, no accumulation (systemic exposure lower at D25 in comparison to D1, 0.38 to 0.56)

Dose (mgA/kg)*	Day	C_{max} (ng/mL)	T_{max} (hours)	AUC_{24} (ng•h/mL)
60	1	16200	0.50	34800
	25	12800	0.50	19200
200	1	35000	1.0	252000
	25	26000	1.0	94900
1000	1	87300	2.0	982000
	25	44500	1.0	548000

Interspecies comparison

Key Response(s)	Dose (mg/kg/day)	C_{max}[a] [µg/mL] (Total)	AUC_{24}[a] [µg•h/mL] (Total)	Exposure Margin[b] C_{max} (Total)	Exposure Margin[b] AUC_{24} (Total)
1-Month Oral Gavage GLP Toxicity Study in Rats (15 sex/group) (21GR122)					
Salivation; ↑ liver weight; thyroid follicular cell hypertrophy; pituitary gland endocrine cells of the pars anterior cytoplasmic vacuolation (M)	60	12.8	19.2	3.1	0.28
All of the above plus: soft feces; ↑ platelets; ↑ PT (M); periportal hepatocellular hypertrophy	200	26.0	94.9	6.3	1.4
All of the above plus: ↑ PT (F); periportal hepatocyte	1000 (NOAEL)	44.5	548	11	8.0

- *4-week toxicity study in monkeys plus a 2-week recovery period*

Table 8 - 4-week toxicity study in monkeys plus a 2-week recovery period

Study ID/GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg/week)/ Route	NOAEL /MTD (mg/kg/day)
4 wk with 2-wk recovery 21GR125 GLP 22/11/2021 (unaudited draft)	Monkey/cynomolgus 5/sex/group (main) Including 2/sex/group (rec, Group vehicle and HD)	0, 40 (20 BID), 100 (50 BID), or 600 (300 BID) Administrated as a 50% spray dried dispersion formulation Twice daily (6h apart) Oral gavage Lot # BREC-2212-124	600 mg/kg/day D28: Cmax = 87.5 µg/mL AUC_{24} = 991 µg.h/mL

Mortality: none

Clinical signs: emesis (sporadic occurrence: 600 M/F (9/10), vehicle (2M/5), 440 (1F/3) and 100 (1F/3)

Body weight: none

Food consumption: none

Ophthalmic observations: None

ECG/heart rate: none

Haematology/coagulation:
↑ fibrinogen (M/F, 600, 1.20x - 1.91x) (fully reversible) also observed in control animals but lower magnitude
↑ ALT (1.63-3.53x) and/or AST (2.68x - 7.41x) (2M+1F, 600) (reversible assessment possible only for 1F: fully reversible)

Urinalysis: none

Organ weights: none

Histopathology: none

TK analysis: No sex differences, dose-dependent increases, no accumulation (1.12 to 1.55x)

Dose (mg/kg/day)	Day	Mean C_{max} (ng/mL)	Mean AUC_{24} (ng•h/mL)
40[a]	1	1250±584	4110±1340
	28	1380±700	5620±1420
100[a]	1	5320±3060	29600±12100
	28	7800±3440	45900±16800
600[b]	1	76600±21300	885000±239000
	28	87500±21000	991000±227000

a. 3 animals/sex/group with serial sampling.
b. 5 animals/sex/group with serial sampling.

Interspecies comparison

Key Response(s)	Dose (mg/kg/day)	C_{max}[a] [µg/mL] (Total)	AUC_{24}[a] [µg•h/mL] (Total)	Exposure Margin[b] C_{max} (Total)	Exposure Margin[b] AUC_{24} (Total)
1-Month BID Oral Gavage GLP Toxicity Study in Cynomolgus Monkeys (3 sex/group) (21GR125)					
No findings	40 (20 BID)	1.38	5.62	0.33	0.08
No findings	100 (50 BID)	7.80	45.9	1.9	0.67
↑ Emesis; ↑ ALT (M); ↑ AST; ↑fibrinogen	600 (300 BID) (NOAEL)	87.5	991	21	14

The toxicity of PF-07321332 was evaluated in two non-pivotal (non-GLP) and 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. All non-adverse test article related clinical findings observed in rats (salivation and soft feces, increases in aPPT, PT, PLT count) or in monkeys (sporadic occurrence of emesis, increases in ALT, AST, fibrinogen) are monitorable in human. Microscopic findings observed in liver, thyroid gland and pituitary gland in rats are consistent with a rat-specific response to hepatic enzyme induction. This mechanism is usually considered to have little to no relevance to humans.

In terms of toxicokinetics, in rats, systemic exposures increased with dose and decreased with treatment duration. In monkeys, while systemic exposures also increased with dose, there was not a clear decrease in exposure with treatment duration. On the contrary, in the 4 weeks 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. There were no quantifiable concentrations of PF-07321332 in plasma samples from control animals from the studies conducted in monkeys (2 and 4 weeks) and the 4 week-study in rats. Regarding the 2-weeks study in rats, there were quantifiable concentrations of PF-07321332 in plasma samples from two control animals, both collected at 2 hours post-treatment. The two concentrations were approximately 5 to 6 times that of the lower limit of quantitation (LLOQ) of the assay (LLOQ = 0.0100 µg/mL) and < 0.5% of the overall mean C_{max} in the lowest dose group (60 mg/kg/day). Furthermore, since these concentrations were only observed at one single time point each, they were considered to not be consistent with inadvertent dose administration and to have no impact on data interpretation.

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 assays up to 1000mg/kg/day. 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. The standard battery performed, and negative results are considered acceptable by CHMP.

Carcinogenicity

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

Reproductive and developmental toxicity

A set of three reproductive and developmental toxicity studies conducted with PF-07321332 administered orally in rats and rabbits were submitted. Fertility and embryo-foetal development studies were completed, while the pre- and postnatal development study is ongoing. For the fertility study, an unaudited draft study report was submitted; final study reports were available for the other completed studies. In all completed studies, PF-07321332 was administered, once daily by oral gavage, as a 50% PF-07321332: 50% HPMCAS-MG (hydroxypropyl methylcellulose acetate succinate-medium granular) spray dried dispersion. Vehicle control animals (0 mg/kg/day) were administered an amount of HPMCAS-MF (medium fine) equivalent to the amount of HPMCAS administered to the PF-07321332 high dose group. The use of medium fine, instead of medium granular, HPMCAS in the control group was justified, by the company, based on the particle size of the 50% PF-07321332: 50% HPMCAS-MG spray dry dispersion.

Table 9 - Overview of completed reproductive toxicity studies with PF-07321332

Study type/ Species Study ID / GLP	Route, duration, doses	Main endpoints
FEED Rat (Wistar) – 20/sex/group 21GR146 GLP: Yes	Oral (gavage) Males: 14 days premating to sacrifice (total 32 days) Females: 14 days premating to GD6 (C-section GD14) 0, 60, 200, 1000 mg/kg/day	F0 animals: mortality, clinical observations, body weight, food consumption, cohabitation, macroscopic examination, ovarian and uterine examination, placental examination, toxicokinetics (C0.5h on GD10)
EFD Rat (Wistar) – 20 timed-pregnant females/ group 21GR132 GLP: Yes	Oral (gavage) GD 6-17 (C-section GD21) 0, 100, 300, 1000 mg/kg/day	F0 animals: mortality, clinical observations, body weight, food consumption, macroscopic examination, ovarian and uterine examination, gravid uterine weight, placental examination, toxicokinetics (GD17) F1 animals: number, sex, body weight, external/visceral/skeletal examinations
EFD Rabbit (NZW) – 20 timed-pregnant females/ group 21GR126 GLP: Yes	Oral (gavage) GD 7-19 (C-section GD29) 0, 100, 300, 1000 mg/kg/day	F0 animals: mortality, clinical observations, body weight, food consumption, macroscopic examination, ovarian and uterine examination, gravid uterine weight, placental examination, toxicokinetics (GD19) F1 animals: number, sex, body weight, external/visceral/skeletal examinations

FEED: fertility and early embryonic development; EFD: embryo-fetal development; GD: day of gestation

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. However, mean control group values for pre- and post-implantation losses seemed rather high, resulting in lower mean number of live embryos. Since a treatment-related effect on post implantation loss was reported neither in rat nor in rabbit embryo-fetal studies at doses up to 1000 mg/kg/day, any treatment-related effect on this endpoint does not seem likely. Regarding preimplantation loss, it is noted that the mean control group value was exceeded in the study control group while the reported values in treated group lied within the historical control range. 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. Fetal examination showed increased litter and fetal incidences of 27th presacral vertebrae (skeletal variation) at the high dose level compared to concurrent controls (litter: 6%, 0%, 5%, 21%; fetal: 0.93%, 0.00%, 0.56%, 4.29%) and outside historical control range (litter: 0-10.5%; fetal: 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 fetal weight (0.91x control) was observed at 1000 mg/kg/day. At fetal examination, the fetal 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. It was however noted that the historical control database in the performing facility is quite limited, and the company clarified further that the abovementioned findings were not considered as treatment-related taking into consideration their incidences in larger historical control databases generated from testing facilities involving animals from the same source and strain and using known foetal procedures. Overall, the developmental NOAEL in rabbits was 300 mg/kg/day and corresponds to an AUC-based exposure ration of 2.8.

In the embryo-fetal development study in rabbits, but not in the other two reproductive toxicity studies, there were quantifiable concentrations of PF-07321332 in plasma from control animals (22/25 samples). These concentrations ranged from just above LLOQ (10.0 ng/mL) up to ~16x LLOQ (157 ng/mL). However, since the concentrations in individual animals did not demonstrate the time-dependent change in concentration relative to time post-dose that was generally observed in animals administered the test article, it was considered unlikely that control rabbits were administered the test article. However, the amount of control plasma samples with quantifiable concentrations of PF-07321332 may lead to question the validity of the toxicokinetic data obtained from this study. This issue will have to be discussed by the company at the time of the MAA procedure.

As for the repeated dose toxicity studies, the company briefly addressed how the PF-07321332 form used in the reproductive toxicity studies - 50% PF-07321332: 50% HPMCAS-MG (hydroxypropyl methylcellulose acetate succinate-medium granular) spray dried dispersion suspension - compares with the PF-07321332 present in the medicine Paxlovid. This issue will be further discussed during the MAA procedure. As applicable, the company is also expected to discuss the impact of any identified differences on safety evaluation.

Regarding ritonavir, developmental toxicity was identified in rats and rabbits mainly at maternally toxic dose levels, whereas there was no effect on fertility in rats[1].

Based on the nonclinical data provided and findings to date, use of Paxlovid is not recommended in pregnant women and women of childbearing potential not using contraception.

Local tolerance

No dedicated local tolerance studies with PF-07321332 have not been conducted. No effect of GI tract was observed in pivotal studies in rats and monkeys.

Phototoxicity

PF-07321332 presents no absorption peaks (UV-Vis) with molar extinction coefficient (MEC) exceeding the threshold of 1000 M^{-1} cm^{-1} thus PF-07321332 does not present with phototoxicity potential.

Impurities

Standalone studies with administration of impurities of PF-07321332 have not been conducted at this early stage of development because the drug substance and drug product processes are still in development and should be discussed as part of the MAA.

Combination toxicity

No combination studies with administration of PF-07321332 with ritonavir have been conducted or have been planned. Ritonavir is already marketed as a PK enhancer with well characterized nonclinical and clinical safety profile. No overlapping or additive toxicities between PF-07321332 and ritonavir are expected since no target organs have been identified after PF-07321332 administration rats and monkeys up to 1-month duration. A combination toxicity study, therefore, will not provide any

[1] SmPC adopted for NORVIR, https://www.ema.europa.eu/en/documents/product-information/norvir-epar-product-information_en.pdf

additional information beyond the known individual toxicity profiles of PF-07321332 and ritonavir. This is considered acceptable by CHMP.

Discussion on non-clinical aspects

PF-07321332 is an orally bioavailable selective for coronavirus the SARS-CoV-2 $3CL^{pro}$ inhibitor showing little or no activity against a panel of human proteases, as well as HIV protease. Since the $3CL^{pro}$ from human coronaviruses are structurally similar and share a high degree of conservation at the active site of the enzyme, the ability of PF-07321332 to inhibit the $3CL^{pro}$ of other coronaviruses (SARS-CoV-1, HCoV-229E, MERS-CoV, HCoV-OC43, HCoV-HKU1, and HCoV-NL63) was also confirmed; thereby, indicating a potential for broad spectrum anti-coronavirus activity. PF-07321332 also demonstrated selectivity for coronavirus $3CL^{pro}$.

The antiviral activity of PF-07321332 against SARS-CoV-2 was evaluated in VeroE6 cells, enriched for expression of the cellular ACE-2 receptor, in the absence or presence of an efflux inhibitor. PF-07321332 exhibited antiviral activity against SARS-CoV-2 infection of the physiologically relevant 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. The antiviral activity of PF-07321332 was measured against SARS-CoV-1 with EC_{50} value 0.151 µM in the presence of an efflux inhibitor, HCoV-229E with EC_{50} value 0.190 µM, and MERS-CoV with EC_{50} value 0.166 µM in the presence of an efflux inhibitor thus suggesting potential for pan-coronavirus treatment.

Ritonavir, as a P-gp and CYP3A4 inhibitor, is recommended by the company to be applied as a booster of PF-07321332 therapeutic effects. Ritonavir had no effect on viral replication in A549-ACE2 cells up to the highest concentration tested, 3 µM. Cell cytotoxicity was also not observed in the A549-ACE2 cells up to 3 µM for PF-07321332 or ritonavir. The potency of PF-07321332 in combination with fixed doses of ritonavir did not exhibit a monotonic relationship as evidenced by less potent EC50 values with 3 and 2 µM ritonavir and more potent EC50 values with 1.33 and 0.889 µM ritonavir. The company will have to clarify the non-monotonic effect of ritonavir and to correlate the effective concentrations of ritonavir *in vitro* with the unbound concentrations attained *in vivo*. This should be addressed as part of the MAA.

An *in vivo* model to evaluate the anti-viral efficacy of PF-07321332 against SARS-CoV-2 using a mouse-adapted virus, SARS-CoV-2-MA10, was conducted in both BALB/c and the 129-mouse. While some impact on viral replication in the lung was suggested in this model, caution is warranted on the interpretation of the data, derived from this model of particular limitations, in terms of clinical relevance.

The activity was tested against SARS-CoV-2 variants.

PF-07321332 had cell culture antiviral activity (with EC50 values in the low nanomolar range ≤3-fold relative to USA-WA1/2020) against SARS-CoV-2 isolates belonging to the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) Lambda (C.37) variants. The Beta (B.1.351) variant was the least susceptible tested variant with approximately 4-fold reduced susceptibility relative to the USA-WA1/2020 isolate.

As a critical limitation given the worldwide increasing circulation of the Omicron variant, the company could not provide any *in vitro* data on the antiviral activity against this VOC. This should be provided at the time of the MAA.

Moreover the data on the activity against Delta VOC had limitations, since not tested against a representative strain derived from GISAID to more completely covering pattern of mutations beyond the key mutations.

Additionally, further investigation is expected to be provided at the time of the MAA on the activity against the Delta sublineage 21J in view of the clinical results by subgroups of patients infected by specific variants.

Finally, at the time of the MAA the company will have to update the data on the *in vitro* activity against SARS-CoV-2 VOC/VOI.

In terms of secondary pharmacology, studies evaluated *in vitro* activity of PF-07321332 against a panel of receptors, transporters, ion channels and enzyme assays, and the results seem to show no significant inhibition of functional or enzyme activity at human relevant concentrations, but this will have to be further investigated at the time of the MAA.

Safety pharmacology studies were conducted in animal to assess potential pharmacodynamic effects on vital organ systems (central nervous, cardiovascular, and respiratory). Translatability of the reported findings to humans is uncertain.

The central nervous system (CNS) and respiratory safety pharmacology studies were conducted in male Wistar Han rats in the same study but in different groups. Relating to the effects on pulmonary system, it was observed 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, 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 on CNS and respiratory system 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.

One dedicated cardiovascular safety pharmacology study 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) . When the QT interval was corrected for HR (QTc), there was a test article-related decrease (down to -7 msec). The 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.

The toxicity of PF-07321332 was evaluated in 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. All non-adverse test article related clinical findings observed in rats (salivation and soft feces, increases in aPPT, PT, PLT count) or in monkeys (sporadic occurrence of emesis, increases in ALT, AST, fibrinogen) are monitorable in human.

Regarding the developmental and reproductive toxicity (DART) studies, adverse treatment-related effects on fertility and early embryonic development and embryo-foetal development were not identified in rats. In rabbits, an adverse decrease in fetal body weight was observed at 7.8-fold the clinical exposure. The company also justified the use of historical control databases larger than that of the performing laboratory to mitigate the increased occurrence of some skeletal and visceral findings in the high dose group. Some issues should be discussed at the MAA, regarding e.g. the validity of the toxicokinetic data obtained from the rabbit EFD study, or the impact on the formulation of the test-article used in DART studies vs. that in the clinical formulation.

PF-07321332 was not genotoxic in either *in vitro* or *in vivo* assays.

The margins of exposure are only indicative at this stage given that the PKPOP available at this stage has particular limitations, notably only based on PK data from health volunteers (see clinical PK part of

this report). The margins of exposure are, therefore, expected to be further substantiated at the time of the MAA.

Conclusion on non-clinical aspects

Overall, the nonclinical studies are considered sufficient for supporting the use of Paxlovid in an emergency setting.

2.4. Clinical aspects

2.4.1. Pharmacokinetics

In the current submission, Paxlovid is intended for the treatment of adult patients with symptomatic, confirmed COVID-19 who are at high risk for progressing to severe disease, including hospitalization and/or death.

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

The clinical pharmacology program (table 10) consisted of seven Phase 1 studies completed or ongoing, performed in healthy volunteers. The following Phase 1 studies have been conducted:

- One SAD and MAD in Caucasian and Japanese healthy subjects (Study **1001** Part 1 and Part 2)
- rBA/ food effect, mass balance study and QTc analysis (Study **1001** Part 3, Part 4 and Part 5)
- Six PK studies investigating intrinsic (Studies **1010** and **1011**) and extrinsic factors (Studies **1012**, **1013**, **1014**, **1015**)

Phase 1 studies **1012**, **1013** and Phase 2/3 studies **1002** and **1006** are ongoing. An update of PK data from these studies will have to be presented at the time of the MAA.

Additional information is planned to be collected from studies performed in adult patients as presented in table 11 with three pivotal Phase 2/3 studies, with one completed, Study **1005** and two ongoing Studies **1002** and **1006**.

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

Table 10 - Clinical Pharmacology studies

Study ID	Study Title	Study Details/Primary Endpoints		Total Sample Size
Study 1001 (Completed)	A Phase 1, randomized, double-blind, sponsor-open, placebo controlled, single- and multiple-dose escalation study to evaluate the safety, tolerability, and pharmacokinetics of PF-07321332 in healthy adult participants	FIH study of PF-07321332 in healthy adult participants. Study 1001 is a 5-part study.		
		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) Will be submitted as part of the MAA	A Phase 1, non-randomized, 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-randomized, 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 ID	Study Title	Study Details/Primary Endpoints	Total Sample Size
Study 1012 (Ongoing) Will be submitted as part of the MAA	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 1013 (Ongoing) Will be submitted as part of the MAA	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

Table 11 - Pivotal clinical studies to support the safety and efficacy assessment for PF-07321332/ritonavir

Study ID	Study Title	Dose and Duration of Study Intervention)	Comparator	Total Planned Sample Size
Study 1002 (Ongoing) Will be submitted as a variation to the future CMA when data are available	An interventional efficacy and safety, phase 2/3, double-blind, 2-arm study to investigate orally administered PF-07321332/Ritonavir compared with placebo in non-hospitalized symptomatic adult participants with COVID-19 who are at low risk of progressing to severe illness.	300/100 mg PF-07321332/ritonavir administered orally q12h for 5 days	PBO	Total ~1140
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-hospitalized symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness	300/100 mg PF-07321332/ritonavir administered orally q12h for 5 days	PBO	Total ~3100
Study 1006 (Ongoing) Will be submitted as a variation to the future CMA when data are available	A Phase 2/3, randomized, double-blind, double-dummy, placebo-controlled study to evaluate the safety and efficacy of 2 regimens of orally administered PF-07321332/Ritonavir in preventing symptomatic SARS-CoV-2 infection in adult household contacts of individuals with symptomatic COVID-19.	300/100 mg PF-07321332/ritonavir administered orally q12h for 5 or 10 days	PBO	Total ~2660 participants

Methods

Throughout the clinical development, two bioanalytical methods were developed to quantify, simultaneously, PF-07321332 and ritonavir, in human K_2EDTA 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) with satisfactory results.

Absorption

Following single or multiple-dosing of PF-07321332/ritonavir as oral suspension at doses between 75 mg/ 100 mg to 500 mg/100 mg in healthy volunteers, absorption was reasonably rapid with Cmax approximately achieved at Tmax of 0.75-2 h (Study **1001**). At the tested dose of PF07321332/ritonavir 250 mg/100 mg, mean Cmax was 2882 ng/mL and AUCinf was 28220 ng.h/mL (Study **1001**).

Following single dose of PF-07321332/ritonavir as tablet formulation at doses between 100 mg/ 100 mg to 300 mg/100 mg in healthy volunteers, absorption was slightly rapid with Cmax approximately achieved at Tmax of 2-3 h (Study **1011** and **1014**).

At the recommended dose of PF-07321332/ritonavir 300 mg/100 mg as tablet (commercial strength of 150 mg), mean Cmax was 2210 ng/mL and AUCinf was 23010 ng.h/mL (Study **1014**).

Absolute bioavailability

The absolute bioavailability of PF-07321332 has not been investigated. However, based on the mass balance study (Part 4 of Study **1001**), absolute bioavailability could be estimated at least at 55 %.

Relative bioavailability / bioequivalence

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

- An extemporaneously prepared oral suspension used for Study **1001, 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 Study **1005** were manufactured at both the Pfizer Groton (Connecticut, USA) and Freiburg (Germany) sites using identical formulation and manufacturing process.

The proposed commercial formulation dosage form for PF-07321332 is two 150 mg IR film-coated tablets manufactured at Freiburg (Germany) and co-packaged with a 100 mg tablet of ritonavir.

Relative bioavailability Study 1001 (Part 3) [Uncoated tablet 250 mg vs 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, randomized, 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.

PK parameters are summarized descriptively in table 12 below. 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.

Table 12 - Descriptive summary of plasma PF-07321332 PK parameters- Part 3 rBA/FE (Study 1001)

Parameter (Unit)[a]	PF-07321332 250 mg (Suspension), Fasted (N=12)	PF-07321332 250 mg (Tablet), Fasted (N=12)	PF-07321332 250 mg (Tablet), Fed (N=12)
N1, N2	12, 7	12, 9	12, 9
AUC_{inf} (ng.hr/mL)	3513 (38)	2958 (50)	4256 (24)
AUC_{inf}(dn) (ng.hr/mL/mg)	14.06 (38)	11.82 (50)	17.03 (24)
AUC_{last} (ng.hr/mL)	3318 (35)	2695 (46)	4012 (27)
AUC_{last}(dn) (ng.hr/mL/mg)	13.27 (35)	10.78 (46)	16.03 (27)
CL/F (L/hr)	71.07 (38)	84.56 (50)	58.70 (24)
C_{max} (ng/mL)	883.1 (37)	497.8 (37)	1219 (55)
C_{max}(dn) (ng/mL/mg)	3.533 (37)	1.992 (37)	4.874 (55)
$t_{1/2}$ (hr)	5.626 ± 3.0407	9.086 ± 4.1570	1.854 ± 0.55166
T_{max} (hr)	1.00 (0.500 - 4.00)	1.00 (0.500 - 4.00)	1.75 (0.500 - 4.00)
V_z/F (L)	493.7 (63)	1004 (41)	151.0 (36)

Comparability testing [film coated 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.

Comparability testing [Manufacturing sites film coated tablet 150 mg]

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 suggesting equivalence in dissolution performance.

Several oral formulations of PF-07321332 were developed and evaluated during the development program (oral suspension, uncoated tablet at 250 mg, film coated tablet of 100 mg and 150 mg). It is essential to ensure a fair PK comparability between formulations in order to guarantee that the whole PK feature is maintained and allow reliable extrapolation of PK properties with later formulations.

Presently only one relative bioavailability study was performed comparing performance of the oral suspension to the uncoated tablet at 250 mg. Based on the results from Study 1001 Part 3, the biocomparison between formulations clearly indicated that they were different with a 44% decrease in Cmax and 19% decrease in AUClast. Such results should be taken 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. However, no *in vitro* dissolution test was performed between these two formulations and should therefore be provided.

The company has proposed to test the formulation effect as a covariate in the future PopPK model development, this is considered acceptable by CHMP provided the PK dataset will include all the formulations used during the clinical development program (oral suspension, 250 mg uncoated tablet, 100 mg and 150 mg film-coated tablets and 150 mg film-coated tablet by manufacturing process). Such analysis should be provided, at the time of the MAA.

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,** results in **Table**) or in combination with ritonavir (Study **1001 Part 1**) in a cross-over design. In combination with ritonavir, PF-07321332 plasma exposures were generally similar for AUCs with an increased 15.3% for Cmax for the fed treatment compared to the fasted state. 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). PF-07321332/ritonavir can therefore be administered with or without food.

Distribution

PF-07321332 was found to be weakly bound to plasma protein (69%). However, it was not mentioned which protein is involved by this binding. The blood/plasma (B/P) ratio was approximately 0.6 indicating limit 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. In patients the Vz/F is unknown.

Elimination

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.

Across clinical studies in healthy volunteers after single or multiple oral doses of PF-07321332/ritonavir as oral suspension CL/F ranged from 5.9 to 12.5 L/h. Based on the PopPK analysis (after correcting by F1 for a 300 m/100 mg dose), CL/F was estimated at 8.17 L/h. After single oral dose PF-07321332/ritonavir as tablet formulation CL/F ranged from 6.9 to 13.0 L/h.

Renal clearance ranged from 2.93 to 3.78 L/h in HV (Caucasian) and was slightly increased in Japanese subjects, estimated at 5.2 L/h.

The main elimination route was renal as unchanged drug, drug metabolism occurs via CYP3A4 enzyme.

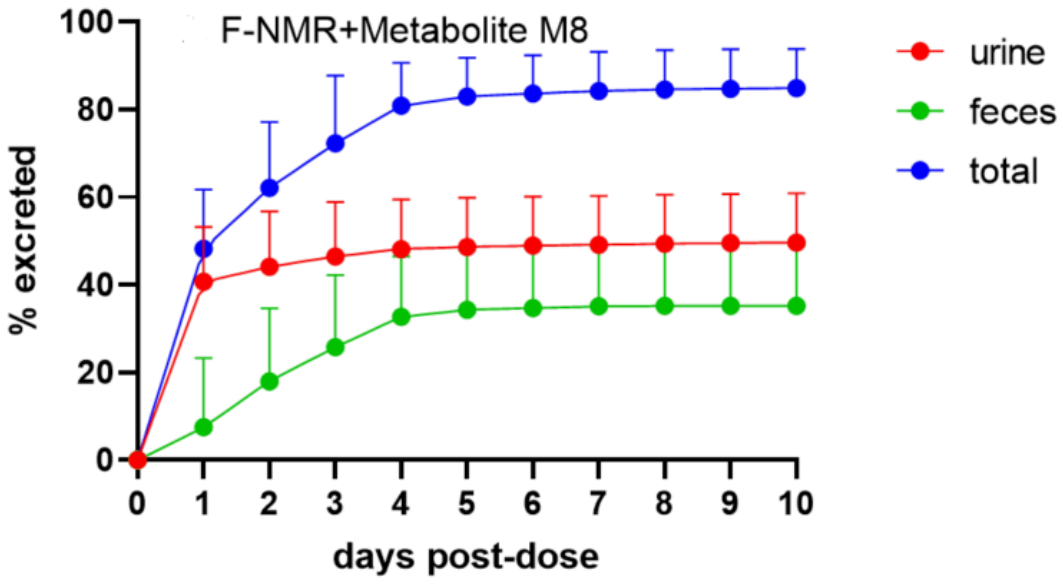
Mass balance

Study **1001 Part 4** was an open label, non-randomized, single period study designed to evaluate the mass balance and metabolism of PF-07321332.

Six male participants with at least 4 completers were enrolled. All participants will receive four doses of 100 mg of ritonavir. Each participant will receive a single dose of 300 mg PF-07321332 on Day 1 along with 100 mg of ritonavir after at least 10h of fasting. Four doses of 100 mg ritonavir were administered at -12h, 0, 12h and 24h. Samples were collected at predetermined time points to determine PF-07321332 concentrations in plasma, urine and feces and metabolite profiling in the three matrix.

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 feces 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 feces in 5 days (figure 4).

Figure 4 - Cumulative mean (+SD) excretion of PF-07321332 and M8 in urine and feces of HV following administration of oral suspension of PF-07321332/ritonavir using 19F-NMR



Metabolism

In vitro

The *in vitro* metabolism of PF-07321332 (10 µM) was investigated by incubation in liver microsomes and hepatocytes from man and animal various species (Report PF-07321332_09Nov20_084546). In all species including human M4 was considered as the main metabolite. All other metabolites found in

human (M1, M2, M3, m/z 498) were generally found in other species. M5 and M8 were only detected following incubation of PF-07321332 (10 µM and 100 µM) in human gut microbiota.

The CYP isoforms involved in the metabolism of PF-07321332 was investigated using recombinant P450 enzymes at a concentration of 10 µM. CYP3A4 mainly and CYP3A5 are involved (Report PF-07321332_12Oct21_082857) with other CYP enzymes contributing in minor amounts. Particularly CYP3A4 was the major contributor to the oxidative metabolism (Report PF 07321332_21Nov20_072016) and mainly in the formation of M4.

M7 the acylglucuronide of M5 was identified in human urine at trace level. The UGT enzymes responsible of its formation was investigated in human liver microsomes. UGT2B4 and 2B7 contributed to 69.8% and 16.7% of the formation of M5.

In vivo

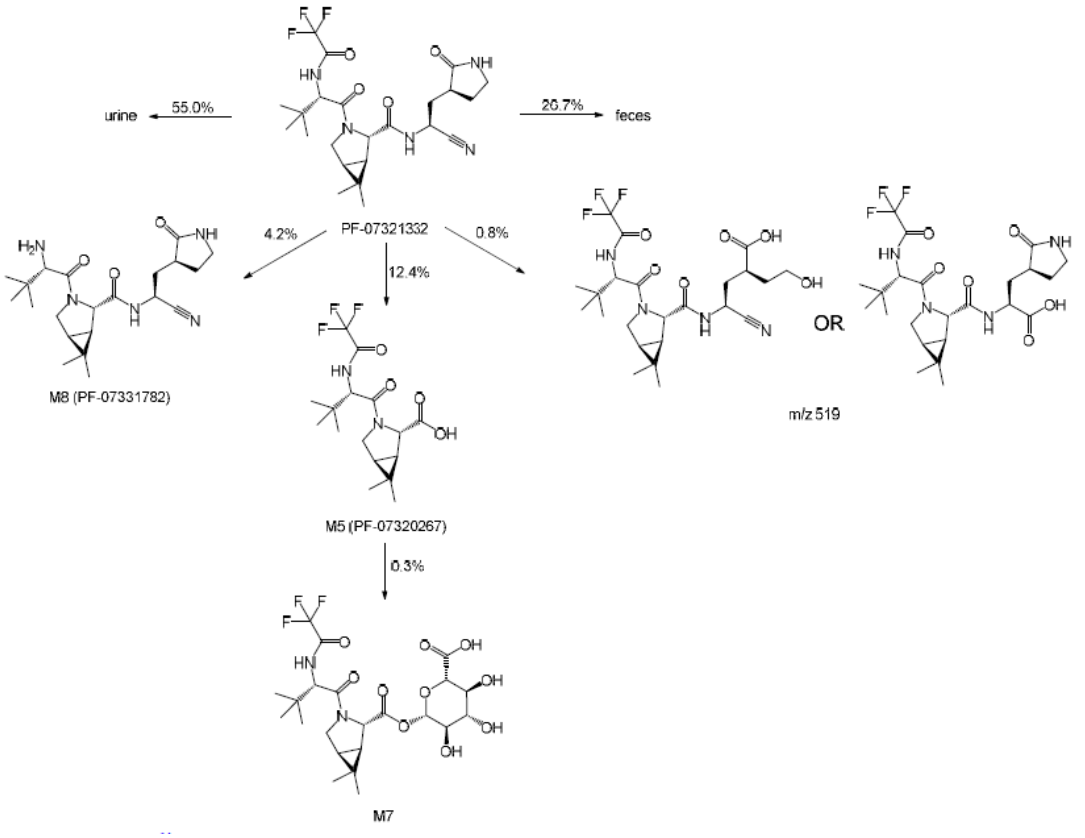
Metabolite profiling was performed in the three matrix (plasma, urine and feces). In plasma unchanged PF-07321332 was the main circulated compound, M4 and M5 were found at trace levels. In urine and feces after normalization of the data to complete mass balance, unchanged PF-07321332 accounted for 82.5% of the drug material (55% in urine and 27.5% in feces). M5 was present at 12.1% in feces, M8 at 4.2% in plasma (table 13). The proposed metabolic scheme is presented in figure 5.

Table 13 - Summary of metabolites of PF-07321332 in urine and feces of healthy participants following oral administration of PF-07321332/ritonavir suspension

Metabolite	% of Normalized Dose[a]		
	Urine	Feces	Total
PF-07321332	55.0	27.5	82.5
M5 (PF-07320267)	0.4	11.7	12.1
M7 (acyl glucuronide of M5)	0.3	ND	0.3
m/z 519	ND	0.8	0.8
M8 (PF-07331782)	2.6	1.6	4.2
Total	58.4[b]	41.6	100[b]

Source: Appendix 16.2.5.10.5

Figure 5 - Summary profile of PF-07321332 metabolism and disposition in healthy participant



Dose proportionality and time dependency

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

- Dose proportionality

Study 1001

Study **1001** was the first-in-human (FIH) study of PF-07321332 in healthy volunteers, which consisted of five parts. **Part 1 (SAD)** and **Part 2 (MAD)** were randomized, double-blind, sponsor open, placebo-controlled triasl to evaluate safety, tolerability and PK.

Part 1 used PF-07321332 (without ritonavir) at a dose range from 150 to 1500 mg, PF-07321332/ritonavir at two dose levels 250 and 750 mg as described in table 14. **Part 2** used PF-07321332/ritonavir from 75 mg/100 mg to 500 mg /100 mg.

Table 14 - Actual dosing regimen evaluated in Study 1001

Part of the study	Dosing regimen evaluated[a]
PART-1: SAD	PF-07321332 150 mg
	PF-07321332 500 mg
	PF-07321332 1500 mg
	PF-07321332 250 mg at 0h + RTV 100 mg at -12, 0 and 12h
	PF-07321332 750 mg at 0h + RTV 100 mg at -12, 0 and 12h
	PF-07321332 250 mg at 0h (Fed) + RTV 100 mg at -12, 0 and 12h
PART-2: MAD	PF-07321332/RTV 75/100 mg BID for 10 days
	PF-07321332/RTV 250/100 mg BID for 10 days
	PF-07321332/RTV 500/100 mg BID for 10 days
	PF-07321332/RTV 250/100 mg BID for 10 days in Japanese participants
PART-3: RBA/FE	PF-07321332 250 mg Tablet
	PF-07321332 250 mg Tablet (Fed)
	PF-07321332 250 mg suspension
PART-4: M&E	PF-07321332 300 mg at 0h + RTV 100 mg at -12, 0, 12 and 24 h
PART-5: SE	PF-07321332 2250 mg (divided into 3 doses of 750 mg administered at 0, 2 and 4h) + RTV 100 mg at -12, 0 and 12 h

a. Unless specified, dosing of PF-07321332 in all parts were done in fasted state (≥7h in all parts except PART-5 in which PF-07321332 was administered approximately 2h after breakfast).

PK parameters following SAD of PF-07321332 (with or without ritonavir) as oral suspension are presented in table 15 and following MAD in table 16.

Table 15 - 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)

Less than dose proportional increases in PF-07321332 exposures was observed following single oral doses of PF-07321332 boosted by 100 mg of ritonavir ranging from 250 mg to 750 mg. Tmax ranged from 2 to 4h, and half-life ranged from 6.93 to 12.8 h.

Less than dose proportional increases in PF-07321332 exposures was observed following multiple oral doses of PF-07321332 boosted by 100 mg of ritonavir ranging from 75 mg to 500 mg during the entire

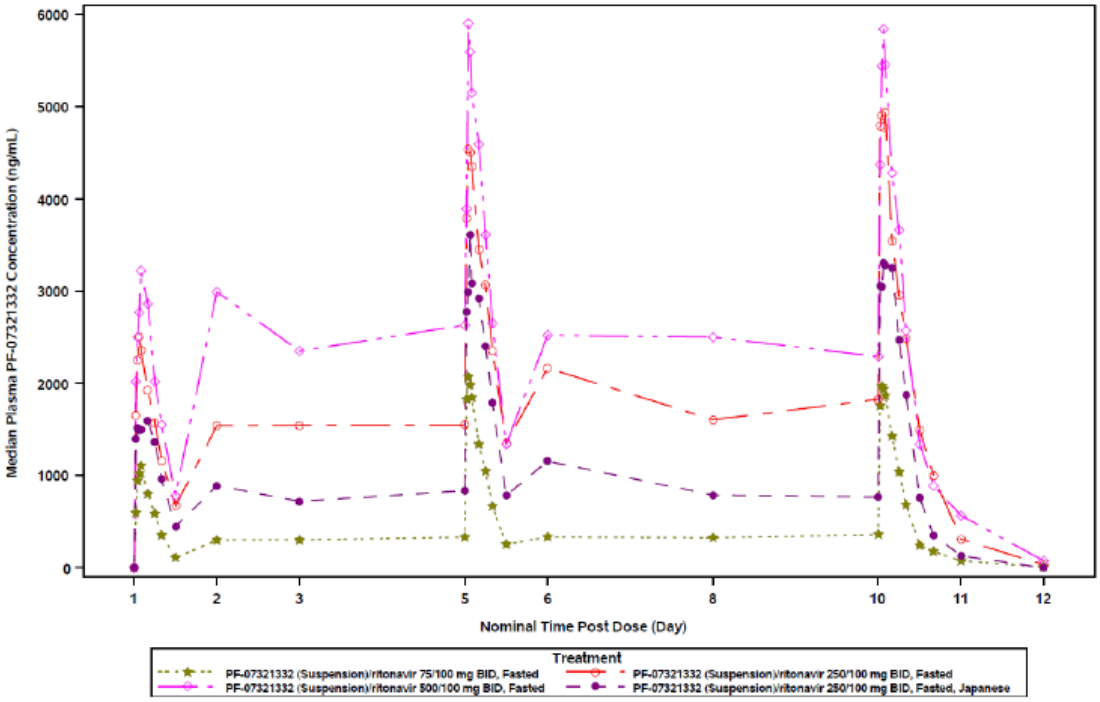
dosing interval (Day 1 to Day 10). Tmax ranged from 0.75 to 2h, and half-life ranged from 6.79 to 8.04 h.

Use of ritonavir as a PK enhancer appeared to considerably increase PF-07321332 exposure. The geometric mean AUCinf, AUClast and Cmax following a single dose of PF-07321332 250 mg in fasted state boosted by ritonavir was 28.22 µg•h/mL, 27.6 µg•h/mL and 2.882 µg/mL, respectively. Comparatively, the geometric mean AUCinf, AUClast and Cmax following a single dose of PF-07321332 250 mg in fasted state (without ritonavir) in PART-3 was 3.51 µg•h/mL, 3.32 µg•h/mL and 0.883 µg/mL, respectively.

- Time dependency

Median plasma PF-07321332 concentration time profiles including Ctrough concentrations are presented in figure 6 and associated PK parameters in table 16.

Figure 6 - Median plasma PF-07321332 concentration -time profiles across all dosing days following MAD of PF-07321332/ritonavir (Part 2, MAD, Study 1001)



Steady-state plasma concentrations appeared to have been achieved by Day 2 for all doses and treatments as shown in figure 6. Plasma PF-07321332 accumulation was approximately 2-fold following multiple dosing and values were similar on Day 5 and Day 10. Geometric mean accumulation ratios ranged from 1.8 to 2.1 for AUCtau (Rac) and Cmax (Rac,Cmax), on Day 10, across all treatments.

Table 16 - 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)

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 cut-off 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 17 - 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-parameterized, 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 $T_{1/2}$ of 15 hours, which is not consistent with that obtained from NCA calculations (mean $T_{1/2}$ =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).

Using the final population PK model and doses from 100 to 500 mg/100mg RTV BID for 5 days, the predicted PK exposures (table 18) 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 18 - 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	1^{st} (Day 1)	458	141	1018	71.5
	2^{nd} (Day 1)	631	175	1546	79.2
	9^{th} (Day 5)	852	238	2276	85.3
200	1^{st} (Day 1)	743	228	1608	85.0
	2^{nd} (Day 1)	1012	281	2443	89.2
	9^{th} (Day 5)	1361	383	3575	93.4
300	1^{st} (Day 1)	987	307	2124	90.7
	2^{nd} (Day 1)	1347	378	3202	93.6
	9^{th} (Day 5)	1800	498	4670	95.7
400	1^{st} (Day 1)	1209	378	2565	94.0
	2^{nd} (Day 1)	1657	468	3879	95.3
	9^{th} (Day 5)	2197	605	5679	97.4
500	1^{st} (Day 1)	1417	449	2979	95.5
	2^{nd} (Day 1)	1952	552	4516	96.5
	9^{th} (Day 5)	2563	704	6640	97.8

The preliminary population PK model and model-based simulations are not considered valid or reliable. Several limitations are highlighted: a) misspecification of the residual error model, b) exclusion of residual errors from the simulation exercise, 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) and d) lack of validity of the PK predictions projected with the tablet formulation while the model was developed using only the suspension formulation and especially given that the tablets appear to have a Cmax on average 44% lower than that of the suspension formulation.

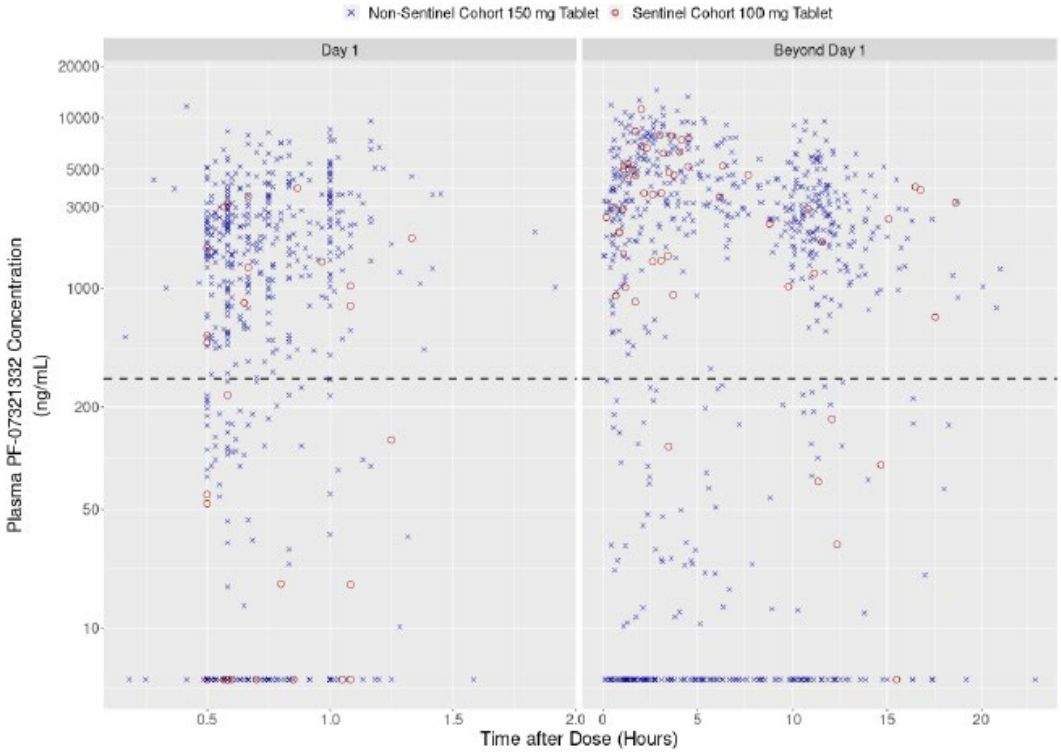
Only very limited data in healthy volunteers (n=20) are part of the analysed dataset. Inclusion of more full data from healthy volunteers and especially from patients in pivotal phase 2/3 studies is deemed essential to better inform the model. Therefore, the company should consider updating the model 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. Clear dosing recommendations (or warning of use if lack of data) for specific subgroups that are not included (elderly, obese and underweighted patients) should be provided. The new relevant population PK analysis should be provided at the time of the MAA.

PK in patients with COVID-19

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 cut-off 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 7.

Figure 7 - 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 19) 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-normalized 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 19 - Summary of Cmin at the Planned Day 5 Visit and Percentage of Participants in Study C4671005 Achieving Cmin ≥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

A predictive check (simulation) approach was performed to assess the adequacy of the preliminary population 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 8) and at steady state (figure 9) appears to be consistent with the model predictions generated population PK model (based on PK data from healthy volunteers). However, as noted above, a high number of unexpected BLQ concentrations after the first dose and at steady was observed.

Figure 8 - 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

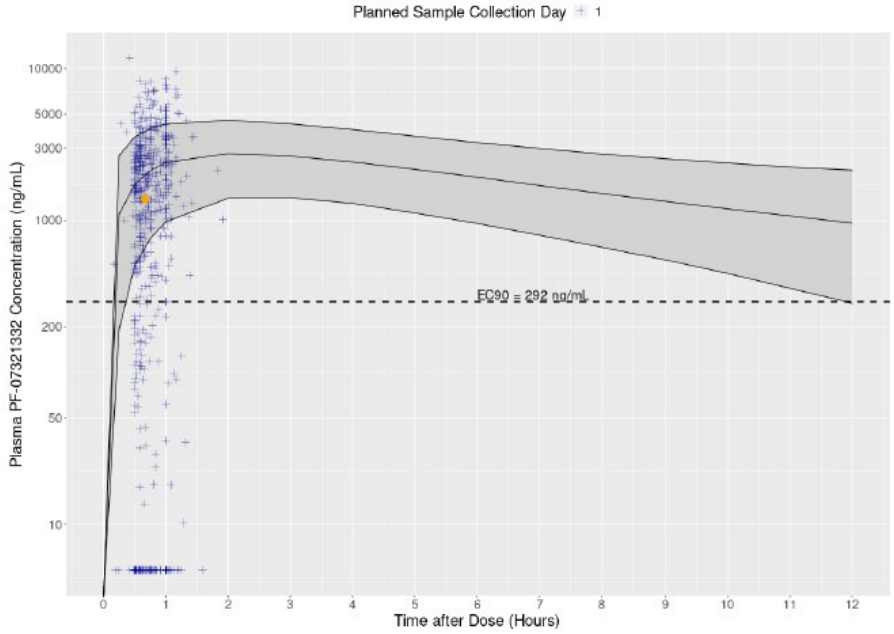
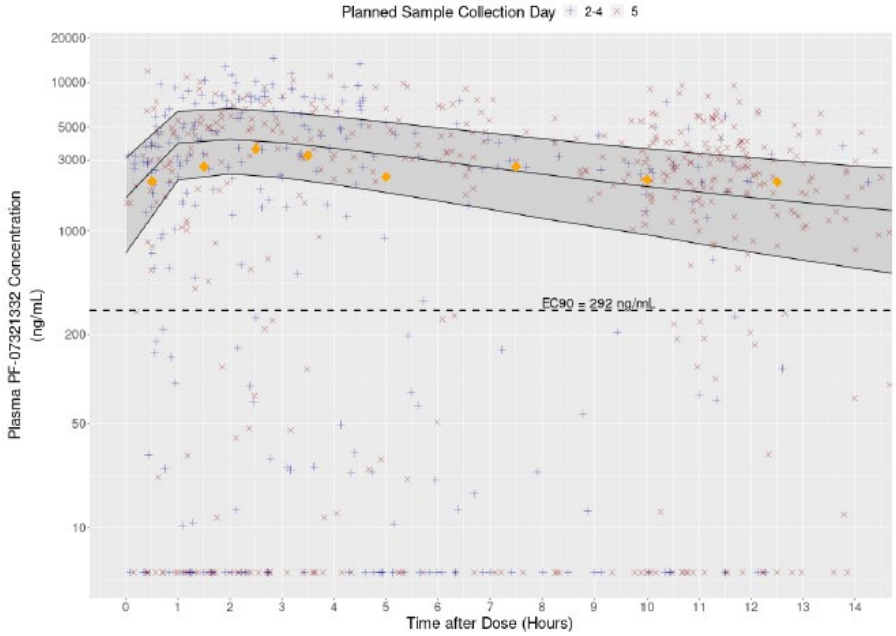


Figure 9 - Median and 90% Prediction Intervals (5th and 95th percentile) for PF-07321332 concentrations at steady-state based on 1000 Simulations (PF-07321332/ritonavir 300 mg/100 mg q12h) overlaid with observed Data from Study C4671005



Special populations

- Race

Race effect on PF-07321332/ritonavir PK was explored as part of Study 1001 in only 4 Japanese subjects. AUCtau and Cmax values were approximately 30% and 21-26%, respectively, lower in Japanese participants compared to Caucasian subjects. Given the very limited data (n=4), this result should be considered with caution and no valid conclusion regarding PK in Japanese subjects could be drawn from this analysis. In order to propose more reliable dosing recommendation in this subgroup, this preliminary result should be confirmed on a large number of patients (by a dedicated study or using the population approach). This will be further investigated at the time of the MAA.

- Renal impairment

A formal study (**C46711011**) 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.

PF-07321332 systemic exposure (AUC and Cmax) increased with increasing severity of renal impairment (figure 10, table 20). Adjusted geometric mean (90% CI) AUCinf, test/reference ratios compared of renal impairment (test) to normal renal function (reference) were 123.84 % (99.64%, 153.91%) for mild renal impairment, 187.40% (148.52%, 236.46%) for moderate renal impairment, and 304.49 % (237.60%, 390.21%) for severe renal impairment. For Cmax, adjusted geometric mean (90% CI) test/reference ratios were 129.78% (101.93%, 165.25%), 138.12% (113.18%, 168.55%) and 148.02% (111.40%, 196.68%) for mild, moderate and severe renal impairment subjects, respectively.

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 CLr decreased 47% and 80% respectively compared to the normal renal functional group.

Figure 10 - Median Plasma PF-07321332 Concentration-Time Plot, Following a Single Oral Dose of PF-07321332/Ritonavir, Protocol C4671011

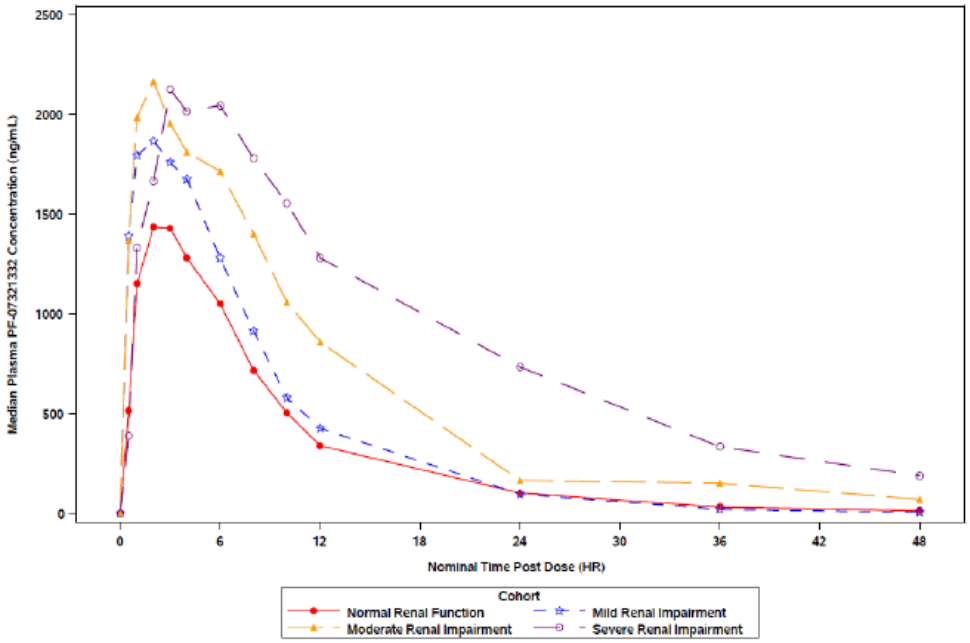


Table 20 - Descriptive Summary of Plasma and Urine PF-07321332 PK Parameters. Protocol C4671011.

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_2/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)

No dose adjustment of PF-07321332 is needed in mild renal impairment, while the dose should be reduced by one-half in moderate renal impairment: PF-07321332/ritonavir 150 mg/100 mg BID.

In severe renal impaired subjects, an increase of AUC by 204% was observed compared to the normal renal group. Appropriate dose for patients with severe renal impairment has not yet been determined. Based on the significant exposure increase, a contraindication regarding use in subjects with severe renal impairment has been included in the Conditions of Use.

- Hepatic impairment

A formal study (**C46711010**) 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. Categorization 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 11 and summarized in table 21.

Figure 11 - Median Plasma PF-07321332 Concentration-Time Profiles Following a Single Oral Dose of PF-07321332 Enhanced with Ritonavir

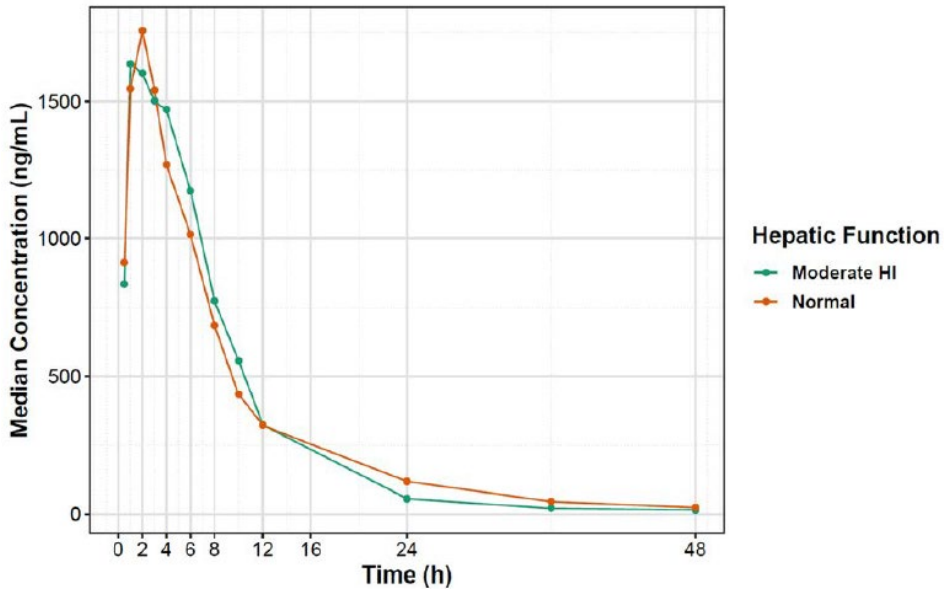


Table 21 - Descriptive Summary of Preliminary (Unaudited) Plasma PK Parameters of PF-07321332 by Hepatic Function in Study C4671010

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

Currently, the preliminary PK data in the moderate hepatic impaired group do not suggest a significant clinical PK change compared to subjects with normal hepatic function. However, these data could not be considered definitive. No data are provided for the severe hepatic impaired group. Pending availability of appropriate dosing recommendations with PF-07321332, a cautionary statement regarding use in subjects with mild and moderate hepatic impairment and a contraindication in subjects with severe hepatic impairment has been added to the Conditions for Use.

- Elderly

Preliminary PK data was provided in patients (study C4671005) between 18 and 86 years. However, the PK data from elderly patients included in the following subgroups of age: [65 to 74 years], [75 to 84 years] and >85 years could not be interpreted in the absence of full descriptive information (including detailed number by subgroup). Given that chronic renal disease is very common in elderly (especially with increasing age) together with the clinically significant increase of PK exposures (AUC and Cmax) for both moderate and severe renal impaired subjects, dosing recommendations in elderly should be further investigated at the time of the MA, notably with updated relevant PKPOP integrating PK data in patients and assessing age in covariate

The PK of PF-07321332 in elderly patients could not be considered elucidated yet.

Overall, among the 608 patients included in the PK dataset of patients, the applicant will be asked to further substantiate the PK profile in the relevant following subgroups of elderly: [65 to 74 years] and [75 to 84 years] and >85 years (including number of patients per category, the number of PK observations per each group of age), the mean and 90% observed interval [5-95th] Cmax at Day 1 and Ctrough at steady state after repeated administration of the recommended dose with comparison to a reference group (adults <65 years old). This is expected to enable providing dosing recommendation for each subgroup. If no or limited clinical / PK data are available in a given subgroup of age and also referring to the clinical data available by age category, restriction and/or warnings would have to be considered.

2.4.2. Pharmacodynamics

PF-07321332 has been shown to be active against SARS-CoV-2 $3CL^{pro}$ (Ki = 0.00311 µM, IC50 = 0.0192 µM) in a biochemical enzymatic assay and against other alpha and betacoronaviruses (SARS-CoV-1, HCoV-229E, MERS-CoV, HCoV-OC43, HCoV-HKU1, and HCoV-NL63).

PF-07321332 binds to the active site SARS-CoV-2 3CL protease and forms a covalent interaction via mainly 13 contact residues in the active site of $3CL^{pro}$. The conservation of these contact residues was assessed across different SARS-COV-2 isolates. These residues were highly conserved, with frequency of mutation <0.024%. The analysis indicates that 9 of 13 contact residues are identical among all alpha/beta CoV strains examined. This could explain the pan-coronavirus $3CL^{pro}$ inhibition by PF-07321332.

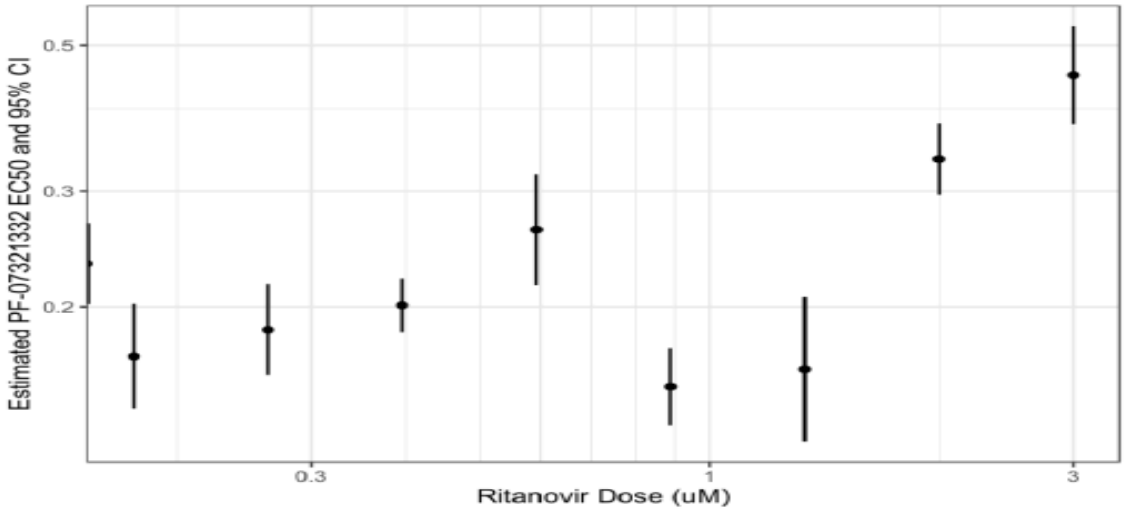
PF-07321332 also demonstrated >521-fold selectivity for coronavirus $3CL^{pro}$, compared with human cellular proteases, showing little or no activity against this panel of mammalian proteases as well as viral HIV protease (IC50>10 µM at human chymotrypsin and >100 µM at all other proteases tested). PF-07321332 did not inhibit enterovirus 71 (EV71) and human rhinovirus 1B (HRV1B) viral-induced CPE in human RD or HeLa cells, respectively (EC50 >100 µM), nor did it demonstrate cytotoxicity (CC50 of >100 µM). The activity of PF-07321332 seems selective to the coronavirus family.

The *in vitro* antiviral activity of PF-07321332 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 which is acceptable, 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 (9-fold less potent than PF-07321332).

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.

Ritonavir had no antiviral effect up to 3 µM in an A549 cell line. Ritonavir does not demonstrate antiviral SARS-CoV-2 activity either alone or in combination with PF-07321332 (figure 12 below). Cell cytotoxicity was not observed up to 3 µM for PF-07321332 or ritonavir in an A549 cell line.

Figure 12 - PF-07321332 in Combination with Fixed Doses of Ritonavir (PF-00346560) Against SARS-CoV-2 nLuc Reporter Virus in A549-ACE2 Cells



Graph made using GeneData EC50 values and 95% CIs (Appendix 12.3) within the R programming environment to represent PF-07321332 potency estimates as a function of ritanovir concentration. The ritanovir dose is plotted on the log-scale, with the PF-07321332 potency with no ritanovir represented by the estimate and confidence interval on the far left of the plot.

Table 22 - 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.

Of note, PF-07321332 is shown to exhibit pan-coronavirus antiviral activity against SARS-CoV-1 (EC50 12.3µM), MERS-CoV (EC50 5.41µM), both in the absence of an efflux inhibitor, that shifted to 0.151µM and 0.166 µM respectively, in the presence of P-gp inhibitor. The EC50 value against HCoV-229E, was of 0.190 µM in MRC-5 cells. The translability of these data in favour of this pan-coronavirus antiviral activity in clinic in uncertain.

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) 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 and 59.5nM 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 71.2 nM, 170 nM, 217 nM, 204 nM, 93 nM and 82.2 nM in the USA-WA1/2020 SARS-CoV-2 strain and alpha, beta, gamma, lamda, and delta variants, respectively.

PF-07321332 activity using a qPCR assay, showed inhibition with mean EC50 values of 32.2 nM, 41.0 nM, 127.2 nM, 24.9 nM, 21.2 nM, 15.9 nM in the USA-WA1/2020 SARS-CoV-2 strain and the Alpha, Beta, Gamma, Delta and Lambda variants, respectively. PF-07321332 is overall active *in vitro* against currently circulating SARS-CoV-2 strains with moderate decrease in PF-07321332 susceptibility against the beta variant (4-fold increase in EC50). The Delta variant represents the most prevalent VOC circulating notably in Europe. Recently, sub lineages of the Delta (B.1.617.2) variant carrying non-silent mutations in different areas of the genome, have emerged. A discussion on the potential impact of $3CL^{pro}$ mutations on the activity of PF-07321332 is considered important and, *in vitro* study in a substantial number of representative sequences will have to be provided at the time of the MA. Further investigation on Delta variant and its sublineages should be provided at the time of the MA. Antiviral activity of PF-07321332 against a fully representative Delta variant and its sublineages taking into account GISAID database remains to be provided. Moreover, investigations of the antiviral activity against the Delta 21J sublineage will have to be provided at the time of the MA, in view of the clinical data by the subgroups of patients with VOC (patients infected with this sublineage tend to show lower efficacy but the enrolled population was almost exclusively infected by the Delta variant (98%), notably including a vast majority of the patients infected with the 21J sublineage.

Table 23 - Activity of PF-07321332 Against Major SARS-CoV-2 Variants

SARS-CoV-2	Drug	Vero E6 P-gp knockout		Vero E6 TMPRSS2	
		Geomean EC_{50} (nM) Range	Geomean EC_{90} (nM) Range	Geomean EC_{50} (nM) Range	Geomean EC_{90} (nM) Range
USA-WA1	PF-07321332	96.3 (86.7 – 110)	195 (174 – 225)	71.2 (51.7 – 92.1)	147 (105 – 191)
	Remdesivir	57.9 (51.8 – 65.0)	122 (109 – 137)	91.4 (61.3 – 150)	196 (134 – 322)
α Variant	PF-07321332	75.3 (58.7 – 90.5)	186 (172 – 199)	170 (145 – 182)	364 (309 – 399)
	Remdesivir	41.7 (36.8 – 53.2)	132 (99.7 – 172)	113 (64.4 – 223)	240 (136 – 465)
β Variant	PF-07321332	171 (138 – 207)	363 (288 – 441)	217 (175 – 243)	460 (378 – 517)
	Remdesivir	50.5 (44.0 – 58.7)	106 (91.4 – 124)	105 (60.2 – 162)	221 (129 – 345)
γ Variant	PF-07321332	87.7 (68.2 – 121)	222 (187 – 251)	204 (137 – 250)	430 (287 – 533)
	Remdesivir	21.1 (17.6 – 26.9	53.6 (41.7– 66.6)	79.8 (52.4 – 116)	171 (111 – 253)
λ Variant	PF-07321332	59.5 (51.2 – 66.6)	171 (129 – 297)	93.0 (87.3 – 97.7)	193 (181 – 203)
	Remdesivir	26.5 (19.6 – 33.2)	64.4 (59.3 – 69.0)	80.3 (38.8 – 119)	171 (80.6 – 254)
Δ Variant	PF-07321332	N.A.	N.A.	82.2 (71.0 – 98.2)	168 (147 – 205)
	Remdesivir	N.A.	N.A.	122 (63.4 – 236)	261 (134 – 511)

N.A. = Not applicable as the Δ-Variant did not kill Vero E6 P-gp Knockout cells efficiently, therefore an EC_{50} could not be generated on this variant using this cell line. Vero-E6 TMPRSS2 cell assay was conducted in the presence of 2 μM P-gp inhibitor drug. Geomeans calculated from N=3, data presented as 3 significant figures

As a critical caveat no *in vitro* data on PF-07321332 against the new-emerging omicron variant were yet available. In view of the very rapidly increasing circulation of omicron, results of these *in vitro* data should be provided at the time of the MAA.

PF-07321332 was only evaluated in resistance selection assay against murine hepatitis virus (MHV) infected L929 cells (10 passages). Antiviral analysis of four mutant viruses harbouring the 5 treatment-emergent mutations in the MHV 3CL protease, shows 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). These preliminary results indicate a possible likelihood of resistance development to PF-07321332 (the mutation S144A is near a catalytic site of the protease). *In vitro* selection of PF-07321332 resistant SARS-CoV-2 is currently underway and should be provided at the time of MA, to notably 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. A resistance selection assay against delta variant and omicron should be provided at the time of the MAA.

Table 24 - 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

A total of 38 mutant SARS-CoV-2 $3CL^{pro}$ enzymes were tested for PF-07321332 inhibition of enzymatic activity (mutants with single point mutations in the PF-07321332 contact residues and highest prevalent mutations circulating in the population). Four mutations (H41Y, C145I, C145F, H163A) of the 13 mutations identified as key contact residues, showed lack of self-cleavage activity and would most likely yield an inactive enzyme. PF-07321332 showed a statistically significant drop in potency for inhibiting five of the 13 mutant enzymes (E166A, F140A, H164N, Q189K, and Y54A) with geomean Ki values of 31.2, 36.4, <5.98, 61.0, and 22.0 nM, respectively, versus wild type SARS-CoV-2 $3CL^{pro}$ (Ki of 1.68 nM). These mutants are being reverse engineered into SARS-Cov-2 and will be evaluated for changes in viral fitness and SARS-CoV-2 activity.

In addition to in-vitro PD data, some PD endpoints were measured amongst the efficacy endpoints in Study 1005, namely Viral Load over Time, allowing for a preliminary analysis on the effect of PF-07321332 in PD biomarkers. An update of those data should be provided at the time of the MAA.

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

A quantitative SARS-CoV-2 RT-PCR assay was used to measure viral load (copies/mL). Participants with samples collected using unvalidated (local) swabs or collected at non-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 mITT1 analysis set were also examined by serology status and baseline viral load. 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 (-

1.15 versus -0.77 Log10 copies/mL on a log-10 scale), and more apparent in participants with higher versus lower (≥107 copies/mL versus <107 copies/mL) viral load at baseline (-1.40 versus -0.79 Log10 copies/mL on a log-10 scale). An update of those data should be provided at the time of the MA.

Descriptive statistics in change in viral load from baseline to Day 5 in the three analysis population are presented below. This should be interpreted with particular caution in terms of magnitude given the descriptive analysis and the limited information.

Table 25 - Statistical analysis of change from baseline in Log10 transformed viral load (copies/mL) data – mITT, mIIT1 and mITT2 (protocol C4671005)

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

n=Number of participants with non-missing data in the analysis population and the covariates in the statistical model.
Infty=Infinity. Only Upper Limit for 80% CI is presented.
Participants are excluded from the analysis for reasons of Not Detected or Missing baseline viral load result, and local swabs use. Results from samples collected at non-nasopharyngeal site are also excluded.
Change from baseline modeled using ANCOVA
For mITT analysis set Model = Treatment + Baseline viral load + geographic region + serology status.
For mITT1 analysis set Model = Treatment + Baseline viral load + geographic region + serology status + symptom onset.
For mITT2 analysis set Model = Treatment + Baseline viral load + COVID-19 mAb treatment + geographic region + serology status + symptom onset.

Variants

The evaluation of the Mu VOC is ongoing. Data on PF-07321332 in the cell-based assay and qPCR assay is expected to be submitted during the MAA.

Antiviral activity data against omicron variant are thus currently unavailable (this has been reflected in the Conditions of Use). Given the epidemiological situation with highly increasing circulation of omicron worldwide, the company should provide this crucial information at the time of the MAA.

In line with prior discussion on the Delta variant and its sublineage, phenotypic antiviral assays will be performed on the subvariant Delta 21J and data will be expected at the time of the MAA.

2.4.3. Interactions

Pharmacodynamic Drug Interactions

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

Pharmacokinetic Drug Interactions

Interactions potential for Paxlovid (PF-07321332 / ritonavir) were only documented for PF-07321332 as, ritonavir interactions are already documented from the already approved ritonavir, NORVIR and have been integrated in the CoU, since it is currently difficult to estimate the net effect of the combination with PF-07321332 and ritonavir. This will be further investigated at the time of the MAA notably with additional expected ddI studies.

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 estimated 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), OATP1B3 (IC50 283.2 µM), OCT1 (IC50 138.1 µM) and MATE1 (IC50 111 µM).

Ritonavir (RTV) interaction profile was based on Norvir SmPC. RTV is an inducer of CYP1A2, CYP2C8, CYP29, 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 seems to be an inhibitor of CYP2D6, P-gp, OATP1B1, OATP1B3, and OCT1 and MATE1. It induces UGTs, CYP3A4, CY2B6, CYP2C8, CYP2C9, CYP1A2, and CYP2C19. This will be further substantiated at the time of the MAA.

Paxlovid net effect on CYP3A4 and P-gp substrates *in vivo* is not 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. The results are expected to be submitted as part of the MAA.

Given the large drug-drug interaction spectrum of Paxlovid, clinical interaction study to assess the magnitude of interaction with MATE1, OATP1B1, OATP1B3, and OCT1 will have to be provided as part of the subsequent MAA.

The recommendations related to co-medications will then have to be updated in the light of the results of these clinical studies expected as part of MAA.

Paxlovid as victim

PF-07321332 is mainly excreted unchanged. Notably, 55.0% and 27.5% of the dose is excreted as parent compound in urine and feces, respectively. Regarding the fraction of PF-07321332 metabolized, CYP3A4 was identified as the major contributor (fm = 0.99) of the oxidative metabolism, based on *in vitro* studies. M5 and M8 metabolites, respectively arising via loss of amide and trifluoro acetyl group from PF-07321332, were the two main metabolites found *in vivo* representing 12.5% (12.1% in feces), and 4.2% (2.6% in urine and 1.6% in feces) of the total drug related material based on the ADME

study. Furthermore, M7 the acyl-glucuronide conjugate of M5, was identified in human urine in trace amounts. In vitro results indicated that UGT2B4 and 2B7 contributed to 69.8% and 16.7% of the total metabolism of M5, respectively.

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 $AUC_{0-\infty}$ and C_{max} of PF-07321332 were decreased by 55% and 43%, respectively, as compared to administration of PF-07321332/ritonavir alone.

Based on these results, a recommendation in case of concomitant use of anti-convulsivant and Paxlovid should take into consideration a risk of efficacy loss caused by carbamazepine induction, and an urgent medical need to treat patients with epilepsy at high risk for progression to severe COVID-19. Because anti-convulsivant treatment in this population cannot be easily interrupted, even for a short period of time, further discussion is needed on the expected efficacy at the proposed therapeutic dose (i.e. 300 mg / 100 mg PF-07321332 / ritonavir) and the therapeutic margin in this particular population. The consequences in terms of efficacy and safety on concentrations 12h after dosing below 3-4 times EC90 on day 1 and below 5 to 6 times EC90 at steady state but above the EC90 (i.e. 292 ng/mL) are unclear. Thus, based on these preliminary data, presently the clinical impact in terms of efficacy at 300/100 mg of Paxlovid is uncertain. Given the available tablet strength of PF-07321332, and given that it is difficult to predict that the PK resulting from a dose increase would enable to strictly avoid a sub-optimal concentration with a critical risk of resistance, a dose increase cannot be proposed. Therefore, a conservative contra-indication with anti-convulsant is agreed and reflected in the Conditions of Use. This needs be further substantiated by the company as part of the MAA, potentially with the help of the ongoing investigation on a more adequate PK/POP model (see PK part) to avoid depriving epileptic patients (impossibility to stop treatment during the COVID treatment course).

After co-administration of PF-07321332/ritonavir (5 oral doses 300/100 mg q12h) and itraconazole (200 mg orally q24h for 8 days), the AUC_{tau} and C_{max} of PF-07321332 were increased by 38% and 19%, respectively, as compared to administration of PF-07321332/ritonavir alone. Such increases 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.

2.4.4. Data on Efficacy

The main clinical study in support of this Article 5(3) review is study C4671005 for which the design and results are presented below.

Other ongoing studies include:

-C4671002 is a ph2/3 pivotal study in non-hospitalised patients who are at low risk of progressing to severe illness (EPIC-SR for standard risk as opposed to High risk for EPIC-HR).

-C4671006 is a Ph2/3 Pivotal study in preventing symptomatic COVID-19 in adults who are household contacts of an individual infected with SARS CoV-2 (EPIC PEP).

No dedicated phase 2 dose-finding study in the intended population was conducted.

Dose selection for the pivotal phase 2/3 study C4671005 (EPIC HR) was based on available preclinical and clinical safety data, from the Phase 1 study (C4671001), and *in vitro* pharmacology studies with PF-07321332.

The rationale for dose selection for the pivotal phase 2/3 study C4671005, based on reaching unbound Ctrough values above EC90 of 90.4 ng/mL determined in dNHBE cells (equivalent to 181 nM, fu, human=0.310) was agreed in principle by the CHMP during a Scientific Advice procedure. At the proposed dose of PF-07321332/ritonavir 300/100 mg BID, more than 95% of the participants are predicted to maintain free PF-07321332 concentrations above the *in vitro* EC90 over the 12-hour dosing interval (for a hypothetical intersubject variability of 60%). The proposed dose results in median Day 1 and steady state trough concentrations 3-4x EC90 and ~5-6 x EC90, respectively.

The use of ritonavir as a PK enhancer is also supported by literature and experimental data. Ritonavir did not demonstrate *in vitro* anti-viral activity toward SARS-CoV-2. The 100 mg dose is deemed appropriate.

The selected duration of treatment (5 days) for the C4671005 clinical study (and consequently for the CoU) is similar to what has been used with other antiviral agents for the treatment of acute respiratory infections. Rationale for treatment duration was based on the viral dynamics of SARS-CoV-2 in humans. To that end, a QSP model capable of describing viral dynamics with time (5d and 10d dosing regimens) was used to confirm the selection of a 5-day dosing duration of oral PF-07321332/ritonavir 300 mg /100 mg BID. The model predicted that a 5-day regimen would be sufficient for the treatment of symptomatic confirmed SARS-CoV-2 participants, with no benefit predicted for longer dosing.

A dosing regimen of 300 mg PF-07321332 coadministered with 100 mg ritonavir q12h administered orally for 5 days was then evaluated in the pivotal study.

Study C4671005

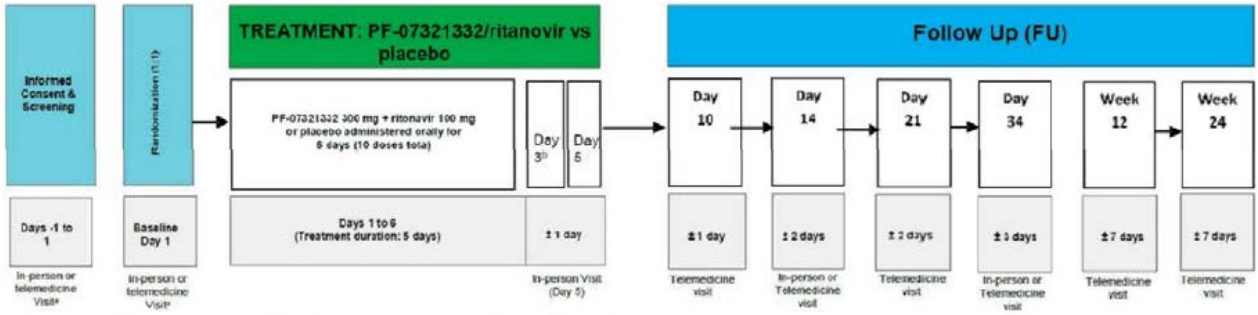
The clinical development for the treatment of non-hospitalized, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness is supported by one Phase 2/3 trial: Study C4671005 (abbreviated Study 1005).

Method

This Phase 2/3, randomized, double-blind, placebo-controlled study in non-hospitalized, 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 to be screened within 48 hours of randomization. Eligible participants received PF-07321332 plus ritonavir or placebo orally q12h for 5 days (10 doses total). 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.

Figure 13 - 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**

Inclusion Criteria

Participants 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 randomization. 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 randomization and at least 1 of the specified signs/symptoms attributable to COVID-19 present on the day of randomization:

  Cough, Shortness of breath or difficulty breathing, Fever (>38°C), Chills or shivering, Fatigue, Muscle or body aches, Diarrhea, 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 (eg, 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 forat least 14 consecutive days within 30 days prior to study entry.
    - Has received treatment with biologics (eg, infliximab, ustekinumab), immunomodulators (eg, methotrexate, 6MP, azathioprine) or cancerchemotherapy 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 (eg, cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (eg, genetic or metabolic syndromes and severe congenital anomalies);
- Active cancer, other than localized 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 (eg, CPAP [not related to COVID-19]).

Exclusion Criteria

Main exclusion criteria were:

Medical Conditions

- History of hospitalization for the medical treatment of COVID-19.
- Current need for hospitalization or anticipated need for hospitalization within 48 hours after randomization 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 nonalcoholic 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 hospitalization 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 randomization.

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).

PF-07321332/ritonavir

A dosing regimen of 300 mg PF-07321332 co-administered with 100 mg ritonavir q12h administered orally for 5 days was evaluated in this study. Dose selection for this study included consideration of all 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 (please see PK and pharmacology sections).

Comparator

The company selected placebo as the comparator since there were no-globally approved Standard of Care (SoC) treatment for this patient population as of June 2021.

Concomitant therapies

Participants in either treatment group could receive SoC therapy so long as it is not prohibited (please see Exclusion criteria).

Eligibility for mAbs was limited to persons meeting EUA-defined (Emergency Use Authorization) criteria of being at high risk for progression to severe COVID-19 or hospitalization, may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction and require patients be monitored during administration and for at least 1 hour after infusion is complete.

Additionally, the company clarified that the case report form was designed to collect supplemental oxygen administered due to COVID-19 illness; therefore, the number of participants on chronic supplementary oxygen for an underlying condition at baseline cannot be characterized.

- **Objectives and outcomes/endpoints**

The primary objective and endpoint were:

Objectives	Endpoints
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 secondary objectives and endpoints were:

Objectives	Endpoints
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.
• 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
• 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.

Additional secondary/endpoints were planned, but not for the interim analysis.

Hospitalization 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 specialized acute medical care unit within an assisted living facility or nursing home. This did not include hospitalization for the purposes of public health and/or clinical trial execution.

While the primary endpoint used the mITT analysis set (all participants treated ≤3 days after COVID-19 symptom onset), the second secondary endpoint used the mITT-1 analysis set (all participants treated ≤3 days and > 3 days after COVID-19 symptom onset) (please see Statistical method section).

- **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 that 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%. Based on the BLAZE study, the proportion of hospitalization/death in the placebo arm was assumed to be 7%.

Using EAST (Version 6.5) for a 2 sample proportion test, 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.

Interim analysis

This report presents the results of the planned interim (IA) analysis of Study 1005. As specified in the protocol, this IA for efficacy and futility with a 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 (ie, 28 days after randomisation).

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

At the time of planning the Phase 2/3 study, there was uncertainty about the rate of COVID-19-related hospitalisation or death in the primary analysis population, and about the treatment effect of PF-07321332. Hence, a sample size re-estimation was to be conducted during the first IA based on conditional power.

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.

- **Randomisation**

Eligible participants with a confirmed diagnosis of SARS-CoV-2 infection were randomized (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.

Geographical region was defined as follows:

- US region: country of the United States, including Puerto Rico.
- Europe region: countries of Bulgaria, Czech Republic, Hungary, Netherlands, Poland, Spain, and Ukraine.
- Brazil region: country of Brazil.
- India region: country of India.
- Rest of the World region: countries of Argentina, Colombia, Japan, Malaysia, Mexico, Peru, Russian Federation, South Africa, Republic of Korea, Taiwan, Thailand, and Turkey.

- **Blinding (masking)**

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 ongoing. 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 was 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.

The independent E-DMC was to review unblinded data to ensure the safety of participants on an ongoing basis throughout the duration of the study, as specified in the E-DMC Charter. In addition, the E-DMC was to review the following:

- Sentinel cohort safety review: The E-DMC reviewed unblinded safety data after approximately the first 60 participants have completed Day 10 of the study, at which point enrolment was paused pending E-DMC review of the safety data.
- Proof-of-concept assessment: The E-DMC reviewed load data when approximately 200 participants in the primary analysis set with evaluable data complete the Day 5 assessments. Enrolment was not be paused during review of these data but could be paused or stopped following E-DMC review.

- Interim analyses (as described above)

- **Statistical methods**

This report includes the results from the planned interim analysis (IA) including the participants randomised through 29 September 2021. A selection of analyses were performed for the IA, in accordance with the company's statistical analysis plan.

Analysis populations

The following efficacy analysis sets were defined for the interim analysis.

Analysis set	Description	Endpoints
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.	Primary endpoint Sensitivity analysis of primary endpoint Supplemental analysis of primary endpoint Subgroup analysis of primary endpoint Secondary analysis of POC Secondary endpoints
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.	First key secondary analysis of the primary endpoint Subgroup analysis of first key secondary endpoint Secondary analysis of POC Secondary endpoints
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.	Sensitivity analysis of primary endpoint Secondary analysis of POC Secondary endpoints

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.

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 hospitalization 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 $p_{PF-7321332}$ and $p_{placebo}$ are the proportions of participants with hospitalization 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:

- Proportion of participants with COVID-19 related hospitalization 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.
- Time (days) to sustained alleviation of all targeted signs/symptoms through Day 28.

Some inconsistencies were found in the company's documentation regarding the sequential testing of the first two secondary endpoints. Indeed, the "proportion of participants with COVID-19 related hospitalization 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" is described as the "first key secondary endpoint". However, the SAP also includes the following text: "The time to sustained alleviation of all targeted signs/symptoms through Day 28 is to be tested first. If this test is positive, then will continue with second endpoint. The hypotheses were to be tested at an overall level of 5% (2-sided)." Given the focus on the primary analysis (mITT) and mITT1 population (part of the key secondary endpoints) at the time of the interim analysis in support of the Art5(3) and the consistency shown in the results as described further, this does not impact the Art5(3) but will have to be clarified at the time of MA.

Other secondary endpoints listed below were to be subsequently tested following the Hochberg procedure1:

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

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

3. 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, ie, 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.

Another discrepancy is noted regarding the stopping boundaries which would have resulted from the potential sample size re-estimation. Although the CHW method would be expected to adequately preserve the type I error and would require fixed stopping boundaries, the SAP also includes the following text: "The actual stopping boundaries will depend on the available percentage of information". In fact there was no sample size re-estimation. The DSMB recommended to stop enrolment in view of efficacy level at the pre-specified interim analysis.

Primary analysis

The cumulative proportion of participants who experienced a COVID-19-related hospitalization 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.

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

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 graphically using Kaplan-Meier plots.

Key secondary analysis

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

Sensitivity analyses of the primary endpoint

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

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 hospitalization and death in a worst-case scenario.

Supplemental analyses of the primary endpoint

Supplemental analyses were performed on the primary endpoint using the mITT analysis set where:

- Participants who received a therapeutic COVID-19 mAb treatment post-baseline were considered as an event for the endpoint (in addition to COVID-19 related hospitalisation and death due to any cause) with mAb treatment date as the time of event.
- A logistic regression model was fitted to the primary endpoint of hospitalisation/death and included treatment and region effect as independent variables

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).

Viral Load Measured via RT-PCR Over Time

The viral load data measured in Day 1 and Day 5 are nasopharyngeal samples. These are the samples to be used on the Proof of Concept (POC) analysis. POC analysis of viral load data was to occur when approximately 200 participants in the mITT population with evaluable data completed the Day 5 assessments.

Descriptive statistics by treatment group for the change from baseline to Day 5 was provided for each treatment group and included the difference between the PF-07321332/ritonavir arm and placebo. An ANCOVA model was used to analyse the change from baseline in Log10 transformed viral load (copies/mL) data which included treatment group, baseline viral load and baseline serology status for the mITT, mITT1 and mITT2 analysis sets. The mAb treatment status and symptom onset to first dose date status (≤3 days, >3 days) was used in the model dependent of population.

Participants were excluded from the analysis due to missing or baseline viral load below the limit of detection (<550 Log10 copies/mL), or collection with an unvalidated (local) swab. Preliminary data suggests swab type is critical and viral load determined with different swab types cannot be combined, therefore, only samples collected with the validated I-Swab-plus were used for formal viral load analysis. Data reported as less than 2.0 Log10 copies/mL was recorded as 1.69 Log10 copies/mL and data reported as "not detected' was recorded as 0 Log10 copies/mL. Results from samples collected at non-NP sites (like nasal, other or missing) were also excluded.

Changes to planned analyses

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

Protocol amendment	Change in planned analyses
Amendment 2	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: - Key secondary endpoint added as a consequence on mITT1 population, i.e. regardless of COVID-19 symptom onset - Sample size increased from 2260 to approximately 3000 (adjusted for updated primary efficacy analysis) - 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	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 randomization). Other impacts include: - Modification of first interim analysis to be planned for efficacy and futility (rather than efficacy and safety) - Sample size increased from 3000 to 3100 participants due to addition of second interim analysis

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 (described previously) was specified in the SAP.

Results

The trial began on 16 July 2021 and the data cut-off for the 45% interim analysis was 26 October 2021.

- **Participant flow**

As of the data cut-off (26 October 2021), all 1361 participants in the interim analysis had entered the treatment phase.

This interim CSR presents the results of a planned interim analysis of participants randomized through 29 September 2021 who completed Day 28 assessments.

Table 26 - Disposition Events Summary - Full Analysis Set (Protocol C4671005_45IA)

Number (%) of Participants	PF-07321332 300 mg + Ritonavir 100 mg (N=678) n (%)	Placebo (N=683) n (%)	Total (N=1361) n (%)
Disposition phase: Treatment			
Participants Entered:	678 (100.0)	683 (100.0)	1361 (100.0)
Discontinued	48 (7.1)	61 (8.9)	109 (8.0)
Reason for discontinuation			
Adverse event	16 (2.4)	29 (4.2)	45 (3.3)
Death	0	0	0
Lack of efficacy	0	0	0
Lost to follow-Up	1 (0.1)	1 (0.1)	2 (0.1)
Noncompliance with study drug	0	0	0
Pregnancy	0	0	0
Protocol deviation	0	0	0
Study terminated by sponsor	0	0	0
Withdrawal by subject	24 (3.5)	23 (3.4)	47 (3.5)
Medication error without associated adverse event	0	1 (0.1)	1 (<0.1)
No longer meets eligibility criteria	1 (0.1)	1 (0.1)	2 (0.1)
Other	6 (0.9)	6 (0.9)	12 (0.9)
Completed	630 (92.9)	622 (91.1)	1252 (92.0)
Ongoing	0	0	0
Disposition phase: Follow-up			
Participants Entered:	678 (100.0)	683 (100.0)	1361 (100.0)
Discontinued	50 (7.4)	57 (8.3)	107 (7.9)
Reason for discontinuation			
Death	0	10 (1.5)	10 (0.7)
Lost to follow-Up	9 (1.3)	7 (1.0)	16 (1.2)
Study terminated by sponsor	0	0	0
Withdrawal by subject	31 (4.6)	32 (4.7)	63 (4.6)
Other	10 (1.5)	8 (1.2)	18 (1.3)
Completed	545 (80.4)	541 (79.2)	1086 (79.8)
Ongoing	83 (12.2)	85 (12.4)	168 (12.3)
Disposition phase: Long-term follow-up			
Participants Entered:	594 (87.6)	597 (87.4)	1191 (87.5)
Discontinued	47 (6.9)	56 (8.2)	103 (7.6)
Reason for discontinuation			
Adverse event	0	0	0
Death	0	10 (1.5)	10 (0.7)
Lost to follow-Up	8 (1.2)	7 (1.0)	15 (1.1)
Study terminated by sponsor	0	0	0
Withdrawal by subject	31 (4.6)	32 (4.7)	63 (4.6)
Other	8 (1.2)	7 (1.0)	15 (1.1)
Completed	0	0	0
Ongoing	547 (80.7)	541 (79.2)	1088 (79.9)

PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (16:07) Source Data: adds Table Generation: 30OCT2021 (19:10)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ./nda_unblinded/C4671005_45IA/adds_s001
Table 14.1.1 PF-07321332 is for Pfizer internal use.

Further enrolment in the study was stopped on 05 November 2021, and at the time of this decision, 2426 of the intended sample size (3100) had been randomized.

- **Recruitment**

1361 participants enrolled in the study through 29 September 2021 are included in this interim analysis.

As a note, as of 09 November 2021, a total of 2426 participants have been randomized into Study 1005, and the final primary analysis has been performed when all participants have completed follow-up through Day. 34. Only preliminary data from the final analysis were provided for this Art5(3) which seem to show consistent effect size with the following described results of the interim analysis.

Results of the final analysis should be provided at the time of the MAA

Halt center's recruitment

The company made a data driven decision to halt recruitment (22 September 2021, total of 193 participants randomized) 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 permitted window in the inclusion criteria for a positive RT-PCR test prior to randomization 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

The most frequently reported important protocol deviations occurred within the procedures/tests (20.6%), investigational product dosing or administration error (16.5%), randomization (2.9%), and inclusion/exclusion criteria (2.4%) categories. All other categories occurred in ≤1.7% of participants.

Protocol deviations were comparable between both treatment groups.

GCP noncompliance

Site 1470, 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 hospitalization/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**

Demographic and baseline characteristics are presented below.

Table 27 - Demographic and Baseline Characteristics - Full Analysis Set

	PF-07321332 300 mg + Ritonavir 100 mg (N=678)	Placebo (N=683)	Total (N=1361)
Age (Years), n (%)			
< 18	0	0	0
18 - 44	361 (53.2)	336 (49.2)	697 (51.2)
45 - 59	208 (30.7)	201 (29.4)	409 (30.1)
60 - 64	38 (5.6)	61 (8.9)	99 (7.3)
65 - 74	54 (8.0)	62 (9.1)	116 (8.5)
≥ 75	17 (2.5)	23 (3.4)	40 (2.9)
Mean (SD)	43.86 (14.93)	45.47 (15.69)	44.67 (15.33)
Median (range)	42.00 (18.00, 86.00)	45.00 (18.00, 84.00)	44.00 (18.00, 86.00)
Gender, n (%)			
Male	344 (50.7)	369 (54.0)	713 (52.4)
Female	334 (49.3)	314 (46.0)	648 (47.6)
Race, n (%)			
White	424 (62.5)	435 (63.7)	859 (63.1)

	PF-07321332 300 mg + Ritonavir 100 mg (N=678)	Placebo (N=683)	Total (N=1361)
Black or African American	37 (5.5)	25 (3.7)	62 (4.6)
Asian	134 (19.8)	140 (20.5)	274 (20.1)
American Indian or Alaska Native	76 (11.2)	77 (11.3)	153 (11.2)
Native Hawaiian or other Pacific Islander	0	0	0
Multiracial	1 (0.1)	0	1 (<0.1)
Other	0	0	0
Not reported	5 (0.7)	4 (0.6)	9 (0.7)
Unknown	1 (0.1)	2 (0.3)	3 (0.2)
Ethnicity, n (%)			
Hispanic or Latino	324 (47.8)	330 (48.3)	654 (48.1)
Not Hispanic or Latino	352 (51.9)	349 (51.1)	701 (51.5)
Not reported	2 (0.3)	4 (0.6)	6 (0.4)
Unknown	0	0	0
Weight (kg)			
Mean (SD)	80.44 (17.59)	81.26 (18.85)	80.85 (18.23)
Median (range)	78.90 (42.00, 158.3)	78.50 (42.00, 166.0)	78.80 (42.00, 166.0)
Height (cm)			
Mean (SD)	166.2 (9.74)	166.4 (10.27)	166.3 (10.00)
Median (range)	166.0 (136.9, 195.6)	166.0 (125.2, 207.3)	166.0 (125.2, 207.3)
BMI (kg/m^2), n (%)			
< 25	142 (20.9)	139 (20.4)	281 (20.6)
25 - < 30	290 (42.8)	291 (42.6)	581 (42.7)
30 - < 35	163 (24.0)	164 (24.0)	327 (24.0)
35 - < 40	45 (6.6)	53 (7.8)	98 (7.2)
≥ 40	38 (5.6)	36 (5.3)	74 (5.4)
Mean (SD)	29.08 (5.65)	29.21 (5.61)	29.14 (5.63)
Median (range)	28.30 (16.58, 58.07)	28.35 (16.05, 59.07)	28.32 (16.05, 59.07)
Duration since first diagnosis (Days), n (%)			
≤ 3	623 (91.9)	642 (94.0)	1265 (92.9)
> 3	55 (8.1)	41 (6.0)	96 (7.1)
Mean (SD)	1.44 (1.33)	1.38 (1.28)	1.41 (1.30)
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	433 (63.9)	426 (62.4)	859 (63.1)
> 3	245 (36.1)	257 (37.6)	502 (36.9)
Mean (SD)	3.02 (1.14)	3.09 (1.10)	3.06 (1.12)
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 (0.3)	0	2 (0.1)

	PF-07321332 300 mg + Ritonavir 100 mg (N=678)	Placebo (N=683)	Total (N=1361)
1	293 (43.2)	267 (39.1)	560 (41.1)
2	240 (35.4)	254 (37.2)	494 (36.3)
3	91 (13.4)	101 (14.8)	192 (14.1)
4	44 (6.5)	49 (7.2)	93 (6.8)
> 4	8 (1.2)	12 (1.8)	20 (1.5)
Comorbidities, n (%)			
Cardiovascular disorder	24 (3.5)	26 (3.8)	50 (3.7)
Chronic kidney disease	3 (0.4)	5 (0.7)	8 (0.6)
Chronic lung disease	40 (5.9)	27 (4.0)	67 (4.9)
Cigarette smoker	244 (36.0)	257 (37.6)	501 (36.8)
Diabetes mellitus	87 (12.8)	88 (12.9)	175 (12.9)
Hypertension	207 (30.5)	234 (34.3)	441 (32.4)
Immunosuppression	6 (0.9)	6 (0.9)	12 (0.9)
Cancer	2 (0.3)	2 (0.3)	4 (0.3)
Neurodevelopmental disorder	2 (0.3)	0	2 (0.1)
HIV infection	0	1 (0.1)	1 (<0.1)
Device dependence	4 (0.6)	1 (0.1)	5 (0.4)
COVID-19 mAb treatment, n (%)			
Received/expected to receive	55 (8.1)	57 (8.3)	112 (8.2)
Not received/not expected to receive	623 (91.9)	626 (91.7)	1249 (91.8)
Geographic region, n (%)			
United States	304 (44.8)	304 (44.5)	608 (44.7)
Europe	122 (18.0)	121 (17.7)	243 (17.9)
Brazil	0	1 (0.1)	1 (<0.1)
India	95 (14.0)	98 (14.3)	193 (14.2)
Rest of World	157 (23.2)	159 (23.3)	316 (23.2)
Serology status, n (%)			
Negative	291 (43.9)	301 (45.0)	592 (44.4)
Positive	372 (56.1)	368 (55.0)	740 (55.6)
Viral load (Log_{10} copies/mL), n (%)			
< 4	237 (37.6)	238 (37.8)	475 (37.7)
≥ 4	393 (62.4)	392 (62.2)	785 (62.3)
≥ 5	331 (52.5)	333 (52.9)	664 (52.7)
≥ 6	259 (41.1)	247 (39.2)	506 (40.2)
< 7	459 (72.9)	464 (73.7)	923 (73.3)
≥ 7	171 (27.1)	166 (26.3)	337 (26.7)
≥ 8	73 (11.6)	69 (11.0)	142 (11.3)
≥ 9	3 (0.5)	1 (0.2)	4 (0.3)
≥ 10	0	0	0
Mean (SD)	4.69 (2.82)	4.72 (2.74)	4.71 (2.78)
Median (range)	5.25 (0.00, 9.13)	5.26 (0.00, 9.06)	5.26 (0.00, 9.13)

All participants had a laboratory confirmed SARS-CoV-2 diagnosis, with 92.9% of participants having a qualifying SARS CoV-2 positive test collected within 3 days of first dose of study intervention.

Across treatment groups, the following could be underlined:

- 91.8% participants did not receive or were not planning to receive mAbs for the disease under study at the time of randomization.
- 55.6% of participants were serological positive at baseline.
- 62.3% participants had baseline viral load ≥4.0 Log10 copies/mL.

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

- BMI >25 kg/m^2: 79.4% (BMI >30 kg/m2: 36.7%)
- Cigarettes smokers: 35.8%
- Hypertension: 32.4%

Across treatment groups, 41.1% and 36.3% had respectively 1 and 2 risk factors.

Variants of concern (VOC)

An analysis was conducted from the first 490 participants with sequencing data. Two participants available for sequencing did not receive either placebo or PF-07321332/ritonavir and are not included in the assessment. The preliminary analysis is described in an interim virology sequencing report.

The primary variant across both treatment arms was Delta (98.0%) and was distributed in high prevalence as subvariants Delta (21J) (72.1%), Delta (21A) (12.5%) and Delta (21I) (13.3%).

Table 28 - Distribution of Variant of Concern by Treatment

CLADE	PF-07321332 300 mg + Ritonavir 100 mg (N=239)	Placebo (N=249)	All (N=488)
20A	0 (0%)	1 (0.4%)	1 (0.2%)
20C	1 (0.4%)	2 (0.8%)	3 (0.6%)
20I (alpha, V1)	1 (0.4%)	0 (0%)	1 (0.2%)
20J (Gamma, V3)	1 (0.4%)	0 (0%)	1 (0.2%)
All Delta (21A, 21I, 21J)	234 (97.9%)	244 (98.0%)	478 (98.0%)
21A (Delta)	35 (14.6%)	26 (10.4%)	61 (12.5%)
21I (Delta)	31 (13.0%)	34 (13.7%)	65 (13.3%)
21J (Delta)	168 (70.3%)	184 (73.9%)	352 (72.1%)
21H (Mu)	1 (0.4%)	0 (0%)	1 (0.2%)
Not Available	1 (0.4%)	2 (0.8%)	3 (0.6%)

Note: 490 participants had Day 1 and/or Day 5 sequencing data available, out of those participants, only 488 received either placebo or PF-07321332/Ritonavir Percentage in parentheses were calculated using a total of 488 participants. For each participant, CLADE is determined from Day 1 Sample, if day 1 sample is not available,

- **Number analysed**

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

Table 29 - Participant Evaluation Groups - All Screened Participants

	PF-07321332 300 mg + Ritonavir 100 mg (N=678) n (%)	Placebo (N=683) n (%)	Total (N=1361) n (%)
Screened: 1361 Screened Failure: 0 Not Screen Failure but not Randomized: 0			
Assigned to Treatment	678 (100.0)	683 (100.0)	1361 (100.0)
Treated	672 (99.1)	677 (99.1)	1349 (99.1)
Not Treated	6 (0.9)	6 (0.9)	12 (0.9)
Safety Analysis Set	672 (99.1)	677 (99.1)	1349 (99.1)
Full Analysis Set	678 (100.0)	683 (100.0)	1361 (100.0)
mITT Analysis Set	389 (57.4)	385 (56.4)	774 (56.9)
mITT1 Analysis Set	607 (89.5)	612 (89.6)	1219 (89.6)
mITT2 Analysis Set	661 (97.5)	669 (98.0)	1330 (97.7)

PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (15:07) Source Data: adsl Table Generation: 16NOV2021 (12:52)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ./nda_unblinded/C4671005_45IA_Secondary/adsl_s002
Table 14.1.1.1 PF-07321332 is for Pfizer internal use.

Of note, screened failure and not randomized participants are not reported in this interim analysis. This will have to be provided at the time of the MAA (notably screening failure in relation to ddI).

Table 30 - Duration of Treatment (Actual Dosing Day) - Safety Analysis Set

	PF-07321332 300 mg + Ritonavir 100 mg (N=672)	Placebo (N=677)	Total (N=1349)
Duration of treatment (Days)[a]			
n	672	677	1349
Mean (SD)	5.04 (0.82)	5.01 (0.89)	5.03 (0.85)
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 (2.2)	10 (1.5)	25 (1.9)
2	5 (0.7)	18 (2.7)	23 (1.7)
3	9 (1.3)	15 (2.2)	24 (1.8)
4	7 (1.0)	5 (0.7)	12 (0.9)
5	508 (75.6)	492 (72.7)	1000 (74.1)
> 5	128 (19.0)	137 (20.2)	265 (19.6)

a. The Total Number of Dosing Days on which study drug was actually administered
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (15:07) Source Data: adex Table Generation: 16NOV2021 (12:52)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ./nda unblinded/C4671005 45IA Secondary/adex s001
Table 14.4.1.1 PF-07321332 is for Pfizer internal use.

- **Outcome and estimations**

Primary Efficacy Analysis

COVID-19-Related Hospitalization 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.

Table 31 - Primary Analysis of Proportion of Participants with COVID-19-Related-Hospitalization 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.
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (15:04) Source Data: adtte Table Generation: 09NOV2021 (09:18)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File:
./nda unblinded/C4671005 45IA adhoc/adtteh s001 mitt
Table 14.2.1.1 PF-07321332 is for Pfizer internal use.

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 hospitalization 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 6.05% (95% CI: -8.90% to -3.19%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 7.35% to 1.30%, 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 Site 1470, the analysis was repeated while excluding data from these sites.

- 3 participants in the PF-07321332/ritonavir group and 27 participants in the placebo group were assumed to have had a primary endpoint event.
- A 7.51% (95% CI: 10.73% to -4.28%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 8.44% to 0.94%, with PF-07321332/ritonavir in comparison with placebo treatment.
- It is to note that, of 193 participants from India randomized, none progressed to hospitalization or death.

Supplemental Analyses

Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 (mITT-2)

This supportive analysis was to assess the treatment effect in a population including participants who received mAb treatment or planned to receive mAb treatment. The population includes patients regardless they received treatment within 3 days and after 3 days since onset of symptom.

Table 32 - Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 - mITT2, Kaplan-Meier Method

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

First Secondary Efficacy Analysis

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

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

3 days. This population analysis is the clinically relevant population in terms of generalizability to clinical practice.

Table 33 - Proportion of Participants with COVID-19-Related-Hospitalization 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.
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (15:04) Source Data: adtte Table Generation: 09NOV2021 (09:18)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ./nda_unblinded/C4671005_45IA_adhoc/adtteh_s001_mitt1
Table 14.2.1.2 PF-07321332 is for Pfizer internal use.

Secondary analysis

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

Please refer to the section on Pharmacodynamics.

- **Ancillary analysis**

Subgroup analysis

Serological status

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

Table 34 - Proportion of Participants with COVID-19-Related-Hospitalization 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	256	272
	Participants with event, n (%)	5 (2.0)	36 (13.2)
	Participants with COVID-19 hospitalization	5 (2.0)	36 (13.2)
	Participants with death	0	9 (3.3)
	Average time at risk for event (Days) [a]	26.7	24.2
	Average study follow-up (Days) [b]	27.1	26.0
	Estimated proportion (95% CI), %	1.980 (0.829, 4.691)	13.433 (9.877, 18.134)
	Difference from Placebo (SE)	-11.453 (2.262)	
	95% CI of difference	-15.886, -7.021	
	p-value	<.0001	
Positive	N	344	332
	Participants with event, n (%)	1 (0.3)	5 (1.5)
	Participants with COVID-19 hospitalization	1 (0.3)	5 (1.5)
	Participants with death	0	1 (0.3)
	Average time at risk for event (Days) [a]	27.2	27.2
	Average study follow-up (Days) [b]	27.2	27.5
	Estimated proportion (95% CI), %	0.291 (0.041, 2.045)	1.513 (0.633, 3.598)
	Difference from Placebo (SE)	-1.223 (0.732)	
	95% CI of difference	-2.657, 0.211	
	p-value	0.0947	

Number of baseline comorbidities

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

Table 35 - Proportion of Participants with COVID-19-Related-Hospitalization 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	488	488
	Participants with event, n (%)	3 (0.6)	26 (5.3)
	Participants with COVID-19 hospitalization	3 (0.6)	26 (5.3)
	Participants with death	0	4 (0.8)
	Average time at risk for event (Days) [a]	27.1	26.0
	Average study follow-up (Days) [b]	27.2	26.9
	Estimated proportion (95% CI), %	0.623 (0.201, 1.919)	5.379 (3.694, 7.801)
	Difference from Placebo (SE)	-4.756 (1.087)	
	95% CI of difference	-6.887, -2.625	
	p-value	<.0001	
2-3	N	115	122
	Participants with event, n (%)	3 (2.6)	15 (12.3)
	Participants with COVID-19 hospitalization	3 (2.6)	15 (12.3)
	Participants with death	0	6 (4.9)
	Average time at risk for event (Days) [a]	26.6	25.1
	Average study follow-up (Days) [b]	27.3	26.6
	Estimated proportion (95% CI), %	2.632 (0.857, 7.940)	12.359 (7.642, 19.662)
	Difference from Placebo (SE)	-9.727 (3.343)	
	95% CI of difference	-16.279, -3.174	
	p-value	0.0036	
≥ 4	N	4	2
	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]	28.0	28.0
	Average study follow-up (Days) [b]	28.0	28.0
	Estimated proportion (95% CI), %	-	-
	Difference from Placebo (SE)	-	
	95% CI of difference	-	
	p-value	-	

Age

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

Table 36 - Proportion of Participants with COVID-19-Related-Hospitalization 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	544	537
	Participants with event, n (%)	5 (0.9)	29 (5.4)
	Participants with COVID-19 hospitalization	5 (0.9)	29 (5.4)
	Participants with death	0	3 (0.6)
	Average time at risk for event (Days) [a]	27.0	26.1
	Average study follow-up (Days) [b]	27.2	27.0
	Estimated proportion (95% CI), %	0.930 (0.388, 2.220)	5.460 (3.826, 7.763)
	Difference from Placebo (SE)	-4.531 (1.069)	
	95% CI of difference	-6.627, -2.434	
	p-value	<.0001	
Age ≥ 65 years	N	63	75
	Participants with event, n (%)	1 (1.6)	12 (16.0)
	Participants with COVID-19 hospitalization	1 (1.6)	12 (16.0)
	Participants with death	0	7 (9.3)
	Average time at risk for event (Days) [a]	26.9	24.4
	Average study follow-up (Days) [b]	27.3	25.9
	Estimated proportion (95% CI), %	1.587 (0.225, 10.738)	16.000 (9.421, 26.452)
	Difference from Placebo (SE)	-14.413 (4.517)	
	95% CI of difference	-23.265, -5.560	
	p-value	0.0014	

Gender

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

Table 37 - Proportion of Participants with COVID-19-Related-Hospitalization 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	306	332
	Participants with event, n (%)	3 (1.0)	24 (7.2)
	Participants with COVID-19 hospitalization	3 (1.0)	24 (7.2)
	Participants with death	0	6 (1.8)
	Average time at risk for event (Days) [a]	27.2	25.7
	Average study follow-up (Days) [b]	27.4	26.8
	Estimated proportion (95% CI), %	0.991 (0.321, 3.042)	7.306 (4.957, 10.704)
	Difference from Placebo (SE)	-6.314 (1.545)	
	95% CI of difference	-9.343, -3.286	
	p-value	<.0001	
Female	N	301	280
	Participants with event, n (%)	3 (1.0)	17 (6.1)
	Participants with COVID-19 hospitalization	3 (1.0)	17 (6.1)
	Participants with death	0	4 (1.4)
	Average time at risk for event (Days) [a]	26.8	26.1
	Average study follow-up (Days) [b]	27.0	26.9
	Estimated proportion (95% CI), %	1.005 (0.325, 3.083)	6.128 (3.854, 9.673)
	Difference from Placebo (SE)	-5.123 (1.552)	
	95% CI of difference	-8.164, -2.082	
	p-value	0.0010	

BMI

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

Table 38 - Proportion of Participants with COVID-19-Related-Hospitalization 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/m²	N	131	130
	Participants with event, n (%)	0	5 (3.8)
	Participants with COVID-19 hospitalization	0	5 (3.8)
	Participants with death	0	1 (0.8)
	Average time at risk for event (Days) [a]	27.1	27.2
	Average study follow-up (Days) [b]	27.1	27.4
	Estimated proportion (95% CI), %	0.000 (0.000, 0.000)	3.858 (1.624, 9.021)
	Difference from Placebo (SE)	-3.858 (1.692)	
	95% CI of difference	-7.175, -0.542	
	p-value	0.0226	
25 - < 30 kg/m²	N	265	272
	Participants with event, n (%)	3 (1.1)	16 (5.9)
	Participants with COVID-19 hospitalization	3 (1.1)	16 (5.9)
	Participants with death	0	3 (1.1)
	Average time at risk for event (Days) [a]	27.0	26.0
	Average study follow-up (Days) [b]	27.3	27.0
	Estimated proportion (95% CI), %	1.136 (0.368, 3.482)	5.908 (3.661, 9.463)
	Difference from Placebo (SE)	-4.771 (1.574)	
	95% CI of difference	-7.857, -1.686	
	p-value	0.0024	
≥ 30 kg/m²	N	211	210
	Participants with event, n (%)	3 (1.4)	20 (9.5)
	Participants with COVID-19 hospitalization	3 (1.4)	20 (9.5)
	Participants with death	0	6 (2.9)
	Average time at risk for event (Days) [a]	26.9	24.8
	Average study follow-up (Days) [b]	27.1	26.3
	Estimated proportion (95% CI), %	1.438 (0.466, 4.392)	9.722 (6.383, 14.667)
	Difference from Placebo (SE)	-8.284 (2.225)	
	95% CI of difference	-12.645, -3.923	
	p-value	0.0002	

Hypertension

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

Table 39 - Proportion of Participants with COVID-19-Related-Hospitalization 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	192	210
	Participants with event, n (%)	4 (2.1)	27 (12.9)
	Participants with COVID-19 hospitalization	4 (2.1)	27 (12.9)
	Participants with death	0	9 (4.3)
	Average time at risk for event (Days) [a]	26.6	24.9
	Average study follow-up (Days) [b]	27.1	26.6
	Estimated proportion (95% CI), %	2.114 (0.799, 5.536)	12.891 (9.028, 18.234)
	Difference from Placebo (SE)	-10.777 (2.541)	
	95% CI of difference	-15.757, -5.796	
	p-value	<.0001	
Hypertension = No	N	415	402
	Participants with event, n (%)	2 (0.5)	14 (3.5)
	Participants with COVID-19 hospitalization	2 (0.5)	14 (3.5)
	Participants with death	0	1 (0.2)
	Average time at risk for event (Days) [a]	27.2	26.4
	Average study follow-up (Days) [b]	27.2	27.0
	Estimated proportion (95% CI), %	0.485 (0.121, 1.925)	3.521 (2.101, 5.874)
	Difference from Placebo (SE)	-3.037 (0.986)	
	95% CI of difference	-4.969, -1.104	
	p-value	0.0021	

Diabetes mellitus

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

Table 40 - Proportion of Participants with COVID-19-Related-Hospitalization 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	Average study follow-up (Days) [b]	27.5	26.7
	Estimated proportion (95% CI), %	2.597 (0.656, 9.988)	8.928 (4.359, 17.819)
	Difference from Placebo (SE)	-6.331 (3.696)	
	95% CI of difference	-13.575, 0.913	
	p-value	0.0867	
Diabetes mellitus = No	N	530	533
	Participants with event, n (%)	4 (0.8)	34 (6.4)
	Participants with COVID-19 hospitalization	4 (0.8)	34 (6.4)
	Participants with death	0	6 (1.1)
	Average time at risk for event (Days) [a]	27.0	25.9
	Average study follow-up (Days) [b]	27.1	26.9
	Estimated proportion (95% CI), %	0.764 (0.287, 2.022)	6.443 (4.647, 8.901)
	Difference from Placebo (SE)	-5.680 (1.135)	
	95% CI of difference	-7.904, -3.456	
	p-value	<.0001	

Cigarette smoker

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

Table 41 - Proportion of Participants with COVID-19-Related-Hospitalization 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	221	239
	Participants with event, n (%)	3 (1.4)	8 (3.3)
	Participants with COVID-19 hospitalization	3 (1.4)	8 (3.3)
	Participants with death	0	1 (0.4)
	Average time at risk for event (Days) [a]	27.1	26.7
	Average study follow-up (Days) [b]	27.4	27.1
	Estimated proportion (95% CI), %	1.366 (0.443, 4.175)	3.381 (1.705, 6.647)
	Difference from Placebo (SE)	-2.015 (1.412)	
	95% CI of difference	-4.783, 0.753	
	p-value	0.1537	
Cigarette smoker = No	N	385	373
	Participants with event, n (%)	3 (0.8)	33 (8.8)
	Participants with COVID-19 hospitalization	3 (0.8)	33 (8.8)
	Participants with death	0	9 (2.4)
	Average time at risk for event (Days) [a]	27.0	25.3
	Average study follow-up (Days) [b]	27.1	26.7
	Estimated proportion (95% CI), %	0.792 (0.256, 2.437)	8.944 (6.443, 12.350)
	Difference from Placebo (SE)	-8.151 (1.554)	
	95% CI of difference	-11.198, -5.105	
	p-value	<.0001	

Supplemental analysis

Analysis to compare efficacy of PF-07321332/ritonavir treatment versus placebo when initiated 4-5 days from symptom onset

This analysis represents participants with onset of symptoms >3 days from treatment initiation who at baseline did not receive nor were expected to receive mAb therapy for COVID-19.

Table 42 - Primary Analysis of Proportion of Participants With COVID-19-Related- Hospitalization or Death From any Cause Through Day 28 by Subgroup of Symptom Onset of > 3 Days - mITT1, Kaplan-Meier Method (Protocol C4671005)

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
N	218	227
Participants with event, n (%)	3 (1.4)	14 (6.2)
Participants with COVID-19 hospitalization	3 (1.4)	14 (6.2)
Participants with death	0	3 (1.3)
Average time at risk for event (Days)[a]	26.7	25.8
Average study follow-up (Days)[b]	26.9	26.7
Estimated proportion (95% CI), %	1.402 (0.454, 4.285)	6.194 (3.716, 10.236)
Difference from Placebo (SE)	-4.792 (1.794)	
95% CI of difference	-8.308, -1.276	
p-value	0.0076	

N = number of participants in the subgroup of the analysis set. Participants 12255001, 14705011 and 14705012 had duration of symptom onset greater than 5 days, and are count in sub-group of symptom onset of > 3 days.

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.

Source: Table 004.1.1 PF-07321332

PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (15:04) Source Data: adtte Table Generation: 07DEC2021 (01:14)

(Data cutoff date : 26OCT2021 Database snapshot date: 29OCT2021) Output File: ./nda_unblinded/SCSC4670004/adtteh_s001_dur_mitt1

Concomitant medication

Overall, 111 (8.3%) participants received corticosteroids with ATC2 classification of "Corticosteroids for systemic use" during the study period (through Day 34). A total of 13 (1.0%) participants received remdesivir.

Table 43 - Concomitant Medications by ATC2 (Corticosteroids for Systemic use) and Preferred Term (Remdesivir) - mITT2 Analysis Set (Protocol C4671005)

ATC2 Preferred Name	PF-07321332 300 mg + Ritonavir 100 mg (N=661) n (%)	Placebo (N=669) n (%)	Total (N=1330) n (%)
Participants with any concomitant medications	40 (6.1)	72 (10.8)	112 (8.4)
ANTIVIRALS FOR SYSTEMIC USE	1 (0.2)	12 (1.8)	13 (1.0)
REMDESIVIR	1 (0.2)	12 (1.8)	13 (1.0)
CORTICOSTEROIDS FOR SYSTEMIC USE	40 (6.1)	71 (10.6)	111 (8.3)
BETAMETHASONE	0	1 (0.1)	1 (0.1)
BETAMETHASONE DIPROPIONATE	0	1 (0.1)	1 (0.1)
BETAMETHASONE;LORATADINE	3 (0.5)	4 (0.6)	7 (0.5)
CORTICOSTEROIDS	0	1 (0.1)	1 (0.1)
DEFLAZACORT	0	1 (0.1)	1 (0.1)
DEXAMETHASONE	13 (2.0)	37 (5.5)	50 (3.8)
DEXAMETHASONE SODIUM PHOSPHATE	0	1 (0.1)	1 (0.1)
HYDROCORTISONE	2 (0.3)	1 (0.1)	3 (0.2)
METHYLPREDNISOLONE	10 (1.5)	12 (1.8)	22 (1.7)
METHYLPREDNISOLONE SODIUM SUCCINATE	0	1 (0.1)	1 (0.1)
PREDNISOLONE	1 (0.2)	6 (0.9)	7 (0.5)
PREDNISONE	13 (2.0)	16 (2.4)	29 (2.2)
STEROIDS	0	1 (0.1)	1 (0.1)
TRIAMCINOLONE	0	1 (0.1)	1 (0.1)
TRIAMCINOLONE ACETONIDE	0	1 (0.1)	1 (0.1)

WHODDG B3 v202103 coding dictionary applied.
a. Medication was pre-specified on CRF.
Source: Table 004.2.1 PF-07321332
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (15:07) Source Data: adcm Table Generation: 06DEC2021 (20:20)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ./nda_unblinded/SCSC4670004/adcm_s003

Variants of concern

For the subset of 488 participants in the interim analysis with sequencing data available, there were 5 events in the PF-07321332/ritonavir treatment group (out of a total of 6 events in the interim analysis) and 17 events in the placebo (out of a total of 41 events in the interim analysis). All 5 events in the PF-07321332/ritonavir participants were infected with the Delta (21J) subvariant. For placebo, 16 events occurred in participants infected with the Delta variant (subvariant:10 in 21J, 5 in 21I, and 1 in 21A) and one event in a participant infected with 20A variant.

Overview of key efficacy data submitted

Table 44 - Overview of key efficacy data submitted

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment	Main efficacy results
Therapeutic indication 1					
Study 1005	Primary objective: • To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in non-hospitalized 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 hospitalization or death from any cause through Day 28.	Non-hospitalized, 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 randomization • Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior randomization • 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, hypertension, sickle	• 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.

			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 hospitalization for the medical treatment of COVID-19 • Current need for hospitalization or anticipated need for hospitalization within 48 hours hours after randomization • 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%		

Discussion on Efficacy

Demonstrated benefits

Method

The main clinical study in support of this procedure was a Phase 2/3, randomized, double-blind, placebo-controlled study (C4671005 or EPIC-HR study) to compare the efficacy, the safety, and the tolerability of PF-07321332/ritonavir, versus placebo, in non-hospitalized, 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.

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 randomization. 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. It has to be noted that patients were to be enrolled on the basis of an 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 to enrich population with very old patients.

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 hospitalization or anticipated need for hospitalization within 48 hours after randomization was an exclusion criterion, as such it might be unlikely that patients with severe illness were recruited at screening. However, SpO2 <94% population could have been likely more clinically at risk of progressing. It has to be underlined that the company did not provide a definition of the population of mild to moderate patients as claimed in the indication of Condition of Use. Nevertheless it is currently acknowledged that non severe patients are rather to be defined as not requiring O2 for COVID19 in clinical practice. Moreover, obviously this study targets non severe patients insofar that requirement of hospitalisation for COVID-19 is part of the exclusion criteria. In this perspective, a rewording of the indication is proposed in the Condition of Use, removing, the statements "mild to moderate" and focusing on the non-requirement of O2.

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 (in fact almost exclusively intended to receive).

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 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 results with this selected dose. Further scrutiny will apply at the time of the MA with PK data some subgroups of patients (notably with BMI>30).

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. While this should be further explored, notably for immunodeficient patients based on kinetic of viral load decrease, this is agreed in the context of an emergency use situation, based on the results of the clinical study with this tested treatment duration However further

discussion might be requested at the time of the MAA (notably if available viral load is available after D5).

The choice of placebo as comparator is considered appropriate.

Overall, the primary objective and the primary endpoints appear acceptable. However, given that this is an interim analysis report, only few secondary endpoints were planned.

The sample size calculations appear to be in line with corresponding protocol assumptions. The assumed proportion of hospitalization/death in the placebo arm (7%) is consistent with the observed rate in these interim results.

The primary analysis population, mITT, was defined as 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. The mITT1 included in addition subjects treated >3 days of COVID-19 onset and therefore is the population of analysis of clinical relevance, better supporting the generalizability to clinical practice. Finally, the mITT2 included on top of all that participants who received or were expected to receive COVID-19 therapeutic mAb treatment.

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.

It should be highlighted that 2 interim analyses were pre-specified in the protocol for decision making (i.e. based on 45% and based on 70% of the overall population).

Results

This study was initiated the 16 July 2021. 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 efficacy had been achieved (primary endpoint met in the mITT population); further enrolment in the study was stopped.

This report includes thus the results from the planned 45% IA, corresponding to 1361 participants (n=678 for PF-07321332/ritonavir, n=683 for placebo), randomised through 29 September (with data cut-off 26 October 2021).

It is highlighted that 1065 additional patients have been enrolled between the date of randomization of the last patients included in the interim analysis (i.e. 29 September 2021) and the time of the stop of the study (i.e. 05 November 2021). The final analysis that should be provided at the time of the MAA will be thus based on 2426 participants.

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 (55.6% vs 43.4%) while any confirmed SARS-CoV-2 infection prior the study and vaccination prior to Visit at day 34 (+/ -3d) were part of the exclusion. This will be further scrutinized at the time of the MA A(notably with discriminant IgG/IgM serology), given the potential impact for generalizability to vaccinated subjects.

8.2% of participants received or were expected to receive COVID-19 therapeutic monoclonal antibody at baseline, which remains a limited proportion.

Across treatment groups, 41.1% and 36.3% had respectively 1 and 2 risk factors. Main risk factors observed in the participants were overweight (79.4% with a BMI >25 kg/m^2, 36.7% with a BMI >30

kg/m2), cigarettes smokers (35.8%), hypertension (32.4%) and diabetes mellitus (12.9%). However, 18.7% were older than 60 years of ages (and 11.4% older than 65). Furthermore, other risks factors are less represented.

62.3% participants had baseline viral load ≥4.0 Log10 copies/mL.

The population enrolled was mainly from US (app. 45%), 17.9% of the subjects were recruited in Europe. The generalizability will be further explored at the time of the MAA.

The Delta variant was largely predominant (i.e. 98.0%) in the subset population with sequencing data (n=490). This is reassuring given this variant is currently predominantly circulating in Europe. However, concerns are raised as regards the Delta (21J) subvariant, since represented in the 5/6 events in the interim analysis, but nevertheless having in mind that it was also the most common (app70%) among the 98 % of patients with delta variant. This will be further scrutinized at the time of the MAA.

Regarding concomitant medication, during the study period (through Day 34), 8.4% of the participants received systemic corticosteroids or remdesivir which remains limited. The administration was numerically higher in the placebo group (10.8%) compared to the PF-07321332/ritonavir group (6.1%), which seems consistent with the observed efficacy of the study treatment. However, the estimation of the effect size across these subgroups is not interpretable, given the very limited number of patients having those comedications.

The number of important protocol deviations through the data cut-off date (26 October 2021) was comparable between the treatment groups as was the number by subcategory of protocol deviations.

The primary endpoint was met with a 6.317% (95% CI: -9.041% to -3.593%; p<0.0001) absolute reduction, reducing the primary endpoint event rate from 7.093% to 0.776% at Day-28, with PF-07321332/ritonavir in comparison with placebo treatment. No patient died in the Paxlovid treatment group whereas 7 deaths occurred in the placebo group. The results are consistent with the analysis conducted in mITT1 and mITT2 populations (respectively -5.765% [95% CI: -7.917% to -3.613%; p<0.0001] and -5.425% [95% CI: -7.460% to -3.390%; p<0.0001]). Additionally, when performing the analysis only in participants with onset of symptoms >3 days from treatment initiation (and who at baseline did not receive nor were expected to receive mAb therapy for COVID-19), the size effect is consistent with above results (-4.792% [95% CI: -8.308% to -1.276%; p=0.0076]).

CHMP discussed the clinical relevance of the analysis in the mITT and mITT1 population. Almost 43% of the patients were not treated ≤3 days of COVID-19 onset and are excluded of the mITT. Moreover, 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 generalization and more representative of the population of interest (notably encompassing patients treated within 5 days since symptoms onset). To this purpose, a time limit for treatment initiation was added in the Condition of Use (i.e. start treatment within 5 days of onset of symptoms).

Sensitivity analysis were generally consistent with primary results; removed data from Indian participants and the GLC non-compliant site would likely not change the conclusions.

Given above considerations regarding the population of interest, together with the much larger number of subjects available in mITT1 than in mITT, subgroup analysis are assessed with mITT1 outcomes.

Overall, results seem consistent in subgroup analysis for the risk factors mainly represented. It can observed an absolute reduction of: -8.28% (95% CI: -12.65% to -3.92%; p=0.0002) in patients with a BMI >30 kg/m2, 10.77% (95% CI: -15.75% to -5.80%; p<0.0001) in patients with hypertension,

-14.41% (95% CI: -13.58% to -5.56%; p=0.0014) in patients older than 65, and -6.33% (95% CI: -23.26% to -0.91%; p=0.0867) in patients with diabetes mellitus.

However, the absolute reduction, -2.01% (95% CI: -4.78% to -0.75%; p=0.1537) in patients who are cigarettes smoker (majority among patients with comorbidities), was more limited.

Likewise, in patients with positive serology status at baseline (55.6%), results make difficult to conclude on the efficacy, with an absolute reduction of -1.22% (95% CI: -2.66% to -0.21%; p=0.0947). However, it is to note that the number of events was low in the placebo group (3 hospitalisation and 0 death).

Finally, a slightly larger reduction of the viral load from baseline to day 5 seems to be observed in the active group versus the placebo group. However, the limited data available at this stage and the descriptive nature of the analysis warrant caution in the interpretation. This will be further substantiated at the time of the MAA.

Overall, the efficacy data submitted are considered sufficient for supporting the use of Paxlovid in an emergency setting. Some uncertainties are however highlighted below that will need complementary data/clarifications from the company at the time of the MAA.

Uncertainty about benefits

In absence or further stratification factors, as commented below, 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. Likewise, there are concerns that participants with SpO_2 ≥92 % but < 94%, thus likely at risk to progress, are in similar proportion in each treatment groups. More broadly, further discussion in the balance of the severity illness at baseline across arms will be needed at the time of the MAA.

A number of risk factors are poorly represented (chronic lung disease, CVD, immunosuppressive disease etc…) making difficult to conclude on the relevance of the results in these subpopulations.

Regarding variants, all five participants with an event in the PF-07321332/ritonavir group were infected with the Delta (21J) subvariant. This is of concern, as this variant, in contrast to the 21A subvariant, harbours mutations in the ORF1a that encodes for nsp5 (the 3CL-protease). This data may point to a potential loss of efficacy in VOCs harbouring mutations in ORF1a. Mutations in ORF1a were also identified in the Omicron variant. These data and the lack of information on the resistance profile of Paxlovid, neither *in vitro* nor *in vivo*. Those limitations will have to be resolved at the time of the MAA.

Finally, the current lack of *in vitro* data of antiviral activity of PF-07321332 on Omicron VOC has become a critical caveat for the early access in view of the evolving epidemiological situation with rapidly increasing circulation of omicron.

Those data will have to be provided at the time of the MAA

Moreover, the reduce effect size in patients with positive serology status and in cigarettes smokers raise concern whether efficacy results to administrate PF-07321332/ritonavir can be translated in a significant benefit in these patients.

Considering that viral loads are not available in all patients, together with the concerns on the methods to handle missing data as commented below, and the logistic issues to perform measurement (kit delays), it seems premature, at this stage, to consider any analysis on this parameter. Additionally, discussion on the clinical relevance of the observed reduction is lacking.

Follow-up data (including Day-34 data) were not yet available in the proposed interim report. In order to ensure that no later events could impact the benefice observed at the primary timepoint, these longer-term data will be needed at the time of the MAA.

More broadly, the analysis based on the total number of the patients enrolled (i.e. n=2426) are awaited to confirm the interim results. The company has provided the top line results from final analysis. However, only few outcomes are available: the primary endpoint (mIIT), the key secondary endpoint (mITT1) and the subgroup analysis by viral load at baseline. The information provided in the preliminary presentation of the interim analysis are too high level and partial to draw a reliable interpretation to draw conclusion on the reliability of the preliminary presentation. While the first final results from this preliminary presentation seem consistent with the interim outcomes, it is preferred to remain cautious awaiting the completed final analysis (notably including sensitivity and subgroup analyses by risk factor, serologic status and variants (including sublineage especially 21J for the almost exclusively reported variant) to be provided at the time of the MAA.

The extent of efficacy in vaccinated patients with breakthrough infection has not been characterised, as such patients were excluded from the pivotal trial. Data in patients with positive SARS-CoV-2 serology status might inform on the potential generalizability to those patients.

The number of participants on chronic supplementary oxygen for an underlying condition at baseline cannot be provided. Uncertainties on the efficacy results thus remains. If such individuals had an oxygen saturation of at least 92% at rest within 24 hours prior to randomisation they were not to be excluded according to the study protocol if this criterion was fulfilled while on their standard home oxygen supplementation. This will be further scrutinized at the time of the MAA.

Statistical methods

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 in which extend this factor is appropriate to defined patients the most 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 be expected as an additional stratification factor of the randomisation. The lack of stratification for the time since symptom onset could raise a concern on 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.

All efficacy populations [mITT, mITT1 (clinically relevant in terms of generalizability to the clinical practice) and mITT2] excluded subjects who were not treated or without at least 1 post-baseline visit through Day 28. This is not in line with the defined estimands that should estimate the treatment effect irrespective of adherence to randomized treatment. 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. Such analysis sets would be more closely aligned with the ITT principle. The difference between mITT2 and FAS (all randomised) consists of subjects either not treated or without at least one post-baseline visit through day 28. It is acknowledged that this appears to represent a relatively small proportion of subjects (2.3% of subjects in the FAS are not included in mITT2).

A discrepancy is also noted in the definition of mITT1 and mITT2 between the SAP/study report and the clinical overview/conditions for use (annex I). The SAP/study report do not specify any criteria regarding COVID-19 symptom onset for mITT1/mITT2 (subjects are included regardless of symptom onset date), whereas the clinical overview/conditions for use specify a ≤ 5 days criterion. The 5 days

onset criteria is understood to be the study inclusion criteria but is not actually used for defining mITT1 and mITT2 populations. In fact, based on demographic summary tables, there appears to be a few subjects with symptom onset > 5 days from treatment that are included in mITT1/mITT2, so the SAP definition seems to be the one actually followed for analyses.

The presentation of missing data is unclear, in particular regarding how many untreated patients and treated patients without post-baseline values were excluded from the different analysis populations. The number of drop-outs and the time to discontinuation was also not presented for the different analysis populations. These uncertainties will be further explored during the assessment of the marketing authorization procedure.

There is some inconsistency in the company's SAP regarding the sequential testing of the first two secondary endpoints. It is not entirely clear which one is meant to be tested first. Again this will be further explored during the assessment of the marketing authorization procedure.

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. Indeed, data from subjects who withdrew early are likely missing not at random, which could lead to biased estimates. It is acknowledged that a post-hoc sensitivity analysis has been performed with subjects not providing follow-up data through Day 21 hypothetically assumed to experience both COVID-19-related hospitalisation and death. This may provide an alternative treatment effect estimate under more conservative assumptions.

Several factors leading to exclusion of participants from the POC viral load analysis were described. Data may be missing not at random (MNAR) which would likely result in biased estimates. These are exploratory analyses and results should be interpreted with caution.

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

2.4.5. Data on Safety

The safety data provided is based on the pivotal Study 1005. Safety results are from the 45% interim analysis which includes 1349 participants (safety analysis set) enrolled through 29 Sep 2021 with the database cut-off on 26 Oct 2021. The safety analysis set is defined as all participants who receive at least 1 dose of study intervention.

Updated safety data from the current data base of 1881 participants for Study 1005 interim analysis was provided during the procedure; the data cut-off date was however not provided.

The safety follow-up period was planned through Day 34.

Visit Identifier Abbreviations used in this table may be found in Appendix 12.	Screening	Baseline (Day 1)	Day 3	Day 5	Day 10	Day 14	Day 21	Day 34	LT F/U		ET (prior to Day 34)	Notes
									Week 12	Week 24		
Visit Window	Day -1 to Day 1	0 days	±1 day	±1 day	±1 day	±2 days	±2 days	±3 days	±7 days	±7 days	±5 days	
												30 days before study entry (considered prior treatment) will be recorded. • Concomitant therapies will be collected through the Day 34 visit. • Refer to Section 6.8.
Adjunctive therapeutic procedures	X	X		X	X	X	X	X			X	• Will be collected through the Day 34 visit.
SERIOUS AND NONSERIOUS AE MONITORING	X	X	[X]	X	X	X	X	X			X	• AEs should be assessed by means of a telemedicine visit if not feasible via an in-person visit • Refer to Section 8.3.

Safety data from supportive Phase 1 studies 1001, 1011, 1014 and 1015 were also submitted.

Clinical safety data

The intended posology is PF- 07321332 300mg and ritonavir 100mg Q12h for 5 days. The extent of exposure was not provided in the submitted data.

Demographic and Baseline Characteristics – Safety analysis set

Overall demographic and baseline characteristics were similar between the two arms of Study 1005. The median age is 44.71 yrs (range 18.00 – 86.00) with a greater proportion of 18-44 (51.1%); subjects ≥60 years of age represented 18.9% of total safety database. The repartition of male and female is comparable (52.3% of male, 47.7% female) and the majority of subjects were White (63.4%). There was 36.6% of subjects with obesity (BMI ≥30) and 42.8% of subjects with overweight (BMI 25≤30). The most reported comorbidities were cigarettes smokers (36.8%), hypertension (32.5%), diabetes mellitus (12.9%), chronic lung disease (4.9%) and cardiovascular disease (3.7%). The other comorbidities defining the high risk of developing severe illness from COVID-19 were reported in <1% of the SAS.

Overview of Adverse Events

Overall, the occurrence of TEAEs in PF1332/ritonavir and placebo arms was comparable, i.e. 19.8% and 22.3% respectively. Serious AEs were less reported in PF-1332/ritonavir arm than placebo arm, i.e. 1.9% and 6.8% respectively. Grade ≥3 TEAEs were also less reported in PF-1332/ritonavir arm than placebo arm, i.e. 3.1% and 8.6% respectively.

No AE leading to study discontinuation occurred in PF-1332/ritonavir arm and occurred at 1.5% subjects in placebo arm. AEs leading to drug interruption were more reported in placebo arm than PF-1332/ritonavir arm, 4.3% and 2.4% respectively. The rate of AEs leading to treatment modifications is however missing in the overview of AEs.

Table 45 - Treatment-emergent adverse events (all causalities) – DAIDS Grade – safety analysis set (protocol C4671005_45IA)

Number (%) of Participants	PF-07321332 300 mg + Ritonavir 100 mg (N=672) n (%)	Placebo (N=677) n (%)
Participants evaluable for adverse events	672	677
Number of adverse events	263	262
Participants with adverse events	133 (19.8)	151 (22.3)
Participants with serious adverse events	13 (1.9)	46 (6.8)
Participants with Maximum Grade 3 or 4 adverse events	21 (3.1)	48 (7.1)
Participants with Maximum Grade 5 adverse events	0	10 (1.5)
Participants discontinued from study due to adverse events[a]	0	10 (1.5)
Participants discontinued study drug due to AE and continue Study[b]	16 (2.4)	29 (4.3)
Participants with dose reduced or temporary discontinuation due to adverse events	1 (0.1)	4 (0.6)

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study
b. Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Participant to be discontinued from Study
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (16:07) Source Data: adae Table Generation: 30OCT2021 (19:13)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ./nda_unblinded/C4671005_45IA/adae_s020

Treatment-related TEAEs were highly reported in PF-1335/ritonavir arm compared to placebo, i.e. 7.3% and 4.3% 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 3 (0.4%) were Grade ≥3. None of the AE leading to study discontinuation or treatment interruption was a treatment-related AE.

Table 46 - Treatment-emergent adverse events (treatment related) – DAIDS Grade – safety analysis set (protocol C4671005_45IA)

Number (%) of Participants	PF-07321332 300 mg + Ritonavir 100 mg (N=672) n (%)	Placebo (N=677) n (%)
Participants evaluable for adverse events	672	677
Number of adverse events	74	35
Participants with adverse events	49 (7.3)	29 (4.3)
Participants with serious adverse events	1 (0.1)	0
Participants with Maximum Grade 3 or 4 adverse events	3 (0.4)	4 (0.6)
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]	7 (1.0)	3 (0.4)
Participants with dose reduced or temporary discontinuation due to adverse events	0	3 (0.4)

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study
b. Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Participant to be discontinued from Study
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (16:07) Source Data: adae Table Generation: 30OCT2021 (19:13)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ./nda_unblinded/C4671005_45IA/adae_s021

Updated safety database (n=1881)

AEs occurred at similar rate across the two treatment groups in the updated safety database, i.e. 19.3% in the PF-07321332/ritonavir group and 20.7% in the placebo group. No additional death was reported in the safety dataset.

Table 47 - Updated safety database

Treatment Emergent Adverse Events

	PF-07321332 300 + Ritonavir 100 mg	Placebo
Participants	945	936
Number of adverse events	339	320
Participants with adverse events	182 (19.3%)	194 (20.7%)
With serious adverse events	16 (1.7%)	62 (6.6%)
With Maximum Grade 3 or 4 AEs	27 (2.9%)	71 (7.6%)
Deaths	0	10 (1.1%)
Discontinued study drug due to AE and continue Study	20 (2.1%)	38 (4.1%)

Analysis of AEs

- All causality TEAEs

The most frequently reported TEAEs in the PF-07321332/ritonavir group (≥1%) were Dysgeusia (4.8%), Diarrhoea (3.9%), Nausea (1.9%), Headache (1.5%), Vomiting (1.3%), and Pyrexia (1.2%), some reported TEAEs may be associated to COVID-19 symptoms. Of these, Dysgeusia, Diarrhoea, Vomiting, and Pyrexia were reported at a higher frequency in the PF-07321332/ritonavir group compared with the placebo group (0.1%, 1.9%, 0.3%, and 1.0%, in the placebo group, respectively).

Hypertension occurred at a low frequency overall (0.9% and 0.1%, in the PF- 07321332/ritonavir and placebo group, respectively, but was more frequent in the PF- 07321332/ritonavir group. A total of 7 AEs of Hypertension were reported; 6 participants in the PF-07321332/ritonavir group and 1 participant in the placebo group. The AEs of Hypertension were non-serious, transient in nature, did not lead to treatment discontinuation and all were assessed as not related to study intervention by the investigator. The AEs were mild or moderate (Grade 1-2) in severity and were resolved/resolving, with exception of 1 participant in the PF-07321332/ritonavir group: This participant had an event of severe (Grade 3) hypertension. The participant also had 2 SAEs (abscess and sepsis), which were not considered by the investigator to be related to study intervention and resolved. The event of severe hypertension was not resolved (Study 1005).

Reported TEAEs with PF-07321332/ritonavir were mostly Grade 1-2.

A summary of all-causality TEAEs that started on or prior to the Day 34 visit, reported by SOC, PT and maximum severity grade is provided in table 48.

Table 48 – Summary of treatment-emergent adverse events by MedDRA system organ class, preferred term, and maximum DAIDS Grade (all causalities) – safety analysis set (protocol C4671005_45IA)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Participants with events	111 (16.5)	15 (2.2)	6 (0.9)	0	1 (0.1)	133 (19.8)	93 (13.7)	37 (5.5)	11 (1.6)	10 (1.5)	0	151 (22.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (0.3)	0	0	0	0	2 (0.3)	1 (0.1)	0	1 (0.1)	0	0	2 (0.3)
Leukocytosis	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
Lymphadenopathy mediastinal	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Microcytic anaemia	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
CARDIAC DISORDERS	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)	4 (0.6)	0	0	0	0	4 (0.6)
Palpitations	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)	2 (0.3)	0	0	0	0	2 (0.3)
Pericardial effusion	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Sinus tachycardia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
EAR AND LABYRINTH DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)
Hyperacusis	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Vertigo	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
EYE DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Eye pain	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
GASTROINTESTINAL DISORDERS	48 (7.1)	0	0	0	0	48 (7.1)	35 (5.2)	1 (0.1)	0	0	0	36 (5.3)
Abdominal pain	2 (0.3)	0	0	0	0	2 (0.3)	2 (0.3)	0	0	0	0	2 (0.3)
Abdominal pain lower	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Abdominal pain upper	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)
Colitis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Constipation	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)
Diarrhoea	26 (3.9)	0	0	0	0	26 (3.9)	13 (1.9)	0	0	0	0	13 (1.9)
Dry mouth	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Dyspepsia	5 (0.7)	0	0	0	0	5 (0.7)	3 (0.4)	0	0	0	0	3 (0.4)
Faeces soft	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Gastrooesophageal reflux disease	3 (0.4)	0	0	0	0	3 (0.4)	2 (0.3)	0	0	0	0	2 (0.3)
Hiatus hernia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hyperchlorhydria	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Large intestine polyp	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Nausea	13 (1.9)	0	0	0	0	13 (1.9)	13 (1.9)	1 (0.1)	0	0	0	14 (2.1)
Rectal haemorrhage	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Vomiting	9 (1.3)	0	0	0	0	9 (1.3)	2 (0.3)	0	0	0	0	2 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	16 (2.4)	0	0	0	0	16 (2.4)	11 (1.6)	1 (0.1)	0	0	0	12 (1.8)
Asthenia	3 (0.4)	0	0	0	0	3 (0.4)	0	1 (0.1)	0	0	0	1 (0.1)
Catheter site pain	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Chest discomfort	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
Chest pain	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Chills	5 (0.7)	0	0	0	0	5 (0.7)	0	0	0	0	0	0

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)
Fatigue	2 (0.3)	0	0	0	0	2 (0.3)	5 (0.7)	0	0	0	0	5 (0.7)
Non-cardiac chest pain	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Oedema due to cardiac disease	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Pain	0	0	0	0	0	0	3 (0.4)	0	0	0	0	3 (0.4)
Pyrexia	8 (1.2)	0	0	0	0	8 (1.2)	7 (1.0)	0	0	0	0	7 (1.0)
HEPATOBILIARY DISORDERS	2 (0.3)	1 (0.1)	0	0	0	3 (0.4)	1 (0.1)	0	0	0	0	1 (0.1)
Cholestasis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hepatitis toxic	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hyperbilirubinaemia	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Liver injury	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
IMMUNE SYSTEM DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Seasonal allergy	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
INFECTIONS AND INFESTATIONS	9 (1.3)	5 (0.7)	1 (0.1)	0	0	15 (2.2)	14 (2.1)	20 (3.0)	6 (0.9)	7 (1.0)	0	47 (6.9)
Abscess	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Atypical pneumonia	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Bronchitis	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
COVID-19	2 (0.3)	1 (0.1)	0	0	0	3 (0.4)	4 (0.6)	5 (0.7)	1 (0.1)	2 (0.3)	0	12 (1.8)
COVID-19 pneumonia	2 (0.3)	3 (0.4)	0	0	0	5 (0.7)	4 (0.6)	10 (1.5)	4 (0.6)	5 (0.7)	0	23 (3.4)
Mumps	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)
Oral herpes	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)
Oropharyngeal candidiasis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Pneumonia	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)	1 (0.1)	5 (0.7)	1 (0.1)	0	0	7 (1.0)
Pneumonia viral	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Respiratory tract infection bacterial	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Respiratory tract infection viral	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Sepsis	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Urinary tract infection	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Viral rhinitis	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Viral sepsis	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Vulvovaginal candidiasis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	0	0	0	2 (0.3)	0	1 (0.1)	0	0	3 (0.4)
Craniocerebral injury	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Eye injury	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Fall	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hand fracture	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)	0	0	2 (0.3)
Road traffic accident	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Wrist fracture	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
INVESTIGATIONS	17 (2.5)	7 (1.0)	5 (0.7)	0	0	29 (4.3)	25 (3.7)	10 (1.5)	5 (0.7)	0	0	40 (5.9)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)
Activated partial thromboplastin time prolonged	2 (0.3)	0	0	0	0	2 (0.3)	1 (0.1)	0	0	0	0	1 (0.1)
Alanine aminotransferase increased	4 (0.6)	0	0	0	0	4 (0.6)	7 (1.0)	3 (0.4)	0	0	0	10 (1.5)
Aspartate aminotransferase increased	2 (0.3)	0	0	0	0	2 (0.3)	1 (0.1)	1 (0.1)	1 (0.1)	0	0	3 (0.4)
Blood creatine phosphokinase increased	0	0	1 (0.1)	0	0	1 (0.1)	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)
Blood fibrinogen decreased	0	2 (0.3)	0	0	0	2 (0.3)	0	0	0	0	0	0
Blood glucose increased	1 (0.1)	0	1 (0.1)	0	0	2 (0.3)	2 (0.3)	1 (0.1)	1 (0.1)	0	0	4 (0.6)
Blood thyroid stimulating hormone increased	2 (0.3)	0	0	0	0	2 (0.3)	1 (0.1)	0	0	0	0	1 (0.1)
Breath sounds abnormal	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
C-reactive protein increased	2 (0.3)	1 (0.1)	0	0	0	3 (0.4)	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)
Creatinine renal clearance abnormal	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Creatinine renal clearance decreased	0	2 (0.3)	1 (0.1)	0	0	3 (0.4)	0	3 (0.4)	1 (0.1)	0	0	4 (0.6)
Differential white blood cell count abnormal	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Fibrin D dimer increased	3 (0.4)	0	0	0	0	3 (0.4)	10 (1.5)	0	1 (0.1)	0	0	11 (1.6)
Glomerular filtration rate abnormal	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Glomerular filtration rate decreased	0	1 (0.1)	0	0	0	1 (0.1)	0	1 (0.1)	1 (0.1)	0	0	2 (0.3)
Glycosylated haemoglobin increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Haematocrit increased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Haemoglobin decreased	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Haptoglobin increased	2 (0.3)	0	0	0	0	2 (0.3)	1 (0.1)	0	0	0	0	1 (0.1)
Hepatic enzyme increased	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)
International normalised ratio abnormal	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)
Neutrophil count increased	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
Oxygen saturation decreased	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Platelet count increased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Prothrombin time prolonged	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Serum ferritin increased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Thyroxine increased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
White blood cell count decreased	1 (0.1)	0	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)
White blood cell count increased	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	8 (1.2)	2 (0.3)	0	0	1 (0.1)	11 (1.6)	7 (1.0)	2 (0.3)	0	0	0	9 (1.3)
Decreased appetite	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Dehydration	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Diabetes mellitus	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Diabetes mellitus inadequate control	0	1 (0.1)	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)
Hyperglycaemia	1 (0.1)	0	0	0	1 (0.1)	2 (0.3)	0	1 (0.1)	0	0	0	1 (0.1)
Hypertriglyceridaemia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hypokalaemia	2 (0.3)	0	0	0	0	2 (0.3)	2 (0.3)	0	0	0	0	2 (0.3)
Hyponatraemia	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
Hypophosphataemia	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Impaired fasting glucose	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Type 2 diabetes mellitus	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	7 (1.0)	0	0	0	0	7 (1.0)	8 (1.2)	0	0	0	0	8 (1.2)
Arthralgia	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Back pain	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Intervertebral disc degeneration	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Intervertebral disc protrusion	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Muscle spasms	0	0	0	0	0	0	2 (0.3)	0	0	0	0	2 (0.3)
Musculoskeletal stiffness	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Myalgia	4 (0.6)	0	0	0	0	4 (0.6)	2 (0.3)	0	0	0	0	2 (0.3)
Pain in extremity	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Spinal osteoarthritis	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Colon adenoma	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
NERVOUS SYSTEM DISORDERS	44 (6.5)	1 (0.1)	0	0	0	45 (6.7)	19 (2.8)	0	0	0	0	19 (2.8)
Anosmia	3 (0.4)	0	0	0	0	3 (0.4)	0	0	0	0	0	0
Dizziness	3 (0.4)	0	0	0	0	3 (0.4)	5 (0.7)	0	0	0	0	5 (0.7)
Dysgeusia	31 (4.6)	1 (0.1)	0	0	0	32 (4.8)	1 (0.1)	0	0	0	0	1 (0.1)
Facial paralysis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Headache	10 (1.5)	0	0	0	0	10 (1.5)	11 (1.6)	0	0	0	0	11 (1.6)
Hypersomnia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)
Migraine	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Restless legs syndrome	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Syncope	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
PSYCHIATRIC DISORDERS	3 (0.4)	0	0	0	0	3 (0.4)	4 (0.6)	0	0	0	0	4 (0.6)
Anxiety	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Confusional state	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Insomnia	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)
Stress	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Vaginal haemorrhage	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	12 (1.8)	1 (0.1)	0	0	0	13 (1.9)	11 (1.6)	10 (1.5)	1 (0.1)	3 (0.4)	0	25 (3.7)
Acute respiratory distress syndrome	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)
Acute respiratory failure	0	1 (0.1)	0	0	0	1 (0.1)	0	2 (0.3)	1 (0.1)	1 (0.1)	0	4 (0.6)
Asthma	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Cough	5 (0.7)	0	0	0	0	5 (0.7)	4 (0.6)	2 (0.3)	0	0	0	6 (0.9)
Dyspnoea	3 (0.4)	0	0	0	0	3 (0.4)	3 (0.4)	3 (0.4)	0	0	0	6 (0.9)
Hiccups	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hypoxia	0	0	0	0	0	0	3 (0.4)	1 (0.1)	0	1 (0.1)	0	5 (0.7)
Interstitial lung disease	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)
Nasal congestion	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
Oropharyngeal pain	3 (0.4)	0	0	0	0	3 (0.4)	0	0	0	0	0	0
Pneumonitis	0	0	0	0	0	0	0	2 (0.3)	0	0	0	2 (0.3)
Respiratory failure	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Rhinorrhoea	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (0.4)	2 (0.3)	0	0	0	5 (0.7)	6 (0.9)	1 (0.1)	0	0	0	7 (1.0)
Acne	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Alopecia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Erythema	0	0	0	0	0	0	4 (0.6)	0	0	0	0	4 (0.6)
Hyperhidrosis	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Hyperkeratosis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Pruritus	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Rash	2 (0.3)	0	0	0	0	2 (0.3)	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)
Rash maculo-papular	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Urticaria	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
SOCIAL CIRCUMSTANCES	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Disease risk factor	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
UNCODED TERM	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
INCREASED PROCALCITONIN VALUE - 0.28 NG/ML - MORE, THAN 3X UNL@@	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing n (%)	Total n (%)
VASCULAR DISORDERS	5 (0.7)	1 (0.1)	0	0	0	6 (0.9)	5 (0.7)	0	0	0	0	5 (0.7)
Hyperaemia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hypertension	5 (0.7)	1 (0.1)	0	0	0	6 (0.9)	1 (0.1)	0	0	0	0	1 (0.1)
Hypotension	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)
Orthostatic hypotension	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (16:07) Source Data: adae Table Generation: 30OCT2021 (19:14)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ./nda_unblinded/C4671005_45IA/adae_s062

Updated safety database (n=1881)

No major difference was noted regarding the most reported TEAEs remained similar between the updated (n=1881) and the initial (n=1349) safety analyses.

Table 49 - Updated safety database

Specific AEs indicating treatment differences

	PF-07321332 300 + Ritonavir 100 mg	Placebo
GI	58 (6.1%)	42 (4.5%) (diarrhea, vomiting)
Dysgeusia	54 (5.7%)	2 (0.2%)
Respiratory AEs	17 (1.8%)	33 (3.5%) (cough, dyspnea, hypoxia)
Hypertension	7 (0.7%)	1 (0.1)%
Pneumonia	2	12
COVID/COVID-19 pneumonia	7	30
COVID-19	3	12

- Treatment-related TEAEs

The most frequently reported treatment-related TEAEs in the PF-07321332/ritonavir group (≥1%) were Dysgeusia (3.7%), and Diarrhoea (1.9%). Of note, dysgeusia and diarrhoea were both reported with ritonavir and mentioned in section 4.8 of SmPC of ritonavir 100 mg at very common frequency. Both of these treatment-related TEAEs were reported with a higher incidence in the PF-07321332/ritonavir group compared with the placebo group (Dysgeusia: 3.7% in the PF-07321332/ritonavir group versus 0.1% in the placebo group, and Diarrhoea: 1.9% in the PF-07321332/ritonavir group versus 0.3% in the placebo group). Most of the treatment related TEAEs experienced by participants in both treatment groups were mild to moderate (Grade 1-2) in severity. One participant in the placebo treatment group had a potentially life-threatening (Grade 4) event (Blood glucose increased) that was considered related to treatment. No participants in either treatment group had an event of death related to an AE (Grade 5).

Table 50 - Summary of treatment-emergent adverse events by MedDRA system organ class, preferred term and maximum DAIDS grade (treatment related) – safety analysis set (protocol C4671005_45IA)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	46 (6.8)	3 (0.4)	0	0	0	49 (7.3)	25 (3.7)	3 (0.4)	1 (0.1)	0	0	29 (4.3)
CARDIAC DISORDERS	0	1 (0.1)	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Palpitations	0	1 (0.1)	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
EAR AND LABYRINTH DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Vertigo	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
GASTROINTESTINAL DISORDERS	26 (3.9)	0	0	0	0	26 (3.9)	12 (1.8)	1 (0.1)	0	0	0	13 (1.9)
Abdominal pain upper	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)
Colitis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Diarrhoea	13 (1.9)	0	0	0	0	13 (1.9)	2 (0.3)	0	0	0	0	2 (0.3)
Dry mouth	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Dyspepsia	5 (0.7)	0	0	0	0	5 (0.7)	2 (0.3)	0	0	0	0	2 (0.3)
Faeces soft	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Gastrooesophageal reflux disease	2 (0.3)	0	0	0	0	2 (0.3)	1 (0.1)	0	0	0	0	1 (0.1)
Nausea	6 (0.9)	0	0	0	0	6 (0.9)	6 (0.9)	1 (0.1)	0	0	0	7 (1.0)
Vomiting	5 (0.7)	0	0	0	0	5 (0.7)	1 (0.1)	0	0	0	0	1 (0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Chest discomfort	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Pyrexia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
INVESTIGATIONS	1 (0.1)	0	0	0	0	1 (0.1)	5 (0.7)	1 (0.1)	1 (0.1)	0	0	7 (1.0)
Activated partial thromboplastin time prolonged	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Alanine aminotransferase increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Blood glucose increased	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Blood thyroid stimulating hormone increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Fibrin D dimer increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Haptoglobin increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hepatic enzyme increased	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
METABOLISM AND NUTRITION DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Decreased appetite	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Myalgia	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
NERVOUS SYSTEM DISORDERS	26 (3.9)	1 (0.1)	0	0	0	27 (4.0)	3 (0.4)	0	0	0	0	3 (0.4)
Dizziness	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
Dysgeusia	24 (3.6)	1 (0.1)	0	0	0	25 (3.7)	1 (0.1)	0	0	0	0	1 (0.1)
Headache	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Hypersomnia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
PSYCHIATRIC DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Anxiety	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Confusional state	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
Dyspnoea	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hiccups	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)	3 (0.4)	1 (0.1)	0	0	0	4 (0.6)
Acne	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Alopecia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Erythema	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Rash	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)
Rash maculo-papular	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
VASCULAR DISORDERS	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Orthostatic hypotension	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (16:07) Source Data: adae Table Generation: 30OCT2021 (19:14)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ./nda unblinded/C4671005 45IA/adae s068

Adverse events leading to study discontinuation

- AEs leading to treatment discontinuation

The AEs leading to treatment discontinuation were more reported in placebo arm than PF-07321332/ritonavir arm, i.e. 4.3% and 2.4% respectively. The most frequently reported AEs leading to discontinuation with PF-07321332/ritonavir treatment were Nausea (0.7%) and Vomiting (0.6%), see table 51.

Table 51 - Summary of treatment-emergent adverse events leading to treatment discontinuation by MedDRA system organ class, preferred term, and maximum DAIDS grade (all causalities) – safety analysis set (protocol C5671005_45IA)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Participants with events	8 (1.2)	7 (1.0)	1 (0.1)	0	0	16 (2.4)	5 (0.7)	18 (2.7)	6 (0.9)	0	0	29 (4.3)
CARDIAC DISORDERS	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Palpitations	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
GASTROINTESTINAL DISORDERS	7 (1.0)	0	0	0	0	7 (1.0)	2 (0.3)	1 (0.1)	0	0	0	3 (0.4)
Abdominal pain lower	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Colitis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Diarrhoea	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Nausea	5 (0.7)	0	0	0	0	5 (0.7)	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)
Vomiting	4 (0.6)	0	0	0	0	4 (0.6)	0	0	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Chest discomfort	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
INFECTIONS AND INFESTATIONS	0	2 (0.3)	0	0	0	2 (0.3)	2 (0.3)	10 (1.5)	3 (0.4)	0	0	15 (2.2)
COVID-19	0	1 (0.1)	0	0	0	1 (0.1)	2 (0.3)	2 (0.3)	0	0	0	4 (0.6)
COVID-19 pneumonia	0	1 (0.1)	0	0	0	1 (0.1)	0	7 (1.0)	3 (0.4)	0	0	10 (1.5)
Pneumonia	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
INVESTIGATIONS	1 (0.1)	3 (0.4)	1 (0.1)	0	0	5 (0.7)	1 (0.1)	2 (0.3)	2 (0.3)	0	0	5 (0.7)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood glucose increased	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Creatinine renal clearance decreased	0	2 (0.3)	0	0	0	2 (0.3)	0	1 (0.1)	0	0	0	1 (0.1)
Differential white blood cell count abnormal	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Glomerular filtration rate abnormal	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Glomerular filtration rate decreased	0	0	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	2 (0.3)
Haemoglobin decreased	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Oxygen saturation decreased	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
White blood cell count decreased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Myalgia	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
NERVOUS SYSTEM DISORDERS	2 (0.3)	0	0	0	0	2 (0.3)	1 (0.1)	0	0	0	0	1 (0.1)
Dizziness	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Dysgeusia	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Restless legs syndrome	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
PSYCHIATRIC DISORDERS	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Insomnia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Vaginal haemorrhage	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	5 (0.7)	2 (0.3)	0	0	7 (1.0)
Acute respiratory failure	0	0	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	2 (0.3)
Cough	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Dyspnoea	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hypoxia	0	0	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	2 (0.3)
Interstitial lung disease	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Respiratory failure	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (0.1)	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)
Rash	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Rash maculo-papular	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (16:07) Source Data: adae Table Generation: 30OCT2021 (19:14)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ./nda_unblinded/C4671005_45IA/adae_s062d

Updated safety data (n=1881)

The updated safety data showed that the rate of discontinuation from study drug due to AE was slightly decreased, i.e. 2.1% (20/945) in PF-07321332/ritonavir arm and 4.1% (38/936) in placebo arm.

- AEs leading to study discontinuation

No participant in the PF-07321332/ritonavir group discontinued the study due to TEAEs (all causalities) compared with 10 participants (1.5%) in the placebo group.

Adverse event of special interest (AESI)

There were pre-specified AESIs in Study 1005 including hemodynamic events, inflammatory events, and thyroid-related events to be reviewed as part of routine safety data review procedures throughout the study and as part of signal detection processes. Analyses of AESI were not provided in the submitted data and will be provided in the final analysis to be provided at the time of MAA once all participants have completed their Day 34 visit.

All AESIs were expected to be reported as an AE or SAE.

Vital signs measurements did not suggest clinically meaningful changes relative to hemodynamic events across treatment groups and cardiac disorders were reported in 2 (0.3%) subject in PF-07321332/ritonavir group (2 cases of palpitations) and 4 (0.6%) subjects in placebo group (2 cases of palpitations, one pericardial effusion and one sinus tachycardia)

The increase of fibrinogen relative to inflammatory events was more reported in placebo arm than PF-07321332/ritonavir, i.e. 21.8% and 14.3% respectively.

No thyroid-related event was reported as AE based on the submitted summary of TEAEs table for study 1005 and the occurrence of TSH and T4 (free) elevations was comparable in the 2 treatment groups.

Serious adverse events (SAE)

All causality SAEs occurred in 13 (1.9%) subjects in the PF-07321332/ritonavir treatment group according to the Clinical Overview while there were 14 subjects having a SAE listed in the table of content of C4671005 Interim Analysis Narratives. SAEs were more reported in placebo arm, i.e. 46 (6.8%) subjects.

Table 52 - Summary of treatment-emergent serious adverse events by MedDRA system organ class, preferred term, and maximum DAIDS grade (all causalities) – safety analysis set (protocol C4671005_45IA)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Participants with events	4 (0.6)	6 (0.9)	3 (0.4)	0	0	13 (1.9)	5 (0.7)	24 (3.5)	7 (1.0)	10 (1.5)	0	46 (6.8)
CARDIAC DISORDERS	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Palpitations	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
GASTROINTESTINAL DISORDERS	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Rectal haemorrhage	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Chest discomfort	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
INFECTIONS AND INFESTATIONS	3 (0.4)	4 (0.6)	1 (0.1)	0	0	8 (1.2)	4 (0.6)	18 (2.7)	6 (0.9)	7 (1.0)	0	35 (5.2)
Abscess	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Atypical pneumonia	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
COVID-19	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)	1 (0.1)	3 (0.4)	1 (0.1)	2 (0.3)	0	7 (1.0)
COVID-19 pneumonia	1 (0.1)	3 (0.4)	0	0	0	4 (0.6)	2 (0.3)	10 (1.5)	4 (0.6)	5 (0.7)	0	21 (3.1)
Pneumonia	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	5 (0.7)	1 (0.1)	0	0	7 (1.0)
Sepsis	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Craniocerebral injury	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Eye injury	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Hand fracture	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Road traffic accident	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Wrist fracture	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
INVESTIGATIONS	0	1 (0.1)	2 (0.3)	0	0	3 (0.4)	1 (0.1)	1 (0.1)	1 (0.1)	0	0	3 (0.4)
Alanine aminotransferase increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Creatinine renal clearance decreased	0	0	1 (0.1)	0	0	1 (0.1)	0	1 (0.1)	1 (0.1)	0	0	2 (0.3)
Haemoglobin decreased	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Oxygen saturation decreased	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Colon adenoma	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
NERVOUS SYSTEM DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Facial paralysis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	8 (1.2)	1 (0.1)	3 (0.4)	0	12 (1.8)
Acute respiratory distress syndrome	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)
Acute respiratory failure	0	0	0	0	0	0	0	2 (0.3)	1 (0.1)	1 (0.1)	0	4 (0.6)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Dyspnoea	1 (0.1)	0	0	0	0	1 (0.1)	0	2 (0.3)	0	0	0	2 (0.3)
Hypoxia	0	0	0	0	0	0	1 (0.1)	1 (0.1)	0	1 (0.1)	0	3 (0.4)
Interstitial lung disease	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Pneumonitis	0	0	0	0	0	0	0	2 (0.3)	0	0	0	2 (0.3)
Respiratory failure	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (16:07) Source Data: adae Table Generation: 30OCT2021 (19:14)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ./nda unblinded/C4671005 45IA/adae s062s

- Deaths

There were no deaths in PF-07321332 + ritonavir arm according to the provided data on Study 1005. A total of 10 deaths were reported in the placebo arm, all related to COVID-19 and respiratory event (hypoxia, acute respiratory distress/failure).

- Other SAEs

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.).

Of the SAEs reported with PF-07321332/ritonavir, one case was considered by the investigator as reasonably possible to be related to the treatment In the opinion of the investigator of this case, 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.

Overall the reported SAEs with PF-07321332/ritonavir treatment were mostly related to COVID-19. Among the non-related COVID-19 SAEs reported, one case was considered as treatment related. The SAEs occurring with PF-07321332/ritonavir treatment in study 1005 were manageable. The majority of the reported SAEs with PF-07321332/ritonavir were considered as resolved/recovered; 2 subjects withdrew from the study and 2 cases were ongoing at the time of the report. The safety profile currently based on the 1349 participants from the safety analysis set from the interim analysis, will be further substantiated on the basis of the data from the approximately 1000 additional patients having achieved primary analysis. This will be analysed at the time of the MAA.

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 hematological 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), neutrophils (>1.2 x ULN), glucose (>1.5 x ULN), thyrotropin (>1.2 x ULN), creatine kinase (>2 x ULN), and bicarbonate (<0.9 x LLN).

Elevations of hepatic transaminases >3xULN were reported at similar rates in both PF-07321332/ritonavir and placebo arms, i.e ASAT at 1.4% and 1.6% respectively; ALAT at 3.3% and 4.3% respectively.

Hemodynamic and inflammatory effects were considered as AESIs. Changes in haemoglobin and platelets were similar between the two arms and reported at low rate. No significative difference was reported in the increase of aPTT and PT between PF-07321332/ritonavir and placebo arms, nevertheless D-dimer increase (>1.5 x ULN) was more reported in placebo arm compared to PF-07321332/ritonavir, i.e. 19.7% and 10.8% respectively. The increase of fibrinogen (> 1.25 x ULN) was more reported in placebo arm than PF-07321332/ritonavir, i.e. 21.8% and 14.3% respectively.

Thyroid-related events were also including among AESIs; TSH and T4 increases (> 1.2 x ULN) were comparable in both treatment groups, i.e. TSH > 1.2 x ULN were reported in 7.1% in PF-07321332/ritonavir arm and 8.1% in placebo arm, and T4 (free) > 1.2 x ULN were reported in 1.1% in PF-07321332/ritonavir arm and 0.8% in placebo arm.

Table 53 - Incidence of laboratory test abnormalities (without regard to baseline abnormalities) – safety analysis set (protocol C467100_45IA)

Laboratory Abnormalities: Number of Participants Evaluable for Laboratory Abnormalities: Number (%) of Participants with Laboratory Abnormalities:			PF-07321332 300 mg + Ritonavir 100 mg 635 451 (71.0%)		Placebo 634 475 (74.9%)	
Group	Parameter (Units)	Primary Criteria	N	n (%)	N	n (%)
HEMATOLOGY	Hemoglobin (g/dL)	<0.8x LLN	537	1 (0.2)	553	4 (0.7)
	Erythrocytes (10^12/L)	<0.8x LLN	537	6 (1.1)	553	8 (1.4)
	Platelets (10^9/L)	<0.5x LLN	530	0	547	3 (0.5)
		>1.75x ULN	530	1 (0.2)	547	4 (0.7)
	Leukocytes (10^9/L)	<0.6x LLN	537	1 (0.2)	553	6 (1.1)
		>1.5x ULN	537	9 (1.7)	553	5 (0.9)
	Lymphocytes (10^9/L)	<0.8x LLN	534	8 (1.5)	546	22 (4.0)
		>1.2x ULN	534	6 (1.1)	546	4 (0.7)
	Neutrophils (10^9/L)	<0.8x LLN	532	14 (2.6)	545	24 (4.4)
		>1.2x ULN	532	30 (5.6)	545	18 (3.3)
	Eosinophils (10^9/L)	>1.2x ULN	534	5 (0.9)	546	5 (0.9)
	Monocytes (10^9/L)	>1.2x ULN	534	4 (0.7)	546	1 (0.2)
	Activated Partial Thromboplastin Time (sec)	>1.1x ULN	580	109 (18.8)	576	95 (16.5)
	Prothrombin Time (sec)	>1.1x ULN	582	28 (4.8)	575	25 (4.3)
CLINICAL CHEMISTRY	Bilirubin (mg/dL)	>1.5x ULN	633	4 (0.6)	630	2 (0.3)
	Aspartate Aminotransferase (U/L)	>3.0x ULN	632	9 (1.4)	630	10 (1.6)
	Alanine Aminotransferase (U/L)	>3.0x ULN	632	21 (3.3)	630	27 (4.3)
	Lactate Dehydrogenase (U/L)	>3.0x ULN	631	1 (0.2)	631	2 (0.3)
	Alkaline Phosphatase (U/L)	>3.0x ULN	632	0	632	1 (0.2)
	Protein (g/dL)	>1.2x ULN	632	1 (0.2)	630	0
	Albumin (g/dL)	<0.8x LLN	635	0	634	1 (0.2)
	Urea Nitrogen (mg/dL)	>1.3x ULN	634	21 (3.3)	633	24 (3.8)
	Creatinine (mg/dL)	>1.3x ULN	634	1 (0.2)	633	3 (0.5)
	Sodium (mEq/L)	<0.95x LLN	634	1 (0.2)	633	2 (0.3)
	Potassium (mEq/L)	<0.9x LLN	630	8 (1.3)	633	8 (1.3)
		>1.1x ULN	630	11 (1.7)	633	14 (2.2)
	Chloride (mEq/L)	<0.9x LLN	634	1 (0.2)	632	1 (0.2)
	Calcium (mg/dL)	<0.9x LLN	630	6 (1.0)	632	6 (0.9)
	Bicarbonate (mEq/L)	<0.9x LLN	632	51 (8.1)	630	52 (8.3)

Laboratory Abnormalities: Number of Participants Evaluable for Laboratory Abnormalities: Number (%) of Participants with Laboratory Abnormalities:			PF-07321332 300 mg + Ritonavir 100 mg 635 451 (71.0%)		Placebo 634 475 (74.9%)	
Group	Parameter (Units)	Primary Criteria	N	n (%)	N	n (%)
	Thyroxine, Free (ng/dL)	<0.8x LLN	630	7 (1.1)	625	5 (0.8)
		>1.2x ULN	630	3 (0.5)	625	7 (1.1)
	Thyrotropin (mIU/L)	<0.8x LLN	632	9 (1.4)	628	11 (1.8)
		>1.2x ULN	632	45 (7.1)	628	56 (8.9)
	Glucose (mg/dL)	<0.6x LLN	631	2 (0.3)	630	0
		>1.5x ULN	631	46 (7.3)	630	42 (6.7)
	Creatine Kinase (U/L)	>2.0x ULN	633	36 (5.7)	630	29 (4.6)
	Fibrinogen (mg/dL)	<0.75x Baseline	623	188 (30.2)	623	184 (29.5)
		>1.25x Baseline	623	89 (14.3)	623	136 (21.8)
	D-Dimer (ng/mL)	>1.5x ULN	622	67 (10.8)	620	122 (19.7)

NOTE: N = total number of participants with at least one observation of the given laboratory test while on study treatment or during lag time.
n = number of participants with a laboratory abnormality meeting specified criteria while on study treatment or during lag time.
Percentages are displayed for the laboratory tests having a category with ≥ 1 evaluable participants.
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2021 (16:07) Source Data: adlb Table Generation: 30OCT2021 (19:17)
(Data cutoff date : 26OCT2021 Database snapshot date : 29OCT2021) Output File: ./nda_unblinded/C4671005_45IA/adlb_s301

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 (Study 1005).

- 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 (Study 1005 Table 14.3.5.3).
- The incidence of participants with diastolic blood >90 mmHg or systolic blood pressure >140 mmHg was comparable across treatment groups.

Table 54 - Categorization of vital signs data – safety analysis set (protocol C4671005_45IA)

		PF-07321332 300 mg + Ritonavir 100 mg		Placebo	
Parameter (units)	Criteria	N	n (%)	N	n (%)
Diastolic Blood Pressure (mmHg)	Value > 90 mmHg	656	69 (10.5)	657	79 (12.0)
Systolic Blood Pressure (mmHg)	Value > 140 mmHg	656	68 (10.4)	657	88 (13.4)

ECGs

No thorough QT study was performed. ECG data were collected in Study 1005 and to be assessed by the E-DMC for the sentinel cohort consisting of the first 60 participants in study. On 12 Aug 2021, the E-DMC reviewed the unblinded safety data for the sentinel cohort of 68 participants which included ECG data for 59 participants. There was no clinically relevant difference between active and placebo groups in changes of QTcF according to the company but the study Blinded Sentinel Safety Summary and Sentinel Cohort ECG Tables were not submitted.

In addition, 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.

Table 55 - Model-derived ΔΔQTcF prediction for concentrations of interest

	Concentration (ng/mL)	Mean ΔΔQTcF (90% CI) (ms)
Therapeutic exposure[a]	4140	-0.37 (-1.84, 1.1)
2x Therapeutic exposure[a]	8280	-0.15 (-1.37, 1.07)
2250 mg mean C_{max} in PART-5: Study 1001	15944	0.27 (-1.42, 1.96)

a. Projected steady-state C_{max} at Phase 2/3 dosing regimen ie, PF-07321332/ritonavir 300/100 q12h

Pregnancy

At the time of the data cut-off in Study 1005 (26 Oct 2021), there was one (1) reported pregnancy in the safety database. This participant was in the placebo group and will continue to be followed for pregnancy outcomes.

Hepatotoxicity

Detailed narratives on all participants included in the safety population from the 45% interim analysis (database cut-off 26 October 2021) with hepatotoxicity in study 1005 were provided upon FDA request on 10 November 2021. Indeed a risk of hepatotoxicity is associated with ritonavir and is 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 cases occurred at similar rate in both arms in Study 1005 and were reported in 7 (1.04%) subjects in PF-07321332/ritonavir arm and 11 (1.62%) subjects in placebo arm. The majority of hepatotoxicity cases reported in the safety population were hepatic transaminase elevation > 5xULN, which might be related to the disease under study.

Post marketing safety data

Not applicable.

Supportive safety data from Phase 1 studies

- Study 1001
    - Part 1 – SAD (n=13)

The median duration of treatment was 1 day for all 9 treatment groups in each period. All participants received treatment for 1 day in PART-1.

There were no TEAEs reported in the PF-07321332 150 mg (suspension, fasted) group, PF-07321332 250 mg (suspension)/ritonavir 100 mg (fed) group and the PF-07321332 750 mg (suspension)/ritonavir 100 mg (fasted) group. 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 in PART-1.

- Part 2 – MAD (n=29)

The median duration of treatment was 10 days for all 6 treatment groups. Almost all participants received treatment for 10 days in PART-2 except 1 participant in the placebo/ritonavir 100 mg BID (fasted) group received study treatment for 7 days. The numbers of all-causality TEAEs and treatment-related TEAEs were similar between 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)

The duration of treatment was 1 day for all participants in each period.

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).

Table 56 - Treatment-emergent adverse event by system organ class and preferred term (all causalities) – part-3: rBA/FE (safety analysis set) (protocol C4671001)

Number of Participants Evaluable for AEs Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	PF-07321332 250 mg (Suspension), Fasted (N=12) n (%)	PF-07321332 250 mg (Tablet), Fasted (N=12) n (%)	PF-07321332 250 mg (Tablet), Fed (N=12) n (%)
With Any Adverse Event	3 (25.0)	3 (25.0)	1 (8.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (16.7)	2 (16.7)	1 (8.3)
Chest discomfort	1 (8.3)	0	0
Vessel puncture site haematoma	0	2 (16.7)	1 (8.3)
Vessel puncture site haemorrhage	1 (8.3)	0	0
NERVOUS SYSTEM DISORDERS	1 (8.3)	1 (8.3)	0
Dizziness	1 (8.3)	0	0
Headache	1 (8.3)	0	0
Hypertonia	0	1 (8.3)	0

Participants were only counted once per treatment per event.
Included all data collected since the first dose of study drug.
MedDRA v24.0 coding dictionary applied.

Table 57 - Treatment-emergent adverse event by system organ class and preferred term (treatment related) – part-3: rBA/FE (safety analysis set) (protocol C4671001)

Number of Participants Evaluable for AEs Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	PF-07321332 250 mg (Suspension), Fasted (N=12) n (%)	PF-07321332 250 mg (Tablet), Fasted (N=12) n (%)	PF-07321332 250 mg (Tablet), Fed (N=12) n (%)
With Any Adverse Event	2 (16.7)	1 (8.3)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (8.3)	0	0
Chest discomfort	1 (8.3)	0	0
NERVOUS SYSTEM DISORDERS	1 (8.3)	1 (8.3)	0
Dizziness	1 (8.3)	0	0
Headache	1 (8.3)	0	0
Hypertonia	0	1 (8.3)	0

Participants were only counted once per treatment per event.
Included all data collected since the first dose of study drug.
MedDRA v24.0 coding dictionary applied.

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.

No participant had an SAE, severe AE, discontinuation from study due to AEs, or dose reduced or temporary discontinuation due to AEs in PART-3.

- Part 4 – M&E (n=6)

The duration of treatment was 1 day for all participants. Only 1 all-causality TEAE (Nasopharyngitis) was reported in PART-4. This AE was not treatment related.

- Part 5 – SE (n=10)

The duration of treatment was 1 day for all participants in each period. 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).

Table 58 - Treatment-emergent adverse event by system organ class and preferred term (all causalities) – part-5: SE (safety analysis set) (protocol C4671001)

Number of Participants Evaluable for AEs	Placebo (Suspension)/ ritonavir 100 mg (N=10)	PF-07321332 2250 mg (Suspension)/ ritonavir 100 mg (N=10)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**
With Any Adverse Event	3 (30.0)	3 (30.0)
EYE DISORDERS	0	1 (10.0)
Photopsia	0	1 (10.0)
GASTROINTESTINAL DISORDERS	2 (20.0)	2 (20.0)
Abdominal pain	1 (10.0)	1 (10.0)
Change of bowel habit	1 (10.0)	0
Diarrhoea	0	1 (10.0)
Nausea	0	1 (10.0)
Vomiting	1 (10.0)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (10.0)	0
Application site erythema	1 (10.0)	0
Application site pruritus	1 (10.0)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (10.0)	0
Back pain	1 (10.0)	0
Pain in extremity	1 (10.0)	0
NERVOUS SYSTEM DISORDERS	1 (10.0)	0
Headache	1 (10.0)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (10.0)	0
Dermatitis contact	1 (10.0)	0

PF-07321332 2250 mg divided into three doses of 750 mg administrated at 0h, 2h and 4h; Ritonavir dosed at -12h, 0h and 12h post-dose.
Participants received first split dose of PF-07321332/placebo oral suspension at least 2h after the morning breakfast.
Participants were only counted once per treatment per event.
Included all data collected since the first dose of study drug.

Table 59 - Treatment-emergent adverse event by system organ class and preferred term (treatment related) – part-5: SE (safety analysis set) (protocol C4671001)

Number of Participants Evaluable for AEs	Placebo (Suspension)/ ritonavir 100 mg (N=10)	PF-07321332 2250 mg (Suspension)/ ritonavir 100 mg (N=10)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)
With Any Adverse Event	1 (10.0)	1 (10.0)
GASTROINTESTINAL DISORDERS	1 (10.0)	1 (10.0)
Nausea	0	1 (10.0)
Vomiting	1 (10.0)	0

PF-07321332 2250 mg divided into three doses of 750 mg administrated at 0h, 2h and 4h; Ritonavir dosed at -12h, 0h and 12h post-dose.
Participants received first split dose of PF-07321332/placebo oral suspension at least 2h after the morning breakfast.
Participants were only counted once per treatment per event.
Included all data collected since the first dose of study drug.

No participant had an SAE, severe AE, discontinuation from study due to AEs, or dose reduced or temporary discontinuation due to AEs in PART-5.

- Study 1011 (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. Treatment related AEs were reported by 2 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. Headache was the most frequently reported AE: 2 participants with normal renal function and 1 participant in the moderate renal impairment group reported headache. In addition, Dysgeusia was reported in 2 participants in the severe renal impairment group. All-causality AEs of other SOCs were reported in 1 participant each. All the all-causality AEs reported in participants with normal renal function, and mild or moderate renal impairment were mild. Most of the all-causality AEs (17 out of 22) were reported by participants in the severe renal impairment group.

There were 4 treatment related AEs under the SOCs of Gastrointestinal disorders (2 participants had Dry mouth) and Nervous system disorders (2 participants had Dysgeusia). All 4 AEs occurred in the severe renal impairment group and were mild in severity

- 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 (Table 14.3.1.2.3). One participant had a treatment related TEAE of Dysgeusia.

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). Eight TEAEs reported by 6 participants were considered treatment related. The most frequently reported treatment related TEAEs by PT were Transaminases increased (5 participants, 41.7%).

No participants had SAE, severe AE, or dose reduced or temporary discontinuation due to

AEs in Period 1 or Period 2. In Period 2 there was 1 participant discontinued from study due to a moderate AE of Inappropriate antidiuretic hormone secretion (Hyponatremia/SIADH), which was considered treatment related.

- Study 1015

Twelve participants received at least 1 study treatment and were thus included in the safety analysis. Except for 1 participant, who withdrew informed consent in Period 1, the remaining 11 participants completed the assigned treatment in both periods (period 1: PF-07321332/ritonavir 300/100 mg; period 2: Itraconazole 200 mg QD + PF-07321332/ritonavir 300/100 mg BID).

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.

Most of the reported AEs were mild in severity. Among the all-causality AEs, 4 participants reported moderate AEs: 2 participants reported 4 moderate AEs in Period 1 and 2 participants reported 5 moderate AEs in Period 2:

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).

All AEs, with concomitant medications given when necessary, were resolved before the end of study, except 1 event of Constipation, which was reported as resolving at the time of the last report.

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. No severe AEs or SAEs were reported.

Overall no notable safety signal was detected with PF- 07321332/ritonavir in Phase 1 studies. Cases of transaminases increases and hyponatremia/SIADH were reported with PF- 07321332/ritonavir + Carbamazepine in Study 1014; both of these reported TEAEs are mentioned in the SmPC of carbamazepine. 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 dyspnea that occurred with Paxlovid in Study 1005, the risk of cardiovascular events should be further discussed by the company during the MAA.

Conditions of use

Three adverse reactions (dysgeusia, diarrhoea and vomiting) have been included in section 6 in Conditions of Use based on Phase 2/3 study 1005 and considered related to Paxlovid according to the presented interim analysis. The proposed list of adverse reactions is agreed based on the submitted data.

However, in section 4.8 of the SmPC of Norvir (ritonavir) a whole range of additional adverse reactions are listed. Taking into account the differences in posology and duration of ritonavir treatment between Norvir and Paxlovid, it is considered unlikely at this stage to identify which of these adverse reactions are related to the dosage of 100 mg ritonavir twice daily. As a conservative measure the CHMP decided to include the adverse reactions from the SmPC of Norvir in the CoU in addition to the adverse reactions reported in the clinical study (467-1005). Nevertheless it is clearly stated in the CoU that the type, severity and frequency of adverse reactions corresponding to higher dose and use for longer duration in the context of chronic HIV infection might not apply to the use of ritonavir during 5 days in Paxlovid.

Discussion on Safety

Demonstrated risks

The safety data was based on the 45% interim analysis of the pivotal Phase II/III Study 1005 (treatment in patients COVID-19 positive at High Risk) which includes 1349 participants (safety analysis set) enrolled through 29 Sep 2021 with the database cut-off on 26 Oct 2021. A total of 672 subjects were enrolled in the PF-07321332/ritonavir arm and 677 subjects were enrolled in the placebo arm. The administered treatment was intended at the posology of PF- 07321332 300mg and ritonavir 100mg Q12h for 5 days, however the extent of exposure was not provided in the submitted data. The safety follow-up period was planned through Day 34. A presentation on updated safety data on a larger safety analysis set (N=1881) was provided during this procedure.

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 with manageable toxicities. From a non-clinical point of view, there were no adverse findings in toxicity studies in rats and cynomolgus monkeys. The incidence of TEAEs was slightly lower in PF-07321332/ritonavir compared to placebo, i.e. 19.8% and 22.3% respectively, and the majority of the adverse events occurring in the study may be confounded with COVID-19 symptoms. The majority of the reported TEAEs with PF-07321332/ritonavir were low grade severity; Grade 3-4 TEAEs were reported in 3.1% of subjects in the PF-07321332/ritonavir arm and 7.1% in subjects in placebo arm. The most reported TEAEs in the PF-07321332/ritonavir group were Dysgeusia (4.8%), Diarrhoea (3.9%), Nausea (1.9%), Headache (1.5%), Vomiting (1.3%), and Pyrexia (1.2%). It is highlighted that these most reported TEAEs were both reported with ritonavir and mentioned in section 4.8 of SmPC of ritonavir 100 mg at very common frequency except for pyrexia (common). The most frequently reported treatment-related TEAEs in the PF-07321332/ritonavir group (≥1%) were Dysgeusia (3.7%), and Diarrhoea (1.9%). Among the cases

of dysgeusia reported with PF-07321332/ritonavir, one led to treatment discontinuation. Most of the treatment-related TEAEs experienced by participants in both treatment groups were mild to moderate (Grade 1-2) in severity.

Hypertension occurred at a low frequency overall (0.9% and 0.1%, in the PF-07321332/ritonavir and placebo group, respectively, but was more frequent in the PF-07321332/ritonavir group. A total of 7 AEs of Hypertension were reported; 6 participants in the PF-07321332/ritonavir group and 1 participant in the placebo group. One participant in the PF-07321332/ritonavir group had an event of severe (Grade 3) hypertension which was not resolved. The number of cases were limited, and causality remains unclear. Ongoing studies are expected to provide more data regarding this issue. Further details should be provided during the MAA such as whether the cases occurred in patients who already had hypertension at baseline, and how often blood pressure was measured.

The AEs leading to treatment discontinuation were more reported in placebo arm than PF-07321332/ritonavir arm, i.e. 4.3% and 2.4% respectively. The most frequently reported AEs leading to discontinuation with PF-07321332/ritonavir treatment were Nausea (0.7%) and Vomiting (0.6%). No participant in the PF-07321332/ritonavir group discontinued the study due to TEAEs (all causalities) compared with 10 participants (1.5%) in the placebo group.

The SAEs were less reported in PF-07321332/ritonavir than placebo and were mostly related to COVID-19. No death occurred in the PF-07321332/ritonavir group while a total of 10 deaths were reported in the placebo arm, all related to COVID-19. Of the SAEs reported with PF-07321332/ritonavir, one case of Chest discomfort, dyspnoea and palpitations was considered by the investigator as reasonably possible to be related to the treatment (ritonavir), the treatment was permanently discontinued on Day 2 and the events were reported as resolved on Day 5.

The overall incidence of laboratory test abnormalities occurring within 34 days of first dose was comparable between both treatment groups. No major hematological and clinical chemistry abnormalities were detected in both PF-07321332/ritonavir and placebo arms.

No in-depth QT study was performed. ECG data were collected in Study 1005 and no clinically relevant difference between active and placebo groups in changes of QTcF was identified by the Applicant according to the Clinical Overview, however the C4671005 Blinded Sentinel Safety Summary and C4671005 Sentinel Cohort ECG Tables were missing. 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.

Due to the risk of hepatotoxicity associated with ritonavir, the company provided detailed narratives on all participants with hepatotoxicity, i.e. Hepatic transaminase elevations exceeding five times the upper limit or normal, clinical hepatitis, and jaundice. Hepatotoxicity cases were reported at similar rate in PF-07321332/ritonavir arm and in placebo arm, i.e. 1.04% and 1.62% respectively. The majority of hepatotoxicity cases that occurred in the safety population were hepatic transaminase elevation > 5xULN. Among the 7 cases of hepatotoxicity reported in the PF-07321332/ritonavir arm, 3 of them had elevations of ALT and/or AST at baseline and there was no hepatotoxicity case considered as related to study intervention by the investigator.

In light of the nonclinical findings, use of Paxlovid is not recommended during pregnancy and in women of childbearing potential not using contraception. This is reflected in section 5.5 of the Conditions for Use.

Uncertainty about risks

Ritonavir is principally metabolized and eliminated by the liver and the primary route of elimination of PF-07321332 when administered with ritonavir was renal excretion of intact drug. 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 1005. There remains uncertainties on the impact of hepatic impairment and severe renal impairment on the safety profile of PF-07321332/ritonavir combination.

Even though Paxlovid is only administered for 5 days, a cardiovascular risk especially in patients with cardiovascular co-morbidities based on the ritonavir component cannot be completely ruled out, especially since only a limited number patients with CVD were included in the Paxlovid group. Therefore, the company will have to discuss at the time of the MAA whether the risk of cardiovascular events should be included as an important potential risk in the RMP.

Some data were missing from the submission and need to be addressed in the MAA, i.e. study drug exposure (duration of exposure, dose intensity, relative dose intensity), AESI analyses, Sentinel Cohort ECG data.

Two still ongoing clinical studies albeit performed in other patients' populations (patients at standard risk of progressing to severe COVID-19 and in Post exposure population) are still ongoing that will provide additional information regarding the safety profile and possible rare adverse reactions.

The Committee considered that this medicine, once it is authorised for use, should be subject to additional monitoring. This enables to stimulate the ADR reporting in order for new safety information to be identified quickly. It is expected that Healthcare Professionals report any suspected adverse reactions

Overall, the safety data submitted are considered sufficient for supporting the use of Paxlovid in an emergency setting.

3. Benefit-risk balance

This procedure, triggered under Article 5(3) of Regulation (EC) No 726/2004, intends to provide a harmonised scientific opinion at EU level on currently available information on Paxlovid and on potential conditions of use with a view to supporting national decisions before a formal marketing authorisation based on the available quality, preclinical and clinical data on the potential use of Paxlovid for the treatment of confirmed COVID-19 in adult patients. This is particularly relevant in the clinical setting in view of the current pandemic situation and the public health interest.

Benefit

The clinical data supporting the use of Paxlovid for treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19 is based on the results of the phase 2/3 study randomized, double blind placebo controlled study (C467- 1005 or EPIC-HR study) with a requiring primary endpoint, difference in percentage of patients with hospitalization for COVID-19 or death for any cause through day 28.

The pre specified interim analysis on 45% of enrolled patients showed an absolute difference in percentage of patients with hospitalization for COVID-19 or death for any cause through day 28 with PF-07321332/ritonavir in comparison with placebo treatment of6.317% (95% CI: -9.041% to -3.593%; p<0.0001) in the primary analysis (mITT). The results in the clinically relevant population, of value for the generalizability to clinical practice (i.e patients who start treatment within 5 days of onset of symptoms) represented by the mITT1 population of analysis were consistent, both the mITT and

mITT are presented in the CoU. On this basis the DSMB recommended to stop the study. The data are considered to support the indication for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

Of note, patients receiving oxygen for other diseases than COVID-19 should not be prevented from being treated with Paxlovid.

It has to be underlined that preliminary presentation of the results of the final analysis were made available at latest stage of the Art5(3) procedure in parallel to the public communication of the company. According to this preliminary presentation the effect size in both the interim and final analyses seem consistent. However, given the high level presentation, no conclusion could be drawn on this final analysis for the CoU, only the results of the interim data are therefore reported in the CoU. The applicant should provide an adequate report of the final analysis at the time of the MAA.

However, some uncertainties regarding the assessment of the data remain and will be further addressed during the MAA.

As regards its pharmacodynamic properties, Paxlovid seems to have a limited barrier to resistance, observed at 10 passages but only based on *in vitro* resistance selection study with murine hepatitis virus (MHV)-3CL protease and are reported in the CoU (requiring caution in interpretation). The resistance pattern (including signature mutations) of SARS-CoV-2 under treatment with Paxlovid remains to be determined. Therefore, *in vitro* data on antiviral resistance to PF-07321332 with SARS-CoV-2 need to be provided at the time of the MAA and will notably enable to substantiate the resistance pattern and the genetic barrier.

Adherence to the treatment schedule is critical to reduce the risk of resistance development. PF-07321332 must be coadministered with ritonavir. Failure to correctly coadministered PF-07321332 with ritonavir will result in plasma levels of PF-07321332 that will be insufficient to achieve the desired therapeutic effect. The recommended dosage is 300 mg PF-07321332 (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally every 12 hours for 5 days. Paxlovid should be administered as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset.

It is noteworthy, that more than half of the enrolled population was seropositive for SARS-CoV-2 (56%) although SARS-COV-2 vaccination and prior episode of SARS-CoV-2 infection were part of the exclusion criteria and scarce use of mAb is reported (only one patient in Paxlovid arm). This will be further scrutinized at the time of the MAA (notably with discriminant IgG/IgM serology to be provided), given the potential impact for generalizability to vaccinated subjects.

As regards the relevant subgroup of patients at high risk, obese patients represented a limited proportion of patients (app 37%), the same applies for patients >65 y/o (11.4%), patients >75 y/o age (app 3%) with a number of patients >80 y/o, being likely scarce and finally for diabetic patients (app 13%). As a matter of fact, among comorbidities cigarette smokers (app 37%) and hypertension (app 30%) were mostly reported.

The complex interaction profile driven by ritonavir is expected to be a notable limiting factor of its use in the target population (likely requiring co-medications, notably for old patients).

Due to the lack of a relevant PK population model integrating PK data from patients, a contra-indication for patient with severe renal impairment and hepatic impairment has been added to the Conditions of Use.

Moreover, based on the available non clinical data, the use in pregnant women is not recommended as well as in WOCBP not using contraception. Moreover, due to the ritonavir driven ddI combined

contraception, use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Therefore, as stated in the CoU, patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment with Paxlovid, and until one menstrual cycle after stopping Paxlovid.

In vitro Data on VOC were provided, with no significant impact on antiviral activity observed against SARS-CoV-2 isolates belonging to the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) Lambda (C.37) variants. This is reflected in the CoU.

However, recently, sublineages of the Delta (B.1.617.2) variant carrying non-silent mutations in different areas of the genome, have emerged. Clinical data have shown that the 5/6 patients with an event in the treated group were all infected with the Delta (21J) subvariant which harbours mutations in the ORF1a that encodes for nsp5 (the 3CL-protease) in contrast to the 21A subvariant. Albeit patients enrolled in the clinical study were almost exclusively infected by the Delta variant (98%) with the vast majority with the sublineage 21J (73%) the applicant will have to provide at the time of MAA adequate *in vitro* data to further investigate this issue, since the clinical data may point to a potential loss of efficacy in VOCs harbouring mutations in ORF1a., In vitro study in a substantial number of representative sequences of the Delta variant and its sublineages (based on GISAID) will have to be provided at the time of the MAA.

In vitro experiment on Mu variant is ongoing with results to be provided at the time of the MAA.

As a critical caveat given the highly increasing circulation of Omicron VOC, the applicant could not provide *in vitro* data for the EU harmonized recommendation for the Article 5(3) (as reflected in the CoU). This will have to be provided at the time of the MAA.

Safety

As regards the security profile, no overlapping or additive toxicities between PF-07321332 and ritonavir are expected since no target organs have been identified after PF-07321332 administration rats and monkeys up to 1 month duration.

Based on the currently limited safety data base (678 patients treated at the recommended dose), the common adverse advents are dysgueusia (being a known AE of ritonavir, with unknown contribution of PF-07321332) diarrhea and vomiting.

The frequency of some adverse events are of higher in the placebo arm, likely reflecting the limited impact on disease progression in this comparator arm.

Overall, based on the provided safety data, the safety profile of PF-07321332/ritonavir combination appears comparable to placebo and manageable with no major concern identified. However there remains uncertainties on the impact of hepatic impairment and severe renal impairment on the safety profile of PF-07321332/ritonavir combination. Additional safety data are expected in the final analysis (from app 1000 additional patients) to be provided at the time of the MAA. This will further substantiate the safety profile of Paxlovid.

Overall conclusion

Considering the data provided by the company on quality aspects, preclinical aspects and the provided clinical dataset from the interim analysis of the phase 2/3 study randomized, double blind placebo controlled study (C467- 1005 or EPIC-HR study), Paxlovid could provide clinical benefit 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 in the context of this procedure and the COVID-19 pandemic, when used in accordance with the conditions of use.

In view of safety reporting for product distribution in the EU supported by CHMP Opinion under Art 5(3) of Reg (EC) No 726/2004, Member States and the company should submit to EudraVigilance Post-Authorisation Module (EVPM) any individual case safety reports (serious non-EEA; serious and non-serious EEA) related to Paxlovid (PF-07321332 - ritonavir) and reported directly to them by patients and healthcare professionals.