COMPREHENSIVE EMERGENCY USE AUTHORIZATION (EUA) REQUEST DOCUMENT FOR PF-07321332/RITONAVIR

EUA 000105

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LIST OF ABBREVIATIONS

Abbreviation	Definition
°C	degree(s) Celsius
1Q2022	first quarter 2022
3CL	3C-like
$3CL^{pro}$	3C-like protease
5d	5-day
10d	10-day
^{19}F	fluorine-19
ACE-2	angiotensin-converting enzyme 2
ADE	antibody-dependent enhancement
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
Ae	amount of unchanged drug excreted in urine
AESI	adverse events of special interest
Al	aluminum
ALB	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
API	active pharmaceutical ingredient
APTT (aPTT)	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under concentration-time curve
AUC_{24}	area under the concentration-time curve from time zero to 24 hours
AUC_{inf}	area under the serum concentration-time profile from time zero extrapolated to infinite time
AUC_{inf} (dn)	Dose normalized AUC_{inf}
AUC_{last}	area under the serum concentration-time profile from time zero to the time of the last quantifiable concentration
AUC_{last} (dn)	area under the serum concentration-time profile from time zero to the time of the last quantifiable concentration, dose normalized
AUC_{tau}/AUC_t	area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval
ACE2	angiotensin converting enzyme 2 receptor
ADR	adverse drug reaction
BCRP	breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BLQ	below limit of quantification
BID	twice daily
BiPAP	Bilevel positive airway pressure
BMI	body mass index
BP	blood pressure
BSA	bovine serum albumin

Abbreviation	Definition
BUN	blood urea nitrogen
C_{12}	plasma concentration at 12 hours post dose
C_{24}	plasma concentration at 24 hours post dose
Caco-2	human colonic adenocarcinoma cells
CC_{50}	cytotoxicity concentration 50%
C_{av}	average free concentration
Cb/Cp	concentration in blood/concentration in plasma
C_{eff}	efficacious concentration
CHOL	cholesterol
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
CL	clearance
CL/F	apparent clearance
Clbile	biliary intrinsic clearance of drug from eg, plasma
CL_r	renal clearance
CMA	conditional marketing authorisation
CMC	Chemistry Manufacturing and Controls
C_{max}	the observed maximum concentration
$C_{max,ss}$	C_{max} at steady-state
C_{min}	minimal concentration (C_{trough})
CoV	coronavirus
COVID-19	coronavirus disease 2019
CPE	cytopathic effect
C-QTc	concentration-QTc
QTc	corrected QT interval
CRP	C-reactive protein
CSR	clinical study report
CT	Connecticut; Computerised tomogram
CTA	clinical trials application
C_{trough}	drug concentration observed at the last planned timepoint prior to dosing
CV	coefficient of variation; cardiovascular
CYP	cytochrome P450
CYP1A2	cytochrome P450 1A2
CYP3A4	cytochrome P450 3A4
CYP2B6	cytochrome P450 2B6
CYP2C9	cytochrome P450 2C9
DAIDS	Division of AIDS
DDI	drug-drug interaction
DBP	diastolic blood pressure
dNHBE	differentiated normal human bronchial epithelial cells
+dP/dT	cardiac contractility

Abbreviation	Definition
EC_{50}	drug concentration at which 50% inhibition of viral replication is observed; Concentration required for 50% effect
EC_{90}	drug concentration at which 90% inhibition of viral replication is observed; Concentration required for 90% effect
ECG	electrocardiogram
E-DMC	external data monitoring committee
ED	Emergency department
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EoT	end of therapy
EPIC	evaluation of protease inhibition for COVID-19
ER	Emergency room
EU	European Union
EUA	Emergency Use Authorization
EV71	Enterovirus 71
F1	relative bioavailability
f2	similarity factor
FC	food consumption
FDA	Food and Drug Administration
FE	food effect
FIB	fibrinogen
FIH	first-in-human
f_m	fraction metabolised
FOB	functional observational battery
f_u	fraction unbound
GD	gestation days
GeoMean	geometric mean
GFR	Glomerular filtration rate
GFR CKD-EPI Equat	Glomerular Filtration Rate Chronic Kidney Disease Epidemiology Collaboration equation
GI	gastrointestinal
GISAID	global initiative on sharing avian influenza data
GLOB	globulin
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
HCl	hydrochloric acid
HCV	Hepatitis C virus
HCoV	human coronavirus
HEK	human embryonic kidney
hERG	human Ether-à-go-go-Related Gene
HHS	Department of Health and Human Services
HIV	human immunodeficiency virus

Abbreviation	Definition
HPD	hours post-dose
HPLC/MS/MS	high-performance liquid chromatography tandem mass spectrometric
HRV1B	Human rhinovirus 1B
HR	heart rate
IB	Investigator's Brochure
IC_{50}	the drug concentration at which 50% inhibition of the 3CL protease enzyme is observed
ICH	International Council for Harmonisation
ICU	intensive care unit
IgG	Immunoglobulin G
IIV	inter-individual variability
IND	Investigational New Drug
INR	International normalized ratio
IOV	inter-occasion variability
IPPV	Intermittent positive pressure ventilation
IR	immediate release
IV	Intravenous
K_a	absorption rate constant
K_i	inhibition constant
K_I	concentration at 50% k_{inact}
Ki^{app}	apparent inhibition constant
K_{inact}	maximal rate of enzyme activation
$k_{p,uu}$	unbound partition coefficient
LC-MS/MS	liquid chromatography tandem mass spectrometry
LLN	Lower limit of normal
LOQ	limit of quantification
LLOQ	lowest limit of quantification
LS	least-squares
LV +dP/dt max	maximum positive slope of the left ventricular pressure wave; an index of cardiac contractility
M	male; metabolite
M&E/ME	metabolism and excretion
MA	marketing authorization
MAA	Marketing Authorisation Application
mAb	monoclonal antibody
MAD	multiple ascending dose
MATE	multidrug and toxic compound extrusion
MDCK	Madin-Darby canine kidney cell line
MDR1	multidrug resistance 1
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
Mfg	manufacturing
MHV	mouse hepatitis virus

Abbreviation	Definition
min	minute
mITT	modified intent-to-treat
mITT1	modified intent-to-treat 1
mITT2	modified intent-to-treat 2
M^{pro}	main protease
MRC-5	human lung epithelial cells-5
mRNA	messenger ribonucleic acid
msec	milliseconds
MT	
N	Number (N = Number of participants; n = Number in tables for sample; No. = Number, when adjective)
ND	not determined
NDA	New Drug Application
NI	non-inferiority
NMR	nuclear magnetic resonance
NOAEL	no-observed-adverse-effect-level
NP	nasopharyngeal
NR	not reported
NTCP	sodium taurocholate cotransporting polypeptide
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
OATP1B	organic anion-transporting polypeptide 1B
OCT	organic cation transporter
OPA	Oriented PolyAmide
PAH	Pulmonary arterial hypertension
P_{app}	apparent permeability coefficient
PBO	placebo
PBPK	physiological based pharmacokinetic modelling and simulation
PD	pharmacodynamic(s)
PDE	phosphodiesterase
PEPT	peptide transporter 1
P-gp	p-glycoprotein
PI	package insert
PK	pharmacokinetic(s)
PMAR	Population Modeling Analysis Report
PO	by mouth
POC	proof of concept
popPK	population pharmacokinetics
PR	time from the onset of the P wave to the start of the QRS complex in the electrocardiogram
PRO	patient reported outcomes
PT	Preferred Term; prothrombin time
PTR	peak to trough ratio

Abbreviation	Definition
PVC	polyvinylchloride
q12h	every 12 hours
q24h	every 24 hours
QC'd	quality controlled
QD	once daily
QRS	Deflections in the tracing of the electrocardiogram comprising the Q, R, and S waves, representing the depolarization of the ventricles
QSP	quantitative systems pharmacology
QT	time from the beginning of the QRS complex to the end of the T wave in the electrocardiogram
QTc	QT interval corrected for heart rate
QTcF	QTc corrected using Fridericia's formula
(Q)SAR	quantitative structure activity relationship
QTPP	quality target product profile
R_{ac}	observed accumulation ratio for AUC_{τ}
$R_{ac,Cmax}$	observed accumulation ratio for C_{max}
rBA	relative bioavailability
RdRp	RNA-dependent RNA polymerase
RH	relative humidity
RNA	Ribonucleic acid
ROW	Rest of the World
RT-PCR	reverse transcriptase–polymerase chain reaction
RTV	ritonavir
RR	respiratory rate
SAD	single ascending dose
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SARS-CoV-2-MA10	Severe acute respiratory syndrome coronavirus 2 (mouse-adapted virus)
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SE	supratherapeutic exposure / standard error
SmPC	summary of product characteristics
SoA	schedule of activities
SoC	standard of care
SOC	System Organ Class
$t_{½}$	terminal elimination half-life
TBD	To be determined
TDI	time-dependent inhibitor / inhibition
TEAE	treatment-emergent adverse event

Abbreviation	Definition
TEM	Treatment-emergent mutation
TI	therapeutic index
TK	toxicokinetic
T_{max}	the time to reach C_{max}
TMPRSS2	transmembrane serine protease 2
TSH	thyroid stimulating hormone
UGT	uridine diphosphate-glucuronosyltransferase
UHPLC-HRMS	Ultra-high performance liquid chromatography - high resolution mass spectrometry
UK	United Kingdom
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VeroE6	monkey kidney cells E6
VOC	variant of concern
VOI	variant of interest
V_{ss}	volume of distribution at steady state
v/v	volume per volume
Vz/F	apparent volume of distribution
WOCBP	woman of child-bearing potential
WHO	World Health Organization
WT	wild type
w/v	weight per volume
w/w	weight per weight

1. DESCRIPTION AND INTENDED USE

1.1. Name of Product

PF-07321332/ritonavir.

1.2. Description of Product

PF-07321332/ritonavir is an oral antiviral drug for the treatment of mild-to-moderate COVID-19 in adult patients with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. The proposed dosing regimen is PF-07321332/ritonavir 300/100 mg q12hr (BID) administered orally for 5 days.

PF-07321332 is a peptidomimetic inhibitor of the coronavirus $3CL^{pro}$, including the SARS-CoV-2 $3CL^{pro}$. Inhibition of the $3CL^{pro}$ renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication. PF-07321332 was shown to be a potent inhibitor of SARS-CoV-2 $3CL^{pro}$ (Ki = 0.00311 μM, or IC_{50} = 0.0192 μM) in a biochemical enzymatic assay.

PF-07321332 will be co-administered with ritonavir (acting as a PK enhancer) to achieve and maintain exposures greater than the in vitro antiviral EC_{90} throughout the duration of the dosing interval. Ritonavir is not active against SARS-CoV-2 $3CL^{pro}$ and is not expected to have any antiviral activity against the SARS-CoV-2 virus. Ritonavir inhibits the CYP3A mediated metabolism of PF-07321332, thereby providing increased plasma concentrations of PF-07321332.

In this document, a leading designation "C467" included in the PF-07321332 study protocol numbers is omitted in text and tables. For example, Study C4671005 (Evaluation of Protease Inhibition for COVID-19 [EPIC]) is referred to as Study 1005.

1.3. Intended Emergency Use Authorization

The intended use of PF-07321332/ritonavir under this EUA is the treatment of mild to moderate COVID-19 in adult patients with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

High risk was defined in the Study C4671005 Protocol Section 5.1 as having at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19[1,2] including:

- ≥60 years of age
- BMI >25 kg/m^2
- Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes
- Chronic kidney disease

- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung disease (eg, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
- 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
- Medical-related technological dependence not related to COVID-19 (eg, tracheostomy, gastrostomy, or positive pressure ventilation)

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19, and authorization of PF-07321332/ritonavir under the EUA is not limited to the medical conditions or factors listed above.

2. UNMET NEED ADDRESSED BY THE EUA

On 04 February 2020, the Secretary of HHS determined that there is a public health emergency that has a significant potential to affect national security or the health and security of US citizens and that involves the virus that causes COVID-19 (virus later named as SARS-CoV-2).[3] On the basis of such determination, the Secretary of HHS declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 pandemic effective 27 March 2020.[4]

Given the ongoing COVID-19 pandemic and the potential for SARS-CoV-2 variants to evade the immune system, even among the fully vaccinated, there is an urgent unmet medical need for a safe and effective therapeutic intervention that can reduce viral transmission, improve time to clinical recovery and prevent the progression of infection to more severe disease, hospitalization, and death. Such a therapeutic would meet these requirements, all whilst decreasing the pressure on the healthcare system by providing an outpatient treatment for COVID-19.

PF-07321332, is a potent and selective inhibitor of the SARS-CoV-2 $3CL^{pro}$, a virally encoded enzyme that is critical to the SARS-CoV-2 replication cycle. The sponsor conducted research in 2003 and again in 2020 to identify potential therapeutic targets for SARS-CoV-1 and SARS-CoV-2, respectively.[5,6] Such research has intentionally targeted the 3C-like/main protease of the coronavirus ($3CL^{pro}/M^{pro}$). The coronavirus $3CL^{pro}$ is a virally encoded

enzyme which is essential for viral replication.[7] $3CL^{pro}$ digests the virus pp1a and pp1ab polyproteins at multiple junctions to generate a series of proteins critical for virus replication and transcription, including RdRp, the helicase, and the $3CL^{pro}$ itself.[5,8] No close human analogs of the coronavirus $3CL^{pro}$ are known.[5,9] The essential functional importance in virus replication cycle together with the absence of closely related homologs in humans, make the $3CL^{pro}$ an attractive antiviral drug target.[10]

PF-07321332 is co-administered with ritonavir (PK enhancer). Ritonavir, by inhibiting the CYP3A-mediated metabolism of PF-07321332, increases plasma concentrations of PF-07321332 throughout the duration of the dosing interval maintaining exposures greater than the in vitro antiviral EC_{90}. Based on the preliminary population PK modeling of FIH data, a dose of approximately 300/100 mg PF-07321332/ritonavir BID would be predicted to provide a median steady-state C_{min} that is >5 fold over the antiviral EC_{90}. Ritonavir (up to 3 μM) is not active against SARS-CoV-2 $3CL^{pro}$ in biochemical assays.

As the ongoing pandemic continues, the coronavirus that causes COVID-19 (SARS-CoV-2) is mutating and thus has the potential to adapt during the current pandemic.[11] Although most mutations in the SARS-CoV-2 genome are expected to be either deleterious to the virus and swiftly purged or relatively neutral, a small proportion may affect functional properties altering infectivity, disease severity or interactions with host immunity.[12] Since late 2020, SARS-CoV-2 evolution has been characterized by the emergence of sets of mutations, in the context of 'variants of concern', that impact virus characteristics, including transmissibility, virulence or escape from the immune system / therapeutics.[12-14] The spike protein receptor binding- domain of SARS-CoV-2 is the molecular target for many vaccines and antibody-based prophylactics aimed at bringing COVID-19 under control. Such a narrow molecular focus raises the specter of viral immune evasion as a potential failure mode for these biomedical interventions.[12] As of October 2021, the WHO has defined four VOCs: B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta).[13] Currently, the Delta variant is displacing all other variants, including the highly dominant and contagious Alpha variant, in numerous countries across the globe.[15]

A recent study assessing the effectiveness of the mRNA vaccines (BNT162b2 and mRNA-1273) undertaken between January and July 2021 found that both protected against severe COVID-19 infections and death against the Delta variant, but a reduction in vaccine efficacy was observed over time.[16] Administration of boost^{er} shots, especially mRNA vaccines specifically targeted against the spike protein of the Delta variant, may improve vaccine effectiveness in those individuals already vaccinated. However, a percentage of the population still chooses not to be vaccinated.[17,18]

There is rising concern following warnings by experts that the Delta and its associated variants may show resistance to mAb cocktail treatments as has already been observed with use of a mAb when administered alone.[19,20] The EUA for bamlanivimab was revoked,[21] based on scientific data showing that SARS-CoV-2 viral variants were resistant to the mAb and increased risk of treatment failure. Laboratory studies also suggest that the combination of bamlanivimab and etesevimab may be less effective for treating cases of COVID-19 caused by variants with certain substitutions or combinations of substitutions in the spike protein. Limitations of Authorized Use has been modified to remove authorization for use in

any state, territory, and US jurisdiction where combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%.[22] Overall, the potential risk is that these new emerging VOC may be able to bypass immunity provided by vaccines, earlier infection,[19] and therapeutic mAbs.

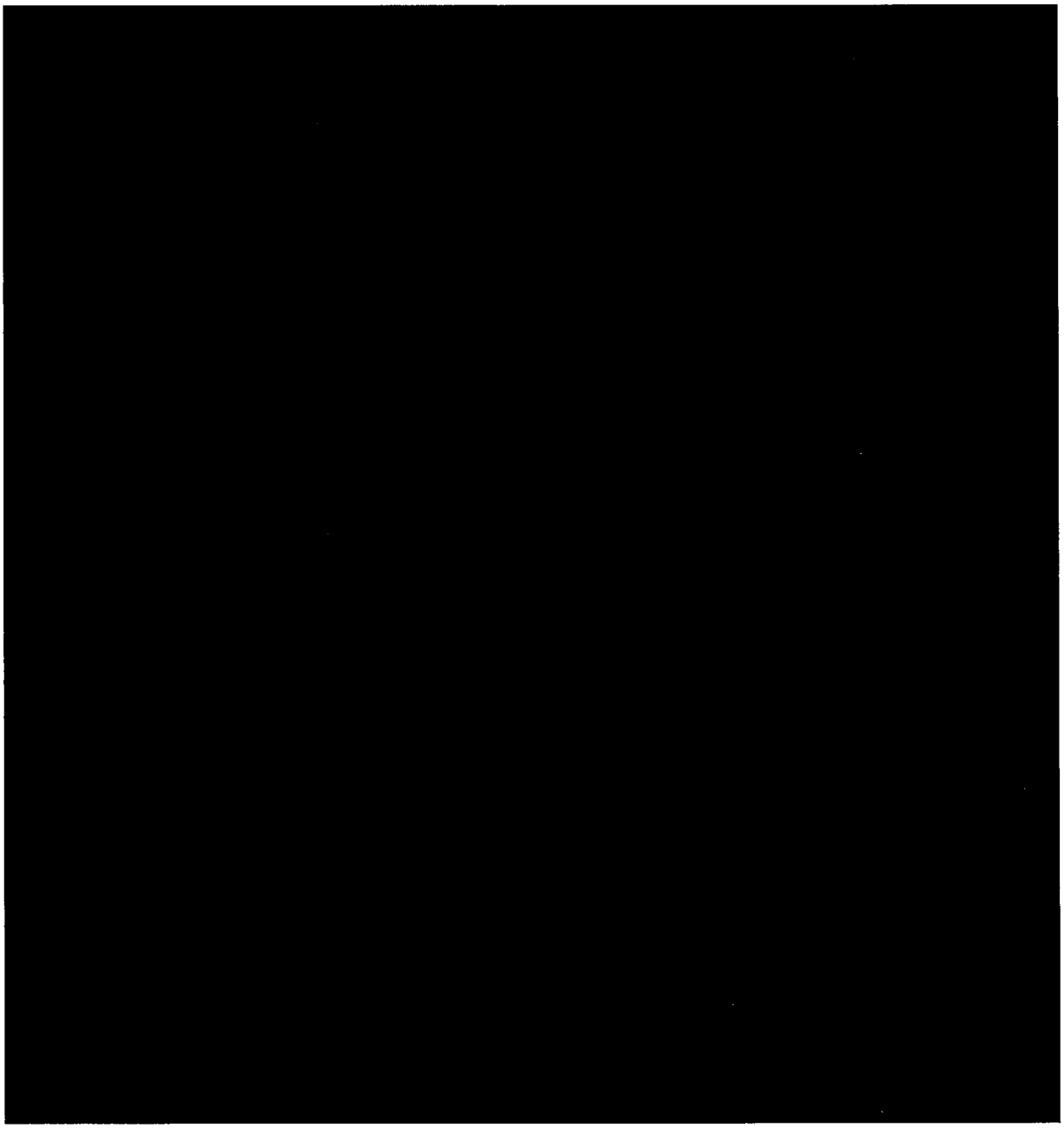
An important advantage of PF-07321332/ritonavir over such therapeutics as mAbs is that by targeting the $3CL^{pro}$, rather than the spike protein, current and future VOC/VOI are expected to remain susceptible to PF-07321332/ritonavir given the critical role the enzyme plays in viral replication. Thus, there is a clear unmet need for an effective and safe oral antiviral agent that can be used either alone or in combination with authorized mAb in both vaccinated and un-vaccinated individuals.

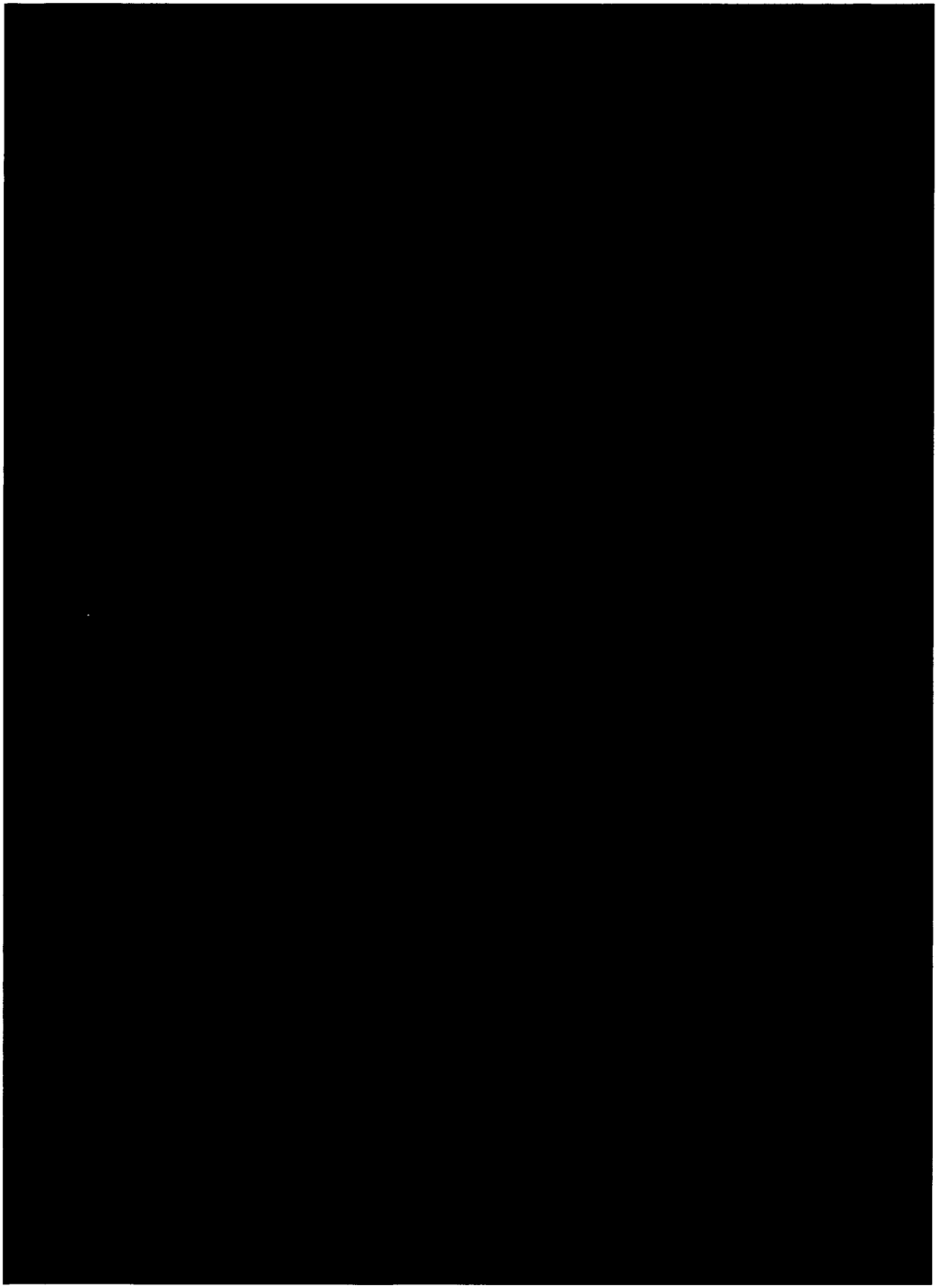
An oral antiviral agent would offer an easy and convenient method of drug administration without requiring attendance at a healthcare setting. Targeting a highly conserved viral target essential for viral replication, would provide an effective therapeutic agent against current and future coronavirus variants. Furthermore, a risk/benefit profile supportive of administration to a broad patient population would significantly add to the treatment armamentarium for COVID-19. Such patient populations would also include but not limited to those who are immunocompromised and cannot be vaccinated or who are fully vaccinated but have breakthrough infections due to a VOC.[23] Such antivirals, when used early on in infection, could limit the impact of SARS-CoV-2 infections on the healthcare system, including overwhelmed hospital facilities and lack of ICU bed space. Overall, development of a pan-coronavirus treatment, has a critical role in global health protection in the current and potential future pandemic(s).

3. APPROVAL/CLEARANCE STATUS

At the present time, PF-07321332/ritonavir is unapproved and not registered or marketed for any disease indication worldwide.

[redacted]





5. ADEQUATE, APPROVED AND ALTERNATIVE PRODUCTS

The following summarizes current antiviral therapies either authorized or undergoing clinical development for treatment of non-hospitalized patients with COVID-19. Note: this is a non-exhaustive list having a focus on therapeutic candidates in Phase 2/3 clinical trials.

5.1. Approved Alternative Products

As of October 2021, there are no approved oral alternatives to PF-07321332/ritonavir for the treatment of mild-to-moderate COVID-19 in adult patients with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

5.2. Alternative Products with EUA for Non-Hospitalized Pediatric Patients (≥12 years old) and Adults with COVID-19

No orally administered antiviral has received an EUA to treat non-hospitalized patients with COVID-19. An EUA application by Merck and Ridgeback for molnupiravir, an orally administered broad spectrum antiviral (see Section 5.3), is pending as of October 2021.[24]

Several recombinant human mAb regimens directed against the SARS-CoV-2 spike protein receptor binding domain (administered by IV infusion or SC injection) have received an EUA to treat mild to moderate COVID-19 in non-hospitalized adults and pediatric patients (≥12 years of age weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death:

- Bamlanivimab 700 mg (IgG1κ with unmodified Fc region) and etesevimab 1400 mg (IgG1κ with modified Fc region): to be administered together as a single IV infusion.[22,25]

- Casirivimab 600 mg (IgG1κ) and imdevimab 600 mg (IgG1λ) both with unmodified Fc region [REGN-COV2]: First authorized at a higher dose for emergency use on 21 November 2020, to be administered together as a single IV infusion. The EUA was subsequently reissued allowing administration by subcutaneous injection (4 separate injection sites) when IV infusion is not feasible and would lead to a delay in treatment.[26,27]

- Sotrovimab 500 mg (IgG1κ with modified Fc region): as a single IV infusion.[28-30]

These mAbs are administered parenterally and only in settings in which health care providers have immediate access to medications to treat a severe infusion reactions.[22,27,29] Serious hypersensitivity reactions including anaphylaxis have been reported with mAbs, and infusion-related reactions occurring during the infusion and up to 24 hours after the infusion have been observed. These reactions may be severe or life-threatening. Clinical worsening of COVID-19 after administration of mAbs has been reported although it is not known whether these events were related to mAb use or were due to progression of COVID-19.[25,26,28] The most commonly reported TEAEs with mAbs were generally similar to placebo.[31]

Other potential challenges for the use and continued effectiveness of mAbs include the possibility of ADE, the potential for attenuation of long-term immunity, and the emergence of resistant viral mutations under selective pressure of mAb treatment.[31-33] Several currently circulating SARS-CoV-2 VOC have substitutions in the spike protein and variants with reduced susceptibility to some mAbs have emerged. This has led to revocation of the EUA for bamlanivimab as a single agent[21] and restriction of the EUA for bamlanivimab plus etesevimab to areas in which the combined frequency of resistant variants is ≤5%.[22]

Monoclonal antibodies are complex to develop and produce, thus limiting supply and increasing cost. Furthermore, intravenous administration and the need for access to emergency care presents challenges in terms of providing specialized clinics and trained staff.

5.3. Alternative Products in Clinical Development for Non-Hospitalized Adults With COVID-19

Many more SARS-CoV-2 monoclonal antibodies are under preclinical or clinical development.[1,34] Three other products currently in clinical development to treat non-hospitalized patients with COVID-19 (molnupiravir, AT-527, and remdesivir) were previously in development or approved to treat other infections (eg, SARS, MERS, influenza, and encephalitic alphaviruses for molnupiravir,[35] HCV for AT-527,[36] and Ebola, SARS, and MERS for remdesivir[37]). All 3 of these products target the viral RNA-dependent RNA polymerase. The potential for the development of viral variants with cross-resistance to these agents is unclear. In addition, high titer convalescent plasma is being investigated in Phase 3 studies in non-hospitalized patients, and ensovibep, a new protein therapeutic, is in early clinical development.[38] Further details are provided below.

Molnupiravir (EIDD-2801/MK-4482), an investigational, orally administered broad spectrum antiviral is currently in Phase 2/3 development in non-hospitalized participants with mild or moderate COVID-19 and at least 1 risk factor for severe illness (Merck and Ridgeback Biotherapeutics; NCT04575597).[39,40] Molnupiravir is a prodrug of the ribonucleoside analogue β-D-N^4-hydroxycytidine (NHC, EIDD-1931), and inhibits viral replication primarily through lethal mutagenesis.[41] However there have been concerns about the mammalian cell mutagenic potential of molnupiravir.[42-44]

- In interim results of a Phase 3 outpatient study 'MOVe-OUT' (NCT04575597; N=775) molnupiravir reduced the risk of hospitalization or death by 48%; 7.3% of

patients who received molnupiravir were either hospitalized or died through Day 29 following randomization (28/385), compared with 14.1% of placebo-treated patients (53/377); p=0.0012 (Merck press release 01 October 2021).[24]

AT-527 (RO7496998), an orally administered guanosine nucleotide prodrug,[36] is in Phase 3 development by Atea and Roche for the treatment of non-hospitalized adult patients with mild or moderate COVID-19 (NCT04889040,[45] NCT04709835[46]). Data from preclinical studies demonstrated that AT-527 inhibits SARS-CoV-2 through unique dual mechanisms targeting both RdRp and the nidovirus RdRp-associated nucleotidyltransferase (NiRAN) of viral nonstructural protein polymerase, which is essential for viral RNA replication and transcription.[47]

- Phase 2/3 studies are ongoing in non-hospitalized patients with mild or moderate COVID-19 (NCT04889040[45] and NCT04709835[46]), although not currently recruiting in the US. Topline results from the global Phase 2 trial evaluating AT-527 in the outpatient setting did not meet its primary endpoint (viral load), which prompted the sponsor to assess potential modifications to the global Phase 3 trial, including the trial's primary endpoint and patient population.[48]

The repurposed drug Remdesivir (Veklury®), is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor approved for IV use in adults and pediatric patients (≥12 years of age and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization.[49] Remdesivir was under investigation in an outpatient setting (NCT04501952), however, the study was terminated in May 2021 due to study enrollment feasibility and changing needs of non-hospitalized patients (decision not based on safety or efficacy concerns).[50]

- The Phase 3 outpatient study was evaluating the efficacy and safety of a 3-day course of IV remdesivir use for treatment of COVID-19 in non-hospitalized patients at high risk for disease progression (NCT04501952). Although enrollment was stopped, the study continued to collect data. Remdesivir demonstrated a significant 87% reduction in risk of COVID-19 related hospitalization or all-cause death by Day 28 compared with PBO.[51]

Ensovibep is a protein therapeutic being developed by Molecular partners and Novartis to target multiple different sites on the SARS-CoV-2 virus simultaneously (Press release March 9, 2021[38]) and is in early clinical development for non-hospitalized patients with COVID-19.

- A Phase 2 study of viral clearance, PK, and tolerability in COVID-19 patients (NCT04834856[52]) has been completed. A Phase 2/3 study is in progress to establish the safety and efficacy of ensovibep in ambulatory adult patients with symptomatic COVID-19 ('Empathy' Study; NCT04828161[53]).

High-titer convalescent plasma against SARS-CoV-2, approved for emergency use for the treatment of hospitalized patients with COVID-19, is under Phase 3 clinical investigation in non-hospitalized patients, with mixed results to date.[54,55] Other studies using convalescent plasma are on-going (eg, NCT04438057,[56] NCT04373460,[57] NCT045899[58]).

6. EFFICACY AND SAFETY INFORMATION

6.1. Nonclinical Studies

- The nonclinical program demonstrates that PF-07321332 has the potential to be efficacious against SARS-CoV-2 virus and has an acceptable toxicity profile.
- PF-07321332 exhibits:
    - In vitro antiviral efficacy against SARS-CoV-2 and associated variants of concern with no measurable cytotoxicity.
    - Pan-coronavirus $3CL^{pro}$ inhibition, likely explained by high conservation of $3CL^{pro}$ active site residues across all human coronaviruses.
    - Selectivity to the $3CL^{pro}$ of the human coronavirus family, showing little or no activity against a panel of human proteases, as well as HIV protease.
    - In vivo antiviral efficacy (reduced lung titer, histopathology, and ameliorated weight loss) in mouse-adapted models of SARS-CoV-2.
    - Acceptable safety pharmacology profile with clinically monitorable nonclinical findings.
- PF-07321332 has no significant inhibition (>50%) of functional or enzymatic activity against a wide panel of receptors, transporters, ion channels, and enzyme assays in vitro.
- In vitro transporter assays indicated that PF-07321332 was a substrate for human MDR1 (P-gp).
- In human liver microsomes, CYP3A4 was the major contributor (f_m = 0.99) to the oxidative metabolism of PF-07321332, when PF-07321332 was tested alone.
- When tested alone, CYP3A mediated oxidation was the primary metabolic route of PF-07321332 and there were no human unique metabolites.
- PF-07321332 has the potential to reversibly and time-dependently inhibit CYP3A4 and inhibit MDR1 (P-gp). Minimum DDI risk is expected from PF-07321332 beyond that posed by ritonavir.
- There were no adverse findings in GLP repeat dose toxicity studies of up to 1 month in duration in rats and cynomolgus monkeys.
- There were no PF-07321332-related effects on male or female fertility up to the highest dose tested in rats.
- There were no PF-07321332-related severe manifestations of developmental toxicity (malformations and embryo-fetal lethality) at the highest dose tested in rats and rabbits.
- PF-07321332 is not mutagenic, aneugenic or clastogenic.

6.1.1. Overview of the Nonclinical Program for PF-07321332

Studies supporting the nonclinical development of PF-07321332/ritonavir and their submission status covering pharmacology, ADME and toxicology studies are summarized in Table 3, Table 4, and Table 5, respectively. Please refer to Module 1.4.4 Cross Reference to Previously Submitted Information to the IND.

As agreed with the Agency as part of the scientific advice, results from the 1-month repeat dose toxicity studies in rats and monkeys are summarized in Section 6.1.2.3. and Section 6.1.2.4. Results from the male and female fertility study are summarized in Section 6.1.2.5, and results from the EFD studies in 2 species (rat and rabbit) are summarized in Section 6.1.2.6.

6.1.1.1. Antiviral Activity and Mechanism of Action of PF-07321332

PF-07321332 is an orally bioavailable $3CL^{pro}$ peptidomimetic inhibitor shown to be active against SARS-CoV-2 $3CL^{pro}$ (Ki = 0.00311 μM) in a biochemical enzymatic assay and displayed broad spectrum anti-coronavirus activity against SARS-CoV-2 in addition to other coronaviruses (SARS-CoV-1, HCoV-229E, MERS-CoV, HCoV-OC43, HCoV-HKU1, and HCoV-NL63). PF-07321332 also demonstrated selectivity for coronavirus $3CL^{pro}$, showing little or no activity against a panel of human proteases, as well as HIV protease.

From the co-crystal structure of PF-07321332 bound to SARS-CoV-2 $3CL^{pro}$, 6 contact residues were identified in the active site of $3CL^{pro}$ to form either covalent or hydrogen bonds between $3CL^{pro}$ and PF-07321332 (Study PF-07321332_[redacted]_054343). Examination of residues within 4 Å from PF-07321332 binding sites identified 7 additional potentially critical residues. The conservation of these contact residues was assessed by aligning SARS-CoV-2 genomes with complete and high coverage sequences (N = 3,163,857; GISAID; last accessed[redacted]2021). This is not a prevalence-based analysis and is biased by regions that are routinely sequencing virus isolates. The 13 residues explored were highly conserved, with frequency of mutation <0.024%. The pan-coronavirus $3CL^{pro}$ inhibition by PF-07321332 could likely be explained by the similarity of the $3CL^{pro}$ across the Coronaviridae family. Although there is only modest sequence similarity overall, the $3CL^{pro}$ active site residues are highly conserved across all human coronaviruses (Study PF-07321332_[redacted]_120222).

Activity was confirmed in the most physiologically relevant antiviral assays of SARS-CoV-2 infection of dNHBE cells with mean EC_{50} and EC_{90} values of 0.0618 μM and 0.181 μM, respectively, at Day 3 post-infection. The in vitro antiviral activity of PF-07321332 against SARS-CoV-2 was also evaluated in VeroE6 cells, enriched for cellular expression of ACE-2 receptor, displaying mean EC_{50} and EC_{90} values of 0.0745 μM and 0.155 μM, respectively, in the presence of efflux inhibitor and no measurable cytotoxicity (CC_{50} > 10 μM). In addition, PF-07321332 was shown to exhibit pan-coronavirus antiviral efficacy with activity against SARS-CoV-1, EC_{50} 0.151 μM, and MERS-CoV, EC_{50} 0.166 μM, both in the presence of an efflux inhibitor, and HCoV-229E, EC_{50} 0.190 μM. PF-07321332 activity is selective to the coronavirus family as PF-07321332 did not inhibit EV71 or HRV1B viral-induced CPE, resulting in EC_{50} >100 μM, nor did it demonstrate cytotoxicity in non-infected RD or HeLa cells up to the top concentration (100 μM) tested producing CC_{50} of >100 μM.

In vivo models for evaluation of PF-07321332 against SARS-CoV-2 use a virus, SARS-CoV-2 virus that has been adapted to infect mice (SARS-CoV-2-MA10). The activity of PF-07321332 has been evaluated in two different laboratories in 2 different models and similar results have been observed for both studies. PF-07321332 has antiviral efficacy (reduced lung titer, histopathology, and ameliorated weight loss) in the mouse-adapted model of SARS-CoV-2 with the data supporting efficacy at exposures ~1xEC_{90} (292 ng/mL [181 nM]) at C_{min}.

6.1.1.2. Secondary Pharmacology

Secondary pharmacology studies evaluated the in vitro activity of PF-07321332 against a wide panel of receptors, transporters, ion channels, and enzyme assays, and the results indicated no significant inhibition (>50%) of functional or enzymatic activity.

6.1.1.3. Safety Pharmacology

Safety pharmacology studies were conducted to assess potential pharmacodynamic effects on vital organ systems (central nervous, cardiovascular, and respiratory). Oral administration of up to 1000 mg/kg of PF-07321332 to male Wistar Han rats produced no test article-related effects on FOB parameters, but at 1000 mg/kg there were test article-related lower number of mean vertical movement counts during the first 5-minute period and a higher number of mean horizontal and vertical movement counts during the last 30-minute period of the quantitative locomotor assessment compared with vehicle control. Translatability of these findings to humans is uncertain. Administration of 1000 mg/kg also resulted in transient test article-related higher respiratory rate and minute volume compared with vehicle control. PF-07321332 administered at 150 (75 BID) mg/kg/day to cynomolgus monkeys produced minor and transient effects such as increased systolic, diastolic, and mean BP, HR decreases, and associated RR, PR, and QT interval increases. When the QT interval was corrected for HR (QTc), there was a test article-related decrease. No arrhythmias were noted. PF-07321332 at 150 (75 BID) mg/kg/day also produced decreases in LV +dP/dt max. All measures returned to vehicle control levels within 24 HPD. There was no clinically meaningful effect of PF-07321332 on hERG, isolated guinea pig heart or isolated rat aorta assays.

The potential effects on safety pharmacology parameters are monitorable in the clinic (eg, ECG) and had no correlating clinical signs or histopathological findings in the repeat dose GLP toxicity studies of up to 1 month duration in rats or monkeys, respectively. ECG data were also collected in the 15-day and 1-month GLP monkey studies and there were no test article-related changes in ECG parameters (HR, RR-, PR-, QRS-, QT-, QTc intervals) or ECG morphology in those studies

6.1.1.4. Pharmacokinetics

PF-07321332 exhibited a moderate CL and t½ of 5 hours in rats with moderate to high bioavailability, while in monkeys the CL was moderate with a short t½ of <1 hour and low bioavailability of <10%. In the pivotal repeat dose toxicity studies in rats and monkeys, mean systemic exposure of PF-07321332 increased with increasing dose and there were no consistent sex-related differences. PF-07321332 exhibited low passive permeability and was moderately bound to plasma proteins in rat, monkey and human and preferentially partitioned

into plasma relative to red blood cells. Concentration-dependent protein binding was observed in rabbit plasma but not in rat, monkey and human. The protein binding of PF-07321332 in human plasma is approximately 69%.

In vitro transporter assays indicated that PF-07321332 was a substrate for human MDR1 (P-gp), but was not a substrate for human BCRP, MATE1, MATE2K, NTCP, OAT1, OAT2, OAT3, OCT1, OCT2, PEPT1, OATPs 1B1, 1B3, 2B1, or 4C1.

In vitro studies indicated that PF-07321332 was principally metabolized via oxidative biotransformation pathways. In vivo, unchanged PF-07321332 was the most prevalent drug-related entity in circulation in rat and monkey plasma, with M4 (PF-07329268) as a primary circulating metabolite in monkey. In human liver microsomes, CYP3A4 was the major contributor (f_m = 0.99) to the oxidative metabolism of PF-07321332 with no significant CYP3A5 contribution. Since clinical data shows PF-07321332 is principally metabolized by CYP3A4, co-administration with the CYP3A4 inhibitor ritonavir increases plasma concentrations of PF-07321332 and maintains trough concentrations above the in vitro EC_{90}, which is likely to increase or prolong its pharmacologic activity.

Based on the preliminary population PK modeling of FIH data, a dose of approximately 300/100 mg PF-07321332/ritonavir BID would provide a median steady-state C_{min} that is >5-fold over the EC_{90} (292 ng/ml [181 nM]) determined in the dNHBE cell assay.

Based on static mechanistic modeling results and FDA guidance, minimal DDI risk is expected from PF-07321332 beyond what is posed by ritonavir. Results of in vitro CYP and transporter inhibition studies indicated PF-07321332 has the potential to reversibly and time-dependently inhibit CYP3A4 and inhibit MDR1 (P-gp) at the clinical dose of 300/100 mg PF-07321332/ritonavir BID. As ritonavir is also an inhibitor of MDR1 (P-gp) and CYP3A, co-administration of PF-07321332/ritonavir with drugs subject to MDR1 efflux and/or primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs. To understand the clinical implications of the in vitro DDI data, clinical DDI studies with PF-07321332/ritonavir with index CYP3A and MDR1 substrates are planned.

6.1.1.5. Toxicology

The toxicity of PF-07321332 was evaluated in 4 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. Nonadverse, test article-related clinical findings included sporadic salivation and soft feces in the 1-month rat study, and sporadic occurrence of emesis with slight body weight decreases in monkeys. In rats, nonadverse, monitorable and reversible clinical pathology findings included those possibly suggestive of low-grade inflammation or alterations in the coagulation pathways without clinical or microscopic correlates. In monkeys, nonadverse, monitorable and reversible clinical pathology findings included increases in ALT (1.63x - 3.53x baseline) and/or AST (2.68x - 7.41x baseline) and increases in fibrinogen (1.20x - 1.91x baseline) at the high dose in the 1-month study without clinical or microscopic correlates. In rats administered 1000 mg/kg/day in the 14-day GLP repeat dose toxicity study, lower mean absolute and relative heart weights were observed in females relative to controls. The lower heart weights had no microscopic correlates and were fully reversed at the end of the 2-week recovery

period, and lower heart weights were not observed in the 1-month GLP rat toxicity study. Higher mean liver weights were observed relative to controls in both 14-day and 1-month rat toxicity studies. Higher liver weights correlated with fully or partially reversible, nonadverse microscopic findings of minimal to mild severity in the liver, thyroid gland, and pituitary gland (males in the 1-month study only). These changes are consistent with a rat-specific response to hepatic microsomal enzyme induction resulting in increased thyroxine catabolism.[59,60,61] This mechanism is considered to have little to no relevance to humans mostly because of the marked differences in plasma half-life of thyroid hormones and in binding to transport proteins between rodents and humans.[61]

The NOAELs in the 1-month rat and monkey studies were the highest doses tested and represented 11x/8.0x (C_{max}/AUC_{24}) and 21x/14x (C_{max}/AUC_{24}) for rats and monkeys, respectively, over the predicted human total PF-07321332 C_{max} and AUC_{24} at a dose of 300/100 mg PF-07321332/ritonavir BID.

PF-07321332 was not mutagenic or clastogenic in in vitro genetic toxicity studies and was negative in the in vivo rat micronucleus assay incorporated into the 14-day GLP repeat-dose rat toxicity study.

There were no effects on male or female fertility when evaluated at doses up to 1000 mg/kg PF-07321332.

The potential embryo-fetal toxicity of PF-07321332 was evaluated in the definitive rat and rabbit studies at doses up to 1000 mg/kg/day. There was no PF-07321332-related effect in any of the parameters in the rat EFD study up to the highest dose of 1000 mg/kg/day (exposure margin of 16x/7.8x based on total C_{max}/AUC_{24}). In the rabbit EFD study, there was no PF-07321332-related effect on fetal morphology or embryo-fetal viability up to the highest dose of 1000 mg/kg/day (exposure margin of 24x/10x based on total C_{max}/AUC_{24}), although lower fetal body weights (0.91x control) were observed at 1000 mg/kg/day in the presence of slight reductions in maternal body weight change and food consumption at this dose. No effects on fetal or maternal body weights were observed at the intermediate dose (10x/2.8x C_{max}/AUC_{24} over the predicted total clinical exposure). The unbound exposure margins at the highest dose in rabbits were 63x/25x C_{max}/AUC_{24} over the predicted human exposures at a dose of 300/100 mg PF-07321332/ritonavir BID.

Therefore, the available data indicate low risk of fetal harm in humans based on lack of malformations or embryofetal lethality in 2 species at 16-24x/7.8-10x (based on total C_{max}/AUC_{24}) the predicted clinical exposure at a dose of 300/100 mg PF-07321332/ritonavir BID.

Evaluation of potential effects of PF-07321332 on PPND is currently ongoing in a dedicated study in rats.

6.1.1.6. Summary of Nonclinical Studies

In summary, the nonclinical package described herein supports the EUA of 300/100 mg of PF-07321332/ritonavir administered orally BID for the proposed clinical treatment duration of mild-to-moderate COVID-19 in adult patients with positive results of direct SARS-CoV-2

viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Table 3. Summary of Completed and Ongoing Pharmacology Studies Supporting the Nonclinical Development of PF-07321332/Ritonavir

Study Type	Study Number (Sponsor Reference Number)	Species / Test System	Submission Status
Primary Pharmacology			
In Vitro Potency in SARS-CoV-2 $3CL^{pro}$ Protease Assay	PF-07321332_[redacted]_090608	Human coronavirus protease	Submitted to the IND
Xray Co-Crystal Structure of PF-07321332 Bound to SARS-CoV-2 $3CL^{PRO}$	PF-07321332_[redacted]_054343	SARS-CoV-2	Submitted to the IND
Sequence Conservation Analyses of PF-07321332 Contact Residues in SARS-CoV-2	PF-07321332_[redacted]_120222	SARS-CoV-2	Submitted to the IND
In Vitro Potency Against Mammalian and Viral Proteases	PF-07321332_[redacted]_091415	Human Alpha and Beta coronavirus, and Mammalian and Viral Proteases	Submitted to the IND
In Vitro Potency in Enterovirus 71 in Human Rhabdomyosarcoma and HRV1B in H1 HeLa cells, CPE and Cytotoxicity Assays	PF-07321332_[redacted]_041406	Enterovirus 71 and HRV1B	Submitted to the IND
In Vitro Potency in SARS-CoV-2 in VeroE6 Cell Line enriched for ACE2 in CPE and Cytotoxicity Assay	PF-07321332_[redacted]_052017	SARS-CoV-2	Submitted to the IND
In Vitro Potency in SARS-CoV-2 in a A549 Cell Line, Alone and in Combination with Ritonivir, and Cytotoxicity Assay	PF-07321332_[redacted]_041209	SARS-CoV-2	Submitted to the IND
In Vitro Potency in dNHBE Cells	PF-07321332_[redacted]_010204	SARS-CoV-2	Submitted to the IND
In Vitro Potency in SARS-COV-1 in VeroE6 Cell Line enriched for ACE2 in CPE and Cytotoxicity Assay	PF-07321332_[redacted]_104426	SARS-COV-1	Submitted to the IND
In Vitro Potency in HCoV-229E in MRC-5 Cells in CPE and Cytotoxicity Assay	PF-07321332_[redacted]_092314	Human CoV ATCC strain	Submitted to the IND
In Vitro Potency in MERS-CoV in Vero81 Cell Line enriched for ACE2 in CPE and Cytotoxicity Assay	PF-07321332_[redacted]_015423	MERS-CoV	Submitted to the IND
In Vivo Efficacy in BALB/c Mouse-Adapted SARS-CoV-2 Models	PF-07321332_[redacted]_105036	BALB/c Mouse-Adapted SARS-CoV-2 Model	Submitted to the IND
In Vivo Efficacy in the 129 Mouse-Adapted SARS-CoV-2 Models	PF-0721332_[redacted]_022652	129 Mouse-Adapted SARS-CoV-2 Model	Submitted to the IND
In Vitro Antiviral Activity In Vero E-6 cells Against SARS-CoV-2 Variants in a Cell-Based CPE Assay	PF-07321332_[redacted]_104040	SARS-CoV-2	Report submitted to the EUA
In Vitro Antiviral Activity in Vero E6 cells Against SARS-CoV-2 Variants in a qPCR-Based Assay	PF-07321332_[redacted]_042713	SARS-CoV-2	Report submitted to the EUA
In Vitro Potency Against SARS-COV-2 3CL Protease Enzyme Containing Mutations	PF-07321332_[redacted]_121015	SARS-CoV-2	Report submitted to the EUA

Table 3. Summary of Completed and Ongoing Pharmacology Studies Supporting the Nonclinical Development of PF-07321332/Ritonavir

Study Type	Study Number (Sponsor Reference Number)	Species / Test System	Submission Status
Evaluation of In Vitro Selected Resistant MHV against PF-07321332	PF-07321332_[redacted]_035634	Mouse Hepatitis Virus	Preliminary report submitted to EUA, study ongoing
Secondary Pharmacology			
In Vitro Pharmacology Study of PF-07321332-00	100054569	Mouse, Rat, and Human	Submitted to the IND
In Vitro Assessment of the Activity of PF-07321332 at Nav1.5 and Cav1.2 Ion Channels	[redacted]J073	Human	Submitted to the IND
In Vitro Assessment of the Activity of PF-07321332 at Phosphodiesterase Subtypes (PDE 1-11)	[redacted]J074	Bovine and Human	Submitted to the IND
In Vitro Safety Pharmacology Studies			
Effect of PF-07321332 on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells	[redacted]0804.QHJ [redacted]J091)	Human	Submitted to the IND
Effects of PF-07321332 on Cardiac Function and Conduction in the Guinea Pig Isolated Langendorff-Perfused Heart Model	[redacted]J075	Guinea Pig	Submitted to the IND
Assessment of the Effects of PF-07321332 on the Rat Isolated Aorta Preparation	[redacted]J076	Wistar Han Rat	Submitted to the IND
Neurofunctional Assessment			
PF-07321332: Neurofunctional and Pulmonary Assessment in Male Wistar Han Rats Following Oral (Gavage) Administration	8455743 [redacted]GR274)	Wistar Han Rat	Submitted to the IND
Pulmonary Function Assessment			
PF-07321332: Neurofunctional and Pulmonary Assessment in Male Wistar Han Rats Following Oral (Gavage) Administration	8455743 [redacted]GR274)	Wistar Han Rat	Submitted to the IND
Cardiovascular Assessment			
Cardiovascular Assessment of Oral Gavage PF-07321332 in Conscious Telemetry-Instrumented Male Cynomolgus Monkeys	[redacted]GR275	Conscious Cynomolgus Monkey	Submitted to the IND

Table 4. Summary of Completed ADME Studies Supporting the Nonclinical Development of PF-07321332/Ritonavir

Study Type	Study Number	Species / Test System	Submission Status
Analytical Method and Pharmacokinetics			
Validation of an LC-MS/MS Assay from 10.0 to 50,000 ng/mL for the Quantitation of PF-07321332 in Rat Plasma	PF-07321332_[redacted]_014313	Rat Plasma	Submitted to IND
Validation of an LC-MS/MS Assay from 10.0 to 50,000 ng/mL for the Quantitation of PF-07321332 in Monkey Plasma	PF-07321332_[redacted]_015142	Monkey Plasma	Submitted to IND
Validation for the quantitation of PF-07321332 in Rabbit Plasma by LC-MS/MS	[redacted]2441VSMB_PGC	Rabbit Plasma	Completed, to be submitted to EUA
Single Dose Pharmacokinetics and Oral Bioavailability of PF-07321332 in Rats Following Oral or Intravenous Administration	PF-07321332_[redacted]_103131	Rat	Submitted to IND
Single Dose Pharmacokinetics and Oral Bioavailability of PF-07321332 in Cynomolgus Monkeys Following Oral or Intravenous Administration	PF-07321332_[redacted]_111728	Monkey	Submitted to IND
Distribution			
Protein Binding of PF-07321332 in Human, Non-Human Primate, and Rat Plasma	PF-07321332_[redacted]_010657	Rat, Monkey, and Human Plasma	Submitted to IND
Definitive Protein Binding of PF-07321332 in Rabbit Plasma	[redacted]067/394	Rabbit Plasma	Submitted to the EUA
Red Blood Cell to Plasma Partitioning of PF-07321332 in Rat, Monkey, and Human Whole Blood	PF-07321332_[redacted]_100444	Rat, Monkey, and Human Whole Blood	Submitted to IND
Metabolism and Excretion			
Preliminary Study of the Biotransformation of PF-07321332	PF-07321332_[redacted]_084546	Mouse, Rat, Hamster, Rabbit, Monkey and Human Liver Microsomes and/or Hepatocytes, Rat Plasma, Urine, Bile, Monkey Plasma	Submitted to IND
Definitive Reaction Phenotyping of Cytochrome P450 Isoforms Involved in the in Vitro Metabolism of PF-07321332	PF-07321332_[redacted]_072016	Human Liver Microsomes	Submitted to IND
Pharmacokinetic Drug Interactions			
In Vitro Evaluation of PF-07321332 as a Reversible and Time-dependent Inhibitor of Cytochrome P450 (CYP) Enzymes	PF-07321332_[redacted]_113907	Human Liver Microsomes	Submitted to IND
In Vitro Evaluation of PF-07321332 as a Time-Dependent Inhibitor (TDI) of Cytochrome P450 3A Enzyme Activity in Human Liver Microsomes	PF-07321332_[redacted]_122202	Human Liver Microsomes	Submitted to IND
In Vitro Evaluation of PF-07321332 as an Inhibitor of UPD Glucuronosyltransferase (UGT) Enzyme Activities in Human Liver Microsomes	PF-07321332_[redacted]_103243	Human Liver Microsomes	Submitted to IND

Table 4. Summary of Completed ADME Studies Supporting the Nonclinical Development of PF-07321332/Ritonavir

Study Type	Study Number	Species / Test System	Submission Status
In Vitro Investigation of the Potential for PF-07321332 to Induce Cytochrome P450 (CYP3A4, CYP2B6, CYP1A2 AND CYP2C) in Cultured Human Hepatocytes	PF-07321332_[redacted]_102559	Human Hepatocytes	Submitted to IND
In Vitro Evaluation of PF-07321332 Transport in CACO-2 Cells	PF-07321332_[redacted]_095737	Caco-2 Cells	Submitted to IND
In Vitro Assessment of Uptake and Billary Excretion of PF-07321332 Using PHH and SCHH	PF-07321332_[redacted]_110227	Plateable Human Hepatocyte Sandwich Cultured Human Hepatocytes	Submitted to IND
In Vitro Evaluation of PF-07321332 as a Substrate of Human Transporters NTCP, OATP1B1, OATP1B3 and OATP2B1	PF-07321332_[redacted]_114514	NTCP, OATP1B1, OATP1B3, OATP2B1 Transfected HEK293 Cells	Submitted to IND
In Vitro Evaluation of PF-07321332 as Substrates of Human Transporters BCRP and MDR1	PF-07321332_[redacted]_124535	MDCKII-BCRP or MDCKI-MDR1 Cells	Submitted to IND
In Vitro Evaluation of PF-07321332 as Substrates of Human MATE1, MATE2K, OAT1, OAT3, OCT1, OCT2, and PEPT1 Transporters	PF-07321332_[redacted]_013448	MATE1, MATE2K, OAT1, OAT3, OCT1, OCT2 transfected HEK293 or MDCKII-PEPT1 cells	Submitted to IND
In Vitro Evaluation of PF-07321332 as Substrates of OATP4C1 in Human Renal Proximal Tubule Epithelial Cells	PF-07321332_[redacted]_124557	Human Renal Proximal Tubule Epithelial Cells	Submitted to IND
In Vitro Transporter Inhibition Study of PF-07321332 on BCRP, MATE1, MATE2K, MDR1, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2	PF-07321332_[redacted]_020944	HEK293 Cells and Vesicles	Submitted to IND

Table 5. Summary of Completed and Ongoing Toxicity Studies Supporting the Nonclinical Development of PF-07321332/Ritonavir

Study Type	Study Number (Sponsor Reference Number)	Species / Test System	Submission Status
Repeat-Dose Toxicity			
4-Day Oral Gavage Exploratory Toxicity Study of PF-07321332 in Wistar Han Rats	[redacted]GR250	Wistar Han Rat	Submitted to IND
4-Day Oral Gavage Exploratory Toxicity of PF-07321332 in Cynomolgus Monkeys	[redacted]GR271	Cynomolgus Monkey	Submitted to IND
2-Week Oral Gavage Toxicity and Micronucleus Assessment Study of PF-07321332 in Wistar Han Rats With a 2-Week Recovery	[redacted]GR276	Wistar Han Rat	Submitted to IND
15-Day Twice Daily (BID) Oral Gavage Toxicity Study of PF-07321332 in Cynomolgus Monkeys	[redacted]GR289	Cynomolgus Monkey	Submitted to IND
1-Month Oral Gavage Toxicity Study of PF-07321332 in Wistar Han Rats With a 2-Week Recovery	[redacted]GR122	Wistar Han Rat	QC-reviewed report submitted with the EUA
1-Month BID Oral Gavage Toxicity Study of PF-07321332 in Cynomolgus Monkeys With a 2-Week Recovery	[redacted]GR125	Cynomolgus Monkey	QC-reviewed report submitted with the EUA
Genotoxicity			
PF-07321332: Bacterial Reverse Mutation Assay	AG48RZ.503ICH.BTL [redacted]GR288)	*Salmonella typhimurium, Escherichia coli*	Submitted to IND
PF-07321332: In Vitro Mammalian Cell Micronucleus Assay in TK6 Cells	AG48RZ.361ICH.BTL [redacted]GR286)	Human	Submitted to IND
2-Week Oral Gavage Toxicity and Micronucleus Assessment Study of PF-07321332 in Wistar Han Rats With a 2-Week Recovery	[redacted]GR276	Wistar Han Rat	Submitted to IND
Development and Reproductive Toxicity			
Oral Gavage Male and Female Fertility Study of PF-07321332 in Wistar Han Rats	[redacted]GR146	Wistar Han Rat	QC-reviewed report submitted with the EUA
Oral Gavage Embryo-Fetal Development Study of PF-07321332 in Pregnant Wistar Han Rats	[redacted]GR132	Wistar Han Rat	Submitted with the EUA
Oral Gavage Embryo-Fetal Development Study of PF-07321332 in Pregnant New Zealand White Rabbits	[redacted]GR126	New Zealand White Rabbit	Submitted with the EUA
An Oral (Gavage) Study of the Effects of PF-07321332 on Pre- and Postnatal Development, Including Maternal Function in Rats	00655272 [redacted]GR149)	Wistar Han Rat	Ongoing[a]

a. Study will be submitted as part of the NDA

6.1.2. Ongoing/Planned Nonclinical Studies

6.1.2.1. PF-07321332 Activity Against Different Coronavirus Species and Variants

PF-07321332 showed inhibition in Vero E6 P-gp knockout cells using a CPE CellTiter-Glo Luminescent Cell Based Assay with mean EC_{50} values of 96.3 nM, 75.3 nM, 171 nM, 87.7 nM, and 59.5 nM in the USA-WA1/2020 SARS-CoV-2 strain and the alpha, beta, gamma, and lambda variants, respectively. Several delta variants have been tested in the Vero E6 P-gp knockout cells, which unexpectedly, did not produce CPE. Therefore, an EC_{50} of the drug could not be obtained by CPE analysis. However, studies were conducted to measure the impact of PF-07321332 on viral load using a qPCR-based method with mean EC_{50} 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, lambda, and delta variants, respectively.

Since the delta variant produced CPE in Vero E6 TMPRSS2 cells, PF-07321332 was tested for antiviral activity in this cell line against the USA-WA1/2020 SARS-CoV-2 strain and alpha, beta, gamma, lambda, and delta to determine the EC_{50}. PF-07321332 showed inhibition in the Vero E6 TMPRSS2 cells using a CPE CellTiter-Glo Luminescent Cell Base Assay with mean EC_{50} values of 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, lambda, and delta variants, respectively.

Evaluation of the Mu VOC is ongoing, and data will be provided as part of the rolling EUA.

6.1.2.2. Viral Resistance Data

Although treatment with PF-07321332 will be of short duration, selection of variants with mutations conferring viral resistance following exposure to PF-07321332 could occur. Several nonclinical approaches are being undertaken by the sponsor to understand the development of drug resistance to PF-07321332 and will be provided per the rolling submission plan.

6.1.2.2.1. In Vitro Potency of PF-07321332 Against SARS-COV-2 3CL Protease Enzyme Containing Different Mutations

A total of 38 mutant SARS-CoV-2 $3CL^{pro}$ enzymes were tested for PF-07321332 inhibition of enzymatic activity using a continuous FRET assay (mutants with single point mutations in the PF-07321332 contact residues and highest prevalent mutations circulating in the population). Of those, 13 mutations were identified as key contact residues elucidated for SARS-CoV-2 3CLpro with PF-07321332 (Section 6.1.1.1, Study PF-07321332_[redacted]_120222). Four mutations (H41Y, C145I, C145F, H163A) showed lack of self-cleavage activity and therefore would most likely yield an inactive enzyme.

PF-07321332 showed a statistically significant drop in potency for inhibiting five of these 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 $3CL^{pro}$ with GeoMean Ki of 1.68 nM.

PF-07321332 also showed a significant drop in potency for inhibiting two additional mutant enzymes which were greater than 4 Å from PF-07321332 in the co-crystal structure (G15S and H172Y), with GeoMean Ki values of 4.07 and 217 nM. These 5 mutations, identified as key contact residues for which PF-07321332 showed reduced inhibitory activity, are being reverse engineered into SARS-CoV-2 and will be evaluated for changes in viral replication fitness and susceptibility to PF-07321332. The remaining mutations within key contact residues elucidated for SARS-CoV-2 $3CL^{pro}$ did not show significant change in potency of PF-07321332. Work is ongoing to reverse engineer these mutations into SARS-CoV-2 to determine viral replication fitness and antiviral activity of PF-07321332 on SARS-CoV-2.

6.1.2.2.2. In Vitro Phenotypic Antiviral Evaluation of PF-07321332 Against SARS-COV-2 Viruses

Studies are in progress to identify amino acid residues using reverse genetics in SARS CoV-2 viruses for phenotypic antiviral evaluation (viral fitness). Data will be provided when available.

6.1.2.2.3. Evaluation of In Vitro PF-07321332 Selected Resistant MHV and SARS-CoV-2

To evaluate the potential for PF-07321332 resistant virus development, in vitro resistance selection studies are being conducted with MHV and SARS-CoV-2. Preliminary results are available for MHV in L929 where in the presence of increasing concentrations of PF-07321332, with initial passaging at 0.5x EC_{50} and incrementally increased to 30x (25.4 µM) and 40x (33.9 µM) EC_{50} drug concentrations, replicating viruses were isolated at each drug concentration step and the virus cultures were sequenced to detect the development of mutations in the $3CL^{pro}$.

A total of 33 mutant viruses were isolated from the 30x and 40x EC_{50} cultures by plaque purification and individually sequenced. Sequence analysis indicates the presence of 5 mutations (Pro55Leu, Ser144Ala, Thr129Met, Thr50Lys, Pro15Ala) in the MHV $3CL^{pro}$, with two mutations located in the active site (Pro55Leu, Ser144Ala) which is highly conserved with SARS-CoV-2. Four mutant viruses which harbor these 5 mutations have been evaluated for virus replication fitness compared to parent MHV and for altered EC_{50} values. At 48 hours post infection, all 4 mutant viruses show reduced viral replication or fitness by 1 - 2 Log PFU/mL compared to parent MHV. Preliminary antiviral analysis using a MHV RT-qPCR assay, in the presence of P-gp inhibitor, shows that PF-07321332 inhibited these 4 mutant viruses with mean EC_{50} values ranging from 2.63-2.93 µM compared to 0.6 µM for parent MHV in murine L929 cells.

These preliminary results indicate that PF-07321332 resistance can develop in MHV under experimental in vitro conditions with multiple passages and gradually increased drug concentrations resulting in the resistant viruses having reduced viral fitness. In a paper by Deng et al,[62] the selection of MHV resistance to a broad-spectrum $3CL^{pro}$ inhibitor revealed that although mutations conferred resistance, the resistant viruses had reduced viral fitness in cell culture but were highly attenuated in mice. This indicates that the essential function of the $3CL^{pro}$ impacts the balance between viral fitness and drug resistance.

In vitro selection of PF-07321332 resistant SARS-CoV-2 is currently underway by passaging virus with increased drug concentrations. Mutations in MHV and SARS-CoV-2 3CLpro that are identified from in vitro selection or that affect 3CLpro activity will be reverse engineered into SARS-CoV-2 and evaluated reduced viral fitness and for phenotypic antiviral activity (Section 6.1.2.2.1). Viral resistance data for SARS CoV-2 will be provided when available.

6.1.2.3. 1-Month GLP Repeat Dose Toxicity Study in Rats

PF-07321332 was administered by oral gavage once daily to male and female Wistar Han rats at doses of 60, 200, or 1000 mg/kg/day for 1 month followed by a 2-week recovery phase.

There was no test article-related unscheduled euthanasias or deaths, or differences in body weights, food consumption, or ophthalmic parameters. Test article-related nonadverse clinical observations were limited to sporadic salivation (all doses) and soft feces (200 [single animal] and 1000 mg/kg/day) typically observed during the dosing phase on Days 25-28; there were no clinical nor anatomic pathology sequelae or correlates for these findings.

PF-07321332 administration resulted in nonadverse findings compared with controls in hematology and coagulation parameters. Dose-dependent higher platelets (1.12x-1.28x) were observed in males and females administered ≥200 mg/kg/day, and dose-dependent prolongations in PT (1.06x-1.15x) were observed in males administered ≥200 mg/kg/day and females administered 1000 mg/kg/day. These findings lacked clinical and microscopic correlates. Differences in platelets and PT were fully recovered at the end of the recovery phase. All clinical pathology findings were nonadverse due to small magnitude, transient nature, and/or absence of adverse clinical and/or microscopic correlates.

Test article-related microscopic findings in this study were present in the liver and thyroid gland (both sexes) and pituitary gland (males only).

In the liver, minimal to mild periportal hepatocellular hypertrophy in males and females at ≥200 mg/kg/day with concomitant increased severity (mild) of periportal hepatocyte cytoplasmic vacuolation (females only) at 1000 mg/kg/day were noted and were associated with higher mean liver weights (1.07x-1.83x control at ≥60 mg/kg/day) and macroscopic findings (enlargement and/or abnormal color [mottled]) in females and 1 male at 1000 mg/kg/day. The hepatocellular hypertrophy was consistent with microsomal enzyme induction.[63] The periportal hepatocellular vacuolation is sometimes observed in livers enlarged following hepatic microsomal induction[63] and so this is considered a secondary change arising from hepatocellular hypertrophy in females at 1000 mg/kg/day.

In the thyroid gland, minimal to mild follicular cell hypertrophy was noted in males and/or females at ≥60 mg/kg/day. In the pituitary gland, minimal to mild cytoplasmic vacuolation was noted in the endocrine cells of the pars anterior (males only) at ≥60 mg/kg/day and possibly reflecting increased secretory activity in one or more subpopulations of the hormone secreting cells (thyrotropin-secreting cells).

The pattern of linked findings in the liver, thyroid and pituitary glands are consistent with a rat specific response to hepatic enzyme induction resulting in increased thyroxine catabolism, raised serum thyroid stimulating hormone and thyroid follicular cell hypertrophy and anterior pituitary vacuolation.[59-61] This mechanism is usually considered to have little to no relevance to humans mostly because of the marked differences in plasma half-life of thyroid hormones and in binding to transport proteins between rodents and humans.[61]

Test article-related effects in the liver, thyroid gland, and pituitary gland were nonadverse based on their limited severity, and lack of microscopic evidence of associated tissue damage (ie, necrosis, or inflammation) or correlating alterations in clinical pathology parameters.

At the end of the recovery phase, the microscopic changes in the liver, thyroid gland, and/or pituitary gland (males only) along with associated higher liver weight completely recovered at all doses in females and at 60 and 200 mg/kg/day in males; partial recovery (lower incidence and/or severity) of the microscopic findings in the liver, thyroid gland, and pituitary gland along with correlating higher liver weights (1.11x- 1.20x) was observed in recovery males at 1000 mg/kg/day. There was complete recovery of the macroscopic liver findings in both sexes by the end of the 2-week recovery phase.

The NOAEL was the highest dose tested and represented 11x/8.0x (C_{max}/AUC_{24}) over the predicted human total PF-07321332 C_{max} and AUC_{24} at a dose of 300/100 mg PF-07321332/ritonavir BID.

6.1.2.4. 1-Month GLP Repeat Dose Toxicity Study in Monkeys

Following administration of PF-07321332 to male and female cynomolgus monkeys by oral gavage twice daily at doses of 40 (20 BID), 100 (50 BID), or 600 (300 BID) mg/kg/day for 28 days, all animals survived the duration of the study. There was no test article-related effects on body weights, qualitative food consumption, or changes in ECG parameters (HR, RR-, PR-, QRS-, QT-, QTc-intervals), ECG morphology, ophthalmic findings, organ weight changes, macroscopic or microscopic findings; and no adverse effects were identified.

Test article-related, nonadverse, clinical observations were limited to sporadic occurrences of emesis at 600 (300 BID) mg/kg/day that was observed after dose administration or following the overnight period.

There were nonadverse PF-07321332-related coagulation and clinical chemistry changes at 600 (300 BID) mg/kg/day. All findings had fully reversed with the exception of ALT and AST which could not be assessed in affected males as those animals were in the main study group euthanized at the end of the dosing phase.

Test article-related clinical pathology findings were limited to increases in ALT (1.63x - 3.53x baseline) and/or AST (2.68x - 7.41x baseline) in males and a female at 600 (300 BID) mg/kg/day and increases in fibrinogen (1.20x - 1.91x baseline) in males and females at 600 (300 BID) mg/kg/day. Fibrinogen increases from baseline were also noted in controls, but the magnitude was slightly greater in test article-treated animals. These findings were considered to be nonadverse based on their small magnitude and absence of clinical or microscopic correlates. No test article-related changes in clinical pathology parameters were

seen the end of the recovery phase, although recovery couldn't be evaluated in males that had increased AST and ALT as those animals were euthanized at the end of the dosing phase.

The NOAEL was the highest dose tested and represented 21x/14x (C_{max}/AUC_{24}) over the predicted human total PF-07321332 C_{max} and AUC_{24} at a dose of 300/100 mg PF-07321332/ritonavir BID.

6.1.2.5. Fertility Study

The potential for PF-07321332 to produce effects on male and female fertility was evaluated in a GLP combined male and female fertility study in Wistar Han rats at doses up to 1000 mg/kg/day. There were no PF-07321332-related effects on male systemic toxicity, estrous cyclicity, days to mating, reproductive indices (mating, fecundity, and fertility), or cesarean section observations. The only PF-07321332-related, nonadverse effect in this study was higher body weight change at 1000 mg/kg/day in the females during the pre-mating phase. Based on the lack of PF-07321332-related adverse effects in this study, the NOAEL for male and female systemic toxicity and fertility was 1000 mg/kg/day (the highest dose tested) representing 12x/4.3x based on the predicted human C_{max}/AUC_{24} at a BID dose of 300/100 mg PF-07321332/ritonavir.

6.1.2.6. Embryo-Fetal Toxicity Studies

PF-07321332 was administered to timed-pregnant female Wistar Han rats or New Zealand White rabbits at doses of 100, 300, or 1000 mg/kg/day on GD 6 to 17 (rats) or GD 7 to 19 (rabbits) to detect potential adverse effects on pregnant females and development of the embryo and fetus consequent to exposure of the female from implantation to closure of the hard palate.

There was no PF-07321332-related maternal toxicity or effects on ovarian or uterine parameters, fetal body weight, or fetal external, visceral, or skeletal morphology in the rat study. In the rabbit study, the only PF-07321332-related maternal effect was lower maternal body weight change and food consumption observed at 1000 mg/kg/day which were not considered adverse based on low magnitude of difference from control and lack of impact on absolute body weights. PF-07321332-related lower fetal weight (0.91x control) was observed at 1000 mg/kg/day and was considered adverse. There were no PF-07321332-related maternal macroscopic observations, effects on ovarian and uterine parameters, fetal viability, fetal external, visceral, or skeletal morphology.

The maternal and developmental NOAEL was 1000 mg/kg/day for the rat study, representing 16x/7.8x based on C_{max}/AUC_{24} over the predicted human total PF-07321332 C_{max} and AUC_{24} at a dose of 300/100 mg PF-07321332/ritonavir BID. For the rabbit study, the maternal NOAEL was 1000 mg/kg/day. The developmental NOAEL based on reduced fetal weights was 300 mg/kg/day (10x/2.8x C_{max}/AUC_{24} over the predicted human total PF-07321332 C_{max} and AUC_{24} at a dose of 300/100 mg PF-07321332/ritonavir BID) but there were no PF-07321332-related severe manifestations of developmental toxicity (malformations and embryo-fetal lethality) at the highest dose tested, 1000 mg/kg/day (24x/10x C_{max}/AUC_{24} over the predicted human total PF-07321332 C_{max} and AUC_{24} at a dose of 300/100 mg PF-07321332/ritonavir BID).

6.2. Overview of the PF-07321332/Ritonavir Clinical Program

Study 1005 is an interventional efficacy and safety, Phase 2/3, double-blind, 2-arm study to investigate orally administered PF-07321332/ritonavir compared with placebo in approximately 3100 non-hospitalized symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness.

This EUA presents the results of a planned interim analysis of Study 1005. As specified in the protocol, an interim analysis was conducted after approximately 45% of participants in the mITT analysis set completed Day 28 assessments. Participants included in the interim analysis are those enrolled on or before 29 September 2021. This represents 774, 1219, and 1330 of participants in the mITT, mITT1 and mITT2 analysis sets, respectively.

On 03 November 2021, the external data monitoring committee reviewed data from the 45% interim analysis and determined that the prespecified 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 enrollment 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.

Additional ongoing pivotal clinical trials (Studies 1002 and 1006) in support of PF-07321332/ritonavir are described in Table 6.

The clinical pharmacology data to support the EUA for PF-07321332/ritonavir are Studies 1001, 1011, 1014 and 1015 (Table 7).

Table 6. Pivotal Clinical Studies to Support the Safety and Efficacy Assessments for PF-07321332/ritonavir

Study ID	Study Title	Dose and Duration of Study Intervention)	Comparator	Total Planned Sample Size
Study 1002 (Ongoing) [redacted]	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) [redacted]	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

Table 7. Clinical Pharmacology Studies Supporting PF-07321332/ritonavir

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) [redacted]	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)

Table 7. Clinical Pharmacology Studies Supporting PF-07321332/ritonavir

Study ID	Study Title	Study Details/Primary Endpoints	Total Sample Size
Study 1012 (Ongoing) [redacted]	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) [redacted]	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

6.3. Clinical Pharmacology

- The PK of PF-07321332/ritonavir has been studied in 3 clinical pharmacology studies (Studies 1001, 1014 and 1015) in healthy adult participants and one study (Study 1011) in renally impaired participants.

- In Study 1001, upon administration of single dose of PF-07321332 at 250 and 750 mg oral suspension, enhanced with 100 mg ritonavir, the increase in exposure was less than dose proportional. Also, following repeat-dose of PF-07321332/ritonavir up to 500 mg/100 mg BID as oral suspension in fasted state, the increase in systemic exposure at steady-state was less than dose proportional. Mean $t_{1/2}$ values across all tested multiple dose regimens ranged between approximately 6.8 hours to 8.0 hours. Mean steady-state was achieved on Day 2 with approximately 2-fold accumulation. Systemic exposures on Day 5 and Day 10 were similar at all doses. The absorption of PF-07321332/ritonavir in fasted state occurred with the median T_{max} ranging between 0.75 hours to 2.75 hours across all doses upon single or repeat dosing.

- The effect of food (eg, high-fat high-calorie meal) on exposures of PF-07321332 after oral administration of a suspension of PF-07321332, enhanced with 100 mg ritonavir, resulted in approximately 1.5% increase in AUC and 15% increase in C_{max} of PF-07321332.

- The exposure of PF-07321332 in Japanese participants was numerically lower but not meaningfully different than in non-Japanese participants. In Study 1001, geometric mean dose normalized AUC_{tau} and C_{max} of PF-07321332 at steady-state following PF-07321332 250/100 mg BID for 10 days was approximately 30% and 21%-26% lower in Japanese participants compared to those observed in non-Japanese participants across all days.

- The primary route of elimination of PF-07321332 when administered with ritonavir was renal excretion of intact drug. A total of 49.6% and 35.3% of the administered dose of PF-07321332 300 mg was recovered in urine and feces, respectively. PF-07321332 was the predominant drug-related entity with small amounts of metabolites arising from hydrolysis reactions in excreta. After normalization of the data to 100% mass balance, unmetabolized PF-07321332 represented 82.5% of the drug-related material, with 55.0% in urine and 27.5% in feces. In plasma, the only drug-related entity quantifiable ^{19}F-NMR was unchanged PF-07321332.

- The exposure of PF-07321332 in renally impaired patients increased with increase in severity of renal impairment. In Study 1011, the exposure (mean AUC_{inf}) in moderately and severely renally impaired patients was higher than those in healthy participants by 87% and 204%, respectively.

- Two DDI studies were conducted to assess the effect of a potent inhibitor (Study 1015) of CYP3A4, itraconazole, as well as a CYP3A4 strong inducer (Study 1014), carbamazepine, with coadministration of PF-07321332/ritonavir 300 mg/100 mg.

    - Co-administration of multiple oral doses of itraconazole 200 mg increased steady-state PF-07321322 adjusted geometric mean AUC_{tau} and C_{max} by approximately 39% and 19%, respectively.

- Co-administration of multiple oral doses of carbamazepine titrated up to 300 mg BID decreased single dose PF-07321332 AUC_{inf} and C_{max} by approximately 55-43%, respectively.
- There was a significant effect of carbamazepine on the systemic exposure of ritonavir as compared to PF-07321332. Carbamazepine titrated up to 300 mg BID decreased single dose ritonavir AUC_{inf} and C_{max} by approximately 83-74%, respectively.

- Simulations using population PK model, developed using healthy participants data from Study 1001, shows that the dose of PF-07321332/ritonavir 300/100 mg BID results in median Day 1 and steady-state C_{12} unbound trough concentrations ~3-4x and ~5-6x in vitro EC_{90}, respectively. A QSP model capable of describing viral dynamics with time was used to confirm the selection of a 5-day dosing duration of oral PF-07321332/ritonavir 300 mg /100 mg BID for the treatment of symptomatic confirmed SARS-CoV-2 participants.

6.3.1. Biopharmaceutics and Plasma/Urine Bioanalytical Assays and Reports

6.3.1.1. Biopharmaceutics

6.3.1.1.1. Formulation Development for PF-07321332

An extemporaneously prepared oral suspension and an uncoated 250 mg IR tablet were developed to support FIH clinical Study 1001. Subsequently, a 100 mg IR film-coated tablet was developed and was used in Phase 1 Study 1011 and only in the sentinel cohort of 68 participants in Phase 2/3 Study 1005. As information on the potential clinical dose became apparent, a 150 mg IR film-coated tablet was developed and is the primary dosage form of PF-07321332 used in Study 1005 and other Phase 2/3 studies (Studies 1002 and 1006) as well as in Phase 1 Study 1014. The clinical study supplies for 150 mg tablets used in Study 1005 were manufactured at [redacted] The proposed EUA dosage form for PF-07321332 is a 150 mg IR film-coated tablet manufactured at [redacted] and co-administered with commercially sourced ritonavir 100 mg tablet.

[redacted] 150 mg tablets.

6.3.1.1.2. BCS Classification of PF-07321332

The anticipated clinical dose of PF-07321332 is 300 mg BID administered with 100 mg ritonavir BID, as a PK enhancer. PF-07321332 can be classified as BCS Class IV (low solubility, low permeability) drug. PF-07321332 is a low solubility compound with measured aqueous solubility of [redacted] across the physiologically relevant pH range. Based on a human mass balance study (Study 1001, PART-4), PF-07321332 is a low permeability compound since unmetabolized PF-07321332 represented 82.5% of the recovered dose (normalized for 100% recovery), with 55.0% in urine representing drug absorbed systemically and 27.5% in feces potentially representing unabsorbed drug (see Section 6.3.2.2.4)

6.3.1.1.3. Clinical Trial Formulae

Detailed description of the formulations for dosage forms used in various clinical trials and for EUA supply is provided in 3.2.P.2.2.1, Formulation Development (EUA CMC).

6.3.1.1.3.1. Extemporaneously Prepared Oral Suspension

PF-07321332 was formulated as an extemporaneously prepared oral suspension for evaluation in FIH study in healthy participants (Module 5.3.3.1 Study C4671001 CSR). The composition of the PF-07321332 oral suspension is provided in Table 8. The oral suspension could achieve doses in the range of 50 - 4500 mg through extemporaneous preparation of the dosage form, but the maximum dose tested in Study 1001 was 1500 mg.

Table 8. Composition of PF-07321332 Extemporaneously Prepared Oral Suspension

[redacted]

The composition of the various tablet strengths of 250 mg, 100 mg, and 150 mg is provided in Table 9.

[redacted]

Table 9. Composition of PF-07321332 Clinical and Proposed EUA Supply Tablets

6.3.1.1.4. Comparison of Formulations

6.3.1.1.4.1. Suspension Versus 250 mg Tablet

The relative bioavailability of the 250 mg tablet versus 250 mg dose of the oral suspension was evaluated in Study 1001 in 12 healthy participants (Section 6.3.2.2.3). This evaluation was done without concomitant ritonavir as a PK enhancer. PF-07321332 plasma exposure for the tablet was lower compared to the suspension, with approximately 19% and 44% lower geometric mean AUC_{last} and C_{max} values, respectively. The ratio of the adjusted geometric means (90% CI) for PF-07321332 AUC_{last} and C_{max} were 81.21% (69.21%, 95.28%) and 56.38% (43.42%, 73.19%), respectively, for the tablet treatment (Test) compared to the suspension treatment (Reference). Geometric mean C_{max} values for both formulations were observed in a median T_{max} of 1.0 hr post-dose.

6.3.1.1.4.2. 100 mg Tablets Versus 150 mg Tablets

[redacted]

The 100 mg tablet was only used in the sentinel cohort of 68 participants in the Phase 2/3 Study 1005 randomized 1:1 for active drug versus placebo. The 150 mg tablets manufactured [redacted] were used for the remainder of Study 1005.

[redacted]

[redacted]

6.3.1.1.4.4. Food Effect

Overall data suggest that PF-07321332/ritonavir, can be dosed without regards to meal, a recommendation that was implemented in Phase 2/3 studies.

The effect of food on the PKs of PF-07321332 was evaluated with the suspension formulation administered *with* ritonavir and the 250 mg tablet administered *without* ritonavir in Study 1001 PART-1 and PART-3, respectively. Since PF-07321332 is intended for administration with ritonavir, the food effect data with co-administration of PF-07321332 with ritonavir was considered for dosing in Phase 2/3 studies.

Food effect of a 250 mg dose of the oral suspension of PF-07321332/ritonavir was examined in 7 healthy participants. The Test/Reference percent ratio of adjusted geometric means (90% CI) for PF-07321332 AUC_{last} and C_{max} was 101.53% (90.18%, 114.31%) and 115.30% (99.36%, 133.79%), respectively, for fed (Test) and fasted (Reference) treatments indicating that there is minimum effect of food on the PK of PF-07321332/ritonavir. These data provided the rationale for recommending dosing of PF-07321332/ritonavir without regards to meal in Phase 2/3 studies. Food slightly delayed the absorption of PF-07321332, with median T_{max} of 4 hours and 2.75 hours for fed and fasted treatment, respectively.

The food effect data for the 250 mg tablet of PF-07321332 is provided in Section 6.3.2.2.3. These data were generated without ritonavir and are therefore superseded by the aforementioned food effect data with the 250 mg suspension of PF-07321332/ritonavir.

Ritonavir PK was not investigated in these studies. According to the ritonavir product label, C_{max} and AUC_{inf} of ritonavir were decreased by 21 to 23% under moderate fat or high fat conditions relative to fasting conditions following administration of 100 mg tablet dose.[64] When ritonavir is used as a PK enhancer for protease inhibitors, the general practice is that the food effect recommendations for the protease inhibitor supersedes ritonavir recommendation.

The Phase 2/3 Study 1005 administered PF-07321332/ritonavir without regards to food requirements based on lack of a food effect from the suspension study.

In summary, it is proposed that PF-07321332/ritonavir be administered without regards to meals for treatment of COVID-19 patients.

6.3.1.2. Plasma and Urine Bioanalytical Assays and Bioanalytical Reports

Specific and sensitive bioanalytical methods using LC-MS/MS were developed and validated for the measurement of PF-07321332 concentrations in human plasma and urine. LC-MS/MS methods for the determination of PF-07321332 has a calibration curve range of 10.0 ng/mL to 50,000 ng/mL in human plasma (Study No. 071459) and a calibration curve range of 10.0 ng/mL to 50,000 ng/mL in human urine (Study No. 074112). These methods were used in support of Study 1001. Subsequently, a specific and sensitive bioanalytical method for simultaneous determination of PF-07321332 and ritonavir in human plasma using LC-MS/MS (Validation Study No. C4679002 [Module 5.3.1.4 - C4679002 - The validation of an HPLC-MS/MS method for the determination of PF-07321332 and Ritonavir in human K2EDTA plasma) was validated at York Bioanalytical Solutions (York, UK). The calibration curve range for the plasma method was 10.0 ng/mL to 10,000 ng/mL for PF-07321332 and 5.00 ng/mL to 5,000 ng/mL for ritonavir. A specific and sensitive bioanalytical method for determination of PF-07321332 in human urine using LC-MS/MS with a calibration range of 100 ng/mL to 200,000 ng/mL (Validation Study No. C4679003 [Module 5.3.1.4 C4679003 -

The Validation of an HPLC-MS/MS Method for the Determination of PF-07321332 in Human Urine]) was also validated at York Bioanalytical Solutions. Assays validated at York Bioanalytical Solutions were used to support clinical Studies 1005, 1011, 1014 and 1015. All assay validations and study sample analysis were conducted in compliance with the current FDA and EMA Guidance requirements and met acceptance criteria.[65,66]

Incurred sample reproducibility assessment was conducted and met acceptance criteria for all studies. All clinical samples in both human plasma and urine were analyzed within established stability interval of the analytes. For details, please refer to bioanalytical report for each study.

6.3.2. Phase 1 Study 1001 – First-in-Human

6.3.2.1. Study Details

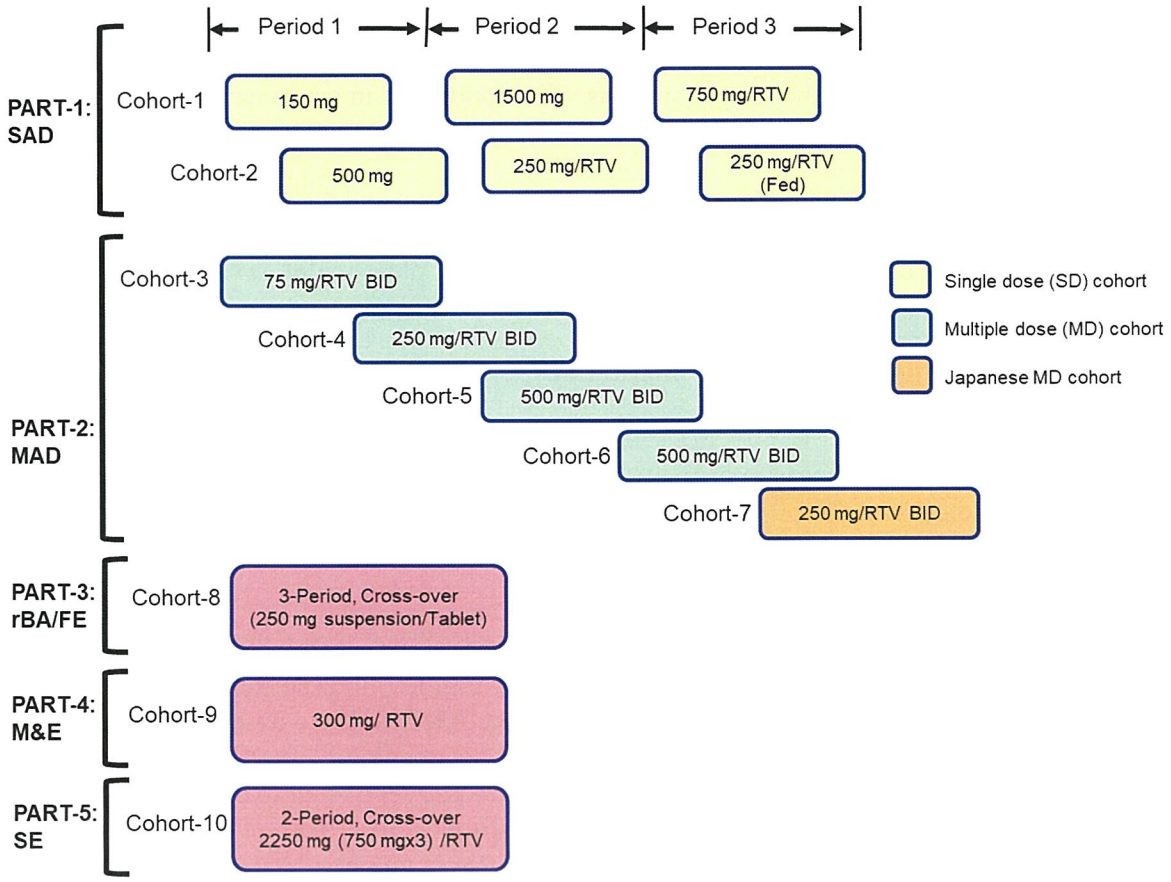
This Phase 1, FIH study was to evaluate safety, tolerability, and PK of PF-07321332 in healthy participants of 18-60 years of age with BMI of 17.5 to 30.5 kg/m^2 and a total body weight >50 kg (Module 5.3.3.1, Study C4671001 CSR).

The study was in 5-parts (Figure 1). PART-1: SAD cohorts, PART-2: MAD cohorts, PART-3: rBA/FE cohort, PART-4: Metabolism and Excretion cohort and PART-5: Supratherapeutic Exposure cohort. PART-1 and 2 were randomized, double-blind (participant and investigator blinded and sponsor open) cohorts. PART-2 also included multiple dose PK and safety assessment in Japanese participants who had 4 Japanese biologic grandparents born in Japan. PART-3 was an open label, randomized, 3 period, crossover design to evaluate relative bioavailability of 250 mg tablet compared to oral suspension and effect of food on PK of tablet when administered without ritonavir. PART-4 was an open-label, non-randomized, single period to evaluate the metabolism and excretion of PF-07321332/ritonavir in healthy male participants. PART-5 was a double-blind, sponsor-open, randomized, 2-period, cross-over cohort to evaluate safety, tolerability, and PK at supratherapeutic exposures.

The actual dosing scheme in PART-1 (SAD), (in Periods 1, 2, and 3) is shown in Table 10 and the dosing regimens evaluated in the 5 different parts of the study are listed in Table 11. Except for 3 doses in the SAD and PART-3: rBA/FE, ritonavir 100 mg was used as PK enhancer in this study.

A total of 70 participants were enrolled in the study. The number of participants in each part of the study is listed in Table 11. One participant in PART-1: SAD, Cohort 1, discontinued after testing COVID-19 positive in a protocol specified test, and was replaced in Period 2. In PART-2, only 1 participant from the placebo (suspension)/ritonavir 100 mg BID (fasted) group discontinued due to 'withdrawal by participant'. No participant discontinued in PART-3, 4 or 5.

Figure 1. Study Design Schema of Study 1001 in Healthy Adult Participants



Source: Study 1001 CSR Appendix 16.1.1 Protocol (Updated based on Table 11)

Table 10. Actual Dosing Scheme of PF-07321332 in Study 1001 PART-1: SAD

Cohort	N	Period 1	Period 2	Period 3
1	2	150 mg	1500 mg	Placebo/ritonavir
	2	150 mg	Placebo	750 mg/ ritonavir
	2	Placebo	1500 mg	750 mg/ ritonavir
2	2	500 mg	250 mg/ ritonavir	250 mg/ ritonavir (fed)
	2	500 mg	Placebo/ ritonavir	Placebo/ ritonavir (fed)
	2	Placebo	250 mg/ ritonavir	250 mg/ ritonavir (fed)

Ritonavir 100 mg was administered at -12h, 0h and 12h with respect to PF-07321332 dosing. Fed represents high-fat high-calorie meal.

Table 11. Actual Dosing Regimens of PF-07321332 (With or Without Ritonavir) Evaluated in Study 1001

Part of the study	N	Dosing regimen evaluated[a]
PART-1: SAD	13	PF-07321332 150 mg PF-07321332 500 mg PF-07321332 1500 mg PF-07321332 250 mg at 0h + ritonavir 100 mg at -12, 0 and 12h PF-07321332 750 mg at 0h + ritonavir 100 mg at -12, 0 and 12h PF-07321332 250 mg at 0h (Fed) + ritonavir 100 mg at -12, 0 and 12h
PART-2: MAD	29	PF-07321332/ritonavir 75/100 mg BID for 10 days PF-07321332/ritonavir 250/100 mg BID for 10 days PF-07321332/ritonavir 500/100 mg BID for 10 days PF-07321332/ritonavir 250/100 mg BID for 10 days in Japanese participants
PART-3: rBA/FE	12	PF-07321332 250 mg Tablet PF-07321332 250 mg Tablet (Fed) PF-07321332 250 mg suspension
PART-4: M&E	6	PF-07321332 300 mg at 0h + ritonavir 100 mg at -12, 0, 12 and 24 h
PART-5: SE	10	PF-07321332 2250 mg (divided into 3 doses of 750 mg administered at 0, 2 and 4h) + ritonavir 100 mg at -12, 0 and 12 h

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

6.3.2.2. PK Results

6.3.2.2.1. Part 1: SAD

PK parameters by treatment are summarized descriptively in Table 12. Statistical analysis of food effect on PK of PF-07321332/ritonavir is presented in Table 13.

Less than dose proportional increases in PF-07321332 exposure was observed following single dose administration of PF-07321332 as an oral suspension at doses of 150 mg, 500 mg, and 1500 mg without ritonavir under fasted conditions. The median T_{max} was observed at 0.634 to 1 hour post-dose across all doses tested without ritonavir. Of the doses administered without ritonavir, mean $t_{½}$ could only be reported for the 150 mg dose, which was 2.02 hours.

Use of ritonavir as PK enhancer appeared to considerably increase PF-07321332 exposure. The geometric mean AUC_{inf}, AUC_{last} and C_{max} following a single dose of PF-07321332 250 mg in fasted state enhanced with ritonavir was 28.22 µg•h/mL, 27.6 µg•h/mL and 2.882 µg/mL, respectively. Comparatively, the geometric mean AUC_{inf}, AUC_{last} and C_{max} following a single dose of PF-07321332 250 mg in fasted state (without ritonavir) in PART-3 (Module 5.3.3.1 Study 1001 CSR Table 35) was 3.513 µg•h/mL, 3.318 µg•h/mL and 0.883 µg/mL, respectively.

Less than dose proportional increase in PF-07321332 exposure was observed following administration of PF-07321332 750 mg as an oral suspension enhanced with 100 mg ritonavir under fasted conditions compared to PF-07321332 250 mg administered under the same condition. The geometric mean dose normalized AUC_{last}, AUC_{inf} and C_{max} values at the 750 mg dose were approximately 22%, 21% and 41% lower respectively compared to the 250 mg dose. The median T_{max} of 2.75 and 2.0 hrs post-dose (Module 5.3.3.1 Study C4671001 CSR Section 11.1.1) was observed at 250 mg and 750 mg dose, respectively, when enhanced with ritonavir in fasted state. Mean $t_{½}$ of 6.94 hours and 12.86 hours was observed at 250 mg and 750 mg dose when boosted with ritonavir in fasted state (Table 12).

Geometric mean AUC_{last} and AUC_{inf} values for PF-07321332 fed treatment were similar to those observed for the fasted treatment with an approximately 15% higher geometric mean C_{max} value observed for the fed treatment compared to the fasted treatment. The test/reference ratios of the adjusted geometric means (90% CI) for PF-07321332 AUC_{last} and C_{max} were 101.53% (90.18%, 114.31%) and 115.30% (99.36%, 133.79%) respectively, for PF-07321332/ritonavir fed treatment (Test) compared to PF-07321332/ritonavir fasted treatment (Reference) indicating that there is minimum effect of food on the PK of PF-07321332 (Table 13).

Table 12. Descriptive Summary of Plasma PF-07321332 PK Parameters - Part-1: SAD (PK Parameter Set) (Protocol C4671001)

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

Ritonavir dosed at -12h, 0h and 12h post-dose.
Source: Table 14.4.5.1.1 and 16.2.5.5.1.1
N = Total number of participants in the treatment group
N1 = Number of participants contributing to the summary statistics
N2 = Number of participants where $t_{1/2}$, AUC_{inf}, AUC_{inf}(dn), CL/F and V_z/F were determined
NR = Not Reported
a. Geometric Mean (Geometric %CV) for all except: Median (Range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$
b. Individual values were listed when there were less than 3 evaluable measurements
Summary statistics were not presented if fewer than 3 participants had reportable parameter values.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](10:06) Source Data: adpp Table Generation: [redacted]
(06:58)
Output File: ./nda1_cdisc/C4671001_CSR_PK/adpp_s102_s
Table 14.4.5.2.1 PF-07321332 is for Pfizer internal use.

Table 13. Statistical Summary of Plasma PF-07321332 PK Parameters - Food Effect, Part-1: SAD (PK Parameter Set) (Protocol C4671001)

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

Source: Table 14.4.5.4.1
Ritonavir dosed at -12h, 0h and 12h post-dose
The model was a mixed effect model with treatment as fixed effect and participant as a random effect.
a. The ratios (and 90% CIs) were expressed as percentages.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](10:06) Source Data: adpp Table Generation: [redacted] (22:51)
Output File: ./nda1_cdisc/C4671001_CSR_PK/adpp_s201_it_s
Table 14.4.5.5.1 is for Pfizer internal use.

6.3.2.2.2. Part 2: MAD

Median plasma PF-07321332 concentration-time profiles including C_{trough} concentrations are presented across all days and treatments in Figure 2. PK parameters by treatment and day are summarized descriptively in Table 14.

Following multiple dose administration of PF-07321332/ritonavir at doses of 75/100 mg, 250/100 mg, and 500/100 mg BID under fasted conditions, a median T_{max} of 0.750 to 2.75 hours post-dose across all treatments on Days 1, 5, and 10 (Table 14).

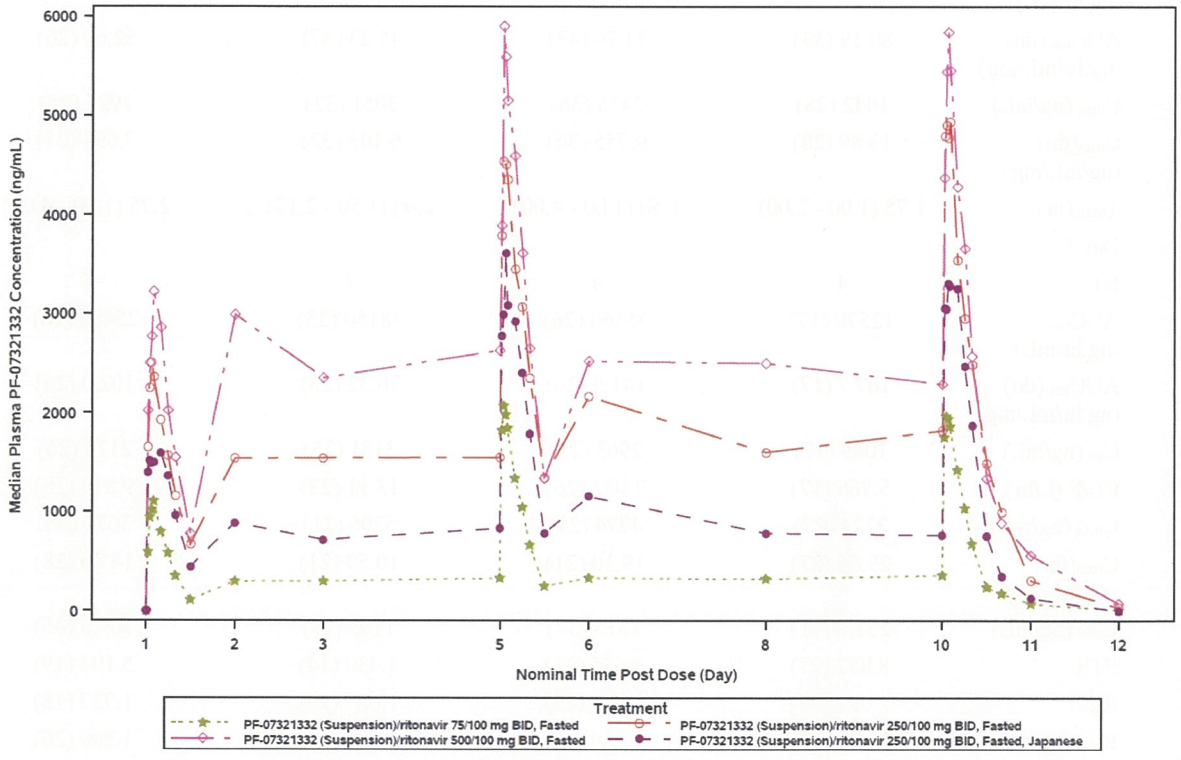
PF-07321332 exposure on Days 1, 5, and 10 appeared to increase in a less than dose proportional manner across the doses studied with dose normalized AUC_{tau} and C_{max} values decreasing as the dose increased. For example, following multiple dose administration of PF-07321332/ritonavir at doses of 75/100 mg, 250/100 mg, and 500/100 mg BID under fasted conditions dose normalized AUC_{tau} on Day 10 was 168.3, 151.1 and 79.56 ng*h/mL/mg, respectively (Table 14).

Steady-state plasma concentrations appeared to have been achieved by Day 2 for all doses and treatments (Figure 2). 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 AUC_{tau} (R_{ac}) and C_{max} ($R_{ac,Cmax}$), on Day 10, across all treatments Table 14).

Following multiple dosing of PF-07321332/ritonavir, PF-07321332 mean t½ values on Day 10 ranged from 6.8 to 8.0 hours across all treatments in non-Japanese participants (Table 14).

Urinary recovery ($\%Ae_{tau}$) of unchanged PF-07321332 decreased with an increase in PF-07321332 dose, with 64%, 52% and 23% of the dose recovered in urine for the 75 mg, 250 mg, and 500 mg PF-07321332 doses enhanced with 100 mg ritonavir, respectively. However, renal clearance (CL_r) was similar across all doses with 3.782, 3.433 and 2.934 L/hr at 75 mg, 250 mg and 500 mg PF 07321332 doses enhanced with 100 mg ritonavir, respectively (Table 14).

Figure 2. Median Plasma PF-07321332 Concentration-Time Profiles on Across All Dosing Days Following Multiple Oral Doses of PF-07321332 Enhanced with Ritonavir in PART-2, Study 1001



Summary statistics had been calculated by setting concentration values below the lower limit of quantification to zero.
The lower limit of quantification was 10 ng/mL.
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Output File: ./nda1_cdisc/C4671001_CSR_PK/adpc_f201_m

Table 14. Descriptive Summary of Plasma and Urine PF-07321332 PK Parameters - Part-2: MAD (PK Parameter Set) (Protocol C4671001)

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)

Table 14. Descriptive Summary of Plasma and Urine PF-07321332 PK Parameters - Part-2: MAD (PK Parameter Set) (Protocol C4671001)

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)
C_{min} (ng/mL)	245.3 (27)	1480 (27)	1279 (31)	12.50 (2.0814162E15)
PTR	8.383 (16)	3.462 (5)	4.385 (17)	6.270 (32)
R_{ac}	2.104 (30)	2.022 (16)	1.757 (26)	2.047 (16)
$R_{ac, Cmax}$	1.971 (34)	2.101 (16)	1.840 (29)	1.962 (14)
$t_{1/2}$ (hr)	7.955 ± 2.0401	6.795 ± 1.7072	8.047 ± 1.7871	5.163 ± 2.0915
T_{max} (hr)	1.00 (1.00 - 2.00)	1.00 (1.00 - 2.00)	1.50 (1.00 - 2.00)	1.50 (0.500 - 2.02)
V_z/F (L)	66.43 (24)	63.40 (13)	142.4 (37)	65.04 (31)
Ae_{tau} (mg)	47.83 (12)	129.9 (4)	116.5 (122)	135.4 (5)
Ae_{tau} %	63.79 (12)	51.81 (4)	23.35 (121)	54.20 (5)
CL_r (L/hr)	3.782 (20)	3.433 (23)	2.934 (128)	5.028 (11)

Source: Table 14.4.5.1.2.1 and 14.4.5.1.2.2
N = Total number of participants in the treatment group
N1 = Number of participants contributing to the summary statistics
N2 = Number of participants where $t_{1/2}$ and V_z/F were determined
a. Geometric Mean (Geometric %CV) for all except: Median (Range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$
For the parameters analyzed on the log scale, zero values had been substituted with 0.0001 prior to log transformation.
Summary statistics were not presented if fewer than 3 participants had reportable parameter values.
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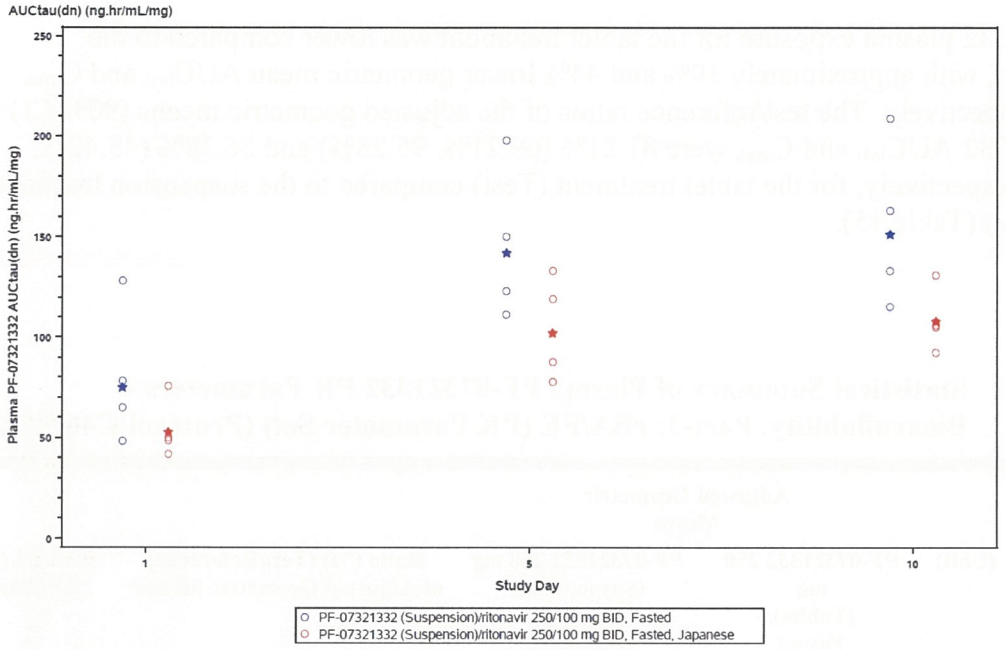
Output File: ./nda1_cdisc/C4671001_CSR_PK/adpp_s102_m
Table 14.4.5.2.2 is for Pfizer internal use.

6.3.2.2.2.1. Multiple Dose PK in Japanese Participants

The exposure of PF-07321332 in Japanese participants was numerically lower but not meaningfully different than in non-Japanese participants (Table 14). As shown in Figure 3, the distribution of dose normalized AUC_{tau} and C_{max} on Day 1, Day 5, and Day 10 following PF-07321332/ritonavir 250/100 mg BID in Japanese and non-Japanese participants is generally comparable. Although, the geometric mean dose normalized AUC_{tau} and C_{max} of PF-07321332 was approximately 30% and 21% to 26% lower in Japanese participants compared to that observed for non-Japanese participants across all days (Table 14 and Figure 3) but those differences are unlikely to be meaningful.

Figure 3. Individual and Geometric Mean Plasma PF-07321332 Dose Normalized AUC_{tau} (Upper Panel) and Cmax (Lower Panel) Values Following Multiple Oral Doses of PF-07321332 Enhanced with Ritonavir in PART-2 - Japanese Cohort Comparison, Study 1001



Circles represented individual participant values and stars represented geometric mean.
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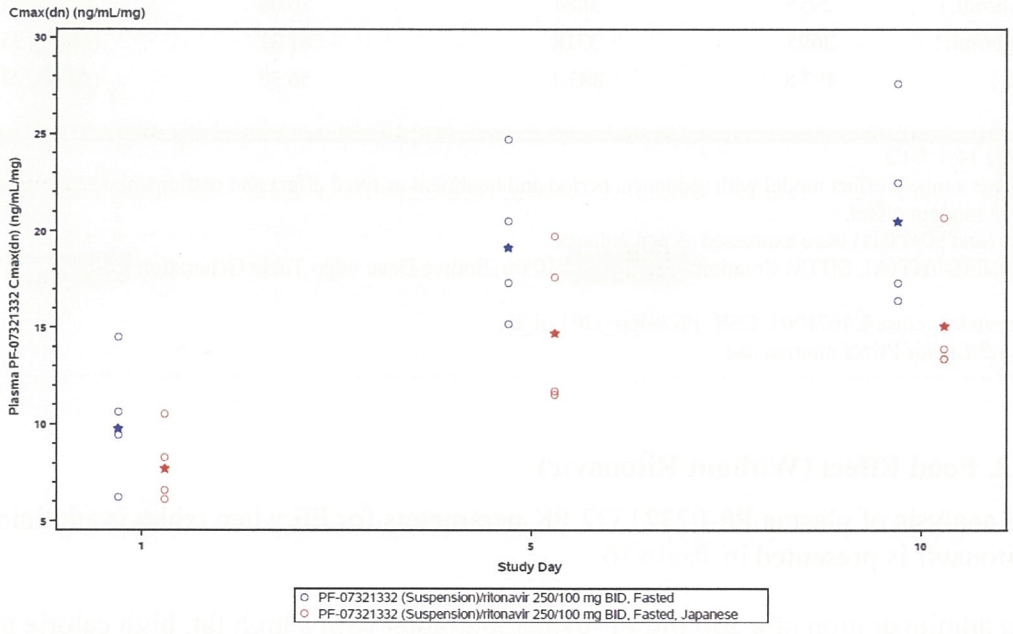

Circles represented individual participant values and stars represented geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: [redacted] (10:06) Source Data: adpp Table Generation: [redacted] (23:24)
Output File: ./nda1_cdisc/C4671001_CSR_PK/adpp_f102_m

6.3.2.2.3. Part 3: rBA/FE

6.3.2.2.3.1. Relative Bioavailability (without ritonavir)

Statistical analysis of plasma PF-07321332 PK parameters for rBA is presented in Table 15.

PF-07321332 plasma exposure for the tablet treatment was lower compared to the suspension, with approximately 19% and 44% lower geometric mean AUC_{last} and C_{max} values, respectively. The test/reference ratios of the adjusted geometric means (90% CI) for PF-07321332 AUC_{last} and C_{max} were 81.21% (69.21%, 95.28%) and 56.38% (43.42%, 73.19%) respectively, for the tablet treatment (Test) compared to the suspension treatment (Reference) (Table 15).

Table 15. Statistical Summary of Plasma PF-07321332 PK Parameters - Bioavailability, Part-3: rBA/FE (PK Parameter Set) (Protocol C4671001)

	Adjusted Geometric Means			
Parameter (Unit)	**PF-07321332 250 mg (Tablet), Fasted (Test)**	**PF-07321332 250 mg (Suspension), Fasted (Reference)**	**Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]**	**90% CI (%) for Ratio[a]**
AUC_{inf} (ng.hr/mL)	2955	3884	76.06	(60.14, 96.20)
AUC_{last} (ng.hr/mL)	2695	3318	81.21	(69.21, 95.28)
C_{max} (ng/mL)	497.8	883.1	56.38	(43.42, 73.19)

Source: Table 14.4.5.4.2
The model was a mixed effect model with sequence, period and treatment as fixed effect and participant nested within sequence as a random effect.
a. The ratios (and 90% CIs) were expressed as percentages.
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Output File: ./nda1_cdisc/C4671001_CSR_PK/adpp_s201_it_ba
Table 14.4.5.5.2 is for Pfizer internal use.

6.3.2.2.3.2. Food Effect (Without Ritonavir)

Statistical analysis of plasma PF-07321332 PK parameters for FE when tablet is administered without ritonavir is presented in Table 16.

Following administration of a 250 mg PF-07321332 tablet with a high fat, high calorie meal, median T_{max} was 1.75 hours post-dose compared to 1.0 hour post-dose for the fasted treatment (Module 5.3.3.1 Study 1001 CSR Table 35).

PF-07321332 plasma exposure was higher for the fed treatment with approximately 1.5 and 2.4-fold higher geometric mean AUC_{last} and C_{max} values respectively compared to the fasted treatment. The test/reference ratios of the adjusted geometric means (90% CI) for PF-07321332 AUC_{last} and C_{max} were 148.91% (126.92%, 174.72%) and 244.84% (188.58%, 317.87%), respectively, for the fed treatment (Test) compared to the fasted treatment (Reference) (Table 16).

Table 16. Statistical Summary of Plasma PF-07321332 PK Parameters - Food Effect, Part-3: rBA/FE (PK Parameter Set) (Protocol C4671001)

Parameter (Unit)	Adjusted Geometric Means		Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI (%) for Ratio[a]
	PF-07321332 250 mg (Tablet), Fed (Test)	PF-07321332 250 mg (Tablet), Fasted (Reference)		
AUC_{inf} (ng.hr/mL)	4337	2955	146.80	(118.80, 181.41)
AUC_{last} (ng.hr/mL)	4012	2695	148.91	(126.92, 174.72)
C_{max} (ng/mL)	1219	497.8	244.84	(188.58, 317.87)

Source: Table 14.4.5.4.3
The model was a mixed effect model with sequence, period and treatment as fixed effect and participant nested within sequence as a random effect.
a. The ratios (and 90% CIs) were expressed as percentages.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](10:06) Source Data: adpp Table Generation: [redacted] (23:01)
Output File: ./nda1_cdisc/C4671001_CSR_PK/adpp_s201_it_fe
Table 14.4.5.5.3 is for Pfizer internal use.

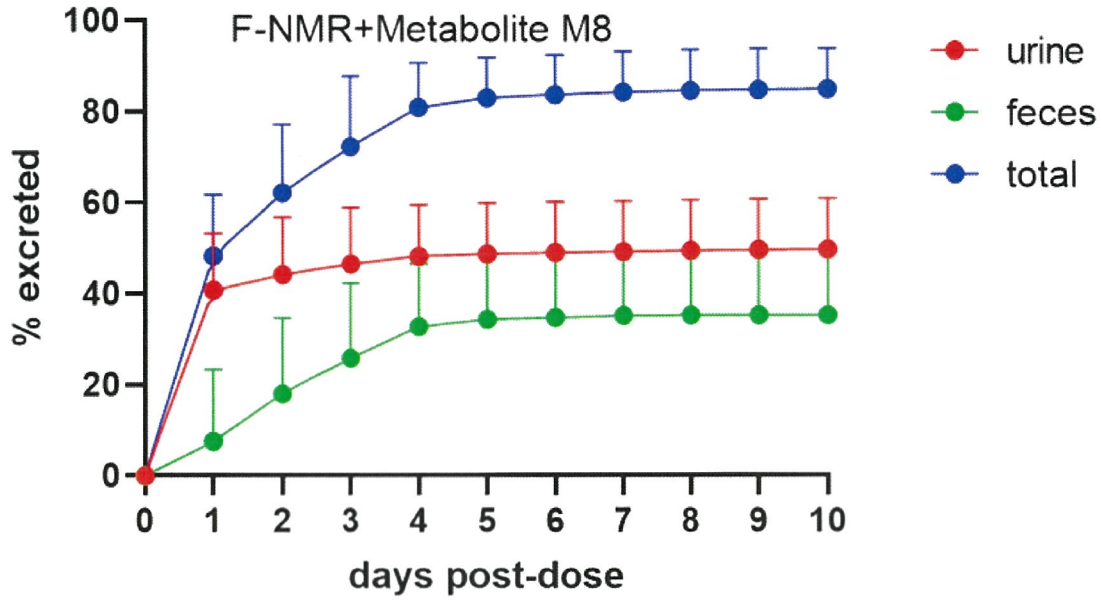
6.3.2.2.4. Part 4: Metabolism & Excretion

The cumulative mean (+SD) excretion of PF-07321332-related material in urine and feces of healthy participants using ^{19}F-NMR method is presented in Figure 4.

Overall mean ± SD (range) mass recovery of PF-07321332-related material in excreta (urine and feces) was calculated at 84.9% ± 8.9% (70.7%, 95.5%) which included 80.7% ± 8.0% by quantitative ^{19}F-NMR and 4.2% ± 1.3% excreted as metabolite M8 (^{19}F-NMR silent due to loss of trifluoroacetyl group) quantified by UHPLC-HRMS. The excretion into urine and feces was 49.6% and 35.3 % of dose, respectively. Almost all of the excretion of drug-related material occurred over the first 5 days following the dose, and most of the drug-related material that was excreted in the urine appeared within the first day following the dose.

The mass recovery of 84.9% is consistent with historical human mass balance data as described for more 100 drugs wherein the mean mass balance recovery by radiolabel ADME studies was 89% (±11%).[67]

Figure 4. Cumulative Mean (+ SD) Excretion of PF-07321332-Related Material in Urine and Feces of Healthy Participants Following Oral Administration of PF-07321332 Suspension Enhanced with Ritonavir Measured by ^{19}F-NMR Spectroscopy



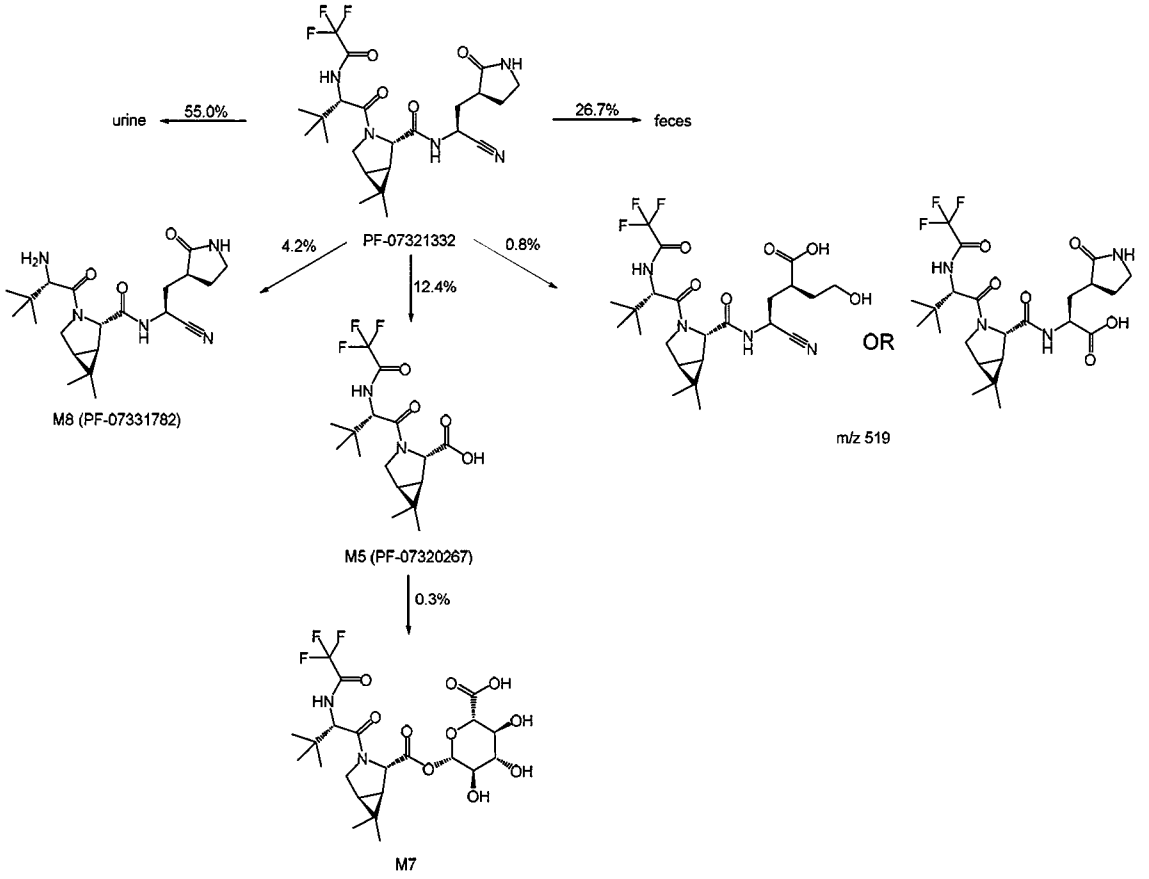
Source: Study 1001 CSR Appendix 16.2.5.10.3
Ritonavir 100 mg was administered at -12 h, 0 h, 12 h and 24 h. PF-07321332 (300 mg) oral suspension was administered at 0 h after at least 10 h of fasting. Data includes metabolite M8, which was ^{19}F-NMR silent, and was quantitated using UHPLC-HRMS/MS.

6.3.2.2.4.1. Metabolic profiling

In plasma, the only drug-related entity quantifiable by ^{19}F-NMR was unchanged PF-07321332 (Module 5.3.3.1. Study 1001 CSR Appendix 16.2.5.10.4).

A metabolic scheme for PF-07321332 is shown in Figure 5 and listing of metabolites in Table 17. In excreta, PF-07321332 was also the predominant drug-related entity. After normalization of the data to 100% mass balance, unmetabolized PF-07321332 represented 82.5% of the drug-related material, with 55.0% in urine and 27.5% in feces. Metabolite M5, arising via hydrolysis, was present at 12.1% of dose with almost all in the feces. All other fluorine-containing metabolites were minor (<1% of dose), and M8 was 4.2% of dose.

Figure 5. Profile of PF-07321332 Metabolism and Disposition in Healthy Participants



Source: Study 1001, Appendix 16.2.5.10.5

Table 17. Summary of Metabolites of PF-07321332 in Urine and Feces of Healthy Participants Following Oral Administration of PF-07321332 Suspension Enhanced with Ritonavir

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]

a.Calculated based on dose normalization to 95.8% mass balance (ie, 100% minus the 4.2% of dose comprised by non-fluorine containing metabolite M8).
b.Sums do not exactly match due to rounding.
Source: Module 5.3.3.1 Study 1001 CSR, Appendix 16.2.5.10.5

6.3.2.2.4.2. Plasma PK

Following administration of a 300 mg oral suspension of PF-07321332 enhanced with 100 mg ritonavir under fasted conditions, PF-07321332 mean AUC_{last} and C_{max} values were 32.96 µg•hr/mL and 4.07 µg/mL, respectively (Module 5.3.3.1 Study 1001 CSR Table 38).

6.3.2.2.5. Part 5: Supratherapeutic Exposure

To achieve supratherapeutic concentrations, considering the less than dose proportional increase in systemic exposure, PF-07321332 dose was divided into 3 doses of 750 mg each administered at 0, 2 and 4 hr. PK parameters for PF-07321332 in PART-5 are presented in Table 18. The C_{max} and AUC_{inf} of PF-07321332 at supratherapeutic dose of 2250 mg were 15.940 µg/mL and 188.800 µg.hr/mL, respectively.

Table 18. Descriptive Summary of Plasma PF-07321332 PK Parameters - Part-5: SE (PK Parameter Set) (Protocol C4671001)

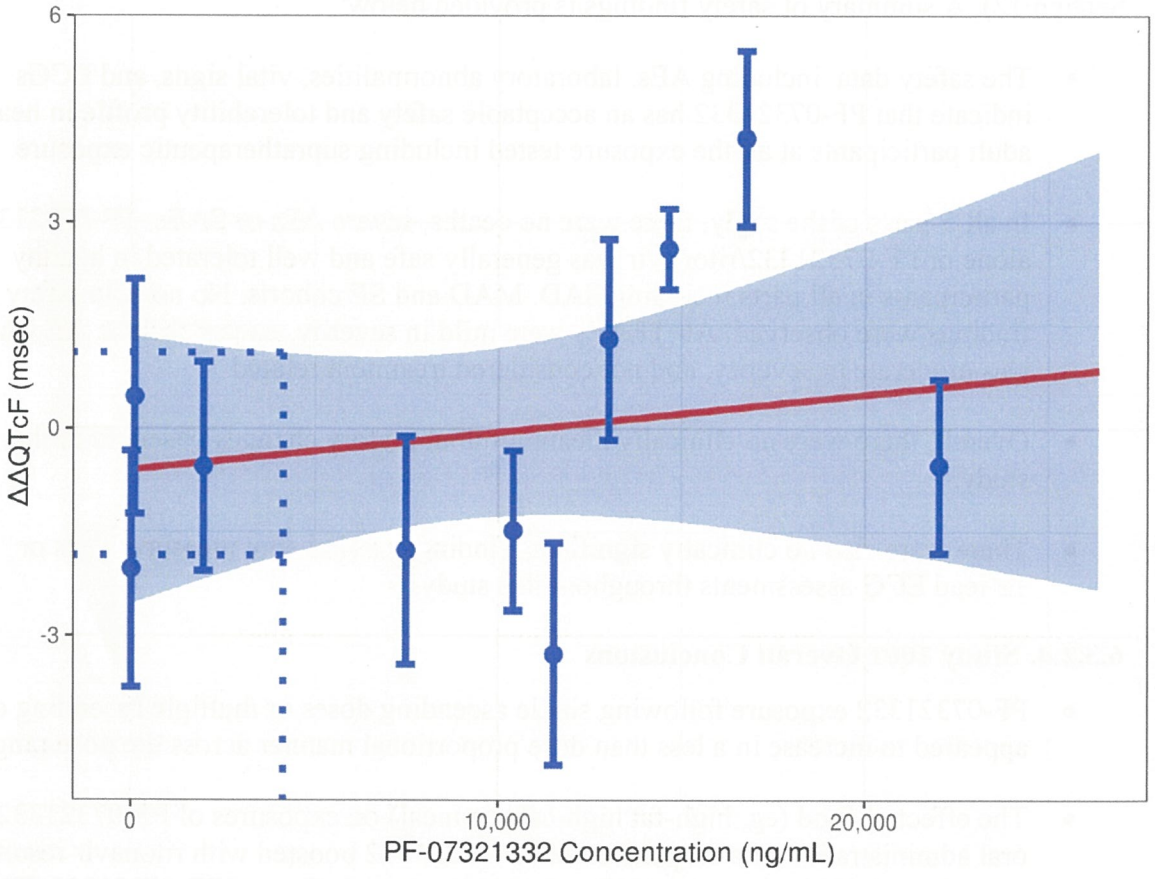
Parameter (Unit)[a]	PF-07321332 2250 mg (Suspension)/ ritonavir 100 mg (N=10)
N1, N2	10, 10
AUC_{inf} (ng.hr/mL)	188800 (35)
AUC_{inf}(dn) (ng.hr/mL/mg)	251.9 (35)
AUC_{last} (ng.hr/mL)	188200 (35)
AUC_{last}(dn) (ng.hr/mL/mg)	251.0 (35)
CL/F (L/hr)	3.970 (35)
C_{max} (ng/mL)	15940 (27)
C_{max}(dn) (ng/mL/mg)	21.27 (27)
$t_{1/2}$ (hr)	7.450 ± 2.9357
T_{max} (hr)	5.00 (3.02 - 6.03)
V_z/F (L)	40.06 (55)

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.
Source: Table 14.4.5.1.5
N = Total number of participants in the treatment group
N1 = Number of participants contributing to the summary statistics
N2 = Number of participants where $t_{1/2}$, AUC_{inf}, AUC_{inf}(dn), CL/F and V_z/F were determined
a. Geometric Mean (Geometric %CV) for all except: Median (Range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$
Summary statistics were not presented if fewer than 3 participants had reportable parameter values.
PFIZER CONFIDENTIAL SDTM Creation: [redacted] (10:06) Source Data: adpp Table Generation: [redacted] (06:17)
Output File: ./nda1_cdisc/C4671001_CSR_PK/adpp_s102_se
Table 14.4.5.2.5 PF-07321332 is for Pfizer internal use.

6.3.2.2.5.1. C-QTcF Modeling

No clinically relevant effect of PF-07321332/ritonavir on QTcF interval is expected based on C-QTc analysis of ECG data collected in the SE part of the study (Module 5.3.3.5 pmar-eqdd-c467a-dp3-1289-exposure-response). The upper bounds of 90% CI for ΔΔQTcF estimates across the entire concentration range were all less than 10 ms, the threshold for potential clinical and regulatory concern (Figure 6). The upper bound of 90% CI for ΔΔQTcF estimate at 2-fold of expected mean $C_{max,ss}$ for the therapeutic dose was 1.07 ms and the value at mean C_{max} of the highest dose in Study 1001, which is approximately 4-fold higher than the expected mean $C_{max,ss}$ for the therapeutic dose, was 1.96 ms (Table 19).

Figure 6. ΔΔQTcF versus Concentration Plot



The red line is the predicted ΔΔQTcF over the range of observed concentrations and shaded region is the 90% CI. Blue circles and error bars represent the observed ΔΔQTcF (using the model-estimated, time-matched placebo effect subtracted from the ΔQTcF of the active treatment group's observations) across the observed concentration bins (n = 10, with equal number of observations in each bin). The blue dotted lines correspond to the predicted lower and upper 90% CI ΔΔQTcF for the projected mean C_{max} at Phase 2/3 dose.
Source: Module 5.3.3.5 pmar-eqdd-c467a-dp3-1289-exposure-response

Table 19. 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
Source: Module 5.3.3.5 pmar-eqdd-c467a-dp3-1289-exposure-response

6.3.2.3. Safety Conclusions

Detailed safety results are included in the Study 1001 CSR (Module 5.3.3.1, Study 1001 CSR Section 12). A summary of safety findings is provided below:

- The safety data, including AEs, laboratory abnormalities, vital signs, and ECGs indicate that PF-07321332 has an acceptable safety and tolerability profile in healthy adult participants at all the exposure tested including supratherapeutic exposure.

- In all 5-parts of the study, there were no deaths, severe AEs or SAEs. PF-07321332 alone or PF-07321332/ritonavir was generally safe and well tolerated in healthy participants in all parts including SAD, MAD and SE cohorts. No notable safety findings were observed. All TEAEs were mild in severity, except for one AE which was moderate in severity, and not considered treatment related.

- Overall, there were no clinically meaningful laboratory changes observed in this study.

- There were also no clinically significant findings in vital sign measurements or 12-lead ECG assessments throughout this study.

6.3.2.4. Study 1001 Overall Conclusions

- PF-07321332 exposure following single ascending doses or multiple ascending doses appeared to increase in a less than dose proportional manner across the dose range.

- The effect of food (eg, high-fat high-calorie meal) on exposures of PF-07321332 after oral administration of a suspension of PF-07321332 boosted with ritonavir resulted in only about 1.5% increase in AUC and 15% increase in C_{max} of PF-07321332. The test/reference ratios of the adjusted geometric means (90% CI) for PF-07321332 AUC_{last} and C_{max} were 101.53% (90.18%, 114.31%) and 115.30% (99.36%, 133.79%) respectively, for PF-07321332/Ritonavir fed treatment (Test) compared to PF-07321332/ritonavir fasted treatment (Reference).

- Steady state was achieved around Day 2 for all treatments in MAD.

- PF-07321332 accumulation was approximately 2-fold following multiple dosing and values were similar on Day 5 and Day 10 across all treatments. Geometric mean

accumulation ratios ranged from 1.8 to 2.1 for AUC_{tau} (R_{ac}) and C_{max} ($R_{ac,Cmax}$), on Day 10, across all treatments.

- Urinary recovery of unchanged PF-07321332 was high and appeared to decrease with an increase in PF-07321332 dose with 64%, 52% and 23% of the dose recovered in urine for the 75 mg, 250 mg, and 500 mg PF-07321332 boosted with 100 mg ritonavir, respectively.

- The exposure of PF-07321332 in Japanese participants was numerically lower but not meaningfully different than those in non-Japanese participants. PF-07321332 exposure in Japanese participants was approximately 30% lower compared to non-Japanese participants based on geometric mean AUC_{tau}. PF-07321332 mean $t_{½}$ was 5.2 hours for the Japanese participants compared to 6.8 hours for the non-Japanese participants. Drug accumulation on Day 10 based on AUC_{tau} (R_{ac}) and C_{max} ($R_{ac}C_{max}$) ratios was similar between the Japanese and non-Japanese participants. Urinary recovery of unchanged PF-07321332 was similar between Japanese and non-Japanese participants.

- PF-07321332 plasma exposure for the tablet treatment was lower compared to the suspension. The test/reference ratios of the adjusted geometric means (90% CI) for PF-07321332 AUC_{last} and C_{max} were 81.21% (69.21%, 95.28%) and 56.38% (43.42%, 73.19%) respectively, for the tablet treatment (Test) compared to the suspension treatment (Reference).

- PF-07321332 plasma geometric mean AUC_{last} and C_{max} in fed state was approximately 1.5 and 2.4-fold higher than fasted state when PF-07321332 tablet was administered without PK enhancing with ritonavir. The test/reference ratios of the adjusted geometric means (90% CI) for PF-07321332 AUC_{last} and C_{max} were 148.91% (126.92%, 174.72%) and 244.84% (188.58%, 317.87%) respectively, for the fed treatment (Test) compared to the fasted treatment (Reference).

- Overall mean ± SD (range) mass recovery of PF-07321332-related material in excreta (urine and feces) was calculated at 84.9% ± 8.9% (70.7%, 95.5%) which included 80.7% ± 8.0% by quantitative ^{19}F-NMR and 4.2% ± 1.3% excreted as metabolite M8 (^{19}F-NMR silent due to loss of trifluoroacetyl group). Almost all the excretion of drug-related material occurred over the first 5 days following the dose, and most of the drug-related material that was excreted in the urine appeared within the first day following the dose.

- In plasma, the only drug-related entity quantifiable by ^{19}F-NMR was unchanged PF-07321332. In excreta, PF-07321332 was also the predominant drug-related entity.

- C-QTc analysis using ECG data from healthy adult participants indicates that treatment with PF-07321332 is not associated with clinically relevant QTc prolongation. The upper bound of 90% CI for ΔΔQTcF estimate was less than 10 ms across the entire investigated concentration range of PF-07321332, including

supratherapeutic concentrations up to 4-times the projected mean C_{max} at the proposed therapeutic dose.

- The safety data, including AEs, laboratory abnormalities, vital signs, and ECGs indicate that PF-073213332 has an acceptable safety and tolerability profile in healthy adult participants.

6.3.3. Study 1011 – Renal Impairment Study

This was a Phase 1, non-randomized, open label, 2-part study to investigate the effect of renal impairment on the plasma and urine PK, safety, and tolerability of a single 100 mg oral dose of PF-07321332 in combination with the PK enhancing agent ritonavir (Module 5.3.3.4, Study C4671011 CSR).

Part 1 was conducted in participants with stable mild (eGFR ≥60 to <90 mL/min) or moderate (eGFR ≥30 to <60 mL/min) renal impairment and a control group of participants with normal (eGFR ≥90 mL/min) renal function. Part 2 was conducted in participants with stable severe (eGFR <30 mL/min and not requiring dialysis) renal impairment. Participants were assigned to mild, moderate, severe renal impairment group or to normal healthy control group based on BSA-adjusted eGFR calculated using CKD-EPI equation. All study participants received a single 100 mg dose of PF-07321332 administered orally 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. Serial blood and urine samples at specified intervals were collected up to 48 hours post-dose for plasma and urine PK assessments. The plasma and urine concentration of PF-07321332 were measured using a validated high-performance liquid chromatography tandem mass spectrometric (HPLC/MS/MS) method (Module 5.3.3.4 C4671011 Analytical Report - PF-07321332 AND RITONAVIR IN HUMAN K2EDTA PLASMA SAMPLES and Module 5.3.3.4 C4671011 Analytical Report - PF-07321332 IN HUMAN URINE SAMPLES). PK parameters were determined from plasma concentration-time data.

A total of 35 participants were assigned to treatment and 34 of them were treated, 8 each in mild, moderate, and severe renal impairment group and 10 in healthy control group. One participant in the moderate renal impairment group was discontinued because of AEs before PF-07321332 administration on Day 1. The mean (SD) age across 4 renal function groups was 62.2 (7.45) years, ranging from 47 to 76 years (Study 1011, Table 14.1.2.1.1). The overall mean (SD) body weight and BMI across the 4 renal function groups was 86.75 (13.88) kg and 29.37 (3.89) kg/m^2, respectively (Study 1011, Table 14.1.2.2.1). Gender and race distribution across the 4 renal function groups was approximately 2:1 for male to female and White to Black/African American (Study 1011, Table 14.1.2.1.1). The healthy participants were matched such that age was within ±10 years and weight was within ±15 kg of the renally impaired participants. Gender and race distribution was similar between the healthy control group and the renal impairment groups.

Descriptive summary of PF-07321332 plasma PK parameters by renal function group are provided in Table 20 (note Study 1011 was undertaken with a single dose of 100 mg PF-07321332, enhanced with ritonavir). Results of the statistical comparisons of PF-07321332 exposure parameters (AUC_{inf}, and C_{max}) are summarized in Table 21.

Mean AUC_{inf} values increased approximately 24%, 87% and 204% in mild, moderate, and severe renal impairment respectively compared to the normal renal function group. PF-07321332 systemic exposure increased with increasing severity of renal impairment. Adjusted geometric mean (90% CI) AUC_{inf}, 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 (Table 21).

Mean C_{max} values increased by approximately 30%, 38%, and 48% for the mild, moderate, and severe renal impairment groups, respectively, compared to the normal renal function group. Adjusted geometric mean (90% CI) test/reference ratios for C_{max} were 129.78% (101.93%, 165.25%) for mild renal impairment, 138.12% (113.18%, 168.55%) for moderate renal impairment, and 148.02% (111.40%, 196.68%) for severe renal impairment participants (Table 21).

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.

Urinary recovery of unchanged PF-07321332 was 31%, 43%, 31%, and 18% for the normal, mild impairment, moderate impairment, and severe impairment renal groups, respectively. Regression plot of CL/F versus eGFR derived from CKD-EPI equation (Figure 7) showed a clear trend of decreasing clearance with a decrease in renal function, with intercept of 1.83 ($P = 0.0009$) and slope of 0.05 ($P<0.0001$).

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

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

Source: Table 14.4.5.1.1 and 14.4.5.1.2
N = Total number of participants in the cohort in the indicated population.
N1 = Number of participants contributing to the summary statistics.
n = Number of participants contributing to the summary statistics for $t_{1/2}$, AUC_{inf}, CL/F and V_Z/F.
a. Geometric mean (Geometric %CV) for all: except Median (Range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](00:43) Source Data: adpp Table Generation: [redacted]
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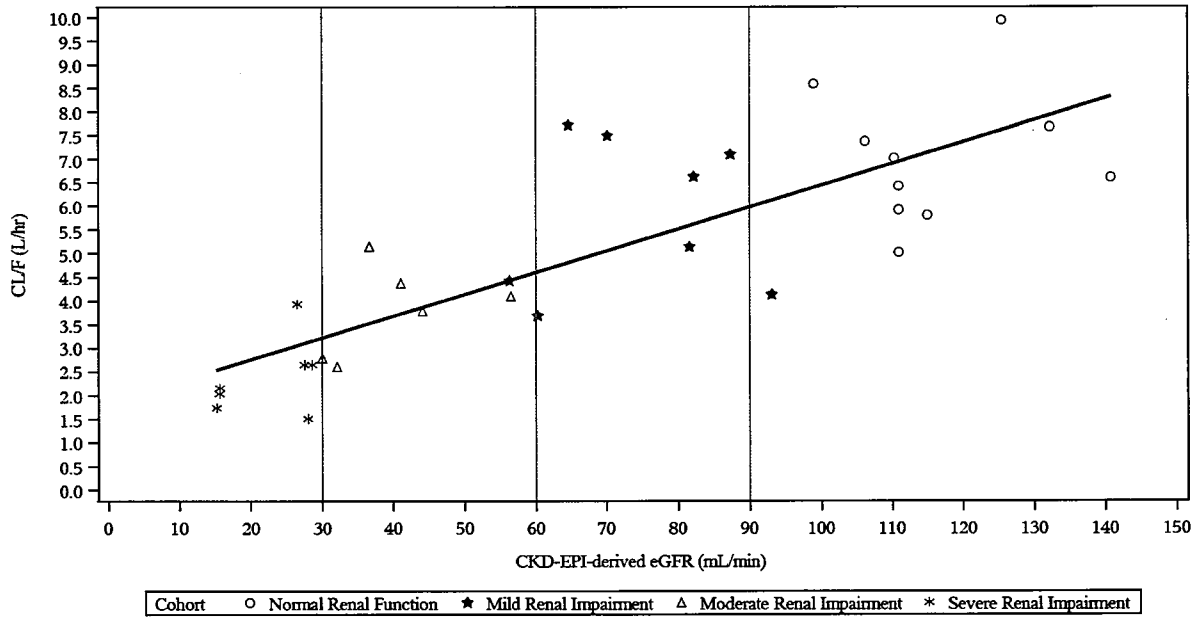
Table 21. Statistical Summary (ANOVA) of Plasma PF-07321332 PK Parameters (AUC_{inf} and C_{max}), Protocol C4671011

Parameter (Units)	Test	Reference	Adjusted Geometric Means		Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI (%) of Ratio[a]
			Test	Reference		
C_{max} (ng/mL)	Mild Renal Impairment	Normal Renal Function	2077	1600	129.78	(101.93, 165.25)
	Moderate Renal Impairment	Normal Renal Function	2210	1600	138.12	(113.18, 168.55)
	Severe Renal Impairment	Normal Renal Function	2369	1600	148.02	(111.40, 196.68)
AUC_{inf} (ng.hr/mL)	Mild Renal Impairment	Normal Renal Function	17910	14460	123.84	(99.64, 153.91)
	Moderate Renal Impairment	Normal Renal Function	27110	14460	187.40	(148.52, 236.46)
	Severe Renal Impairment	Normal Renal Function	44040	14460	304.49	(237.60, 390.21)

Source: Table 14.4.5.3.1.1
Natural log-transformed AUC_{inf} and C_{max} for PF-07321332 were analyzed using a mixed effect model with cohort as a fixed effect and assuming unequal variances.
a. The ratios (and 90% CIs) were expressed as percentages.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](00:43) Source Data: adpp Table Generation: [redacted] (07:02)
(Database snapshot date : [redacted] Output File: ./nda_ph1/C4671011/adpp_s201_it

Figure 7. Plot of Plasma PF-07321332 CL/F Versus CKD-EPI-derived eGFR (mL/min)



Day -1 eGFR calculated from CKD-EPI equation was used in this presentation.
CL/F=1.83 + 0.05* eGFR
R-squared=0.6568; Slope p-value= <0.0001.
The solid line was the predicted line of the response variable.
The shadow area was 90% confidence region for the response variable.
PFIZER CONFIDENTIAL SDTM Creation: [redacted] (00:43) Source Data: adpp Table Generation: [redacted] (09:46)(Database snapshot date : [redacted] Output File: . /nda_ph1/C4671011/adpp_f302

The number of all-causality TEAEs were similar between the mild (1 AE), moderate (1 AE) and normal renal function (3 AEs) groups. All AEs in these 3 groups were mild and not considered treatment related. There were 17 AEs experienced by 5 participants in the severe renally impaired group (Study 1011, Table 14.3.1.2.3 and Study 1011, Table 14.3.1.3.3). This included 3 SAEs in 1 participant, pneumonia, pulmonary edema, and acute kidney injury, and 8 non-serious AEs, in 1 participant who was discontinued from the study due to the SAE; none of these AEs were considered treatment related (Study 1011, Table 16.2.7.1).

Summary of the treatment related TEAEs by SOC and PT are provided in Table 22. There were 4 treatment related TEAEs in the SOC Gastrointestinal Disorders and Nervous System Disorders, which occurred in the severe renal impairment group and were mild. Two participants experienced 2 AEs of Dry mouth and 2 AEs of Dysgeusia. There were no deaths in this study.

There were 4 AEs of laboratory abnormalities (anemia, thrombocytopenia, hyperkalemia, and hyponatremia) in 1 participant (who had a history of [redacted] in the severe renally impaired group, and these were not considered treatment related (Study 1011, Table 16.2.7.1). There were no clinically meaningful laboratory findings or trends observed in this study. There were no clinically significant treatment related changes in ECG assessments or vital sign measurements in this study.

Table 22. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Treatment Related) - Safety Analysis Set (Protocol C4671011)

Number of Participants Evaluable for AEs	Normal Renal Function (N=10)	Mild Renal Impairment (N=8)	Moderate Renal Impairment (N=8)	Severe Renal Impairment (N=8)
Number (%) of Participants: by System Organ Class and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
With Any adverse event	0	0	0	2 (25.0)
GASTROINTESTINAL DISORDERS	0	0	0	2 (25.0)
Dry mouth	0	0	0	2 (25.0)
NERVOUS SYSTEM DISORDERS	0	0	0	2 (25.0)
Dysgeusia	0	0	0	2 (25.0)

Participants were only counted once per treatment per event.
Totals for the number of participants at a higher level were not necessarily the sum of those at the lower levels since a participant may report two or more different adverse events within the higher level category.
Included all data collected since the first dose of study treatment.
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](07:08) Source Data: adae Table Generation: [redacted] (23:33)
(Database snapshot date : [redacted] Output File: ./nda_ph1/C4671011/adae_s032
Table 14.3.1.3.2 PF-07321332 is for Pfizer internal use.

Conclusions:

- Overall systemic exposure of PF-07321332 increased with increasing severity of renal impairment; specifically, in the moderately and severely impaired participants the ratios of the adjusted geometric means (90% CI) for PF-07321322 AUC_{inf} were 187.40% (148.52%, 236.46%) and 304.49% (237.6%, 390.21%), respectively compared to the healthy control group.

- PF-07321332/ritonavir was generally safe and well-tolerated in both healthy and renally impaired adult participants.

6.3.4. Study 1014 – Carbamazepine DDI

This was a Phase-1, open label, fixed sequence, 2 period crossover study to estimate the effect of a strong CYP3A4 inducer, carbamazepine, on the PK of PF-07321332/ritonavir and ritonavir in healthy participants (Module 5.3.3.4, Study C4671014 CSR).

In Period 1, participants received a single oral dose of PF-07321332/ritonavir 300/100 mg followed by PK sampling up to 48 hours. In Period 2, participants received carbamazepine in a titrated schedule as follows: On Days 1-3 carbamazepine 100 mg BID, Days 4-7 carbamazepine 200 mg BID, and on Days 8-15 carbamazepine 300 mg BID. On Day 14, a

single dose of PF-07321332/ritonavir 300/100 mg was administered and followed by up to 48 hours of PK sampling. The plasma concentration of PF-07321332 and ritonavir were measured using a validated high-performance liquid chromatography tandem mass spectrometric (HPLC/MS/MS) method (Module 5.3.3.4 C4671014 Analytical Report – PF-07321332 AND RITONAVIR IN HUMAN K2EDTA PLASMA SAMPLES). PK parameters were calculated for each participant and treatment, as applicable, using noncompartmental analysis of concentration-time data for both PF-07321332 and ritonavir.

All 12 study participants were enrolled in the study. Ten participants completed Period 1 (Study 1014, Table 14.1.1.2). In Period 1, 2 participants discontinued before PF-07321332/ ritonavir 300 mg/100 mg dosing and thus were not part of the PK analysis. Most of the participants were White (58.3%) and the mean (SD) age was 41.1 (10.04) years, ranging from 22.0 to 56.0 years (Study 1014, Table 14.1.2.1). The overall mean (SD) weight and BMI were 77.7 (11.35) kg and 25.1 (2.98) kg/m^2, respectively.

A descriptive summary of PF-07321332 plasma PK parameters by treatment group are provided in Table 23. Results of the statistical comparisons of PF-07321332 exposure parameters (AUC_{inf}, and C_{max}) are summarized in Table 24.

Table 23. Descriptive Summary of Plasma PF-07321332 PK Parameters, Protocol C4671014

	Parameter Summary Statistics[a] by Treatment	
Parameter (Unit)	**PF-07321332 300 mg/ritonavir 100 mg (N=12)**	**Carbamazepine + PF-07321332 300 mg/ritonavir 100 mg (N=12)**
N2, N3	12, 12	10, 10
AUC_{inf} (ng.hr/mL)	23010 (23)	10280 (58)
AUC_{last} (ng.hr/mL)	22450 (23)	10050 (58)
CL/F (L/hr)	13.06 (23)	29.17 (58)
C_{max} (ng/mL)	2210 (33)	1300 (43)
$t_{1/2}$ (hr)	6.053 ± 1.7939	3.845 ± 0.99642
T_{max} (hr)	3.00 (1.02-6.00)	1.50 (0.500-4.00)
V_Z/F (L)	109.4 (38)	157.2 (69)

Source: Table 14.4.5.1.1
N = Total number of participants in the treatment group in the indicated population
N2 = Number of participants contributing to the summary statistics
N3 = Number of participants contributing to the summary statistics for AUC_{inf}, CL/F, $t_{1/2}$ and V_Z/F.
a. Geometric mean (Geometric %CV) for all except Median (Range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.
PFIZER CONFIDENTIAL SDTM Creation: [redacted] (23:43) Source Data: adpp Table Generation: [redacted] (05:26)
(Database snapshot date : [redacted] Output File: ./nda_ph1/C4671014/adpp_s101_1

Table 24. Statistical Summary of Plasma PF-07321332 PK Parameters (AUCinf, AUClast and Cmax), Protocol C4671014

Parameter (Unit)	Adjusted Geometric Means: Carbamazepine + PF-07321332 300 mg/ritonavir 100 mg (Test)	Adjusted Geometric Means: PF-07321332 300 mg/ritonavir 100 mg (Reference)	Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI (%) of Ratio[a]
AUC_{inf} (ng.hr/mL)	10240	23010	44.50	(33.77, 58.65)
AUC_{last} (ng.hr/mL)	10010	22450	44.59	(33.99, 58.50)
C_{max} (ng/mL)	1256	2210	56.82	(47.04, 68.62)

Source: Table 14.4.5.3.1
Natural log-transformed AUC_{inf}, AUC_{last} and C_{max} for PF-07321332 are analyzed using a mixed effect model with treatment as fixed effect and participant as a random effect.
a. The ratio (and 90% CIs) are expressed as percentages.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](23:43) Source Data: adpp Table Generation: [redacted] (04:26)
(Database snapshot date : [redacted] Output File: ./nda_ph1/C4671014/adpp_s201_i

Following a single oral dose of PF-07321332/ritonavir 300 mg/100 mg given without or with multiple oral doses of carbamazepine, C_{max} of PF-07321332 was observed at a median T_{max} of 3.0 hours post dose for PF-07321332/ritonavir administered alone, compared to a median T_{max} of 1.50 hours post dose following co-administration with carbamazepine. PF-07321332 plasma concentrations appeared to decline at a faster rate following co-administration with carbamazepine, with a mean $t_{½}$ of 3.8 hours as compared to 6.05 hours when PF-07321332/ritonavir 300 mg/100 mg was administered alone. In addition, the mean CL/F of PF-07321332 was approximately 50% higher (29 L/hr) following co-administration with carbamazepine compared to the mean CL/F (13 L/hr) of PF-07321332/ritonavir 300 mg/100 mg administered alone (Table 23).

Overall, PF-07321332 systemic exposure based on geometric mean AUC_{inf} and C_{max} values, decreased by approximately 55% and 43% respectively, following multiple dose co-administration with carbamazepine as compared to dosing of PF-07321332/ritonavir alone. The test/reference ratios of the adjusted geometric means for PF-07321332 AUC_{inf} and C_{max} were 44.59 % and 56.82%, respectively, following PF-07321332/ritonavir 300 mg/100 mg co-administration with multiple oral doses of carbamazepine (Test) compared to PF-07321332/ritonavir administered alone (Reference) (Table 24).

Inter-individual variability for PF-07321332 exposure was higher following co-administration with carbamazepine; geometric %CV for AUC_{inf} and C_{max} of 23% and

33% for PF-07321332/ritonavir administered alone, respectively, and 58% and 43% following co-administration with carbamazepine, respectively (Table 23).

Descriptive summary of ritonavir plasma PK parameters by treatment group are provided in Table 25. Results of the statistical comparisons of ritonavir exposure parameters (AUC_{inf}, and C_{max}) are summarized in Table 26.

Table 25. Descriptive Summary of Plasma Ritonavir PK Parameters, Protocol C4671014

	Parameter Summary Statistics[a] by Treatment	
Parameter (Unit)	PF-07321332 300 mg/ritonavir 100 mg (N=12)	Carbamazepine + PF-07321332 300 mg/ritonavir 100 mg (N=12)
N2, N3	12, 12	10, 8
AUC_{inf} (ng.hr/mL)	3599 (47)	677.6 (61)
AUC_{last} (ng.hr/mL)	3414 (47)	466.2 (104)
CL/F (L/hr)	27.78 (48)	147.6 (61)
C_{max} (ng/mL)	359.3 (46)	96.07 (71)
$t_{1/2}$ (hr)	6.149 ± 2.2413	3.345 ± 0.79964
T_{max} (hr)	3.98 (1.48-4.20)	1.98 (0.983-4.00)
V_Z/F (L)	234.0 (36)	697.5 (51)

Source: Table 14.4.5.1.2
N = Total number of participants in the treatment group in the indicated population
N2 = Number of participants contributing to the summary statistics
N3 = Number of participants contributing to the summary statistics for AUC_{inf}, CL/F, $t_{1/2}$ and V_Z/F.
a. Geometric mean (Geometric %CV) for all except Median (Range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](23:43) Source Data: adpp Table Generation: [redacted]
(05:26)
(Database snapshot date : [redacted]Output File: ./nda_ph1/C4671014/adpp_s101_a_1

Table 26. Statistical Summary of Plasma Ritonavir PK Parameters (AUCinf, AUClast and Cmax), Protocol C4671014

	Adjusted Geometric Means			
Parameter (Unit)	Carbamazepine + PF-07321332 300 mg/ritonavir 100 mg (Test)	PF-07321332 300 mg/ritonavir 100 mg (Reference)	Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI (%) of Ratio[a]
AUC_{inf} (ng.hr/mL)	596.4	3599	16.57	(13.32, 20.60)
AUC_{last} (ng.hr/mL)	441.1	3414	12.92	(9.28, 17.99)
C_{max} (ng/mL)	91.94	359.3	25.59	(18.76, 34.91)

Table 26. Statistical Summary of Plasma Ritonavir PK Parameters (AUCinf, AUClast and Cmax), Protocol C4671014

Parameter (Unit)	Adjusted Geometric Means: Carbamazepine + PF-07321332 300 mg/ritonavir 100 mg (Test)	Adjusted Geometric Means: PF-07321332 300 mg/ritonavir 100 mg (Reference)	Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI (%) of Ratio[a]

Source: Table 14.4.5.3.2
Natural log-transformed AUC_{inf}, AUC_{last} and C_{max} for Ritonavir are analyzed using a mixed effect model with treatment as fixed effect and participant as a random effect.
a. The ratio (and 90% CIs) are expressed as percentages.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](23:43) Source Data: adpp Table Generation: [redacted] (04:26)
(Database snapshot date : [redacted] Output File: ./nda_ph1/C4671014/adpp_s201_1_i

The effect of multiple dose carbamazepine was significantly greater on ritonavir PK as compared to PF-07321332. Overall, there was a significant effect of carbamazepine on the systemic exposure of ritonavir with an approximately 83% and 74% decrease in ritonavir geometric mean AUC_{inf} and C_{max} respectively, following co-administration of PF-07321332/ritonavir 300 mg/100 mg with carbamazepine as compared to administration of PF-07321332/ritonavir alone (Table 25 and Table 26).

The test/reference ratios of the adjusted geometric means for ritonavir AUC_{inf} and C_{max} (90% CI) were 16.57% (90% CI: 13.32%, 20.60%) and 25.59% (90% CI: 18.76%, 34.91%), respectively, following PF-07321332/ritonavir 300 mg/100 mg co-administration with multiple oral doses of carbamazepine (Test) compared to administration of PF-07321332/ritonavir alone (Reference) (Table 26). The mean $t_{½}$ values for ritonavir were 6.15 hours in the absence of carbamazepine and 3.35 hours in the presence of carbamazepine (Table 25).

Summary of treatment related TEAEs by SOC are provided in Table 27. Most treatment related TEAEs (1, and 6 after receiving PF-07321332/ritonavir, and PF-07321332/ritonavir co-administered with carbamazepine, respectively) were mild. The most commonly reported treatment related TEAEs by SOC across the 2 treatment groups was Nervous system disorders (Dysgeusia) reported by 1 participant after receiving PF-07321332/ritonavir, and 1 participant after receiving PF-07321332/ritonavir co-administered with carbamazepine. Only 1 participant discontinued the study due to a treatment related AE of Inappropriate antidiuretic hormone secretion (Hyponatremia). There were no deaths, SAEs or severe TEAEs in this study.

Five participants had mild elevations of transaminases in the PF-07321332/ritonavir when co-administered with carbamazepine (Table 27). No participants met the categorical criteria of concern for ECGs. There were 2 instances that met the categorical criteria of concern for vital signs; one instance of SBP absolute value <90 mm Hg was reported in Period 1 and one instance of DBP increase ≥20 mm Hg was reported in Period 2.

Table 27. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Treatment Related) - Safety Analysis Set (Protocol C4671014)

Number of Participants Evaluable for AEs	PF-07321332 300 mg/ritonavir 100 mg (N=12)	Carbamazepine + PF-07321332 300 mg/ritonavir 100 mg (N=12)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**
With Any adverse event	1 (8.3)	6 (50.0)
ENDOCRINE DISORDERS	0	1 (8.3)
Inappropriate antidiuretic hormone secretion	0	1 (8.3)
GASTROINTESTINAL DISORDERS	0	1 (8.3)
Dry mouth	0	1 (8.3)
INVESTIGATIONS	0	5 (41.7)
Transaminases increased	0	5 (41.7)
NERVOUS SYSTEM DISORDERS	1 (8.3)	1 (8.3)
Dysgeusia	1 (8.3)	1 (8.3)

Safety Analysis Set - All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.
Participants are only counted once per treatment per event.
Totals for the No. of Participants at a higher level are not necessarily the sum of those at the lower levels since a participant may report two or more different adverse events within the higher level category.
Includes data up to lag days after last dose of study drug.
MedDRA v24.0 coding dictionary applied.
Two participants only took Carbamazepine at the time of withdrawn, and did not take PF-07321332 300 mg/ritonavir 100 mg at Period 2.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](21:48) Source Data: adae Table Generation: [redacted] (02:12)
(Database snapshot date : [redacted] Output File: ./nda_ph1/C4671014/adae_s0311_1
Table 14.3.1.3.2 PF-07321332 is for Pfizer internal use.

Conclusion(s):

- The test/reference ratios of the adjusted geometric means for PF-07321332 AUC_{inf} and C_{max} (90% CI) were 44.50 % (90% CI: 33.77%, 58.65%) and 56.82% (90% CI: 47.04%, 68.62%), respectively, following PF-07321332/ritonavir 300 mg/100 mg co-administration with multiple oral doses of carbamazepine (Test) compared to PF-07321332/ritonavir administered alone (Reference).

- The test/reference ratios of the adjusted geometric means for ritonavir AUC_{inf} and C_{max} (90% CI) were 16.57% (90% CI: 13.32%, 20.60%) and 25.59% (90% CI: 18.76%, 34.91%), respectively, following PF-07321332/ritonavir 300 mg/100 mg co-administration with multiple oral doses of carbamazepine (Test) compared to administration of PF-07321332/ritonavir alone (Reference).

- Treatments were generally safe and well tolerated for participants administered either PF-07321332/ritonavir with or without carbamazepine.

6.3.5. Study 1015 – Itraconazole DDI

This was a Phase 1, open-label, fixed sequence, 2-period crossover study to estimate the effect of a strong CYP3A4 inhibitor, itraconazole, on the PK of PF-07321332/ritonavir in healthy participants (Module 5.3.3.4, Study C4671015 CSR).

In Period 1, participants received PF-07321332/ritonavir 300/100 mg orally q12h for a total of 5 doses, with the last dose administered on the morning of Day 3. In Period 2, participants received itraconazole 200 mg orally q24h for 8 days. On Days 4 through 6 of Period 2, participants received PF-07321332/ritonavir 300/100 mg orally q12h for a total of 5 doses.

Intensive blood samples for PF-07321332 and ritonavir PK characterization were collected at pre-dose and up to 48-hours post dose following the fifth dose on Day 3 of Period 1 and Day 6 of Period 2. The plasma concentration of PF-07321332 and ritonavir were measured using a validated high-performance liquid chromatography tandem mass spectrometric (HPLC/MS/MS) method (Module 5.3.3.4 C4671015 Analytical Report - PF-07321332 AND RITONAVIR IN HUMAN K2EDTA PLASMA SAMPLES). PK parameters were determined from plasma concentration-time data using standard non-compartmental methods.

A total of 12 participants were assigned to treatment and 11 of them completed the study as planned. Most of the participants were White (10/12) and Male (11/12) (Study 1015, Table 14.1.2.1). The mean (SD) age was 41.5 (12.03) years, ranging from 28 to 60 years (Study 1015, Table 14.1.2.1). The overall mean (SD) weight and BMI were 79.86 (13.121) kg and 25.43 (3.434) kg/m^2, respectively (Study 1015, Table 14.1.2.2).

Descriptive summary of PF-07321332 plasma PK parameters by treatment group are provided in Table 28. Results of the statistical comparisons of PF-07321332 exposure parameters (AUC_{tau}, and C_{max}) are summarized in Table 29.

Overall, PF-07321332 systemic exposure based on the adjusted geometric mean AUC_{tau} and C_{max} increased by approximately 39% and 19% respectively, when PF-07321332/ritonavir was co-administered with itraconazole compared of PF-07321332 /ritonavir administered alone. The test/reference ratios of the adjusted geometric means (90% CI) for PF-07321332 AUC_{tau} and C_{max} were 138.82 % (129.25%, 149.11%) and 118.57% (112.50 %, 124.97%), respectively, when PF-07321332/ritonavir was co-administered with itraconazole (Test) versus of PF-07321332/ritonavir administered alone (Reference).

Table 28. Descriptive Summary of Plasma PF-07321332 PK Parameters, Protocol C4671015

	Parameter Summary Statistics[a] by Treatment	
Parameter (Unit)	**PF-07321332 (suspension)/ritonavir 300/100 mg BID, Fasted (N=11)**	**Itraconazole 200 mg QD + PF-07321332 (suspension)/ritonavir 300/100 mg BID, Fasted (N=11)**
N1, n	11, 11	11, 10
AUC_{last} (ng.hr/mL)	41840 (21)	74430 (21)
AUC_{tau} (ng.hr/mL)	33350 (20)	46290 (18)
CL/F (L/hr)	8.990 (20)	6.478 (18)
C_{max} (ng/mL)	4678 (17)	5546 (15)
$t_{1/2}$ (hr)	8.255 ± 1.9465	7.793 ± 0.89019
T_{max} (hr)	1.020 (0.500 - 2.08)	1.700 (0.500 - 4.00)
V_Z/F (L)	104.7 (33)	72.07 (16)

Source: Table 14.4.5.1.1.1
N = Total number of participants in the treatment group in the indicated population.
N1 = Number of participants contributing to the summary statistics.
n = Number of participants contributing to the summary statistics for $t_{1/2}$ and V_Z/F.
a. Geometric mean (Geometric %CV) for all: except Median (Range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.
PFIZER CONFIDENTIAL SDTM Creation: [redacted] (22:11) Source Data: adpp Table Generation: [redacted] (09:40)
Output File: ./nda_ph1/C4671015/adpp_s101_it

Table 29. Statistical Summary of Plasma PF-07321332 PK Parameters (AUC_{tau} and C_{max}), Protocol C4671015

Parameter (Unit)	Adjusted Geometric Means: Itraconazole 200 mg QD + PF-07321332 (suspension)/ritonavir 300/100 mg BID, Fasted (Test)	Adjusted Geometric Means: PF-07321332 (suspension)/ritonavir 300/100 mg BID, Fasted (Reference)	Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI (%) of Ratio[a]
AUC_{tau} (ng.hr/mL)	46292	33346	138.82	(129.25, 149.11)
C_{max} (ng/mL)	5546.1	4677.5	118.57	(112.50, 124.97)

Source: Table 14.4.5.1.2.1
Natural log-transformed AUC_{tau} and C_{max} for PF-07321332 were analyzed using a mixed effect model with treatment as fixed effect and participant as a random effect.
a. The ratios (and 90% CIs) were expressed as percentages.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](22:11) Source Data: adpp Table Generation: [redacted] (09:40)
Output File: ./nda_ph1/C4671015/adpp_s201_it

Itraconazole had minimum effect on the overall systemic exposure of ritonavir with a 21% and 15% increase in ritonavir exposure (AUC_{tau} and C_{max}, respectively) observed in the presence of itraconazole. Mean $t_{½}$ values for ritonavir was 5.720 hours when PF-07321332/ritonavir administered alone versus 7.645 hours when co-administered with itraconazole. Mean ritonavir CL/F values were 13.92 L/hr when PF-07321332/ritonavir administered alone versus 11.50 L/hr when co-administered with itraconazole (Study 1015, Table 14.4.5.2.1.1).

A summary of the treatment related TEAEs by SOC is provided in Table 30.

A total of 24 treatment related AEs (21 mild AEs and 3 moderate AEs) were reported in Period 1 and 43 (38 mild and 5 moderate) treatment related AEs in Period 2, respectively. Most of the TEAEs were mild in nature (Study 1015, Table 14.3.1.3.3). The most reported TEAEs by SOC across 2 treatments were Gastrointestinal disorders (5 participants in Period 1 and 7 in Period 2), General disorders and administration site conditions (1 participant in Period 1 and 4 in Period 2), and Nervous system disorders (6 participants in Period 1 and 6 in Period 2).

Two participants reported 3 treatment related moderate AEs in Period 1 and 2 participants reported 5 treatment related moderate AEs in Period 2. In Period 1, 1 participant reported vomiting and headache and 1 participant reported headache. In Period 2, 1 participant reported constipation and 1 participant reported anorectal discomfort, constipation, diarrhoea, and gastrointestinal motility (Study 1015, Table 14.3.1.3.3).

There were no deaths, SAEs or severe TEAEs in this study. None of the laboratory findings were considered as clinically meaningful. No participants met the categorical criteria for

ECG changes, though one had a borderline first degree heart-block at baseline that slightly increased during the study (Study 1015, Table 16.2.8.3.4 and Table 14.3.1.3.3). Vital signs remained stable throughout the trial for all participants.

Table 30. Treatment-Emergent Adverse Events by System Organ Class (Treatment Related) (Protocol C4671015)

Number of Participants Evaluable for AEs	PF-07321332 (suspension)/ritonavir 300/100 mg BID, Fasted (N=12)	Itraconazole 200 mg QD + PF-07321332 (suspension)/ritonavir 300/100 mg BID, Fasted (N=11)
Number (%) of Participants: by SYSTEM ORGAN CLASS	**n (%)**	**n (%)**
With Any adverse event	7 (58.3)	7 (63.6)
CARDIAC DISORDERS	1 (8.3)	0
GASTROINTESTINAL DISORDERS	5 (41.7)	7 (63.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (8.3)	4 (36.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (9.1)
NERVOUS SYSTEM DISORDERS	6 (50.0)	6 (54.5)
PSYCHIATRIC DISORDERS	0	1 (9.1)
RENAL AND URINARY DISORDERS	1 (8.3)	1 (9.1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	1 (9.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	1 (9.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (9.1)

Participants were only counted once per treatment per event.
Totals for the number of participants at a higher level were not necessarily the sum of those at the lower levels since a participant may report two or more different adverse events within the higher level category.
Included all data collected since the first dose of study drug.
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](21:42) Source Data: adae Table Generation: [redacted] (10:25)
Output File: ./nda_ph1/C4671015/adae_s032
Table 14.3.1.3.2 PF-07321332 is for Pfizer internal use.

Conclusions:

- Co-administration of multiple oral 200 mg doses of itraconazole increased PF-07321322 AUC_{tau} and C_{max}. The ratios of the adjusted geometric means (90% CI) for PF-07321322

AUC_{tau} and C_{max} were 138.82% (129.25%, 149.11%) and 118.57% (112.50%, 124.97%), respectively, when PF-07321332/ritonavir was co-administered with multiple doses of itraconazole (Test) as compared to PF-07321332/ritonavir administered alone (Reference).

- PF-07321332/ritonavir was generally safe both in the absence and presence of multiple doses of itraconazole with no deaths or SAEs reported. With respect to toleration, the most frequent AEs noted were predominantly gastrointestinal and nervous system disorder and mostly mild.

6.3.6. Drug Interactions with PF-07321332/Ritonavir

An assessment of risk for in vivo DDIs between PF-07321332 and co-administered substrates based on the 2020 FDA drug interaction guidance[68] is provided in Module 4.2.2.6 DDI assessments R values.

6.3.6.1. Drug Interaction Studies Conducted with PF-07321332/Ritonavir

6.3.6.1.1. Effect of other drugs on PF-07321332/ritonavir

Preclinical data suggest that CYP3A4 was the major contributor (fm = 0.99) to the oxidative metabolism of PF 07321332, when PF-07321332 was tested alone in human liver microsomes (Section 6.1.1.4). Ritonavir is an inhibitor of CYP3A and increases plasma concentrations of drugs that are primarily metabolized by CYP3A. Data from Study 1001 indicates that ritonavir markedly increased the plasma concentration of PF-07321332. Despite being co-administered with ritonavir as a PK enhancer, there is potential for strong inhibitors and inducers to alter the pharmacokinetics of PF-07321332. Therefore, clinical drug interaction studies were conducted with itraconazole as strong CYP3A inhibitor (Section 6.3.5) and with carbamazepine as a strong CYP3A inducer (Section 6.3.4).

The effects of co-administration of PF-07321332/ritonavir with itraconazole (CYP3A inhibitor) and carbamazepine (CYP3A inducer) on the PF-07321332 AUC and C_{max} are summarized in Table 31.

Table 31. Effect of Co-administered Drugs on Pharmacokinetics of PF-07321332.

Co-administered Drug	Co-administered Drug Dose (Schedule)	PF-07321332/Ritonavir Drug Dose (Schedule)	N	Ratio of PF-07321332 Pharmacokinetic Parameters (90% CI)	
				C_{max}	AUC[a]
Carbamazepine[b]	300 mg twice daily (16 doses)	300/100 mg [redacted]	9	56.82 (47.04, 68.62)	44.50 (33.77, 58.65)
Itraconazole	200 mg once daily (8 doses)	300/100 mg twice daily (5 doses)	11	118.57 (112.50, 124.97)	138.82 (129.25, 149.11)

a. For carbamazepine, $AUC=AUC_{inf}$, for itraconazole, $AUC=AUC_{tau}$
b. carbamazepine titrated up to 300 mg twice daily on Day 8 through Day 15 (eg, 100 mg twice daily on Day 1 through Day 3 and 200 mg twice daily on Day 4 through Day 7).
Source: Section 6.3.3 and Section 6.3.4

6.3.6.1.2. Effect of PF-07321332/Ritonavir on Other Drugs

Preclinical data indicates that PF-07321332 has the potential to reversibly and time-dependently inhibit CYP3A4 and inhibit MDR1 (P-gp) (Section 6.1.1.4). As ritonavir is also a potent inhibitor of CYP3A4 MDR1 (P-gp), administration of PF-07321332/ritonavir with drugs primarily metabolized by CYP3A4 and/or subject to MDR1 efflux may result in increased plasma concentrations of such drugs. Because of the potent inhibitory effect of ritonavir compared to PF-07321332, administration of PF-07321332/ritonavir is unlikely to cause an incremental risk of drug interactions beyond that posed by ritonavir alone. To that end, clinical drug interaction studies to assess the effect of PF-07321332/ritonavir on midazolam as a CYP3A4 substrate (Study 1013) and dabigatran as a P-gp substrate (Study 1012) are currently ongoing. [redacted]

6.3.6.2. Drug Interactions Known to be Associated with Ritonavir

The drug interactions associated with the use of ritonavir as a pharmacokinetic enhancer as well as for treatment of HIV infection is well established and adequately covered in several drug product labels [redacted]

6.3.6.2.1. Contraindications

The sponsor's recommendations are generally aligned with the ritonavir labels for drugs that would be contraindicated (Appendix Table 53). Accordingly, co-administration of PF-07321332/ritonavir with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events are contraindicated. Co-administration with drugs that induce CYP3A which may decrease

PF-07321332 and ritonavir plasma concentrations, thereby reducing the therapeutic effect of PF-07321332, are also contraindicated. For easy reference, the list of drugs that would be contraindicated with PF-07321332/ritonavir includes the following:

[redacted]

6.3.6.2.2. Potentially Significant Drug Interactions

The use of ritonavir 100 mg BID as PK enhancer for PF-07321332 for treatment of COVID-19 is for a short-term duration (5 days) compared to its use as PK enhancer for treatment of HIV or HCV infection for much longer duration. Therefore, it is expected that the clinical management of potentially significant drug interactions for treatment of COVID-19 would be different compared to the current ritonavir labels which are meant for use of ritonavir as a PK enhancer for HIV or HCV treatment.[redacted]

Approximately [redacted] different drug classes are listed in Appendix Table 54 that cover a wide range of drugs used in clinical practice for a wide range of indications. Notably, this is not a comprehensive list of all possible drugs that may interact with PF-07321332/ritonavir, but in the view of the sponsor, are representative of those included in the ritonavir product labels.

6.3.7. Population Pharmacokinetic Analyses

A preliminary population PK model (Module 5.3.3.5 PMAR-EQDD-C467a-Proof of Concept-1246) was developed based on healthy adult data from Study 1001 (data cutoff date [redacted] 2021). Only PK data collected from the PF-07321332/ritonavir treatment arms (536 evaluable PF-07321332 plasma concentrations from 20 participants) were included in the population PK analysis.

The PK of PF-07321332/ritonavir following oral administration were adequately characterized by a two-compartment disposition model with first-order absorption. The population PK model included an allometric model of baseline body weight on clearance and volume of distribution with exponents fixed to 0.75 and 1, respectively. Separate power functions were used to describe the dose effect on k_a and F1.

The parameter estimates after adjustment by F1 at a PF-07321332 dose of 300 mg are: CL 8.2 L/h, volume of distribution 111 L, and k_a 1.1 h^{-1}. This gives a population mean $t_{½}$ of approximately 15 hours (the individual post-hoc $t_{½}$ ranged from 8.7 to 32.8 hours). The IIV in CL was low at 26.4% comparing with IIV in central and peripheral volume of distribution V2 30.7%, V3 69.9%, k_a 54.3%, and IOV in k_a 60.7%.

With the preliminary population PK model, a PF-07321332 dose of 300 mg with ritonavir is projected based on simulations to have >90% of participants achieve a concentration at C_{12h} above EC_{90} of 292 ng/mL after the first dose (Table 32).

The dose of PF-07321332/ritonavir 300/100 mg BID resulted in median Day 1 and steady state C_{12h} concentrations ~3-4 x EC_{90} and ~5-6 x EC_{90}, respectively (Table 32). The EC_{90} target was derived from the antiviral activity of PF-07321332 against SARS-CoV-2 evaluated in the most physiologically relevant antiviral assay of SARS-CoV-2 infection in dNHBE cells. The geometric mean EC_{90} of 0.181 μM at 3 days post-infection was used and adjusted by PF-07321332 molecular weight (499.54 Daltons) and protein binding in human ($f_{u,human}$=0.310).

Table 32. Predicted C_{12h} and Percentage of Simulated Subjects Achieving C_{12h} $\geq EC_{90}$ of 292 ng/mL.

PF-07321332 dose (mg), with ritonavir	Dose Number	C_{12h} (ng/mL)[a] Median	10^{th} percentile	90^{th} percentile	% Subjects achieved $C_{12h} \geq EC_{90}$
100	1st (Day 1)	458	141	1018	71.5
	2nd (Day 1)	631	175	1546	79.2
	9th (Day 5)	852	238	2276	85.3
200	1st (Day 1)	743	228	1608	85.0
	2nd (Day 1)	1012	281	2443	89.2
	9th (Day 5)	1361	383	3575	93.4
300	1st (Day 1)	987	307	2124	90.7
	2nd (Day 1)	1347	378	3202	93.6
	9th (Day 5)	1800	498	4670	95.7
400	1st (Day 1)	1209	378	2565	94.0
	2nd (Day 1)	1657	468	3879	95.3
	9th (Day 5)	2197	605	5679	97.4
500	1st (Day 1)	1417	449	2979	95.5
	2nd (Day 1)	1952	552	4516	96.5
	9th (Day 5)	2563	704	6640	97.8

a IIV on CL inflated to 60%

In conclusion, the preliminary modelling and simulation analyses support a PF-07321332 dose of 300 mg with 100 mg ritonavir administered orally q12h.

6.3.8. Dose and Duration Selection Rationale

The proposed dosing regimen for the treatment of high-risk symptomatic SARS-CoV-2 is primarily supported by the data from Study 1005 that the dose of PF-07321332/ritonavir 300/100 mg BID is generally safe and well-tolerated and effective at reducing the risk of hospitalization/death (Section 6.4.4.1). This dose was the only dose evaluated in Study 1005 since it was desired to maximize efficacy in the patient population while maintaining adequate safety margins over preclinical safety margins.

In the mouse-adapted SARS-CoV-2 model, dose-dependent efficacy was observed in lung vial titers, body weight and lung histopathology. Efficacy was observed in the mouse model at concentrations approximating the in vitro EC_{90} with greater efficacy observed at concentrations at approximately 4 times higher than the in vitro EC_{90} (Section 6.1.1.1). These observations are consistent with human data for protease inhibitors for the treatment of HCV and HIV were concentrations maintained $>EC_{90}$ are associated with efficacy.[71,72] Given these data, the selected dose would maintain concentrations above EC_{90} (based on unbound plasma concentrations) in most participants (Section 6.3.7). The dose of PF-07321332/ritonavir 300/100 mg BID results in median Day 1 and steady state trough concentrations 3-4x EC_{90} and ~5-6 x EC_{90}, respectively (Section 6.3.7).

The dose of 100 mg ritonavir was selected as this is the dose that has previously been used as a PK enhancer in approved products.[73] The safety of this dose is well established and results in nearly full CYP3A4 inhibition, maximizing the enhancing potential of the ritonavir dose.

As ritonavir is used as a PK enhancer and is not expected to have any anti-viral activity toward SARS-CoV-2, the 100 mg dose was deemed as appropriate.

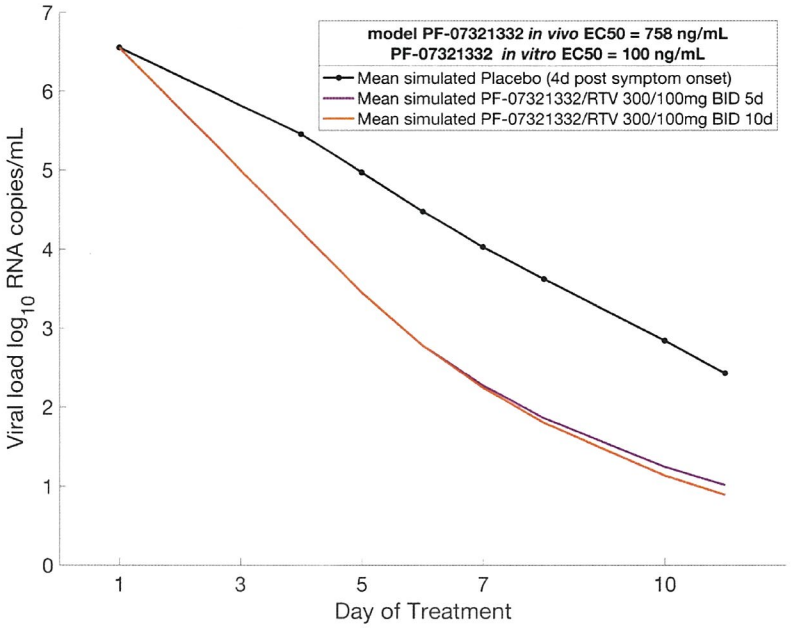
The duration of the regimen selected was based on the viral dynamics of SARS-CoV-2 in humans. To that end, a QSP model[74] capable of describing viral dynamics with time was used to confirm the selection of a 5-day dosing duration of oral PF-07321332/ritonavir 300 mg /100 mg BID for the treatment of symptomatic confirmed SARS-CoV-2 participants.

The previously published model included viral dynamics, and the effect of innate and adaptive immunity, and tissue damage. Parameters of the model were informed by literature data, and both in vivo and in vitro PK/PD data for PF-07321332. Uncertainty in the model and heterogeneity in disease pathogenesis were captured by a virtual population approach.[75] The model was updated to incorporate the following:

- The observed PK profile of PF-07321332/ritonavir 300 mg/100 mg BID
- Preclinical data on PF-07321332 pharmacology in a mouse model of SARS-CoV-2 that was used to estimate the in vivo potency of PF-07321332 with the QSP model
- A virtual population (N=502) that matched the placebo and treatment response of viral load and severity as reported in publicly available data[22,76-78]

To assess the efficacy of different dosing durations, symptomatic out-patient COVID-19 population and dosing 4 days post viral load peak/symptom onset was assumed.[22] Given the estimated in vivo potency of PF-07321332, QSP model simulations predicted that a 5-day regimen of oral PF-07321332/ritonavir 300 mg/100 mg BID would be sufficient for the treatment of symptomatic confirmed SARS-CoV-2 participants, with no benefit predicted for longer dosing (Figure 8).[22]

Figure 8. QSP Model Predictions for Symptomatic COVID-19 Patients.[a]

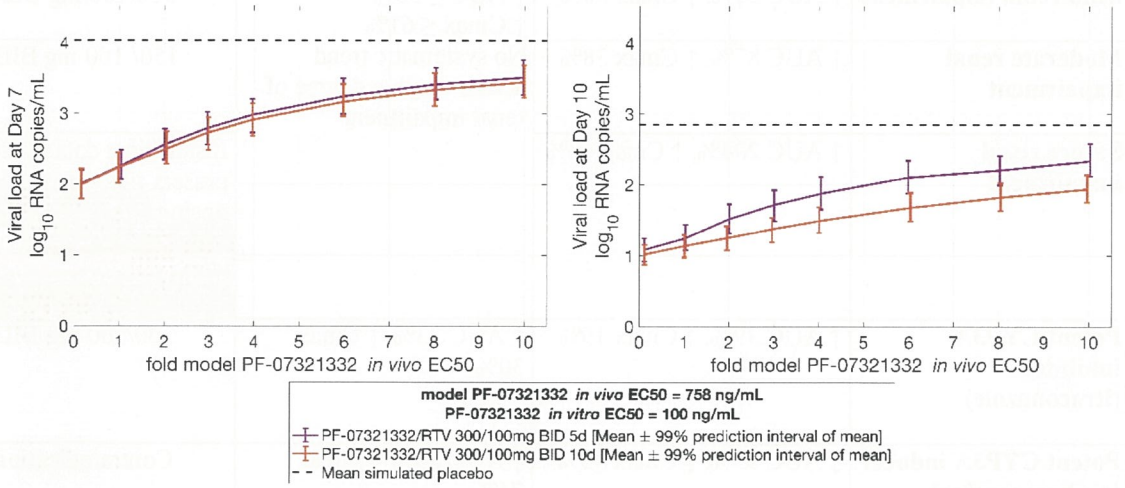


[a] QSP model-predicted viral load time course upon simulated treatment with 5d and 10d dosing regimens of oral PF-07321332/ritonavir 300/100 mg BID, respectively, where the in vivo potency is estimated from preclinical data in a mouse model of SARS-CoV-2.

Given the uncertainty on the clinical potency of PF-07321332 at the time of Phase 2/3 dose and regimen selection, sensitivity analysis was conducted to evaluate if the predicted lack of benefit for longer dosing is maintained across a range of potencies simulated in the model. The model predicted that a longer dosing regimen would provide no further meaningful increase in viral load lowering efficacy at Day 7 or Day 10 regardless of clinical potency (Figure 9).

The physiological rationale for this observation is that after 5 days of dosing (~9 days post symptom onset, and ~2 weeks post infection) viral dynamics are predicted to be almost entirely driven by the rate of clearance of virus, and not replication of virus. At 10 days post treatment, a ~0.4 Log_{10} difference in viral load is predicted between the 5 day and 10 day dosing regimens for a greater than 3-fold shift in the estimated in vivo potency of PF-07321332. However, in this case, the predicted viral load for both the 5 day and 10 day dosing regimens is below the typical limits of quantification, and hence the difference is presumed to be not clinically meaningful or measurable.[78] Given this analysis, greater than 5 days of dosing was not tested in this patient population. Less than 5 days of dosing was not considered due to the risk of stopping dosing too early in patients recruited closer to symptom onset. Based on this information, it was decided to test 5 days of PF-07321332/ritonavir 300 mg/100 mg BID administration for the treatment of symptomatic COVID-19.

Figure 9. Sensitivity of QSP Model-Predicted Viral Load Lowering Efficacy at A) Day 7 and B) Day 10 Post Treatment to the Fold Shift of In Vitro to In Vivo EC_{50} of PF-07321332



In summary, based on this information, the 300 mg/100 mg PF-07321332/ritonavir BID for 5 days was selected for further clinical evaluation in Phase 2/3 studies for treatment of symptomatic COVID-19 patients.

6.3.9. Dosing Recommendation in Specific Populations

Key PK from renal impairment Study 1011 and DDI Studies 1014 and 1015 along with proposed dosing in these populations is summarized in Table 33.

Table 33. Summary of Results and Dosing Recommendations in Specific Populations

Populations	Change in PF-07321332[a]	Change in Ritonavir	Proposed dosing PF-07321332/Ritonavir
Mild renal impairment	↑ AUC 24%, ↑ Cmax 30%	↑ AUC ≤ 38% ↑ Cmax ≤ 61% No systematic trend across varying degree of renal impairment[64]	300/100 mg BID
Moderate renal impairment	↑ AUC 87%, ↑ Cmax 38%		150/ 100 mg BID
Severe renal impairment	↑ AUC 204%, ↑ Cmax 48%		Insufficient data at the present time to propose dosing. [redacted]
Potent CYP3A inhibitor (itraconazole)	↑ AUC 39%, ↑ Cmax 19%	↑ AUC 23%, ↑ Cmax 30%	300/100 mg BID
Potent CYP3A inducer (carbamazepine)	↓ AUC 55%, ↓ Cmax 43%	↓ AUC 83%, ↓ Cmax 74%	Contraindication

a. Change relative to reference arm in each respective study Values represent change in geometric mean C_{max} and AUC_{inf} for mild, moderate, and severe renal impairment, change in geometric mean C_{max} and AUC_{tau} for itraconazole DDI study, and change in geometric mean C_{max} and AUC_{inf} for carbamazepine DDI study.

These recommendations are based on the following:

- Maintaining PF-07321332 C_{trough} levels at or above those in healthy participants with normal renal function receiving 300/100 mg BID for 5 days, a dose that maintains concentration above EC_{90} over the dosing interval and shown to be efficacious in Study 1005.

- Safety data from Phase 2/3 Study 1005 which enrolled participants with eGFR >45 mL/min/1.73 m^2 receiving 300/100 mg PF-07321332/ritonavir BID for 5 days

The metabolism and excretion data from Part-4 of Study 1001 showed that PF-07321332 is the primary drug-related entity present in systemic circulation and is primarily eliminated as unchanged drug in urine following administration of PF-07321332/ritonavir (Section 6.3.2.2.4). Therefore, it is reasonable to use the preliminary population PK model (Module 5.3.3.5 PMAR-EQDD-C467a-Proof of Concept-1246) to simulate scenarios of reduced clearance of PF-07321332 for dose recommendations in renal impairment. For drug interaction with itraconazole that resulted in an increased AUC roughly similar to the increase in mild renal impairment, the approach for dose recommendation in mild renal impairment can be applied to strong inhibitors of CYP3A4. The preliminary population PK model was used to predict the Day 5 C_{trough} plasma concentration of PF-07321332/ritonavir BID to simulate the following scenarios:

- Reference group with no change in clearance and dosed with 300/100 mg PF-07321332/ritonavir BID

- Reduction in the clearance of PF-07321332 by one-third since AUC in mild renal impairment was higher by 24%. This scenario mathematically accounts for the 39% higher AUC noted with itraconazole even if the change is due to CYP3A4 inhibition (ie, change in CLT/F rather than CL_r)

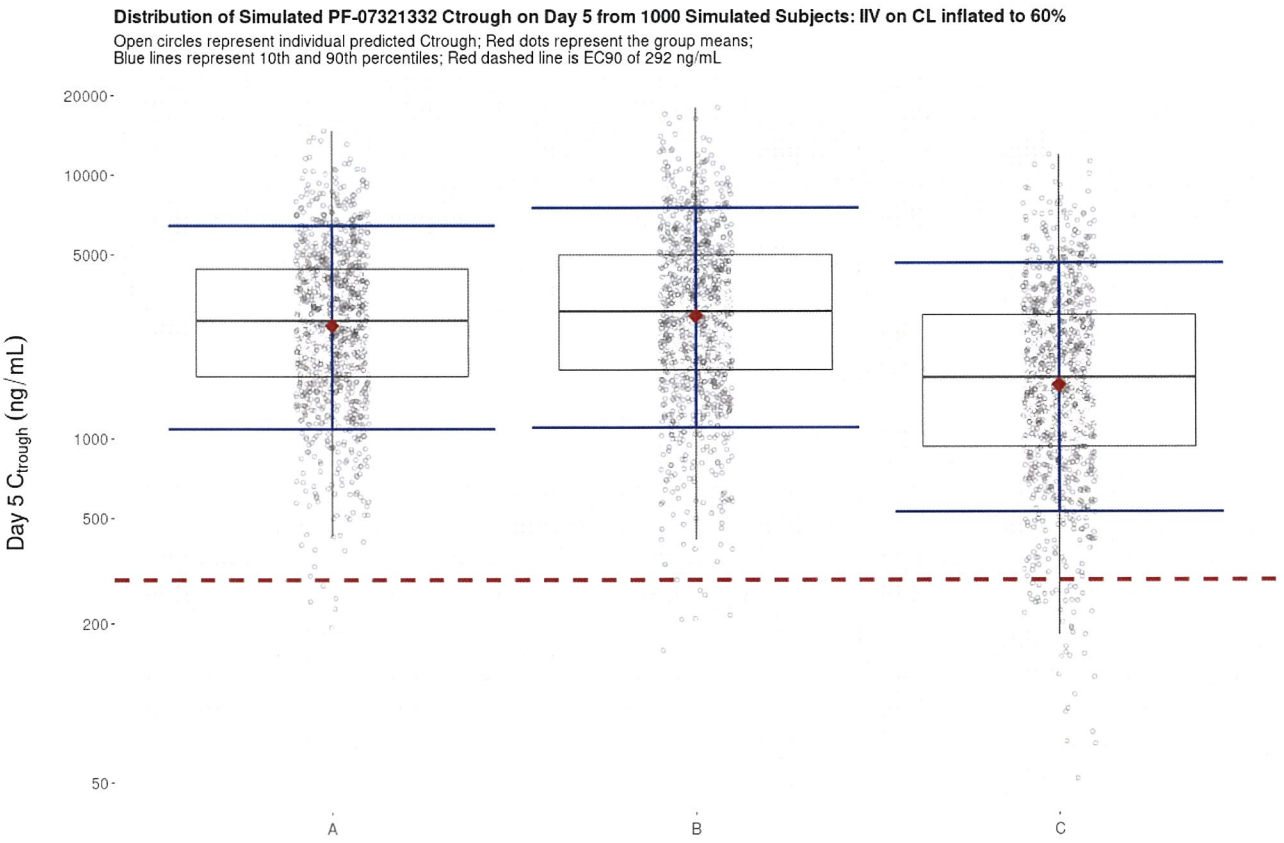
- Reduction in the clearance of PF-07321332 by one-half, since AUC in moderate renal impairment was higher by 87%

Since PF-07321332 tablets are only available in 150 mg strength, the dosing regimens simulated were either 300/100 mg or 150/100 mg PF-07321332/ritonavir BID for 5 days. Once daily regimens of PF-07321332 were also explored but were deemed unsuitable because ritonavir needs to be administered BID which complicates dosing and potentially increases the chance of non-compliance.

6.3.9.1. Renal Impairment

Figure 10 shows the predicted C_{trough} concentrations of PF-07321332 with reduced clearance and with doses which provided a close approximation to C_{trough} concentration to that of a reference group (ie no reduction in CL). There was significant overlap in the individual predicted PF-07321332 C_{trough} values when clearance was reduced by one-third and dosed with 300/100 mg PF-07321332/ritonavir BID, and when clearance was reduced by one-half and dosed with 150/100 mg PF-0732132/ritonavir BID (Figure 10). In both scenarios, the median C_{trough} values were slightly higher than the reference group, and the vast majority of individual predicted C_{trough} values were above EC_{90} (292 ng/ml). It is presumed that maintaining C_{trough} values above EC_{90} for SARS-CoV-2 would be necessary for therapeutic activity, and hence slightly higher C_{trough} values are not expected to compromise therapeutic activity of PF-07321332/ritonavir.

Figure 10. Precited PF-07321332 C_{trough} Plasma Concentrations by Dosing Regimen and Clearance



Source: Repository artifact ID FI-26931791

The Phase 2/3 Study 1005 enrolled participants with eGFR ≥45 mL/min/1.73 m^2, and all study participants including mild and moderate renal impairment, received PF-07321332/ritonavir 300/100 mg BID or PBO for 5 days. The safety data from this study is presented in Section 6.4.6. Overall, the safety data suggest that PF-07321332/ritonavir was well tolerated and supports the PK-derived dosing recommendation mentioned in Table 33 for mild and moderate renal impairment.

For participants with severe renal impairment, AUC was higher by 204% suggesting an approximate 3-fold reduction in clearance in this population. [redacted]

6.3.9.2. CYP3A4 Inhibitors

Administration of PF-07321332/ritonavir with the strong CYP3A4 inhibitor (itraconazole) results in an increase in AUC of 39%. This situation is mathematically similar to the mild

renal impairment group and simulations results (Figure 10) and supports the dosing recommendation of 300/100 mg PF-07321332/ritonavir BID when used concomitantly with strong CYP3A4 inhibitors.

Administration of PF-07321332/ritonavir is contraindicated with potent CYP3A4 inducers like carbamazepine (section 6.3.4). This is due to a differential effect of the inducer on the PK of PF-07321332 and ritonavir and due to the risk, that a lower C_{trough} may potentially affect efficacy and/or development of viral resistance.

6.3.9.3. CYP3A4 Inducers

Administration of PF-07321332/ritonavir is contraindicated with potent CYP3A4 inducers like carbamazepine due a differential effect of the inducer on the PK of PF-07321332 and ritonavir and due to the risk that lower C_{trough} may potentially affect efficacy. Furthermore, since it takes several days for the induction effect to dissipate, stopping the inducer to start treatment with PF-07321332/ritonavir should not be considered.

6.3.9.4. HIV-Infected Patients

The dosing recommendations of 300/100 mg PF-07321332/ritonavir BID with concomitant strong CYP3A4 inhibitor itraconazole would also apply to HIV-infected patients on ritonavir or cobicistat as PK enhancer. Adding a second drug that inhibits CYP3A4 (cobicistat or additional 100 mg BID dose of ritonavir) in anticipated to provide results similar to those observed with itraconazole and PF-07321332/ritonavir.

Importantly, it is essential to administer ritonavir together with PF-07321332 to get the PK enhancement of PF-07321332. Separating these two could potentially lead to sub-therapeutic concentrations of PF-07321332. With complex HIV-regimens, there is a chance that administration of PF-07321332 with a PK enhancer (ritonavir or cobicistat) gets separated in time. For instance, cobicistat is indicated to increase systemic exposure of atazanavir or darunavir (once daily dosing regimen) in combination with other antiretroviral agents in the treatment of HIV-1 infection.[79] Similarly, ritonavir 100 mg is used as a PK enhancer for HIV-protease inhibitors that are administered twice daily (eg, lopinavir, darunavir in treatment experienced patients) or once daily (eg, atazanavir, darunavir in treatment naïve patients).[70,80,81]

In a poly-pharmacy setting, to avoid the possibility that PF-07321332 is administered without ritonavir (or cobicistat) or is separated in time relative to administration of a PK enhancer (ritonavir or cobicistat), it is proposed that PF-07321332/ritonavir be administered together at a dose of 300/100 mg as indicated for treatment of COVID-19, regardless of other PK enhancers indicated for HIV therapy.

6.3.9.5. Population Pharmacokinetics (Dose Recommendation) in Adolescent Subjects (≥12 to <18 years of Age)

Population PK simulations suggests that a PF-07321332/ritonavir 300 mg/100 mg BID dose in adolescents (ie, ≥12 to < 18 years of age) provides reasonably comparable exposures in adults receiving the same dose.

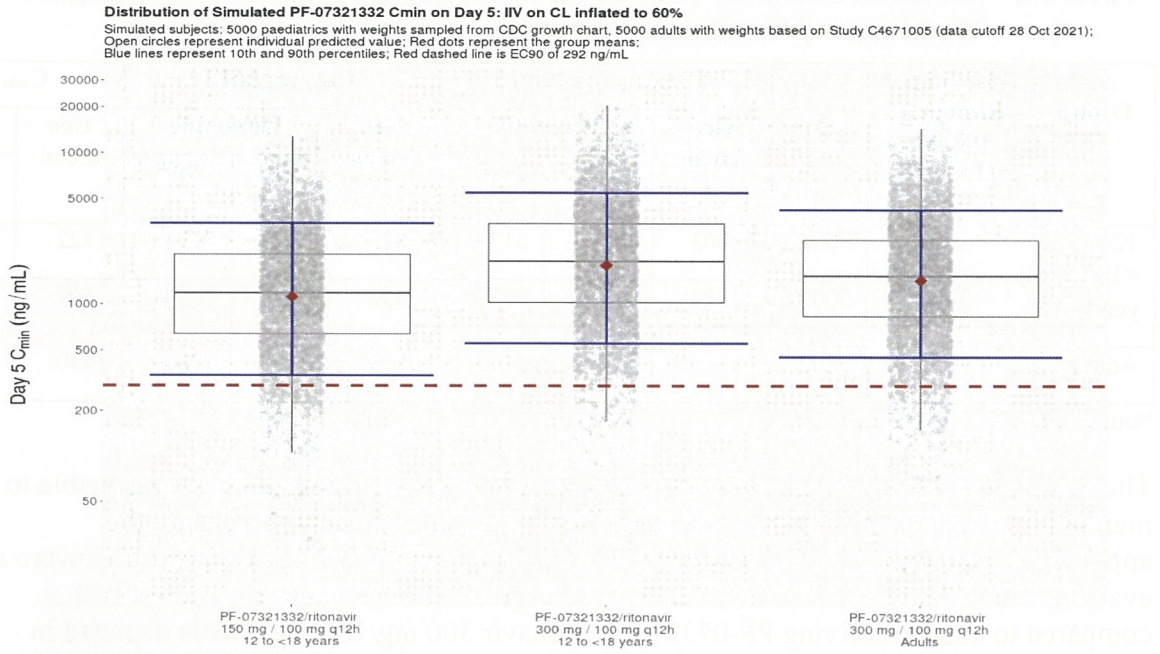
A preliminary population PK model based on healthy adult data (Module 5.3.3.5 PMAR-EQDD-C467a-Proof of Concept-1246) with interindividual variability on clearance inflated to 60% was used to simulate the plasma PF-07321332 concentration-time profiles. The model included standard allometric functions of body weight for clearances and volumes with exponents fixed to 0.75 and 1, respectively.

A simulation data set was created for adults by using the observed body weight distribution of adult participants in Study 1005 (data cutoff date 28 Oct 2021), and a separate simulation data set for adolescents using the CDC National Center for Health Statistics growth chart.[82] Simulations were performed with 5000 subjects in each age group (adults or adolescent) assuming a dose regimen of PF-07321332/ritonavir 300 mg/100 mg q12h given orally for 5 days (single dose on Day 5, a total of 9 doses). Additionally, a dose regimen of PF-07321332/ritonavir 150 mg/100 mg q12h given orally for 5 days (a total of 9 doses) was simulated for adolescents. A fine grid of time points (every 1 hour) over the 0–12 hour profile after the first dose on Day 1, and the last dose on Day 5 was simulated. Derived PK parameters (AUC, C_{max}, C_{min}) were obtained and graphically compared with the adult reference group. It is noted that these simulations of adults and adolescents were based on the preliminary population PK model generated using adult healthy participant PK data.

It is presumed that maintaining plasma concentration above EC_{90} over the entire dosing interval is linked to pharmacodynamic activity of antivirals. Hence the simulations focused on selecting a dose in adolescents that maintains C_{min} levels at or above those seen in adults receiving 300/100 mg BID for 5 days. The distribution of simulated C_{min} on Day 5 by dose of either PF-07321332/ritonavir 150 mg/100 mg BID or 300 mg/100 mg BID regimen in adolescent subjects are depicted in Figure 11. The distribution of simulated C_{min} on Day 5 based on adults from the Study 1005 is provided for reference.

In general, there is considerable overlap in C_{min} values of PF-07321332 between the PF-07321332/ritonavir 150 mg/100 mg BID and PF-07321332/ritonavir 300 mg/100 mg BID administrations in adolescents as compared to C_{min} values in adults receiving PF-07321332/ritonavir 300 mg/100 mg BID. Importantly, a dose of PF-07321332/ritonavir 300 mg/100 mg BID in adolescents will achieve a larger distribution of subjects above the in vitro EC_{90} of 292 ng/mL as compared to those receiving a dose of PF-07321332/ritonavir 150 mg/100 mg BID (Figure 11)

Figure 11. Distribution of C_{min} on Day 5 by Treatment in Simulated Adolescent Subjects



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Summary statistics for simulations results for all exposure parameters are presented in Table 34. These simulations suggests that a dose of PF-07321332/ritonavir 300 mg/100 mg BID in adolescents provide higher PF-07321332 AUC, C_{max} and C_{min} by 32%, 37% and 25%, respectively, as compared to adults receiving the same dose (Table 34). In comparison, a dose of PF-07321332/ritonavir 150 mg/100 mg BID in adolescents provide lower PF-07321332 AUC, C_{max} and C_{min}, by 14%, 6% and 22%, respectively, as compared to adults.

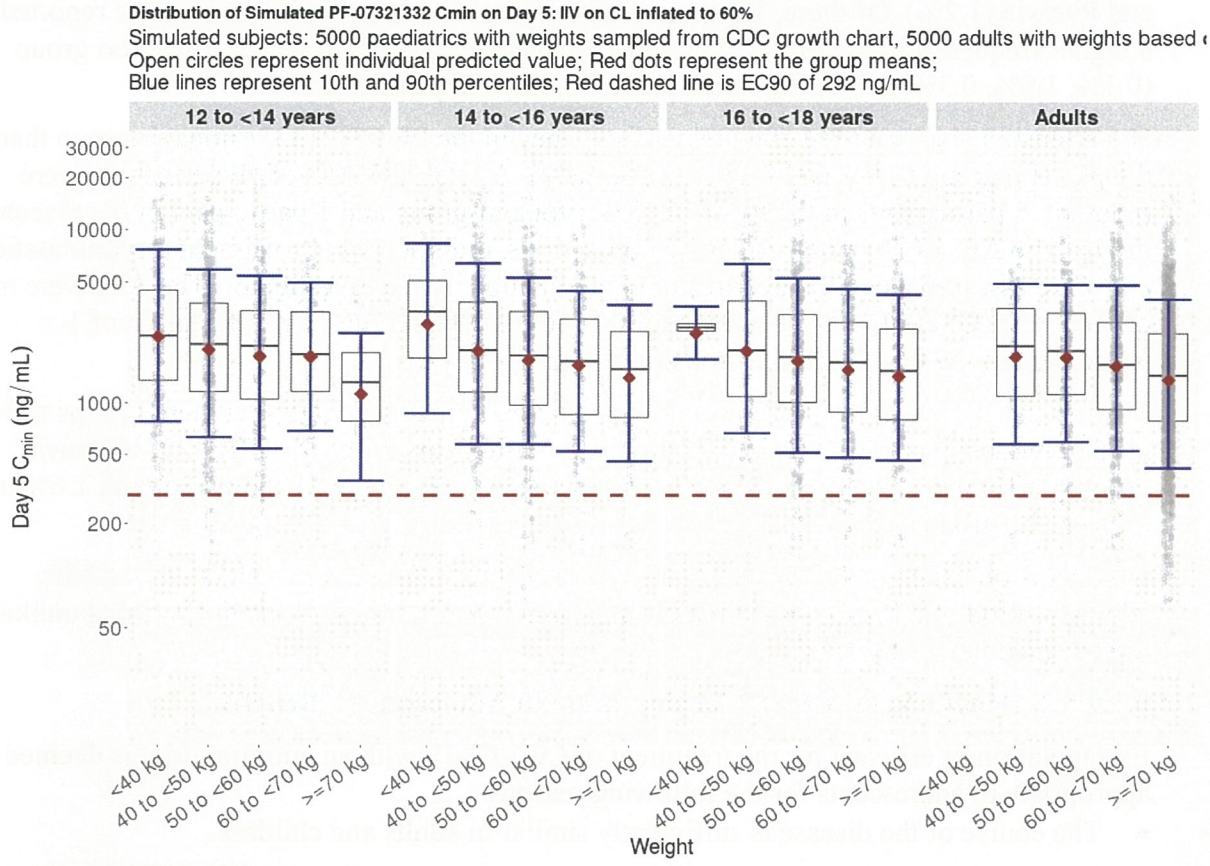
Table 34. Statistical Summary (Geometric Mean and Percentiles) of the Output of the Modeling and Simulation Evaluation

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

Source: CP1:FI-27152936

The dose of PF-07321332/ritonavir 300/100 mg BID in adolescents appears reasonable to maintain C_{min} comparable to adults without compromising efficacy. To ensure the appropriateness of the dose, assessment for both body weight and age on exposures were also evaluated. The distribution of C_{min} on Day 5 by age and body weight for adolescents as compared to adults receiving PF-07321332/ritonavir 300 mg/100 mg BID is depicted in Figure 12. For reference, the median body weight for 12, 14, 16, and 18 year old boys based on the CDC charts is 40.67, 51.23, 61.09, and 67.28 kg, respectively.[83] Regardless of age or body weight, C_{min} values appear to be consistent with that in adults and above the in vitro EC_{90}. It is important to note that those adolescents <40 kg appear to have the higher simulated exposures.

Figure 12. Distribution of C_{min} on Day 5 by Age and Body Weight in Simulated Adolescents and Adults Receiving PF-07321332/ritonavir 300/100 mg BID



Source: CP1:FI-27155210

6.3.9.5.1. Benefit Versus Risk Considerations in Adolescents - Risks

The safety and tolerability of PF-07321332/ritonavir in adolescents in not currently known but can be contextualized from the observed safety and tolerability profile in adults. This is because the pharmacologic target for PF-07321332, the SARS-CoV-2 $3CL^{pro}$ enzyme, is not different between adults and adolescents. In the secondary pharmacology assessments (Section 6.1.1.2), PF-07321332 had no significant inhibition (>50%) of functional or enzymatic activity against a wide panel of receptors, transporters, ion channels, and enzyme assays in vitro. The use of ritonavir as PK enhancer is well established in pediatric populations and is safe and well tolerated.

In Study 1005, adult patients have generally depicted an acceptable safety and tolerability profile (Section 6.4.6). In the 45% interim analysis of Study 1005, the most frequently reported TEAEs were GI-related and were mild to moderate in severity. All-causality TEAEs were most common (reported in ≥3% of participants in either treatment group) in the SOCs of Gastrointestinal disorders, Infections and Infestations, Investigations, Nervous system disorders, and Respiratory, Thoracic, and Mediastinal disorders. The overall incidence of all-causality TEAEs was comparable between the PF-07321332/ritonavir group and the placebo group.

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%). 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 also occurred at a greater frequency in the PF 07321332/ritonavir group than in the placebo group (0.9% and 0.1%, respectively). 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, did not lead to treatment discontinuation and 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.

Most of the all-causality TEAEs experienced by participants in both treatment groups were mild to moderate (Grade 1-2) in severity. Few participants in the PF-07321332/ritonavir group (0.9%) reported potentially life-threatening events (Grade 4) compared with 1.6% in the placebo group.

In conclusion, since PF-07321332/ritonavir 300/100 mg BID is well tolerated in adults, administration of a PK exposure-matched dose of 300/100 mg BID in adolescent is unlikely to pose an unnecessary risk.

6.3.9.5.2. Benefit Versus Risk Consideration in Adolescents - Benefit

Extrapolation of efficacy for the treatment of COVID-19 with an antiviral drug is deemed appropriate in adolescents for the following reasons:

- The course of the disease is sufficiently similar in adults and children.
- The response to treatment is sufficiently similar in adults and children; and
- Adults and children have a sufficiently similar exposure-response relationship (ie, similar PK-PD target of maintaining C_{min} above in vitro EC_{90}).

Hence, the population PK model can be utilized for dose selection in adolescents by matching exposures across both adolescents and adult groups. This is acceptable as the route of elimination of PF-07321332 when given with ritonavir, is mainly by renal clearance. GFR increases rapidly during the first two weeks of life and then rises steadily until adult values are reached at 8 to 12 months of age.[84] Similarly, tubular secretion is immature at birth and reaches adult capacity during the first year of life. Results of the simulation performed suggest that the PF-07321332/ritonavir 300 mg/100 mg dose in adolescents maintains similar or higher C_{min} levels above the in vitro EC_{90} as compared to adults and provides a suitable dose for exposure matching to adults. Lastly, even though the pediatric dose of ritonavir is based on body surface area, a fixed dose of 100 mg in adolescents is supported by precedented labels (lopinavir/ritonavir, darunavir/ritonavir). These labels support that pediatric patients ≥40 kg (~12 years and older) receive 100 mg ritonavir as a PK enhancer.

In conclusion, simulations suggest a dose of PF-07321332/ritonavir 300 mg/100 mg in adolescents will provide similar exposures to that observed as the same dose in adults and is

anticipated to provide a favorable benefit-risk profile for treatment of COVID-19 in adolescents.

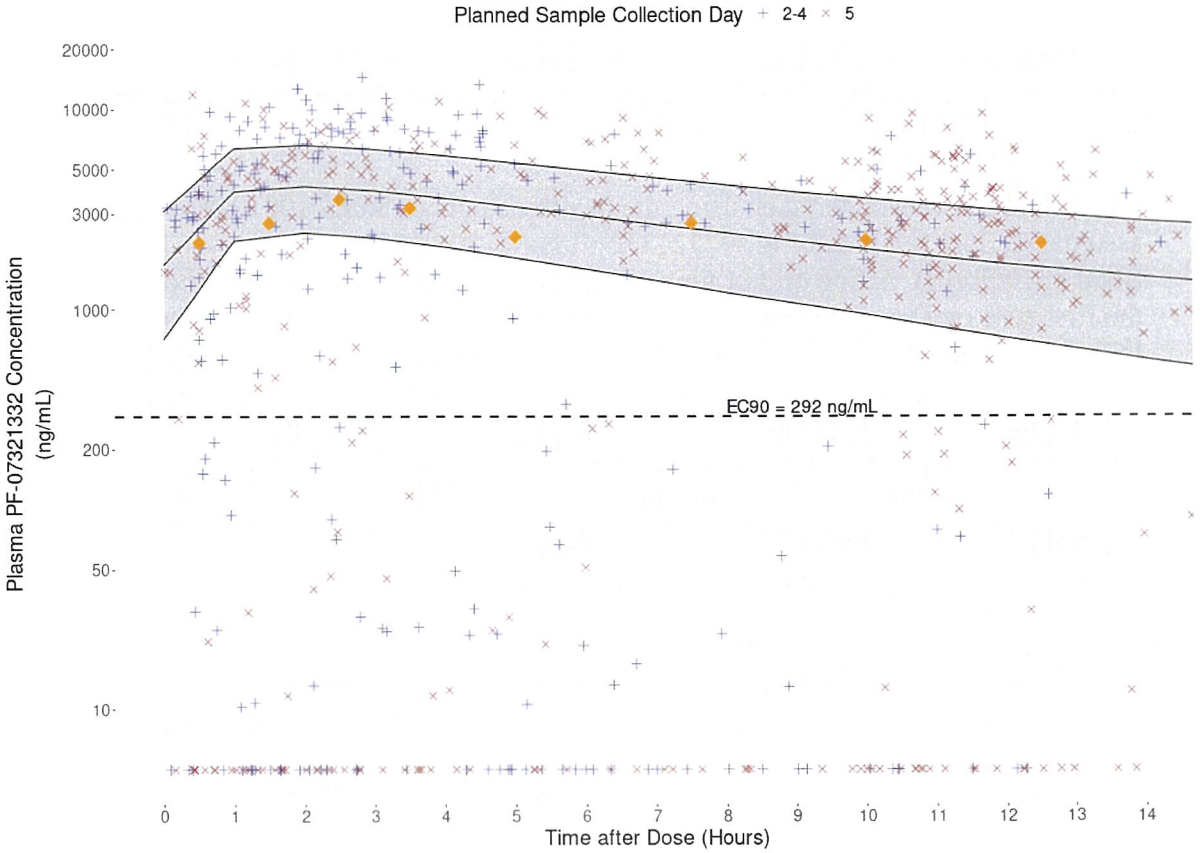
6.3.10. Phase 2/3 Study 1005 – Pharmacokinetics

A predictive check (simulation) approach was used to assess the adequacy of the preliminary population PK model (Module 5.3.3.5 PMAR-EQDD-C467a-Proof of Concept-1246), developed based on the preliminary healthy adult data (Study 1001), in describing the patient data from Study 1005.

The simulation was undertaken using the healthy adults in Study 1001 (Part 1-3), and assuming a dose regimen of PF-07321332/ritonavir 300/100 mg q12h given orally for 5 days (total of 10 doses). A fine grid of time points (every 1 hour) over the 0-12 hour profile after the first dose on Day 1 and the last dose on Day 5 was simulated. Assessment was based on the median and 90% prediction interval constructed from a simulation with 1000 subproblems (ie, healthy participants) and overlaid with the observed plasma PF-07321332 concentration-time data from Study 1005 in COVID-19 patients. In Study 1005, venous blood samples for analyses of plasma concentration of PF-07321332 were collected during site visit on Day 1 (0.5 to 1.5 hr post dose), and on Day 5 (up to 2 hours pre-dose; otherwise, collected anytime post dose). Optional PK samples were collected via home health or during in-person site visit at any time on Days 2, 3, or 4.

Since steady-state is reached by Day 2, the observed plasma PF-07321332 concentrations on Days 2-4 and on Day 5 in Study 1005 are depicted along with the median and 90% prediction interval based on population PK simulations (Figure 13). In general, the majority of the observed plasma PF-07321332 concentrations from Study 1005 fall within the 90% prediction interval. The median observed data from samples collected during the planned Day 5 visit were in good agreement with the model predictions generated by the preliminary population PK model (Figure 13) (Module 5.3.3.5 PMAR-EQDD-C467a-DP4-1307).

Figure 13. Median and 90% Prediction Intervals (5th and 95th percentile) for PF-07321332 Concentration Based on 1000 Simulations (PF-07321332/ritonavir 300/100 mg q12h at Steady-State) Overlaid with Observed Data From Study 1005.



Symbols represent individual observations; Blue symbols represent PK samples collected on Day 2 to Day 4, and red symbols represent PK samples collected on Day 5. Orange diamonds represent median of Day 5 observations binned by intervals (0, 1, 2, 3, 4, 6, 9, 11, and 14 hours post dose); Dashed horizontal line represents the in vitro EC_{90} value. Excluded observations with time after dose >14 hours. BLQ samples are shown below the LLOQ of 10 ng/mL
Source: Figure 4 PMAR-EQDD-C467a-DP4-1307

These data suggests that the pharmacokinetics of PF-07321332/ritonavir appears to be generally similar between healthy subjects and patients with COVID-19.