6.4. Pivotal Phase 2/3 Study 1005

- Study 1005 met the primary endpoint, demonstrating overwhelming efficacy at the pre-planned 45% interim analysis in the mITT population.
  - In the mITT analysis set, PF-07321332/ritonavir significantly reduced ($p<0.0001$) the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 by 89.1% compared to placebo in non-hospitalized symptomatic adult participants who were at increased risk of progression to severe illness at baseline.
- A first key secondary analysis supports the findings for the primary endpoint:
  - In the mITT1 analysis set, PF-07321332/ritonavir significantly reduced ($p<0.0001$) the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 by 85.2% compared to placebo.
- A sensitivity analysis supports the findings for the primary endpoint:
  - In the mITT2 analysis set, PF-07321332/ritonavir significantly reduced ($p<0.0001$) the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 by 83.6% compared to placebo.
- Secondary analyses showed that the adjusted mean reduction in Log_{10}(viral load) from baseline to Day 5 for the mITT, mITT1 and mITT2 analysis sets was significantly greater for participants who received PF-07321332/ritonavir compared to those who received placebo, with adjusted mean difference (SE) of -1.03 (0.16), -0.93 (0.13) and -0.96 (0.12) Log_{10}(copies/mL), respectively.
  - The additional viral load reduction from PF-07321332/ritonavir treatment relative to placebo was more apparent in participants who were seronegative than participants who were seropositive, and more apparent in participants with higher versus lower viral load at baseline.
- Treatment with PF-07321332/ritonavir was safe and well tolerated.
  - The incidence of all-causality TEAEs was comparable between the PF-07321332/ritonavir group and the placebo group (19.8% and 22.3%, respectively).
  - 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.
  - The proportion of participants with all-causality SAEs was lower in the PF-07321332/ritonavir group (1.9%) compared with the placebo group (6.8%).
  - There were 10 events of deaths among participants in this study. All 10 death events were in the placebo group and were related to the disease under study.
  - Fewer participants discontinued study intervention due to an AE in the PF-07321332/ritonavir group compared with the placebo group (2.4% and 4.3%, respectively).
  - PF-07321332/ritonavir was not associated with clinically meaningful changes in laboratory values, vital signs, or ECGs (including QT_c).

6.4.1. Study Design

This EUA presents the results of an interim analysis which includes 774 participants (~45% of participants in the primary [mITT] analysis set) enrolled through 29 September 2021 who completed Day 28 assessments (data cutoff 26 October 2021). At the time of the cutoff for the 45% interim analysis, 1219 participants were in the mITT1 analysis set and 1330 participants were in the mITT2 analysis set and are included in this EUA. As of 09 November 2021, a total of 2426 participants have been randomized into Study 1005, and the final primary analysis will be performed when all participants have completed follow-up through Day 34. A long-term follow-up analysis will be performed once all participants have completed the Week 24 visit.

Study 1005, as detailed in Table 6, is a Phase 2/3, randomized, double-blind, placebo-controlled, efficacy and safety study targeting approximately 3100 symptomatic participants with COVID-19 who were non-hospitalized.

Eligible participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection were randomized (1:1) to receive PF-07321332/ritonavir or placebo orally q12h for 5 days (10 doses total). Randomization was stratified by geographic region and by whether participants had received/were expected to receive treatment with COVID-19 therapeutic mAbs based on the investigator's assessment at time of randomization. Detailed inclusion and exclusion criteria are provided in Study 1005 Protocol Section 5.

The total study duration was up to 24 weeks and included a screening period of no more than 48 hours, study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow up at Weeks 12 and 24. A total of 15 countries across 5 geographical regions (US, Europe, Brazil, India, and ROW) contributed to the data in this 45% interim analysis.

The sponsor made a data driven decision to halt recruitment (22 September 2021, total of 193 participants randomized) in India due to observations in a blinded data review of a >90% rate of serology positive participants at baseline (92% versus 45% in patients from India versus ROW, respectively), with corresponding low levels of viral load measured at baseline from a blinded assessment (mean baseline viral load [Log_{10} copies/mL] = 2.36 versus 5.25 copies/mL in patients from India versus ROW, respectively), and the high frequency of participants experiencing mild COVID-19 symptoms at baseline (73% versus 15% of participants with only mild symptoms at baseline, India versus ROW, respectively). Lastly, of 193 participants from India randomized, none progressed to hospitalization or death, despite the presence of risk factors for progression to severe disease. A sensitivity analysis of the mITT population, excluding data from India sites, was consistent with the results in the overall mITT population. [redacted]

6.4.2. Endpoints and Analysis Methods

6.4.2.1. Efficacy

6.4.2.1.1. Efficacy Endpoints

For purposes of the 45% interim analysis, the following efficacy analysis sets are defined:

Table 35. Efficacy Analysis Sets Defined for the 45% Interim Analysis of Study 1005

Analysis Set	Description	Analysis Set Applies to Following Endpoints
mITT	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, with at least 1 postbaseline visit through Day 28, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days after COVID-19 symptom onset. Participants will be analyzed according to the study intervention to which they were randomized.	• Primary endpoint • Sensitivity analysis of primary endpoint • Supplemental analysis of primary endpoint • Subgroup analysis of primary endpoint • Secondary analysis of POC • Secondary endpoints
mITT1	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, with at least 1 postbaseline visit through Day 28 visit and who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤5 days after COVID-19 symptom onset. Participants will be analyzed according to the study intervention to which they were randomized.	• First key secondary analysis of the primary endpoint • Subgroup analysis of first key secondary endpoint • Secondary analysis of POC • Secondary endpoints
mITT2	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, and with at least 1 postbaseline visit through Day 28 and were treated ≤5 days after COVID-19 symptom onset regardless of mAb treatment status. Participants will be analyzed according to the study intervention to which they were randomized.	• Sensitivity analysis of primary endpoint • Secondary analysis of POC • Secondary endpoints

The primary endpoint for Study 1005 was:

- Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 in the mITT analysis set.

The first key secondary endpoint for Study 1005 was:

- Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 in the mITT1 analysis set.

Sensitivity analyses of the primary endpoint for Study 1005 presented within this EUA were:

- Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 in the mITT2 analysis set.

- Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 in the mITT analysis set whereby participants that did not have follow-up data through Day 21 were hypothetically assumed to experience both COVID-19-related hospitalization and death in a worst-case scenario.

The secondary analysis for the POC for Study 1005 presented within this EUA that used the mITT, mITT1 and mITT2 analysis sets was:

- Viral load measured via RT-PCR in NP samples at baseline (Day 1) and EoT (Day 5).

6.4.2.1.2. Efficacy Assessments

Efficacy assessments for participants in Study 1005 were collected at planned timepoints as described in Study C4671005 Protocol Section 1.3. Full details regarding efficacy assessments for Study 1005 are found in Study C4671005 Protocol Section 8.

Key efficacy assessments for the endpoints presented in this 45% interim analysis for the EUA are summarized below:

- COVID-19-Related Hospitalizations or Death from any cause through Day 28.

- **Viral Load Over Time:** NP swabs were collected per the SoA and analyzed to measure SARS-CoV-2 RNA by RT-PCR at baseline (Day 1) and EoT (Day 5). Nasal (MT) swabs were collected by the participant as specified in the SoA on Day 3, Day 10 and Day 14 but were not used in the viral POC analysis. Residual viral load samples will be utilized for viral sequencing to assess prevalence of VOC/VOI in the study population and to determine the efficacy of study treatment against different VOC/VOI present at baseline and the frequency of treatment emergent mutations (eg, 3CL gene) compared to placebo.

[redacted]

6.4.2.1.3. Statistical Methods for Efficacy Analyses

Primary Analysis of the Primary Endpoint

The cumulative proportion of participants who experienced a COVID-19-related hospitalization or death due to any cause during the first 28 days of the study was estimated for each treatment group of the mITT analysis set using the Kaplan-Meier method to consider losses to follow-up and patients who discontinued early. The estimand was the difference of the proportions of the 2 treatment groups without regard to adherence to randomized treatment.

First Key Secondary Analysis of the Primary Endpoint

A first key secondary analysis of the primary endpoint was performed using the mITT1 analysis set.

Sensitivity Analyses of the Primary Endpoint

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

Per the Agency's request, a sensitivity analysis was performed using the mITT analysis set whereby participants that did not have follow-up data through Day 21 were hypothetically assumed to experience both COVID-19-related hospitalization and death in a worst-case scenario.

Supplemental Analyses of the Primary Endpoint

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

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

Subgroup Analyses of the Primary and First Key Secondary Endpoints

Prespecified subgroup analyses of the primary and first key secondary endpoints using the mITT and mITT1 analysis sets, respectively, were conducted by age (<65, ≥65 years), gender, race, BMI (<25, 25-29, ≥30 kg/m^2), baseline serology status (antibody negative, antibody positive), baseline viral load ([<10^4, ≥10^4 copies/mL] and [<10^7, ≥10^7 copies/mL]), baseline comorbidities and number of baseline comorbidities present (0-1, 2-3, ≥4).

Viral Load Measured via RT-PCR Over Time

Descriptive statistics by treatment group for the change from baseline to Day 5 was provided for each treatment group and included the difference between the PF-07321332/ritonavir arm

and placebo. An ANCOVA model was used to analyze the change from baseline in Log_{10} transformed viral load (copies/mL) data which included treatment group, baseline viral load and baseline serology status for the mITT, mITT1 and mITT2 analysis sets, as detailed in Section 6.4.4.8. The mAb treatment status and symptom onset to first dose date status (≤3 days, >3 days) was used in the model dependent of population.

Participants were excluded from the analysis due to missing or baseline viral load below the limit of detection (<550 Log_{10} copies/mL), or collection with a unvalidated (local) swab. Preliminary data suggests swab type is critical and viral load determined with different swab types cannot be combined, therefore, only samples collected with the validated I-Swab-plus were used for formal viral load analysis. Data reported as less than 2.0 Log_{10} copies/mL was recorded as 1.69 Log_{10} copies/mL and data reported as "not detected' was recorded as 0 Log_{10} copies/mL. Results from samples collected at non-NP sites (like nasal, other or missing) were also excluded.

6.4.2.2. Safety

6.4.2.2.1. Safety Endpoints

The safety endpoints for Study 1005 include:

- Incidence of TEAEs.
- Incidence of SAEs and AEs leading to discontinuations.

6.4.2.2.2. Safety Assessments

Safety assessments for participants in Study 1005 were collected at planned timepoints as described in Study C4671005 Protocol Section 1.3. Full details regarding safety assessments for Study 1005 are found in Study C4671005 Protocol Section 8.

Key safety assessments are summarized below:

- Complete medical history including COVID-19 disease history and smoking status was collected.
- AEs and SAEs were collected at the time of informed consent before participation in the study, through 28 days after last dose of study drug, or Day 34 ('active collection period'). In addition, post-study completion, any SAEs, including events of death that the investigator considered reasonably related to the study intervention were reported. Follow-up was continued until the AE or SAE or its sequelae resolved or stabilized. An AE was defined as "serious" when it met at least 1 of the predefined outcomes as described in the definition of an SAE, not when it was rated as severe.
- Vital signs (including temperature, pulse rate, respiratory rate, oxygen saturation level, and blood pressure), ECGs and clinical safety laboratory assessments were assessed as specified in the protocol.

- Routine pregnancy tests were performed in WOCBP as detailed in the protocol and positive tests were reported.

- AESIs including hemodynamic events, inflammatory events, and thyroid-related events were examined as part of routine safety data review procedures throughout the study and as part of signal detection processes. All AESIs were reported as an AE or SAE as described in the protocol.

Narratives

- Narratives are provided for all deaths, SAEs, and AEs resulting in permanent discontinuation from study intervention (Module 5.3.5.1 C4671005 Interim Analysis Narratives). In addition, per FDA request, narratives are provided for all participants included in the safety population from the 45% interim analysis (database cutoff 26 Oct 2021) with reported hepatotoxicity (ie, hepatic transaminase elevations exceeding 5 times the upper limit of normal, clinical hepatitis, and/or jaundice; Module 5.3.5.1 C4671005 Interim Analysis Narratives: Hepatotoxicity). Narratives for participants with hepatotoxicity, enrolled after 29 Sep 2021 will be provided [redacted] once all participants have completed their Day 34 visit.

6.4.2.2.3. Statistical Methods for Safety Analyses

Disposition and demographics data are provided for the full analysis set, defined as: all participants randomly assigned to study intervention regardless of whether or not study intervention was administered. Safety analyses are provided for the safety analysis set, defined as: all participants who received at least 1 dose of study intervention. Participants were analyzed according to the intervention received. A randomized but not treated participant was excluded from the safety analyses.

Adverse Events

All AE analyses were conducted using treatment-emergent AEs. All AEs were coded using MedDRA version 24.0. The incidence of TEAEs is summarized by treatment group, by SOC and PT using the safety analysis set population.

Pre-specified AESI are provided in Study C4671005 Statistical Analysis Plan, Appendix 4. Analyses of AESI are not provided in this EUA and will be provided in the final analysis once all participants have completed their Day 34 visit.

The incidence of SAEs and AEs leading to discontinuation are summarized by treatment group using the safety analysis set population.

Laboratory, Vital Sign and ECG Data

For laboratory and vital sign data, descriptive statistics are summarized by treatment group as well as mean change from baseline for laboratory parameters.

Laboratory shift tables from baseline are presented for the following laboratory abnormalities: TSH, T4 (free), fibrinogen, platelets, PT, aPTT, albumin, total proteins, D-dimer levels, liver function tests (ALT/AST), creatinine clearance (derived using Cockcroft-Gault Equation).

For ECGs, all ECG parameters were provided by a central reader. Details on ECG assessments are provided in Study C4671005 Statistical Analysis Plan Section 6.6.4. ECG analyses were provided to the E-DMC and FDA for their assessment of ECG data from the sentinel cohort in Study 1005. Based on E-DMC and FDA assessment of ECG data collected from the sentinel cohort, ECG collections were stopped after the sentinel cohort in Study 1005. A summary of the ECG data from the sentinel cohort is provided in Section 6.4.6.4.

6.4.3. Study Participants

6.4.3.1. Disposition of Participants

As of the data cutoff (26 Oct 2021) 1361 (100.0%) participants in the interim analysis had entered the treatment phase, 1086 (79.8%) participants had completed the safety follow-up (Day 34) and no participants had completed the long-term safety follow-up (Table 36).

- The proportion of participants who discontinued the treatment phase was similar between treatment groups (7.1% versus 8.9% in the PF-07321332/ritonavir group and placebo group, respectively). The most common reasons for discontinuation during the treatment phase of the study in either treatment group were 'withdrawal by subject' (3.5%) followed by AE (3.3%). Fewer participants in the PF-07321332/ritonavir group (2.4%) discontinued the treatment phase due to an AE compared with the placebo group (4.2%).

- The proportion of participants who completed the safety follow-up (Day 34) was similar between treatment groups. The most common reason for discontinuation during the safety follow-up phase of the study in either treatment group was 'withdrawal by subject' (4.6%). The proportion of participants ongoing in the safety follow-up phase, defined as participants that have not yet completed Day 34 visit, were similar between treatment groups (12.3%).

- The number of participants who entered the long-term follow-up phase was balanced across the treatment groups.

Table 36. Disposition Events Summary - Full Analysis Set (Protocol C4671005_45IA)

Number (%) of Participants	PF-07321332 300 mg + Ritonavir 100 mg (N=678) n (%)	Placebo (N=683) n (%)	Total (N=1361) n (%)
Disposition phase: Treatment			
Participants Entered:	678 (100.0)	683 (100.0)	1361 (100.0)
Discontinued	48 (7.1)	61 (8.9)	109 (8.0)
Reason for discontinuation			
Adverse event	16 (2.4)	29 (4.2)	45 (3.3)
Death	0	0	0
Lack of efficacy	0	0	0
Lost to follow-Up	1 (0.1)	1 (0.1)	2 (0.1)
Noncompliance with study drug	0	0	0
Pregnancy	0	0	0
Protocol deviation	0	0	0
Study terminated by sponsor	0	0	0
Withdrawal by subject	24 (3.5)	23 (3.4)	47 (3.5)
Medication error without associated adverse event	0	1 (0.1)	1 (<0.1)
No longer meets eligibility criteria	1 (0.1)	1 (0.1)	2 (0.1)
Other	6 (0.9)	6 (0.9)	12 (0.9)
Completed	630 (92.9)	622 (91.1)	1252 (92.0)
Ongoing	0	0	0
Disposition phase: Follow-up			
Participants Entered:	678 (100.0)	683 (100.0)	1361 (100.0)
Discontinued	50 (7.4)	57 (8.3)	107 (7.9)
Reason for discontinuation			
Death	0	10 (1.5)	10 (0.7)
Lost to follow-Up	9 (1.3)	7 (1.0)	16 (1.2)

Table 36. Disposition Events Summary - Full Analysis Set (Protocol C4671005_45IA)

Number (%) of Participants	PF-07321332 300 mg + Ritonavir 100 mg (N=678) n (%)	Placebo (N=683) n (%)	Total (N=1361) n (%)
Study terminated by sponsor	0	0	0
Withdrawal by subject	31 (4.6)	32 (4.7)	63 (4.6)
Other	10 (1.5)	8 (1.2)	18 (1.3)
Completed	545 (80.4)	541 (79.2)	1086 (79.8)
Ongoing	83 (12.2)	85 (12.4)	168 (12.3)
Disposition phase: Long-term follow-up			
Participants Entered:	594 (87.6)	597 (87.4)	1191 (87.5)
Discontinued	47 (6.9)	56 (8.2)	103 (7.6)
Reason for discontinuation			
Adverse event	0	0	0
Death	0	10 (1.5)	10 (0.7)
Lost to follow-Up	8 (1.2)	7 (1.0)	15 (1.1)
Study terminated by sponsor	0	0	0
Withdrawal by subject	31 (4.6)	32 (4.7)	63 (4.6)
Other	8 (1.2)	7 (1.0)	15 (1.1)
Completed	0	0	0
Ongoing	547 (80.7)	541 (79.2)	1088 (79.9)

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

6.4.3.2. Demographics and Other Characteristics of Study Population

Full Analysis Set

Demographic characteristics for the full analysis set were similar between the PF-07321332/ritonavir and placebo groups (Table 37).

As of the data cutoff, 44.7%, 17.9%, <0.1%, 14.2%, and 23.2% of participants were from the US, Europe, Brazil, India and ROW, respectively. Over half of the participants (52.4%) were male and were White (63.1%). Approximately half of the participants in each treatment group were Hispanic or Latino. The median age was 44.00 (18.00, 86.00) years and 255 (18.7%) patients were 60 years of age or greater at the time of randomization.
The mean (SD) BMI was 29.14 (5.63), and the majority of participants had a BMI of 25 or greater at the time of screening.

The participant population of Study 1005 reflected the patient population that would be treated with PF-07321332/ritonavir in clinical practice and who are at high risk for progressing to severe disease. Across treatment groups, 63.1% of participants received their first dose of study intervention within 3 days of symptom onset, and 100% of participants had a laboratory confirmed SARS-CoV-2 diagnosis, with 92.9% of participants having a qualifying SARS-CoV-2 positive test collected within 3 days of first dose of study intervention. Across treatment groups, 44.4% of participants were serological negative at baseline. Most participants (91.8% across treatment groups) did not receive or were not planning to receive monoclonal antibodies for the disease under study at the time of randomization.

With the exception of 2 participants, all other participants had at least one risk factor for severe COVID-19 with approximately 41.1% of participants with 1 prespecified risk factor and 494 (36.3%) participants with 2 pre-specified risk factors. A total of 192 (14.1%) and 93 (6.8%) participants presented at screening with 3 and 4 risk factors, respectively. The most common risk factor at baseline was BMI >25 (79%). A total of 501 participants were cigarette smokers (36.8%), 441 participants (32.4%) presented at screening with hypertension, and 175 participants (12.9%) presented with diabetes mellitus.

Across treatment groups, the median Log_{10}(viral load) in Log_{10}(copies/mL) was 5.26. Approximately 37.7% of participants had a low baseline viral load (<4.0 Log_{10} copies/mL), 62.3% of participants had a high baseline viral load (≥4.0 Log_{10} copies/mL) and 26.7% of participants had a very high baseline viral load (≥7.0 Log_{10} copies/mL).

Further details of risk factors are provided in Study 1005 Listing 16.2.4.2.3. Additional details on significant medical history can be found in Study 1005 Table 14.1.3.1.

Efficacy Analysis Sets

Demographic and baseline characteristics were similar for the mITT, mITT1 and mITT2 analysis sets (Study 1005 Tables 14.1.2.2, 14.1.2.4, and 14.1.2.5, respectively).

In the mITT analysis set, by definition, all participants received their first dose of study intervention within 3 days of symptom onset and no participants received or were expected to receive COVID-19 mAb treatment at the time of randomization. All participants had a laboratory-confirmed SARS-CoV-2 diagnosis, with 99.5% of participants having their qualifying SARS-CoV-2 positive test collected within 3 days of the first dose of study intervention. 66.5% of participants had high baseline viral load ($\geq Log10^4$ copies/mL) and 8.9% of participants had a baseline viral load <LOQ.

In the mITT1 analysis set, 63.5% of participants received their first dose of study intervention within 3 days of symptom onset, and all participants had a laboratory confirmed SARS-CoV-2 diagnosis, with 93.4% of participants having their qualifying SARS-CoV-2 positive test collected within 3 days of first dose of study intervention. By analysis set definition, no participants received or were expected to receive COVID-19 mAb treatment, and 61.6% of participants had high baseline viral load ($\geq Log10^4$ copies/mL) and 10.3% of participants had a baseline viral load <LOQ.

In the mITT2 analysis set, 63.6% of participants received their first dose of study intervention within 3 days of symptom onset, and 100% of participants had a confirmed SARS-CoV-2 diagnosis, with 92.9% of participants having their qualifying SARS-CoV-2 positive test collected within 3 days of first dose of study intervention. 8.3% of participants received or were expected to receive COVID-19 mAb treatment at the time of randomization, 61.9% of participants had high baseline viral load ($\geq Log10^4$ copies/mL) and 10.0% of participants had a baseline viral load <LOQ.

Safety Analysis Set

Demographic and baseline characteristics for the safety analysis set were similar to the full analysis set (Study 1005 Table 14.1.2.3).

Table 37. Demographic and Baseline Characteristics - Full Analysis Set (Protocol C4671005_45IA)

	PF-07321332 300 mg + Ritonavir 100 mg (N=678)	Placebo (N=683)	Total (N=1361)
Age (Years), n (%)			
< 18	0	0	0
18 - 44	361 (53.2)	336 (49.2)	697 (51.2)
45 - 59	208 (30.7)	201 (29.4)	409 (30.1)
60 - 64	38 (5.6)	61 (8.9)	99 (7.3)
65 - 74	54 (8.0)	62 (9.1)	116 (8.5)
≥ 75	17 (2.5)	23 (3.4)	40 (2.9)
Mean (SD)	43.86 (14.93)	45.47 (15.69)	44.67 (15.33)
Median (range)	42.00 (18.00, 86.00)	45.00 (18.00, 84.00)	44.00 (18.00, 86.00)
Gender, n (%)			
Male	344 (50.7)	369 (54.0)	713 (52.4)
Female	334 (49.3)	314 (46.0)	648 (47.6)
Race, n (%)			
White	424 (62.5)	435 (63.7)	859 (63.1)
Black or African American	37 (5.5)	25 (3.7)	62 (4.6)
Asian	134 (19.8)	140 (20.5)	274 (20.1)
American Indian or Alaska Native	76 (11.2)	77 (11.3)	153 (11.2)
Native Hawaiian or other Pacific Islander	0	0	0
Multiracial	1 (0.1)	0	1 (<0.1)
Other	0	0	0
Not reported	5 (0.7)	4 (0.6)	9 (0.7)
Unknown	1 (0.1)	2 (0.3)	3 (0.2)
Ethnicity, n (%)			
Hispanic or Latino	324 (47.8)	330 (48.3)	654 (48.1)
Not Hispanic or Latino	352 (51.9)	349 (51.1)	701 (51.5)
Not reported	2 (0.3)	4 (0.6)	6 (0.4)
Unknown	0	0	0
Weight (kg)			
Mean (SD)	80.44 (17.59)	81.26 (18.85)	80.85 (18.23)
Median (range)	78.90 (42.00, 158.3)	78.50 (42.00, 166.0)	78.80 (42.00, 166.0)
Height (cm)			
Mean (SD)	166.2 (9.74)	166.4 (10.27)	166.3 (10.00)
Median (range)	166.0 (136.9, 195.6)	166.0 (125.2, 207.3)	166.0 (125.2, 207.3)

Table 37. Demographic and Baseline Characteristics - Full Analysis Set (Protocol C4671005_45IA)

	PF-07321332 300 mg + Ritonavir 100 mg (N=678)	Placebo (N=683)	Total (N=1361)
BMI (kg/m^2), n (%)			
< 25	142 (20.9)	139 (20.4)	281 (20.6)
25 - < 30	290 (42.8)	291 (42.6)	581 (42.7)
30 - < 35	163 (24.0)	164 (24.0)	327 (24.0)
35 - < 40	45 (6.6)	53 (7.8)	98 (7.2)
≥ 40	38 (5.6)	36 (5.3)	74 (5.4)
Mean (SD)	29.08 (5.65)	29.21 (5.61)	29.14 (5.63)
Median (range)	28.30 (16.58, 58.07)	28.35 (16.05, 59.07)	28.32 (16.05, 59.07)
Duration since first diagnosis (Days), n (%)			
≤ 3	623 (91.9)	642 (94.0)	1265 (92.9)
> 3	55 (8.1)	41 (6.0)	96 (7.1)
Mean (SD)	1.44 (1.33)	1.38 (1.28)	1.41 (1.30)
Median (range)	1.00 (0.00, 5.00)	1.00 (0.00, 9.00)	1.00 (0.00, 9.00)
Duration since first symptom (Days), n (%)			
≤ 3	433 (63.9)	426 (62.4)	859 (63.1)
> 3	245 (36.1)	257 (37.6)	502 (36.9)
Mean (SD)	3.02 (1.14)	3.09 (1.10)	3.06 (1.12)
Median (range)	3.00 (0.00, 7.00)	3.00 (0.00, 9.00)	3.00 (0.00, 9.00)
Number of risk factors of interest, n (%)			
0	2 (0.3)	0	2 (0.1)
1	293 (43.2)	267 (39.1)	560 (41.1)
2	240 (35.4)	254 (37.2)	494 (36.3)
3	91 (13.4)	101 (14.8)	192 (14.1)
4	44 (6.5)	49 (7.2)	93 (6.8)
> 4	8 (1.2)	12 (1.8)	20 (1.5)
Comorbidities, n (%)			
Cardiovascular disorder	24 (3.5)	26 (3.8)	50 (3.7)
Chronic kidney disease	3 (0.4)	5 (0.7)	8 (0.6)
Chronic lung disease	40 (5.9)	27 (4.0)	67 (4.9)
Cigarette smoker	244 (36.0)	257 (37.6)	501 (36.8)
Diabetes mellitus	87 (12.8)	88 (12.9)	175 (12.9)
Hypertension	207 (30.5)	234 (34.3)	441 (32.4)
Immunosuppression	6 (0.9)	6 (0.9)	12 (0.9)
Cancer	2 (0.3)	2 (0.3)	4 (0.3)
Neurodevelopmental disorder	2 (0.3)	0	2 (0.1)
HIV infection	0	1 (0.1)	1 (<0.1)

Table 37. Demographic and Baseline Characteristics - Full Analysis Set (Protocol C4671005_45IA)

	PF-07321332 300 mg + Ritonavir 100 mg (N=678)	Placebo (N=683)	Total (N=1361)
Device dependence	4 (0.6)	1 (0.1)	5 (0.4)
COVID-19 mAb treatment, n (%)			
Received/expected to receive	55 (8.1)	57 (8.3)	112 (8.2)
Not received/not expected to receive	623 (91.9)	626 (91.7)	1249 (91.8)
Geographic region, n (%)			
United States	304 (44.8)	304 (44.5)	608 (44.7)
Europe	122 (18.0)	121 (17.7)	243 (17.9)
Brazil	0	1 (0.1)	1 (<0.1)
India	95 (14.0)	98 (14.3)	193 (14.2)
Rest of World	157 (23.2)	159 (23.3)	316 (23.2)
Serology status, n (%)			
Negative	291 (43.9)	301 (45.0)	592 (44.4)
Positive	372 (56.1)	368 (55.0)	740 (55.6)
Viral load (Log_{10} copies/mL), n (%)			
< 4	237 (37.6)	238 (37.8)	475 (37.7)
≥ 4	393 (62.4)	392 (62.2)	785 (62.3)
≥ 5	331 (52.5)	333 (52.9)	664 (52.7)
≥ 6	259 (41.1)	247 (39.2)	506 (40.2)
< 7	459 (72.9)	464 (73.7)	923 (73.3)
≥ 7	171 (27.1)	166 (26.3)	337 (26.7)
≥ 8	73 (11.6)	69 (11.0)	142 (11.3)
≥ 9	3 (0.5)	1 (0.2)	4 (0.3)
≥ 10	0	0	0
Mean (SD)	4.69 (2.82)	4.72 (2.74)	4.71 (2.78)
Median (range)	5.25 (0.00, 9.13)	5.26 (0.00, 9.06)	5.26 (0.00, 9.13)

Age at Screening (years) = (date of given informed consent - date of birth + 1)/365.25.
The denominator to calculate percentages is N, the number of participants in the full analysis set within each treatment group.
Risk Factors include Age ≥ 60, BMI > 25 and Verbatim from pre-specified Medical History (Cigarette Smoker, Immunosuppression, Chronic Kidney Disease,Hypertension, Diabetes Mellitus, Cardiovascular Disorder, Chronic Lung Disease, HIV Infection, Sickle Cell Disease, Neurodevelopmental Disorder, Cancer and Device Dependence).
Duration since First Diagnosis is days from qualifying positive SARS-CoV-2 test.
Duration since first diagnosis and duration since first symptom are computed from the start of dosing.
Missing category is not included in the table.
Rest of World: Argentina, Colombia, Japan, Malaysia, Mexico, Peru, Russian Federation, South Africa, Republic of Korea, Taiwan, Thailand, and Turkey.
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Table 14.1.2.1 PF-07321332 is for Pfizer internal use.

6.4.4. Efficacy Results

6.4.4.1. Primary Endpoint: COVID-19-Related Hospitalization or Death from Any Cause Through Day 28 in Participants at High Risk of Progression to Severe Disease When Treated Within 3 Days of Symptom Onset (mITT Population)

At the 45% interim analysis, the event rate of a COVID-19-related hospitalization or death from any cause through Day 28 in the mITT analysis set who received treatment within 3 days of symptom onset was 27/385 (7.01%) in the placebo group, and 3/389 (0.77%) in the PF-07321332/ritonavir group (Table 38).

After accounting for premature study discontinuation (ie, participant discontinued study before Day 28 without having experienced a primary endpoint event) by using the follow-up time in the Kaplan-Meier calculation, treatment with PF-07321332/ritonavir showed a 6.32% (95% CI: -9.04% to -3.59%; $p<0.0001$) absolute reduction, or 89.1% relative reduction in primary endpoint events compared to placebo. The reduction was statistically significant, at α-level of 0.002, which was pre-specified for the interim analysis.

There were 0 and 7 reported events of death from any cause through Day 28 in the PF-07321332/ritonavir and placebo groups, respectively. Additional details are described in Section 6.4.6.1.4.

Further details on hospitalizations and deaths at the time of the cutoff for the 45% interim analysis are provided in Study 1005 Listing 16.2.6.1.1 and Study 1005 Listing 16.2.6.1.2, respectively.

Table 38. Primary Analysis of Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 - mITT, Kaplan-Meier Method (Protocol C4671005_45IA)

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

Table 38. Primary Analysis of Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 - mITT, Kaplan-Meier Method (Protocol C4671005_45IA)

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo

N – number of participants in the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.
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Table 14.2.1.1 PF-07321332 is for Pfizer internal use.

6.4.4.2. First Key Secondary Endpoint: COVID-19-Related Hospitalization or Death from Any Cause Through Day 28 in Participants at High Risk of Progression to Severe Disease When Treated Within 5 Days of Symptom Onset (mITT1 Population)

As specified in the protocol, the first key secondary endpoint to be tested sequentially after the primary endpoint tested significant is the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 in the mITT1 analysis set who received treatment within 5 days of symptom onset. The event rate of a COVID-19-related hospitalization or death from any cause through Day 28 in the mITT1 analysis set who received treatment within 5 days of symptom onset was 41/612 (6.70%) in the placebo group, and 6/607 (0.99%) in the PF-07321332/ritonavir group (Table 39).

After accounting for premature study discontinuation (ie, participant discontinued study before Day 28 without having experienced a primary endpoint event) by using the follow-up time in the Kaplan-Meier calculation, treatment with PF-07321332/ritonavir showed a 5.77% (95% CI: -7.92% to -3.61%; $p<0.0001$) absolute reduction, or 85.2% relative reduction in primary endpoint events compared to placebo.

There were 0 and 10 reported events of death from any cause through Day 28 in the PF-07321332/ritonavir and placebo groups, respectively. Additional details are described in Section 6.4.6.1.4.

Table 39. Secondary Analysis of Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 - mITT1, Kaplan-Meier Method (Protocol C4671005_45IA)

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

N – number of participants in the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.
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Table 14.2.1.2 PF-07321332 is for Pfizer internal use.

6.4.4.3. Sensitivity Analysis of the Primary Endpoint: COVID-19-Related Hospitalization or Death from Any Cause Through Day 28 in Participants at High Risk of Progression to Severe Disease When Treated Within 5 Days of Symptom Onset Regardless of mAb Treatment Status (mITT2 Population)

As specified in the protocol, a sensitivity analysis was planned as a secondary analysis of the primary endpoint to include participants regardless of COVID-19 therapeutic mAb treatment (mITT2 analysis set). This sensitivity analysis or supportive analysis was to assess if the treatment effect of PF-07321332/ritonavir would extend to participants who received mAb treatment or planned to receive mAb treatment. At the 45% interim analysis, the event rate of a COVID-19-related hospitalization or death from any cause through Day 28 in the mITT2

analysis set who received treatment within 5 days of symptom onset regardless of mAb antibody treatment was 43/669 (6.43%) in the placebo group, and 7/661 (1.06%) in the PF-07321332/ritonavir group (Study 1005 Table 14.2.1.3).

After accounting for premature study discontinuation (ie, participant discontinued study before Day 28 without having experienced a primary endpoint event) by using the follow-up time in the Kaplan-Meier calculation, treatment with PF-07321332/ritonavir showed a 5.43% (95% CI: -7.46% to -3.39%; p<0.0001) absolute reduction, or 83.6% relative reduction in primary endpoint events compared to placebo.

There were 0 and 10 reported events of death from any cause through Day 28 in the PF-07321332/ritonavir and placebo groups, respectively. Additional details are described in Section 6.4.6.1.4.

6.4.4.4. Supplemental Analyses of the Primary Endpoint (mITT Population)

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

- When participants who received a therapeutic COVID-19 mAb treatment post-baseline were considered to have experienced a primary endpoint event, treatment with PF-07321332/ritonavir showed 6.06% absolute reduction, or 85.4% relative reduction compared to placebo (Study 1005 Table 14.2.1.4),

- When results were computed from a logistic regression model, participants treated with PF-07321332/ritonavir were 0.10 times as likely to have a primary endpoint event compared to placebo. That is, the PF-07321332/ritonavir treatment reduced the odds of having COVID-19-related hospitalization or death from any cause by 90% compared to placebo (Study 1005 Table 14.2.1.5).

6.4.4.5. Subgroup Analyses of the Primary Endpoint (mITT Population)

The prespecified subgroup analyses of the primary endpoint by age (Study 1005 Table 14.2.1.8) and gender (Study 1005 Table 14.2.1.9) were consistent with the overall mITT population. The treatment effect from PF-07321332/ritonavir versus placebo was significant among participants <65 years of age (0.59% versus 5.47%, a 4.88% absolute reduction, p=0.0002), but was larger in terms of absolute reduction among participants ≥65 years of age due to the expected higher event rate (2.27% versus 17.65%, a 15.37% absolute reduction, p=0.0079). Similarly, due to the higher event rate within the group, males had larger absolute reduction due to PF-07321332/ritonavir treatment (7.51%, p=0.0004) than females (4.99%, p=0.0049).

The prespecified subgroup analysis of the primary endpoint by race was consistent with the overall mITT population for the subgroup of White (Study 1005 Table 14.2.1.10). No participant had an event in the subgroup of Black or African American and a statistical test could not be performed. Few participants had events in the subgroup of Asian (0 for PF-07321332/ritonavir; 3 for placebo) and Others (0 for PF-07321332/ritonavir; 3 for placebo) and p-values were p=0.0772 and p=0.0732, respectively.

The prespecified subgroup analysis of the primary endpoint by BMI was consistent with the overall mITT population for the subgroup of BMI 25 to <30 kg/m^2 (p=0.0187) and ≥30 kg/m^2 (p=0.0003) (Study 1005 Table 14.2.1.11). For the subgroup of BMI <25 kg/m^2, the p-value was p=0.0778. Few participants in the subgroup of BMI <25 kg/m^2 had events (0 for PF-07321332/ritonavir; 3 for placebo).

The prespecified subgroup analysis of the primary endpoint by serology negative subgroup was consistent with the overall mITT population. The p-value for the serology positive subgroup was p=0.0810 (Table 40). Few participants in the serology positive subgroup had events (0 for PF-07321332/ritonavir; 3 for placebo).

The prespecified subgroup analysis of the primary endpoint by baseline viral load was consistent with the overall mITT population for the subgroups of high baseline viral load (≥Log10^4 copies/mL), very high baseline viral load (≥Log10^7 copies/mL) and baseline viral load <Log10^7 copies/mL (Study 1005 Table 14.2.1.13). The p-value for the low baseline viral load subgroup (<Log10^4 copies/mL) was p=0.3153. Few participants in the subgroup of low baseline viral load had events (0 for PF-07321332/ritonavir; 1 for placebo).

The prespecified subgroup analysis of the primary endpoint by baseline comorbidities was consistent with the overall mITT population for the subgroups of diabetes mellitus, hypertension, and cardiovascular disorder (Study 1005 Table 14.2.1.14). No participant had an event in the subgroups of immunosuppression, chronic lung disease, chronic kidney disease, device dependence, neurodevelopmental disorder or cancer, and a p-value could not be calculated. The p-value for the subgroup of cigarette smoker was p=0.2820. Few participants in the cigarette smoker subgroup had events (2 for PF-07321332/ritonavir; 5 for placebo). No participant in the mITT analysis set had HIV infection or sickle cell disease, and therefore these subgroup analyses could not be performed.

The prespecified subgroup analysis of the primary endpoint by number of baseline comorbidities was consistent with the overall mITT population for participants with 0-1 and 2-3 baseline comorbidities (Study 1005 Table 14.2.1.15). No participant had an event in the subgroup of ≥4 baseline comorbidities and a p-value could not be calculated.

In summary, treatment with PF-07321332/ritonavir showed no inconsistent effect in any subgroup of participants. Significant or larger event reductions were observed in subgroups with an increased sample size and/or a higher event rate.

Table 40. Analysis of Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28, by Subgroup of Serology Status - mITT, Kaplan-Meier Method (Protocol C4671005_45IA)

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Negative	N	168	175
	Participants with event, n (%)	3 (1.8)	24 (13.7)
	Participants with COVID-19 hospitalization	3 (1.8)	24 (13.7)
	Participants with death	0	7 (4.0)
	Average time at risk for event (Days)[a]	26.9	24.2
	Average study follow-up (Days)[b]	27.2	26.1
	Estimated proportion (95% CI), %	1.797 (0.583, 5.467)	13.970 (9.587, 20.121)
	Difference from Placebo (SE)	-12.173 (2.840)	
	95% CI of difference	-17.739, -6.607	
	p-value	<.0001	
Positive	N	217	204
	Participants with event, n (%)	0	3 (1.5)
	Participants with COVID-19 hospitalization	0	3 (1.5)
	Participants with death	0	0
	Average time at risk for event (Days)[a]	27.4	27.3
	Average study follow-up (Days)[b]	27.4	27.6
	Estimated proportion (95% CI), %	0.000 (0.000, 0.000)	1.478 (0.479, 4.512)
	Difference from Placebo (SE)	-1.478 (0.847)	
	95% CI of difference	-3.138, 0.182	
	p-value	0.0810	

N – number of participants in the subgroup of the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.
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Table 14.2.1.12 PF-07321332 is for Pfizer internal use.

6.4.4.6. Subgroup Analyses of the First Key Secondary Endpoint (mITT1 Population)

The prespecified subgroup analyses of the first key secondary endpoint by age (Study 1005 Table 14.2.1.16), gender (Study 1005 Table 14.2.1.17) and BMI (Study 1005 Table 14.2.1.19) were consistent with the overall mITT1 population.

The prespecified subgroup analysis of the first key secondary endpoint by race was consistent with the overall mITT1 population for the subgroups of White, Asian and Others (Study 1005 Table 14.2.1.18). Few participants had events in the subgroup of Black or African American (0 for PF-07321332/ritonavir; 1 for placebo) and the p-value was p=0.3055.

The prespecified subgroup analysis of the first key secondary endpoint by serology negative subgroup was consistent with the overall mITT1 population. The p-value for the serology positive subgroup was p=0.0947 (Study 1005 Table 14.2.1.20). Few participants in the serology positive subgroup had events (1 for PF-07321332/ritonavir; 5 for placebo).

The prespecified subgroup analysis of the first key secondary endpoint by baseline viral load was consistent with the overall mITT1 population for subgroups of high baseline viral load ($\geq Log10^4$ copies/mL), very high baseline viral load ($\geq Log10^7$ copies/mL) and baseline viral load $<Log10^7$ copies/mL (Study 1005 Table 14.2.1.21). The p-value for the subgroup of low baseline viral load ($<Log10^4$ copies/mL) was p=0.3064. Few participants in the subgroup with low baseline viral load had events (1 for PF-07321332/ritonavir; 3 for placebo).

The prespecified subgroup analysis of the first key secondary endpoint by baseline comorbidities was consistent with the overall mITT1 population for the subgroups of hypertension and cardiovascular disorder (Study 1005 Table 14.2.1.22). No participant had an event in the subgroups of immunosuppression, chronic kidney disease, device dependence, HIV infection, neurodevelopmental disorder or cancer, and a p-value could not be calculated. P-values for the subgroups of cigarette smoker, diabetes mellitus, and chronic lung disease were p=0.1537, p=0.0867, and p=0.3066, respectively. In the subgroup of cigarette smokers, there were 3 events in the PF-07321332/ritonavir arm and 8 in placebo. In the subgroup of diabetes mellitus there were 2 events in the PF-07321332/ritonavir arm and 7 in placebo). Few participants had events in the chronic respiratory disease subgroup (0 for PF-07321332/ritonavir; 1 for placebo). One participant in the mITT1 analysis set had HIV infection and did not have an event, and no participant had sickle cell disease, and therefore these subgroup analyses could not be performed.

The prespecified subgroup analysis of the first key secondary endpoint by number of baseline comorbidities was consistent with the overall mITT1 population for participants with 0-1 and 2-3 baseline comorbidities (Study 1005 Table 14.2.1.22.1). No participant had an event in the subgroup of ≥ 4 baseline comorbidities and a p-value could not be calculated.

6.4.4.7. Sensitivity Analysis of the Primary Endpoint: COVID-19-Related Hospitalization or Death from Any Cause Through Day 28 in Participants at High Risk of Progression to Severe Disease When Treated Within 3 Days of Symptom Onset, Event Imputation for Missing Data (mITT Population)

Per the Agency's request, a sensitivity analysis was performed in the mITT analysis set whereby participants that did not have follow-up data through Day 21 were hypothetically assumed to experience both COVID-19-related hospitalization and death in a worst-case scenario. Two participants in the PF-07321332/ritonavir group and one in the placebo group were assumed to have had a primary endpoint event. Consistent with what was observed in the primary analysis, a statistically significant reduction ($p<0.0001$) in COVID-19-related hospitalization and death was shown in the PF-07321332/ritonavir group relative to placebo (Study 1005 Table 14.2.1.1s).

6.4.4.8. Secondary Endpoint: Change from Baseline in Viral Load

As described in the protocol, the statistical analysis of viral load first occurred when a sufficient number of participants (approximately 200 were required) in the mITT analysis set completed the viral load assessment at Day 5 and had valid viral load measurements at both Day 1 and Day 5 available for the POC assessment. A snapshot of the database took place on [redacted]2021 and the POC assessment included all participants who had data in the database at the time.

A validated quantitative SARS-CoV-2 RT-PCR assay was used to measure viral load (copies/mL). Participants with samples collected using unvalidated (local) swabs or collected at non-NP sites were excluded from this POC assessment, as were participants with no virus detected at baseline (0 copies/mL). Viral load below the detection limit of 100 copies/mL was imputed as approximately 50 copies/mL, ie, using 1.69 Log_{10} (copies/mL) for Log_{10} (viral load) values below 2 Log_{10} (copies/mL) (Study 1005 Tables 14.1.3p, 14.1.4p and 14.1.5p).

In the mITT1 analysis set, baseline Log_{10} (viral load) in Log_{10} (copies/mL) averaged 5.11 among the 303 participants in the placebo group, and 5.41 among the 269 participants in the PF-07321332/ritonavir group (Study 1005 Table 14.2.1.1p). At Day 5, after accounting for baseline viral load, geographic region, serology status and symptom onset, the adjusted mean (SE) reduction in Log_{10} (viral load) was -1.75 (0.09) Log_{10} (copies/mL) in the placebo group, and -2.69 (0.10) in the PF-07321332/ritonavir group, reflecting an additional average reduction (SE) of -0.93 (0.13) Log_{10} (copies/mL) (Table 41).

Similar findings were observed in the mITT analysis set, a subset of the mITT1 analysis set. The adjusted mean reduction in Log_{10} (viral load) from baseline to Day 5 for the mITT analysis set was significantly greater for participants who received PF-07321332/ritonavir than those who received placebo with adjusted mean difference (SE) of -1.03 (0.16) Log_{10} (copies/mL) (Table 41 and Study 1005 Table 14.2.1.1p).

The adjusted mean reductions in viral load from baseline to Day 5 in the mITT2 analysis set were comparable to that for the mITT and mITT1 analysis sets (Table 41 and Study 1005 Table 14.2.1.1p).

Results in the mITT1 analysis set were also examined by serology status (Study 1005 Table 14.2.1.2p and Study 1005 Table 14.2.1.5p) and baseline viral load (Study 1005 Table 14.2.1.3p and Study 1005 Table 14.2.1.6p). As expected, the additional viral load reduction from PF-07321332/ritonavir treatment relative to placebo were more apparent in participants who were seronegative than participants who were seropositive (-1.15 versus -0.77 Log_{10} copies/mL on a log-10 scale) (Study 1005 Table 14.2.1.5p), and more apparent in participants with higher versus lower ($\geq 10^7$ copies/mL versus $<10^7$ copies/mL) viral load at baseline (-1.40 versus -0.79 Log_{10} copies/mL on a log-10 scale) (Study 1005 Table 14.2.1.6p).

Table 41. Statistical Analysis of Change from Baseline in Log10 Transformed Viral Load (copies/mL) Data - mITT, mITT1 and mITT2 (Protocol C4671005)

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

n=Number of participants with non-missing data in the analysis population and the covariates in the statistical model.
Infty=Infinity. Only Upper Limit for 80% CI is presented.
Participants are excluded from the analysis for reasons of Not Detected or Missing baseline viral load result, and local swabs use. Results from samples collected at non-nasopharyngeal site are also excluded.
Change from baseline modeled using ANCOVA
For mITT analysis set Model = Treatment + Baseline viral load + geographic region + serology status.
For mITT1 analysis set Model = Treatment + Baseline viral load + geographic region + serology status + symptom onset.
For mITT2 analysis set Model = Treatment + Baseline viral load + COVID-19 mAb treatment + geographic region + serology status + symptom onset.
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Table 14.2.1.4p PF-07321332 is for Pfizer internal use.

6.4.5. Biomarkers

6.4.5.1. Viral Sequencing

Interim viral sequencing analysis for Study 1005 has been undertaken to determine the distribution of SARS-CoV-2 variants including a preliminary evaluation of the mutational pressure of PF-07321332 on the $3CL^{pro}$ gene for the first 490 study participants treated with PF-07321332/ritonavir (Module 5.3.5.1 PF-07321332 C4671005 Interim Viral Sequencing Study Report)

All data to support clinical virology was derived from nasal swab collections. In brief, swabs were assessed for SARS-CoV-2 RT-PCR (viral load) and viral sequencing as well as downstream infectivity and phenotypic analysis. In brief, samples collected from Day 1 (Baseline) and Day 5 (End of Treatment) were sequenced if the samples met the criteria of greater than 2.7 Log_{10} copies/mL viral load detected by RT-PCR. Viral mutations at Baseline were flagged if the sequence differed from the reference sequence (NCBI: NC_045512.2) and, at Post-dose Day 5 samples as TEMs, if the sequence differed from the Day 1 sequence (Module 5.3.5.1 PF-07321332 C4671005 Interim Viral Sequencing Study Report). The clinical endpoint of treatment failure was defined as progression to COVID-19-related hospitalization or death from any cause through Day 28. More details can be found in Module 5.3.5.1 PF-07321332 Biomarker Statistical Analysis Plan for Study C4671005.

6.4.5.2. Distribution of Variants of Concern and by Treatment and Treatment Failure

The first 490 participants that received treatment were analyzed for variants designated by the WHO as VOC and VOI by treatment group. Preliminary findings show that Delta variants were most prevalent (97.95%) in study participants and distributed with high prevalence as Delta subvariants 21J, 21A, and 21I (Module 5.3.5.1 PF-07321332 C4671005 Interim Viral Sequencing Study Report Table 3). Additionally, within the treatment group receiving PF-07321332/ritonavir, all 5 participants that experienced treatment failure were identified as infected by the Delta variant.

6.4.5.3. Associations between treatment and TEMs

Mutational pressure of PF-07321332 on the $3CL^{pro}$ gene was evaluated for 216 out of the first 490 study participants that had sequencing data available at both Day 1 and Day 5. In brief, the initial mutation analysis was grouped into four genomic regions of interest: 1) PF-07321332 contact sites within 3CLpro gene; 2) $3CL^{pro}$ cleavage sites (including cleavage sites not within 3CLpro gene); 3) The entire $3CL^{pro}$ gene excluding region 1 and 2, and 4) Region 1-3 combined (all $3CL^{pro}$ gene and cleavage sites not within $3CL^{pro}$ gene). Preliminary findings showed no significant associations between treatment and TEMs across the $3CL^{pro}$ gene regions of interest (Module 5.3.5.1 PF-07321332 C4671005 Interim Viral Sequencing Study Report Table 4). Additionally, no clear associations were observed between TEMs and treatment failure in participants who received PF-07321332/ritonavir participants and in placebo (Module 5.3.5.1 PF-07321332 C4671005 Interim Viral Sequencing Study Report Table 5). Further analysis is ongoing and will include

characterization of post-dose TEMs outside of the $3CL^{pro}$ gene. Data will be provided as it becomes available.

6.4.6. Safety Results

Safety results from the 45% interim analysis which includes 1349 participants (safety analysis set) enrolled through 29 Sep 2021, with the database cutoff on 26 Oct 2021 are presented below. Safety outputs from all participants (N=1881 in the safety analysis set) enrolled as of the database cutoff of 26 Oct 2021 are provided in Section 6.4.6.6.

6.4.6.1. Adverse Events

PF-07321332/ritonavir was safe and well-tolerated. The proportion of participants with all-causality TEAEs was comparable between the PF-07321332/ritonavir group and the placebo group (19.8% and 22.3%, respectively). The proportion of participants with all-causality SAEs was lower in the PF-07321332/ritonavir group (1.9%) compared with the placebo group (6.8%). Fewer participants discontinued study intervention due to an AE in the PF-07321332/ritonavir group compared with the placebo group (2.4% and 4.3%, respectively). The reported safety data indicates that PF-07321332/ritonavir has a favorable safety profile.

6.4.6.1.1. Overview of Adverse Events

An overview of all-causality TEAEs that started on or prior to the Day 34 visit is shown in Table 42. The proportion of participants with all-causality TEAEs was comparable between the PF-07321332/ritonavir group (19.8%) and the placebo group (22.3%).

- The proportion of participants with all-causality severe or potentially life-threatening TEAEs (Grade 3 or 4) was lower in the PF-07321332/ritonavir group (3.1%) compared with the placebo group (7.1%).
- The proportion of participants with all-causality SAEs was lower in the PF-07321332/ritonavir group (1.9%) compared with the placebo group (6.8%).
- No participants in the PF-07321332/ritonavir group experienced an AE resulting in death compared with 10 participants (1.5%) in the placebo group.
- The proportion of participants who discontinued study intervention or discontinued the study due to an AE was lower in the PF-07321332/ritonavir group (2.4% and 0%, respectively) compared with the placebo group (4.3% and 1.5%, respectively). Similar findings were observed for those participants who had a temporary discontinuation due to an AE.

An overview of treatment-related TEAEs that started on or prior to the Day 34 visit is shown in Table 43. The proportion of participants with treatment-related TEAEs was higher in the PF-07321332/ritonavir group (7.3%) compared with the placebo group (4.3%). The overall numbers of participants with treatment-related severe or potentially life-threatening TEAEs (Grade 3 or 4) or SAEs were low and comparable between treatment groups.

A listing of all adverse events is provided in Study 1005 Listing 16.2.7.1.

Table 42. Treatment-Emergent Adverse Events (All Causalities) - DAIDS Grade - Safety Analysis Set (Protocol C4671005_45IA)

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

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study
b. Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Participant to be discontinued from Study
PFIZER CONFIDENTIAL SDTM Creation: [redacted](16:07) Source Data: adae Table Generation: [redacted] (19:13)
(Data cutoff date : 26OCT2021 Database snapshot date : [redacted] Output File: ./nda_unblinded/C4671005_45IA/adae_s020
Table 14.3.1.1 PF-07321332 is for Pfizer internal use.

Table 43. Treatment-Emergent Adverse Events (Treatment Related) - DAIDS Grade - Safety Analysis Set (Protocol C4671005_45IA)

Number (%) of Participants	PF-07321332 300 mg + Ritonavir 100 mg (N=672) n (%)	Placebo (N=677) n (%)
Participants evaluable for adverse events	672	677
Number of adverse events	74	35
Participants with adverse events	49 (7.3)	29 (4.3)
Participants with serious adverse events	1 (0.1)	0
Participants with Maximum Grade 3 or 4 adverse events	3 (0.4)	4 (0.6)
Participants with Maximum Grade 5 adverse events	0	0
Participants discontinued from study due to adverse events[a]	0	0
Participants discontinued study drug due to AE and continue Study[b]	7 (1.0)	3 (0.4)
Participants with dose reduced or temporary discontinuation due to adverse events	0	3 (0.4)

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study
b. Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Participant to be discontinued from Study
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](16:07) Source Data: adae Table Generation: [redacted] (19:13)
(Data cutoff date : 26OCT2021 Database snapshot date : [redacted] Output File: ./nda_unblinded/C4671005_45IA/adae_s021
Table 14.3.1.2 PF-07321332 is for Pfizer internal use.

6.4.6.1.2. Analysis of Adverse Events

6.4.6.1.2.1. All-Causality TEAEs

A summary of all-causality TEAEs that started on or prior to the Day 34 visit, reported by SOC, PT and maximum severity grade is provided in Table 44. The overall incidence of all-causality TEAEs was comparable between the PF-07321332/ritonavir group and the placebo group.

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

    - This participant had an event of severe (Grade 3) hypertension. The participant also had 2 SAEs (abscess and sepsis), which were not considered by the investigator to be related to study intervention and resolved. The event of severe hypertension was not resolved (Study 1005 Listing 16.2.7.1).

- 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.

- There were no events of death related to an AE (Grade 5) in the PF-07321332/ritonavir group compared with 10 events (1.5%) in the placebo group.

Table 44. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum DAIDS Grade (All Causalities) - Safety Analysis Set (Protocol C4671005_45IA)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Participants with events	111 (16.5)	15 (2.2)	6 (0.9)	0	1 (0.1)	133 (19.8)	93 (13.7)	37 (5.5)	11 (1.6)	10 (1.5)	0	151 (22.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (0.3)	0	0	0	0	2 (0.3)	1 (0.1)	0	1 (0.1)	0	0	2 (0.3)
Leukocytosis	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
Lymphadenopathy mediastinal	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Microcytic anaemia	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
CARDIAC DISORDERS	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)	4 (0.6)	0	0	0	0	4 (0.6)
Palpitations	1 (0.1)	1 (0.1)	0	0	0	2 (0.3)	2 (0.3)	0	0	0	0	2 (0.3)
Pericardial effusion	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Sinus tachycardia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
EAR AND LABYRINTH DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)
Hyperacusis	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Vertigo	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
EYE DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Eye pain	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
GASTROINTESTINAL DISORDERS	48 (7.1)	0	0	0	0	48 (7.1)	35 (5.2)	1 (0.1)	0	0	0	36 (5.3)
Abdominal pain	2 (0.3)	0	0	0	0	2 (0.3)	2 (0.3)	0	0	0	0	2 (0.3)
Abdominal pain lower	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0

Table 44. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum DAIDS Grade (All Causalities) - Safety Analysis Set (Protocol C4671005_45IA)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Abdominal pain upper	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)
Colitis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Constipation	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.3)	0	0	0	0	2 (0.3)
Diarrhoea	26 (3.9)	0	0	0	0	26 (3.9)	13 (1.9)	0	0	0	0	13 (1.9)
Dry mouth	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Dyspepsia	5 (0.7)	0	0	0	0	5 (0.7)	3 (0.4)	0	0	0	0	3 (0.4)
Faeces soft	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Gastrooesophageal reflux disease	3 (0.4)	0	0	0	0	3 (0.4)	2 (0.3)	0	0	0	0	2 (0.3)
Hiatus hernia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hyperchlorhydria	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Large intestine polyp	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Nausea	13 (1.9)	0	0	0	0	13 (1.9)	13 (1.9)	1 (0.1)	0	0	0	14 (2.1)
Rectal haemorrhage	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Vomiting	9 (1.3)	0	0	0	0	9 (1.3)	2 (0.3)	0	0	0	0	2 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	16 (2.4)	0	0	0	0	16 (2.4)	11 (1.6)	1 (0.1)	0	0	0	12 (1.8)
Asthenia	3 (0.4)	0	0	0	0	3 (0.4)	0	1 (0.1)	0	0	0	1 (0.1)
Catheter site pain	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Chest discomfort	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
Chest pain	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Chills	5 (0.7)	0	0	0	0	5 (0.7)	0	0	0	0	0	0

Table 44. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum DAIDS Grade (All Causalities) - Safety Analysis Set (Protocol C4671005_45IA)

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

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

Table 44. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum DAIDS Grade (All Causalities) - Safety Analysis Set (Protocol C4671005_45IA)

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

Table 44. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum DAIDS Grade (All Causalities) - Safety Analysis Set (Protocol C4671005_45IA)

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

Table 44. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum DAIDS Grade (All Causalities) - Safety Analysis Set (Protocol C4671005_45IA)

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

Table 44. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum DAIDS Grade (All Causalities) - Safety Analysis Set (Protocol C4671005_45IA)

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

Table 44. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum DAIDS Grade (All Causalities) - Safety Analysis Set (Protocol C4671005_45IA)

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

Table 44. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum DAIDS Grade (All Causalities) - Safety Analysis Set (Protocol C4671005_45IA)

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

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](16:07) Source Data: adae Table Generation: [redacted](19:14)
(Data cutoff date : 26OCT2021 Database snapshot date : [redacted] Output File: ./nda_unblinded/C4671005_45IA/adae_s062
Table 14.3.1.3 PF-07321332 is for Pfizer internal use.

6.4.6.1.2.2. Treatment-related TEAEs

A summary of treatment-related TEAEs that started on or prior to the Day 34 visit, reported by SOC, PT and maximum severity grade is provided in Table 45. The overall incidence of treatment-related TEAEs was higher in the PF-07321332/ritonavir group (7.3%) compared with the placebo group (4.3%).

- The most frequently reported treatment-related TEAEs (reported in ≥3% of participants in either treatment group) occurred in the SOCs of Nervous system disorders and Gastrointestinal disorders.

- The most frequently reported treatment-related TEAEs in the PF-07321332/ritonavir group (≥1%) were Dysgeusia (3.7%), and Diarrhoea (1.9%). Both of these treatment-related TEAEs were reported with a higher incidence in the PF-07321332/ritonavir group compared with the placebo group (Dysgeusia: 3.7% in the PF-07321332/ritonavir group versus 0.1% in the placebo group, and Diarrhoea: 1.9% in the PF-07321332/ritonavir group versus 0.3% in the placebo group).

- Most of the treatment-related TEAEs experienced by participants in both treatment groups were mild to moderate (Grade 1-2) in severity. One (1) participant in the placebo treatment group had a potentially life-threatening (Grade 4) event (Blood glucose increased) that was considered related to treatment. No participants in either treatment group had an event of death related to an AE (Grade 5).

Table 45. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Maximum DAIDS Grade (Treatment Related) - Safety Analysis Set (Protocol C4671005_45IA)

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

Table 45. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Maximum DAIDS Grade (Treatment Related) - Safety Analysis Set (Protocol C4671005_45IA)

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

Table 45. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Maximum DAIDS Grade (Treatment Related) - Safety Analysis Set (Protocol C4671005_45IA)

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

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
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(Data cutoff date : 26OCT2021 Database snapshot date : [redacted] Output File: ./nda_unblinded/C4671005_45IA/adae_s068
Table 14.3.1.5 PF-07321332 is for Pfizer internal use.

6.4.6.1.3. Serious Adverse Events

The overall incidence of participants with all causality SAEs was lower in the PF-07321332/ritonavir treatment group (1.9%) compared with placebo (6.8%) (Table 46).

- No participants in the PF-07321332/ritonavir group had an SAE that resulted in death compared with 10 participants (1.5%) in the placebo group (Table 47).

- The most frequently reported treatment emergent SAEs in the PF-07321332/ritonavir group (≥2 participants) were COVID-19 (2 participants, 0.3% [compared with 7 participants, 1% in the placebo group]), and COVID-19 pneumonia (4 participants, 0.6% [compared with 21 participants, 3.1% in the placebo group]). All of these SAEs were considered related to the disease under study.

- One participant in the PF-07321332/ritonavir group had treatment-emergent SAEs of Palpitations, Chest discomfort and Dyspnoea (Table 48). In the opinion of the investigator, there was a reasonable possibility that the events of Chest discomfort, Dyspnoea, and Palpitations were related to the study intervention (ritonavir); there was not a reasonable possibility that the events were related to the study intervention (PF-07321332), concomitant drug or clinical trial procedure. A narrative for this participant is provided in Module 5.3.5.1 C4671005 Interim Analysis Narratives.

A listing of SAEs is provided in Study 1005 Table 16.2.7.1 and narratives for all participants who experienced an SAE are provided in Module 5.3.5.1 C4671005 Interim Analysis Narratives.

Table 46. Summary of Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum DAIDS Grade (All Causalities) - Safety Analysis Set (Protocol C4671005_45IA)

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

Table 46. Summary of Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum DAIDS Grade (All Causalities) - Safety Analysis Set (Protocol C4671005_45IA)

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

Table 46. Summary of Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum DAIDS Grade (All Causalities) - Safety Analysis Set (Protocol C4671005_45IA)

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

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
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Table 14.3.1.7 PF-07321332 is for Pfizer internal use.

Table 47. Summary of Treatment-Emergent Serious Adverse Events with an Outcome of Fatal by MedDRA System Organ Class, Preferred Term, and Maximum DAIDS Grade (All Causalities) - Safety Analysis Set (Protocol C4671005_45IA)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Participants with events	0	0	0	0	0	0	0	0	0	10 (1.5)	0	10 (1.5)
INFECTIONS AND INFESTATIONS	0	0	0	0	0	0	0	0	0	7 (1.0)	0	7 (1.0)
COVID-19	0	0	0	0	0	0	0	0	0	2 (0.3)	0	2 (0.3)
COVID-19 pneumonia	0	0	0	0	0	0	0	0	0	5 (0.7)	0	5 (0.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	0	0	0	0	0	0	0	3 (0.4)	0	3 (0.4)
Acute respiratory distress syndrome	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)
Acute respiratory failure	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)
Hypoxia	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: [redacted] (16:07) Source Data: adae Table Generation: [redacted] (19:14)
(Data cutoff date : 26OCT2021 Database snapshot date : [redacted] Output File: ./nda_unblinded/C4671005_45IA/adae_s062sf
Table 14.3.1.9 PF-07321332 is for Pfizer internal use.

Table 48. Summary of Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class, Preferred Term and Maximum DAIDS Grade (Treatment Related) - Safety Analysis Set (Protocol C4671005_45IA)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
CARDIAC DISORDERS	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Palpitations	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Chest discomfort	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Dyspnoea	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](16:07) Source Data: adae Table Generation: [redacted](19:14)
(Data cutoff date : 26OCT2021 Database snapshot date : [redacted] Output File: ./nda_unblinded/C4671005_45IA/adae_s068s
Table 14.3.1.8 PF-07321332 is for Pfizer internal use.

6.4.6.1.4. Deaths

There were 10 events of deaths among participants in this study (Study 1005 Listing 16.2.6.1.2).

- All 10 death events (1.5%) were in the placebo group and were related to the disease under study (events reported as COVID-19 pneumonia [5 participants], COVID-19 [2 participants], Hypoxia [1 participant], Acute respiratory distress syndrome [1 participant], and Acute respiratory failure [1 participant]), and none were considered by the investigator to be related to study intervention.

Narratives for these participants are provided in Module 5.3.5.1 C4671005 Interim Analysis Narratives.

6.4.6.1.5. Adverse Events Leading to Discontinuation

Discontinuations of Study Intervention Due to AEs

Fewer participants discontinued study intervention due to an AE in the PF-07321332/ritonavir group compared with the placebo group (2.4% and 4.3%, respectively) (Table 49).

- TEAEs that led to discontinuation of study intervention in more than one participant in a treatment group were Nausea, Vomiting, COVID-19 pneumonia, Creatinine renal clearance decreased, Glomerular filtration rate decreased, Acute respiratory failure, COVID-19, and Hypoxia. Of these, Nausea and Vomiting are considered COVID-19-related symptoms based on FDA Guidance for Industry[85] (Study C4671005 Protocol Appendix 9).

Of the participants in the PF-07321332/ritonavir group who discontinued study intervention due to AEs, 8 (1.2%) participants had AEs that were reported as mild to moderate (Grade 1-2) and 7 (1.0%) had AEs that were reported as severe (Grade 3). One participant (0.1%) in the PF-07321332/ritonavir group had an AE that led to discontinuation that was reported as Grade 4. In the placebo group, a greater proportion of participants who discontinued study intervention due to an AE had AEs that were reported as Grade 3 (18 participants, 2.7%) and Grade 4 (6 participants, 0.9%) (Table 49).

A greater proportion of TEAEs leading to discontinuation from study intervention were considered treatment related in the PF-07321332/ritonavir group (1%) compared with the placebo group (0.4%) (Table 50).

Further details for participants who discontinued study intervention due to AEs and continued in the study are provided in Study 1005 Listing 16.2.7.3.

Narratives for non-serious AEs resulting in permanent discontinuation from study intervention are provided in Module 5.3.5.1 C4671005 Interim Analysis Narratives.

Discontinuation of Study Due to AE

No participants in the PF-07321332/ritonavir group discontinued the study due to TEAEs (all causalities) compared with 10 participants (1.5%) in the placebo group (Table 42).

A listing of AEs for participants who discontinued from Study due to AEs is provided (Study 1005 Listing 16.2.7.2).

Table 49. Summary of Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by MedDRA System Organ Class, Preferred Term, and Maximum DAIDS Grade (All Causalities) - Safety Analysis Set (Protocol C4671005_45IA)

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

Table 49. Summary of Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by MedDRA System Organ Class, Preferred Term, and Maximum DAIDS Grade (All Causalities) - Safety Analysis Set (Protocol C4671005_45IA)

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

Table 49. Summary of Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by MedDRA System Organ Class, Preferred Term, and Maximum DAIDS Grade (All Causalities) - Safety Analysis Set (Protocol C4671005_45IA)

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

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](16:07) Source Data: adae Table Generation: [redacted](19:14)
(Data cutoff date : 26OCT2021 Database snapshot date : [redacted]Output File: ./nda_unblinded/C4671005_45IA/adae_s062d
Table 14.3.1.4 PF-07321332 is for Pfizer internal use.

Table 50. Summary of Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by MedDRA System Organ Class, Preferred Term and Maximum DAIDS Grade (Treatment Related) - Safety Analysis Set (Protocol C4671005_45IA)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	5 (0.7)	2 (0.3)	0	0	0	7 (1.0)	0	2 (0.3)	1 (0.1)	0	0	3 (0.4)
CARDIAC DISORDERS	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Palpitations	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
GASTROINTESTINAL DISORDERS	5 (0.7)	0	0	0	0	5 (0.7)	0	1 (0.1)	0	0	0	1 (0.1)
Colitis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Diarrhoea	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Nausea	4 (0.6)	0	0	0	0	4 (0.6)	0	1 (0.1)	0	0	0	1 (0.1)
Vomiting	3 (0.4)	0	0	0	0	3 (0.4)	0	0	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Chest discomfort	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
INVESTIGATIONS	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Blood glucose increased	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0

Table 50. Summary of Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by MedDRA System Organ Class, Preferred Term and Maximum DAIDS Grade (Treatment Related) - Safety Analysis Set (Protocol C4671005_45IA)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=672)						Placebo (N=677)					
	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total	Grade 1-2	Grade 3	Grade 4	Grade 5	Missing	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Myalgia	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
NERVOUS SYSTEM DISORDERS	2 (0.3)	0	0	0	0	2 (0.3)	0	0	0	0	0	0
Dizziness	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Dysgeusia	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Dyspnoea	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (0.1)	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)
Rash	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Rash maculo-papular	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](16:07) Source Data: adae Table Generation: [redacted](19:14)
(Data cutoff date : 26OCT2021 Database snapshot date : [redacted] Output File: ./nda_unblinded/C4671005_45IA/adae_s068d
Table 14.3.1.6 PF-07321332 is for Pfizer internal use.

6.4.6.2. Clinical Laboratory Evaluations

PF-07321332/ritonavir was not associated with clinically meaningful changes in laboratory values. In general, observed laboratory values were consistent with those expected from participants with disease under study.

6.4.6.2.1. Evaluation of Each Laboratory Parameter

No clinically meaningful differences were observed between the PF-07321332/ritonavir and placebo groups with respect to hematology, and clinical chemistry laboratory test results.

Baseline abnormalities (elevations) in laboratory parameters were comparable across treatment groups (Study 1005 Table 14.3.4.3). Baseline abnormalities (elevations) in D-Dimer, fibrinogen, aPTT, ALT, AST, LDH, creatinine, and CK have been reported in COVID-19 patients.[86]

The overall incidence of laboratory test abnormalities during the study was comparable between both treatment groups (Table 51).

- The most frequently occurring laboratory test abnormalities (occurring in ≥5% participants in any treatment group) were fibrinogen (<0.75 x baseline; >1.25 x baseline), aPTT (>1.1 x ULN), D-Dimer (>1.5 x ULN), neutrophils (>1.2 x ULN), glucose (>1.5 x ULN), thyrotropin (>1.2 x ULN), creatine kinase (>2 x ULN), and bicarbonate (<0.9 x LLN).

- The incidences of abnormalities in the following laboratory parameters were comparable across treatment groups: fibrinogen (<0.75x Baseline; 30.2% and 29.5% in the PF-07321332/ritonavir and placebo groups, respectively), aPTT (>1.1 x ULN; 18.8% and 16.5% in the PF-07321332/ritonavir and placebo groups, respectively), neutrophils (>1.2 x ULN; 5.6% and 3.3% in the PF-07321332/ritonavir and placebo groups, respectively), glucose (>1.5 x ULN; 7.3% and 6.7% in the PF-07321332/ritonavir and placebo groups, respectively), thyrotropin (>1.2 x ULN; 7.1% and 8.9% in the PF-07321332/ritonavir and placebo groups, respectively), creatine kinase (>2 x ULN; 5.7% and 4.6% in the PF-07321332/ritonavir and placebo groups, respectively), and bicarbonate (<0.9 x LLN; 8.1% and 8.3% in the PF-07321332/ritonavir and placebo groups, respectively).

- Abnormalities in laboratory tests for fibrinogen (>1.25 x Baseline) and D-dimer (>1.5 x ULN) both occurred more frequently in the placebo group (21.8% and 19.7%, respectively) compared with the PF-07321332/ritonavir group (14.3% and 10.8%, respectively).

Table 51. Incidence of Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) - Safety Analysis Set (Protocol C4671005_45IA)

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

Table 51. Incidence of Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) - Safety Analysis Set (Protocol C4671005_45IA)

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

NOTE: N = total number of participants with at least one observation of the given laboratory test while on study treatment or during lag time.
n = number of participants with a laboratory abnormality meeting specified criteria while on study treatment or during lag time.
Percentages are displayed for the laboratory tests having a category with ≥ 1 evaluable participants.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](16:07) Source Data: adlb Table Generation: [redacted](19:17)
(Data cutoff date : 26OCT2021 Database snapshot date : [redacted] Output File: ./nda_unblinded/C4671005_45IA/adlb_s301
Table 14.3.4.1 PF-07321332 is for Pfizer internal use.

6.4.6.2.2. Laboratory Values Over Time

TSH changes were observed with the administration of PF-07321332/ritonavir during Phase 1 Study 1001. Low-level inflammation (increase in fibrinogen) in the 15-day NHP toxicology study and changes in platelets, globulin and albumin/globulin ratio and coagulation system (increase in prothrombin time and aPTT) in the 14-day rat toxicology study were reported. Based on these observations, TSH and T4 (free) in addition to AEs, fibrinogen, platelets, D-dimer, prothrombin time and aPTT, albumin, and total protein were monitored in Study 1005 (Study C4671005 Protocol Section 2.3.1).

The incidence of participants shifting from an out-of-range value to a within-range value for the following laboratory parameters was similar across treatment groups: TSH (Study 1005 Table 14.3.4.2.1), free T4 (thyroxine; Study 1005 Table 14.3.4.2.2), prothrombin time (Study 1005 Table 14.3.4.2.5), total protein (Study 1005 Table 14.3.4.2.8), platelets (Study 1005 Table 14.3.4.2.4), fibrinogen (Study 1005 Table 14.3.4.2.3), D-dimer (Study 1005 Table 14.3.4.2.12), creatinine clearance (Study 1005 Table 14.3.4.2.9), AST (Study 1005 Table 3.4.2.10), ALT (Study 1005 Table 14.3.4.2.11), albumin (Study 1005 Table 14.3.4.2.7), and aPTT (Study 1005 Table 14.3.4.2.6).

6.4.6.3. Vital Signs

No clinically meaningful findings in vital sign measurements were observed in this study. The assessments and observations were comparable across treatment groups. In general, observed vital sign values were consistent with those expected from participants with disease under study.

Baseline values for systolic and diastolic blood pressure, heart rate, oxygen saturation (%), body temperature, and respiratory rate, were similar across both treatment groups, and there were no clinically meaningful differences between treatment groups in the mean changes from baseline in vital signs assessments (Study 1005 Table 14.3.5.1).

- The mean maximum change from baseline in vital signs were comparable for participants in the PF-07321332/ritonavir treatment group compared with the placebo group (Study 1005 Table 14.3.5.3).

- The incidence of participants with diastolic blood >90 mmHg or systolic blood pressure >140 mmHg was comparable across treatment groups (Study 1005 Table 14.3.5.2).

6.4.6.4. ECGs

On 12 Aug 2021, the E-DMC reviewed the unblinded safety data for the sentinel cohort of 68 participants which included ECG data for 59 participants. No notable changes in ECG intervals were observed. A summary of maximum change of QTcF and descriptive statistics of changes of QTcF (msec) observed over time indicated no clinically relevant changes from baseline by Day 5 and no clinically relevant difference between active and placebo groups (previously submitted C4671005 Blinded Sentinel Safety Summary and C4671005 Sentinel Cohort ECG Tables).

6.4.6.5. Pregnancy

At the time of the data cutoff in Study 1005 (26 Oct 2021), there was one (1) reported pregnancy in the safety database. This participant was in the placebo group and will continue to be followed for pregnancy outcomes. A narrative for this participant is provided in Module 5.3.5.1 C4671005 Interim Analysis Narratives.

6.4.6.6. Safety Data from All Participants Enrolled as of Database Cutoff

Safety data for 1881 participants (safety analysis set) who were enrolled as of the database cutoff of 26 Oct 2021 were reviewed by the E-DMC. Safety outputs for this larger safety population have previously been submitted (E-DMC Safety Summary Tables).

6.4.6.7. Safety Conclusions

- Treatment with PF-07321332/ritonavir was safe and well tolerated.
    - The proportion of participants with all-causality TEAEs was comparable between the PF-07321332/ritonavir group and the placebo group (19.8% and 22.3%, respectively).
    - 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.
    - The proportion of participants with all-causality SAEs was lower in the PF-07321332/ritonavir group (1.9%) compared with the placebo group (6.8%).
    - There were 10 events of deaths among participants in this study. All 10 death events were in the placebo group and were related to the disease under study.
    - Fewer participants discontinued study intervention due to an AE in the PF-07321332/ritonavir group compared with the placebo group (2.4% and 4.3%, respectively).
    - PF-07321332/ritonavir was not associated with clinically meaningful changes in laboratory values, vital signs, or ECGs (including QT_c).

6.4.7. Continuation of Study Plan if Emergency Use Authorization is Granted

Study 1002 (low risk participants) and Study 1006 (household contact study) are still ongoing [redacted] Status of these studies is summarized in the EUA submission (Module 5.2 Tabular Listing – Monthly Clinical Trial Summary Table_Nov2021).

7. POTENTIAL BENEFITS AND RISKS

7.1. Benefit-Risk Summary

Overall, appraisal of the benefit-risk for PF-07321332/ritonavir is positive. Moreover, there remains an unmet medical need for an effective oral antiviral therapeutic during the current COVID-19 pandemic.

PF-07321332/ritonavir is a potential new oral antiviral therapeutic for non-hospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe illness. The medical need and the benefit-risk summary for the treatment of COVID-19 are presented in Table 52.

Table 52. Medical Need and Benefit-Risk Summary for PF-07321332/Ritonavir for Treatment of Patients at Increased Risk of Developing Severe COVID-19

Decision Factors	Evidence and Uncertainties	Conclusion and Reasons
Analysis of Condition		
Prevalence	Worldwide 250 million confirmed cases including 5 million deaths, as of 12 November 2021.[2]	Although remdesivir is the only approved treatment of hospitalized patients with moderate and severe COVID-19, its efficacy is debated, and toxicity concerns (risk of elevation in liver function test) [87]might limit the therapeutic range of the drug. A recent study found no clinical benefit observed with remdesivir when used in patients who were admitted to hospital for COVID-19, were symptomatic for more than 7 days, and required oxygen support,[88] supporting the conclusion from the interim WHO solidarity trial consortium.[89] Nevertheless, recent remdesivir data in non-hospitalized individuals supports the concept that antiviral medications provide maximal benefit (reduced hospitalization and death) when used early in the disease course.[51]
Clinical Manifestations	COVID-19 presentation can range from a mild to moderately severe, self-limited acute respiratory illness with fever, cough, and shortness of breath to severe life-threatening symptoms resulting in pneumonia, severe acute respiratory syndrome, hypercoagulation, kidney failure and death.	
Comorbidities	Older age (>60), obesity (BMI >25 kg/m^2), current smoker, CKD, diabetes, immunosuppressive disease or immunosuppressive treatment, CV or hypertension, CLD, SCD, neurodevelopmental disorders, active cancer.	
Approved available therapies for COVID-19	Only the antiviral agent remdesivir is approved for IV use in adults and pediatric patients (≥12 years of age) for the treatment of COVID-19 requiring hospitalization. In a systematic review and meta-analysis, remdesivir has positive effects on clinical improvement, and reduction of the risk of serious adverse events. However, it did not influence the mortality at day 14 of treatment.[90] Although enrollment was stopped, recent data in an outpatient setting indicates that remdesivir following 3 days of IV administration, demonstrated a significant 87% reduction of COVID-19 related hospitalization compared with PBO.[51]	Given the potential for SARS-CoV-2 variants to evade the immune system despite natural infection or vaccination, and limitations with remdesivir treatment, there is an urgent unmet medical need for a safe and effective oral therapeutic intervention for non-hospitalized patients with COVID-19. The antiviral would be able to reduce viral transmission, improve time to clinical recovery and prevent the progression of infection to more severe disease, hospitalization, and death, in addition to lowering the strain on the healthcare system caused by SARS-CoV-2, by:

Table 52. Medical Need and Benefit-Risk Summary for PF-07321332/Ritonavir for Treatment of Patients at Increased Risk of Developing Severe COVID-19

Decision Factors	Evidence and Uncertainties	Conclusion and Reasons
Current treatment Options Emergency use authorization of therapeutic mAbs (bamlanivimab and etesevimab; casirivimab and imdevimab; sotrovimab) using either IV or SC administration.	mAb cocktails have been shown to be an effective therapy for treatment of mild to moderate COVID-19. Most reported TEAE with mAbs were generally similar to placebo. Concerns over reduced effectiveness against VOCs and safety issues 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. 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.	- Targeting a highly conserved viral target essential for viral replication, would provide an effective therapeutic agent against current and future coronavirus variants. - Offering an oral antiviral agent with an easy and convenient method of drug administration, taken outside of the hospital setting. This helps keep patients out of hospitals lowering the impact on the healthcare setting especially with the rise in severe COVID-19 hospitalizations. - Providing clear safety benefits over an IV therapeutic by minimizing complications of IV administration and reducing IV-related medication errors.
Benefit of PF-07321332/ritonavir An interventional efficacy and safety, Phase 2/3, double blind, placebo-controlled trial planned in ~3100 non-hospitalized symptomatic participants with COVID-19 who were at increased risk of progression to severe illness. - 1361 participants had entered the treatment phase as of the data cutoff for the 45% interim analysis.	Study 1005 45% Interim Analysis: The primary efficacy analysis result (mITT population) demonstrated that PF-07321332/ritonavir reduced hospitalization or death from any cause by 89.1% compared to placebo when treatment was initiated within 3 days of symptom onset in participants with COVID-19 when compared to placebo. The first key secondary analysis (mITT1 population) similarly showed that PF-07321332/ritonavir reduced hospitalization or death from any cause by 85.2% when treatment was initiated within 5 days of symptom onset. Allowing patients who had	PF-07321332/ritonavir was effective in reducing hospitalization and death, meeting the primary and the first key secondary efficacy endpoints. A significant reduction in viral load was also seen in participants who received PF-07321332/ritonavir versus PBO within 5 days of symptom onset. PF-07321332/ritonavir is an effective antiviral agent for treatment of COVID-19.

Table 52. Medical Need and Benefit-Risk Summary for PF-07321332/Ritonavir for Treatment of Patients at Increased Risk of Developing Severe COVID-19

Decision Factors	Evidence and Uncertainties	Conclusion and Reasons
	received or expected to be receive mAb treatment (mITT2 population) did not alter this conclusion. At the end of the 5-day treatment period, PF-07321332/ritonavir reduced viral load on the Log_{10} scale by 0.93 Log_{10} (copies/mL) when treatment was initiated within 5 days of symptom onset, and by 1.03 Log_{10} (copies/mL) when treatment was initiated within 3 days of symptom onset, indicating PF-07321332/ritonavir reduced the number of viruses by approximately 90%, similar to the amount of reduction in hospitalization or death. In subgroup analysis, PF-07321332/ritonavir was effective in participants with negative serology, and baseline viral load $\geq Log_{10}^4$ copies/mL, $< Log_{10}^7$ copies/mL and $\geq Log_{10}^7$ copies/mL. Treatment differences were not significant for subgroups with positive serology or low baseline viral load $< Log10^4$ copies/mL; however, the results were attributable to a low event rate for these subgroups.	

Table 52. Medical Need and Benefit-Risk Summary for PF-07321332/Ritonavir for Treatment of Patients at Increased Risk of Developing Severe COVID-19

Decision Factors	Evidence and Uncertainties	Conclusion and Reasons
Risk and Risk Management with PF-07321332/ritonavir		
Tolerability	PF-07321332/ritonavir was well tolerated for the 5 days of dosing. PF-07321332/ritonavir is an oral antiviral protease inhibitor for use in the outpatient setting. Results of nonclinical toxicology studies undertaken further support the favorable safety profile of PF07321332.	Safety results from the 45% interim analysis of Study 1005 includes 1349 participants. The frequency of all-causality SAEs was lower with PF-07321332/ritonavir compared with PBO. Overall, PF-07321332/ritonavir has a favorable safety profile. PF -07321332/ritonavir was not associated with clinically meaningful changes in laboratory values, vital signs, or ECGs (including QTc).
Deaths	No deaths were reported in participants receiving PF-07321332/ritonavir compared to PBO.	
SAEs	The overall incidence of SAEs with PF-07321332/ritonavir was low (<2%) with the most frequently reported treatment-emergent SAEs considered related to the disease under study. Serious and unexpected AEs may occur that have not been previously reported with PF-07321332/ritonavir.	Risk mitigation through labeling is considered sufficient to communicate and minimize the risks associated to PF-07321332/ritonavir treatment.
Laboratory Effects	No clinically meaningful treatment-emergent laboratory test abnormalities were observed. PF-07321332/ritonavir has not been studied in pediatrics, pregnancy, and lactation at time of EUA submission.	

7.2. Benefit-Risk Summary Assessment

7.2.1. General Summary of the Benefits/Risks Conclusions

A 5-day treatment of PF-07321332/ritonavir decreases viral load and improves clinical outcome as observed by a significant 85.2% reduction in hospitalization and deaths in participants with risk factors for progressing to severe disease when compared to participants receiving SoC. The reported safety data indicates that PF-07321332/ritonavir has a favorable safety profile.

7.2.2. Benefits

COVID-19 is a serious and potentially fatal or life-threatening human infection. Based on clinical data to date, it is expected that PF-07321332/ritonavir will be an effective antiviral agent against the Delta variant and other VOC as confirmed by generated nonclinical data (Section 6.1.2.1).

Efficacy of PF-07321332/ritonavir was demonstrated at the formal interim analysis of 1361 participants who were at increased risk to develop severe illness. Both the primary and the first key secondary analyses showed significant treatment benefit ($p<0.0001$) in a sequential testing procedure pre-specified in the protocol. The relative reduction in COVID-19-related hospitalization or death from any cause through Day 28 was 89.1% when treatment was initiated within 3 days of symptom onset, and 85.2% when treatment was initiated within 5 days of symptom onset.

The treatment benefit reflected the anti-viral effect of PF-07321332/ritonavir. Compared with placebo, PF-07321332/ritonavir reduced the viral load on the Log_{10} scale by an additional 0.93 Log_{10} (copies/mL) at Day 5 when treatment was initiated within 5 days of symptom onset, and by an additional 1.03 Log_{10} (copies/mL) when treatment was initiated within 3 days of symptom onset. Reduction of 1 Log_{10} (copies/mL) indicates 90% reduction in the virus count. The antiviral effect was more apparent in patients who were seronegative or who had high viral load at baseline.

- As both the primary analysis and key secondary analysis of the primary endpoint for hospitalization or death were met, time from symptom onset to initiation of treatment did not negatively affect the antiviral efficacy of PF-07321332/ritonavir, with treatment indicated for use in patients with COVID-19 symptom onset $\leq$5 days.

- In sensitivity analysis, there was minimal impact on the reduction in hospitalization or death of including participants who received or were expected to receive mAb (mITT2).

- In subgroup analysis, PF-07321332/ritonavir was effective in participants with negative serology, high baseline viral load ($\geq Log_{10}^4$ copies/mL), very high baseline viral load ($\geq Log_{10}^7$ copies/mL), and irrespective of sex, age group, and BMI category $\geq$25 kg/m^2. Although treatment differences were not significant for subgroups with positive serology or low baseline viral load $<Log_{10}^4$, analysis was compromised by a low event rate. The clinical significance of the lack of treatment difference in the subgroup with BMI<25 kg/m^2 is unknown.

Additional data are pending final study completion and will assess the effect of treatment on symptom duration and severity.

7.2.3. Risks

The reported safety data indicates that PF-07321332/ritonavir has a favorable safety profile.

The most frequently reported TEAEs were GI-related and were mild to moderate in severity. The overall incidence of SAEs with PF-07321332/ritonavir was low (<2%) with the most frequently reported treatment-emergent SAEs considered related to the disease under study. No deaths were reported in the PF-07321332/ritonavir group. In addition, few participants in the PF-07321332/ritonavir group discontinued study intervention due an AE and no participants discontinued the study due to an AE.

PF-07321332/ritonavir has not been studied in pediatrics, pregnancy, and lactation at time of EUA submission.

Serious and unexpected AEs may occur that have not been previously reported with PF-07321332/ritonavir.

Overall, PF-07321332/ritonavir was well tolerated for 5 days of dosing in high-risk individuals with COVID-19.

Given no safety signals of concerns were identified in the clinical program, the sponsor proposes using routine pharmacovigilance to support further risk assessment and characterization of the safety profile for PF-07321332/ritonavir under the EUA (for further details see Section 12).

7.2.3.1. Laboratory Effects

No clinically meaningful changes in laboratory values, vital signs, or ECGs (including QTc) were observed with PF-07321332/ritonavir administration.

7.2.4. Conclusions

Overall, the potential benefits and risks, as assessed by the efficacy and safety profile of PF-07321332/ritonavir, are balanced in favor of the potential benefits to reduce hospitalizations and death in high-risk individuals with COVID-19. The public health impacts also weigh in favor of an EUA for PF-07321332/ritonavir.

7.3. Contraindications

Refer to the Full EUA Prescribing Information (Full EUA PI) provided in Module 1.14.1 and includes contraindications for PF-07321332/ritonavir administration.

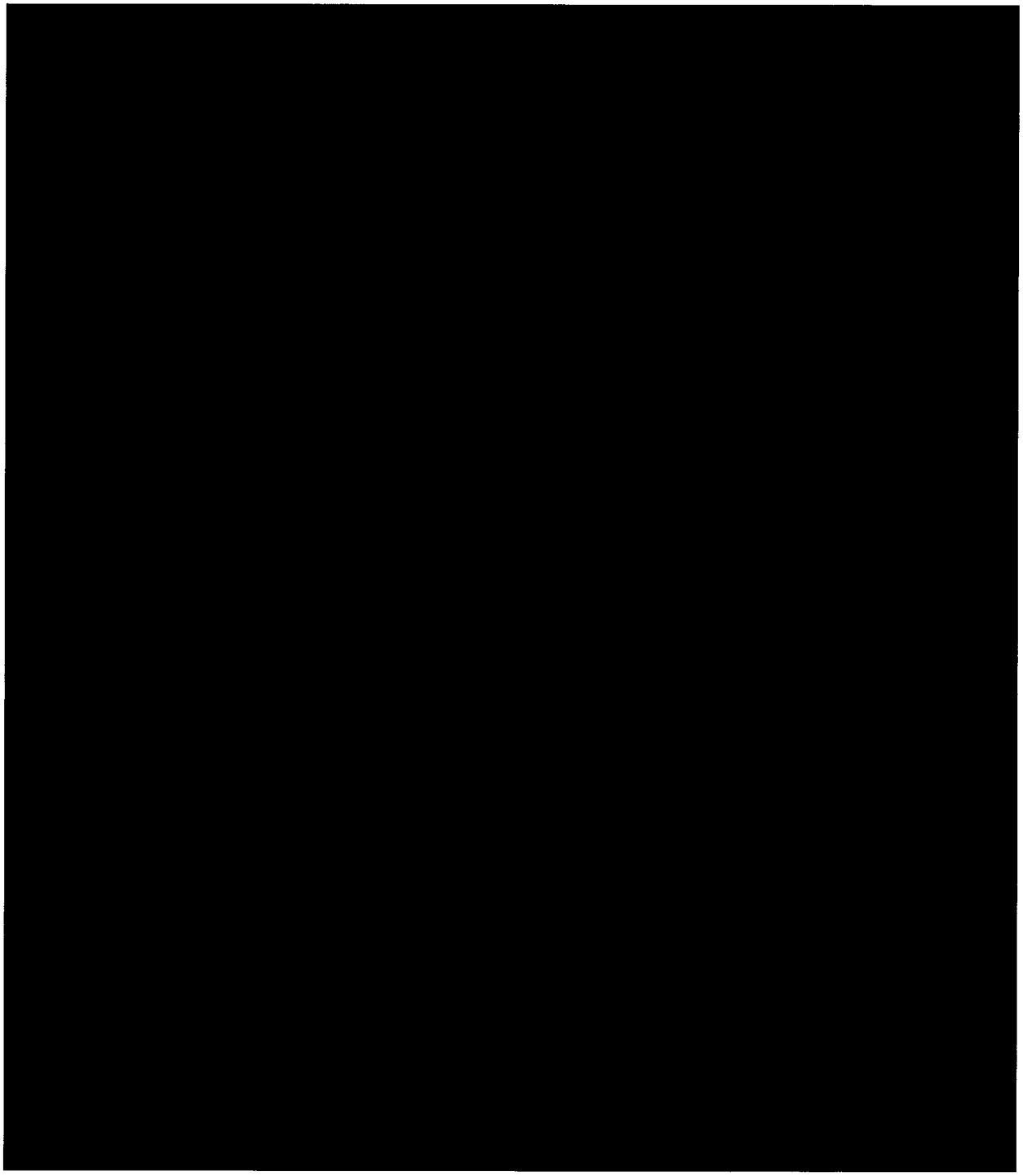
7.4. Special Populations

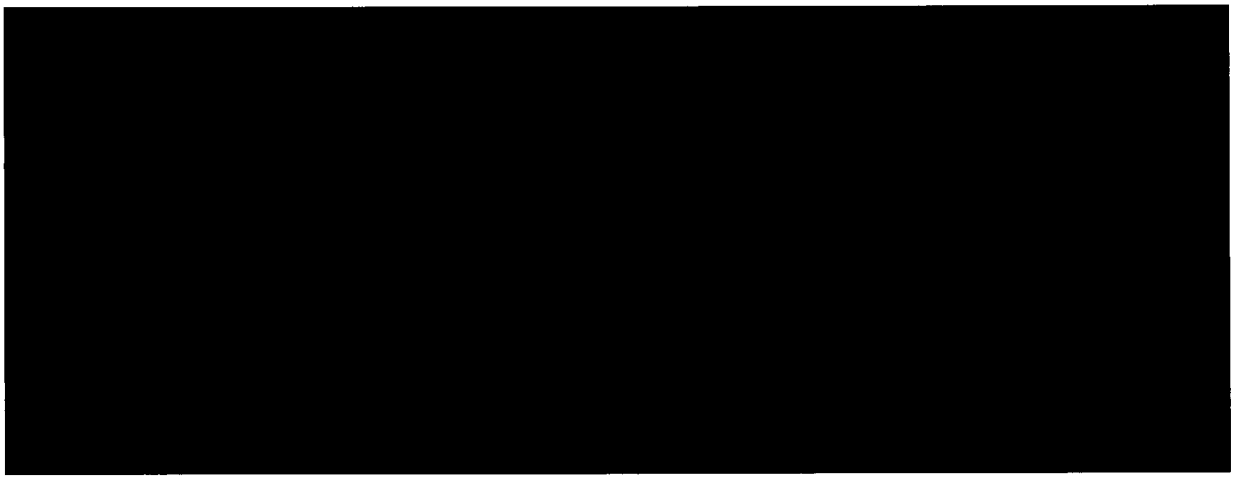
The Full EUA PI (located in Module 1.14.1) includes information on administration to special populations.

8. CHEMISTRY, MANUFACTURING, AND CONTROLS

This application introduces manufacturing sites, manufacturing process details, characterization, control strategies, quality attributes, analytical validation data, drug product dissolution data, updated specifications, and descriptions of analytical procedures for release and stability testing of emergency supply PF-07321332 drug substance and drug product.

[redacted]





9. FACT SHEET FOR THERAPEUTIC PROVIDERS

Refer to the Fact Sheet for Healthcare Providers located in Module 1.14.1.

10. FACT SHEET FOR RECIPIENTS AND CAREGIVERS

Refer to the Fact Sheet for Recipients and Caregivers located in Module 1.14.1.

12. ADVERSE EVENT AND MEDICATION ERROR MONITORING

PF-07321332/ritonavir is an oral antiviral protease inhibitor for use in the outpatient setting with a favorable safety profile. Previous human experience of protease inhibitors, albeit with a higher dose and longer duration and in different patient populations, supports the characterization of the safety profile, in terms of identifying known and potential risks of PF-07321332/ritonavir for treatment of patients with COVID-19.

As a result, given no safety concerns were identified in the clinical program, the sponsor proposes using routine pharmacovigilance to support further risk assessment and characterization of the safety profile for PF-07321332/ritonavir under the EUA.

The sponsor's routine pharmacovigilance processes include the ongoing timely collection, processing, follow-up, and analysis of individual adverse event reports. As per the sponsor's policy, the safety profile of PF-07321332/ritonavir will be monitored; evaluating in a timely manner issues potentially impacting product benefit-risk profiles such as those that may arise during clinical development, registration and authorization; and ensure that appropriate communication of relevant information is conveyed in a timely manner to the FDA, prescribers and patients.

The sponsor conducts numerous scientific and data gathering activities for the detection and evaluation of adverse events to provide safety monitoring commensurate with product characteristics. Signal detection activities include medical review of reports during individual case processing as well as periodic aggregate data review based on the known safety profile of the drug and the life cycle for the product. Safety signal evaluation requires the collection and assessment of information to evaluate whether there is a potential causal link between an event and the administration of the product and includes subsequent qualitative and/or quantitative characterization of the identified safety risk and/or determination that the safety risk may require further action.

13. LABELING

Refer to Module 1.14.1 PI.

Please refer to the Fact Sheet for Recipients and Caregivers for additional patient information that will be provided to the sponsor's COVID-19 Oral Anti-Viral recipients.

13.1. Draft Blister and Carton Artwork

Please refer to Module 1.14.1.1 and information in Module 1.14.1.1 draft blister and Module 1.14.1.1 carton artwork.

15. APPENDIX

Table 53. List of Drugs that are Contraindicated for Concomitant Use with PF-07321332/ritonavir

Table 53. List of Drugs that are Contraindicated for Concomitant Use with PF-07321332/ritonavir

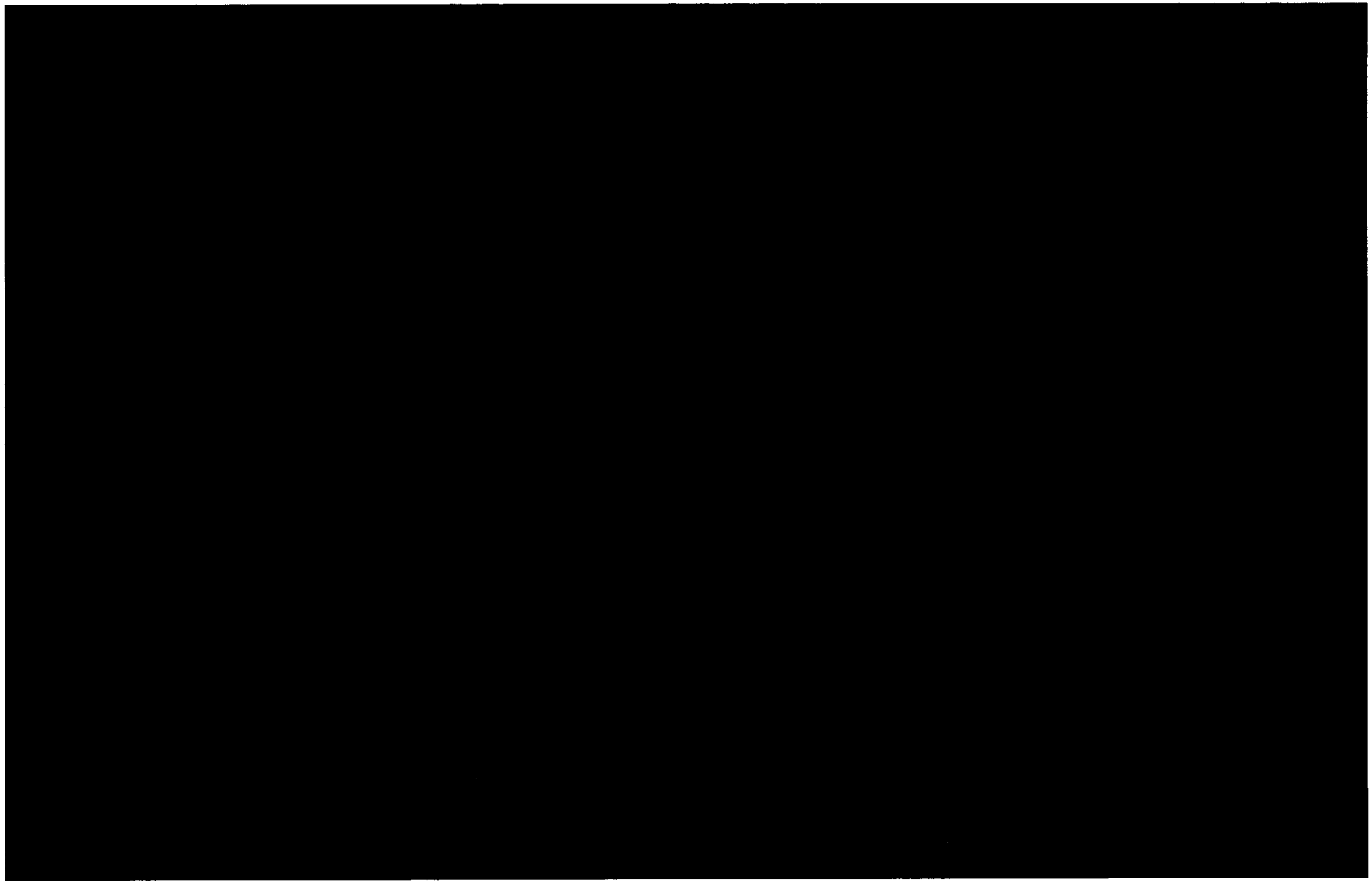


Table 53. List of Drugs that are Contraindicated for Concomitant Use with PF-07321332/ritonavir

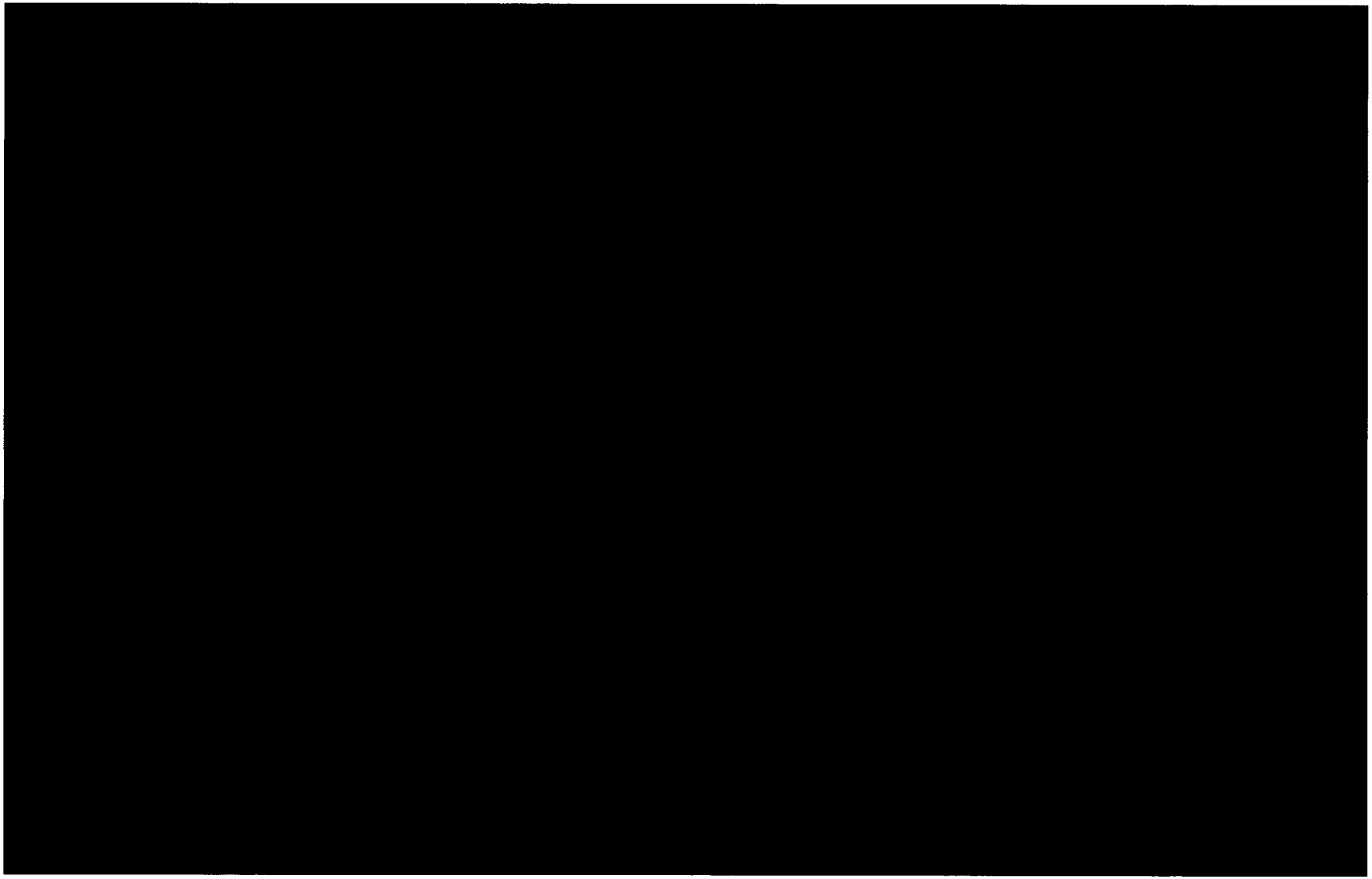


Table 53. List of Drugs that are Contraindicated for Concomitant Use with PF-07321332/ritonavir

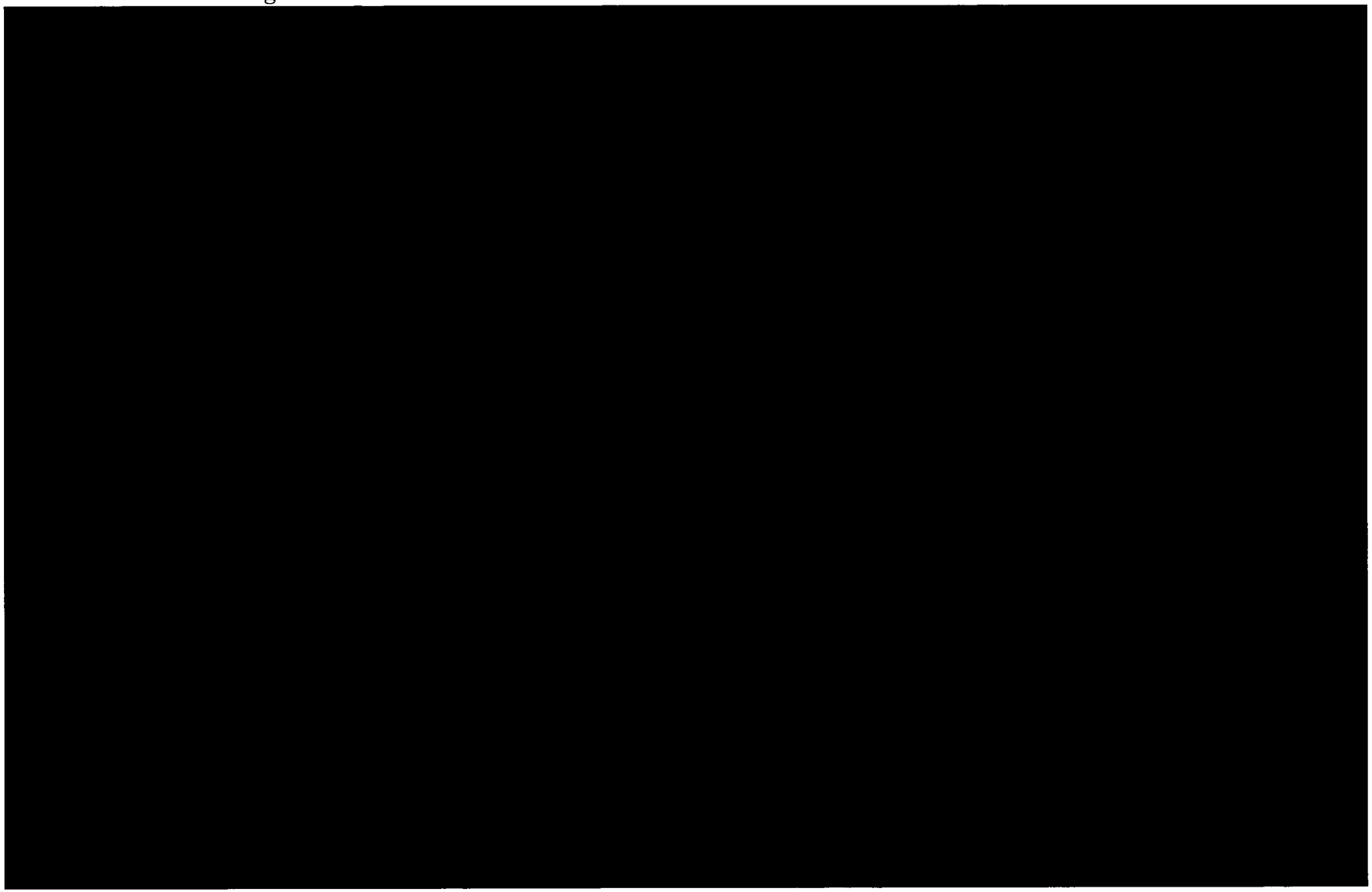


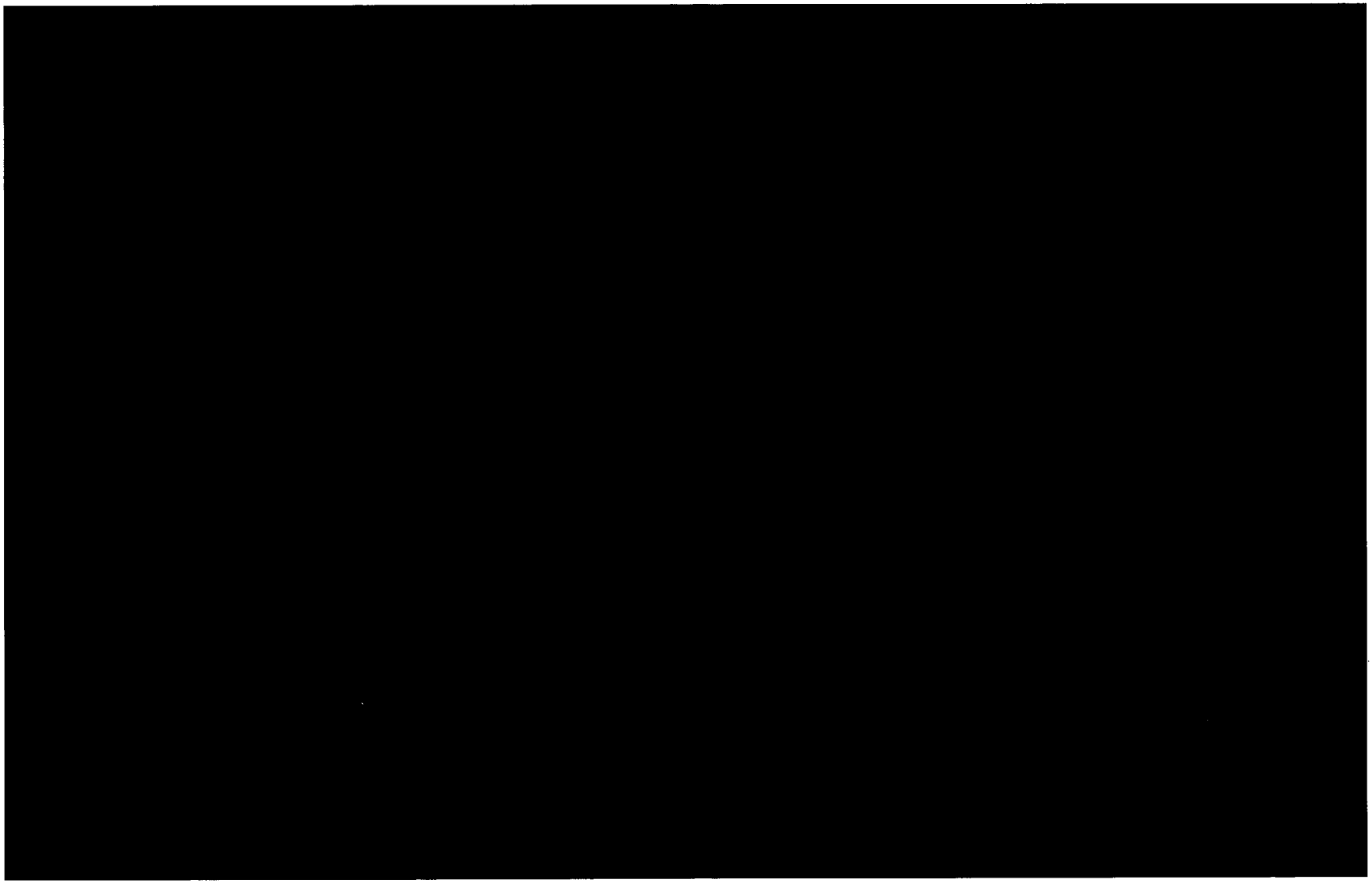
Table 53. List of Drugs that are Contraindicated for Concomitant Use with PF-07321332/ritonavir

[redacted]

Table 54. Other Potentially Significant Drug Interactions

[redacted]

Table 54. Other Potentially Significant Drug Interactions



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PRELIMINARY COMPLETION DATE SUMMARY REPORT
STUDY C4671005

AN INTERVENTIONAL EFFICACY AND SAFETY, PHASE 2/3, DOUBLE-BLIND, 2-ARM STUDY TO INVESTIGATE ORALLY ADMINISTERED PF-07321332/RITONAVIR COMPARED WITH PLACEBO IN NONHOSPITALIZED SYMPTOMATIC ADULT PARTICIPANTS WITH COVID-19 WHO ARE AT INCREASED RISK OF PROGRESSING TO SEVERE ILLNESS

First Subject First Visit:	16 Jul 2021
Study Primary Completion Date:	09 Dec 2021
Database Snapshot:	[redacted]Dec 2021
PCD Summary Report Date:	[redacted]Dec 2021

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This is a top line report (TLR) summarizing primary efficacy and key safety data from the primary completion date (PCD) analysis of Study 1005 for all participants enrolled. The report includes efficacy assessments through Day 28 and follow-up safety assessments through Day 34.

1. OBJECTIVES

The primary efficacy objective was to compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of COVID-19 in non-hospitalized symptomatic adult participants with COVID-19 who were at increased risk of progression to severe disease in the Modified Intent-To-Treat (mITT) analysis set.

The safety objectives were to describe the safety and tolerability of PF-07321332/ritonavir relative to placebo in the treatment of non-hospitalized symptomatic adult participants with COVID-19 who were at increased risk of progression to severe disease.

2. STUDY DESIGN

This Phase 2/3, randomized, double-blind, placebo-controlled study in ~3000 symptomatic participants with COVID-19 who are non-hospitalized is to determine the efficacy, safety, and tolerability of PF-07321332/ritonavir compared with placebo. Eligible participants with a confirmed diagnosis of SARS-CoV-2 infection were randomized (1:1) to receive PF-07321332/ritonavir or placebo orally q12h for 5 days (10 doses total). Randomization was stratified by geographic region and by whether participants had received/were expected to receive treatment with COVID-19 therapeutic monoclonal antibodies (mAbs) based on the investigator's assessment at time of randomization.

The analysis population set (mITT, mITT1, and mITT2) is defined in Table 1. These definitions differ from what was used in the interim analysis (IA) but was changed in the latest statistical analysis plan prior to database lock using the agreed FDA Biometrics suggested definitions.

Table 1. Efficacy Analysis Sets Defined for Study 1005

Analysis Set	Description
mITT	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days after COVID-19 symptom onset. Participants will be analyzed according to the study intervention to which they were randomized.
mITT1	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, and who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤5 days after COVID-19 symptom onset. Participants will be analyzed according to the study intervention to which they were randomized.
mITT2	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, and were treated ≤5 days after COVID-19 symptom onset regardless of mAb treatment status. Participants will be analyzed according to the study intervention to which they were randomized.

The total study duration was up to 24 weeks and includes a screening period of no more than 48 hours, study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow-up at Weeks 12 and 24.

3. SUBJECT POPULATION

The number of participants within each analysis set for the PCD analysis is outlined in Table 2.

Table 2. Participant Evaluation Groups – All Screened Participants

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

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As of the data cutoff (11 Dec 2021) 2246 (100.0%) participants were randomized into Study 1005, and 2102 (93.6%) participants had completed the safety follow-up (Day 34). (Table 3).

- The proportion of participants who discontinued the treatment phase was similar between treatment groups (6.0% versus 7.7% in the PF-07321332/ritonavir group and placebo group, respectively). The most common reasons for discontinuation during the treatment phase of the study in either treatment group were adverse event (AE) (3.1%) followed by 'withdrawal by subject' (2.6%). Fewer participants in the PF-07321332/ritonavir group (2.1%) discontinued the treatment phase due to an AE compared with the placebo group (4.2%).

- The proportion of participants who completed the safety follow-up (Day 34) was similar between treatment groups.

Table 3. Disposition Events Summary - Full Analysis Set

Number (%) of Participants	PF-07321332 300 mg + Ritonavir 100 mg (N=1120) n (%)	Placebo (N=1126) n (%)	Total (N=2246) n (%)
Disposition phase: Treatment			
Participants Entered:	1120 (100.0)	1126 (100.0)	2246 (100.0)
Discontinued	67 (6.0)	87 (7.7)	154 (6.9)
Reason for discontinuation			
Adverse event	23 (2.1)	47 (4.2)	70 (3.1)
Death	0	0	0
Lack of efficacy	0	0	0
Lost to follow-up	0	0	0
Noncompliance with study drug	0	0	0
Pregnancy	0	0	0
Protocol deviation	0	0	0
Study terminated by sponsor	0	0	0
Withdrawal by subject	32 (2.9)	27 (2.4)	59 (2.6)
Medication error without associated adverse event	0	1 (<0.1)	1 (<0.1)
No longer meets eligibility criteria	3 (0.3)	1 (<0.1)	4 (0.2)
Other	9 (0.8)	11 (1.0)	20 (0.9)
Completed	1053 (94.0)	1039 (92.3)	2092 (93.1)
Ongoing	0	0	0
Disposition phase: Follow-up			
Participants Entered:	1120 (100.0)	1126 (100.0)	2246 (100.0)
Discontinued	67 (6.0)	77 (6.8)	144 (6.4)
Reason for discontinuation			
Death	0	13 (1.2)	13 (0.6)
Lost to follow-up	11 (1.0)	9 (0.8)	20 (0.9)
Study terminated by sponsor	0	0	0
Withdrawal by subject	43 (3.8)	43 (3.8)	86 (3.8)
Other	13 (1.2)	12 (1.1)	25 (1.1)
Completed	1053 (94.0)	1049 (93.2)	2102 (93.6)
Ongoing	0	0	0
Disposition phase: Long-term follow-up			
Participants Entered:	1120 (100.0)	1126 (100.0)	2246 (100.0)
Discontinued	64 (5.7)	75 (6.7)	139 (6.2)
Reason for discontinuation			

Number (%) of Participants	PF-07321332 300 mg + Ritonavir 100 mg (N=1120) n (%)	Placebo (N=1126) n (%)	Total (N=2246) n (%)
Adverse event	0	0	0
Death	0	13 (1.2)	13 (0.6)
Lost to follow-up	10 (0.9)	10 (0.9)	20 (0.9)
Study terminated by sponsor	0	0	0
Withdrawal by subject	43 (3.8)	42 (3.7)	85 (3.8)
Other	11 (1.0)	10 (0.9)	21 (0.9)
Completed	0	0	0
Ongoing	1056 (94.3)	1051 (93.3)	2107 (93.8)

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4. DEMOGRAPHIC AND BASELINE CHARACTERISTICS - FULL ANALYSIS SET

Demographic and baseline characteristics for the full analysis set (FAS) were similar between the PF-07321332/ritonavir and placebo groups (Table 4).

As of the data cutoff, 41.3%, 29.8%, 8.5%, and 20.4% of participants were from the US, Europe, India and Rest of the World, respectively. Over half of the participants (51.1%) were male and were White (71.5%). Just under half of the participants in each treatment group were Hispanic or Latino. The median age was 46.0 (18.0, 88.0) years and 288 (12.8%) patients were 65 years of age or greater at the time of randomization. The mean (SD) body mass index (BMI) was 29.17 (5.62), and the majority of participants had a BMI of 25 or greater at the time of screening.

The participant population of Study 1005 reflected the patient population that would be treated with PF-07321332/ritonavir in clinical practice and who are at high risk for progressing to severe disease. Across treatment groups, 47.0% of participants were serological negative at baseline. Most participants (93.8% across treatment groups) did not receive or were not planning to receive monoclonal antibodies for the disease under study at the time of randomization.

With the exception of 2 participants, all participants had at least 1 risk factor for severe COVID-19 with 38.9% of participants with 1 prespecified risk factor and 35.7% participants with 2 pre-specified risk factors. A total of 375 (16.7%) and 152 (6.8%) participants presented at screening with 3 and 4 risk factors, respectively. The most common risk factor at baseline was BMI ≥25 (80.5%).

Across treatment groups, the median baseline viral load (Log_{10} copies/mL) was 5.35. Approximately 36.5% of participants had a low baseline viral load (<4.0 Log_{10} copies/mL), 60.2% of participants had a high baseline viral load (≥4.0 Log_{10} copies/mL) and 25.6% of participants had a very high baseline viral load (≥7.0 Log_{10} copies/mL).

Table 4. Demographic and Baseline Characteristics - Full Analysis Set

	PF-07321332 300 mg + Ritonavir 100 mg (N=1120)	Placebo (N=1126)	Total (N=2246)
Age (Years), n (%)			
< 18	0	0	0
18 - 44	556 (49.6)	517 (45.9)	1073 (47.8)
45 - 59	338 (30.2)	349 (31.0)	687 (30.6)
60 - 64	86 (7.7)	112 (9.9)	198 (8.8)
65 - 74	104 (9.3)	117 (10.4)	221 (9.8)
≥ 75	36 (3.2)	31 (2.8)	67 (3.0)
Mean (SD)	45.33 (15.40)	46.34 (15.51)	45.84 (15.46)
Median (range)	45.00 (18.00, 86.00)	46.50 (18.00, 88.00)	46.00 (18.00, 88.00)
Gender, n (%)			
Male	566 (50.5)	582 (51.7)	1148 (51.1)
Female	554 (49.5)	544 (48.3)	1098 (48.9)
Race, n (%)			
White	800 (71.4)	807 (71.7)	1607 (71.5)
Black or African American	60 (5.4)	50 (4.4)	110 (4.9)
Asian	154 (13.8)	161 (14.3)	315 (14.0)
American Indian or Alaska Native	96 (8.6)	95 (8.4)	191 (8.5)
Native Hawaiian or other Pacific Islander	0	0	0
Multiracial	1 (<0.1)	2 (0.2)	3 (0.1)
Other	0	0	0
Not reported	8 (0.7)	9 (0.8)	17 (0.8)
Unknown	1 (<0.1)	2 (0.2)	3 (0.1)
Ethnicity, n (%)			
Hispanic or Latino	499 (44.6)	505 (44.8)	1004 (44.7)
Not Hispanic or Latino	616 (55.0)	614 (54.5)	1230 (54.8)
Not reported	5 (0.4)	7 (0.6)	12 (0.5)
Unknown	0	0	0
Weight (kg)			
Mean (SD)	81.39 (17.51)	82.28 (18.85)	81.84 (18.19)
Median (range)	80.00 (42.00, 158.3)	80.00 (42.00, 173.0)	80.00 (42.00, 173.0)
Height (cm)			
Mean (SD)	167.1 (9.64)	167.5 (10.24)	167.3 (9.94)
Median (range)	167.0 (136.9, 196.0)	167.6 (125.2, 207.3)	167.6 (125.2, 207.3)
BMI (kg/m^2), n (%)			
< 25	220 (19.6)	217 (19.3)	437 (19.5)
25 - < 30	492 (43.9)	489 (43.4)	981 (43.7)

	PF-07321332 300 mg + Ritonavir 100 mg (N=1120)	Placebo (N=1126)	Total (N=2246)
30 - < 35	276 (24.6)	268 (23.8)	544 (24.2)
35 - < 40	78 (7.0)	88 (7.8)	166 (7.4)
≥ 40	53 (4.7)	63 (5.6)	116 (5.2)
Mean (SD)	29.09 (5.50)	29.25 (5.74)	29.17 (5.62)
Median (range)	28.20 (16.58, 58.07)	28.34 (16.05, 59.07)	28.30 (16.05, 59.07)
Duration since first diagnosis (Days), n (%)			
≤ 3	1044 (93.2)	1072 (95.2)	2116 (94.2)
> 3	76 (6.8)	54 (4.8)	130 (5.8)
Mean (SD)	1.30 (1.29)	1.31 (1.23)	1.30 (1.26)
Median (range)	1.00 (0.00, 5.00)	1.00 (0.00, 9.00)	1.00 (0.00, 9.00)
Duration since first symptom (Days), n (%)			
≤ 3	754 (67.3)	735 (65.3)	1489 (66.3)
> 3	366 (32.7)	391 (34.7)	757 (33.7)
Mean (SD)	2.93 (1.12)	2.99 (1.09)	2.96 (1.10)
Median (range)	3.00 (0.00, 7.00)	3.00 (0.00, 9.00)	3.00 (0.00, 9.00)
Number of risk factors of interest, n (%)			
0	2 (0.2)	0	2 (<0.1)
1	449 (40.1)	425 (37.7)	874 (38.9)
2	393 (35.1)	408 (36.2)	801 (35.7)
3	183 (16.3)	192 (17.1)	375 (16.7)
4	77 (6.9)	75 (6.7)	152 (6.8)
> 4	16 (1.4)	26 (2.3)	42 (1.9)
Comorbidities, n (%)			
Cardiovascular disorder	42 (3.8)	50 (4.4)	92 (4.1)
Chronic kidney disease	6 (0.5)	8 (0.7)	14 (0.6)
Chronic lung disease	62 (5.5)	41 (3.6)	103 (4.6)
Cigarette smoker	428 (38.2)	448 (39.8)	876 (39.0)
Diabetes mellitus	135 (12.1)	138 (12.3)	273 (12.2)
Hypertension	359 (32.1)	380 (33.7)	739 (32.9)
Immunosuppression	6 (0.5)	7 (0.6)	13 (0.6)
Cancer	5 (0.4)	6 (0.5)	11 (0.5)
Neurodevelopmental disorder	2 (0.2)	1 (<0.1)	3 (0.1)
Sickle cell disease	0	0	0
HIV infection	0	1 (<0.1)	1 (<0.1)
Device dependence	4 (0.4)	3 (0.3)	7 (0.3)
COVID-19 mAb treatment, n (%)			
Received/expected to receive	70 (6.3)	70 (6.2)	140 (6.2)
Not received/not expected to receive	1050 (93.8)	1056 (93.8)	2106 (93.8)

	PF-07321332 300 mg + Ritonavir 100 mg (N=1120)	Placebo (N=1126)	Total (N=2246)
Geographic region, n (%)			
United States	463 (41.3)	465 (41.3)	928 (41.3)
Europe	334 (29.8)	335 (29.8)	669 (29.8)
India	95 (8.5)	98 (8.7)	193 (8.6)
Rest of World	228 (20.4)	228 (20.2)	456 (20.3)
Serology status, n (%)			
Negative	518 (46.3)	537 (47.7)	1055 (47.0)
Positive	581 (51.9)	568 (50.4)	1149 (51.2)
Unknown	21 (1.9)	21 (1.9)	42 (1.9)
Viral load (Log_{10} copies/mL), n (%)			
0	191 (17.1)	184 (16.3)	375 (16.7)
< 2.7	300 (26.8)	332 (29.5)	632 (28.1)
< 4	406 (36.3)	413 (36.7)	819 (36.5)
≥ 4	677 (60.4)	676 (60.0)	1353 (60.2)
≥ 5	583 (52.1)	582 (51.7)	1165 (51.9)
≥ 6	442 (39.5)	441 (39.2)	883 (39.3)
< 7	783 (69.9)	814 (72.3)	1597 (71.1)
≥ 7	300 (26.8)	275 (24.4)	575 (25.6)
≥ 8	118 (10.5)	113 (10.0)	231 (10.3)
≥ 9	4 (0.4)	5 (0.4)	9 (0.4)
≥ 10	0	0	0
Mean (SD)	4.67 (2.88)	4.59 (2.86)	4.63 (2.87)
Median (range)	5.41 (0.00, 9.16)	5.30 (0.00, 9.15)	5.35 (0.00, 9.16)

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

5.1. Primary Analysis Set – mITT

At the PCD analysis, the event rate of a COVID-19-related hospitalization or death from any cause through Day 28 in the mITT analysis set in participants who received treatment within 3 days of symptom onset was 44/682 (6.45%) in the placebo group, and 5/697 (0.72%) in the PF-07321332/ritonavir group (Table 5).

After accounting for premature study discontinuation (ie, participant discontinued study before Day 28 without having experienced a primary endpoint event) by using the follow-up time in the Kaplan-Meier calculation, treatment with PF-07321332/ritonavir showed a 5.81% (95% CI: -7.78% to -3.84; p<0.0001) absolute reduction, or 88.9% relative reduction in primary endpoint events compared to placebo.

There were 0 and 9 reported events of death from any cause through Day 28 in the PF-07321332/ritonavir and placebo groups, respectively.

Table 5. Primary Analysis of Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 - mITT, Kaplan-Meier Method

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
N	697	682
Participants with event, n (%)	5 (0.717)	44 (6.452)
Participants with COVID-19 hospitalization	5 (0.717)	44 (6.452)
Participants with death	0	9 (1.320)
Average time at risk for event (Days)[a]	27.288	26.188
Average study follow-up (Days)[b]	27.448	27.245
Estimated proportion (95% CI), %	0.723 (0.302, 1.729)	6.531 (4.901, 8.676)
Difference from Placebo (SE)	-5.807 (1.005)	
95% CI of difference	-7.777, -3.837	
p-value	<.0001	

N = number of participants in the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.
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5.2. Secondary Analysis Sets – mITT1 and mITT2

The event rate of a COVID-19-related hospitalization or death from any cause through Day 28 in the mITT1 analysis set in participants who received treatment within 5 days of

symptom onset was 66/1046 (6.31%) in the placebo group, and 8/1039 (0.77%) in the PF-07321332/ritonavir group (Table 6).

After accounting for premature study discontinuation (ie, participant discontinued study before Day 28 without having experienced a primary endpoint event) by using the follow-up time in the Kaplan-Meier calculation, treatment with PF-07321332/ritonavir showed a 5.62% (95% CI: -7.21% to -4.03%; p<0.0001) absolute reduction, or 87.8% relative reduction in primary endpoint events compared to placebo.

There were 0 and 12 reported events of death from any cause through Day 28 in the PF-07321332/ritonavir and placebo groups, respectively.

Table 6. Secondary Analysis of Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 - mITT1, Kaplan-Meier Method

	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
N	1039	1046
Participants with event, n (%)	8 (0.770)	66 (6.310)
Participants with COVID-19 hospitalization	8 (0.770)	65 (6.214)
Participants with death	0	12 (1.147)
Average time at risk for event (Days)[a]	27.048	25.972
Average study follow-up (Days)[b]	27.203	27.046
Estimated proportion (95% CI), %	0.781 (0.391, 1.556)	6.400 (5.063, 8.075)
Difference from Placebo (SE)	-5.619 (0.810)	
95% CI of difference	-7.207, -4.031	
p-value	<.0001	

N = number of participants in the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.
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The event rate of a COVID-19-related hospitalization or death from any cause through Day 28 in the mITT2 analysis set in participants who received treatment within 5 days of symptom onset regardless of mAb antibody treatment was 68/1115 (6.10%) in the placebo group, and 9/1109 (0.81%) in the PF-07321332/ritonavir group (Table 7).

After accounting for premature study discontinuation (ie, participant discontinued study before Day 28 without having experienced a primary endpoint event) by using the follow-up time in the Kaplan-Meier calculation, treatment with PF-07321332/ritonavir showed a 5.36%

(95% CI: -6.88% to -3.84%; p<0.0001) absolute reduction, or 86.7% relative reduction in primary endpoint events compared to placebo.

There were 0 and 12 reported events of death from any cause through Day 28 in the PF-07321332/ritonavir and placebo groups, respectively.

Table 7. Sensitivity Analysis of Proportion of Participants with COVID-19- Related-Hospitalization or Death From any Cause Through Day 28 - mITT2, Kaplan-Meier Method

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

N = number of participants in the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](10:10) Source Data: adtte Table Generation: [redacted](11:37)
(Data cutoff date : 11DEC2021 Database snapshot date : [redacted] Output File:
./nda/C4671005_EUA/adtteh_s001_mitt2

5.3. Subgroup Analysis – mITT by Baseline Viral Load

The prespecified subgroup analysis of the primary endpoint by baseline viral load was consistent with the overall mITT population for the subgroups of high baseline viral load (≥4.0 Log_{10} copies/mL), very high baseline viral load (≥7.0 Log_{10} copies/mL) and baseline viral load <7.0 Log_{10} copies/mL (Table 8). The p-value for the low baseline viral load subgroup (<4.0 Log_{10} copies/mL) was p=0.3162. Few participants in the subgroup of low baseline viral load had events (0 for PF-07321332/ritonavir; 1 for placebo).

Table 8. Analysis of Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28, by Subgroup of Baseline Viral Load - mITT, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Viral load < 4	N	231	219
	Participants with event, n (%)	0	1 (0.457)
	Participants with COVID-19 hospitalization	0	1 (0.457)
	Participants with death	0	0
	Average time at risk for event (Days)[a]	27.619	27.740
	Average study follow-up (Days)[b]	27.619	27.840
	Estimated proportion (95% CI), %	0.000 (0.000, 0.000)	0.459 (0.065, 3.211)
	Difference from Placebo (SE)	-0.459 (0.458)	
	95% CI of difference	-1.356, 0.438	
	p-value	0.3162	
Viral load ≥ 4	N	446	445
	Participants with event, n (%)	5 (1.121)	40 (8.989)
	Participants with COVID-19 hospitalization	5 (1.121)	40 (8.989)
	Participants with death	0	7 (1.573)
	Average time at risk for event (Days)[a]	27.105	25.508
	Average study follow-up (Days)[b]	27.354	27.016
	Estimated proportion (95% CI), %	1.132 (0.473, 2.698)	9.141 (6.789, 12.252)
	Difference from Placebo (SE)	-8.009 (1.467)	
	95% CI of difference	-10.884, -5.133	
	p-value	<.0001	
Viral load < 7	N	452	460
	Participants with event, n (%)	3 (0.664)	21 (4.565)
	Participants with COVID-19 hospitalization	3 (0.664)	21 (4.565)
	Participants with death	0	2 (0.435)
	Average time at risk for event (Days)[a]	27.400	26.583
	Average study follow-up (Days)[b]	27.569	27.457
	Estimated proportion (95% CI), %	0.664 (0.215, 2.045)	4.613 (3.032, 6.987)
	Difference from Placebo (SE)	-3.949 (1.055)	
	95% CI of difference	-6.016, -1.881	
	p-value	0.0002	
Viral load ≥ 7	N	225	204

Subgroup	PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Participants with event, n (%)	2 (0.889)	20 (9.804)
Participants with COVID-19 hospitalization	2 (0.889)	20 (9.804)
Participants with death	0	5 (2.451)
Average time at risk for event (Days)[a]	27.040	25.480
Average study follow-up (Days)[b]	27.196	26.907
Estimated proportion (95% CI), %	0.917 (0.230, 3.618)	9.964 (6.545, 15.019)
Difference from Placebo (SE)	-9.046 (2.211)	
95% CI of difference	-13.380, -4.713	
p-value	<.0001	

5.4. Subgroup Analysis – mITT by Serology Status

The prespecified subgroup analysis of the primary endpoint by serology negative subgroup was consistent with the overall mITT population (Table 9). The p-value for the serology positive subgroup was p=0.0442. Few participants in the serology positive subgroup had events (0 for PF-07321332/ritonavir; 4 for placebo).

Table 9. Analysis of Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28, by Subgroup of Baseline SARS-CoV-2 Serology Status - mITT, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Negative	N	342	342
	Participants with event, n (%)	5 (1.462)	40 (11.696)
	Participants with COVID-19 hospitalization	5 (1.462)	40 (11.696)
	Participants with death	0	9 (2.632)
	Average time at risk for event (Days)[a]	27.058	24.924
	Average study follow-up (Days)[b]	27.383	26.787
	Estimated proportion (95% CI), %	1.473 (0.616, 3.504)	11.903 (8.874, 15.872)
	Difference from Placebo (SE)	-10.430 (1.884)	
	95% CI of difference	-14.123, -6.736	
	p-value	<.0001	
Positive	N	350	332
	Participants with event, n (%)	0	4 (1.205)
	Participants with COVID-19 hospitalization	0	4 (1.205)
	Participants with death	0	0
	Average time at risk for event (Days)[a]	27.503	27.446
	Average study follow-up (Days)[b]	27.503	27.699
	Estimated proportion (95% CI), %	0.000 (0.000, 0.000)	1.211 (0.456, 3.195)
	Difference from Placebo (SE)	-1.211 (0.602)	
	95% CI of difference	-2.391, -0.031	
	p-value	0.0442	

N = number of participants in the subgroup of the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](10:10) Source Data: adtte Table Generation: [redacted](11:37)
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./nda/C4671005_EUA/adtteh_s001_sub_ser

5.5. Subgroup Analysis – mITT by Age

The prespecified subgroup analysis of the primary endpoint by age was consistent with the overall mITT population (Table 10). The treatment effect from PF-07321332/ritonavir versus placebo was significant among participants <65 years of age (0.66% versus 4.80%, a 4.19% absolute reduction, p<0.0001), but was larger in terms of absolute reduction among participants ≥65 years of age due to the expected higher event rate (1.06% versus 16.33%, a 15.26% absolute reduction, p<0.0001).

Table 10. Analysis of Proportion of Participants with COVID-19-Related-Hospitalization or Death From any Cause Through Day 28, by Subgroup of Age - mITT, Kaplan-Meier Method

Subgroup		PF-07321332 300 mg + Ritonavir 100 mg	Placebo
Age < 65 years	N	603	584
	Participants with event, n (%)	4 (0.663)	28 (4.795)
	Participants with COVID-19 hospitalization	4 (0.663)	28 (4.795)
	Participants with death	0	3 (0.514)
	Average time at risk for event (Days)[a]	27.325	26.447
	Average study follow-up (Days)[b]	27.466	27.329
	Estimated proportion (95% CI), %	0.670 (0.252, 1.774)	4.861 (3.382, 6.963)
	Difference from Placebo (SE)	-4.191 (0.956)	
	95% CI of difference	-6.065, -2.317	
	p-value	<.0001	
Age ≥ 65 years	N	94	98
	Participants with event, n (%)	1 (1.064)	16 (16.327)
	Participants with COVID-19 hospitalization	1 (1.064)	16 (16.327)
	Participants with death	0	6 (6.122)
	Average time at risk for event (Days)[a]	27.053	24.643
	Average study follow-up (Days)[b]	27.330	26.745
	Estimated proportion (95% CI), %	1.064 (0.151, 7.312)	16.327 (10.339, 25.259)
	Difference from Placebo (SE)	-15.263 (3.881)	
	95% CI of difference	-22.869, -7.657	
	p-value	<.0001	

N = number of participants in the subgroup of the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
a. Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.
b. Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.
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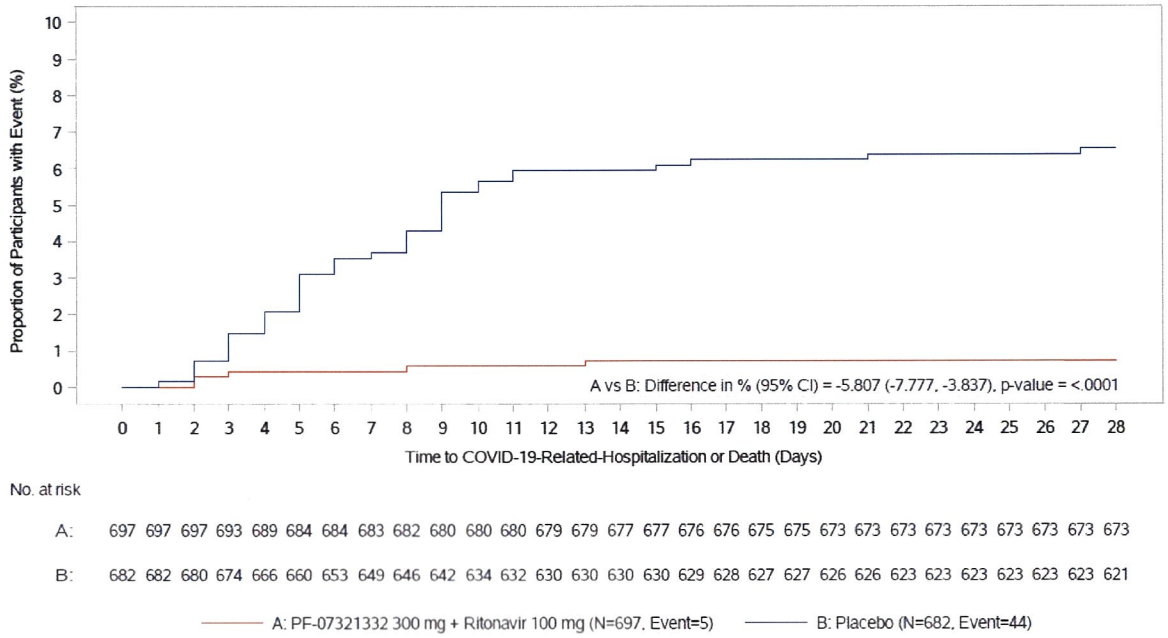
(Data cutoff date : 11DEC2021 Database snapshot date : [redacted] Output File:
./nda/C4671005_EUA/adtteh_s001_sub_age

5.6. Cumulative Proportions of Primary Events – mITT

As demonstrated in Figure 1, there is a strong separation of risk of primary events (COVID-19 related hospitalization or death from any cause) for PF-07321332/ritonavir compared to placebo from Day 3 of study treatment.

Figure 1. Time to COVID-19-Related-Hospitalization or Death From any Cause Through Day 28 - mITT Analysis Set



N = number of participants in the analysis set.
The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method. The difference of the proportions in the 2 treatment groups and its 95% confidence interval, and p-value based on Normal approximation of the data are presented.
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(Data cutoff date : 11DEC2021 Database snapshot date : [redacted]) Output File: ./nda/C4671005_EUA/adtteh_f001_mitt

6. SAFETY- SAFETY ANALYSIS SET

No safety concerns for PF-07321332/ritonavir were identified during the review of safety data through the PCD of this study (data cutoff date: 11 Dec 2021).

There was one participant that had a hospitalization on Day 3 with an outcome of death on Day 32. As the primary analysis evaluates hospitalization and death through Day 28, this death was outside the event window but was within the 'follow-up' window through the Day 34 visit. Therefore, this participant was included as a death in the safety analysis set giving a total of 13 deaths in the placebo group (Table 11).

PF-07321332/ritonavir was safe and well-tolerated. The proportion of participants with all-causality TEAEs was comparable between the PF 07321332/ritonavir group and the placebo group (22.6% and 23.9%, respectively).

Most of the all-causality TEAEs experienced by participants in both treatment groups were mild (Grade 1) to moderate (Grade 2) in severity (Table 12). The proportion of participants with all-causality SAEs was lower in the PF-07321332/ritonavir group (1.6%) compared with the placebo group (6.6%). Fewer participants discontinued study intervention due to an AE in the PF-07321332/ritonavir group compared with the placebo group (2.1% versus 4.2%), respectively; Table 11).

Table 11. Treatment-Emergent Adverse Events (All Causalities) - DAIDS Grade - Safety Analysis Set

Number (%) of Participants	PF-07321332 300 mg + Ritonavir 100 mg n (%)	Placebo n (%)
Participants evaluable for adverse events	1109	1115
Number of adverse events	476	525
Participants with adverse events	251 (22.6)	266 (23.9)
Participants with serious adverse events	18 (1.6)	74 (6.6)
Participants with Maximum Grade 3 or 4 adverse events	45 (4.1)	93 (8.3)
Participants with Maximum Grade 5 adverse events	0	13 (1.2)
Participants discontinued from study due to adverse events[a]	0	13 (1.2)
Participants discontinued study drug due to AE and continue study[b]	23 (2.1)	47 (4.2)
Participants with dose reduced or temporary discontinuation due to adverse events	4 (0.4)	4 (0.4)

Includes AEs that started on or prior to Day 34 visit.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study.
b. Participants who have an AE record that indicates that action taken with study treatment was drug withdrawn but AE did not cause the participants to be discontinued from study.
MedDRA v24.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](10:10) Source Data: adae Table Generation: [redacted](12:02)
(Data cutoff date : 11DEC2021 Database snapshot date : [redacted] Output File: ./nda/C4671005_EUA/adae_s020

The most frequently reported TEAEs in the PF-07321332/ritonavir group (≥1%) were Diarrhoea (3.1%), Nausea (1.4%), Vomiting (1.1%), Alanine aminotransferase increased (1.5%), Creatinine renal clearance decreased (1.4%), and Fibrin D-dimer increased (1.9%), Dysgeusia (5.6%), and Headache (1.4%). Of these, Diarrhoea, Vomiting, Dysgeusia, and Headache were reported at a higher frequency in the PF-07321332/ritonavir group compared with the placebo group (1.6%, 0.8%, 0.3%, and 1.3% in the placebo group, respectively; Appendix Table 12).

The reported safety data indicates that PF-07321332/ritonavir has a favorable safety profile.

7. CONCLUSION

Since the IA conducted at approximately 45% of participants met pre-specified efficacy criteria, the primary statistical interpretation for this study is from the IA. The results of the IA showed an 89.1%, 85.2%, and 83.6% relative reduction in primary endpoints events for the mITT, mITT1 and mITT2 analysis sets, respectively. The relative risk reduction was similar for the PCD analysis being 88.9%, 87.8% and 86.7%, respectively. Overall, the PCD analysis is supportive and confirms the results from the IA. Furthermore, the overall treatment effect was similar for the participants included in the IA and participants included post-IA.

This report presents the efficacy and safety data from the PCD analysis (data cutoff: 11 Dec 2021) of 2246 participants randomized through 06 November 2021 of which 1379 were included in the mITT analysis set.

The PCD analysis showed an 88.9% relative reduction in risk of COVID-19-related hospitalization or death from any cause compared to placebo in participants treated with PF-07321332/ritonavir within 3 days of symptom onset (primary endpoint); 0.72% (5/697) of participants who received PF-07321332/ritonavir were hospitalized or died through Day 28 following randomization, compared to 6.45% (44/682) of participants who received placebo; $p<0.0001$.

Similar reductions in COVID-19-related hospitalization or death were observed in participants treated within 5 days of symptom onset; 0.77% (8/1039) of participants who received PF-07321332/ritonavir were hospitalized or died through Day 28 following randomization, compared to 6.31% (66/1046) of participants who received placebo; $p<0.0001$.

In the overall study population through Day 28, 0 deaths were reported in participants who received PF-07321332/ritonavir as compared to 12 deaths in participants who received placebo. No safety concerns for PF-07321332/ritonavir were identified during the review of safety data.

8. APPENDIX

Table 12. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum DAIDS Grade (All Causalities) - Safety Analysis Set

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=1109)						Placebo (N=1115)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Participants with events	138 (12.4)	68 (6.1)	34 (3.1)	11 (1.0)	0	251 (22.6)	88 (7.9)	72 (6.5)	75 (6.7)	18 (1.6)	13 (1.2)	266 (23.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3 (0.3)	2 (0.2)	0	0	0	5 (0.5)	4 (0.4)	2 (0.2)	1 (0.1)	2 (0.2)	0	9 (0.8)
Anaemia	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	1 (0.1)	0	1 (0.1)
Leukocytosis	2 (0.2)	0	0	0	0	2 (0.2)	0	0	0	0	0	0
Leukopenia	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	2 (0.2)	0	0	0	0	2 (0.2)
Lymphadenopathy mediastinal	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Microcytic anaemia	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)
Neutropenia	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)	0	0	2 (0.2)
Thrombocytopenia	0	0	0	0	0	0	1 (0.1)	2 (0.2)	0	0	0	3 (0.3)
CARDIAC DISORDERS	0	1 (0.1)	1 (0.1)	0	0	2 (0.2)	5 (0.4)	0	1 (0.1)	0	0	6 (0.5)
Palpitations	0	1 (0.1)	1 (0.1)	0	0	2 (0.2)	2 (0.2)	0	0	0	0	2 (0.2)
Pericardial effusion	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Sinus bradycardia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Sinus tachycardia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Ventricular arrhythmia	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
EAR AND LABYRINTH DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.2)	0	0	0	0	2 (0.2)
Hyperacusis	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Vertigo	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
EYE DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Eye pain	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
GASTROINTESTINAL DISORDERS	53 (4.8)	13 (1.2)	0	0	0	66 (6.0)	35 (3.1)	16 (1.4)	2 (0.2)	0	0	53 (4.8)
Abdominal pain	2 (0.2)	0	0	0	0	2 (0.2)	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)
Abdominal pain lower	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Abdominal pain upper	3 (0.3)	0	0	0	0	3 (0.3)	2 (0.2)	0	0	0	0	2 (0.2)
Aphthous ulcer	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Colitis	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Constipation	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)
Diarrhoea	29 (2.6)	5 (0.5)	0	0	0	34 (3.1)	13 (1.2)	5 (0.4)	0	0	0	18 (1.6)
Dry mouth	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Dyspepsia	4 (0.4)	2 (0.2)	0	0	0	6 (0.5)	5 (0.4)	0	0	0	0	5 (0.4)
Faeces soft	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Gastritis	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Gastrooesophageal reflux disease	3 (0.3)	0	0	0	0	3 (0.3)	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)
Hiatus hernia	0	0	0	0	0	0	2 (0.2)	0	0	0	0	2 (0.2)
Hyperchlorhydria	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Large intestine polyp	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Nausea	12 (1.1)	4 (0.4)	0	0	0	16 (1.4)	10 (0.9)	7 (0.6)	2 (0.2)	0	0	19 (1.7)
Rectal haemorrhage	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Vomiting	8 (0.7)	4 (0.4)	0	0	0	12 (1.1)	6 (0.5)	3 (0.3)	0	0	0	9 (0.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	15 (1.4)	2 (0.2)	0	0	0	17 (1.5)	12 (1.1)	3 (0.3)	1 (0.1)	0	0	16 (1.4)
Asthenia	3 (0.3)	0	0	0	0	3 (0.3)	2 (0.2)	0	1 (0.1)	0	0	3 (0.3)
Catheter site pain	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Chest discomfort	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	0	0	0	0	0
Chest pain	2 (0.2)	0	0	0	0	2 (0.2)	1 (0.1)	0	0	0	0	1 (0.1)
Chills	4 (0.4)	1 (0.1)	0	0	0	5 (0.5)	0	0	0	0	0	0
Fatigue	2 (0.2)	0	0	0	0	2 (0.2)	5 (0.4)	0	0	0	0	5 (0.4)
Non-cardiac chest pain	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Oedema due to cardiac disease	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Pain	0	0	0	0	0	0	1 (0.1)	2 (0.2)	0	0	0	3 (0.3)
Peripheral swelling	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Pyrexia	8 (0.7)	0	0	0	0	8 (0.7)	5 (0.4)	2 (0.2)	0	0	0	7 (0.6)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=1109)						Placebo (N=1115)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
HEPATOBILIARY DISORDERS	1 (0.1)	2 (0.2)	1 (0.1)	0	0	4 (0.4)	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)
Cholestasis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hepatic function abnormal	0	1 (0.1)	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)
Hepatitis toxic	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Hyperbilirubinaemia	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Liver injury	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
IMMUNE SYSTEM DISORDERS	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	0	0	0	0	0
Mycotic allergy	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Seasonal allergy	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
INFECTIONS AND INFESTATIONS	6 (0.5)	8 (0.7)	7 (0.6)	2 (0.2)	0	23 (2.1)	7 (0.6)	15 (1.3)	36 (3.2)	7 (0.6)	11 (1.0)	76 (6.8)
Abscess	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Atypical pneumonia	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)
Bronchitis	0	1 (0.1)	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)
Bronchopulmonary aspergillosis	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
COVID-19	0	2 (0.2)	1 (0.1)	0	0	3 (0.3)	1 (0.1)	4 (0.4)	5 (0.4)	1 (0.1)	3 (0.3)	14 (1.3)
COVID-19 pneumonia	0	2 (0.2)	5 (0.5)	0	0	7 (0.6)	1 (0.1)	5 (0.4)	22 (2.0)	5 (0.4)	8 (0.7)	41 (3.7)
Gastroenteritis viral	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Influenza	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Mumps	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Nasopharyngitis	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	0	0	0	0	0
Oral candidiasis	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Oral herpes	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.2)	0	0	0	0	2 (0.2)
Oropharyngeal candidiasis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Pharyngitis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Pneumonia	1 (0.1)	0	1 (0.1)	0	0	2 (0.2)	0	5 (0.4)	9 (0.8)	1 (0.1)	0	15 (1.3)
Pneumonia viral	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Pyelonephritis chronic	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	0	0	0
Respiratory tract infection bacterial	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Respiratory tract infection viral	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	0	0	0	0	0
Sepsis	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	0	0	0
Staphylococcal bacteraemia	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Tonsillitis	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Upper respiratory tract infection	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Urinary tract infection	0	1 (0.1)	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Viral rhinitis	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Viral sepsis	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Vulvovaginal candidiasis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	0	0	0	1 (0.1)	2 (0.2)	0	1 (0.1)	0	4 (0.4)
Craniocerebral injury	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)
Eye injury	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)
Fall	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Hand fracture	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)	0	2 (0.2)
Meniscus injury	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Road traffic accident	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)
Wrist fracture	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)
INVESTIGATIONS	26 (2.3)	32 (2.9)	23 (2.1)	8 (0.7)	0	89 (8.0)	27 (2.4)	41 (3.7)	30 (2.7)	6 (0.5)	0	104 (9.3)
Activated partial thromboplastin time prolonged	5 (0.5)	3 (0.3)	1 (0.1)	0	0	9 (0.8)	10 (0.9)	0	2 (0.2)	0	0	12 (1.1)
Alanine aminotransferase increased	2 (0.2)	13 (1.2)	2 (0.2)	0	0	17 (1.5)	4 (0.4)	18 (1.6)	5 (0.4)	0	0	27 (2.4)
Aspartate aminotransferase increased	4 (0.4)	5 (0.5)	1 (0.1)	0	0	10 (0.9)	4 (0.4)	6 (0.5)	3 (0.3)	1 (0.1)	0	14 (1.3)
Blood albumin decreased	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Blood alkaline phosphatase increased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Blood bicarbonate decreased	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Blood calcium decreased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Blood creatine phosphokinase increased	1 (0.1)	0	0	1 (0.1)	0	2 (0.2)	3 (0.3)	0	2 (0.2)	0	0	5 (0.4)
Blood creatinine decreased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Blood creatinine increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Blood fibrinogen decreased	1 (0.1)	1 (0.1)	2 (0.2)	0	0	4 (0.4)	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)
Blood glucose decreased	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Blood glucose increased	0	1 (0.1)	0	1 (0.1)	0	2 (0.2)	0	3 (0.3)	3 (0.3)	1 (0.1)	0	7 (0.6)
Blood lactate dehydrogenase increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=1109)						Placebo (N=1115)					
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Blood potassium decreased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Blood potassium increased	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Blood pressure increased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Blood sodium decreased	0	0	0	0	0	0	2 (0.2)	0	0	0	0	2 (0.2)
Blood thyroid stimulating hormone decreased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Blood thyroid stimulating hormone increased	6 (0.5)	0	0	0	0	6 (0.5)	5 (0.4)	2 (0.2)	0	0	0	7 (0.6)
Blood urea increased	0	1 (0.1)	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Breath sounds abnormal	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
C-reactive protein	2 (0.2)	0	0	0	0	2 (0.2)	1 (0.1)	0	0	0	0	1 (0.1)
C-reactive protein increased	6 (0.5)	1 (0.1)	2 (0.2)	0	0	9 (0.8)	11 (1.0)	1 (0.1)	1 (0.1)	0	0	13 (1.2)
Creatinine renal clearance abnormal	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Creatinine renal clearance decreased	0	5 (0.5)	9 (0.8)	2 (0.2)	0	16 (1.4)	0	6 (0.5)	10 (0.9)	2 (0.2)	0	18 (1.6)
Creatinine renal clearance increased	0	0	1 (0.1)	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Differential white blood cell count abnormal	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Fibrin D dimer	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	0	0	0	0	0
Fibrin D dimer increased	11 (1.0)	6 (0.5)	4 (0.4)	0	0	21 (1.9)	14 (1.3)	11 (1.0)	4 (0.4)	2 (0.2)	0	31 (2.8)
Glomerular filtration rate abnormal	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Glomerular filtration rate decreased	0	0	3 (0.3)	0	0	3 (0.3)	0	0	1 (0.1)	1 (0.1)	0	2 (0.2)
Glycosylated haemoglobin increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Haematocrit increased	1 (0.1)	0	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)
Haemoglobin decreased	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	0	0	0
Haemoglobin increased	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Haptoglobin	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Haptoglobin increased	3 (0.3)	0	0	0	0	3 (0.3)	3 (0.3)	0	0	0	0	3 (0.3)
Hepatic enzyme abnormal	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hepatic enzyme increased	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	1 (0.1)	2 (0.2)	0	0	3 (0.3)
International normalised ratio abnormal	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	0	0	0
International normalised ratio increased	1 (0.1)	0	0	2 (0.2)	0	3 (0.3)	3 (0.3)	1 (0.1)	1 (0.1)	0	0	5 (0.4)
Liver function test increased	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Lymphocyte count decreased	0	0	0	0	0	0	1 (0.1)	1 (0.1)	1 (0.1)	0	0	3 (0.3)
Neutrophil count decreased	0	0	0	0	0	0	2 (0.2)	0	0	0	0	2 (0.2)
Neutrophil count increased	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	0	0	0	0	0
Oxygen saturation decreased	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Platelet count decreased	1 (0.1)	0	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)
Platelet count increased	2 (0.2)	0	0	0	0	2 (0.2)	0	1 (0.1)	0	0	0	1 (0.1)
Procalcitonin	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Procalcitonin increased	0	0	0	0	0	0	2 (0.2)	0	0	0	0	2 (0.2)
Prothrombin time prolonged	1 (0.1)	0	0	2 (0.2)	0	3 (0.3)	1 (0.1)	2 (0.2)	2 (0.2)	0	0	5 (0.4)
Red blood cell count increased	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Serum ferritin decreased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Serum ferritin increased	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	5 (0.4)	0	1 (0.1)	0	0	6 (0.5)
Thyroxine free increased	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Thyroxine increased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Transaminases increased	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Weight increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
White blood cell count decreased	0	2 (0.2)	0	0	0	2 (0.2)	0	2 (0.2)	1 (0.1)	0	0	3 (0.3)
White blood cell count increased	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	0	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	5 (0.5)	9 (0.8)	3 (0.3)	0	0	17 (1.5)	4 (0.4)	6 (0.5)	4 (0.4)	0	0	14 (1.3)
Decreased appetite	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Dehydration	0	2 (0.2)	0	0	0	2 (0.2)	0	1 (0.1)	0	0	0	1 (0.1)
Diabetes mellitus	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	0	0	0	0	0
Diabetes mellitus inadequate control	0	0	1 (0.1)	0	0	1 (0.1)	0	0	1 (0.1)	0	0	1 (0.1)
Glucose tolerance impaired	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Gout	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hyperglycaemia	0	1 (0.1)	1 (0.1)	0	0	2 (0.2)	1 (0.1)	1 (0.1)	2 (0.2)	0	0	4 (0.4)
Hyperkalaemia	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Hypertriglyceridaemia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hypervolaemia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hypokalaemia	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)
Hypomagnesaemia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hyponatraemia	0	2 (0.2)	0	0	0	2 (0.2)	0	0	0	0	0	0

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=1109)						Placebo (N=1115)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hypophosphataemia	0	0	1 (0.1)	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Impaired fasting glucose	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Lack of satiety	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Type 2 diabetes mellitus	0	1 (0.1)	0	0	0	1 (0.1)	1 (0.1)	2 (0.2)	0	0	0	3 (0.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	10 (0.9)	3 (0.3)	0	0	0	13 (1.2)	9 (0.8)	2 (0.2)	0	0	0	11 (1.0)
Arthralgia	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)	1 (0.1)	0	0	0	0	1 (0.1)
Back pain	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)	2 (0.2)	0	0	0	0	2 (0.2)
Intervertebral disc degeneration	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Intervertebral disc protrusion	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Muscle spasms	0	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)
Musculoskeletal stiffness	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Myalgia	6 (0.5)	1 (0.1)	0	0	0	7 (0.6)	2 (0.2)	0	0	0	0	2 (0.2)
Pain in extremity	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)
Spinal osteoarthritis	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Colon adenoma	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
NERVOUS SYSTEM DISORDERS	70 (6.3)	8 (0.7)	2 (0.2)	0	0	80 (7.2)	20 (1.8)	6 (0.5)	0	0	0	26 (2.3)
Amnesia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Anosmia	3 (0.3)	0	0	0	0	3 (0.3)	0	0	0	0	0	0
Brain stem stroke	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Dizziness	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)	5 (0.4)	1 (0.1)	0	0	0	6 (0.5)
Dysgeusia	58 (5.2)	3 (0.3)	1 (0.1)	0	0	62 (5.6)	3 (0.3)	0	0	0	0	3 (0.3)
Facial paralysis	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Headache	14 (1.3)	1 (0.1)	0	0	0	15 (1.4)	11 (1.0)	3 (0.3)	0	0	0	14 (1.3)
Hypersomnia	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Memory impairment	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Parosmia	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Restless legs syndrome	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Syncope	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Tremor	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Vascular dementia	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
PRODUCT ISSUES	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)	0	0	0	0	0	0
Product after taste	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)	0	0	0	0	0	0
PSYCHIATRIC DISORDERS	4 (0.4)	3 (0.3)	0	0	0	7 (0.6)	2 (0.2)	2 (0.2)	0	0	0	4 (0.4)
Anxiety	3 (0.3)	0	0	0	0	3 (0.3)	0	1 (0.1)	0	0	0	1 (0.1)
Confusional state	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Depression	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Insomnia	0	2 (0.2)	0	0	0	2 (0.2)	2 (0.2)	0	0	0	0	2 (0.2)
Stress	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
RENAL AND URINARY DISORDERS	0	0	0	1 (0.1)	0	1 (0.1)	0	1 (0.1)	1 (0.1)	1 (0.1)	0	3 (0.3)
Chronic kidney disease	0	0	0	1 (0.1)	0	1 (0.1)	0	0	1 (0.1)	0	0	1 (0.1)
Renal impairment	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)	0	2 (0.2)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)
Heavy menstrual bleeding	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Intermenstrual bleeding	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Vaginal haemorrhage	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	17 (1.5)	5 (0.5)	1 (0.1)	0	0	23 (2.1)	9 (0.8)	5 (0.4)	13 (1.2)	5 (0.4)	2 (0.2)	34 (3.0)
Acute respiratory failure	0	0	1 (0.1)	0	0	1 (0.1)	0	0	3 (0.3)	1 (0.1)	1 (0.1)	5 (0.4)
Allergic cough	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Asthma	1 (0.1)	0	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)
Cough	5 (0.5)	1 (0.1)	0	0	0	6 (0.5)	4 (0.4)	1 (0.1)	2 (0.2)	0	0	7 (0.6)
Dyspnoea	4 (0.4)	3 (0.3)	0	0	0	7 (0.6)	3 (0.3)	2 (0.2)	4 (0.4)	0	0	9 (0.8)
Epistaxis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Haemoptysis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hiccups	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hypoxia	0	0	0	0	0	0	1 (0.1)	2 (0.2)	1 (0.1)	0	0	4 (0.4)
Interstitial lung disease	1 (0.1)	0	0	0	0	1 (0.1)	0	0	2 (0.2)	0	0	2 (0.2)
Nasal congestion	2 (0.2)	2 (0.2)	0	0	0	4 (0.4)	0	0	0	0	0	0

Number of Participants Evaluable for AEs	PF-07321332 300 mg + Ritonavir 100 mg (N=1109)						Placebo (N=1115)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Oropharyngeal pain	4 (0.4)	0	0	0	0	4 (0.4)	0	0	0	0	0	0
Pneumonitis	0	0	0	0	0	0	0	0	2 (0.2)	2 (0.2)	1 (0.1)	5 (0.4)
Pulmonary embolism	0	0	0	0	0	0	0	0	0	2 (0.2)	0	2 (0.2)
Respiratory failure	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Rhinorrhoea	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	7 (0.6)	0	2 (0.2)	0	0	9 (0.8)	7 (0.6)	1 (0.1)	1 (0.1)	0	0	9 (0.8)
Acne	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Alopecia	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Erythema	0	0	0	0	0	0	4 (0.4)	0	0	0	0	4 (0.4)
Hyperhidrosis	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Hyperkeratosis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Pruritus	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Rash	2 (0.2)	0	0	0	0	2 (0.2)	2 (0.2)	0	1 (0.1)	0	0	3 (0.3)
Rash maculo-papular	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Skin exfoliation	2 (0.2)	0	0	0	0	2 (0.2)	0	0	0	0	0	0
Skin oedema	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Urticaria	0	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)
SOCIAL CIRCUMSTANCES	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Disease risk factor	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
VASCULAR DISORDERS	3 (0.3)	3 (0.3)	1 (0.1)	1 (0.1)	0	8 (0.7)	6 (0.5)	5 (0.4)	1 (0.1)	0	0	12 (1.1)
Deep vein thrombosis	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Embolism	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)	0	0	2 (0.2)
Hyperaemia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hypertension	4 (0.4)	2 (0.2)	1 (0.1)	0	0	7 (0.6)	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)
Hypertensive crisis	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	0	0	0
Hypotension	0	1 (0.1)	0	0	0	1 (0.1)	1 (0.1)	3 (0.3)	0	0	0	4 (0.4)
Orthostatic hypotension	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Thrombophlebitis	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Vein collapse	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)

Includes AEs that started on or prior to Day 34 visit.
MedDRA v24.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: [redacted](10:10) Source Data: adae Table Generation: [redacted](12:02)
(Data cutoff date : 11DEC2021 Database snapshot date : [redacted] Output File: ./nda/C4671005_EUA/adae_s062

PF-07321332

治験薬概要書

第[redacted]版　　20[redacted]年　[redacted]月　[redacted]日　発行

[redacted]

本治験薬概要書はファイザー社 20[redacted]年[redacted]月発行の Investigator's Brochure PF-07321332 Version [redacted]を翻訳したものである。

ファイザー株式会社

第[redacted]版　　20[redacted]年　[redacted]月　[redacted]日　発行

1. 目次

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[redacted]

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略号・用語の定義一覧

略号，用語	省略していない表現または定義
3CL	3C-like：3C 様
A-B	apical-to-basolateral：頂端膜側から基底膜側
ACE2	angiotensin converting enzyme 2：アンジオテンシン変換酵素 2
ADME	absorption, distribution, metabolism and excretion：吸収，分布，代謝および排泄
Ae_{tau}	amount excreted unchanged in urine during dosing interval (12h)：投与間隔（12 時間）の尿中未変化体排泄量
A/G	albumin/globulin：アルブミン/グロブリン
ALP	alkaline phosphatase：アルカリホスファターゼ
APTT	activated partial thromboplastin time：活性化部分トロンボプラスチン時間
ATP	adenosine triphosphate：アデノシン三リン酸
AUC	area under the plasma concentration-time curve：血漿中濃度 - 時間曲線下面積
AUC_{inf}	area under the plasma concentration-time curve from zero to infinity：0 時間から無限大時間までの血漿中濃度 - 時間曲線下面積
AUC_{last}	area under the plasma concentration-time curve from zero to time of last measurable concentration：0 時間から最終定量可能時間までの血漿中濃度 - 時間曲線下面積
AUC_t	area under the plasma concentration-time curve from zero to t hours：0 時間から t 時間までの血漿中濃度 - 時間曲線下面積
AUC_{tau}	area under the plasma concentration-time curve over dosing interval τ：投与間隔の血漿中濃度 - 時間曲線下面積
BCRP	breast cancer resistance protein
BID	twice daily：1 日 2 回（投与）
BSA	bovine serum albumin：ウシ血清アルブミン
Caco-2	human colonic adenocarcinoma cells：ヒト結腸癌由来細胞
C_{av}	average plasma concentration：平均血漿中濃度
Cb/Cp	concentration in blood/concentration in plasma：血液/血漿中濃度比
CC_{50}	concentration required for 50% cytotoxicity：50%細胞毒性濃度
$CCID_{50}$	cell culture infectious dose required for 50% cell death：50%細胞培養感染量
CI	confidence interval：信頼区間
CL_{bile}	biliary intrinsic clearance of drug from eg, plasma：血漿中（例）からの胆汁排泄固有クリアランス
CL_r	renal clearance：腎クリアランス
C_{max}	maximum plasma concentration：最高血漿中濃度
C_{min}	minimum plasma concentration：最低血漿中濃度
CoV	coronavirus：コロナウイルス
COVID-19	coronavirus disease 2019：新型コロナウイルス感染症
CPE	cytopathic effect：細胞変性効果
C_{trough}	plasma concentration pre-dose (during multiple dosing)：血漿中トラフ濃度
CV	coefficient of variation：変動係数
CYP	cytochrome P450
dNHBE	differentiated normal human bronchial epithelial cells：分化正常ヒト気道上皮細胞
+dP/dT	cardiac contractility：心収縮性
EC_{50}	concentration corresponding to 50% of the maximum effect：最大効果の 50%の効果を示す 濃度

略号・用語の定義一覧

略号，用語	省略していない表現または定義
EC_{90}	concentration corresponding to 90% of the maximum effect：最大効果の 90%の効果を示す 濃度
EMA	European Medicines Agency：欧州医薬品庁
F	bioavailability：バイオアベイラビリティ
FDA	Food and Drug Administration：米国食品医薬品局
FIH	first-in-human
f_m	fraction metabolized：当該酵素で代謝される割合
FOB	functional observational battery：機能観察総合評価法
FRET	fluorescence resonance energy transfer：蛍光共鳴エネルギー移動
fu	fraction unbound：非結合型分率
$f_{u,human}$	fraction unbound in human：ヒト非結合型分率
$f_{u,rat}$	fraction unbound in rat：ラット非結合型分率
GISAID	Global Initiative on Sharing All Influenza Data：インフルエンザウイルス遺伝子データベース
GLP	Good Laboratory Practice：医薬品の安全性に関する非臨床試験の実施の基準
HCoV	human coronavirus：ヒトコロナウイルス
HCV	hepatitis C virus：C 型肝炎ウイルス
HEK	human embryonic kidney：ヒト胎児由来腎臓
hERG	human ether-a-go-go-related gene：ヒト ether-a-go-go 関連遺伝子
HIV	human immunodeficiency virus：ヒト免疫不全ウイルス
IC_{50}	50% inhibitory concentration：50%阻害濃度
k_a	absorption rate constant：吸収速度定数
K_I	concentration at 50% kinact：50%不活性化濃度
K_i	inhibition constant：阻害定数
K_{iapp}	inhibitor concentration that supports half the maximal rate of inactivation：酵素と阻害薬の見かけの解離定数
k_{inact}	maximal rate of enzyme inactivation：最大酵素不活性化速度定数
$k_{p,uu}$	unbound partition coefficient：組織/血漿間非結合型薬物濃度比
LC/MS/MS	liquid chromatography/tandem mass spectrometry：液体クロマトグラフィー/タンデム質量分析
LV +dP/dt max	maximum positive slop of the left ventricular pressure wave：左心室内圧最大上昇速度
MAD	multiple ascending dose：用量漸増反復投与
MA-SARS-CoV-2	mouse-adapted severe acute respiratory syndrome coronavirus 2：マウス馴化重症急性呼吸器症候群コロナウイルス 2
MATE	multidrug and toxin extrusion
mBcrp	mouse breast cancer resistance protein：マウス Bcrp
MDCK	Madin-Darby canine kidney：Madin-Darby イヌ腎臓
MDR1	multidrug resistant protein 1
MedDRA	Medical Dictionary for Regulatory Activities：ICH 国際医薬用語集
MERS	Middle East respiratory syndrome-related coronavirus：中東呼吸器症候群関連コロナウイルス
MRC-5	Medical Research Council cell strain 5
mRNA	messenger ribonucleic acid：メッセンジャーRNA
MTBE	methyl tert-butyl ether

略号・用語の定義一覧

略号，用語	省略していない表現または定義
MTD	maximum tolerated dose：最大耐量
NA	not applicable：該当せず
ND	not determined：算出せず
NOAEL	no-observed-adverse-effect level：無毒性量
NOEL	no-observed-effect level：無作用量
NR	not reported：報告なし
NTCP	Na taurocholate cotransporting polypeptide
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OECD	Organisation for Economic Co-operation and Development：経済協力開発機構
P450	cytochrome P450：シトクロム P450
P_{app}	apparent permeability coefficient：見かけの透過係数
PD	pharmacodynamics：薬力学
PDE	phosphodiesterase：ホスホジエステラーゼ
P-gp	p-glycoprotein：P-糖タンパク質
PK	pharmacokinetics：薬物動態
PR	time from the beginning of the P wave to the beginning of the QRS complex in the electrocardiogram：心電図上の P 波の開始から QRS 群の開始までの時間
PT	prothrombin time：プロトロンビン時間
QRS	time from the beginning of the Q wave to the end of the S wave in the electrocardiogram：心電図上の Q 波の開始から S 波の終了までの時間
QT	time from the beginning of the QRS complex to the end of the T wave in the electrocardiogram：心電図上の QRS 群の開始から T 波の終了までの時間
QTc	QT interval corrected for heart rate：心拍数で補正した QT 間隔
RdRp	RNA dependant RNA polymerase：RNA 依存性 RNA ポリメラーゼ
RR	time from the peak of one QRS complex to the peak of the next：2 つの QRS 波の頂点の間の時間
RT-PCR	reverse transcription-polymerase chain reaction：逆転写 DNA ポリメラーゼ連鎖反応
RTV	ritonavir：リトナビル
SAD	single ascending dose：用量漸増単回投与
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1：重症急性呼吸器症候群コロナウイルス 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2：重症急性呼吸器症候群コロナウイルス 2
SUSAR	suspected unexpected serious adverse reaction：予期せぬ重篤な副作用の疑い
$t_{½}$	terminal phase half-life：終末相の消失半減期
TI	therapeutic index：治療指数
TK	toxicokinetics：トキシコキネティクス
TSH	thyroid stimulating hormone：甲状腺刺激ホルモン
UGT	uridine diphosphate-glucuronosyltransferase：UDP グルクロン酸転移酵素
ULN	upper limit of normal：基準値上限
Vero	monkey kidney cells：サル腎臓細胞
V_{ss}	volume of distribution at steady state：定常状態時の分布容積
WHO	World Health Organization：世界保健機関

2. 要約

2.1. 総合的概要および結論

COVID-19は，2019年12月に，SARS-CoV-2に起因する新たな死に至る可能性のある呼吸器感染症として特定された[1]。SARS-CoV-2はACE2受容体を介して細胞に感染し，主な感染部位は肺および気管支の上皮細胞である[2]。SARS-CoV-2の3CLプロテアーゼはウイルスに組み込まれている，ウイルス複製に不可欠な酵素である[3]。3CLプロテアーゼは，ウイルスのp1aおよびp1abポリタンパク質を複数の接合部位で消化し，RdRp，ヘリカーゼおよび3CLプロテアーゼ自体を含むウイルス複製および転写に重要な一連のタンパク質を生成する[4]。コロナウイルスの3CLプロテアーゼに近縁のヒト類似体は知られていない[5]。3CLプロテアーゼは，ウイルスの複製サイクルにとって必須の機能を持つ重要な酵素であり，また，近縁のヒト相同体が存在しないことから，抗ウイルス薬の標的として有望視されている[6]。

PF-07321332は，生化学的酵素アッセイでSARS-CoV-2 3CLプロテアーゼに対して有効であることが示された（K_i = 0.00311 μmol/L）経口投与可能な3CLプロテアーゼ阻害薬である。ヒトコロナウイルスの3CLプロテアーゼは構造的に類似しており，酵素の活性部位が高度に保存されていることから，その他のコロナウイルス（SARS-CoV-1，HCoV-229E，MERS，HCoV-OC43，HCoV-HKU1およびHCoV-NL63）の3CLプロテアーゼに対するPF-07321332の阻害能も確認され，広範な抗コロナウイルス活性スペクトルの可能性が示されている。PF-07321332はまた，コロナウイルスの3CLプロテアーゼに対して選択性を示し，一連のヒトプロテアーゼおよびHIVプロテアーゼに対してはほとんどまたは全く活性を示さなかった。

ACE2受容体を高発現させたVeroE6細胞を用いて，排出阻害薬の非存在下または存在下でSARS-CoV-2に対するPF-07321332の抗ウイルス活性を評価した。PF-07321332のEC_{50}値およびEC_{90}値は排出阻害薬の存在下でそれぞれ0.0748 μmol/Lおよび0.156 μmol/Lであり，測定可能な細胞毒性は認められなかった（in vitro細胞毒性のCC_{50}は100 μmol/L超）。この活性は生理学的に最も適切なdNHBE細胞を用いたSARS-CoV-2感染の抗ウイルスアッセイの結果（感染後3日のEC_{50}およびEC_{90}の幾何平均値はそれぞれ0.0618 μmol/Lおよび0.181 μmol/L）により確認された。また，HCoV-229Eに対するPF-07321332の抗ウイルス活性も確認されたことから，本薬が汎コロナウイルス治療薬となる可能性があることが示された。

副次的薬理試験では，広範囲の受容体，トランスポーター，イオンチャネルおよび酵素アッセイに対するPF-07321332のin vitro活性を評価した結果，機能的活性または酵素活性に対する有意な阻害（50%超）は認められなかった。

重要な臓器系（中枢神経系，心血管系および呼吸系）に対する薬力学的作用の有無を評価するため，安全性薬理試験を実施した。雄のWistar Hanラットに PF-07321332を1000 mg/kgの用量まで経口投与したとき，FOBパラメータへの影響は認められなかったが，自発運動量の定量的評価では，1000 mg/kg群で溶媒対照群と比較して，評価期間の最初の5分間に垂直運動の平均回数の減少，評価期間の最後の30分間に水平運動および垂直運動の平均回数の増加が認められた。これらの所見のヒトへの外挿性は不明である。1000 mg/kg群では，溶媒対照群と比較して，一過性の呼吸数および分時換気量の増加も認められた。カニクイザルにPF-07321332を150（75 BID）mg/kg/日の用量で投与したとき，収縮期，拡張期および平均血圧の上昇ならびに心拍数減少などの軽微かつ一過性の影響が認められ，これに伴いRR，PRおよびQT間隔が延長し

た。QTc 間隔には短縮が認められた。不整脈は認められなかった。PF-07321332 を 150（75 BID）mg/kg/日の用量で投与したとき，LV +dP/dt max の低下も認められた。測定値はすべて初回投与後 24 時間以内に溶媒対照を投与したときのレベルに回復し，また，hERG，モルモット摘出心臓またはラット摘出大動脈を用いたアッセイでは臨床的に意味のある PF-07321332 の影響は認められなかった。

安全性薬理パラメータへの影響は臨床試験でモニタリング可能であり，ラットを用いた GLP 適用 14 日間反復投与毒性試験およびサルを用いた GLP 適用 15 日間反復投与毒性試験では，関連する一般状態の変化または病理組織学的所見は認められなかった。サルを用いた GLP 適用 15 日間投与試験では心電図データも収集しており，この試験では，心電図パラメータ（心拍数ならびに RR，PR，QRS，QT および QTc 間隔）または心電図波形の変化は認められなかった。

細胞を用いない生化学的アッセイで，主要酸化代謝物である PF-07329268（M4）も SARS-CoV-2 の主要なプロテアーゼ（3CL プロテアーゼ）を阻害し，K_i 値は 0.00315 μmol/L であった。同じ VeroE6 細胞系において P-gp 排出阻害薬の存在下および非存在下で PF-07329268 の抗ウイルス効果が示され，EC_{50} 値はそれぞれ 0.525 μmol/L および 3.33 μmol/L 超であったことから，P-gp 阻害薬の存在下では PF-07321332 の効力が 7 分の 1 になることが示された。

PF-07321332 は，ラットでは CL は中程度，$t_{½}$ は 5 時間，バイオアベイラビリティは中程度から高度であり，サルでは，CL は中程度，$t_{½}$ は 1 時間未満と短く，バイオアベイラビリティは 10%未満であった。ラットおよびサルを用いた重要な反復投与毒性試験では，PF-07321332 の曝露量は用量の増加に伴って増加し，一貫した性差は認められなかった。PF-07321332 の受動的膜透過性は低く，ラット，サルおよびヒトの血漿タンパクとの結合率は中程度であり，赤血球と比較して血漿中に多く分布した。In vitro のトランスポーターアッセイでは，PF-07321332 は MDR1（P-gp）および BCRP の基質となるが，NTCP，OATP1B1，OATP1B3 または OATP2B1 の基質とはならないことが示された。

CYP3A を介した酸化が PF-07321332 の主要代謝経路であり，ヒト特有の代謝物は認められなかった。In vivo では，PF-07321332 の未変化体がラットおよびサルの血漿中に最も多く認められた薬物関連物質であり，M4（PF-07329268）がサルの血中の主要代謝物であった。ヒトでは，in vitro での PF-07321332 の酸化的代謝に寄与する主要な酵素は CYP3A4 であると予想され（f_m = 0.99），CYP3A5 の寄与は大きくないと予想された。PF-07321332 は主に CYP3A4 によって代謝されることを考慮すると，リトナビルなどの強い CYP3A4 阻害薬と併用投与すると血漿中の PF-07321332 濃度が上昇し，これにより治療効果が増強または延長される可能性がある。

FIH 試験データの予備的な母集団 PK モデリングに基づくと，約 300/100 mg の PF-07321332/リトナビルを 1 日 2 回投与したときの定常状態の C_{min} の中央値は，dNHBE 細胞アッセイで得られた EC_{90}（0.181 μmol/L）の 5 倍超になると考えられる。

薬物相互作用に関する FDA および EMA のガイダンスに従い，PF-07321332/リトナビルの臨床用量（300/100 mg BID）での基礎的な静的モデルに基づくと，PF-07321332 は，CYP2C8，CYP2C9 および CYP2C19 を誘導，CYP3A4 を可逆的および時間依存的に阻害ならびに MDR1（P-gp），MATE1，OCT1 および OATP1B1 を阻害する可能性がある。メカニズムに基づく静的モデルを用いて追加の評価を行ったところ，PF-07321332 が CYP2C8，CYP2C9 および CYP2C19 を誘導または MATE1，OCT1 および OATP1B1 を阻害するリスクは低いことがさらに示唆され

た。しかし，メカニズムに基づく静的モデルを用いた場合も，PF-07321332 が CYP3A4 を可逆的および時間依存的に阻害ならびに MDR1（P-gp）を阻害する可能性は残っている。リトナビルも MDR1（P-gp）および CYP3A の阻害薬であるため，PF-07321332/リトナビルを，MDR1 により排出されるおよび（または）主に CYP3A によって代謝される薬剤と併用すると，それらの薬剤の血漿中濃度が上昇する可能性がある。PF-07321332 による薬物相互作用がリトナビルによって引き起こされる薬物相互作用を超えるリスクは極めて低いと考えられる。

PF-07321332 の毒性は，ラットを用いた GLP 適用 14 日間反復投与毒性試験およびサルを用いた GLP 適用 15 日間反復投与毒性試験で評価した。いずれの試験においても毒性所見は認められず，NOAEL は投与した最高用量であった。サルでは，毒性学的意義の乏しい一般状態所見として，散発的な嘔吐の発現およびこれに伴うわずかな体重減少が認められた。モニタリング可能かつ可逆的な臨床病理所見として，関連する一般状態所見または病理組織学的所見を伴わない，低グレードの炎症（ラットおよびサル）または凝固経路の変化（ラットのみ）を示唆する可能性のある所見が認められた。サルで認められたその他の臨床病理所見は，嘔吐およびそれに続く脱水に起因するものであった可能性が高く，毒性学的意義の乏しい所見と判断された。ラットでは，1000 mg/kg/日群で，対照群と比較して心臓の絶対重量および相対重量の平均値が低値を示し（雌），肝臓の絶対重量および相対重量の平均値が高値を示した（雌雄）。心臓重量の減少は，関連する病理組織学的所見を伴うことなく，2 週間の休薬期間終了時までに完全に回復した。肝臓重量の増加に関連する所見として，肝臓および甲状腺に，ミクロソーム酵素の誘導に関連した適応性変化に一致する軽微から軽度の可逆的かつ毒性学的意義の乏しい病理組織学的所見が認められた[7]。

PF-07321332 は，in vitro 遺伝毒性試験で変異原性および染色体異常誘発性を示さず，ラットを用いた GLP 適用反復投与毒性試験の一部として実施した in vivo 小核試験でも陰性であった。

ラットを用いた 14 日間投与試験およびサルを用いた 15 日間投与試験における NOAEL は検討した PF-07321332 の最高用量であった。NOAEL における曝露量（C_{max} および AUC_{24}）は，ヒトに 300/100 mg の PF-07321332/リトナビルを 1 日 2 回投与したときに推定される PF-07321332 の非結合型 C_{max} および AUC_{24} と比較してそれぞれ，ラットでは 19 倍および 6.6 倍，サルでは 36 倍および 25 倍であった。

実施した非臨床試験により，臨床試験における最長 14 日間の PF-07321332 の経口投与が十分に支持される。

C4671001 臨床試験は，健康成人治験参加者を対象に PF-07321332 の安全性，忍容性および PK を評価する，進行中の SAD・MAD 試験であり，予備的な安全性および PK データにより，臨床試験における PF-07321332 の研究の継続が支持される。

3. 序文

非臨床試験計画の概要

PF-07321332 は，COVID-19 患者の治療のために経口薬として投与することを目的とした強力かつ選択的な SARS-CoV-2 プロテアーゼ（3CL プロテアーゼ）阻害薬である。

一連の in vitro 生化学的酵素アッセイおよびウイルス細胞培養アッセイで PF-07321332 の主要な薬力学的特性を評価し，SARS-CoV-2 に対する効力および特異性を検討した。X 線共結晶構造解析では PF-07321332 の SARS-CoV-2 3CL プロテアーゼへの結合が認められ，PF-07321332 とその標的が特異的に相互作用することが確認された。SARS-CoV-2 の 3CL プロテアーゼはシステインプロテアーゼであることから，哺乳類のシステインプロテアーゼ（カスパーゼ 2，カテプシン B およびカテプシン L），セリンプロテアーゼ（キモトリプシン，エラスターゼおよびトロンビン a）およびアスパルチルプロテアーゼ（カテプシン D および HIV-1）に対する PF-07321332 の活性も評価した。SARS-CoV-2 はβコロナウイルスであることから，他のβコロナウイルス［SARS-CoV-1（SARS），HCoV-HKU1（HKU1），HCoV-OC43（OC43），MERS など］の 3CL プロテアーゼに対する PF-07321332 の活性も測定した。さらに，αコロナウイルスに属する HCoV-229E（229E）および HCoV-NL63（NL63）を評価した。PF-07321332 およびその主要酸化代謝物（PF-07329268）の SARS-CoV-2 に対する抗ウイルス活性および細胞毒性は，hACE2 受容体を高発現させたアフリカミドリザル腎臓由来 VeroE6 細胞を用いて評価した。PF-07321332 および PF-07329268 は P-gp の基質となり，また，Vero 細胞は P-gp を高度に発現していることから，P-gp 排出阻害薬である CP-100356 の存在下で SARS-CoV-2 に対する抗ウイルス活性を評価した。また，生理学的に近いとされる dNHBE 細胞を用い，ウイルス産生の阻害（Vero76 細胞に対する力価で定量）に関して，SARS-CoV-2 に対する PF-07321332 の抗ウイルス活性を評価した。さらに，ヒト肺線維芽細胞（MRC-5 細胞）に対する CPE をモニタリングすることにより，HCoV-229E に対する PF-07321332 の抗ウイルス活性を評価した。

臨床開発計画

現在計画している PF-07321332 の臨床試験には，健康成人治験参加者を対象として PK および安全性を評価する進行中の SAD・MAD，第 1 相試験がある。

健康治験参加者を対象とした第 1 相試験で安全性および忍容性を評価したのち，以下の効能・効果に対する承認取得を支持するための主要な試験を開始する。

- コロナウイルス陽性確定の症候性の成人患者の治療
- コロナウイルス感染疑い（例：COVID-19 陽性患者への濃厚接触）に対する先行治療

Table 1.　承認取得を支持するためのPF-07321332/リトナビル臨床試験計画

試験ID	タイトル	主要評価項目	症例数
[redacted]	[redacted]	[redacted]	[redacted]
C4671002	重症化リスクの低い成人COVID-19外来患者を対象にPF-07321332/RTV経口投与の有効性，安全性およびPKを評価する，無作為化，二重盲検，プラセボ対照，第2/3相試験	すべての評価対象とするCOVID-19徴候または症状の持続的な緩和が得られるまでの期間（日数）（第28日まで）	N = 800
C4671005	重症化リスクの高い成人COVID-19外来患者を対象にPF-07321332/RTV経口投与の有効性，安全性およびPKを評価する，無作為化，二重盲検，プラセボ対照，第2/3相試験	COVID-19に関連した入院または全死亡が認められた治験参加者の割合（第28日まで）	N = 2200
C4671006	SARS-CoV-2感染者と接触した同居者を対象にSARS-CoV-2感染予防を目的として，PF-07321332経口投与の有効性，安全性，忍容性およびPKを評価する，無作為化，二重盲検，プラセボ対照，第2/3相試験	症候性かつRT-PCRによりSARS-CoV-2感染が確定された治験参加者の割合	N = 1600

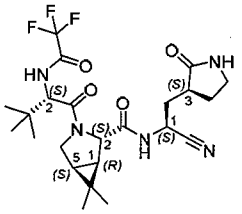
上記の第 2/3 相試験に加え，次の臨床薬理試験を計画している。

Table 2.　PF-07321332/リトナビル臨床薬理試験計画

試験ID	タイトル	主要評価項目	症例数
C4671010	中等度の肝機能障害を有する成人治験参加者および正常な肝機能を有する健康治験参加者を対象として，RTV（ブースター）併用時のPF-07321332のPK，安全性および忍容性を評価する，非無作為化，非盲検，第1相試験	AUC_{inf}およびC_{max}	健康治験参加者約8例および肝機能障害を有する治験参加者約8例
C4671011	腎機能障害を有する成人治験参加者および正常な腎機能を有する健康治験参加者を対象として，RTV（ブースター）併用時のPF-07321332のPK，安全性および忍容性を評価する，非無作為化，非盲検，第1相試験	AUC_{inf}およびC_{max}	治験参加者約32例
C4671014	健康治験参加者を対象として，RTV（ブースター）併用時にリファンピシンがPF-07321332のPKに及ぼす影響を評価する，非盲検，固定順序，2期，クロスオーバー，第1相試験	PF-07321332のC_{max}およびAUC_{tau}をリファンピシン併用（試験）時とリファンピシン非併用（対照）時で比較	健康治験参加者約12例
C4671015	健康治験参加者を対象として，イトラコナゾールがPF-07321332/RTVのPKに及ぼす影響を評価する，非盲検，固定順序，2期，クロスオーバー，第1相試験	PF-07321332のC_{max}およびAUC_{tau}をイトラコナゾール併用（試験）時とイトラコナゾール非併用（対照）時で比較	健康治験参加者約12例
C4671013	PF-07321332/RTVがCYP3A4の指標基質（ミダゾラム）のPKに及ぼす影響を評価する，非盲検，第1相試験	ミダゾラムのAUC_{inf}およびC_{max}	健康治験参加者約12例
C4671012	PF-07321332/RTVがP-gpの指標基質（ダビガトラン）のPKに及ぼす影響を評価する，非盲検，第1相試験	ダビガトランのAUC_{inf}およびC_{max}	健康治験参加者約12例

4. 物理的・化学的および薬剤学的性質ならびに製剤組成

PF-07321332 は経口製剤として投与される。

研究コード：	PF-07321332
分子量：	499.54 Daltons (Da.)
化学構造式：	 PF-07321332
IUPAC 名：	(1R,2S,5S)-N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-6,6-dimethyl-3- [3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide
分子式：	$C_{23}H_{32}F_3N_5O_4$
性状：	異物の無い白色～わずかに着色した粉末

製剤

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[a] 添加剤として結晶セルロース，乳糖水和物，クロスカルメロースナトリウム，軽質無水ケイ酸およびフマル酸ステアリルナトリウムを含む。

5. 非臨床試験

5.1. 非臨床薬理

5.1.1. 要約

COVID-19 パンデミックの原因病原体である SARS-CoV-2 は，コロナウイルス科に属するウイルスである[1]。SARS-CoV-2 は ACE2 受容体を介して細胞に感染し，主な感染部位は肺および気管支の上皮細胞である[1,2]。SARS-CoV-2 は，他のコロナウイルスと同様に，主要なプロテアーゼ（MPro）である 3CL プロテアーゼをコードしている[8,9]。SARS-CoV-2 に近縁の他のコロナウイルスおよびピコルナウイルス（ピコルナウイルス様スーパークラスター）を用いた突然変異誘発実験により，3CL プロテアーゼ（または対応するピコルナウイルス 3C 酵素）の活性がウイルス複製に不可欠であることが示されている[3]。3CL プロテアーゼは，ウイルスの p1a および p1ab ポリタンパク質を複数の接合部位で消化し，RdRp，ヘリカーゼおよび 3CL プロテアーゼ自体を含むウイルス複製および転写に重要な一連のタンパク質を生成する[4]。コロナウイルスの 3CL プロテアーゼに近縁のヒト類似体は知られていない[5]。3CL プロテアーゼは，ウイルスの複製にとって必須の機能を持つ重要な酵素であり，また，近縁のヒト相同体が存在しないことから，抗ウイルス薬の標的として有望視されている[6]。

PF-07321332 は強力かつ選択的な SARS-CoV-2 3CL プロテアーゼ阻害薬であり［K_i（幾何平均値）= 0.00311 μmol/L］，コロナウイルス科全体の 3CL プロテアーゼに対して広範な阻害活性を示すことから，抗ウイルス効果を発揮する可能性が示唆されている。酵素と阻害薬との結合相互作用に関与する重要なアミノ酸残基は，このウイルス科内で特によく保存されている[10]。

PF-07321332 の in vitro 抗ウイルス活性は，ACE2 受容体を高発現させた正常に分化したアフリカミドリザル腎由来 VeroE6，dNHBE 細胞および胎児肺組織由来のヒト二倍体細胞株（MRC-5 細胞）を用いて評価している。

サル腎由来 Vero 細胞を用いたアッセイで，PF-07321332 は SARS-CoV-2 によるウイルス誘導性 CPE を阻害し，Vero 細胞の P-gp トランスポーター活性を抑制したときの EC_{50} 値は 0.0748 μmol/L，EC_{90} 値は 0.156 μmol/L であった。生理学的に近いとされる dNHBE 細胞では，同じ薬物処置期間（3 日間）を用いたときの SARS-CoV-2 に対する PF-07321332 の抗ウイルス活性は，EC_{50} の幾何平均値が 0.0618 μmol/L，EC_{90} の幾何平均値が 0.181 μmol/L であった。総合すると，PF-07321332 の SARS-CoV-2 に対するこれらの in vitro 抗ウイルスデータにより，EC_{90} 値をヒトにおける非結合型最小有効濃度の推定値として用いることができ，用量選択の参考となる情報が得られた。

PF-07321332 の主要酸化代謝物である PF-07329268 も SARS-CoV-2 3CL プロテアーゼを強力に阻害した［K_i（幾何平均値）= 0.00315 μmol/L］。PF-07329268 は，サル腎由来 Vero 細胞を用いたアッセイで SARS-CoV-2 によるウイルス誘導性 CPE を阻害し，Vero 細胞の P-gp トランスポーター活性が十分に抑制されているときの EC_{50} 値は 0.525 μmol/L（PF-07321332 の効力の 7 分の 1）であった。さらに，PF-07321332 は，ヒト MRC-5 細胞において HCoV-229E によるウイルス誘導性 CPE も阻害し，EC_{50} 値は 0.190 μmol/L，EC_{90} 値は 0.620 μmol/L であり，検出可能な細胞毒性は認められなかった。これにより，PF-07321332 がαおよびβコロナウイルス属全体に対する抗ウイルス活性を有することが確認された。

5.1.2. 効力を裏付ける試験

PF-07321332（未変化体）およびPF-07329268（主要酸化代謝物）の非臨床薬理を評価するために実施した試験の概要を以下の項に示す。

5.1.2.1. In vitro での薬力学

5.1.2.1.1. 作用機序

PF-07321332 の作用機序は，さまざまな生化学的，結晶学的および細胞を用いた方法によって示されている。PF-07321332 は完全長 SARS-CoV-2 3CL プロテアーゼの酵素活性を阻害し，IC_{50} の幾何平均値は 0.0192 μmol/L，K_i の幾何平均値は 0.00311 μmol/L であった。PF-07321332 の主要酸化代謝物である PF-07329268 も SARS-CoV-2 3CL プロテアーゼを強力に阻害し，IC_{50} の幾何平均値は 0.0175 μmol/L，K_i の幾何平均値は 0.00315 μmol/L であった。また，PF-07321332 は，Table 3 に示すように SARS-CoV-1 3CL プロテアーゼも 0.0289 μmol/L の IC_{50} 値で阻害し（PF-07321332_[redacted]_090608 試験，PF-07321332_[redacted]_091415 試験），Table 4 に示すように HCoV-229E 3CL プロテアーゼも 0.113 μmol/L の IC_{50} 値で阻害した（PF-07321332_[redacted]_091415 試験）。

Table 3.　SARS 3CL プロテアーゼに対する PF-07321332 および PF-07329268 の生化学的活性

由来	化合物	IC_{50} μmol/L (CI)	K_{iapp} μmol/L (95% CI)
SARS-CoV-1[a]	PF-07321332	0.0289 (0.0244–0.0342)	ND
	PF-07329268	ND	ND
SARS-CoV-2[b]	PF-07321332	0.0192 (0.0135–0.0250)	0.00311 (0.00131–0.00491)
	PF-07329268	0.0175 (0.0153–0.0200)[c]	0.00315 (0.00236–0.00422)[c]

PF-07321332 は未変化体であり，その主要酸化代謝物は PF-07329268 である。
a. PF-07321332_[redacted]_091415 試験
b. PF-07321332_[redacted]_090608 試験
c. n = 2 の場合，CI の代わりに値の範囲を示す。

3CL プロテアーゼはすべてのコロナウイルスの複製サイクルにおいて不可欠な役割を担っていることから[3]，FRET によるプロテアーゼ活性アッセイを用いて，他のヒトコロナウイルスの 3CL プロテアーゼ（β コロナウイルス属の SARS-CoV-2，SARS-CoV-1，MERS，HCoV-OC43，HCoV-HKU1，α コロナウイルス属の HCoV-229E，HCoV-NL63 の 3CL プロテアーゼを含む）に対する PF-07321332 の活性を評価した。このデータにより，PF-07321332 が α および β コロナウイルス属に対し広範な阻害活性を有する強力な化合物であることが確認された（Table 4，PF-07321332_[redacted]_091415 試験）。

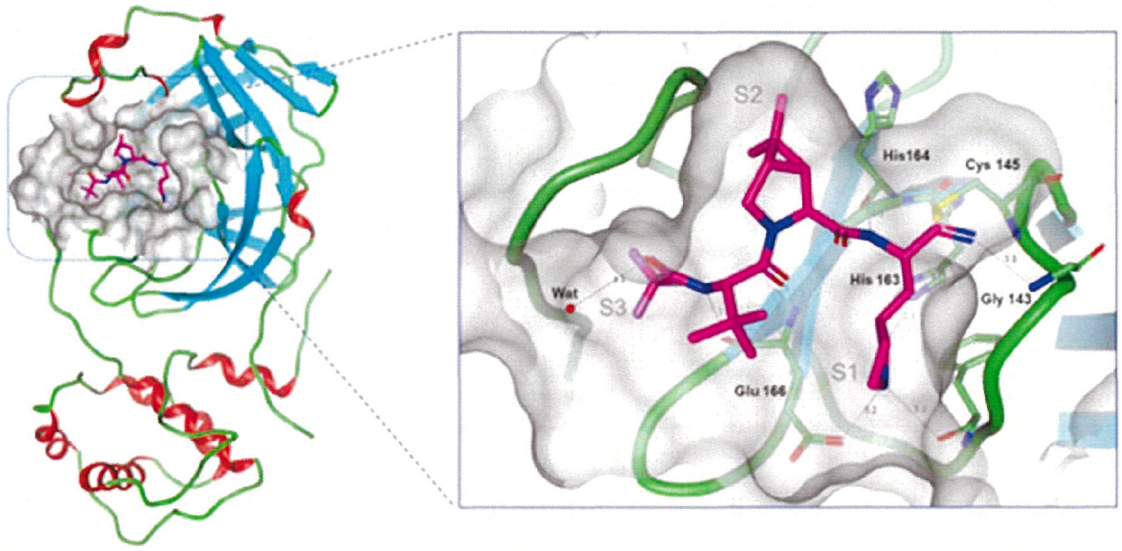
Table 4.　コロナウイルスの 3CL プロテアーゼに対する PF-07321332 の生化学的活性

ウイルス		IC_{50} μmol/L (95% CI)[a]
α-CoV[b]	NL63-CoV	0.479 (0. 242–0.949)
	229E-CoV-2	0.113 (0.0417–0.304)
	MERS-CoV	0.402 (0. 218–0.741)
β-CoV[b]	HKU1-CoV	0.0391 (0.0256–0.0598)
	OC43-CoV	0.0777 (0.0312–0.194)

a. PF-07321332 の力価は 3 回の測定から求めた。
b. PF-07321332_[redacted]_091415 試験

共結晶構造により示されるとおり，PF-07321332 は SARS-CoV-2 3CL プロテアーゼの活性部位に結合し，3CL プロテアーゼと PF-07321332 との間に共有結合性相互作用を形成する（C-S 結合長は 1.90 Å）（Figure 1，PF-07321332_[redacted]_054343 試験）。PF-07321332 の結合様式は基質結合を模倣していることから，酵素と基質の接触に類似する多くのタンパク質相互作用を形成する[10]。

Figure 1.　SARS-CoV-2 3CL プロテアーゼに結合する PF-07321332 の共結晶構造



PF-07321332 は SARS-CoV-2 3CL プロテアーゼの基質部位と結合し，触媒システイン残基（Cys 145）と共有結合性相互作用を形成する。さらに，PF-07321332 は活性部位の S1，S2 および S3 部位の結合ポケットを占有する。リガンドと水素結合相互作用（破線）を形成する残基を標識している（PF-07321332_[redacted]_054343 試験）。

PF-07321332 が SARS-CoV-2 3CL プロテアーゼと結合している共結晶構造から，3CL プロテアーゼの活性部位に，3CL プロテアーゼと PF-07321332 との間に共有結合または水素結合を形成する 6 個の接触残基が特定された（PF-07321332_[redacted]_054343 試験）。PF-07321332 結合部位から 4 Å 以内の残基を検討したところ，必須残基である可能性がある 7 個の残基がさらに特定された。これらの接触残基の保存度を，利用できる SARS-CoV-2 ゲノム（N = 263,975,

GISAID）と比較することにより評価した（PF-07321332_[redacted]_120222 試験）。この解析は現在流行しているものに関するデータを提供するが，これは有病率に基づいた解析ではなく，日常的に分離株のシークエンシングが行われている地域によりバイアスを受けていることに注意する必要がある。検討した 13 残基は高度に保存されており，突然変異の頻度は 0.017%未満であった。アミノ酸残基，突然変異およびその頻度の一覧を次の表に要約する（PF-07321332_[redacted]_120222 試験）。

Table 5.　SARS-CoV-2 3CL プロテアーゼの主な PF-07321332 接触残基における突然変異

残基の位置	参照アミノ酸	突然変異	例数	PF-07321332 との相互作用
41	His (H)	H41Y	1	触媒部位，疎水性接触
49	Met (M)	M49I, M49T, M49V	47	側鎖疎水性接触
54	Tyr (Y)	Y54*	1	直接接触なし
140	Phe (F)	なし	0	主鎖水素結合
143	Gly (G)	G143S, G143C	4	主鎖水素結合
145	Cys (C)	C145F, C145I, C145Y	3	触媒部位（共有結合）
163	His (H)	なし	0	側鎖水素結合
164	His (H)	H164N	1	主鎖水素結合
165	Met (M)	M165I, M165K	4	側鎖疎水性接触
166	Glu (E)	なし	0	主鎖および側鎖接触
167	Leu (L)	L167*, L167I	37	側鎖疎水性接触
168	Pro (P)	P168S, P168K	22	側鎖疎水性接触
189	Gln (Q)	Q189K	3	直接接触なし

* 指名終止コドン
PF-07321332_[redacted]_120222 試験

PF-07321332 が広範なコロナウイルス 3CL プロテアーゼに対して阻害作用を示す理由は，コロナウイルス科全体での 3CL プロテアーゼの類似性によって説明できる可能性が高い。全体としての配列の類似性はわずかであるが，3CL プロテアーゼの活性部位の残基はすべてのヒトコロナウイルスではるかに高度に保存されている（Table 5，PF-07321332_[redacted]_120222 試験）。

5.1.2.1.2. PF-07321332 の選択性

種々のヒト，哺乳類およびウイルスのプロテアーゼ（主にシステインプロテアーゼおよびセリンプロテアーゼ酵素）ならびに非近縁ウイルスである HIV-1 のプロテアーゼと比較して，SARS の 3CL プロテアーゼに対する PF-07321332 の選択性を検討した（PF-07321332_[redacted]_091415 試験）。これらの実験の結果により，PF-07321332 の SARS-CoV-2 3CL プロテアーゼに対する選択性（IC_{50} = 0.0192 μmol/L）は，ヒトキモトリプシンおよびその他のヒト細胞プロテアーゼならびに HIV プロテアーゼと比較すると 521 倍超であることが示された（Table 6）。

Table 6.　他の哺乳類およびウイルスのプロテアーゼに対する PF-07321332 の選択性

プロテアーゼ[a]	IC_{50} μmol/L
ヒトカテプシン B[b]	>100
ヒトカテプシン D	>100
ヒトカテプシン L[b]	>100
ヒトカスパーゼ 2	>100
ウシキモトリプシン	>100
ヒトキモトリプシン	>10
ヒトエラスターゼ	>100
ヒト免疫不全ウイルス-1	>100
ヒトトロンビン a	>100

a. PF-07321332_[redacted]_091415 試験
b. n = 3。試験した他のヒトおよびウイルスのプロテアーゼはすべて n = 2。

5.1.2.1.3. PF-07321332 の抗ウイルス活性

ACE2 受容体を高発現させた VeroE6 細胞を用いた CPE アッセイで，PF-07321332 およびその主要酸化代謝物（PF-07329268）の SARS-CoV-2 に対する抗ウイルス活性を評価した（PF-07321332_[redacted]_052017 試験）。また，非感染 VeroE6 細胞を用いて PF-07321332 の細胞毒性を評価した。PF-07321332 は P-gp の基質となることから，生理学的により適切な細胞となるよう，P-gp 阻害薬である CP-100356 を用いて VeroE6 細胞に高発現している P-gp を抑制した。したがって，被験物質の評価は，単独または CP-100356 の存在下で実施した。細胞の生存率は，CPE および細胞毒性のエンドポイントの双方に存在する ATP を定量することにより生存細胞数を測定する CellTiter-Glo（Promega 社）発光細胞生存率アッセイを用いてモニタリングした。

PF-07321332 は，CP-100356 の非存在下で SARS-CoV-2 CPE を阻害し，EC_{50} 値は 4.78 μmol/L，EC_{90} 値は 10.1 μmol/L であった。2.0 μmol/L の CP-100356 存在下でも，PF-07321332 は SARS-CoV-2 CPE を阻害し，EC_{50} 値は 0.0748 μmol/L，EC_{90} 値は 0.156 μmol/L であった。細胞毒性は，本薬単独（100 μmol/L の濃度まで）でも 2.0 μmol/L の CP-100356 存在下でも認められなかった。SARS-CoV-2 に対する TI は，2.0 μmol/L の CP-100356 存在下で 1380 超であった（Table 7）。

PF-07329268 は，CP-100356 の非存在下で SARS-CoV-2 CPE を阻害し，EC_{50} 値および EC_{90} 値はともに 3.33 μmol/L 超であった。2.0 μmol/L の CP-100356 存在下でも，PF-07329268 は SARS-CoV-2 CPE を阻害し，EC_{50} 値は 0.525 μmol/L（PF-07321332 の効力の 7 分の 1），EC_{90} 値は 1.09 μmol/L であった。細胞毒性は，PF-07329268 単独（最高 3.33 μmol/L の濃度まで）でも 2.0 μmol/L の CP-100356 存在下でも認められなかった（Table 7）。

Table 7.　VeroE6 細胞における SARS-CoV-2 に対する PF-07321332 および PF-07329268 の in vitro 抗ウイルス活性，細胞毒性および TI

PF-07321332				PF-07321332 + CP-100356[a]			
EC_{50} 幾何平均値[b] µmol/L (95% CI)	EC_{90} 幾何平均値[b] µmol/L (95% CI)	CC_{50} 幾何平均値[b] µmol/L (95% CI)	TI[c]	EC_{50} 幾何平均値[b] µmol/L (95% CI)	EC_{90} 幾何平均値[b] µmol/L (95% CI)	CC_{50} 幾何平均値[b] µmol/L (95% CI)	TI[c]
4.78 n = 18 (3.79–6.02)	10.1 n = 18 (8.17–12.5)	>100 n = 9 (ND)	>23.5	0.0748 n = 18 (0.0661–0.0847)	0.156 n = 18 (0.138–0.176)	>100 n = 9 (ND)	>1380
PF-07329268				**PF-07329268 + CP-100356[a]**			
EC_{50} 幾何平均値[b] µmol/L (95% CI)	EC_{90} 幾何平均値[b] µmol/L (95% CI)	CC_{50} 幾何平均値[b] µmol/L (95% CI)	TI[c]	EC_{50} 幾何平均値[b] µmol/L (95% CI)	EC_{90} 幾何平均値[b] µmol/L (95% CI)	CC_{50} 幾何平均値[b] µmol/L (95% CI)	TI[c]
>3.33 n = 2 (ND)	>3.33 n = 2 (ND)	>3.33 n = 2 (ND)	ND	0.525 n = 2 (0.487–0.567)[d]	1.09 n = 2 (1.01–1.10)[d]	>3.33 n = 2 (ND)	>6.36

PF-07321332_[redacted]_052017 試験

a. CP-100356は，2.0 µmol/Lの固定濃度で本試験に使用したP-gp阻害薬である。

b. EC_{50}曲線はHill係数が3を超えた場合は3でフィッティングし，最高用量で50%以上の効果を示す場合に定義された。30%を超える細胞毒性が検出された場合は，対応する濃度のデータをEC_{50}値の算出から除外した。

c. CC_{50}値をEC_{50}値で除して個々のTI値を算出し，累積TIの平均値を求めた。[redacted]作成データ（20[redacted]）。SARS-CoV-2（ワシントン）株

d. n = 2 の場合は，CI ではなく値の範囲を示す。>で表された CC_{50} の幾何平均値については CI を求めていない。

dNHBE 細胞の SARS-CoV-2 感染に対する PF-07321332 の抗ウイルス活性を評価した（PF-07321332_[redacted]_010204 試験）。ウイルス感染時に薬剤の投与を開始して感染後 3 日および 5 日に dNHBE 培養細胞から感染子孫ウイルスを収集し，CPE に基づいた Vero76 細胞の $CCID_{50}$ アッセイを用いて複製可能なウイルスを定量した。感染後 3 日および 5 日における PF-07321332 の抗ウイルス効果の EC_{50} の幾何平均値はそれぞれ 0.0618 µmol/L および 0.0326 µmol/L，EC_{90} の幾何平均値はそれぞれ 0.181 µmol/L および 0.0561 µmol/L であった。レムデシビルの EC_{50} 値は，同様のアッセイで報告されている値と一致していた（Table 8）。

Table 8.　感染後 3 日および 5 日の dNHBE 細胞における PF-07321332 およびレムデシビルの EC_{50} 値

	PF-07321332							
ウイルス	EC_{50} [a,b] (μmol/L)			幾何平均値	EC_{90} [a,b] (μmol/L)			幾何平均値
収集日	N = 1	N = 2	N = 3	(95% CI)	N = 1	N = 2	N = 3	(95% CI)
3	0.0757	0.0678	0.0461	0.0618 (0.0324–0.118)	0.157	0.141	0.2676	0.181 (0.0769–0.425)
5	0.0555	0.0231	0.0271	0.0326 (0.0102–0.104)	0.0924	0.0436	0.0440	0.0561 (0.0192–0.164)
	レムデシビル							
ウイルス	EC_{50} [a,b] (μmol/L)			幾何平均値	EC_{90} [a,b] (μmol/L)			幾何平均値
収集日	N = 1	N = 2	N = 3	(95% CI)	N = 1	N = 2	N = 3	(95% CI)
3	0.0019	0.0053	0.0026	0.00297 (0.000805–0.0109)	0.0043	0.0099	0.0322	0.0111 (0.000901–0.137)
5	0.0024	0.0069	0.0098	0.00545 (0.000885–0.0336)	0.008	0.0136	0.0349	0.0156 (0.0024–0.0993)

a. EC_{50} 曲線は Hill 係数が 3 を超えた場合は 3 でフィッティングし，最高用量で 50%以上の効果を示す場合に定義された。
b. [redacted]作成データ（20[redacted]）。SARS-CoV-2（USA_WA1/2020，ワシントン株）

MRC-5 細胞を用いた CPE アッセイで，HCoV-229E に対する PF-07321332 の抗ウイルス活性も評価した（Table 9，PF-07321332_[redacted]_092314 試験）。また，非感染 MRC-5 細胞を用いて PF-07321332 の細胞毒性も評価した。細胞の生存率は，CellTiter-Glo（Promega 社）を用いて，CPE および細胞毒性のエンドポイントの双方についてモニタリングした。MRC-5 細胞では，PF-07321332 はウイルスによる CPE を阻害し，EC_{50} 値は 0.190 μmol/L，EC_{90} 値は 0.620 μmol/L であった。また，MRC-5 細胞に対する細胞毒性の CC_{50} は 100 μmol/L 超であった。したがって，MRC-5 細胞における PF-07321332 の TI は 567 超であった。

Table 9.　MRC-5 細胞における HCoV-229E に対する PF-07321332 の抗ウイルス活性，細胞毒性および TI

宿主細胞	EC_{50} 幾何平均値 μmol/L (95% CI)	EC_{90} 幾何平均値 μmol/L (95% CI)	CC_{50} 幾何平均値 μmol/L (95% CI)[a]	TI[b]
MRC-5	0.190, n = 3 (0.0583–0.621)	0.620, n = 3 (0.166–2.32)	>100, n = 3 (ND)	>567

PF-07321332_[redacted]_092314試験
EC_{50} 曲線は Hill 係数が 3 を超えた場合は 3 でフィッティングし，最高用量で 50%以上の効果を示す場合に定義された。30%を超える細胞毒性が検出された場合は，対応する濃度のデータを EC_{50} 値の算出から除外した。
a. >で表された CC_{50} の幾何平均値については CI を求めていない。
b. CC_{50} 値を EC_{50} 値で除して各実験の TI を算出し，次いで TI の平均値を求めた。

5.1.2.2. In vivo での薬力学

5.1.2.2.1. 動物モデルでの有効性

In vivo での有効性を評価するための SARS-CoV-2 動物モデルを用いた PF-07321332 の試験は進行中であるが，3CL プロテアーゼ阻害薬クラスの PF-00835231 では，マウスの SARS-CoV-1 感染モデルにおいて proof of concept が示されている（PF-00835231_[redacted]_033653 試験）。これらの試験では PK-PD 相関が認められ，用量依存的な肺ウイルス力価の低下および疾患の軽減がみられた。また，投与開始を感染後 1 日まで遅延させた場合も肺ウイルス力価に対する顕著な効果が認められた。これらの結果により，このクラスの分子は感染動物の肺内のウイルス力価を低下および疾患を軽減させ得ることが示唆される。SARS-CoV-2 に対する PF-07321332 の活性を評価する第 2 のモデルでは，マウスに感染可能なマウス馴化株である MA-SARS-CoV-2 を使用している。2 つの異なる研究室で PF-07321332 の活性が評価されており，いずれも同様の結果が得られている。

最初の試験（PF-07321332_[redacted]_105036 試験）の予備的な結果から，PF-07321332 投与による肺ウイルス量の用量依存的な減少が示され，体重減少の抑制のほか，肺障害が低減した。本試験では，マウス馴化株である MA-SARS-CoV-2 MA10 を感染させた BALB/c マウスを用いて，リトナビル併用時および非併用時の PF-07321332 の抗ウイルス活性を評価した。マウスに 1×10^5 $CCID_{50}$ の MA-SARS-CoV-2 を経鼻接種した。感染後 4 時間から感染後 4 日まで，PF-07321332 を 1 日 2 回経口投与した。感染に伴う体重減少を測定するため，試験 0 日から連日マウスの体重を測定した。PF-07321332 がウイルス増殖を in vivo で阻害するか否かを評価するため，感染後 4 日にマウスを安楽殺し，$CCID_{50}$ アッセイにより肺ウイルス力価を評価した。

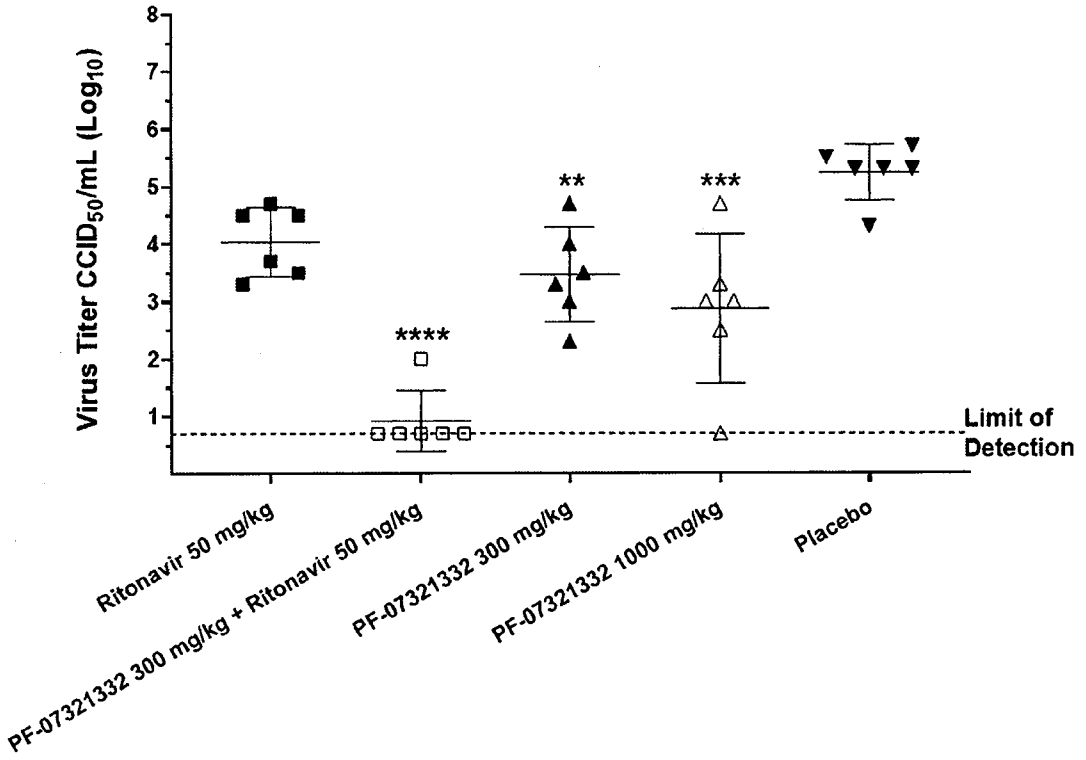
無処置群のマウスでは，感染後 4 日の肺ウイルス力価は約 10^5 $CCID_{50}$/mL であった。300 mg/kg または 1000 mg/kg の PF-07321332 を 1 日 2 回経口投与した感染マウスの肺ウイルス力価の平均値は，無処置の感染マウス（対照）よりも統計的に有意に低下した（Figure 2）。300 mg/kg の PF-07321332 および 50 mg/kg のリトナビルを 1 日 2 回併用投与したマウスでは，肺ウイルス力価が検出限界に近い値まで統計的に有意に低下した（Figure 2）。同様に，PF-07321332 を投与したマウスでは，無処置の感染マウスと比較して体重減少の抑制が認められた（データは示していない）。50 mg/kg のリトナビルを投与したマウスでは，無処置の感染マウスと比較して肺ウイルス力価が約 10 分の 1 に低下した（PF07321332_[redacted]_105036 試験）。しかし，in vitro では，リトナビルは 3 μmol/L の濃度まで SARS-CoV-2 に対する抗ウイルス活性を示さなかった。本試験では，肺の病理組織学的検査の結果はまだ得られていない。

本モデルを用いて，曝露量と PD の関係を評価した。初代培養 dNHBE を用いた分析法により，PF-07321332 の抗ウイルス活性を in vitro で評価したところ，EC_{90} 値は 90.4 ng/mL（181 nmol/L，$f_{u,human}$ = 0.310 に相当）であった（PF-07321332_[redacted]_010204 試験，過去に提出した試験結果）。

感染マウスへの投与と並行して，非感染マウスを用いて PF-07321332 の曝露量を評価した。サテライト群のマウスに 300 mg/kg および 1000 mg/kg の PF-07321332 を 1 日 2 回投与したところ，非結合型薬物の血漿中曝露量はそれぞれ EC_{90} 値の約 0.6 倍および約 4 倍を上回る値で持続した。リトナビルと併用して 300 mg/kg の PF-07321332 を 1 日 2 回投与したところ，PF-

07321332 の非結合型 C_{min} は EC_{90} 値の約 10 倍に増加した（PF07321332_[redacted]_105036 試験）。

Figure 2.　SARS-CoV-2 のマウス馴化株（MA10）を感染させた BALB/c マウスでのリトナビル併用時および非併用時の PF-07321332 の評価



MA-SARS-CoV-2 を感染させたマウスに PF-07321332 を投与したときの肺ウイルス力価：マウス（各群 6 例）に 1×10^5 $CCID_{50}$ の MA-SARS-CoV-2 を経鼻接種した。その後，各群のマウスに 300 mg/kg PF-07321332（▲），1000 mg/kg PF-07321332（Δ），50 mg/kg リトナビル（■），300 mg/kg PF-07321332 + 50 mg/kg リトナビル（□）またはプラセボ（▼）を 1 日 2 回経口投与した。試験 4 日にマウスを安楽殺し，肺ウイルス力価を評価して結果を $CCID_{50}$/mL（Log_{10}）で表示した。実薬群の結果をプラセボ群と統計的に比較した際に，**は $p < 0.01$，***は $p < 0.001$，****は $p < 0.0001$ であることを示す。

5.1.3. 副次的薬理試験

安全性上の懸念が示唆されている標的（G タンパク質共役型受容体，イオンチャネル，トランスポーターおよび酵素など）を含む広範な標的プロファイリングパネルを用い，PF-07321332 の in vitro オフターゲット薬理作用を 100 μmol/L の濃度で評価した（100054569 試験）。この結果，50%を超える活性は認められなかった。この評価に用いた PF-07321332 の濃度は，ヒトに PF-07321332/リトナビルの予定治療用量（300/100 mg BID）を投与したときの推定非結合型 C_{max} の 39 倍であった。

Nav1.5（ピーク）ナトリウムチャネルおよびCav1.2カルシウムチャネルの電流に対するPF-07321332の阻害のIC_{50}値はいずれも，検討した最高用量である300 µmol/Lを上回り（[redacted]LJ073試験），この用量における曝露量はヒトに予定治療用量を投与したときの推定非結合型C_{max}の117倍超であった。

11種類のPDEサブタイプ（1～11）に対するPF-07321332の阻害活性も評価したところ，IC_{50}値は，検討したすべてのPDEサブタイプにおいて200 µmol/L（検討した最高用量）を上回り（[redacted]LJ074試験），この用量における曝露量はヒトに予定治療用量を投与したときの推定非結合型C_{max}の78倍超であった。

これらの結果により，PF-07321332が臨床的に意味のある曝露量において副次的（オフターゲット）薬理作用を示す可能性は極めて低いことが示された。

5.1.4. 安全性薬理試験

Table 10に示す一連の安全性薬理試験でPF-07321332を評価した。In vivo試験での投与経路には，予定臨床投与経路である経口投与を選択した。In vivo試験では，曝露量を増加させるためPF-07321332を1：1のMTBE溶媒和物として動物に投与し，別に，MTBEを投与する対照群も設定した。

Table 10.　PF-07321332の安全性薬理試験の概要

試験	試験番号（ファイザー社試験番号）	濃度または用量	GLP
In vitroスクリーニング試験			
hERG阻害能評価	[redacted]LJ091	30 µmol/L, 300 µmol/L	適用
モルモット摘出ランゲンドルフ灌流心モデルにおける心機能および心伝導に対するPF-07321332の効果	[redacted]LJ075	0.03 µmol/L–100 µmol/L	非適用
ラット摘出大動脈に対するPF-07321332の効果の評価	[redacted]LJ076	0.000002 µmol/L–100 µmol/L	非適用
神経機能 – ラット[a]			
FOB 体温 自発運動	8455743 ([redacted]GR274)	0, 0 (150 MTBE)[b], 60, 1000 mg/kg	適用
肺機能 – ラット[a]			
一回換気量，呼吸数および分時換気量	8455743 ([redacted]GR274)	0, 0 (150 MTBE)[b], 60, 1000 mg/kg	適用
心血管 – 無麻酔サル[c]			
血圧，心拍数，心電図および左室パラメータ	[redacted]GR275	0, 0[22.5 (11.25 BID) MTBE][b], 40 (20 BID), 150 (75 BID) mg/kg	適用

すべてのGLP適用試験はデータ相互受け入れ制度に参加するOECD加盟国で実施した。
a. 単回投与
b. 対照群のMTBE量は，高用量群のMTBE量（15% MTBE）に基づいた。これは，8455743試験では150 mg/kgのMTBE，[redacted]GR275試験では22.5（11.25 BID）mg/kg/日のMTBEに相当した。
c. 約6時間間隔で1日2回投与した。

安全性薬理試験での所見は，高用量群のラットで認められた自発運動量の変化ならびに一過性の呼吸数および分時換気量の増加，高用量群のカニクイザルで認められた軽微かつ一過性の血行動態の変化（血圧上昇および心拍数減少）であった。安全性薬理パラメータへの影響は臨床試験ではモニタリング可能であり，ラットまたはサルを用いたGLP適用14日間または15日間反復投与毒性試験では，関連する一般状態の変化および該当する臓器の病理組織学的所見は認められていない（5.3項，[redacted]GR276試験および[redacted]GR289試験）。サルを用いたGLP適用15日間投与試験では心電図データも収集しており，この試験では，心電図パラメータ（心拍数ならびにRR，PR，QRS，QTおよびQTc間隔）または心電図波形の変化は認められていない。

神経系への影響を評価するため，雄ラットに溶媒または60 mg/kgもしくは1000 mg/kgのPF-07321332を単回経口投与し，ラットの神経機能（投与1時間後に実施したFOBおよびその後に実施した60分間の自発運動量の定量的評価を含む）を評価した（[redacted]GR274試験）。FOBパラメータへの影響は，1000 mg/kgの用量まで認められなかった。自発運動量の定量的評価では，PF-07321332の1000 mg/kg群で，溶媒対照群と比較して，評価期間の最初の5分間に垂直運動の平均回数の減少（-36%），評価期間の最後の30分間に水平運動（+298%）および垂直運動（+838%）の平均回数の増加が認められた。ラットを用いた14日間投与毒性試験（[redacted]GR276試験）の試験1日における雄の非結合型C_{max}に基づくと，1000 mg/kgおよび60 mg/kg（NOEL）を投与したときの曝露量は，ヒトにPF-07321332/リトナビルの予定治療用量（300/100 mg BID）を投与したときに推定されるPF-07321332の非結合型C_{max}のそれぞれ27倍および4.1倍であった。

呼吸系への影響を評価するため，雄ラットに溶媒または60 mg/kgもしくは1000 mg/kgのPF-07321332を単回経口投与し，その後6時間，連続的にモニタリングした。この結果，PF-07321332の1000 mg/kg群で，投与後40分から160分の間に溶媒対照群と比較して呼吸数（最大で+44%）および分時換気量（最大で+38%）が増加した（[redacted]GR274試験）。ラットを用いた14日間投与毒性試験（[redacted]GR276試験）の試験1日における雄のC_{max}に基づくと，1000 mg/kgおよび60 mg/kg（NOEL）を投与したときの曝露量は，ヒトに予定治療用量を投与したときに推定されるPF-07321332の非結合型C_{max}のそれぞれ27倍および4.1倍であった。

心血管系への影響を評価するため，一連のin vitro，ex vivoおよびin vivo試験を実施した。hERG阻害試験（[redacted]LJ091試験）では，PF-07321332を300 μmol/Lの濃度で投与したとき，溶媒対照群（2.0 ± 0.4%）と比較してわずかではあるが統計的に有意（$p < 0.05$）なhERG阻害（5.9 ± 0.3%）が認められたが，30 μmol/Lを投与したときのhERG阻害（2.5 ± 0.4%）は統計的に有意ではなかった。hERGカリウム電流に対するPF-07321332の阻害作用のIC_{50}値は算出しなかったが，300 μmol/L（ヒトに予定治療用量を投与したときに推定されるPF-07321332の非結合型C_{max}の117倍超）を上回ると推定された。モルモットから摘出したランゲンドルフ灌流心モデル（[redacted]LJ075試験）では，PF-07321332は，検討したいずれの濃度［最高100 μmol/L（ヒトに予定治療用量を投与したときの推定非結合型C_{max}の39倍）］においても心機能（+dP/dT，左室圧および冠動脈潅流圧）または心伝導（PR，QRSおよびQT間隔）に統計的に有意な変化を及ぼさなかった。ラットから摘出した大動脈組織の標本（[redacted]LJ076試験）についてティッシュバスを用いた評価では，PF-07321332により，対照と比較して統計的に有意かつ濃度依存的な血管緊張低下が認められた。IC_{50}値は50.3 μmol/Lであり，この濃度は，ヒトにPF-07321332/リトナビルの予定治療用量（300/100 mg BID）を投与したときに推定されるPF-07321332の非結合型C_{max}の20倍であった。

心血管系安全性薬理試験として，独立した GLP 適用試験も実施した。この試験では，テレメトリーを装着した雄の無麻酔サルに PF-07321332 を 0，40（20 BID）または 150（75 BID）mg/kg/日の用量でクロスオーバーデザインにより投与し，初回投与後約 24 時間にわたって各動物から心血管データを得た。PF-07321332 を 40（20 BID）mg/kg/日の用量で経口投与したとき，測定したいずれのパラメータにも変化は認められなかった。PF-07321332 を 150（75 BID）mg/kg/日の用量で投与したときには，心拍数の-14 bpm までの減少が初回投与後 0.75～16.00 時間に認められ，収縮期，拡張期および平均血圧の上昇（最大で+5 mmHg）が初回投与後 0.75～5.5 時間（拡張期血圧のみ）および初回投与後 7.25～9.00 時間に認められた。初回投与後 0.75～16.00 時間に RR 間隔の延長（最大で+52 msec）が認められ，同時点で心拍数減少がみられたことと一致していた。初回投与後 0.75～9.00 時間に PR 間隔（+3 msec）および QT 間隔（最大で+13 msec）の延長が認められ，これは，心拍数の減少に伴う二次的な変化と考えられた。QTc 間隔には，初回投与後 7.25～16.00 時間に短縮（-7 msec まで短縮）が認められた。PF-07321332 を 150（75 BID）mg/kg/日の用量で投与したとき，初回投与後 0.75～9.00 時間に LV +dP/dt max も低下（-364 mmHg/sec まで低下）した。測定値はすべて，初回投与後 24 時間以内に溶媒対照を投与したときのレベルに回復した（[redacted]GR275 試験）。この試験で得られた PK データ（150 mg/kg 投与時）およびサルを用いた 15 日間投与毒性試験の試験 1 日における雄のデータ（40 mg/kg 投与時，[redacted]GR289 試験）に基づくと，150 mg/kg および 40 mg/kg（NOEL）を投与したときの曝露量は，ヒトに PF-07321332/リトナビルの予定治療用量（300/100 mg BID）を投与したときに推定される PF-07321332 の非結合型 C_{max} のそれぞれ 5.0 倍および 0.58 倍であった。

5.1.5. 薬力学的薬物相互作用試験

In vivo での PF-07321332 の薬力学的薬物相互作用試験は実施していない。In vitro での PF-07321332 の抗ウイルス活性については 5.1.1 項および 5.1.2 項に示す。

5.2. 動物における薬物動態

5.2.1. 分析法

ラットおよびサルを用いたGLP適用毒性試験における血漿中PF-07321332濃度を定量するために用いるLC/MS/MS法（濃度範囲10～50000 ng/mL）をバリデートした（PF-07321332_[redacted]_014313試験およびPF-07321332_[redacted]_015142試験）。

5.2.2. 吸収

5.2.2.1. In vitroでの吸収

MDCK低排出細胞株を用いた予備的な評価で，PF-07321332のA-B P_{app}は0.78×10^{-6} cm/secであったことから，受動的膜透過性は低いことが示された[11]。また，予備試験では，MDR1遺伝子（MDR1-MDCK）およびmBcrp遺伝子（mBcrp-MDCK）をトランスフェクトしたMDCK細胞株でPF-07321332の膜透過性に対称性が認められたことから，PF-07321332はヒトMDR1およびmBcrp排出トランスポーターの基質となることも示された。

Caco-2細胞におけるPF-07321332のA-B P_{app}（平均値）は，測定した濃度範囲（0.03～81 μmol/L）全体にわたって$0.66 \sim 1.2 \times 10^{-6}$ cm/secであり，MDCK低排出細胞で受動的膜透過性が低かったことと一致していた。排出トランスポーター阻害薬のカクテルで前処理したCaco-2細胞では0.32 μmol/Lの濃度におけるPF-07321332のA-B P_{app}は4.05×10^{-6} cm/secであったことから，PF-07321332は能動輸送を受けることが示された（PF-07321332_[redacted]_095737試験）。

5.2.2.2. 単回投与時の薬物動態

ラット（PF-07321332_[redacted]_103131試験）およびサル（PF-07321332_[redacted]_111728試験）にPF-07321332（MTBEとの溶媒和結晶）を単回静脈内または経口投与した。また，ラットにはPF-07321332の無水結晶も経口投与した。両動物種ともに，静脈内投与後の血漿CLは中程度，V_{ss}は中程度から低値であり，$t_{½}$はラットで5時間，サルで1時間未満であった（Table 11）。経口投与時の全体的なバイオアベイラビリティは，ラットでは中程度から高値であったが（29%～100%超），サルでは低値を示した（10%未満）。

Table 11.　ラットおよびサルにおける PF-07321332 の PK

動物種	投与量[a] (mg/kg)	投与経路	N	CL (mL/min/kg)	V_{ss} (L/kg)	$t_{½}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{inf} (ng•h/mL)	AUC_{last} (ng•h/mL)	%F
ラット	1	IV	2	27.2	1.8	5.1	–	–	632	630	–
	10	PO	2	–	–	4.0	1.5	1290	3190	3170	50
	10[b]	PO	3	–	–	2.8	0.25	1450	2170	2160	34
	100	PO	2	–	–	14[c]	0.75	29100	58600[c]	68500	>100
	100[b]	PO	3	–	–	5.7	1.4	5300	18100	18000	29
	300	PO	2	–	–	NR[d]	0.38	48900	153000	153000	81
	1000	PO	2	–	–	8.7	1.0	88300	750000	749000	>100
サル	1	IV	2	17.1	0.33	0.8	–	–	977	976	–
	10	PO	2	–	–	NR[d]	0.25	1450	NR[e]	831	8.5

a. 特記しない限り，PF-07321332 の処方 2（MTBE との溶媒和結晶）を投与した。
b. PF-07321332 の処方 1（無水結晶）を投与した。
c. N = 1
d. 識別可能な消失相が得られなかったため，パラメータは報告しなかった。
e. 最後の測定時点で濃度が上昇したため，パラメータは報告しなかった。

5.2.2.3. 反復投与時の薬物動態（トキシコキネティクス）

ラットおよびサルを用いた重要な毒性試験で，14 日間または 15 日間の投与後に PF-07321332 の TK データを評価した（Table 12）。

両動物種ともに，PF-07321332 の全身曝露量に一貫した性差は認められず，曝露量は用量の増加に伴って増加した。ラットに反復投与したとき，試験 14 日における PF-07321332 の AUC_{24} はすべての用量群で試験 1 日と比較して減少し，累積係数は 0.18～0.74 であった。サルでは，PF-07321332 の AUC_{24} の減少は主に中用量群の雌でみられ（累積係数は 0.56），高用量群では，試験 14 日における PF-07321332 の AUC_{24} は試験 1 日と比較して増加した（累積係数は最大で 1.7）。

Table 12.　PF-07321332（MTBE 溶媒和物）を経口投与したときの PF-07321332 の平均（雌雄）TK データの要約

動物種 試験番号	試験日	投与量 (mg/kg/日)	T_{max} (h)	C_{max} (μg/mL) 総濃度	 非結合型濃度 [a]	AUC_{24} (μg•h/mL) 総濃度	 非結合型濃度 [a]
ラット [b]	1	60	0.50	12.9	6.18	27.3	13.1
[redacted]GR276		200	0.50	37.0	17.7	291	139
		1000	2.0	62.1	29.7	796	381
	14	60	0.50	13.3	6.37	17.2	8.24
		200	0.50	27.1	13.0	80.5	38.6
		1000	2.0	51.5	24.7	292	140
サル [c]	1	40 (20 BID)	NR[d]	1.79	0.779	10.4	4.52
[redacted]GR289		100 (50 BID)	NR[d]	11.3	4.92	84.2	36.6
		600 (300 BID)	NR[d]	59.6	25.9	723	315
	15	40 (20 BID)	NR[d]	2.42	1.05	9.61	4.18
		100 (50 BID)	NR[d]	11.8	5.13	52.6	22.9
		600 (300 BID)	NR[d]	106	46.1	1220	531

a. 非結合型濃度の測定には，ラットでは 0.479，サルでは 0.435 の全 fu 値（試験した 4 つの濃度の平均値）を用いた。
b. 雌雄各 15 匹/群による非連続サンプリング（n = 5/測定時点）
c. 雌雄各 3 匹/群による連続サンプリング
d. 1 日 2 回投与のため，T_{max} の報告はなかった。個々の T_{max} 値はおおむね 1 日 2 回投与の 1 回目投与後 0.5～2 時間または 1 日 2 回投与の 2 回目投与後 1 時間だった。

5.2.3. 分布

5.2.3.1. In vitro での血漿タンパク結合率

ラット，サルおよびヒトにおける PF-07321332 の血漿タンパク結合率は 0.3～10 μmol/L の濃度範囲で中程度であり，評価した動物種を通じて同程度であった（Table 13，PF-07321332_[redacted]_010657 試験）。

Table 13.　PF-07321332 の血漿タンパク結合率

動物種（系統）	血漿 fu 0.3 μmol/L[a]	 1 μmol/L[a]	 3 μmol/L[a]	 10 μmol/L[a]	 平均値 [b]
ラット（Wistar Han）	0.490	0.474	0.484	0.467	0.479
サル（カニクイザル）	0.386	0.404	0.449	0.499	0.435
ヒト	0.296	0.300	0.311	0.333	0.310

a. 幾何平均値（n = 12）
b. 試験した 4 つの濃度の平均値

5.2.3.2. In vitro での Cb/Cp

1 μmol/L の濃度では，PF-07321332 は赤血球と比較して血漿中に多く分布し，Cb/Cp は 0.83（ラット），0.68（サル）および 0.60（ヒト）であった（PF-07321332_[redacted]_100444 試験）。

5.2.4. 代謝

PF-07321332 の代謝は，in vitro で肝ミクロソーム（マウス，ラット，ハムスター，ウサギ，サルおよびヒト）および肝細胞（ラット，サルおよびヒト）を用いて評価し，in vivo でラットおよびサルに反復経口投与した後に評価した（PF-07321332_[redacted]_084546 試験）。

計 6 種の代謝物が検出された。このうち 5 種は酸化的代謝［M1～M3 および M4（PF-07329268）］，1 種は加水分解［M5（PF-07320267）］により生成されたものであり，すべての動物種で同様に認められた。主要代謝物は，ピロリジノン環の C-5 位のモノヒドロキシル化により生成された M4 であり，相互変換するジアステレオマーが認められた。また，他の部位の酸化および加水分解により生成された微量の代謝物が検出された。ヒト特有の代謝物は認められなかった。In vivo では，未変化体がラットおよびサルの血漿中ならびにラットの尿中および胆汁中に最も多く認められた薬物関連物質であり，サルの血漿中で最も多く認められた代謝物は M4 であった。加水分解物 M5 を含む他の代謝物は in vivo ではすべて微量であった（Table 14）。

細胞を用いない生化学的アッセイで，M4 は SARS-CoV-2 の主要なプロテアーゼ（3CL プロテアーゼ）を PF-07321332 と同程度の効力で阻害した。また，M4 は，VeroE6 細胞においても既知の MDR1（P-gp）排出阻害薬の存在下で SARS-CoV-2 を阻害したが，抗ウイルス活性は PF-07321332 の 7 分の 1 であった（5.1.2.1 項）。

遺伝子組換えヒト P450 分子種パネルを用いた検討において，酸化代謝物 M1～M4 は CYP3A4/5 によって生成され，その他の P450 分子種の関与はごくわずかであった。また，PF-07321332 から M5 への加水分解は，評価したいずれのヒト由来 in vitro 試験系（ヒト血液，腸液ならびに肝臓，腎臓，腸および肺の S9 画分）でも認められなかった。

ヒト肝ミクロソームを用いて選択的 P450 阻害薬の存在下で実施した代謝酵素の同定試験では，CYP3A4 が in vitro での PF-07321332 の酸化的代謝に寄与する主要な酵素であると予想され（f_m = 0.99），CYP3A5 の PF-07321332 代謝への寄与は大きくないと予想された（PF-07321332_[redacted]_072016 試験）。

Table 14.　PF-07321332 をインキュベートまたは経口投与したときに in vitro および in vivo で認められた代謝物

	肝ミクロソーム						肝細胞			In vivo			
										ラット			サル
代謝物 ID	マウス[a]	ラット[a]	ハムスター	ウサギ	サル	ヒト	ラット	サル	ヒト	血漿[b]	尿	胆汁	血漿[b]
PF-07321332	NR	NR	NR	NR	NR	NR	NR	NR	NR	+++	+++	+++	+++
M1 (PF-07329265)	+	+	+	++	t	+	+	t	t	t	t	t	t
M2 (PF-07329266)	+	+	+	+	t	+	t	t	t	t	-	-	t
M3 (PF-07329267)	+	t	-	t	t	+	-	t	t	+	-	-	+
M4 (PF-07329268)	+++	+++	+++	+++	+++	+++	+++	+++	+++	+	t	t	++
M5 (PF-07320267)	NR	NR	NR	NR	NR	NR	NR	NR	NR	+	t	t	+
m/z 498	+	t	+	+	t	+	-	-	-	+	-	-	+

-：検出できず，+：質量分析法による軽微な UV ピークの検出，++：質量分析法による中程度の UV ピークの検出，
+++：質量分析法による主な UV ピークの検出，t：トレース，質量分析法のみで検出
a. 雌雄の試料で結果は類似しており，差が認められた場合には相対存在量がより大きかった。
b. 雌雄の試料で相対存在量は同じであった。

5.2.5. 排泄

単回投与薬物動態試験で，ラット（PF-07321332_[redacted]_103131 試験）およびサル（PF-07321332_[redacted]_111728 試験）に静脈内または経口投与したときの PF-07321332 の尿中および胆汁中への排泄を評価した。PF-07321332 の投与量に対する未変化体の排泄率は，ラットでは尿中で 17%，胆汁中で 9%，糞便中で最大 11%であり，サルでは尿中で 7%，糞便中で 4%であった。

5.2.6. 薬物動態学的薬物相互作用

PF-07321332 は主に CYP3A4 によって代謝されることから（5.2.4 項），CYP3A4 の強い阻害薬または誘導薬と併用すると PF-07321332 の曝露量が変化すると予想される。

PF-07321332 による in vitro での主要な P450 分子種および UGT 分子種の阻害，主要な P450 分子種の誘導ならびに種々の排出，肝取込みおよび腎トランスポーターの阻害を検討した。PF-07321332 が相互作用薬として薬物相互作用を引き起こすリスクは，薬物相互作用に関する FDA および EMA のガイダンスに従い，PF-07321332/リトナビルの予定治療用量（300/100 mg BID）および推定総 C_{max}［4.14 µg/mL（非結合型は 1.28 µg/mL），7.2 項］に基づいて評価した。

基礎的な静的モデルに基づくと，PF-07321332 が CYP1A2 および CYP2B6 を誘導するかまたは CYP1A2，CYP2B6，CYP2C8，CYP2C9，CYP2C19，CYP2D6，UGT1A1，UGT1A4，UGT1A6，UGT1A9，UGT2B7，UGT2B15，BCRP，MATE2K，OAT1，OAT3，OATP1B3 および OCT2 を可逆的に阻害するリスクは低い。しかし，PF-07321332 は，CYP2C8，CYP2C9 および CYP2C19 を誘導するおそれがあり，CYP3A4 を可逆的および時間依存的に阻害する可能性が高く，MDR1（P-gp），MATE1，OCT1 および OATP1B1 を阻害する可能性がある。

さらに，メカニズムに基づく静的モデルを用いて，推定 C_{max} に基づいた可逆的阻害ならびに血漿，腸管腔，腸細胞，肝臓および門脈流入部の C_{av}（$k_{p,uu}$ および k_a を含む）に基づいた時間依存的阻害を評価し，PF-07321332 が薬物相互作用を引き起こす可能性をより詳細に検討した。このモデルに基づくと，PF-07321332 が P450 分子種（CYP3A4 以外），UGT 分子種およびトランスポータータンパク質を阻害するリスクは極めて低いが，ヒトに予定治療用量を投与したときに CYP3A4 の可逆的および時間依存的な阻害ならびに P-gp の阻害が生じる可能性は残る。リトナビルも MDR1（P-gp）および CYP3A の阻害薬であるため，PF-07321332 による薬物相互作用がリトナビルによって引き起こされる薬物相互作用を超えるリスクは極めて低いと考えられる。

5.2.6.1. P450 に対する阻害能

ヒト肝ミクロソームを用いた試験で，PF-07321332 は CYP3A4/5 を可逆的に阻害することが示され，IC_{50} 値はそれぞれ 58.3 µmol/L（ミダゾラム），106 µmol/L（テストステロン）および 45.1 µmol/L（ニフェジピン）であった（PF-07321332_[redacted]_113907 試験）。PF-07321332 は CYP1A2，CYP2C8，CYP2C9，CYP2C19 および CYP2D6 を可逆的に阻害しなかった（IC_{50} 値は 300 µmol/L 超）。

加えて，PF-07321332 は，ミダゾラムをプローブ基質として用いたときには 3.16 µmol/L 以上の濃度で，テストステロンをプローブ基質として用いたときには 0.562 µmol/L 以上の濃度で，CYP3A4/5 を時間依存的に阻害することが示された（PF-07321332_[redacted]_122202 試験）。こ

のときの PF-07321332 の K_I 値および k_{inact} 値は，テストステロン 6β-ヒドロキシラーゼに対してそれぞれ 13.9 μmol/L および 0.0165 min^{-1}，ミダゾラム 1'-ヒドロキシラーゼに対しては 15.5 μmol/L および 0.0142 min^{-1} であった。したがって，予定治療用量において，CYP3A4/5 の可逆的阻害および時間依存的阻害が生じるリスクがある。

5.2.6.2. P450 に対する誘導能

ヒト肝細胞を PF-07321332 で処理したとき，評価したいずれの肝細胞ロットにおいても CYP1A2 の mRNA または活性の誘導は認められず，CYP2C19 の誘導が起こらないことも確認された（PF-07321332_[redacted]_102559 試験）。PF-07321332 は，CYP3A4（最大 41 倍）および CYP2B6（最大 3.9 倍）の mRNA 活性および酵素活性を誘導し，CYP2C8 および CYP2C9 に対しては mRNA 活性を誘導した（4.4 倍未満）。予定治療用量では，臨床的に意味のあるこれらの P450 分子種の誘導が起こるリスクは極めて小さい。

5.2.6.3. UGT に対する阻害能

プールしたヒト肝ミクロソームを用いた試験では，PF-07321332 は 2% BSA の存在下でも非存在下でも，UGT1A1，UGT1A4，UGT1A6，UGT1A9，UGT2B7 および UGT2B7 の触媒酵素活性に対して可逆的阻害をほとんどまたは全く示さなかった（IC_{50} 値は 100 μmol/L 超，PF-07321332_[redacted]_103243 試験）。したがって，予定治療用量で，これらの UGT 分子種が阻害されるリスクはほとんどまたは全くない。

5.2.6.4. トランスポーターの基質となる可能性

NTCP，OATP1B1，OATP1B3 および OATP2B1 を安定的に発現している HEK293 細胞を用いて最高 7.7 μmol/L までの濃度で評価したとき，PF-07321332 はこれらの取込みトランスポーターの基質とならなかった（PF-07321332_[redacted]_114514 試験）。さらに，プレートに播種したヒト肝細胞およびサンドイッチ培養ヒト肝細胞を用いて PF-07321332 の肝取込みおよび胆汁中排泄を評価したとき，PF-07321332 は OAT2，NTCP および OATP に対する既知の阻害薬によって有意に阻害されなかったことから，これらのトランスポーターの取込みによる輸送を受けないことが示された[12]（PF-07321332_[redacted]_110227 試験）。サンドイッチ培養ヒト肝細胞では PF-07321332 の胆汁中排泄も認められ，CL_{bile} は 2.1 μL/min/mg protein であった。この結果により，おそらく MDR1（P-gp）および BCRP を介して，PF-07321332 の一部が未変化体として胆汁中に排泄される傾向があることが示唆された。

5.2.6.5. トランスポーターに対する阻害能

安定的にトランスフェクトされた HEK293 細胞または小胞系を用いて検討した結果，種々の排出トランスポーターおよび取込みトランスポーターの大部分に対し，PF-07321332 が阻害する可能性は低いことが示された（PF-07321332_[redacted]_020944 試験，Table 15）。PF-07321332 は予定治療用量で，MDR1（P-gp），MATE1，OCT1 および OATP1B1 を阻害する可能性がある。

Table 15.　各種トランスポーターに対する PF-07321332 の in vitro での特性

トランスポーター	試薬系	プローブ基質	PF-07321332 IC_{50}[a] (μmol/L)
BCRP	HEK293 小胞	0.2 μmol/L ロスバスタチン	>1000
MATE1	HEK293 細胞	15 μmol/L [^{14}C]メトホルミン	112
MATE2K	HEK293 細胞	15 μmol/L [^{14}C]メトホルミン	872
MDR1	HEK293 小胞	0.2 μmol/L N-メチルキニジン	70.6
OAT1	HEK293 細胞	0.5 μmol/L [^{3}H]パラアミノ馬尿酸	>1000
OAT3	HEK293 細胞	0.1 μmol/L [^{3}H]エストロン-3-硫酸	521
OATP1B1	HEK293 細胞	0.3 μmol/L ロスバスタチン	44.4
OATP1B3	HEK293 細胞	0.3 μmol/L ロスバスタチン	283
OCT1	HEK293 細胞	10 μmol/L [^{14}C]メトホルミン	138
OCT2	HEK293 細胞	15 μmol/L [^{14}C]メトホルミン	955

a. すべてのトランスポーター阻害アッセイで推定 K_i 値は IC_{50} 値と等しいと仮定した。ただし，MDR1 については換算係数 1.28 を用いた（$K_i = IC_{50}/1.28$）。

5.2.7. 最小有効濃度

他の抗ウイルス薬で得られている知見に基づくと，SARS-CoV-2 に対する PF-07321332 の最小有効用量は，in vitro の EC_{90} 値を超える非結合型血漿中曝露量が維持される用法用量であると予想される[13]。最も外挿性の高い初代培養 dNHBE 細胞アッセイの SARS-COV-2 モデルにおける PF-07321332 の EC_{90} 値は 0.181 μmol/L であり（5.1.2 項），この値は，P-gp 阻害薬の存在下での VeroE6 細胞のデータ（EC_{90} が 0.156 μmol/L）により裏付けられている。この in vitro 抗ウイルス阻害データをカバーするため，最小有効濃度の目標値は 0.181 μmol/L（非結合型血漿中濃度）と定義した。

5.3. 毒性

5.3.1. 要約

一連の非臨床試験でPF-07321332を評価した（Table 16）。

ADME試験の結果によりラット，サルおよびヒトの間でPF-07321332の代謝および血漿タンパク結合に類似性が認められたことから，毒性試験に用いる動物種としてラットおよびサルを選択した。また，PF-07321332の標的はウイルス特異的タンパク質であることおよび実施した副次的薬理試験の結果に基づくとPF-07321332がオフターゲット作用を示す可能性は低いことから，薬理学的に毒性試験に適切な動物種は存在しない。In vivo試験での投与経路には，予定臨床投与経路である経口投与を選択した。重要な反復投与毒性試験では，全身曝露量を増加させるためPF-07321332を1：1のMTBE溶媒和物として動物に投与し，別に，MTBEを投与する対照群も設定した。

Table 16.　毒性試験の概要

試験[a,b]	試験番号（ファイザー社試験番号）	濃度または用量[c]	GLP
反復投与毒性試験			
重要な試験以外の試験			
ラットを用いた4日間投与試験	[redacted]GR250	0, 30, 100, 1000	非適用
カニクイザルを用いた4日間投与試験	[redacted]GR271	0, 30 (15 BID), 300 (150 BID), 1000 (500 BID)[d]	非適用
重要な試験			
ラットを用いた2週間投与試験	[redacted]GR276	0, 0 (150 MTBE)[e], 60, 200, 1000	適用
カニクイザルを用いた15日間投与試験	[redacted]GR289	0, 0 [90 (45 BID) MTBE][e], 40 (20 BID), 100 (50 BID), 600 (300 BID)[d]	適用
遺伝毒性試験			
In vitro試験			
細菌を用いる復帰突然変異試験	AG48RZ.503ICH.BTL ([redacted]GR288)	1.50–5000 µg/plate	適用
ヒト培養リンパ芽球様TK6細胞を用いた小核誘導試験	AG48RZ.361ICH.BTL ([redacted]GR286)	62.5–500 µg/mL	適用
In vivo試験			
ラットを用いたin vivo小核試験[f]	[redacted]GR276[f]	0, 0 (150 MTBE)[e], 60, 200, 1000	適用

a. すべてのGLP適用試験はデータ相互受け入れ制度に参加するOECD加盟国で実施した。
b. すべてのin vivo試験で雌雄を用いた。
c. 特記しない限り，すべての用量をmg/kgで表す。
d. 1日2回投与の間隔は約6時間である。
e. 対照群の溶媒量は高用量群の溶媒量（15%溶媒）に基づいた。これは，[redacted]GR276試験では150 mg/kg/日の溶媒，[redacted]GR289試験では90（45 BID） mg/kg/日の溶媒に相当した。
f. ラットを用いた重要な2週間投与試験（[redacted]GR276試験）の一環として実施した。

PF-07321332 の毒性は，ラットおよびカニクイザルを用いた探索的反復投与毒性試験 2 試験および重要な GLP 適用反復投与毒性試験 2 試験で評価した。ラットを用いた重要な試験で炎症状態を示唆する所見が探索的試験よりも長期にわたって認められたほかは，各動物種における所見は探索的試験および重要な試験でおおむね同様であった。重要な GLP 適用反復投与試験（ラットでは 14 日間，サルでは 15 日間）では毒性所見は認められず，投与した最高用量が NOAEL であった。サルでみられた一般状態の変化は，散発的な嘔吐の発現およびこれに伴うわずかな体重減少であり，毒性学的意義の乏しい所見と判断された。ラットでは，雌のみで，対照群と比較して体重がわずかに増加した。ラットおよびサルで，関連する一般状態所見または病理組織学的所見を伴わない，モニタリング可能かつ可逆的な臨床病理所見が認められた。サルでみられたその他の臨床病理所見は，嘔吐およびそれに続く脱水に起因するものであった可能性が高く，毒性学的意義の乏しい所見と判断された。ラットでは，1000 mg/kg/日群で，対照群と比較して心臓の絶対重量および相対重量の平均値が低値を示し（雌），肝臓の絶対重量および相対重量の平均値が高値を示した（雌雄）。心臓重量の減少は，関連する病理組織学的所見を伴うことなく，2 週間の休薬期間終了時までに完全に回復した。肝臓重量の増加については，関連する軽微から軽度の病理組織学的所見が肝臓および甲状腺に認められたが毒性学的意義の乏しい所見であり，これに伴う組織損傷または臨床病理検査パラメータの変化は認められなかった。ラットの肝臓および甲状腺で認められたこれらの所見は，ミクロソーム酵素の誘導に関連した適応性変化に一致するものであり[7]，2 週間の休薬期間後には完全に回復していた。

PF-07321332 は，in vitro 遺伝毒性試験で変異原性および染色体異常誘発性を示さず，ラットを用いた GLP 適用反復投与毒性試験の一部として実施した in vivo 小核試験でも陰性であった。

ラットを用いた 14 日間投与試験およびサルを用いた 15 日間投与試験における NOAEL は検討した最高用量であった。NOAEL における曝露量は，ヒトに PF-07321332/リトナビルの予定治療用量（300/100 mg BID）を投与したときに推定される PF-07321332 の非結合型 C_{max} および AUC_{24} と比較してそれぞれ，ラットでは 19 倍および 6.6 倍，サルでは 36 倍および 25 倍であった。

5.3.2. 単回投与毒性試験

PF-07321332 の単回投与毒性試験は実施していない。

5.3.3. 反復投与毒性試験

PF-07321332 の探索的および重要な反復投与毒性試験はラットおよびカニクイザルを用いて実施した。

5.3.3.1. ラットを用いた試験

探索的毒性試験で，Wistar Han ラットに PF-07321332 を 1000 mg/kg/日までの用量で 4 日間強制経口投与したところ，一般状態の変化，体重，血液学的検査および血液生化学的検査パラメータへの影響，剖検所見ならびに胸骨骨髄（評価した唯一の臓器）の病理組織学的所見は認められなかった（[redacted]GR250 試験）。

Wistar Han ラットを用いて実施した GLP 適用 14 日間強制経口投与試験では，60，200 または 1000 mg/kg/日の用量で 1 日 1 回投与して PF-07321332 の毒性，TK および染色体異常誘発性・異

数性誘発性を検討した。2 週間の休薬期間後に投与の影響の可逆性を評価した（[redacted]GR276 試験）。

GLP 適用試験で投与した PF-07321332 の投与液は 1：1 の MTBE 溶媒和物であったことから，本試験で認められた影響への MTBE の寄与を評価するため，PF-07321332 の最高用量群に用いた製剤と同濃度の MTBE を添加した溶媒を投与する対照群を設けた。対照群では，MTBE による影響が腎臓に認められたが，これらは MTBE 投与時に起こることが知られている雄ラットに特有の影響であり，毒性学的意義の乏しい変化であった[14,15]。

この試験では，一般状態の変化ならびに摂餌量または眼科学的パラメータへの影響は認められなかった。体重パラメータへの影響は雄では認められず，200 mg/kg/日以上の群の雌でわずかな体重増加（対照群の平均値の 1.04～1.12 倍）が認められたが，変化の程度が小さかったことから毒性学的意義の乏しい所見と判断された。PF-07321332 は，雄または雌ラットの末梢血中の網状赤血球に小核を誘発しなかった。

投与期間終了時に，60 mg/kg/日以上の群の雄および 1000 mg/kg/日群の雌で血液学的検査および凝固検査パラメータに毒性学的意義の乏しい変化が認められた。また，1000 mg/kg/日群のみで，毒性学的意義の乏しい血液生化学検査値の変化（雌雄）および尿検査値の変化（雄のみ）が認められた。凝固検査では，用量依存的な PT 延長が 60 mg/kg/日以上の群の雄（最大 2.50 倍）および 1000 mg/kg/日群の雌（1.40 倍）で認められ，APTT の延長が 200 mg/kg/日以上の群の雄（最大 1.19 倍）および 1000 mg/kg/日群の雌（1.11 倍）で認められた。これらの PT および APTT の延長の機序は明らかになっていない。1000 mg/kg/日群で，血小板数の増加（雌雄，最大 1.25 倍），赤血球パラメータの減少（雌のみ，ヘモグロビン値が 0.95 倍）およびフィブリノゲン値の上昇（雌のみ，1.10 倍）が認められた。血液生化学検査では，1000 mg/kg/日群のみで毒性学的意義の乏しい変化がみられ，これらは，雌雄でみられたグロブリン上昇（1.07 倍），コレステロール上昇（1.33 倍）および ALP 低下（0.66 倍）ならびに雌のみでみられた A/G 比の低下（0.90 倍）であった。尿検査では，1000 mg/kg/日群の雄で尿 pH の低下（0.90 倍）が認められた。これらの所見のいずれにおいても，関連する一般状態の変化または病理組織学的所見は認められず，休薬期間終了時にはすべての所見が完全に回復していた。

投与期間終了後の剖検時に，1000 mg/kg/日群の雌で心臓の絶対重量および相対重量平均値の低値（対照群の0.85～0.88倍）が認められたが，関連する病理組織学的所見がみられなかったため，毒性学的意義の乏しい変化であると判断された。休薬期間終了時には心臓重量に対照群との差は認められなかったことから，この変化は完全に回復することが示された。

病理組織学的検査で認められた所見は，投与期間終了時に雌雄の肝臓および甲状腺にみられた毒性学的意義の乏しい影響のみであり，これらの影響は休薬期間終了時には完全に回復していた。肝臓の所見として，200 mg/kg/日以上の群の雌および 1000 mg/kg/日群の雄で軽微から軽度の門脈周囲肝細胞肥大が認められ，1000 mg/kg/日群の雌では，これと同時に，門脈周囲肝細胞空胞化の発現頻度および程度（軽微から軽度）も上昇した。肝臓におけるこれらの病理組織学的所見は，1000 mg/kg/日群の雌雄でみられた肝臓重量の増加（対照群の 1.35～1.59 倍）および肝腫大の剖検所見に相関して認められ，肝細胞肥大および肝細胞空胞化はミクロソーム酵素の誘導に一致する所見であった[7]。1000 mg/kg/日群では，肝臓重量の増加および肝細胞肥大に相関する所見として，甲状腺濾胞細胞の肥大（軽微から軽度）が雌雄で認められた。まとめると，

肝臓および甲状腺に認められた上記の所見は，肝臓におけるミクロソーム酵素誘導による甲状腺ホルモンクリアランスの上昇に関連した二次的な適応反応と一致する。ラットはヒトと比較して，この機序に対して特に高い感受性を示すことが知られている[16]。肝臓および甲状腺に認められた影響はすべて，程度が低く，また，組織の損傷を示す病理組織学的所見または関連する臨床病理検査パラメータの変化を伴わなかったこと，また，いずれの所見も 2 週間の休薬期間後に完全に回復したことから毒性学的意義の乏しい変化であると判断された。

NOAEL は 1000 mg/kg/日であり，この NOAEL における曝露量は，ヒトに PF-07321332/リトナビルの予定治療用量（300/100 mg BID）を投与したときに推定される PF-07321332 の非結合型 C_{max} および AUC_{24} のそれぞれ 19 倍および 6.6 倍であった。

5.3.4. サルを用いた試験

5.3.4.1. カニクイザルを用いた PF-07321332 の探索的 1 日 2 回 4 日間強制経口投与試験

カニクイザルを用いて実施した探索的 4 日間強制経口投与試験では，30（15 BID），300（150 BID）または 1000（500 BID）mg/kg/日の用量で PF-07321332 の忍容性および TK を評価した（[redacted]GR271 試験）。

すべての用量群で忍容性が認められ，摂餌量への影響はなかった。300 mg/kg/日以上の群で嘔吐が認められた。この所見はおおむね用量依存的であり，反復投与により改善した。また，1000 mg/kg/日群では体重減少も認められ，嘔吐に関連した変化である可能性が高いと考えられた。

300 mg/kg/日以上の群でフィブリノゲン値の上昇および単球数の増加が認められ，1000 mg/kg/日群では，白血球数の増加（好中球数の増加による）および網状赤血球絶対数の減少も認められた。これらの変化は，急性期・炎症反応を示す所見であり，産生低下に起因する可能性が高い網状赤血球数の減少を伴っていた。

高用量群の雌では，赤血球数増加，ヘモグロビン上昇，アルブミンおよびグロブリンの双方の上昇に起因する総タンパク質増加，尿素窒素ならびにクレアチニン上昇も認められ，いずれも血液濃縮・脱水を示す所見であった。これらの変化は，嘔吐による体液喪失に起因するものであり，この結果としてナトリウム，カリウムおよびクロールも低下した。また，ビリルビン，トリグリセリドおよびグルコースの上昇も認められた。

最高用量の 1000 mg/kg/日における曝露量は，ヒトに PF-07321332/リトナビルの予定治療用量（300/100 mg BID）を投与したときに推定される PF-07321332 の非結合型 C_{max} および AUC_{24} のそれぞれ 49 倍および 36 倍であった。嘔吐に関連する一般状態所見および臨床検査所見が認められたことから，1000 mg/kg/日は長期投与試験での MTD を上回る可能性が高いと考えられた。そのため，カニクイザルを用いた GLP 適用 15 日間反復投与毒性試験では高用量として 600 mg/kg/日を選択した。

5.3.4.2. カニクイザルを用いた PF-07321332 の 1 日 2 回 15 日間強制経口投与試験

カニクイザルを用いて実施した GLP 適用 15 日間強制経口投与試験では，40（20 BID），100（50 BID）または 600（300 BID）mg/kg/日の用量で PF-07321332 の毒性および TK を検討した（[redacted]GR289 試験）。

GLP 適用試験で投与した PF-07321332 の投与液は 1：1 の MTBE 溶媒和物であったことから，本試験で認められた影響への MTBE の寄与を評価するため，PF-07321332 の最高用量群に用いた製剤と同濃度の MTBE を添加した溶媒を投与する対照群を設けた。この試験では，MTBE に関連した影響は認められなかった。

すべての動物が試験終了時まで生存し，摂餌量への影響も，心電図パラメータ（心拍数ならびに RR，PR，QRS，QT および QTc 間隔），心電図波形，眼科学的検査所見，臓器重量，剖検所見および病理組織学的所見の変化も認められなかった。

認められた一般状態の変化は，100 mg/kg/日以上の群でみられた散発的な嘔吐の発現のみであり，毒性学的意義の乏しい所見と判断された。嘔吐の発現はおおむね用量依存的であり，1 日 2 回投与したときの 2 回目投与後または一晩経過した後にみられた。600（300 BID）mg/kg/日群の雄 1 例で体重減少（試験 1 日の 0.91 倍）が認められたが，減少の程度が小さく，また，嘔吐の一般状態所見に起因するものであったことから，毒性学的意義の乏しい変化と判断された。

600（300 BID）mg/kg/日群の雄および 1 例の雌でフィブリノゲン値の上昇（個々の動物の投与前値との比較）が認められ（最大 2.09 倍），これにより炎症過程の存在が示唆されたが，関連する病理組織学的所見は認められなかった。また，600（300 BID）mg/kg/日群の雄 1 例でナトリウム（0.96 倍）およびクロール（0.93 倍）の低下（投与前値との比較）が認められた。これらの低下は消化管からの喪失によるものであり，嘔吐の一般状態所見と一致する変化であった。さらに，600（300 BID）mg/kg/日群の雌雄では，尿 pH の平均値が対照群と比較して低値を示したが（0.73～0.80 倍），これに関連する一般状態の変化または病理組織学的所見は認められなかった。これらの臨床病理検査値の変化は，変化の程度が小さく，また，関連する病理組織学的所見が認められなかったことから，毒性学的意義の乏しい変化と判断された。

NOAEL は 600 mg/kg/日（検討した最高用量）であり，この NOAEL における曝露量は，ヒトに PF-07321332/リトナビルの予定治療用量（300/100 mg BID）を投与したときに推定される PF-07321332 の非結合型 C_{max} および AUC_{24} のそれぞれ 36 倍および 25 倍であった。

5.3.5. 遺伝毒性試験

細菌を用いる復帰突然変異試験，in vitro染色体異常誘発試験（ヒトリンパ芽球様TK6細胞を用いる小核試験）およびラットを用いたin vivo小核試験からなる一連の遺伝毒性試験でPF-07321332を評価した。In vitro試験はすべて，適用されるガイドラインの上限濃度または細胞毒性もしくは不溶性により制限された濃度を最高濃度とし，外因性代謝活性化系の存在下および非存在下で実施した。PF-07321332は，in vitroまたはin vivoのいずれの試験においても遺伝毒性を示さなかった（AG48RZ.503ICH.BTL，AG48RZ.361ICH.BTLおよび[redacted]GR276試験）。

5.3.6. がん原性試験

PF-07321332 のがん原性試験は実施していない。

5.3.7. 生殖発生毒性試験

PF-07321332 の生殖発生毒性試験は実施していない。重要な毒性試験では評価した雌雄の生殖器で所見はみられなかった。

5.3.8. 局所刺激性試験

PF-07321332 の局所刺激性試験は実施していない。

5.3.9. その他の毒性試験

5.3.9.1. 光毒性試験

紫外可視吸光度を評価したところ，モル吸光係数は閾値である 1000 L mol^{-1} cm^{-1} を上回らなかったことから，PF-07321332 は光毒性のリスクを有しないことが示された。

5.3.9.2. 抗原性試験

PF-07321332 の抗原性試験は実施していない。

5.3.9.3. 免疫毒性試験

PF-07321332 の免疫毒性試験は実施していない。

5.3.9.4. 毒性発現の機序に関する試験

PF-07321332 の毒性発現の機序に関する試験は実施していない。

5.3.9.5. 依存性試験

PF-07321332 の依存性試験は実施していない。

5.3.9.6. 代謝物の毒性試験

PF-07321332 の代謝物を投与する独立した試験は実施していない。PF-07321332 のヒト特有の代謝物は認められていない。ヒト肝ミクロソームおよびヒト肝細胞で形成されるすべての代謝物が毒性試験で用いた非臨床動物種（ラットおよびサル）で認められた。

5.3.9.7. 不純物の毒性試験

原料および製剤の製造工程は開発中であり開発の初期である現時点で，PF-07321332 の不純物を投与する独立した試験は実施していない。

5.3.9.8. その他の試験

PF-07321332 のその他の試験は実施していない。

5.3.10. 所見と薬物動態の関係

ラットおよびサルへの経口投与後に PF-07321332 の血漿中濃度を測定したところ，曝露量（C_{max} および AUC_{24}）に一貫した性差は認められず，PF-07321332 の曝露量は用量の増加に伴って増加した。

各用量で得られたTKパラメータに関連するPF-07321332の曝露量比（ヒトの推定曝露量との比）をTable 17に示す。各用量で認められた主な所見も記載する。曝露量比は，動物で得られたPF-07321332の非結合型濃度を用いて，ヒトにPF-07321332/リトナビルの予定治療用量（300/100 mg BID）を投与したときに推定されるPF-07321332の非結合型C_{max}およびAUC_{24}と比較することにより算出した。

Table 17.　主な所見と PF-07321332 投与量

主な所見	投与量（mg/kg/日）	非結合型 C_{max} (μg/mL)[a]	非結合型 AUC_{24} (μg•h/mL)[a]	曝露比（非結合型 C_{max}）[b]	曝露比（非結合型 AUC_{24}）[b]
ラット（雌雄各 3 匹/群）を用いた探索的 4 日間強制経口投与毒性試験（[redacted]GR250 試験）					
所見なし	30	2.49	3.40	1.9	0.16
所見なし	100	6.99	15.6	5.5	0.73
所見なし	1000	17.3	199	14	9.3
カニクイザル（雌雄各 1 匹/群）を用いた探索的 1 日 2 回 4 日間強制経口投与毒性試験（[redacted]GR271 試験）					
所見なし	30 (15 BID)	0.87	2.67	0.68	0.13
嘔吐，フィブリノゲン↑，単球絶対数↑	300 (150 BID)	19.4	196	15	9.2
上記に加えて，体重↓，白血球数↑，網状赤血球絶対数↓	1000 (500 BID)	62.6	770	49	36
ラット（雌雄各 15 匹/群）を用いた GLP 適用 14 日間強制経口投与毒性試験（[redacted]GR276 試験）					
PT↑（雄）	60	6.37	8.24	5.0	0.39
上記に加えて，APTT↑（雄），門脈周囲肝細胞肥大（雌）	200	13.0	38.6	10	1.8
上記に加えて，PT↑（雌），APTT↑（雌），血小板数↑，赤血球パラメータ↓（雌），フィブリノゲン↑（雌），グロブリン↑，コレステロール↑（雌），ALP↓（雌），A/G 比↓（雌），尿 pH↓（雄），心臓重量↓（雌），肝臓重量↑，門脈周囲肝細胞肥大（雄），門脈周囲肝細胞空胞化（雌），甲状腺濾胞細胞肥大	1000	24.7	140	19	6.6
カニクイザル（雌雄各 3 匹/群）を用いた GLP 適用 1 日 2 回 15 日間強制経口投与毒性試験（[redacted]GR289 試験）					
所見なし	40 (20 BID)	1.05	4.18	0.82	0.20
嘔吐↑	100 (50 BID)	5.13	22.9	4.0	1.1
上記に加えて，体重↓（雄），フィブリノゲン↑，尿 pH↓	600 (300 BID)	46.1	531	36	25

a. AUC および C_{max} の値は血漿中濃度で示す。各値は特記しない限り投与期間終了付近で得られたものである。非結合型 AUC および C_{max} は各動物種のタンパク結合率に基づいている（PF-07321332 の fu は Wistar Han ラットで 0.479，カニクイザルで 0.435 およびヒトで 0.310）。

b. ヒトに PF-07321332/リトナビルの予定治療用量（300/100 mg BID）を投与したときの推定非結合型曝露量［C_{max}：1.28 μg/mL，AUC_{24}：21.3 μg•h/mL（PF-07321332）］と動物での曝露量との比較から，曝露量比を算出した。

5.3.11. 標的臓器毒性（その他）

実施した非臨床試験の結果に基づき，ラットを用いた GLP 適用 14 日間投与試験で病理組織学的所見が認められたことから，肝臓および甲状腺が，標的臓器の可能性がある臓器として特定された。肝臓の所見として，200 mg/kg/日以上の群の雌および 1000 mg/kg/日群の雄で軽微から

軽度の門脈周囲肝細胞肥大が認められ，1000 mg/kg/日群の雌では，これと同時に，門脈周囲肝細胞空胞化の発現頻度および程度（軽微から軽度）も上昇した。肝臓におけるこれらの病理組織学的所見は，1000 mg/kg/日群の雌雄でみられた肝臓重量の増加および肝腫大の剖検所見に関連して認められ，肝細胞肥大および肝細胞空胞化はミクロソーム酵素の誘導に一致する所見であった[7]。1000 mg/kg/日群では，肝臓重量の増加および肝細胞肥大に関連する所見として，甲状腺濾胞細胞の肥大（軽微から軽度）が雌雄で認められた。まとめると，肝臓および甲状腺に認められた上記の所見は，肝臓におけるミクロソーム酵素誘導による甲状腺ホルモンクリアランスの上昇に関連した二次的な適応反応と一致する。ラットはヒトと比較して，この機序に対して特に高い感受性を示すことが知られている[16]。肝臓および甲状腺に認められた影響はすべて，程度が低く，組織の損傷を示す病理組織学的所見または関連する臨床病理検査パラメータの変化を伴わなかったこと，また，いずれの所見も2週間の休薬期間後に完全に回復したことから毒性学的意義の乏しい変化であると判断された。

6. 臨床試験

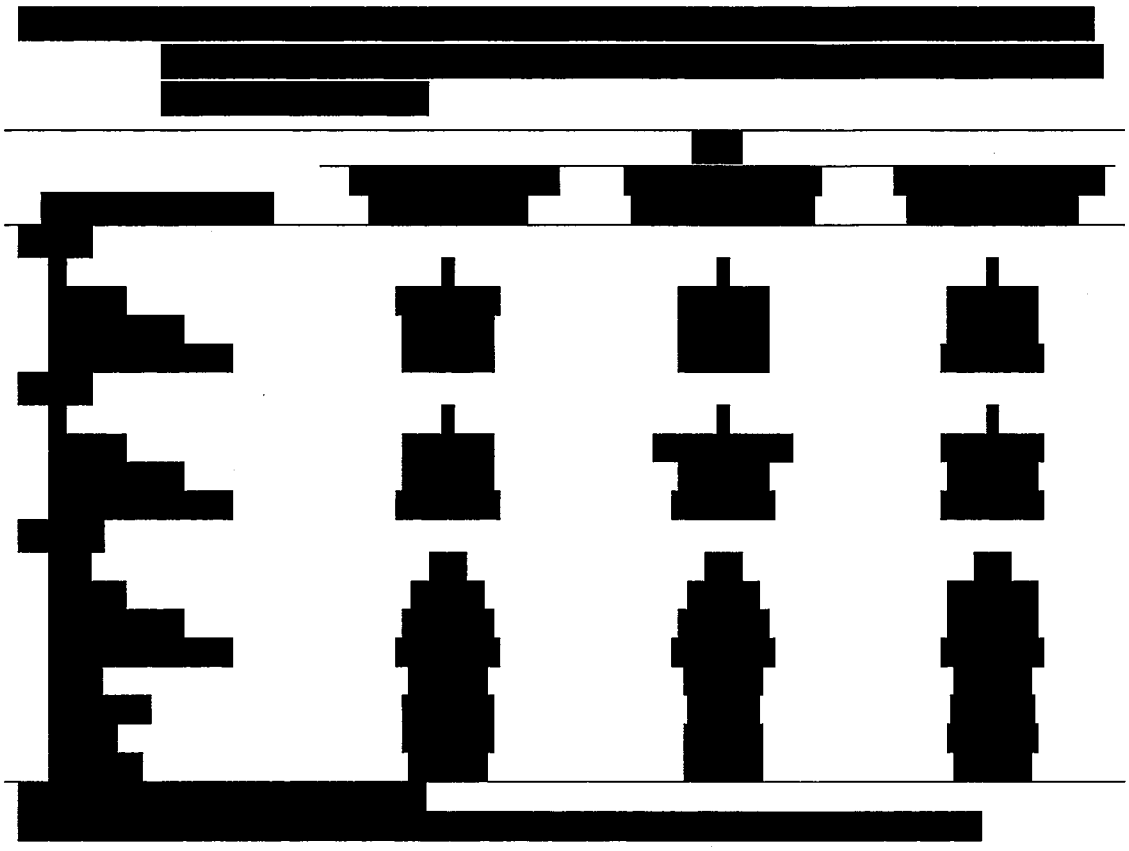
[redacted]

6.1. ヒトにおける薬物動態

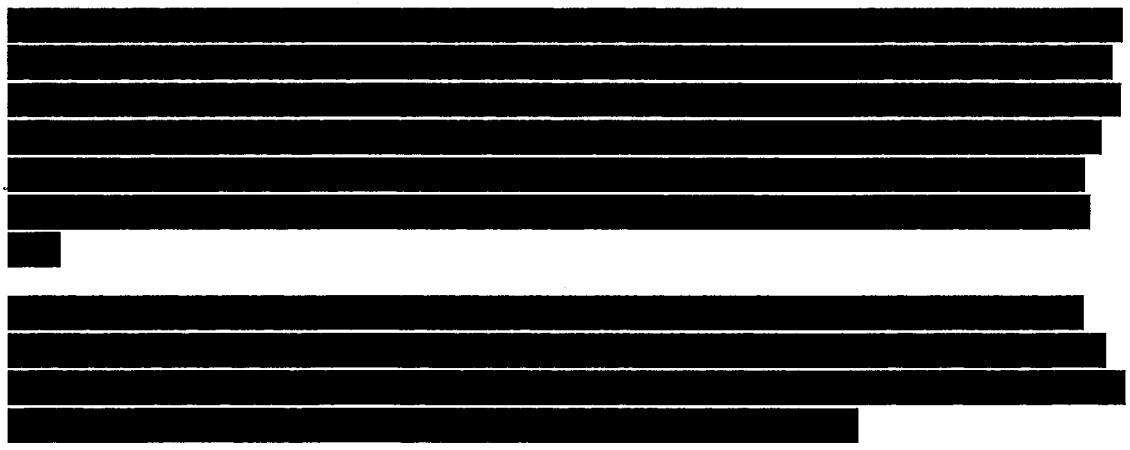
6.1.1. 薬物動態

[redacted]

[redacted]



[redacted]



[redacted]

6.1.2. 薬物相互作用

[redacted]

6.2. 安全性および有効性

6.2.1. 健康治験参加者での安全性

6.2.1.1. 全体的な安全性プロファイル

[redacted]

パート 1：SAD

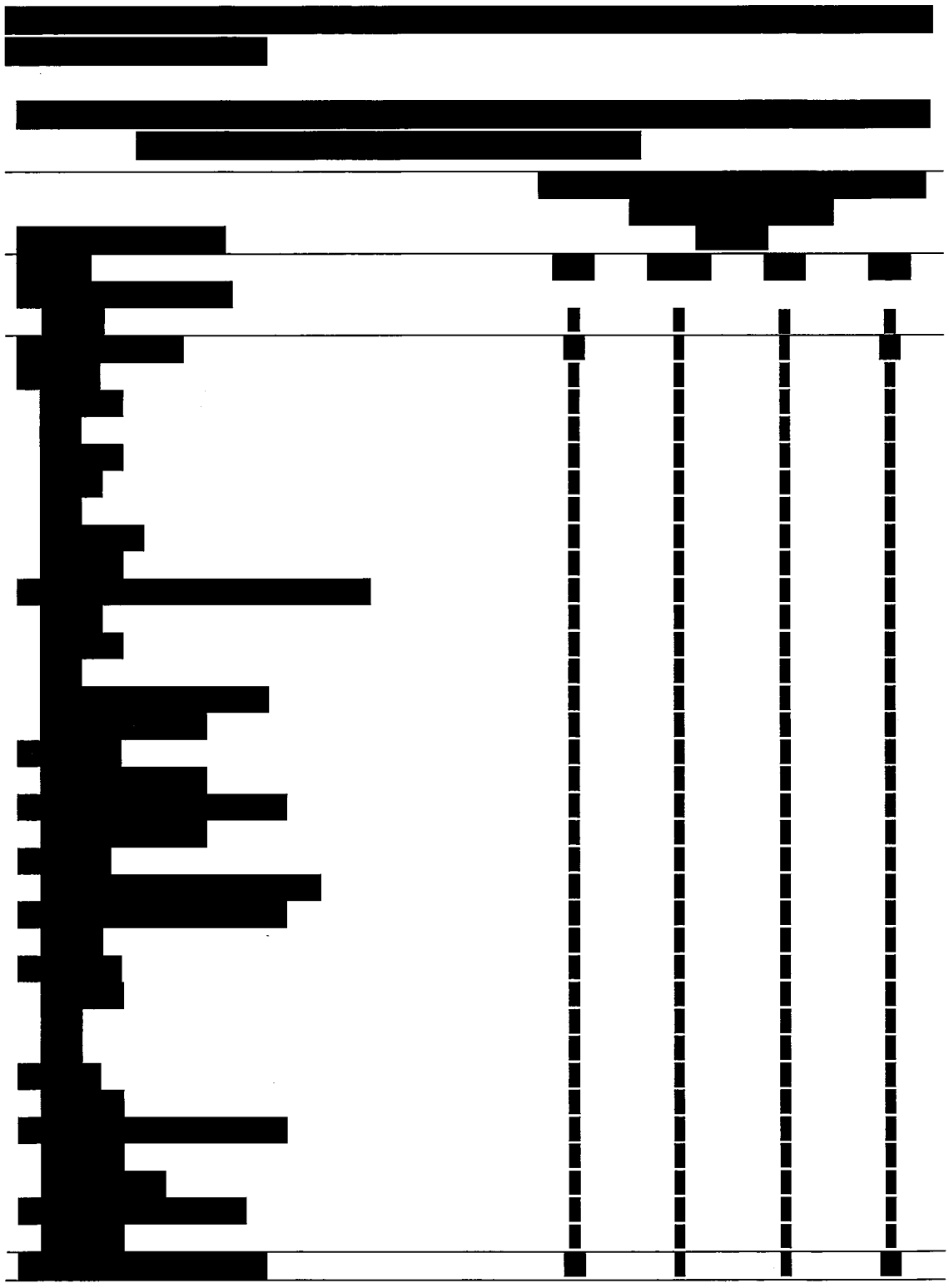
[redacted]

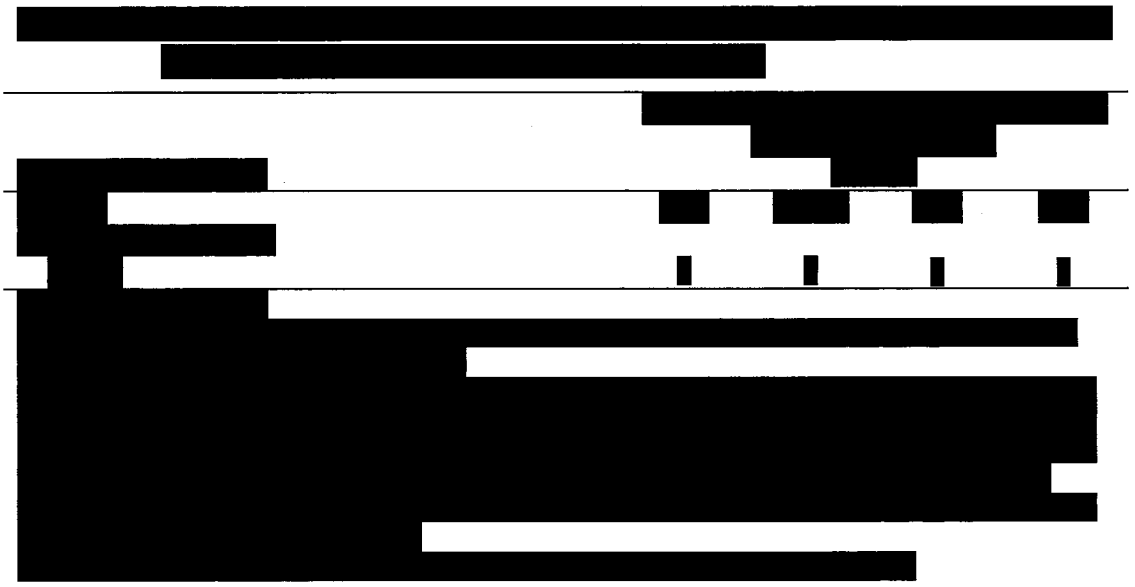
[redacted]

[redacted]

パート 2 : MAD

[redacted]





6.2.1.2. 臨床検査値異常

[redacted]

6.2.2. 第 2/3 相試験での安全性および有効性

[redacted]

6.2.3. 安全性の懸念

[redacted]

6.3. 市販後の使用経験

[redacted]

7. データの要約および治験責任医師に対するガイダンス

7.1. 作用機序，予定される効能・効果

PF-07321332 は，COVID-19 患者の治療のために経口薬として開発中の強力かつ選択的な SARS-CoV-2 3CL プロテアーゼ阻害薬である。

7.1.1. COVID-19 の治療

PF-07321332 は，COVID-19 の治療を目的とした経口抗ウイルス薬として開発中である。COVID-19 は，2019 年 12 月に，新型コロナウイルス SARS-CoV-2 に起因する新たな死に至る可能性のある呼吸器感染症として特定された。WHO は，2020 年 1 月 20 日に COVID-19 を国際的に懸念される公衆衛生上の緊急事態と宣言し，2020 年 3 月 11 日には COVID-19 のアウトブレイクを受けてパンデミックの状況にあると発表した[17]。

COVID-19 は，無症候性感染から重度の肺炎，急性呼吸促迫症候群および死亡に至るまで，幅広い臨床症状を示す疾患である。大多数の症例（約 80%）は無症候性または軽度[18]であるが，COVID-19 で入院した患者は，重大な病的状態および死亡に至る可能性があり[19,20]，炎症性サイトカインの増加を伴う重度の炎症，急性呼吸促迫症候群，急性心障害，血栓塞栓症，凝固亢進，腎障害などの合併症の発現リスクが高い[21,22,23,24,25]。

本治験薬概要書（英語版 Version [redacted]）の作成時点で，SARS-CoV-2 に活性を示す抗ウイルス薬として，RNA ポリメラーゼ阻害薬であるレムデシビルの 1 剤のみが COVID-19 の入院患者に対して承認されている[26]。モノクローナル抗体（casirivimab および imdevimab または bamlanivimab および estesevimab を含む）は，最近診断された高リスク非入院患者における軽度から中等度の COVID-19 に対する緊急使用許可を受けた。これらの投与経路はいずれも静脈内であり，医療従事者による投与が必要である。本治験薬概要書（英語版 Version [redacted]）の作成時点で，最近診断された COVID-19 患者に対して承認または緊急使用許可を受けた経口投与可能な治療薬はない。

コロナウイルスの 3CL プロテアーゼはウイルス自身がコードする酵素であり，ウイルス自身がコードする他の必須のプロテアーゼ（HIV プロテアーゼ，HCV プロテアーゼなど）と同様に，SARS-CoV-2 の複製サイクルにおいて不可欠な機能を担っている[5]。SARS-CoV-2 に近縁の他のコロナウイルスおよびピコルナウイルス（ピコルナウイルス様スーパークラスター）を用いた突然変異誘発実験により，3CL プロテアーゼ（または対応するピコルナウイルス 3C 酵素）の活性がウイルス複製に不可欠であることが示されている。コロナウイルスの 3CL プロテアーゼに近縁のヒト類似体は知られていないことから，適切な 3CL プロテアーゼ阻害薬は，SARS-CoV-2 および他のコロナウイルスに対する選択的阻害薬として機能する治療薬となる可能性が示唆される。

SARS-CoV-2 3CL プロテアーゼの阻害は，SARS-CoV-2 の RdRp を阻害するアデノシンヌクレオシド類似体のプロドラッグであるレムデシビルの作用機序とは異なる作用機序である。

7.2. 用法・用量

300/100 mg の用量による PF-07321332/リトナビル 1 日 2 回 5 日間の経口投与は安全かつ有効であると予想される。

C4671001 試験の予備的な食事の評価で食事の影響がわずかであったことを考慮すると，本薬は空腹時または食後に服用可能と考えられる。

7.3. 禁忌

20[redacted]年[redacted]月[redacted]日のデータカットオフ時点で特定されている PF-07321332 の投与に対する禁忌はない。

7.4. 警告および使用上の注意

これまでに実施された非臨床毒性試験の結果に基づくと，PF-07321332 の投与に関する警告または既知の注意事項はない。PF-07321332 の毒性は，5.3 項に詳述したとおり，ラットおよびカニクイザルを用いた安全性薬理試験 2 試験および重要な GLP 適用反復投与毒性試験 2 試験で評価した。重要な GLP 適用反復投与試験（ラットでは 14 日間，サルでは 15 日間）では毒性所見は認められず，投与した最高用量が NOAEL であった。

モニタリング可能かつ可逆的な臨床病理所見として，関連する一般状態所見または病理組織学的所見を伴わない，低グレードの炎症（ラットおよびサル）または凝固経路の変化（ラットのみ）を示唆する可能性のある所見が認められた。ラットでは，1000 mg/kg/日群で，対照群と比較して心臓の絶対重量および相対重量の平均値が低値を示し（雌），肝臓の絶対重量および相対重量の平均値が高値を示した（雌雄）。心臓重量の減少は，関連する病理組織学的所見を伴うことなく，2 週間の休薬期間終了時までに完全に回復した。肝臓重量の増加に関連する所見として，肝臓および甲状腺に，ミクロソーム酵素の誘導に関連した適応性変化に一致する軽微から軽度の可逆的かつ毒性学的意義の乏しい病理組織学的所見が認められた[7]。

初期の臨床試験では，安全性評価として重篤な有害事象，標準的な臨床検査，身体的診察ならびにバイタルサインおよび心電図の評価など，潜在的な有害作用を検討するために頻回のモニタリングを行っている。毒性試験で認められた低レベルの炎症および凝固検査における変化の機序については不明であるが，毒性学的意義は乏しく，可逆的でモニタリング可能であった。進行中の健康治験参加者を対象とした試験（C4671001 試験）では，凝固検査における変化は認められなかった。治験薬と関連のある有害事象として，パート 2（MAD）の投与群全体で TSH 増加が 3 例に認められた。これら 3 例には TSH 値の上昇に伴う臨床症状は認められず，遊離型 T4 値は正常範囲内であった。C4671001 試験の MAD パートで PF-07321332 投与に伴い認められた TSH 値の変化の意義を評価するデータは限られているため，PF-07321332 が甲状腺機能に影響を及ぼす可能性についてより多くのデータが利用可能になるまで PF-07321332 を反復投与する試験で甲状腺機能検査（TSH および遊離型 T4）をモニタリングする予定である。

7.5. 薬物相互作用

[redacted]

PF-07321332 の初期の in vitro 代謝試験により，CYP3A4 がヒトでの代謝の主要な代謝酵素であることが示された。PK ブースターとして使用されているリトナビルも CYP3A4 により代謝される。したがって，中程度および強い CYP3A4 の誘導薬の併用は禁止する。

PF-07321332 は CYP3A4 に対して時間依存的阻害を起こす可能性が示されおり，リトナビルは CYP3A4 を阻害することが知られている。したがって，クリアランスが CYP3A4 に大きく依存しており，血漿中濃度の上昇が重篤な事象および（または）生命を脅かす事象と関連している可能性がある薬剤の使用は，PF-07321332/リトナビルの投与中および PF-07321332/リトナビルの最終投与後 4 日間禁止する。

PF-07321332 とリトナビルは P-gp を可逆的に阻害する可能性があり，P-gp 基質の曝露量を増加させる可能性がある。したがって，PF-07321332/リトナビルの投与中は，血漿中濃度の上昇が重篤な事象および（または）生命を脅かす事象と関連している可能性がある P-gp 基質と PF-07321332 の併用を禁止する。

7.6. 妊娠，妊婦，授乳婦等への影響

妊婦に投与したときに PF-07321332 が胎児に影響を及ぼすかどうかは現時点では明らかになっていない。PF-07321332 の動物を用いた生殖発生毒性試験は実施していない。また，PF-07321332 のヒト乳汁中への移行性も明らかになっていない。PF-07321332 は治験薬であるため，妊婦や授乳婦には投与しないこと。避妊の要件および妊娠可能な女性の臨床試験への組み入れについては，治験実施計画書に規定されている制限および条件に従う。

7.7. 自動車の運転，機械の操作

PF-07321332 が自動車の運転能力および機械の操作能力に及ぼす影響は明らかになっていない。

7.8. 副作用

7.8.1. 副作用

PF-07321332 の副作用はこれまでに特定されていない。

7.8.2. 重篤な副作用の予測性判断のための安全性参照情報

SUSAR の緊急報告の目的で治験依頼者が予測できると判断した重篤な副作用はない。

7.9. 過量投与

これまでに PF-07321332 が過量投与された報告はない。

7.10. 薬物乱用，薬物依存

PF-07321332 の乱用のリスクまたは依存性についての情報は得られていない。

7.11. 治験薬の安全性

7.11.1. ヒトにおける安全性

7.11.1.1. ヒトへの投与

20[redacted]年[redacted]月[redacted]日時点で，健康成人治験参加者を対象にPF-07321332の安全性，忍容性およびPKを検討する臨床試験1試験（C4671001試験）が開始され，進行中である。20[redacted]年[redacted]月[redacted]日時点で，SADコホートで13例，MADコホートで12例がPF-07321332の単独投与またはリトナビル（PKブースター）との併用投与を受けている。

これまでのところ，PF-07321332のベネフィット - リスクは許容されると治験依頼者は評価している。

7.11.1.2. 特記すべき有害事象

本治験薬概要書（英語版Version[redacted]）の作成時点で，C4671001試験では特記すべき有害事象はなかった。

7.11.1.3. 既知の薬剤クラスエフェクト，その他のヒトへの使用経験

プロテアーゼ阻害薬は，HIV感染症やC型肝炎など他のウイルス感染症の治療に使用されており，その効果が認められている。C4671001試験はPF-07321332のヒトを対象とした最初の臨床試験であるため，その臨床効果は不明である。PF-07321332はin vitroでSARS-CoV-2の抗ウイルス活性を有することが示されており，SARS-CoV-2に感染した患者のウイルス力価を低下させることにより疾患の重症度および死亡リスクを低減することを目的としている。PF-07321332の投与に関連して特定されているリスクは，SARS-CoV-2に感染した治験参加者にもたらされる可能性があると予想されるベネフィットを考慮すると許容可能であると考えられる。

7.11.2. 特記すべき非臨床所見

ラットおよびカニクイザルを用いた安全性薬理試験2試験および重要なGLP適用反復投与毒性試験2試験で，PF-07321332の毒性プロファイルを評価した（7.4項および5.3項）。重要なGLP適用反復投与試験（ラットでは14日間，サルでは15日間）で毒性学的意義のある所見は認められず，NOAELは投与した最高用量であった。

実施した非臨床試験により，臨床試験における最長14日間のPF-07321332の経口投与が十分に支持される。

7.12. 結論

以上のように，PF-07321332の非臨床試験および臨床試験から得られた安全性の結果から，臨床試験におけるPF-07321332の評価の継続が支持されると考える。

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