A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO CONTROLLED, SINGLE- AND MULTIPLE-DOSE ESCALATION STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF PF-07321332 IN HEALTHY ADULT PARTICIPANTS

Study Intervention Number:	PF-07321332
Study Intervention Name:	N/A
US IND Number:	CCI [redacted]
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Phase:	Phase 1

Short Title: A Phase 1 Single Ascending Dose and Multiple Ascending Dose Study of PF-07321332 in Healthy Adult Participants

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 3	24 June 2021	• CCI [redacted]
Amendment 2	02 June 2021	• CCI [redacted]
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Original protocol	28 January 2021	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1 Single Ascending Dose and Multiple Ascending Dose Study of PF-07321332 in Healthy Adult Participants

Rationale

The current study is the first clinical administration with PF-07321332. It is a 5-part study combining PART-1: SAD, PART-2: MAD, PART-3: relative bioavailability/food effect, PART-4: metabolism and excretion (M&E) and PART-5: Supratherapeutic Exposure (SE). PART-1 and 2 are randomized, double-blind, sponsor-open, placebo-controlled trial to evaluate safety, tolerability and PK of single and multiple escalating oral doses of PF-07321332 in healthy adult participants and PART-3 is a randomized open label study to evaluate relative bioavailability and food effect of an oral tablet formulation. PART-2 of the study may also evaluate the safety tolerability and PK in Japanese participants. PART-4 is an open-label, non-randomized, single period to evaluate the metabolism and excretion of PF-07321332. PART-5 is a double-blind, sponsor-open, randomized, cross-over study to evaluate safety and tolerability at supratherapeutic exposures.

Objectives and Endpoints

PART-1: SAD

Objectives	Endpoints
Primary:	**Primary:**
• To assess the safety and tolerability following a single dose of PF-07321332 alone or in combination with a PK boosting agent (ritonavir).	• Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs. • Frequency and magnitude of abnormal laboratory findings. • Changes from baseline in vital sign measurements and 12-lead ECG parameters.
Secondary:	**Secondary:**

• To assess the plasma PK profile of PF-07321332 following single ascending doses of PF-07321332 alone or in combination with a PK boosting agent (ritonavir).	• Plasma PK parameters of PF-07321332:
	  • C_{max}, T_{max}, AUC_{last}, C_{max}(dn), AUC_{last}(dn).
	  • If data permit, AUC_{inf}, AUC_{inf}(dn), $t_{½}$, V_z/F, and CL/F.

Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To explore metabolites in plasma, urine, and feces, if data permit.	• Qualitative characterization of metabolites of PF-07321332 in pooled plasma, urine, and feces if data permit.
• Quantitative excretion of drug-related material using ^{19}F-NMR spectroscopy, if data permit.	• Total excretion of drug-related material in urine and feces separately, and both routes combined, expressed as a percent of total dose administered, if data permit.

• To determine the oral bioavailability of a tablet formulation of PF-07321332 relative to suspension, if evaluated (Optional).	• The ratio of AUC_{last}, AUC_{inf} and C_{max} of tablet formulation and suspension.
• To evaluate the effect of food (high fat meal) on the exposure of PF-07321332 following a single oral dose of PF-07321332 tablet formulation, if evaluated (Optional).	• The ratio of AUC_{last}, AUC_{inf} and C_{max} under fed condition and fasted condition.

PART-2: MAD (including optional Japanese cohort)

Objectives	Endpoints
Primary:	**Primary:**
• To assess the safety and tolerability following multiple ascending doses of PF-07321332 alone or in combination with a PK boosting agent (ritonavir).	• Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs. • Frequency and magnitude of abnormal laboratory findings. • Changes from baseline in vital sign measurements and 12-lead ECG parameters.
Secondary:	**Secondary:**

• To assess the plasma PK profile of PF-07321332 on Days 1, 5 and 10 following multiple ascending doses of PF-07321332 alone or in combination with a PK boosting agent (ritonavir).	• Plasma PK parameters of PF-07321332:
	  • C_{max}, T_{max}, AUC_{tau} (where tau=8 hours for TID dosing or 12 hours for BID dosing), C_{min}, C_{max}(dn), AUC_{tau}(dn), C_{av}, R_{ac}, $R_{ac,Cmax}$, PTR,CL/F and V_z/F.
	  • If data permit, $t_{½}$.

• To assess the urinary PK profile of PF-07321332 on Day 10 following multiple ascending doses of PF-07321332 alone or in combination with a PK boosting agent (ritonavir).	• PF-07321332 urinary PK parameters: • Ae_{tau} and Ae_{tau}%, CL_r.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To explore metabolites in plasma if data permit.	• Qualitative characterization of metabolites of PF-07321332 in pooled plasma if data permit.
• To explore PK by microsampling technique(s), if evaluated (Optional).	• Concentration of PF-07321332, if evaluated.

PART-3: Relative Bioavailability/Food Effect Cohort

Objectives	Endpoints
Primary:	**Primary:**
• To determine the oral bioavailability of a tablet formulation of PF-07321332 relative to suspension.	• The ratio of AUC_{last}, AUC_{inf} and C_{max} of tablet formulation and suspension.
Secondary:	**Secondary:**
• To evaluate the effect of food (high-fat high-calorie meal) on the exposure of PF-07321332 following a single oral dose of PF-07321332 tablet formulation.	• The ratio of AUC_{last}, AUC_{inf} and C_{max} of tablet formulation under fed condition and fasted condition.
• To determine the pharmacokinetics of PF-07321332 following oral administration of tablet and suspension of PF-07321332.	• Plasma PK parameters of PF-07321332: T_{max}, C_{max}, AUC_{last}, C_{max}(dn), AUC_{last}(dn), if data permit AUC_{inf}, AUC_{inf}(dn), $t_{½}$, CL/F, V_z/F.
• To determine the safety and tolerability of PF-07321332 following oral administration of tablet and suspension of PF-07321332.	• Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs. • Frequency and magnitude of abnormal laboratory findings. • Changes from baseline in vital sign measurements and 12-lead ECG parameters.
CCI [redacted]	[redacted]
[redacted]	[redacted]

PART-4: Metabolism and Excretion

Objectives	Endpoints
Primary:	**Primary:**
• To determine the extent of excretion of drug related material in urine and feces after a single oral administration of PF-07321332 with PK boosting agent ritonavir.	• Total recovery of drug related material in urine and feces separately, and both routes combined, expressed as a percent of total oral dose administered.
Secondary:	**Secondary:**
• To determine the pharmacokinetics of PF-07321332 following oral administration of PF-07321332 with PK boosting agent ritonavir.	• Plasma PK parameters of PF-07321332: T_{max}, C_{max}, AUC_{last}, if data permit AUC_{inf}, $t_{½}$, CL/F, V_z/F.

• To determine the safety and tolerability of PF-07321332 after a single oral administration of PF-07321332 with PK boosting agent ritonavir.	• Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs. • Frequency and magnitude of abnormal laboratory findings. • Changes from baseline in vital sign measurements and 12-lead ECG parameters.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To characterize the metabolic profile and identify circulating and excreted metabolites following administration of a single oral dose of PF-07321332 with PK boosting agent ritonavir, if possible.	• Metabolic profiling/identification and determination of relative abundance of PF-07321332 and the metabolites of PF-07321332 in plasma, urine, and feces, if possible.

PART-5: Supratherapeutic Exposure (NH CRU only)

Objectives	Endpoints
Primary:	**Primary:**
• To assess the safety and tolerability of a supratherapeutic exposure of PF-07321332 with a PK boosting agent (ritonavir) administered as split dosing.	• Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs. • Frequency and magnitude of abnormal laboratory findings. • Changes from baseline in vital sign measurements and 12-lead ECG parameters.
Secondary:	**Secondary:**

• To assess the plasma PK of PF-07321332 at a supratherapeutic exposure of PF-07321332 with a PK boosting agent (ritonavir) administered as split dosing.	• Plasma PK parameters of PF-07321332:
	  • C_{max}, T_{max}, AUC_{last}
	  • If data permit, AUC_{inf}, $t_{½}$.

Overall Design

The study will combine PART-1: single ascending dose (SAD), PART-2: multiple ascending dose (MAD, including optional Japanese cohort), PART-3: relative bioavailability and food effect cohort, PART-4: metabolism and excretion study and PART-5: supratherapeutic exposure cohort. PART-1 and 2 are randomized, double-blind (participant and investigator blinded), sponsor open, placebo controlled, single and multiple dose escalation study. PART-3 is a randomized open label study to evaluate relative bioavailability and food effect. PART-4 is an open-label, non-randomized, single period to evaluate the metabolism and excretion of PF-07321332. PART-5 is a double-blind, sponsor-open, randomized, cross-over study to evaluate safety and tolerability at supratherapeutic exposures to be conducted at NH CRU only.

PART-1: SAD

SAD will include 2 interleaving cohorts with a total of approximately 12 participants planned (approximately 6 participants in each cohort), with 4-period cross-over in each cohort. Period 3 and 4 are optional periods which may be used to further explore PK at additional doses or PK in combination with ritonavir or relative bioavailability of a new formulation or food effect (high-fat high-calorie meal), etc, based on emerging safety, tolerability and PK assessments.

There will be a washout interval of ≥5 days between dosing to a given participant. Participants will be required to stay at the CRU for the duration of the washout interval. However, they may be released at the discretion of the investigator. The washout interval may be adjusted based on data emerging from previous cohorts/periods.

PART-2:MAD

The first MAD cohort may start after a same total daily dose, which provides comparable or higher total daily exposure (24 h) in SAD than the projected total daily steady-state exposure (over 24 h) at the starting dose in MAD, is found safe and well tolerated in PART-1 of the study. The proposed MAD study design will be parallel cohorts, with 10 days of dosing. PART-2 will consist of approximately 2 to 5 cohorts including up to 3 optional cohorts (Cohort 5, 6 and 7) with approximately 6 participants in each cohort. Cohort 7 is an optional Japanese participants cohort.

PART-3: RBA and Food effect

If conducted, this cohort will be an open label, randomized, 3-period, 3-sequence cross-over single dose cohort evaluating the relative bioavailability of PF-07321332 tablet compared to PF-07321332 oral suspension and to evaluate the effect of food on the bioavailability of the PF-07321332 tablet in healthy adult participants. A maximum of 18 participants may be enrolled in PART-3 of the study with approximately equal number of participants randomized to each sequence. There will be a washout interval of at least 2 days between dosing in each period. Participants will be required to stay at the CRU until discharge in the last period. The washout interval may be adjusted based on data emerging from SAD and MAD cohorts.

PART-4: Metabolism and Excretion

This part will include a single cohort of approximately 6 male participants with at least 4 completers. All participant will receive 4 doses of 100 mg ritonavir as specified in the SoA. Each participant will receive a single dose of 300 mg of PF-07321332 on Day 1 0h along with 100 mg of ritonavir after at least 10h of fasting. The participants will be discharged on Day 11.

In PART-1 and 2, treatment sequences, actual doses, dose increments and dosing regimen may be adjusted, and intermediate or alternative dose levels may be substituted during the study based on emerging safety, tolerability, and PK data.

PART-5: Supratherapeutic Exposure (NH CRU only)

This cohort will include up to 12 participants in a 4-period (Periods 3 and 4 are optional), double-blind, sponsor-open, randomized, 2-sequence, cross-over design to explore safety, tolerability and PK at supratherpeutic exposure. For each period, participants will receive split dosing administration (3 doses) of PF-07321332 or placebo at short intervals (approximately 2 h of the previous dose) after at least 2 hours after the breakfast on Day 1. Baseline ECGs, vitals [redacted] will be collected before breakfast. The first 2 periods will be a cross-over where participants will be given PF-07321332 at 0, 2 and 4 hours at the dose of 750 mg (or placebo) with ritonavir. Periods 3 and 4 (if conducted) will only be conducted if supratherapeutic concentrations are not reached in Period 1. In periods 3 and 4 (if conducted) doses may be given up to 4 times for a total daily dose not exceeding 3000 mg, with or without food.

Number of Participants

A total of up to 78 participants (12 in PART-1: SAD, up to 30 [with 2 cohorts and 3 optional cohorts] in PART-2: MAD, a maximum of 18 in PART-3: Relative Bioavailability/Food Effect cohort,6 participants in PART-4: Metabolism and Excretion cohort and up to 12 participants in PART-5: Supratherapeutic Exposure) are planned to be randomized in this study. At the discretion of the sponsor and investigator, participant who were enrolled in PART-2 may be enrolled in PART-5.

Intervention Groups and Duration

In all 5 parts, participants will be screened within 28 days of their first dose of investigational product. Participants will be admitted to the CRU on Day -1 or earlier and may be discharged at investigator discretion following completion of assessments per SoA.

PART-1: SAD

For each period, approximately 4 participants will receive a single oral dose of PF-07321332, and approximately 2 participants will receive placebo after at least 10h of fast. Each participant may receive either a single dose of PF-07321332 or a placebo during each period. In each period, participants on active treatment in Cohort 1 will receive D1, D3, D5 and D7 (optional) dose levels (Section 4.3, Table 9) and Cohort 2 will receive D2, D4, D6 and D8 (optional) dose levels (Section 4.3) in dose escalation format. In SAD cohorts requiring co-administration of PF-07321332/placebo with ritonavir, all participants (active and placebo) will receive 3 doses of 100 mg of ritonavir at -12h, 0h (coadministered with PF-07321332) and 12h.

PART-2: MAD

In each cohort, approximately 4 participants will receive one of the escalating doses of PF-07321332 and approximately 2 participants will receive matching placebo after at least 7h of fast for the morning dose and 2h of fast for the next dose(s). From Day 1 – Day 9, PF-07321332/placebo will be administered every 8h (ie, TID) when administered alone and every 12h (ie, BID) when co-administered with ritonavir; however, PF-07321332/placebo alone may also be administered every 12h (ie, BID), if needed, based on emerging PK data. On Day 10, PF-07321332/placebo will be administered at approximately 0h for TID or BID regimen. In MAD cohorts requiring co-administration of PF-07321332/placebo with ritonavir, all participants (active and placebo) will receive 100 mg of ritonavir as specified in the SoA.

PART-3: RBA and Food effect

The dose level to be evaluated in relative bioavailability/food effect cohort will be determined based on emerging PK and safety data from SAD and MAD cohorts. The selected dose will be equal or lower than the highest tolerated dose already evaluated in SAD. There will be a washout interval of at least 2 days between dosing in each period. Participants will be required to stay at the CRU until the discharge in last period. The washout interval may be adjusted based on data emerging from SAD and MAD cohorts.

PART-4: Metabolism and Excretion

This part will include a single cohort of approximately 6 male participants with at least 4 completers. All participants will receive 4 doses of 100 mg ritonavir as specified in the SoA. Each participant will receive a single dose of 300 mg of PF-07321332 on Day 1 0h along with 100 mg of ritonavir after at least 10h of fasting. The plasma for PK and metabolic profiling will be collected as specified in SoA. The urine and feces will be collected for 10 days as specified in SoA to determine excretion routes and metabolite profiling. Dietary fiber supplementation and use of laxative (Section 5.3.1.1) should be considered with the goal to facilitate at least once daily bowel movement. The participants will be discharged on Day 11.

PART-5: Supratherapeutic Exposure

In this part, for each period, participants will receive split dosing (3 doses) of PF-07321332 or placebo at short intervals (within 2 h of the previous dose). Participants will receive first split dose of PF-07321332/placebo oral suspension at approximately 08:00 hours (±2 hours) at least 2h after the morning breakfast per the So. The second and third split doses will be administered at approximately 2h and 4h after the first dose, respectively.

A total of 3 doses of 100 mg ritonavir tablet will be administered as a PK boosting agent as per SoA (approximately 12 hours before the first split dose, concurrently with the first split dose and approximately 12 hours after the first split dose).

For all Parts, a telephone follow-up contact will occur between 28 to 35 days from the day of last administration of study intervention. At the discretion of the investigator, telephone follow-up contact may be substituted with an on-site visit in case of additional follow-up of open AEs or clinically significant laboratory findings.

The total planned duration of participation, from Screening visit to the Follow-up phone call, may be approximately 12 weeks for PART-1 and PART-5, 10 weeks for PART-2 and PART-3 and 8 weeks for PART-4.

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

The sample size for PART-1 and PART-2 of the study has been chosen based on the need to minimize exposure of healthy participants to a new chemical entity and the requirements to provide adequate safety and toleration and PK information at each dose level.

For PART-3, the sample size will provide adequate precision to compare the relative bioavailability of a tablet formulation of PF-07321332 relative to oral suspension.

For Part 4: A sample size of approximately 6 male participants (with at least 4 completers) is chosen based on the industry standard sample size for metabolism and excretion studies. This sample size was not justified by any empirical data or hypothesis testing criteria.

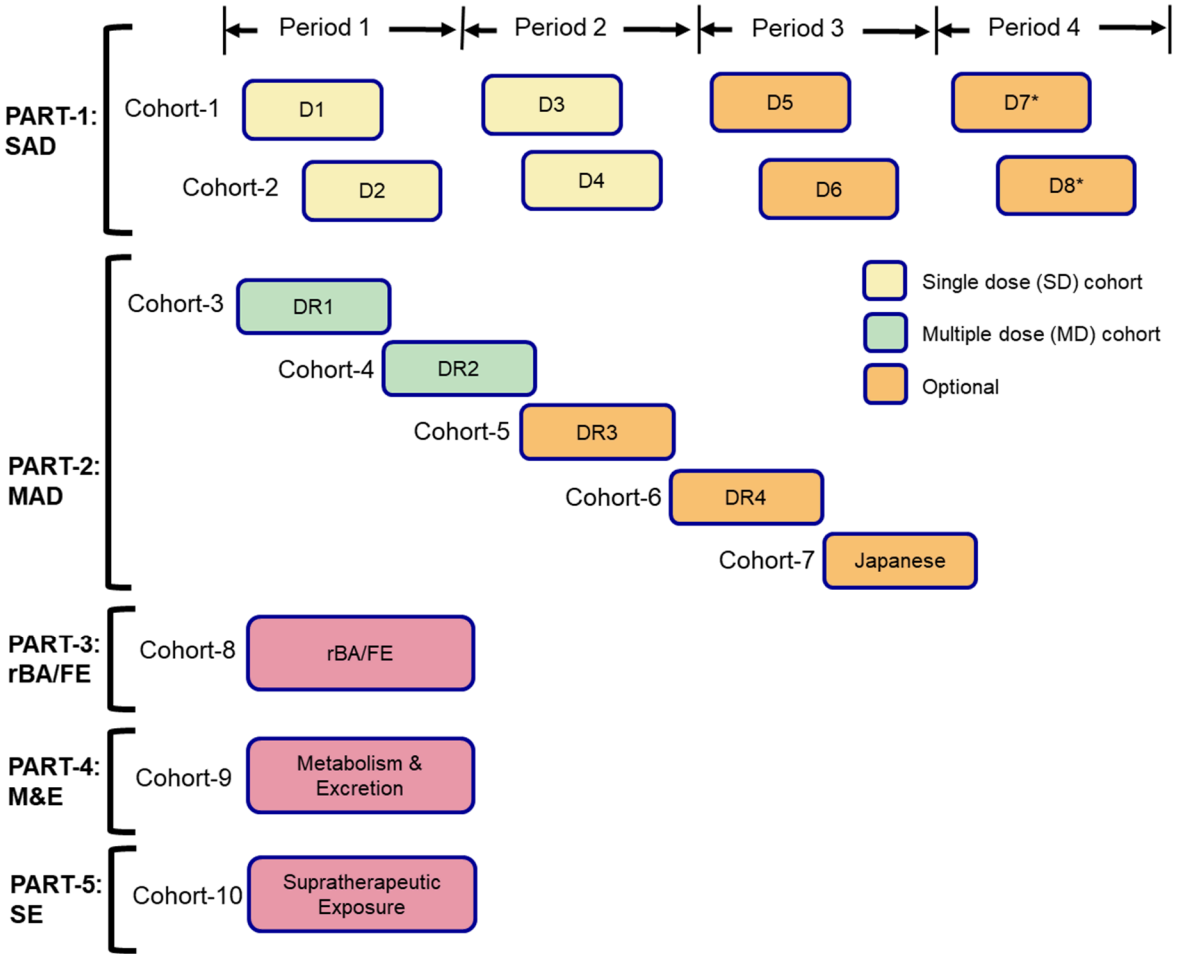
For Part 5: A sample size of up to 12 participants (with at least 10 completers) is chosen based on the need to provide adequate safety, tolerability and PK information at each dose level and/or administration schedule.

The data from the 5 parts of this study will be analyzed and reported separately in a single CSR.

All safety analyses will be performed on the safety analysis set, which is defined as all participants randomly assigned to study intervention and who receive at least one dose of study intervention. Participants will be analyzed according to the product they actually received. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. Plasma concentrations will be listed and summarized descriptively by PK sampling time and treatment. The plasma PK parameters will be summarized descriptively by dose. No formal inferential statistics will be applied to the PK data apart from the comparisons of formulation and food effect in either PART-1 or PART-3, if conducted.

1.2. Schema

Figure 1. C4671001 Study Design



*Optional dose levels in SAD/MAD may be used to explore higher doses or food effect or relative bioavailability or in combination with ritonavir (see more details in Section 4.1). Dosing with food may be done in one or more cohorts in SAD/MAD based on the emerging PK/safety data. PART-4: Metabolism and Excretion (M&E) is an open-label single dose cohort (see more details in Section 4.1). PART-5: supratherapeutic exposure (SE) is a double-blind, sponsor-open, randomized, cross-over cohort (See more details in Section 4.1).

SAD dose levels D1 to D8 and MAD dosing regimens DR1 to DR4 are listed in Table 9 and Table 10, respectively in Section 4.3.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Table 1. PART-1: Single Ascending Dose Cohorts

Visit Identifier[a]	**Screening**	**Periods 1-4**[b]																**F/U Contact**[c,j]	**E/T**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**											**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 29-36**	
Planned Hours Post Dose			**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24h**	**48h**	**72h**	**96h**	**120h**		
Informed consent	X																			
Inclusion/exclusion criteria	X	X[d]																		
Demographics (including height & weight)	X																			
Medical/Medicine history	X	X[d]																		
SARS-CoV-2 RT-PCR[e]	X	X[d]														X[d]				
COVID-19 Assessment[r]	X	X	X											X	X	X	X[h]			
CRU Confinement[f]		X	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X[h]			
Physical exam[g]	X	X																		X
Vital signs (temperature, respiratory rate, pulse rate, blood pressure)	X		X		X	X	X	X	X	X		X		X						X
12-Lead ECG (triplicate)	X		X		X	X	X	X	X	X		X		X						X
Continuous cardiac telemetry monitoring[i]			X	→	→	→	→	→	→	→	X									
Contraception check	X	X[d]														X[j]			X	X
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		X	X
Study intervention administration																				
PF-07321332 or Placebo[q]			X																	
Ritonavir (if used)		X[k]	X									X								

Table 1. PART-1: Single Ascending Dose Cohorts

Visit Identifier[a]	Screening	Periods 1-4[b]																F/U Contact[c,j]	E/T
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**											**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 29-36**	
Planned Hours Post Dose			**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24h**	**48h**	**72h**	**96h**	**120h**		
Blood Samples for:																				
Pregnancy test (WOCBP only)	X	X[d]														X[j]				X
Safety laboratory (4h fasting except 6h sample)	X	X								X				X	X	X				X
HIV, HBsAg, HBsAb,[l] HBcAb and HCVAb	X																			
Serum FSH (post-menopausal females only)	X																			
CCI																				
Plasma Pharmacokinetics (PF-07321332)			X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
^{19}F-NMR measurements and metabolite profiling[p]			X			X			X			X		X						
Urine Samples for:																				
Drug screen testing	X	X[d]																		
Urinalysis	X	X								X				X	X	X				X
^{19}F-NMR Measurement and metabolic profiling[n,p]		X	X	→	→	→	→	→	→	→	→	→	→	X	X	X	X	X		
Feces Collection for:																				
^{19}F-NMR Measurement and metabolic profiling[o,p]		X	X	→	→	→	→	→	→	→	→	→	→	X	X	X	X	X		

a. **Visit Identifier:** Day relative to start of study treatment (Day 1).

b. **Period 1 to Period 4:** Washout duration of at least 5 days between dosing. May be adjusted based on emerging data. Period 3 and 4 are optional.

c. **F/U Contact:** Follow-up phone call may occur via telephone 28-35 days after the last dose of investigational product in the final period.

d. **Period 1 only.** If participants are discharged and readmitted, follow all Period 1 activities **except I/E criteria, medical history update** CCI

e. **SARS-CoV-2 RT-PCR:** Screening, admission (Day -1), 4 days following admission (Day 4), ad hoc test based on symptoms, and for ambulatory on-site visits.

f. **CRU Confinement:** Participants will be required to stay at CRU from Day -1 in Period 1 until completing Day 4 (72h) activities in the final period.

g. **Physical Examination:** Complete physical examination will be conducted at Screening or upon admission (Day -1) in Period 1. Brief physical examination may be performed at other times, as appropriate, for findings during previous examination or new/open AEs, at investigator's discretion.

h. **COVID-19 assessment and PCRU confinement**: Not done in the last period.

i. **Continuous cardiac telemetry monitoring:** Baseline telemetry to be recorded for at least 2 hours between admission and prior to dosing in Period 1 only while awake. Post dose telemetry will continue for 8 hours after the start of dosing for each period.

j. **Last Period only,** unless discharged at the discretion of the investigator.

k. **Ritonavir:** To be administered approximately 12 hours before PF-07321332 administration on Day 1.

l. **HBsAb:** Can be done either automatically or only if HBcAb or HBsAg is positive, as per local practices.

c
cl [redacted]

n. **Urine Sample Collection:** "Blank" pre-dose urine sample to be collected within 24h prior to dosing and at each subsequent 24h interval until dosing in next period or up to 120 h, whichever is earlier. Forced void into the collection container at the end of each collection period.

o. **Feces Sample Collection:** "Blank" fecal sample to be collected at baseline from at least one bowel movement during the 48h predose interval. Fecal samples will also be collected at intervals of 0-24 h post oral dose, and at each subsequent 24h interval until dosing in next period or up to 120 h, whichever is earlier.

p. **Metabolite profiling and quantitative F-NMR:** conducted for Cohort 1, Period 2 only.

q. **Study Drug Administration:** The study drug should be administered after approximately at least 10h of fast in the morning dose (0h). For dosing in fed condition, please refer Section 5.3.1.

r. **COVID-19 Assessment:** Temperature check as per local requirement. Questionnaire before admission.

Table 2. PART-2: Multiple Ascending Dose Cohorts (Including Optional Japanese Cohort)

Visit Identifier[a]	Screening														F/U Contact[b]	ET
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1[k]**	**Day 2**	**Day 3**	**Day 4**	**Day 5[k]**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10[k]**	**Day 11**	**Day 12**	**Day 38-45**	
Informed consent	X															
Inclusion/exclusion criteria	X	X														
Demographics (including height & weight)	X															
Medical/Medicine history	X	X														
SARS-CoV-2 RT-PCR[c]	X	X				X										
COVID-19 Assessment[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CRU Confinement[d]		X	→	→	→	→	→	→	→	→	→	→	→	X		
Physical exam[e]	X	X														X
Supine Vital signs (temperature, respiratory rate, pulse rate, blood pressure)[f]	X		X	X			X			X		X		X		X
12-Lead ECG (triplicate)[f]	X		X	X			X			X		X		X		X
Contraception check	X	X												X	X	X
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	X	X	X
Study intervention administration																
PF-07321332 or Placebo (BID or TID)[g]			X	X	X	X	X	X	X	X	X	X				
Ritonavir BID (if used)[l]			X	X	X	X	X	X	X	X	X	X				
Blood samples for:																
Pregnancy test (WOCBP only)	X	X												X		X
Safety laboratory (4h fasting)[o]	X	X		X			X	X		X		X		X		X
TSH and Free T4	X[q]	X[q]										X				
HIV, HBsAg, HBsAb[n], HBcAb and HCVAb	X															
Serum FSH (post-menopausal females only)	X															
CCI [redacted]			[redacted]													
Plasma Pharmacokinetics (PF-07321332)			X	Xj	Xj		X	Xj		Xj		X	Xj	Xj		X
Metabolite profiling			X									X				

Table 2. PART-2: Multiple Ascending Dose Cohorts (Including Optional Japanese Cohort)

Visit Identifier[a]	Screening														F/U Contact[b]	ET
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1[k]**	**Day 2**	**Day 3**	**Day 4**	**Day 5[k]**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10[k]**	**Day 11**	**Day 12**	**Day 38-45**	
Optional Microsampling Pharmacokinetics (PF-07321332)[p]								X[j]		X[j]						
Urine samples for:																
Drug screen testing	X	X														
Urinalysis[o]	X	X		X			X	X		X		X		X		X
Pharmacokinetics			X									X				

a. **Visit Identifier:** Day relative to start of study treatment (Day 1).

b. **F/U Contact:** Follow-up contact may occur via telephone and must occur 28 to 35 days after the last dose of investigational product.

c. **SARS-CoV-2 RT-PCR:** Screening, admission (Day -1), 4 days following admission (Day 4), ad hoc test based on symptoms, and for ambulatory on-site visits.

d. **CRU Confinement:** Participants will be required to stay at CRU from Day-1 until completing Day 12 activities.

e. **Physical Examination:** Complete physical examination will be conducted at Screening or upon admission (Day -1). Brief physical examination may be performed at other times, as appropriate, for findings during previous examination or new/open AEs, at investigator's discretion.

f. **Vital signs and 12-lead ECG:** Except on D1, D5 and D10, all vital signs and ECGs are to be collected pre-dose. on D12, collected 48h after last dose of PF-07321332/placebo.

g. **Study drug administration:** From Day 1 – Day 9 at approximately 0, 8 and 16 h for TID regimen (ie, every 8 h) of PF-07321332/placebo alone and at 0 and 12h for BID regimen (ie, every 12h). On Day 10, at approximately 0h for TID or BID regimen of PF-07321332/placebo. The study drug should be administered after approximately at least 7h of fast in the morning dose (0h) and at least 2 hours of fast for afternoon and/or evening doses. For dosing in fed condition, please refer Section 5.3.1.

[redacted]

j. **Plasma PK sample and optional microsampling PK sample collections:** To be collected prior to morning dosing, except D11 and 12 which is at 24h and 48 h after last dose of PF-07321332/placebo, respectively.

k. **Day 1; 5 and 10:** Refer to Table 3.

l. **Ritonavir dosing:** To be used with BID dosing of PF-07321332/placebo only. On Day 10 12h Ritonavir will be administered without PF-07321332/placebo.
m. **COVID-19 Assessment:** Temperature check as per local requirement. Questionnaire before admission.
n. **HBsAb:** Can be done either automatically or only if HBcAb or HBsAg is positive, as per local practices.
o. **Safety labs and urinalysis:** should be taken pre-dose only, except on Day 5 (refer to Table 3).
p. **Optional Microsampling exploratory PK sample:** To be collected only at NH CRU.
q. **TSH and Free T4**: Must be collected at least once before dosing. PI may choose to either collect at screening or Day -1 or both.

Table 3. PART-2: PK Days (Day 1, Day 5, Day 10) in MAD Cohorts

Visit Identifier[a]	Treatment Period on PK Days																													
Days Relative to Day 1	**Day 1**										**Day 5**										**Day 10**									
Planned Hours Post 1st Dose on that day	**0[b]**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**0[b]**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**0[b]**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**
COVID-19 assessment[c]	X								X		X								X		X								X	
Supine Vital signs (temperature, pulse rate, respiratory rate, blood pressure)	X										X		X		X						X		X		X					
12-Lead ECG (Triplicate)	X										X		X		X						X		X		X					
Study intervention administration																														
PF-07321332 or Placebo (TID dosing)[d]	X							X		X	X							X		X	X									
PF-07321332 or Placebo (BID dosing)[d]	X								X		X								X		X									
Ritonavir BID (if used)[h]	X								X		X								X		X								X	
Blood samples for:																														
Safety laboratory (4h fasting except 6h sample on Day 5)											X						X				X									
TSH and Free T4																					X									
CCI [redacted]	[redacted]																													
Plasma Pharmacokinetics (PF-07321332) if TID dosing	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X
Plasma Pharmacokinetics (PF-07321332) if BID dosing	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Metabolite Profiling	X																				X		X			X		X	X	
Urine samples for:																														
Urinalysis											X						X				X									
Pharmacokinetics and metabolic profiling (TID dosing)	X[e]																				X	→	→	→	→	→	→	X		
Pharmacokinetics and metabolic profiling (BID dosing)	X[e]																				X	→	→	→	→	→	→	→	X	

a. **Visit Identifier**: Day relative to start of study treatment (Day 1).

b. **Day 1-0H, Day 5-0H and Day 10-0H**: Predose sample collection/procedure, except for study intervention administration.

c. **COVID-19 assessment:** Temperature check as per local requirement. Questionnaire before admission.

d. **PF-07321332 or placebo administration:** Morning dose (0h) to be administered after at least 7h of fast. Afternoon dose (8h) and/or evening doses (12h or 16h) require at least 2h fast before dosing. For dosing in the fed condition, please refer Section 5.3.1.

e. **Urine sample for PK and metabolic profiling:** A single aliquot of blank urine to be collected before dosing.

[redacted]

h. **Ritonavir dosing**: To be used with BID dosing of PF-07321332/placebo only. On Day 10, 12h Ritonavir will be administered without PF-07321332/placebo.

Table 4. PART-3: Relative Bioavailability/Food Effect Cohort

Visit Identifier[a]	Screening	Periods 1-3[b]											F/U Contact[c]	E/T
Days Relative to Day 1	**Days -28 to -2**	**Day -1[d]**	**Day 1**									**Day 2**	**Day 3[i]**	**Day 29-36**	
Planned Hours Post Dose			**0**	**0.5**	**1**	**1.5**	**2**	**4**	**8**	**12**	**16**	**24h**	**48h**		
Informed consent	X														
Inclusion/exclusion criteria	X	X													
Demographics (including height & weight)	X														
Medical/Medicine history	X	X													
SARS-CoV-2 RT-PCR[e]	X	X													
COVID-19 Assessment[n]	X	X	X							X		X	X		
CRU Confinement[f]		X	→	→	→	→	→	→	→	→	→	→	X		
Physical exam[g]	X	X													X
Supine Vital signs[h] (temperature, respiratory rate, pulse rate, blood pressure)	X		X										X		X
12-Lead ECG (single)[h]	X		X										X		X
Contraception check	X	X											X	X	X
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	X	X	X
Study intervention administration															
PF-07321332[m]			X												
Blood Samples for:															
Pregnancy test (WOCBP only)	X	X											X		X
Safety laboratory (4h fasting)	X	X											X		X
HIV, HBsAg, HBsAb,[j] HBcAb and HCVAb	X														
Serum FSH (post-menopausal females only)	X														
CCI [redacted]			[redacted]												
Plasma Pharmacokinetics (PF-07321332)			X	X	X	X	X	X	X	X	X	X	X		X
Urine samples for:															
Urine drug screen testing	X	X													
Urinalysis	X	X											X		X
Other Assessments															
CCI [redacted]			[redacted]												

a. **Visit Identifier:** Day relative to start of study treatment (Day 1).

b. **Period 1 to Period 3:** Washout duration of at least 2 days between dosing. May be adjusted based on emerging data.

c. **F/U Contact:** Follow-up phone call may occur via telephone approximately 28 to 35 days after the last dose of investigational product in the final period.

[redacted]

e. **SARS-CoV-2 RT-PCR:** Screening, admission (Day -1), 4 days following admission in Period 1, ad hoc test based on symptoms, and for ambulatory on-site visits.

f. **CRU Confinement:** Participants will be required to stay at CRU from Day-1 until completing Day 3 (48h) activities in the final period.

g. **Physical Examination:** Complete physical examination will be conducted at Screening or upon admission (Day -1) in Period 1. Brief physical examination may be performed at other times, as appropriate, for findings during previous examination or new/open AEs, at investigator's discretion.

h. **12-lead ECG and Vitals:** Single ECG. Based on emerging safety data, additional ECGs (including triplicate ECG) and/or vital measurements may be added.

i. Last Period only.

j. **HBsAb:** Can be done either automatically or only if HBcAb or HBsAg is positive, as per local practices.

[redacted]

m. **Study Drug Administration:** The study drug should be administered after approximately at least 10h of fast. For dosing in fed condition, please refer Section 5.3.1.

n. **COVID-19 Assessment:** Temperature check as per local requirement. Questionnaire before admission.

Table 5. PART-4: Metabolism and Excretion Cohort

Visit Identifier[a]	Screening																	F/U Contact[b]	E/T
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**										**Day 2**	**Day 3**	**Day 4**	**Day 5-10**	**Day 11**	**Day 29-36**	
Planned Hours Post Dose			**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24h**	**48h**	**72h**	**96h-216h**	**240h**		
Informed consent	X																		
Inclusion/exclusion criteria	X	X																	
Demographics (including height & weight)	X																		
Medical/Medicine history	X	X																	
SARS-CoV-2 RT-PCR[c]	X	X													X				
COVID-19 Assessment[k]	X	X	X											X	X	X	X	X		
CRU Confinement		X[l]	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	X		
Physical exam[d]	X	X																	X
Vital signs (pulse rate, blood pressure)	X		X															X		X
12-Lead ECG (Single)	X		X															X		X
Contraception check	X	X																X	X	X
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Study intervention administration																				
PF-07321332[j]			X																	
Ritonavir		X[e]	X									X		X						
Blood Samples for:																				
Safety laboratory (4h fasting)	X	X																X		X
TSH and Free T4	X[m]	X[m]																X		
HIV, HBsAg, HBsAb,[f] HBcAb and HCVAb	X																			
CCI [redacted]			[redacted]																	
Plasma Pharmacokinetics (PF-07321332)			X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Drug-related material measurement and metabolite profiling			X			X		X	X		X	X		X						
Urine Samples for:																				
Drug screen testing	X	X																		

Table 5. PART-4: Metabolism and Excretion Cohort

Visit Identifier[a]	Screening																	F/U Contact[b]	E/T
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**										**Day 2**	**Day 3**	**Day 4**	**Day 5-10**	**Day 11**	**Day 29-36**	
Planned Hours Post Dose			**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24h**	**48h**	**72h**	**96h-216h**	**240h**		
Urinalysis	X	X																X		X
Drug related material measurement and metabolic profiling[h]		X	X	→	→	→	→	→	→	→	→	→	→	X	X	X	X	X		
Feces Collection for:																				
Drug related material measurement and metabolic profiling[i]		X	X	→	→	→	→	→	→	→	→	→	→	X	X	X	X	X		

a. **Visit Identifier:** Day relative to start of study treatment (Day 1).
b. **F/U Contact:** Follow-up phone call may occur via telephone 28-35 days after the last dose of investigational product.
c. **SARS-CoV-2 RT-PCR:** Screening, admission, 4 days following admission, ad hoc test based on symptoms.
d. **Physical Examination:** Complete physical examination will be conducted at Screening or upon admission (Day -1). Brief physical examination may be performed at other times, as appropriate, for findings during previous examination or new/open AEs, at investigator's discretion.
e. **Ritonavir:** To be administered approximately 12 hours before PF-07321332 administration on Day 1.
f. **HBsAb:** Can be done either automatically or only if HBcAb or HBsAg is positive, as per local practices.
[redacted]
h. **Urine Sample Collection:** A "Blank" pre-dose urine sample to be collected within 24h prior to dosing. Post-dose urine samples need to be collected at intervals of 0-24h post oral dose, and at each subsequent 24h intervals until discharge. Forced void into the collection container at the end of each collection period.
i. **Feces Sample Collection:** A "Blank" fecal sample to be collected at baseline from at least 1 bowel movement during the 48h predose interval. Post-dose fecal samples will also be collected at intervals of 0-24h post oral dose, and at each subsequent 24h interval until discharge.
j. **Study Drug Administration:** The study drug should be administered after approximately at least 10h of fast in the morning dose (0h).
k. **COVID-19 Assessment:** Temperature check as per local requirement. Questionnaire before admission.
l. **CRU Confinement:** May be admitted earlier to facilitate pre-dose fecal collection. At the discretion of the investigator, one or more Day -1 assessments may be conducted at admission if admitted earlier.
m. **TSH and Free T4**: Must be collected at least once before dosing. PI may choose to either collect at screening or Day -1 or both.

Table 6. PART-5: Supratherapeutic Exposure (NH CRU only)

Visit Identifier[a]	Screening	Periods 1-4[b]													F/U Contact[c,i]	E/T
Days Relative to Day 1	Days -28 to -2	Day -1	Day 1											Day 2	Day 3	Day 4	Day 5	Day 29-36	
Planned Hours Post Dose			0	1	2	3	3.5	4	4.5	5	5.5	6	8	12	24h	48h	72h	96h		
Informed consent	X																			
Inclusion/exclusion criteria	X	X[d]																		
Demographics (including height & weight)	X																			
Medical/Medicine history	X	X[d]																		
SARS-CoV-2 RT-PCR[e]	X	X[d]															X[d]			
COVID-19 Assessment[n]	X	X	X												X	X	X	X		
CRU Confinement[f]		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X		
Physical exam[g]	X	X[d]																		X
Vital signs (temperature, respiratory rate, pulse rate, blood pressure)	X		X		X	X		X		X		X	X	X	X	X	X	X		X
12-Lead ECG (triplicate)[r]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Continuous cardiac telemetry monitoring[h]			X	→	→	→	→	→	→	→	→	→	→	X						
Contraception check	X	X[d]																X[i]	X	X
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Standardized meal[q]			X										X	X	X	X	X	X		
Study intervention administration																				
PF-07321332 or Placebo[m]			X		X			X												
Ritonavir		X[j]	X											X						
Blood Samples for:																				
Pregnancy test (WOCBP only)	X	X[d]																X[i]		X
Safety laboratory (fasted for 4 h)	X	X													X			X[i]		X
HIV, HBsAg, HBsAb,[k] HBcAb and HCVAb	X																			

Table 6. PART-5: Supratherapeutic Exposure (NH CRU only)

Visit Identifier[a]	Screening	Periods 1-4[b]																F/U Contact[c,i]	E/T
Days Relative to Day 1	Days -28 to -2	Day -1	Day 1												Day 2	Day 3	Day 4	Day 5	Day 29-36	
Planned Hours Post Dose			0	1	2	3	3.5	4	4.5	5	5.5	6	8	12	24h	48h	72h	96h		
Serum FSH (post-menopausal females only)	X																			
CCI [redacted]			[redacted]																	
Plasma Pharmacokinetics (PF-07321332)			X[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
TSH and free T4	X[o]	X[o]																X[i]		
Urine Samples for:																				
Drug screen testing	X	X[d]																		
Urinalysis	X	X[d]													C [redacted]		X	X[i]		X

a. **Visit Identifier:** Day relative to start of study treatment (Day 1).

b. **Period 1 to Period 4:** Washout duration of at least 5 days between 1st dosing in each period. Periods 3 and 4 are optional.

c. **F/U Contact:** Follow-up phone call may occur via telephone 28 to 35 days after the last dose of investigational product in the final period.

d. **Period 1 only.** If participants are discharged and readmitted, follow all Period 1 activities **except I/E criteria, medical history update** CCI [redacted]

e. **SARS-CoV-2 RT-PCR:** Screening, admission (Day -1), 4 days following admission (Day 4), ad hoc test based on symptoms, and for ambulatory on-site visits.

f. **CRU Confinement:** Participants will be required to stay at CRU from Day -1 in Period 1 until completing Day 5 (96h) activities in the final period.

g. **Physical Examination:** Complete physical examination will be conducted at Screening or upon admission (Day -1) in Period 1. Brief physical examination may be performed at other times, as appropriate, for findings during previous examination or new/open AEs, at investigator's discretion.

h. **Continuous cardiac telemetry monitoring:** Baseline telemetry to be recorded for at least 2 hours between admission and prior to dosing while awake. Post dose telemetry will continue for 12 hours after the start of dosing for each period.

i. **Last Period only,** unless discharged at the discretion of the investigator.

j. **Ritonavir:** To be administered approximately 12 hours before PF-07321332 administration on Day 1.

k. **HBsAb:** Can be done either automatically or only if HBcAb or HBsAg is positive, as per local practices.

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m. **Study Drug Administration:** The first split dosing of study drug should be at approximately 2h after the breakfast.

n. **COVID-19 Assessment:** Temperature check as per local requirement. Questionnaire before admission.

o. **TSH and Free T4**: Must be collected at least once before dosing in each period. PI may choose to either collect at screening or Period 1 Day -1 or both.

p. Pre-dose sample.

q. **Standardized meal:** On Day 1, the breakfast to be provided after collection of vitals, ECGs CCI and approximately 2h before the administration of study intervention at 0h and lunch to be provided at approximately 4h after the last administration of PF-07321332/placebo.

r. **ECG (triplicate):** To be collected in fasted state (>3h after the previous meal).

2. INTRODUCTION

PF-07321332 is a potent and selective inhibitor of the SARS-CoV-2 3CL protease, that is being developed as an oral treatment in patients with COVID-19.

2.1. Study Rationale

The current study is the first in human (FIH) study of PF-07321332 in healthy adult participants. It is a 5-part study combining PART-1: SAD, PART-2: MAD, PART-3: relative bioavailability/food effect, PART-4: metabolism and excretion and PART-5: supratherapeutic exposure (SE). PART-1 and 2 are a randomized, double-blind, sponsor-open, placebo-controlled trial to evaluate safety, tolerability and PK of single and multiple escalating oral doses of PF-07321332 in healthy adult participants and PART-3 is a randomized open label study to evaluate relative bioavailability and food effect of an oral tablet formulation. PART-2 of the study may also evaluate the safety, tolerability and PK in Japanese participants. PART-4 is an open-label, non-randomized, single period to evaluate the metabolism and excretion of PF-07321332. PART-5 is a double-blind, sponsor-open, randomized, cross-over cohort to evaluate safety and tolerability at supratherapeutic exposures.

2.2. Background

Disease Overview

In December 2019, COVID-19 was identified as a new, potentially fatal, respiratory infection caused by the novel coronavirus, SARS-CoV-2. The WHO declared COVID-19 a Public Health Emergency of International Concern on 20 January 2020 and further characterized the disease outbreak as a pandemic on 11 March 2020.[1]

COVID-19 manifests as a wide range of illnesses, from asymptomatic infection to severe pneumonia, ARDS and death. While the majority of cases (approximately 80%) are asymptomatic or mild,[2] patients who are hospitalized with COVID-19 may have significant morbidity and mortality,[3,4] and are at increased risk of developing complications such as severe inflammation associated with elevations in pro-inflammatory cytokines, ARDS, acute cardiac injury, thromboembolic events, hypercoagulability, and/or kidney injury.[5-9]

Current Treatment Options

As of the date of issuance of this protocol, only 1 anti-viral drug with activity against SARS-CoV-2, Remdesivir, an RNA polymerase inhibitor, has received approval in hospitalized patients with COVID-19.[10]

Antibody cocktails (containing casirivimab and imdevimab) and bamlanivimab received emergency use authorization for recently diagnosed patients with mild to moderate COVID-19 in high risk patients. Both these options are administered intravenously and require administration by healthcare professionals. As of the date of issuance of the protocol, no orally administered therapeutic intervention has been approved or received emergency use authorization in recently diagnosed individuals with COVID-19.

Despite these advances, there remains an urgent need for additional safe and more effective therapeutic interventions that shorten time to clinical recovery and prevent the progression of infection to more severe disease and death. The direct reduction of viral replication, through inhibition of other critical viral enzymes, offers an important mechanism as monotherapy or in combination, to achieve greater patient benefit.

Rationale for Development of PF-07321332

The coronavirus 3CL protease is a virally encoded enzyme that is critical to the SARS-CoV-2 replication cycle, analogous to other obligatory virally encoded proteases (eg, HIV Protease, HCV Protease).[11] Mutagenesis experiments with other coronaviruses and picornaviruses that are related to SARS-CoV-2 (picornavirus-like supercluster) have demonstrated that the activity of the 3CL protein (or the corresponding picornaviral 3C enzyme) is essential for viral replication. No close human analogs of coronavirus 3CL enzymes are known, suggesting that appropriate 3CL inhibitors may function as selective inhibitors of SARS-CoV-2 and other coronaviruses as therapeutic agents.

Inhibition of the SARS-CoV-2 3CL protease is a mechanism of action distinct from that of Remdesivir, which is a prodrug of an adenosine nucleoside analogue that interferes with SARS-CoV-2 RNA-dependent RNA polymerase.

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2.3. Benefit/Risk Assessment

PF-07321332 is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, and pharmacokinetic data for further clinical development.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07321332 may be found in the IB, which is the SRSD for this study. The SRSD for the Ritonavir[19] is the US FDA approved label and SmPC.

CCI [redacted]

	CCI	

2.3.2. Benefit Assessment

For healthy participants in this study, no clinical benefit is expected.

2.3.3. Overall Benefit/Risk Conclusion

PF-07321332 is not expected to provide any clinical benefit to healthy participants in this study. Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with administration of PF-07321332 is clinically acceptable.

3. OBJECTIVES AND ENDPOINTS

PART-1: SAD

Objectives	Endpoints
Primary:	**Primary:**
• To assess the safety and tolerability following a single dose of PF-07321332 alone or in combination with a PK boosting agent (ritonavir).	• Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs. • Frequency and magnitude of abnormal laboratory findings. • Changes from baseline in vital sign measurements and 12-lead ECG parameters.
Secondary:	**Secondary:**

• To assess the plasma PK profile of PF-07321332 following single ascending doses of PF-07321332 alone or in combination with a PK boosting agent (ritonavir).	• Plasma PK parameters of PF-07321332:
	  • C_{max}, T_{max}, AUC_{last}, C_{max}(dn), AUC_{last}(dn).
	  • If data permit, AUC_{inf}, AUC_{inf}(dn), $t_{½}$, V_z/F, and CL/F.

Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To explore metabolites in plasma, urine, and feces, if data permit.	• Qualitative characterization of metabolites of PF-07321332 in pooled plasma, urine, and feces if data permit.
• Quantitative excretion of drug-related material using ^{19}F-NMR spectroscopy, if data permit.	• Total excretion of drug-related material in urine and feces separately, and both routes combined, expressed as a percent of total dose administered, if data permit.
• To determine the oral bioavailability of a tablet formulation of PF-07321332 relative to suspension, if evaluated (Optional).	• The ratio of AUC_{last}, AUC_{inf} and C_{max} of tablet formulation and suspension.
• To evaluate the effect of food (high fat meal) on the exposure of PF-07321332 following a single oral dose of PF-07321332 tablet formulation, if evaluated (Optional).	• The ratio of AUC_{last}, AUC_{inf} and C_{max} under fed condition and fasted condition.

PART-2: MAD (including optional Japanese cohort)

Objectives	Endpoints
Primary:	**Primary:**
• To assess the safety and tolerability following multiple ascending doses of PF-07321332 alone or in combination with a PK boosting agent (ritonavir).	• Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs. • Frequency and magnitude of abnormal laboratory findings. • Changes from baseline in vital sign measurements and 12-lead ECG parameters.
Secondary:	**Secondary:**

• To assess the plasma PK profile of PF-07321332 on Days 1, 5 and 10 following multiple ascending doses of PF-07321332 alone or in combination with a PK boosting agent (ritonavir).	• Plasma PK parameters of PF-07321332:
	  • C_{max}, T_{max}, AUC_{tau} (where tau=8 hours for TID dosing or 12 hours for BID dosing), C_{min}, C_{max}(dn), AUC_{tau}(dn), C_{av}, R_{ac}, $R_{ac,Cmax}$, PTR,CL/F and V_z/F.
	  • If data permit, $t_{½}$.

• To assess the urinary PK profile of PF-07321332 on Day 10 following multiple ascending doses of PF-07321332 alone or in combination with a PK boosting agent (ritonavir).	• PF-07321332 urinary PK parameters: • Ae_{tau} and Ae_{tau}%, CL_r.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To explore metabolites in plasma if data permit.	• Qualitative characterization of metabolites of PF-07321332 in pooled plasma if data permit.
• To explore PK by microsampling technique(s), if evaluated (Optional).	• Concentration of PF-07321332, if evaluated.

PART-3: Relative Bioavailability/Food Effect Cohort

Objectives	Endpoints
Primary:	**Primary:**
• To determine the oral bioavailability of a tablet formulation of PF-07321332 relative to suspension.	• The ratio of AUC_{last}, AUC_{inf} and C_{max} of tablet formulation and suspension.
Secondary:	**Secondary:**
• To evaluate the effect of food (high-fat high-calorie meal) on the exposure of PF-07321332 following a single oral dose of PF-07321332 tablet formulation.	• The ratio of AUC_{last}, AUC_{inf} and C_{max} of tablet formulation under fed condition and fasted condition.
• To determine the pharmacokinetics of PF-07321332 following oral administration of tablet and suspension of PF-07321332.	• Plasma PK parameters of PF-07321332: $T_{max,}$ $C_{max,}$ AUC_{last}, C_{max}(dn), AUC_{last}(dn), if data permit AUC_{inf}, AUC_{inf}(dn), $t_{½}$, CL/F, V_z/F.

• To determine the safety and tolerability of PF-07321332 following oral administration of tablet and suspension of PF-07321332.	• Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs. • Frequency and magnitude of abnormal laboratory findings. • Changes from baseline in vital sign measurements and 12-lead ECG parameters.
CCI [redacted]	[redacted]
[redacted]	[redacted]

PART-4: Metabolism and Excretion

Objectives	Endpoints
Primary:	**Primary:**
• To determine the extent of excretion of drug related material in urine and feces after a single oral administration of PF-07321332 with PK boosting agent ritonavir.	• Total recovery of drug related material in urine and feces separately, and both routes combined, expressed as a percent of total dose administered.
Secondary:	**Secondary:**
• To determine the pharmacokinetics of PF-07321332 following oral administration of PF-07321332 with PK boosting agent ritonavir.	• Plasma PK parameters of PF-07321332: T_{max}, C_{max}, AUC_{last}, if data permit AUC_{inf}, $t_{½}$, CL/F, V_z/F.
• To determine the safety and tolerability of PF-07321332 after a single oral administration of PF-07321332 with PK boosting agent ritonavir.	• Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs. • Frequency and magnitude of abnormal laboratory findings. • Changes from baseline in vital sign measurements and 12-lead ECG parameters.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To characterize the metabolic profile and identify circulating and excreted metabolites following administration of a single oral dose of PF-07321332 with PK boosting agent ritonavir, if possible.	• Metabolic profiling/identification and determination of relative abundance of PF-07321332 and the metabolites of PF-07321332 in plasma, urine, and feces, if possible.

PART-5: Supratherapeutic Exposure (NH CRU only)

Objectives	Endpoints
Primary:	**Primary:**
• To assess the safety and tolerability of a supratherapeutic exposure of PF-07321332 with a PK boosting agent (ritonavir) administered as split dosing.	• Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs. • Frequency and magnitude of abnormal laboratory findings. • Changes from baseline in vital sign measurements and 12-lead ECG parameters.
Secondary:	**Secondary:**

• To assess the plasma PK of PF-07321332 at a supratherapeutic exposure of PF-07321332 with a PK boosting agent (ritonavir) administered as split dosing.	• Plasma PK parameters of PF-07321332:
	  • C_{max}, T_{max}, AUC_{last}
	  • If data permit, AUC_{inf}, $t_{½}$.

4. STUDY DESIGN

4.1. Overall Design

This study may be conducted at 1-3 sites in the USA and/or European Union.

This Phase 1 first-in-human (FIH) study will evaluate safety, tolerability, and PK of PF-07321332 in healthy participants. This 5-part study will combine PART-1: single ascending dose (SAD), PART-2: multiple ascending dose (MAD, including optional Japanese cohort), PART-3: relative bioavailability and food effect cohort, PART-4: metabolism and excretion cohort and PART-5: supratherapeutic exposure cohort. PART-1 and 2 are randomized, double-blind (participant and investigator blinded and sponsor open) and PART-3 is open label. PART-4 is an open-label, non-randomized, single period to evaluate the metabolism and excretion of PF-07321332. PART-5 is a double-blind, sponsor-open, randomized, cross-over cohort to evaluate safety and tolerability at supratherapeutic exposures to be conducted at NH CRU only.

In all 5 parts, participants will be screened within 28 days of their first dose of investigational product. Participants will be admitted to the CRU on Day -1 or earlier and may be discharged at investigator discretion following completion of assessments per SoA. In PART-4, participants may be admitted earlier to facilitate collection of pre-dose fecal sample. If a participant has any clinically significant, study related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the participant may be asked to remain in the CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up.

Participants who discontinue for non-safety related reasons prior to completion of the study may be replaced, at the discretion of the PI and sponsor. The replacement participant(s) may or may not be required to complete all periods of the cohort in which they are participating at the discretion of the PI and sponsor.

Study schema is shown in Section 1.2. In PART-1 and 2, treatment sequences, actual doses, dose increments and dosing regimen may be adjusted, and intermediate or alternative dose levels may be substituted during the study based on emerging safety, tolerability, and PK data.

PART-1: SAD

SAD will include 2 interleaving cohorts with a total of approximately 12 participants planned (approximately 6 participants in each cohort), with 4-period cross-over in each cohort. Period 3 and 4 are optional periods which may be used to further explore PK at additional doses or PK in combination with ritonavir or relative bioavailability of a new formulation or food effect (high-fat high-calorie meal), etc, based on emerging safety, tolerability and PK assessments. For each period, approximately 4 participants will receive a single oral dose of PF-07321332, and approximately 2 participants will receive placebo after at least 10 hours of fasting. In order to improve gastrointestinal tolerability, if required based on emerging safety data, PF-07321332 may also be dosed with standard meal (Section 5.3.1). If required to be dosed in fed state, the participants will be required to eat a meal before drug administration as specified in Sections 5.3.1 and 6.1. Each participant may receive either a single dose of PF-07321332 or a placebo during each period. In each period, participants on active treatment in Cohort 1 will receive D1, D3, D5 and D7 dose levels and Cohort 2 will receive D2, D4, D6 and D8 dose levels in dose escalation format as specified in Table 9 (Section 4.3). Provisional dosing scheme in PART-1 is provided in Table 6. In SAD cohorts requiring co-administration of PF-07321332/placebo with ritonavir, all participants (active and placebo) will receive 3 doses of 100 mg of ritonavir as specified in the SoA. Except D1 of Cohort 1 in SAD, all other dose levels and/or meal condition may be changed based on emerging PK and safety data. Dose escalation to subsequent dose levels in SAD cohorts will be based on all available (a minimum of 48 hours post-dose) safety data and PK over approximately ≥6 hours in a minimum of 4 participants (3 active and 1 placebo) at previous dose levels.

Table 6. Provisional Dosing Scheme in Part-1:SAD

		Period 1	**Period 2**	**Period 3[a]**	**Period 4[a]**
Cohort 1	N=2	Placebo (PL)	D3	D5	D3 (Tablet)[b]
	N=2	D1	PL	D5	PL
	N=2	D1	D3	PL	D3 (Tablet)[b]
Cohort 2	N=2	PL	D4	D6	PL+Food
	N=2	D2	PL	D6	D2+Food[b]
	N=2	D2	D4	PL	D2+Food[b]

Dose levels D1 to D6 are specified in Table 9.

a. Period 3 and 4 are optional. These periods may be used for evaluation of additional dose levels or combination with ritonavir or relative bioavailability of tablet formulation or food effect etc.

b. Period and dose levels for relative bioavailability of tablet or administration with food may be changed based on emerging PK data. If relative bioavailability and food effect conducted in Period 3 or 4, the active/Placebo allocation will be the same as equivalent dose used in period 1 or 2.

There will be a washout interval of ≥5 days between dosing to a given participant. Participants will be required to stay at the CRU for the duration of the washout interval. However, they may be released at the discretion of the investigator. The washout interval may be adjusted based on data emerging from previous cohorts/periods.

Optional Period 3 or 4 of Cohort 1 or 2 may be used to explore food effect (high-fat high-calorie meal) and/or relative bioavailability. If conducted, the active/Placebo allocation will be the same as equivalent dose used in Period 1 or 2.

At dose level of D3 (Cohort-1, Period 2), the urine and feces will be collected for 5 days as specified in SoA for ^{19}F-NMR spectroscopy and metabolite profiling. Based on the emerging PK data, the dose level for urine and feces collection may be changed. If needed, the feces and urine may also be collected at an additional dose level.

PART-2: MAD

The first MAD cohort may start after a total daily dose, which provides comparable or higher total daily exposure (24h) in SAD to the projected total daily steady-state exposure (over 24h) at the starting dose in MAD, is found safe and well tolerated in the PART-1 of the study. The proposed MAD study design will be parallel cohorts, with 10 days of dosing. PART-2 will consist of approximately 2 to 5 cohorts including up to 3 optional cohorts (Cohort 5, 6 and 7) with approximately 6 participants in each cohort. Cohort 7 is an optional Japanese participants cohort. In each cohort, approximately 4 participants will receive one of the escalating doses of PF-07321332 as specified in Table 10 (Section 4.3) and approximately 2 participants will receive matching placebo after at least 7h of fast for the morning dose and 2h of fast for the next dose(s). From Day 1 – Day 9, PF-07321332/placebo will be administered every 8h (ie, TID) when administered alone and every 12h (ie, BID) when co-administered with ritonavir; however, PF-07321332/placebo alone may also be administered every 12h, if needed, based on emerging PK data. On Day 10, PF-07321332/placebo will be administered at approximately 0h for TID or BID regimen. In MAD cohorts requiring co-administration of PF-07321332/placebo with ritonavir, all participants (active and placebo) will receive 100 mg of ritonavir as specified in the SoA. If required to be dosed in fed state, the participants will be required to eat a meal before drug administration (as specified in Sections 5.3.1 and 6.1). Dose escalation to subsequent dose levels in MAD cohorts will be based on a minimum of 6 days safety data and PK over approximately ≥6 hours on Day 5 in a minimum of 4 participants (3 active and 1 placebo) at previous dose levels.

Safety, tolerability and PK may be evaluated in participants of Japanese descent (defined as having 4 biological Japanese grandparents who were born in Japan) after multiple oral administration of PF-07321332 in PART-2. If conducted, this cohort will have all evaluations as specified in SoA for MAD cohorts and the dose level in this cohort will be equal or lower than the highest dose level already evaluated in healthy western participants. Frequency of administration and meal condition will be based on safety, tolerability and PK data from MAD cohorts.

If possible, microsampling PK and/or metabolite profiling may also be done.

PART-3: RBA and Food effect

If conducted, this cohort will be an open label, randomized, 3-period, 3-sequence cross-over single dose cohort evaluating the relative bioavailability of PF-07321332 tablet compared to PF-07321332 oral suspension and to evaluate the effect of food on the bioavailability of the PF-07321332 tablet in healthy adult participants (Table 7). CCI [redacted] Number of participants required in this part of the study will be determined based on the variability observed in PK data emerging from SAD cohorts. A maximum of 18 participants may be enrolled in PART-3 of the study with approximately equal number of participants randomized to each sequence. The dose level to be evaluated in PART-3 will be determined based on emerging PK and safety data from SAD and MAD cohorts. The selected dose will be equal or lower than the highest tolerated dose already evaluated in PART-1. In this part, there will be a washout interval of at least 2 days between dosing to a given participant in each period. Participants will be required to stay at the CRU until the discharge in the last period. The washout interval may be adjusted based on data emerging from SAD and MAD cohorts.

Table 7. Randomization Sequence in Relative Bioavailability/Food Effect Cohort

Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	B	C	A
3	C	A	B

A: PF-07321332 oral suspension in fasted state.
B: PF-07321332 tablet formulation in fasted state.
C: PF-07321332 tablet formulation in fed (high-fat high-calorie meal) state.

PART-4: Metabolism and Excretion

This part will include a single cohort of approximately 6 male participants. All participants will receive 4 doses of 100 mg ritonavir as specified in the SoA. Each participant will receive a single dose of 300 mg of PF-07321332 on Day 1 0 hr along with 100 mg of ritonavir after at least 10 hr of fasting. The plasma for PK and metabolic profiling will be collected as specified in the SoA. The urine and feces will be collected for 10 days as specified in SoA to determine excretion routes and metabolite profiling. A fecal sample is required prior to dosing on Day 1. Dietary fiber supplementation anduse of laxative (Section 5.3.1.1) should be considered with the goal to facilitate at least once daily bowel movement. The use of the laxative should be recorded. The participants will be discharged on Day 11.

PART-5: SE (NH CRU only)

This cohort will include up to 12 participants in a 4-period (Periods 3 and 4 are optional), double-blind, sponsor-open, 2-sequence, cross-over design to explore safety, tolerability and PK at supratherpeutic exposure. For each period, participants will receive split dosing

administration (3 doses) of PF-07321332 or placebo at short intervals (approximately 2 h of the previous dose) after at least 2 hours after breakfast on Day 1. The first 2 periods will be a cross-over where participants will be given PF-07321332 at 0, 2 and 4 hrs at the dose of 750 mg (or placebo). Periods 3 and 4 (if conducted) will only be conducted if supratherapeutic concentrations are not reached in Period 1. In Periods 3 and 4 (if conducted) doses may be given up to 4 times for a total daily dose not exceeding 3000 mg, with or without food. The timing of the food, ECGs, PK collection in Periods 3 and 4 may be modified based on the data from Period 1 but the total number of these assessments will remain the same.

In each period, participants will receive 3 doses of 100 mg ritonavir as specified in SoA. Provisional dosing scheme in PART-5 is provided in Table 8.

Table 8. Provisional Dosing Scheme in Part-5:Supratherpeutic Exposure

Sequence	Period 1	Period 2	Period 3[a]	Period 4[a]
1	Placebo (PL)	Treatment P	PL	Treatment Q
2	Treatment P	PL	Treatment Q	PL

a. Periods 3 and 4 are optional.
Treatment P=750 mg of PF-07321332 to be administered at 0, 2 and 4h and PK enhancer (ritonavir) administered at -12, 0 and 12h. Treatment Q = To be determined

There will be a washout interval of ≥5 days between dosing of PF-07321332/placebo to a given participant. Participants will be required to stay at the CRU for the duration of the washout interval. However, they may be released at the discretion of the investigator.

Dose escalation, if required, to subsequent dose levels (Treatment Q) in Periods 3 and 4 will be based on all available (a minimum of 48 hours post-dose) safety data and PK data over approximately ≥6 hours (after the first dose on Day 1) in Period 1.

The dose escalation stopping criteria are specified in Section 6.6.1. The total daily dose in this part will not exceed 3000 mg.

In PART-1 and PART-2 of the study, the dose levels, frequency of administration and/or meal condition may be changed based on emerging PK and safety data. During the SAD and MAD the dose increments and planned doses may be adjusted, as the study progresses dependent upon emerging PK, safety, and tolerability data. Other intermediate doses or lower doses may be administered instead of the planned doses, or changes in dosing frequency or titration schemes may be proposed for MAD cohorts if safety/tolerability or PK issues become apparent, if evidence of nonlinear PK dictates the need to escalate more slowly, or if subsequent doses are predicted to result in exposures that exceed the target limits. Any potential altered dose scheme will be equal to or less than a 3.3-fold increase in exposure from the previous highest dose if a higher dose is warranted to achieve exposure. If gastrointestinal tolerability issue becomes dose-limiting in PART-1 or 2, dosing with food (standard meal) or pre-dosing with anti-emetics may be considered. The projected average exposure of the altered dose scheme will not exceed the exposure limit specified in Section 6.1.1.

In all cohorts (all parts of the study), participants can be released after completing activities specified in SoA. A telephone follow-up contact will occur between 28 to 35 days after the day of last administration of study intervention. At the discretion of the investigator, telephone follow-up contact may be substituted with an on-site visit in case of additional follow-up of open AEs or clinically significant laboratory findings.

The total planned duration of participation, from Screening visit to the Follow-up phone call, may be approximately 12 weeks for PART-1 and PART-5, 10 weeks for PART-2 and PART-3 and 8 weeks for PART-4.

Participants who discontinue from the study (due to non-safety reasons) may be replaced at the Sponsor's discretion.

4.2. Scientific Rationale for Study Design

Given the current study is the first to dose PF-07321332 to healthy participants, an escalating single dose design with careful assessment and ongoing review of safety and PK data of PF-07321332 is planned. The 5-part combined SAD, MAD, RBA/FE, M&E and SE design was selected because it provides the opportunity to shorten the drug development timeline, without compromising the safety of the participants.

Male and female of 18-60 years of age was selected to better represent COVID-19 patient population. PF-07321332 is a non-genotoxic but its effect on embryo-fetal development is currently not known. Therefore, male and female are required to follow contraception requirements as specified in Section 5.3.4 and Appendix 4.

In addition to the standard safety assessments, fibrinogen, PT and aPTT will also be monitored [redacted]

PART-1: SAD

The crossover design will permit both a within and between participant assessment of safety, tolerability, and PK. Furthermore, 2 interleaving cohorts will permit assessment of safety and PK over a wider dose range within a given participant compared to a sequential cohort design. To permit an unbiased assessment of safety, the administration of active versus placebo in each period will be double blinded to site staff (except those involved in preparation of doses) as well as the study participants.

For a given participant, dosing will be separated by ≥5 days. This planned dosing interval is deemed sufficient to permit washout of previous treatment. Based on the projected PF-07321332 effective $t_{½}$ of ~2 hours (see Section 2.2.1.4), almost complete PK washout is expected within 24 hours of dosing.

In SAD period, the urine and feces may be collected to calculate total excretion of drug-related material using ^{19}F-NMR technique and understand metabolic profile as described in previous publications.[15]

If a reasonable dose of PF-07321332 is not able to achieve desired concentrations in the efficacious range, ritonavir may be used as PK boosting agent. If required, 3 doses of 100 mg ritonavir at -12h, 0h (co-administered with PF-07321332) and 12h may be used as boosting agent to increase the exposure of PF-07321332 because the primary route of elimination of PF-07321332 is expected to be via CYP3A4 mediated metabolism. This dose of ritonavir is a subtherapeutic dose and provides maximum CYP3A4 inhibition. In SAD, participants will begin receiving ritonavir dose approximately 12 hours before the PF-07321332 dose to maximize the PK boosting potential of ritonavir. Although ritonavir is generally recommended to be dosed under fed condition for better gastrointestinal tolerability, lower dose of ritonavir (100 mg) is expected to provide acceptable gastrointestinal tolerability based on the fact that lopinavir/ritonavir combination are recommended to be dosed with or without food.

PART-2: MAD

The safety and tolerability will be collected up to 12 days to evaluate the impact of PF-07321332 on relatively longer dosing; however, the dose escalation decision will be based on Day 5 PK. PBPK simulations (including time dependent induction and inhibition potential) showed that the PK concentration after 5 days of dosing is expected to be very close to the steady state. Therefore, the Day 5 PK and all available safety will be used to dose escalate to the next cohort in order to rapidly collect the PK and safety data to initiate the study in COVID-19 patients. By Day 10, the PK of PF-07321332 is expected to achieve steady-state and therefore, the steady-state plasma and urine PK will be determined on Day 10.

Exploratory microsampling PK sample may be collected to evaluate the microsampling techniques which may be employed in future clinical trials.

In order to understand the qualitative metabolic profile of PF-07321332 at steady-state, exploratory plasma samples may be collected on Day 10.

PART-3: RBA and FE

This part of the study will evaluate bioavailability of a tablet formulation relative to the formulation used in PART-1 and/or PART-2 of the study and explore the food effect on the PK of a new formulation in healthy participants.

Based on the projected half-life of 2h, the 48h washing interval should be sufficient to provide the concentration <5% of C_{max} in the subsequent period.

CCI [redacted]

PART-4: Metabolism and Excretion

This part is an open-label, non-randomized, single period cohort to evaluate the metabolism and excretion of PF-07321332 in healthy male participants. Only males will be included in this study given the desire to enroll a homogeneous population due to the small sample size.

A single dose of PF-07321332 is considered appropriate as available data do not indicate PF-07321332 PK are time-dependent, and hence, single dose data are considered predictive of steady state.

The urine and feces samples collected will only be analyzed at the end of the study to determine the amount of drug related material excreted. Considering the half-life and variability in gastrointestinal transit time, feces and urine will be collected up to 10 days after dosing to allow near complete collection of the drug or drug related materials.

PART-5: Supratherapeutic exposure (NH CRU only)

This part is a double-blind, sponsor-open, randomized, 2-sequence, cross-over cohort to evaluate safety, tolerability and PK at supratherapeutic exposures. The dose currently being evaluated in Phase 2/3 studies is PF-07321332/ritonavir 300/100 mg BID which is expected to achieve a geometric mean C_{max} of approximately CCI [redacted] and it is desirable to establish safety and tolerability at least 2 fold exposure margins to cover the impact of DDI or organ impairment. In SAD and MAD, the increase in exposure of PF-07321332 was less than dose proportional and therefore the supratherapeutic exposure was not achieved. In this cohort, PF-07321332 will be administered into split doses at time around expected T_{max} to achieve higher C_{max} of PF-07321332. The projected exposures at the dosing regimen used in this part will not exceed PK stopping limits as defined in Section 6.6.1.

Extensive PK and triplicate ECGs are collected to enable potential exposure-response modeling with PF-07321332 concentration and ECG parameters. The cross-over, randomized design provides an intrasubject comparison of placebo for exposure-response analysis using PF-07321332 concentration and ECG parameters. The timing of the food was selected to avoid the effect of food on QTc ie, ≥4h before and after T_{max}, while avoiding very long fasting requirements for the participants.

Considering half-life and inter-individual variability in PART-1 of this study, a wash out of ≥5 days was deemed sufficient.

CCI [redacted]

4.3. Justification for Dose

4.3.1. Justification of Dose for PART-1, PART-2 and PART-3 (Original Protocol, 28 January 2021)

The approach for dose selection for this study includes consideration of all relevant information obtained in non-clinical pharmacology and toxicity studies with PF-07321332.

Similar to other antiviral therapies, PF-07321332 is expected to exhibit therapeutic anti-SARS-CoV-2 activity in patients when the free plasma exposure is maintained at or above the in vitro EC_{90} values.[16-18] The primary dNHBE cell assay is considered the most relevant for translation and has an EC_{90} value CCI [redacted] This potency is also consistent with the SARS-CoV-2 VeroE6 monkey kidney cell line assay EC_{90} CCI [redacted] in the presence of a P-gp inhibitor. Since high levels of P-gp expression are not expected in lung cells, the primary site of viral replication during SARS-CoV-2 infection, the potency in the presence of the P-gp inhibitor is considered most relevant. Based on this antiviral data the target C_{eff} was defined CCI [redacted]

The human PK of PF-07321332 after single and multiple dose administration (with and without ritonavir) was predicted using physiology based pharmacokinetic (PBPK) modeling by scaling in vitro hepatic clearance obtained from human liver microsomes (HLM) and CL_{bile} from human hepatocytes under sandwich-cultured conditions in SimCyp® ADME simulator Version 19 release 1 (Certara, NJ, USA). The predicted plasma CL and Vss of PF-07321332 are CCI [redacted] and 1 L/kg, respectively, providing CCI [redacted]. In addition, inhibition (reversible and time dependent inhibition of CYP3A), induction potential and transporter interaction potential of PF-07321332 were also included in the PBPK model. For ritonavir, in-built PBPK model in SimCyp simulator was used.

CCI [redacted]

The planned starting dose of PF-07321332 as a single dose is 150 mg. Being an anti-viral agent, the target (3CL-protease) is not expressed in healthy participants hence primary pharmacology related effect is not expected in healthy participants. The projected average free concentration ($C_{average,free}$) of approximately CCI [redacted] at 150 mg is more than 1000 times lower than the observed IC_{50} (IC_{50} >100 µM) in off-target pharmacology screening panel. The projected total C_{max} and the AUC_{inf} of PF-07321332 at the proposed starting dose of 150 mg is CCI [redacted] and CCI [redacted], which provides approximately

CCI safety margins (based on free concentrations), respectively. The maximum recommended starting dose based on human equivalent dose (HED) approach with safety factor of CCI. Given the absence of target from healthy participants, absence of off-target pharmacology and high safety margin based on pre-clinical toxicology study, the proposed starting dose of 150 mg is expected to be safe.

Dose escalation is aimed to occur in incremental increases of ≤½ log (ie, up to approximately 3.3-fold) based on predicted exposures. The margins for the highest proposed single dose (3000 mg) established on the free exposures in rats are projected to be approximately CCI for C_{max} and CCI for AUC_{inf} which are well within the NOAEL exposure. In the presence of ritonavir, the projected exposure is lower than the projected exposures at the highest proposed dose of 3000 mg.

The nominal doses, projected PK exposure parameters and safety margins of PF-07321332 relative to PK stopping limits at the planned doses in SAD are listed in Table 9. Doses presented are projected based on nonclinical data and may be modified based on emerging safety, tolerability, and PK data. The projected exposures (adjusted based on observed PK) at the modified doses will not exceed the PK stopping limits (Section 6.6.1).

CCI

The starting dose in MAD cohort is planned at 500 mg TID; however, the starting dose in MAD may be adjusted based on available PK and safety data from the SAD cohorts. Based on the current human PK predictions, a dose of approximately 500 mg TID would provide the C_{min} consistently above C_{eff}. Since the target is not expressed in healthy participants, a dose that is expected to be efficacious is proposed as a starting dose in MAD in order to minimize the exposure of healthy participants at subtherapeutic dose levels.

Based on the predicted steady state exposures ($C_{max,ss}$ and $AUC_{24,ss}$), 500 mg TID is expected to provide margins of approximately CCI for $C_{max,ss}$ and CCI for $AUC_{24,ss}$ relative to the free exposure in rats on Day 14 at the NOAEL. All dose levels listed are nominal since doses will be driven by exposure. Dose escalation is aimed to occur in incremental increases of ≤½ log (ie, up to approximately 3.3-fold) based on predicted exposures.

Due to the uncertainties in the in vitro potencies and PK parameters scaling and anticipated interpatient variability, the current intent of the development program is to explore dosing regimens resulting in a multiple of this C_{min} target. Highest daily dose of PF-07321332 is expected to be 3000 mg/day (ie, 1000 mg TID), which is expected to provide margins of approximately CCI for $C_{max,ss}$ and CCI for $AUC_{24,ss}$ relative to the free exposure in rats on Day 14 at the NOAEL.

The nominal dosing regimen, projected PK exposure parameters and safety margins of PF-07321332 relative to PK stopping limits at the planned doses in MAD are listed in Table 10.

CCI

All the doses in SAD or MAD cohorts except starting dose of 150 mg in SAD cohort are nominal and may be adjusted, as the study progresses depending upon emerging PK, PD, safety, and tolerability data. Other intermediate doses or lower doses or repeat doses may be administered instead of the planned doses, or changes in dosing frequency or titration schemes may be proposed for MAD cohorts if safety/tolerability issues become apparent, if evidence of nonlinear PK dictates the need to escalate more slowly, or if subsequent doses are predicted to result in exposures that exceed the target limits. However, the projected exposure for the modified doses or additional cohorts following either single dose or multiple dose administration will not exceed PK stopping limit.

The dosing regimen to be evaluated in optional Japanese cohort will be equal to or lower than the safe and tolerated dosing regimen in western healthy adult participants in MAD cohorts. Similarly, the dose to be evaluated in relative bioavailability cohort will be the dose which will be projected to provide the exposure (in fed condition) equal to or lower than the exposure already observed in SAD or MAD cohorts at safe and tolerated doses.

4.3.2. Justification of Dose for PART-4:Metabolism and Excretion (Protocol Amendment 2, 2 June 2021)

In PART-4: Metabolism and Excretion cohort, a single oral dose of 300 mg PF-07321332, pharmacokinetically enhanced with ritonavir (4 doses of 100 mg at -12, 0, 12, and 24 hours relative to PF-07321332), is planned. This dose is anticipated to be a clinically effective dose and currently planned to be evaluated in Phase 2/3 studies.

CCI [redacted]

The dose of ritonavir to be used in this study is 100 mg. This dose is the typical dose of ritonavir when dosed as a PK enhancer.

CCI [redacted]

4.3.3. Justification of Dose for PART-5: Supratherapeutic Exposure (Protocol Amendment 3, 24 June 2021)

In PART-5, the total dose planned for PF-07321332 is 2250 mg administered as 3 split doses of 750 mg at 0, 2h and 4h, pharmacokinetically enhanced with ritonavir (3 doses of 100 mg at -12, 0 and 12 hours relative to PF-07321332). Based on the simulations using preliminary population PK model, this dose is anticipated to provide a supratherapeutic exposure CCI [redacted].

CCI [redacted]

The dose of ritonavir to be used in this study is 100 mg. This dose is the typical dose of ritonavir as a PK enhancer.

The projected exposure for the proposed dose / regimen of PF-07321332 was based on a preliminary population PK model. The model for PF-07321332 750 mg (administered at 0h, 2h and 4h) with PK enhancement predicts the total AUC_{24} and C_{max} to be CCI µg•hr/mL and CCI µg/mL, which is less than CCI higher than the observed exposure at PF-07321332 750 mg (with ritonavir), and approximately CCI and CCI lower, respectively, in terms of unbound concentration than the observed NOAEL CCI in rats in the 14-day toxicity study.

Using the same preliminary population PK model, the projected AUC_{24} and C_{max} at the maximum allowed dose in this protocol (3000 mg total daily dose administered as 4 split doses of 750 mg at every 2 hour intervals) are approximately CCI µg•hr/mL and CCI, which is approximately CCI and CCI below the PK stopping limit.

At this dosing regimen, the supratherapeutic exposure is expected to be achieved while being safe.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit.

The end of the study is defined as the date of the last visit of the last participant in the trial globally.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male and female participants must be 18 to 60 years of age, inclusive, at the time of signing the ICD. Only Male participants will be included in PART-4.

- Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and vital signs and standard 12-lead ECGs.

3. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

4. **For optional Japanese cohort only:** Japanese participants who have 4 Japanese biologic grandparents who were born in Japan.

Weight:

5. BMI of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb).

Informed Consent:

6. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy, intestinal resection).

3. Positive test result for SARS-CoV-2 infection at the time of screening or Day-1.

4. History of HIV infection, hepatitis B, or hepatitis C; positive testing at screening for HIV, HBsAg, HBcAb, or HCVAb. As an exception a positive HBsAb test due to Hepatitis B vaccination is allowed.

5. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

6. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. (Refer to Section 6.5 for additional details).

7. Participants who have received a COVID-19 vaccine within 7 days before screening or admission, or who are to be vaccinated with a COVID-19 vaccine at any time during the study confinement period

Prior/Concurrent Clinical Study Experience:

8. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

9. A positive urine drug test at screening or admission.

10. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

11. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTcF interval >450 msec, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >450 msec, this interval should be rate-corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants. In PARTs-1, 2 and 5, the average of triplicate measurement should be used for eligibility determination.

    In PART-3 and PART-4 only: If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility.

12. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

    - AST **or** ALT level ≥1.5 × ULN;
    - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

Other Exclusions:

13. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit or 3 ounces (90 mL) of wine).
14. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.
15. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.
16. Use of tobacco or nicotine containing products in excess of the equivalents of 5 cigarettes per day or 2 chews of tobacco per day.
17. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.
18. Pregnant or breastfeeding women.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to safety laboratory evaluations (except 6h post dose on Day 1 in PART-1 and Day 5 in PART-2) and at least 10 hours in PART-1, PART-3 and PART-4 and at least 7 hours before morning doses in PART-2.
- PART-5: On Day 1, the breakfast to be provided after collection of vitals, ECGs CCI [redacted] and approximately 2h before the administration of study intervention at 0h and lunch to be provided at approximately 4h after the last administration of PF-07321332/placebo.

- PART-1, PART-3, PART-4 and on PK days in PART-2 (**if dosed under fasted condition**):

  - Water is permitted until 1 hour prior to study intervention administration at 0h on PK days. Water may be consumed without restriction beginning 1 hour after dosing at 0h on PK days. Water consumption is not restricted on afternoon and/or evening dose(s) on PK days and on all doses of non-PK days.

  - No food will be allowed for approximately 4 hours post-dose in PART-1, PART-3 and after the morning dose on PK days (Days 1, 5, 10) in PART-2. For all other doses in PART-2, no food will be allowed approximately 2 hours before and after dosing.

- Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices (see below) may be consumed with meals and the evening snack.

- Lunch will be provided approximately 4 hours after morning dosing.

- Dinner will be provided approximately 9 to 10 hours after morning dosing.

- An evening snack may be permitted.

- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.

- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

PART-5 only:

- On Day 1 in all periods, following an overnight fast of at least 10 hours and collection of ECGs, vitals [redacted], participants should finish a standard breakfast approximately 2 hours prior to the administration of the investigational product. Participants will be encouraged to eat the full standard meal. If participants are unable to complete the entire meal, the approximate portion of the meal consumed will be documented.

- Water is restricted for 30 minutes prior and 1 hour after dosing (1st, 2nd and 3rd split dose). Ambient temperature water may be consumed without restriction 1 hour after 3rd split dose.

- Participants will be restricted to consuming ambient temperature or warm drinks form Day 1 (prior to baseline ECG measurements) until final ECG measurements have been collected in each study period. Hot or cold drinks are prohibited during this time frame.

- Non-caffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices) may be consumed with meals and evening snacks.

- Participants will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (eg, Seville oranges, pomelos) from 7 days prior to the first dose of investigational product until collection of the final PK blood sample in the last period.

- On Day 1 in Periods 1 and 2, lunch will be provided approximately 4 hours after last dosing (ie, **following** the scheduled 8 hour ECG and PK assessments).

- On Day 1 in all Periods, dinner will be provided approximately 8 hours after last split dosing (ie, after collection of the ECG and PK measurements scheduled at 12 hours postdose).

- The timing of meals should be standardized between period 1 and 2 and between period 3 and 4. The timing of the meals and snacks must be recorded. It should be noted if subject fails to consume the majority of a meal.

- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

If dosed under standard meal condition in PART-1 or PART-3:

Following an overnight fast of at least 10 hours, participants should start a standard breakfast approximately 30 minutes prior to the administration of the investigational product. The breakfast will be consumed over approximately 20 minutes with investigational product administered within approximately 10 minutes after completion of the meal. Participants will be encouraged to eat the full standard meal. If participants are unable to complete the entire meal, the approximate portion of the meal consumed will be documented. No food will be allowed for at least 2 hours post-dose.

- Water can be allowed as desired except for 1 hour after investigational product administration. There are no water restrictions prior to dosing for participants dosed under fed conditions.

If dosed under high fat meal condition in PART-1 or PART-3:

- Following an overnight fast of at least 10 hours, participants should start a high-fat/high-calorie breakfast approximately 30 minutes prior to administration of the investigational product. The breakfast will be consumed over approximately

20 minutes with investigational product administered within approximately 10 minutes after completion of the meal. Participants will be encouraged to eat the full meal. If participants are unable to complete the entire meal, the approximate portion of the meal consumed will be documented. No food will be allowed for at least 2 hours post-dose.

- The breakfast will be a high-calorie/high-fat test meal. The test meal should derive approximately 150, 250 and 500-600 calories from protein, carbohydrate and fat, respectively. The following breakfast as a representative example of a high-fat, high-calorie meal: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, 8 fluid ounces (240 mL) of whole milk.

- Water can be allowed as desired except for 1 hour after investigational product administration. There are no water restrictions prior to dosing for participants dosed under fed conditions.

If dosed under standard meal condition in PART-2:

Morning dosing condition:

Following an overnight fast of at least 7 hours, participants should start a standard breakfast approximately 30 minutes prior to the morning administration of the investigational product. The breakfast will be consumed over approximately 20 minutes with investigational product administered within approximately 10 minutes after completion of the meal. Participants will be encouraged to eat the full standard breakfast. If participants are unable to complete the entire breakfast on PK profile assessment days (Days 1, 5 and 10), the approximate portion of the breakfast consumed will be documented. On non-PK days, it is not required to document the approximate portion of food consumed. No food will be allowed for at least 2 hours post-dose.

Water can be allowed as desired except for 1 hour after investigational product administration on PK days. There are no water restrictions on non-PK days neither prior to dosing for participants dosed under fed conditions.

Afternoon and/or evening dosing condition:

A snack consisting of at least 400 kcal will be provided approximately 20 minutes before dosing in the afternoon and/or evening. The snacks will be consumed over approximately 10 minutes with investigational product administered within approximately 10 minutes after completion of the snack. Participants will be encouraged to eat the full snack. There is no food restrictions on afternoon and/or evening dose(s).

There are no water restrictions on afternoon and/or evening dose(s) on PK days and on non-PK days.

5.3.1.1. Dietary Fiber Supplementation (PART-4 and PART-5 only)

To help assure regularity in bowel movements, nutritional composition should include high fiber content. This may include consumption of fiber capsules, at a frequency dictated by investigator, starting with the evening meal (ie, approximately 8 or 9 hours post dose) on Day 1, for duration of inpatient stay to ensure at least 1 bowel movement per day.

If an individual participant has not experienced a bowel movement in the first 24 hours after dosing water intake should be increased and prune juice should be offered on Day 2.

Despite these measures, if bowel movement does not occur regularly (ie, at least once daily bowel movement), consideration should be given to administration of mild laxative/stool softener (eg, milk of magnesia or docusate), at investigator's discretion.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine containing products for 24 hours prior to the start of dosing of PF-07321332/placebo until collection of the final PK sample of each study period.

- Participants will abstain from alcohol for 24 hours prior (or as specified above for red wine) to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample of each study period. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Participants will abstain from the use of tobacco or nicotine containing products for 24 hours prior to dosing of PF-07321332/placebo and during confinement in the CRU.

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down (except when required for BP, pulse rate, respiratory rate and ECG measurements) for first 4 hours after morning dose, and may be required to follow meals and dietary restrictions as specified in Section 5.3.1.

- **PART-1 and PART-5 only:** Participants will be confined to the procedure room for the first 4 hours after last PF-07321332/placebo dosing on Day 1 during continuous cardiac monitoring, except to use the bathroom. After this, if the equipment setup allows, participants may be ambulatory during the ECG monitoring period, but should not engage in strenuous activities. If equipment does not allow ambulation, appropriate accommodations will be made by the investigator site to facilitate continuous monitoring (eg, bedside urinals should be provided to accommodate participants' excretory needs).

5.3.4. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/enrolled in the study. Screen failure data are collected and remain as source and are not reported to the clinical database.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study intervention refers to all of the following:

- PF-07321332;
- Placebo for PF-07321332;
- Ritonavir.

6.1. Study Intervention(s) Administered

PF-07321332 and placebo will be provided by Pfizer as bulk powders for extemporaneous preparation of oral suspensions at the CRU.

PF-07321332 or placebo will be presented to the participants in individual dosing containers.

In addition, PF-07321332 and matching placebo may also be supplied as tablets. If provided, tablets will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

Ritonavir 100 mg tablets will be supplied locally by the CRU.

6.1.1. Administration

Dosing of PF-07321332/placebo (placebo for PART-1 only) and ritonavir (if used) in PART-1 and PART-3

If dosed under fasted condition, participants will receive PF-07321332/placebo (placebo for PART-1 only) at approximately 08:00 hours (±2 hours) per the SoA following an overnight fast of at least 10h. In PART-1, if required, 3 doses of 100 mg ritonavir may be administered as a PK boosting agent as per SoA. At a time point when PF-07321332/placebo (placebo for PART-1 only) will be dosed with ritonavir (ie, at 0h), both PF-07321332/placebo (placebo for PART-1 only) and ritonavir will be dosed simultaneously (within no more than 5 minutes of each other). Participants will swallow ritonavir and PF-07321332/placebo (placebo for PART-1 only) tablets whole (if administered as tablet) and will not chew prior to swallowing.

Investigator site personnel will administer with ambient temperature water to a total volume of approximately 240 mL. Study intervention will be administered according to the EDR.

If dosed under fed condition (standard meal or high-fat high-calorie meal), the PF-07321332/placebo (placebo for PART-1 only) should be administered approximately 10 minutes after finishing the meal/snack (refer Section 5.3.1 for further details).

Dosing of PF-07321332/placebo and ritonavir (if used) in PART-2

If dosed under fasted condition, participants will receive PF-07321332/placebo at approximately 08:00 hours (plus or minus 2 hours) per the SoA following an overnight fast of at least 7 hours. At least 2h of fast is required for afternoon and/or evening dosing for BID and TID dosing regimen. When dosed with ritonavir, both PF-07321332/placebo and ritonavir will be dosed simultaneously (within no more than 5 minutes of each other). Participants will swallow ritonavir and PF-07321332/placebo tablets whole (if administered as tablet) and will not chew prior to swallowing.

Investigator site personnel will administer with ambient temperature water to a total volume of approximately 240 mL. Study intervention will be administered according to the EDR.

If dosed under fed condition (meal/snack), the PF-07321332/placebo should be administered approximately 10 minutes after finishing the meal/snack (refer Section 5.3.1 for further details).

Dosing of PF-07321332 and ritonavir in PART-4

Participants will receive PF-07321332 and ritonavir at approximately 08:00 hours (±2 hours) per the SoA following an overnight fast of at least 10h. Participants will receive 4 doses of 100 mg ritonavir as a PK boosting agent as per SoA. At a time point when PF-07321332 will be dosed with ritonavir (ie, at 0h), both PF-07321332 and ritonavir will be dosed

simultaneously (within no more than 5 minutes of each other) in fasted state. Except when dosed with PF-07321332, ritonavir may be administered with or without food. Participants will swallow ritonavir tablets whole and will not chew prior to swallowing.

Investigator site personnel will administer PF-07321332 oral suspension and ritonavir tablets with ambient temperature water to a total volume of approximately 240 mL. PF-07321332 oral suspension will be administered according to the EDR.

Dosing of PF-07321332/placebo and ritonavir in PART-5

In this part, for each period, participants will receive split administrations (3 doses) of PF-07321332 or placebo at short intervals (within 2 h of the previous dose).

Participants will receive first split dose of PF-07321332/placebo oral suspension at approximately 08:00 hours (±2 hours) at least 2h after the morning breakfast per the SoA. The second and third split doses will be administered at approximately 2h and 4h after the first dose, respectively. A total of 3 doses of 100 mg ritonavir tablet will be administered as a PK boosting agent as per SoA. At a time point when PF-07321332/placebo will be dosed with ritonavir (ie, at 0h), both PF-07321332/placebo and ritonavir will be dosed simultaneously (within no more than 5 minutes of each other). Participants will swallow ritonavir tablets whole and will not chew prior to swallowing.

Investigator site personnel will administer with ambient temperature water to a total volume of approximately 240 mL. PF-07321332/placebo will be administered according to the EDR.

Intervention Name	PF-07321332	Placebo	Ritonavir (if used)
ARM Name (group of patients receiving a specific treatment (or no treatment)	PF-07321332	Placebo	NA
Type	Drug	Placebo	Boosting agent
Dose Formulation	Suspension or Tablet	Suspension or Tablet	Tablet
Unit Dose Strength(s)	Planned nominal unit doses strength for tablets: 25 mg, 100 mg, and 250 mg	0 mg	100 mg
Dosage Level(s)	Planned nominal unit doses strength for tablets: 25 mg, 100 mg, and 250 mg	0 mg	100 mg
Route of Administration	Oral	Oral	Oral
Use	Experimental	Placebo	PK Boosting agent
IMP or NIMP	IMP	IMP	NIMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided locally by the trial site, subsidiary, or designee
Packaging and Labeling	Materials (API and components) for extemporaneous prep of oral suspensions will be provided in bulk. Tablets will be provided in bulk. PCRU staff will prepare individual doses for administration. Individual dose containers will be labeled by site staff per country requirement	Materials for extemporaneous prep of oral suspensions will be provided in bulk. Tablets will be provided in bulk. PCRU staff will prepare individual doses for administration. Individual dose containers will be labeled by site staff per country requirement	PCRU will procure commercially labeled materials
Current/Former Name(s) or Alias(es)	PF-07321332	Placebo	Norvir® or other local commercialized product

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage

conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the PCRU site procedures.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the EDR for storage conditions of the study intervention once prepared.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the PCRU's site procedures. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, participant in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

PF-07321332 and placebo oral dosing suspensions will be prepared in the CRU by 2 operators, 1 of whom is a pharmacist. Details of dose preparation will be given in a separate EDR. Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator site's labeling requirements.

PF-07321332 and placebo tablets, if used, will be dispensed at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

Ritonavir will be administered to the participant in an unblinded (open-label) fashion. Ritonavir tablets will be dispensed at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

Investigators and participants will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third party (for example, pharmacist) will be responsible for the preparation and dispensing of all study intervention according to the randomization schedule and assigned treatment for the individual participant.

This third party will instruct the participant to avoid discussing the taste, or packaging of the study intervention with the investigator.

Blinding procedures do not apply to PART-3 and PART-4 of this study because it will be conducted as open-label. Where the design is open-label, the investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

6.3.2. Breaking the Blind

The method for breaking the blind in this study will be manual. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. When the blinding code is broken, the reason must be fully documented in a CRF.

Blood specimens will be obtained from all participants for PK analysis to maintain the study blind at the investigator site. Only the investigator site staff and blinded study monitor, if assigned, will be blinded to study treatment. A limited number of Pfizer study team personnel will be unblinded to participant treatments in order to permit real-time interpretation of the safety and PK data; and provide information necessary to potentially alter the dose escalation sequence. The blinded study monitor, if assigned, will remain blinded to treatment until all monitoring for the study has been completed. Specimens from participants randomized to placebo will not be routinely analyzed. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer unblinded personnel and will not be released to the blinded investigator or blinded investigator site personnel until the study database has been locked or the investigator requests unblinding for safety reasons.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

Females using hormonal contraceptives or taking hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study. Depo-Provera® must be discontinued at least 6 months prior to the first dose of study treatment. Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (See Appendix 4).

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of study intervention will be documented as a prior treatment. Treatments taken after the first dose of study intervention will be documented as concomitant treatments.

6.5.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with study intervention; standard medical supportive care must be provided to manage the AEs.

6.6. Dose Modification

Progression to the next dose in PART-1 will occur if the last dose was well tolerated and after satisfactory review of the available safety and PK data. Each dose escalation will be based on review of the safety data up to a minimum of 48-hours post dose plus PK assessments up to 6-hours post dose, in at least 3 actively treated participants and at least 1 placebo-treated participant dosed in the previous dose-level.

Progression to the next dose in PART-2 will occur if the last dose was well tolerated and after satisfactory review of the available safety and PK data. Each dose escalation will be based on review of the safety data up to a minimum of 6-days plus PK assessments up to 6-hours post dose on Day 5, in at least 3 actively treated participants and at least 1 placebo-treated participant dosed in the previous dose-level.

6.6.1. Dose Escalation and Stopping Rules

Dose escalation stopping rules will be used to determine whether the maximal tolerated dose has been attained. Dose escalation may be stopped if it is determined that the limits of safety and/or tolerability have been reached. This decision will be made after a discussion takes place between the sponsor study team and the investigator. The sponsor study team may not overrule the investigator's decision to stop dose escalation. If dose escalation is stopped because of any of these criteria, additional cohorts may receive the same or lower doses of the study intervention.

The dose escalation will be terminated based on the following criteria:

- If 50% or more of the participants receiving active drug at a given dose level (but not participants receiving placebo) develop similar clinically significant laboratory, ECG, or vital sign abnormalities, in the same organ class, indicating dose-limiting intolerance.

- Severe nonserious AEs, considered as, at least, possibly related to study intervention administration, in 2 participants at a given dose level (but not participants receiving placebo), independent of within or not within the same system organ class, indicating dose-limiting intolerance.

- Dosing will be paused for any SAE that occurs in a participant receiving active treatment until causality is fully assessed by the PI and sponsor. Dosing may resume if the SAE is determined to be not drug-related by the PI and sponsor. If the SAE is determined to be either drug-related or unknown, either dosing will cease or the SAE will be evaluated by the sponsor's protocol review committee (or similar review group), which is independent of the study team and investigators. If the protocol review committee determines that dosing may resume, a plan that mitigates risks to participants with the resumption of dosing will be implemented. Such a plan could include a revision of inclusion/exclusion criteria, repeating or reducing the dose, or adding appropriate safety monitoring.

- It is determined that the limit of safety and/or tolerability has been reached. This decision will be made following discussions between the study team and the investigator.

- Other findings that, at the discretion of the study team and investigator, indicate that dose escalation should be halted.

- If, at any dose level, the average exposure reaches or exceeds the PK stopping limits, total plasma AUC (AUC_{inf} in PART-1 and PART-5 and AUC_{tau} in PART-2) and C_{max} of CCI µg•h/mL and CCI µg/mL.

- If, based on the observed data, the group mean C_{max} or AUC (based on total plasma concentration) of the next planned dose is projected to exceed the escalation limits, that dose will not be explored. Modified doses may be explored if they are not expected to exceed PK stopping criteria.

Progression to the next dose will occur if the last dose was well tolerated and after satisfactory review of the available safety and PK data.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following

- AE requiring discontinuation in investigator's view;

- Pregnancy;

- Positive COVID-19 test.

If study intervention is definitively discontinued, the participant will not remain in the study for further evaluation. See the SoA for data to be collected at the time of discontinuation of study intervention.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

ECG Changes

A participant who meets either bulleted criteria based on the average of triplicate ECG readings will be withdrawn from the study intervention.

- QTc, QTcB, QTcF >500 msec.
- Change from baseline: QTc >60 msec.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Potential Cases of Acute Kidney Injury

Abnormal values in SCr concurrent with presence or absence of increase in BUN that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

An increase of ≥0.3 mg/dL (or ≥26.5 µmol/L) in SCr level relative to the participant's own baseline measurement should trigger another assessment of SCr as soon as practically feasible, preferably within 48 hours from awareness.

If the second assessment (after the first observations of ≥0.3 mg/dL [or ≥26.5 µmol/L] in SCr relative to the participant's own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 µmol/L), the participant should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include serum BUN, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium,

phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If ≥2 healthy participants in a given period in PART-1 and 3 and in a treatment arm in PART-2 are noted to have 2 *consecutive* SCr results of ≥0.3 mg/dL (or ≥26.5 µmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Investigator's decision;
- Pregnancy.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for/attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical assessments or specimen collections, eg, banked biospecimens, may be used without repeat collection, as appropriate.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study may be up to approximately 480 mL, 290 mL, 160 mL, 205 mL and 485 mL in PART-1, PART-2, PART-3, PART-4 and PART-5, respectively. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Concomitant Therapy sections of the protocol.

8.1. Efficacy Assessments

No efficacy assessment is planned in this study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the SoA. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

8.2.2. Vital Signs

Supine BP will be measured with the participant’s arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

8.2.2.1. Respiratory Rate

Respiratory rate will be measured after approximately 5 minutes of rest in a supine position by observing and counting the respirations of the participant for 30 seconds and multiplying by 2. When BP is to be taken at the same time, respiration measurement will be done during the 5 minutes of rest and before BP measurement.

8.2.2.2. Temperature

Temperature will be measured orally. No eating, drinking, or smoking is allowed for 15 minutes prior to the measurement.

8.2.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) is not recommended given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

In PART-1 and PART-5, triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected before dose administration on Day 1 of each period will serve as each participant's baseline QTc value.

In PART-2, triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected at each nominal time point on Day 1 in MAD cohorts will serve as each participant's time-controlled baseline QTc value.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) the mean value from the triplicate measurements for any postdose QTcF interval is increased by ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then a single ECG measurement must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

For PART-3 and PART-4 only (when Single ECGs are conducted): To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a postdose QTc interval is increased by ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTc values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTc interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.3.1. Continuous Cardiac Monitoring by Telemetry (PART-1 and PART-5 only)

All abnormal rhythms will be recorded and reviewed by the study physician for the presence of rhythms of potential clinical concern. The time, duration, and description of the clinically significant event will be recorded in the CRF. In addition, a printed record of the tracing(s) of the clinically significant rhythm(s) will be made and retained with other source documents.

Telemetry should be collected using a centralized system that also allows for the storage and advanced analysis of all recorded data in order to preserve important events for future evaluations. Holter monitoring should not be used in parallel with continuous telemetry, unless it is the only means of data storage available at the investigator site, or verifiable arrhythmia quantification is required. To establish a baseline, telemetry should be recorded for at least 2 hours before dosing in Period 1. This may be done immediately prior to dosing or at some 2-hour continuous interval in the 24 hours prior to dosing, as long as the recording is performed when the participant is awake. Telemetry may be stopped within a reasonably short period of time prior to dosing, in order to avoid interference with study operations conducted immediately before dosing. However, it is expected that the telemetry leads will be in place and the system connected prior to dosing.

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with

the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 48h after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for participants to receive study intervention.

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant’s receiving the study treatment. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at discharge. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AE or SAE after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion, inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

All AESIs must be reported as an AE or SAE following the procedures described in Section 8.3.1 through Section 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.3.8.1. Lack of Efficacy

This section is not applicable because efficacy is not expected in the study population.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of PF-07321332 greater than 3000 mg within a 24-hour [-2 hour] time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of study intervention (whichever is longer).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

5. Obtain a blood sample for PK analysis within 2 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

8.5.1. Plasma for Analysis of PF-07321332 PK, ^{19}F-NMR measurement and Metabolic Profiling

Blood samples of approximately 4 mL, to provide approximately 1.5 mL of plasma, will be collected for measurement of plasma concentrations of PF-07321332 as specified in the SoA. In PART-2 MAD portion of the study conducted at NH CRU only, exploratory microsampling PK blood samples for the measurement of PF-07321332 concentrations may be collected in order to evaluate one or more approach(es). Total blood volume for exploratory microsampling PK will not exceed 0.4 mL at each time point specified in the SoA. In Cohort 1, Period 2 in PART-1 and PART-2 of the study, blood samples of approximately 6 mL, to provide a minimum of 2 mL of plasma, may be collected for ^{19}F-NMR measurement of drug related materials and/or metabolic profiling as specified in the SoA. In PART-4, 10 mL blood samples will be collected for metabolite identification as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

Samples collected for analyses of PF-07321332 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for the measurement of ritonavir or for other internal exploratory purposes.

Genetic analyses will not be performed on these plasma samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of PF-07321332 will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples collected for exploratory PK may be analyzed with either validated or qualified methods.

This exploratory data will not be included in the clinical study report. Potential metabolites may be analyzed with either validated or exploratory methods.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Drug concentration information that would unblind the study will not be reported to investigator sites or blinded personnel until the respective cohort of study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.5.2. Urine Pharmacokinetics (PART-2 only)

Urine samples will be collected for an interval as specified in the SoA and mixed thoroughly and the total volume will be measured and recorded on the CRF. An aliquot of 5 mL will be collected for the measurement of urine concentrations of PF-07321332. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of start and end of each collection interval will be recorded.

The urine blank (approximately 5 mL) for PK will be obtained prior to dosing.

Samples collected for measurement of urine concentrations of PF-07321332 will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Drug concentration information that would unblind the study will not be reported to investigator sites or blinded personnel until the respective cohort of the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

As part of understanding the pharmacokinetics of the study drug, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the CSR.

8.5.3. Urine and Feces for Measurement of Drug-Related Material by ^{19}F-NMR and Metabolic Profiling (PART-1: Cohort-1, Period 2 only)

Urine will be collected in Cohort 1, Period 2 of PART-1 for determination of total drug related material by ^{19}F-NMR spectroscopy and metabolite profiling as specified in the SoA. The participants will force void before oral dosing. Prior to dosing on Day 1 (within 24 hours), each participant must empty his urinary bladder; an aliquot from this urine will serve as the "urine blank". The details regarding the collection, processing, storage and shipping of the urine samples will be provided in the lab manual and supporting documentation.

Feces will be collected for determination of total drug related material by ^{19}F-NMR spectroscopy and metabolite profiling as specified in the SoA. If possible, a pre-dose fecal sample within 48 hours prior to dosing should be collected.

Details of the collection of aliquots, volume, processing, storage and shipping of the urine and feces samples will be provided in the lab manual and supporting documentation. The actual date and time (24-hour clock time) of each sample will be recorded.

At the discretion of the Sponsor, one or more assessments on urine and feces may not be conducted if deemed unnecessary by the Sponsor.

8.5.4. Urine and Feces for Measurement of Drug-Related Material and Metabolic Profiling (PART-4 only)

Urine will be collected in PART-4 for determination of total drug-related material and metabolite profiling as specified in the SoA. The participants will force void before oral dosing. Prior to dosing on Day 1 (within 24 hours), each participant must empty his urinary bladder; an aliquot from this urine will serve as the "urine blank". The details regarding the collection, processing, storage and shipping of the urine samples will be provided in the lab manual and supporting documentation.

Feces will be collected for determination of total drug-related material and metabolite profiling as specified in the SoA. A pre-dose fecal sample within 48 hours prior to PF-07321332 dosing is required before dosing drug.

Details of the collection of aliquots, volume, processing, storage and shipping of the urine and feces samples will be provided in the lab manual and supporting documentation. The actual date and time (24-hour clock time) of each sample will be recorded.

At the discretion of the Sponsor, one or more assessments on urine and feces may not be conducted if deemed unnecessary by the Sponsor.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

CCI [redacted]

CCI [redacted]

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

CCI [redacted]

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

There are no statistical hypotheses for this study.

9.2. Sample Size Determination

A total of up to 78 participants (12 in PART-1: SAD, up to 30 [with 2 cohorts and 3 optional cohorts] in PART-2: MAD, a maximum of 18 in PART-3: Relative Bioavailability/Food Effect cohort,6 in PART-4: metabolism and excretion and up to 12 in PART-5: Supratherapeutic Exposure) are planned to be randomized in this study. Participants who discontinue for reasons other than safety during the study may be replaced at the discretion of the sponsor and Investigator.

9.2.1. PART-1: SAD

A sample size of 6 participants per cohort for this single, dose-escalating, 4-period cross-over, with placebo substitution study (4 active, 2 placebo per dose level) has been chosen based on the need to minimize first exposure of healthy participants to a new chemical entity and the requirement to provide adequate safety and toleration information and PK information at each dose level.

9.2.2. PART-2: MAD

A sample size of 6 participants per cohort, with 4 participants randomized to PF-07321332 plus 2 participants to placebo per cohort, has been selected as a compromise between the need to minimize exposure to PF-07321332 and the need to have sufficient participants randomized to provide adequate safety and toleration information and PK.

This sample size has been judged sufficient to obtain a preliminary evaluation of safety, tolerability, and PK data in these populations.

9.2.3. PART-3: Relative Bioavailability/Food Effect

A sample size of up to 18 participants will provide adequate precision to compare the relative bioavailability of a tablet formulation of PF-07321332 relative to oral suspension. This sample size assumes that the within-participant SD for log-transformed PK parameters would not increase beyond approximately 0.3. The expected widths of the 90% CIs with 80% coverage probability for the comparison of tablet formulation of PF-07321332 relative to oral suspension are shown in Table 11 for a range of possible effects. The sample size ultimately decided for Relative Bioavailability, by the sponsor, will depend on observed variability in plasma PK observed in PART-1: SAD.

Table 11. Probable 90% CI with 80% coverage probability for Varying SDs, Effect Sizes and Sample Sizes – in PART-3: Relative Bioavailability

Effect Size	SD = 0.2		SD = 0.3	
	N = 12	N = 18	N = 12	N = 18
0.75	0.64 – 0.88	0.66 – 0.85	0.59 – 0.95	0.62 – 0.90
1.0	0.85 – 1.17	0.88 – 1.13	0.79 – 1.27	0.83 – 1.20
1.25	1.07 – 1.46	1.10 – 1.41	0.99 – 1.58	1.04 – 1.51

9.2.4. PART-4: Metabolism and Excretion

A sample size of approximately 6 participants (with at least 4 completers) is chosen based on the industry standard sample size for metabolism and excretion studies. This sample size was not justified by any empirical data or hypothesis testing criteria.

9.2.5. PART-5: Supratherapeutic Exposures

A sample size of up to 12 participants (with at least 10 completers) is chosen based on the need to provide adequate safety, tolerability and PK information at each dose level and/or administration schedule. At the discretion of the sponsor and investigator, participant who were enrolled in PART-2 may be enrolled in PART-5.

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Evaluable	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention for the given part of the study.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
PK Concentration Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported for the given part of the study.
PK Parameter Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of interest are reported for the given part of the study.
Excretion analysis set	In PART-4, excretion analysis population will be defined by evaluable participants who have received 1 dose of PF-07321332 and who have completed drug related material concentration (urinary and fecal) data and who had no protocol deviations that may have affected the mass balance analysis.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. General Considerations

The data from each part of the study will be analyzed and reported separately in a single CSR issued at the end of this study.

9.4.2. Primary Endpoint(s)

The primary endpoints in PART-1,PART-2 and PART-5 are related to safety/tolerability with analyses as described in Section 9.4.5.

The primary endpoints in PART-3 are the plasma PK endpoints whose analyses are described in Sections 9.4.3.1 and 9.4.3.2.

The primary endpoints in PART-4 are percent recovery and cumulative recovery of drug-related material in urine, feces determined based on total administered dose. Percent recovery of drug-related material in urine and feces will be determined based on total administered dose. The total recovery of drug-related material in urine and feces and their combination will be listed and summarized.

9.4.3. Secondary Endpoint(s)

The secondary endpoints in PART-1, PART-2 and PART-5 as well as the primary endpoints in PART-3 related to PK are described herein.

9.4.3.1. PK Analysis

9.4.3.1.1. Derivation of PK Parameters

Plasma PK parameters for PF-0732332 will be derived (if data permit) from the concentration-time data using standard noncompartmental methods following a single oral dose (Table 12) and multiple oral doses (Table 13). Urine PF-07321332 PK parameters are described in Table 13. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 12. Plasma PF-07321332 PK Parameters For PART-1: Single Ascending Doses, PART-3: Relative Bioavailability/Food Effect, PART-4: Metabolism and Excretion and PART-5: Supratherapeutic Exposure

Parameter	Part of The Study	Definition	Method of Determination
AUC_{last}[b]	1, 3, 5	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}[a]	1, 3, 5	Area under the concentration-time curve from time zero extrapolated to infinity	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point from the log-linear regression analysis
C_{max}	1, 3, 5	Maximum plasma concentration	Observed directly from data
T_{max}	1, 3, 5	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$[a]	1, 3, 5	Terminal half-life	$Log_e(2)/k_{el}$,

			where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline are used in the regression.
CL/F^a	1, 3	Apparent clearance	$Dose/AUC_{inf}$
V_z/F^a	1, 3	Apparent volume of distribution	$Dose/(AUC_{inf} \bullet k_{el})$
$AUC_{last}(dn)$	1, 3	Dose normalized AUC_{last}	$AUC_{last}/Dose$
$AUC_{inf}(dn)^a$	1, 3	Dose normalized AUC_{inf}	$AUC_{inf}/Dose$
$C_{max}(dn)$	1, 3	Dose normalized C_{max}	$C_{max}/Dose$

a. If data permit.
b. In PART-3, pre-dose (0h) sample from Periods 2 and 3 will also be considered as 48h PK sample for Periods 1 and 2, respectively.

dn=dose normalized to a 1 mg dose.

Table 13. Plasma and Urine PF-07321332 PK Parameters for PART-2: Multiple Ascending Doses

Parameter	Day(s)	Definition	Method of Determination
Plasma			
AUC_{τ}	1, 5, 10	Area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval, where τ = 8 for TID dosing or 12 hours for BID dosing	Linear/Log trapezoidal method
C_{max}	1, 5, 10	Maximum plasma concentration during the dosing interval	Observed directly from data
T_{max}	1, 5, 10	Time for C_{max}	Observed directly from data as time of first occurrence
C_{min}	5, 10	Minimum observed concentration during the dosing interval	Observed directly from data
PTR	5, 10	Peak-to-trough ratio	C_{max}/C_{min}
R_{ac}	5, 10	Observed accumulation ratio for AUC_{τ}	Day 5 or Day 10 AUC_{τ}/Day 1 AUC_{τ}
$R_{ac,Cmax}$	5, 10	Observed accumulation ratio for C_{max}	Day 5 or Day 10 C_{max}/Day 1 C_{max}
CL/F	5, 10	Apparent clearance	Dose/AUC_{τ}
$t_{½}$[a]	10	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline are used in the regression
V_Z/F[a]	10	Apparent volume of distribution	Dose/(AUC_{τ} • k_{el})
AUC_{τ}(dn)	1, 5, 10	Dose normalized AUC_{τ}	AUC_{τ}/Dose
C_{max}(dn)	1, 5, 10	Dose normalized C_{max}	C_{max}/Dose
Urine			
Ae_{τ}	10	Amount excreted in urine as unchanged drug over the dosing interval τ	Sum of (urine volume × urine concentration) for each collection over the dosing interval
Ae_{τ}%	10	Percent of dose excreted in urine as unchanged drug over the dosing interval τ	100 * Ae_{τ}/Dose
CL_r	10	Renal clearance	Ae_{τ}/AUC_{τ}

a. If data permit.

dn=dose normalized to a 1 mg dose.

9.4.3.2. Statistical Methods for PK Data

No formal inferential statistics will be applied to the plasma PK data apart from the comparisons of formulation and food effect in either Part 1 or Part 3.

For all parts of the study, plasma concentrations will be listed and summarized descriptively by PK sampling time and treatment. Individual participant and median profiles of the concentration-time data will be plotted by treatment. For summary statistics and median plots by sampling time, the nominal PK sampling time will be used, for individual participant plots by time, the actual PK sampling time will be used for plasma samples. Median profiles will be presented on both linear-linear and log-linear scales.

The plasma PK parameters listed in Table 12 and Table 13 will be summarized descriptively by dose.

For PART-1,PART-2 and PART-5, dose normalized (to 1 mg) AUC_{inf} or AUC_{tau} and C_{max} of PF-07321332 will be plotted against dose (using a logarithmic scale) and will include individual participant values as well as the geometric means for each dose. These plots may be used to help understand the relationship between the PK parameters and dose.

For PART-2, urine amounts as listed in Table 13 of PF-07321332 will be listed and summarized descriptively, if data permit.

For PART-3, natural log transformed AUC_{last}, C_{max}, and AUC_{inf} (if data permit) for PF-07321332 will be analyzed using a mixed effect model with sequence, period, and treatment included as fixed effects and participant nested within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

The following comparisons will be made:

Comparison	Test	Reference
Formulation	PF-07321332 tablet formulation in fasted state (B)	PF-07321332 oral suspension in fasted state (A)
Food Effect	PF-07321332 tablet formulation in fed (high fat meal) state (C)	PF-07321332 tablet formulation in fasted state (B)

Additional specifications about the tables, listings, and figures will be outlined in the SAP.

9.4.4. Tertiary/Exploratory Endpoint(s)

Exploratory endpoints may not be reported in the CSR and may be reported separately.

9.4.5. Safety Analyses

9.4.5.1. Standard Safety Analyses

In this study, assessment of safety and tolerability following single- and multiple-ascending doses forms the primary objective for PART-1,PART-2 and PART-5. In all 5 parts of the study, all safety analyses will be performed on the ***Safety Analysis Set***.

All AEs, ECGs, BP, pulse rate, continuous cardiac monitoring, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and PE and neurological examination information, as applicable, collected during the course of the study will be considered source data and will ***not*** be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.4.5.2. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS complex will be summarized by treatment and time.

The number (%) of participants with maximum post dose QTcF values and maximum increases from baseline in the categories outlined in Table 14 will be tabulated by treatment.

Table 14. Safety QTcF Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

CCI [redacted]

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is a sponsor-open study, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, facilitating PK modeling, and/or supporting clinical development. Unblinded results will be reviewed by a designated limited number of sponsor colleagues within the study team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a DMC.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 10 days from the previous ICD signature date.

For NH CRU only: unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage

period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the IQMP.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in source document locator.

Description of the use of computerized system is documented in source document locator.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer-intervention related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.9. Sponsor’s Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the CTMS.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant’s participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it

should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 15. Protocol -Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	• Urine drug screening[c] • SARS-CoV-2 RT-PCR • eGFR [CKD EPI] • Pregnancy test (β-hCG)[d] • aPTT • PT-INR • Fibrinogen • TSH • Free T4 <u>At screening only:</u> • FSH[b] • Hepatitis B surface antigen • Hepatitis B surface antibody[e] • Hepatitis B core antibody • Hepatitis C antibody • Human immunodeficiency virus

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. For confirmation of postmenopausal status only, at screening only.
c. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
d. Serum or urine β-hCG for female participants of childbearing potential.
e. Can be done either automatically or only if HBcAb or HBsAg is positive, as per local practices.

Investigators must document their review of each laboratory safety report.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. CCI [redacted]

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10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and

(3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female.

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
     - High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
     - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent (for WOCBP partners only)

1. Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation.

    - Oral;

    - Intravaginal;

    - Transdermal;

2. Progestogen-only hormone contraception associated with inhibition of ovulation.

    - Oral;

    - Injectable.

3. Sexual abstinence.

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

One of the following effective barrier methods must be used in addition to the highly effective methods listed above that are user dependent:

- Male or female condom with or without spermicide;

- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

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- [redacted]

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and

monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

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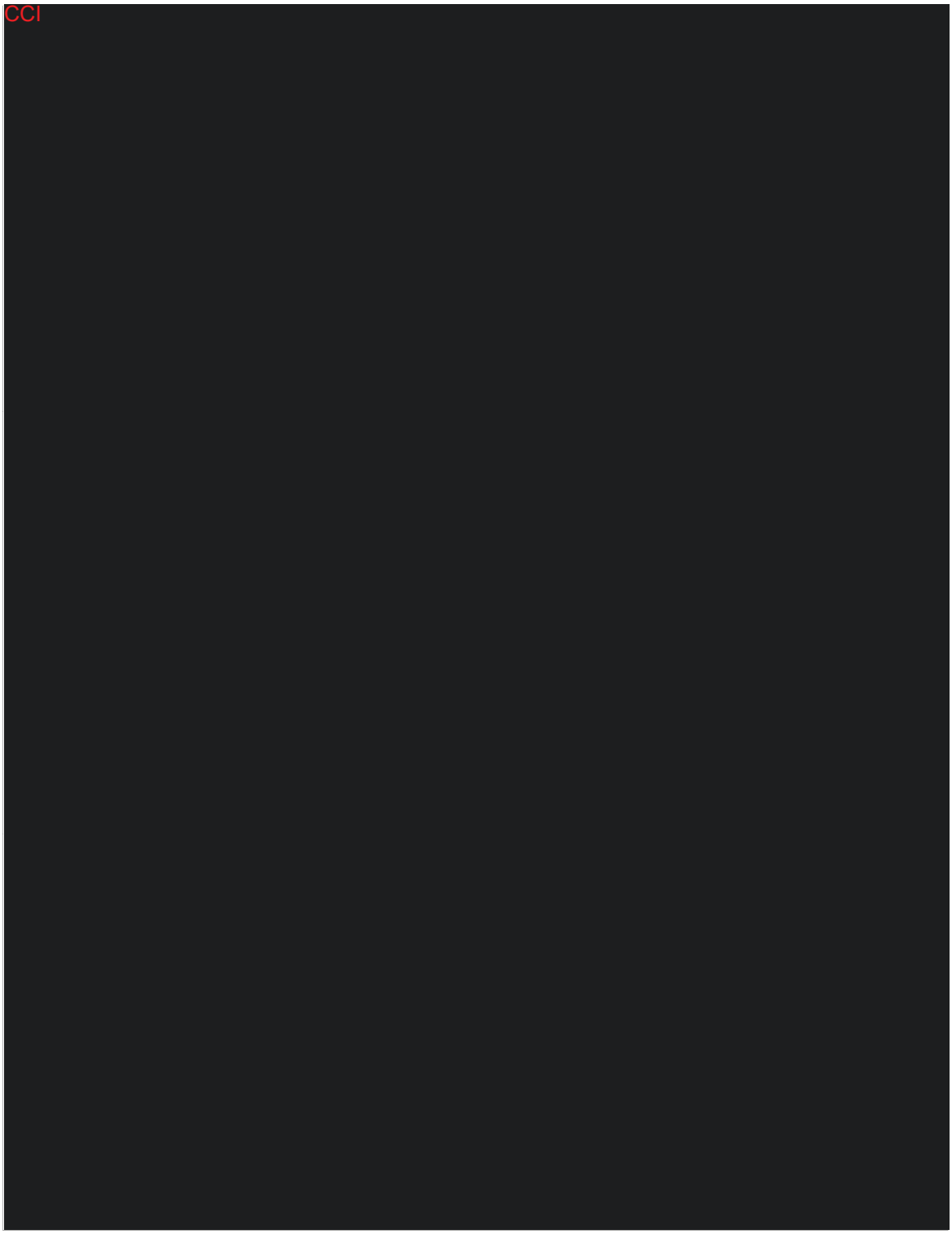
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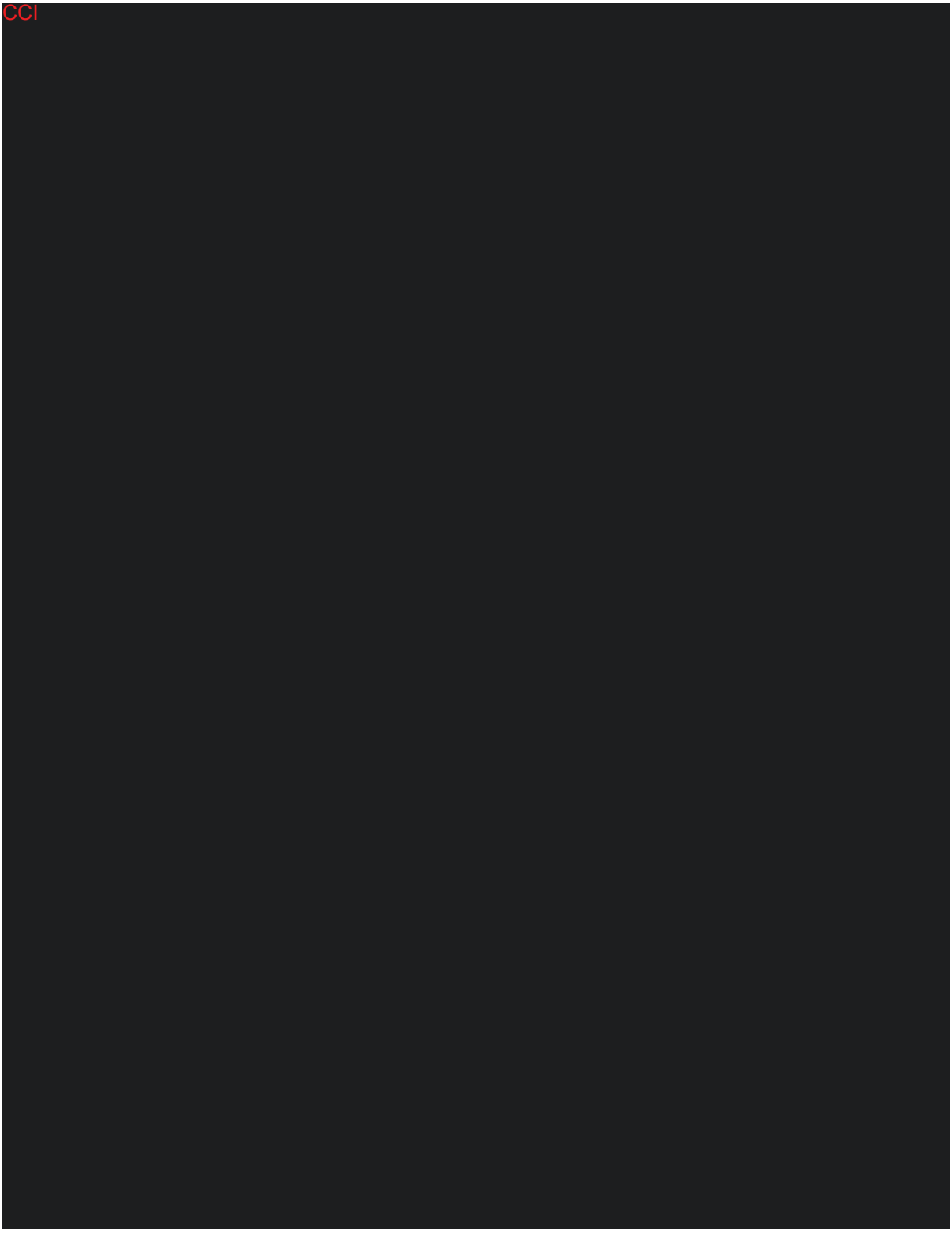

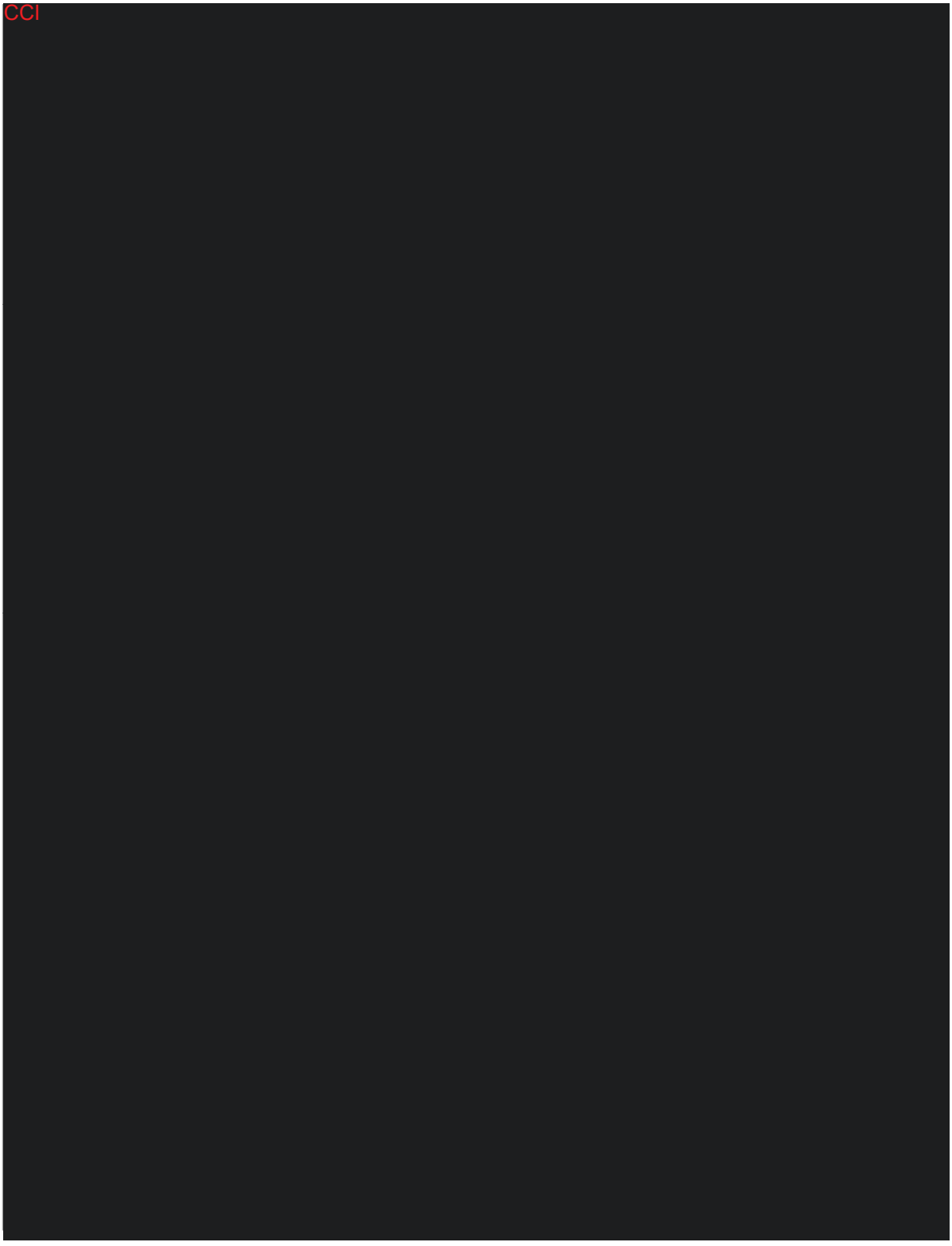
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10.9. Appendix 9: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
$3CL^{pro}$	3C-like protein
Abs	absolute
ADE	adverse device effect
AE	adverse event
Ae_{tau}/Ae_{τ}	amount excreted in urine as unchanged drug over the dosing interval τ/tau
$Ae_{tau}\%/Ae_{\tau}\%$	percent of dose excreted in urine as unchanged drug over the dosing interval
AESI	adverse events of special interest
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the plasma concentration-time profile from time zero to the time 24 hours
$AUC_{24,ss}$	area under the plasma concentration-time profile from time zero to the time 24 hours at steady state
AUC_{inf}	area under the plasma concentration-time curve from time 0 extrapolated to infinite time
AUC_{inf}(dn)	dose normalized AUC_{inf}
AUC_{last}	area under the plasma concentration time curve from time 0 to the time of the last quantifiable concentration
AUC_{last}(dn)	dose normalized AUC_{last}
AUC_{tau}/AUC_{t}	area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval
AV	atrioventricular
BA	bioavailability
BBS	Biospecimen Banking System
BCRP	breast cancer resistance protein
BE	bioequivalence
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
C_{av}	average concentration

Abbreviation	Term
Cb/Cp ratio	blood to plasma ratio
C_{eff}	efficacious concentration
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD EPI	chronic kidney disease epidemiology collaboration
CL	clearance
C_{last}	last quantifiable concentration
CL/F	apparent clearance
CL_r	renal clearance
C_{max}	maximum plasma concentration
C_{max}(dn)	dose normalized C_{max}
C_{min}	minimum plasma concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	Corona Virus Disease 2019
CPP	coronary perfusion pressure
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	clinical trial management system
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
CCI	[redacted]
dHNBE	differentiated normal human bronchial epithelial
dP/dT	rate of rise of left ventricular pressure
DR	dosing regimen
DU	dispensable unit
EC	ethics committee
EC_{50}	half maximal effective concentration
EC_{90}	90% maximal effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency

Abbreviation	Term
E/T	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FAMHP	Federal Agency for Med
FDA	US Food and Drug Administration
FIH	first-in-human
^{19}F-NMR	fluorine-19 nuclear magnetic resonance
FOB	functional observational battery
FSH	follicle-stimulating hormone
fu	free fraction
F/U	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HAE	human airway epithelial
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HED	human equivalent dose
hERG	human ether-a-go-go related gene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLM	human liver microsome
HPD	hours post first dose
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	inhibitory concentration 50%
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
I/E	inclusion/exclusion
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IQMP	Integrated Quality Management Plan
IRB	Institutional Review Board
IV	intravenous
k_{el}	rate constant for terminal phase

Abbreviation	Term
K_I	inhibition constant
k_{inact}	rate of enzyme inactivation
LBBB	left bundle branch block
LFT	liver function test
LVP	left ventricular pressure
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MD	multiple dose
MDR1	multidrug resistance mutation 1
M&E	Metabolism and Excretion
msec	millisecond
N/A	not applicable
Nab	neutralizing antibodies
NH	New Haven
NHP	non-human primates
NIMP	non-investigational medicinal product
NMR	nuclear magnetic resonance
NOAEL	no-observed-adverse-effect level
NTCP	human sodium taurocholate co-transporting polypeptide
OATP	organic anion transporting polypeptides
PBPK	physiology based pharmacokinetic
PCRU	Pfizer clinical research unit
PD	pharmacodynamic(s)
PDE	phosphodiesterase
PE	physical examination
P-gp	P-glycoprotein
PI	principal investigator
PK	pharmacokinetic(s)
PL	placebo
PT	prothrombin time
PTR	peak to trough ratio
PVC	premature ventricular contraction/complex
QTc	corrected QT
QTcB	corrected QT (Bazetts method)
QTcF	corrected QT (Fridericia method)
qual	qualitative
R_{ac}	observed accumulation ratio for AUC_{τ}
$R_{ac,Cmax}$	observed accumulation ratio for C_{max}
RBA/FE	relative bioavailability/food effect
RBC	red blood cell

Abbreviation	Term
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
RTV	ritonavir
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCr	serum creatinine
SD	single dose standard deviation stable disease (based on content)
SE	supratherapeutic exposure
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single-reference safety document
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal half-life
T4	thyroxine
TBili	total bilirubin
TEAE	treatment-emergent adverse events
THC	tetrahydrocannabinol
TID	three times daily
T_{max}	time for C_{max}
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
V_{ss}	volume at steady-state
V_z/F	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman of childbearing potential

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