A PHASE 1, NON-RANDOMIZED, OPEN-LABEL STUDY TO ASSESS THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF PF-07321332 BOOSTED WITH RITONAVIR IN ADULT PARTICIPANTS WITH MODERATE HEPATIC IMPAIRMENT AND HEALTHY PARTICIPANTS WITH NORMAL HEPATIC FUNCTION

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Brief Title: Study to Estimate the Effects of Hepatic Impairment on the Pharmacokinetics of PF-07321332

Document History

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: Study to Estimate the Effects of Hepatic Impairment on the Pharmacokinetics of PF-07321332.

Rationale

The purpose of this study is to estimate the effect of hepatic impairment on the plasma PK of PF-07321332/ritonavir. Findings from this study will be used to develop dosing recommendations so that the dose and/or dosing interval may be adjusted appropriately in the presence of hepatic impairment.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To compare the PK of PF-07321332, following a single oral dose administration of PF-07321332 pharmacokinetically boosted with ritonavir in adult participants with moderate hepatic impairment and age and body weight-matched participants without hepatic impairment.	• Plasma PF-07321332 PK parameters: C_{max}, AUC_{last}, AUC_{inf} (if data permit)
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of PF-07321332 and ritonavir, following a single oral dose administration of PF-07321332 pharmacokinetically boosted with ritonavir, in participants with moderate hepatic impairment and in healthy participants with normal hepatic function.	• Incidence of TEAEs, abnormal ECGs, vital signs, and laboratory values
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[redacted]	[redacted]

Overall Design

Brief Summary

This is a Phase 1, non-randomized, open-label study to investigate the effect of hepatic impairment on the plasma PK, safety and tolerability of a single oral dose of PF-07321332 in combination with the PK boosting agent ritonavir in approximately 16 participants. The study will be conducted in adult participants with stable, moderate hepatic impairment and a control group of participants with normal hepatic function.

Enrollment will be in a staged manner such that participants with hepatic impairment (Cohort 2) will begin enrollment first. Participants without hepatic impairment (Cohort 1) will begin recruitment towards the end of Cohort 2 or earlier, at the sponsor's discretion such that the enrollment in both cohorts may overlap. Participants in Cohort 1 will match the average demographics (at a minimum, age and weight; gender and race as much as practically possible) of participants in Cohort 2.

All participants in both cohorts will provide informed consent and undergo Screening evaluations to determine their eligibility. Categorization of participants into hepatic impairment cohort, Cohort 2, will be done based on Child-Pugh scores as described in Appendix 9, at the Screening visit.

Participants who prematurely discontinue for non-safety related reasons may be replaced, at the discretion of the PI and sponsor study team.

Eligible participants will be admitted to the CRU on Day -1 (at least 12 hours prior to the dosing of PF-07321332 on Day 1) and will be confined in the CRU until Day 3. On the evening of Day -1, participants will receive a single 100 mg dose of ritonavir (-12 hour relative to PF-07321332 dosing). On the morning of Day 1, the participants will receive a single dose of 100 mg PF-07321332 with a 100 mg dose of ritonavir after an overnight (or a minimum of 6 hours) fast. Ritonavir, 100 mg, will continue to be dosed at 12 and 24 hours post PF-07321332 dosing to ensure maintenance of the PK boosting effect. Serial blood CCI [redacted] samples at specified intervals will be collected up to 24 hours post-dose for PK assessments.

Safety assessments will be performed during Screening, on Day -1 prior to dosing and on Day 3. Physical examinations, vital sign measurements, and clinical laboratory tests will be conducted, and AEs will be monitored to assess safety. The total participation time (eg, CRU confinement time for study procedures) for each participant in this study is approximately 3 nights/4 days (excluding screening & Follow-Up contact).

A safety follow-up call will be made to participants 28 to 35 days from administration of the last dose of PF-07321332.

Number of Participants

Approximately 16 participants will be enrolled to study intervention.

Note: "Enrolled" means a participant's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. 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.

Intervention Groups and Duration

Each enrolled participant will receive a single 100 mg dose of PF-07321332 administered orally in combination with the PK boosting agent ritonavir administered as a 100 mg dose at -12, 0, 12, and 24 hours relative to PF-07321332 dosing.

The total planned duration of participation, from the Screening visit to the last Follow-up phone call, is approximately up to 9 weeks.

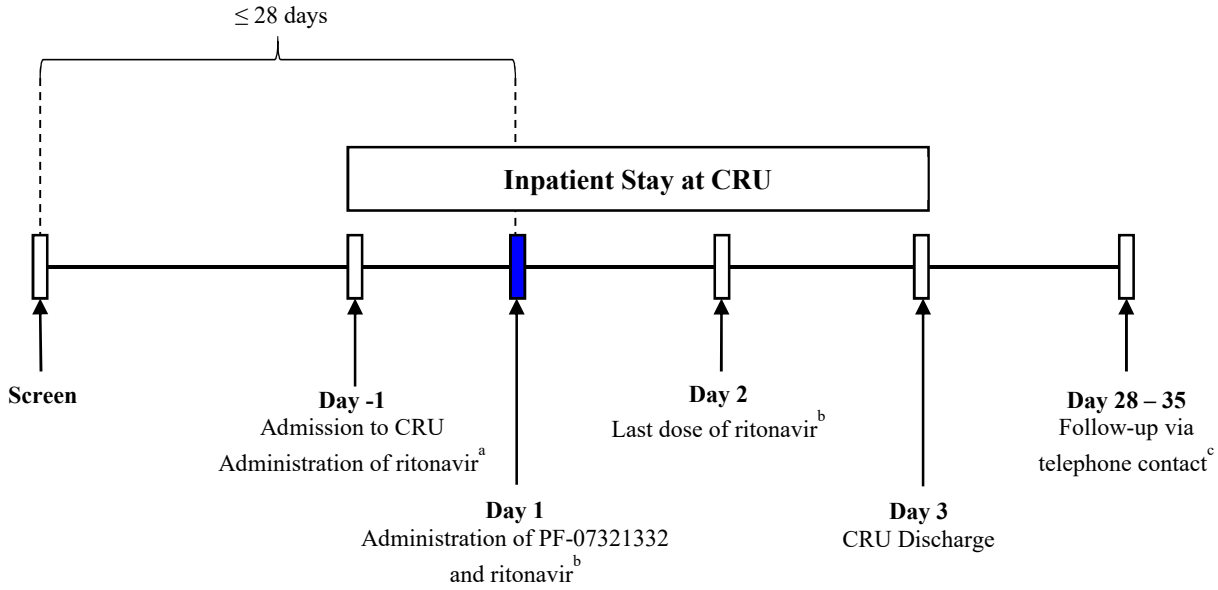
Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

One-way ANOVA will be used to compare the natural log transformed AUC_{last}, AUC_{inf} (if data permit) and C_{max} for PF-07321332 between Cohort 2 with moderate hepatic impairment (Test) and Cohort 1 with normal hepatic function (Reference). Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CI 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 the adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

1.2. Schema

Figure 1. Treatment and Schema



a. Admission can occur at any time of day; once admitted, participants to be provided inpatient meal(s). On the evening of Day -1, participants will receive a single 100 mg dose of ritonavir (-12-hour relative to PF-07321332 dosing).
b. On the morning of Day 1, participants will receive a single dose of 100 mg PF-07321332 with a 100 mg dose of ritonavir after a fast of at least 6 hours, followed by ritonavir (100 mg) to be dosed at 12 and 24 hours post PF-07321332 dosing.
c. Contact may occur via telephone contact and must occur 28 to 35 days from administration of PF-07321332 or from the time of early termination/discontinuation.

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.

Visit Identifier[a]	**Screening**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Early Termination/ DC**	**Follow-up Contact**
Days Relative to Day 1 Abbreviations used in this table can be found in Appendix 10	**Day -28 to Day -2**						**28-35 Days**[b]
Informed consent	X						
Admission to CRU		X					
Confinement to CRU		X	→	→	X		
Inclusion/exclusion criteria	X	X					
Medical history	X	X					
Demography[c]	X						
Physical examination[d]	X	X			X	X	
Height and weight assessment	X						
Safety laboratory tests[e]	X	X			X	X	
Child-Pugh classification[f]	X						
History of illegal drug/tobacco/alcohol use	X	X					
Urine alcohol test or alcohol breath test	X	X					
Urine or serum pregnancy test (WOCBP only)	X	X			X	X	
Contraception check[g]	X	X			X	X	X
Serum FSH in post-menopausal females amenorrheic ≥12 months and under 60 years of age	X						
Urine drug screen	X	X					
Single supine 12-Lead ECG[h]	X		X		X	X	

Visit Identifier[a]	Screening	Day -1	Day 1	Day 2	Day 3	Early Termination/ DC	Follow-up Contact
Days Relative to Day 1 Abbreviations used in this table can be found in Appendix 10	**Day -28 to Day -2**						**28-35 Days[b]**
Single, seated vital signs (BP, and pulse rate)[i]	X		X		X	X	
HIV, HBsAg, HBcAb, HCVAb testing[j]	X						
PF-07321332 administration			X				
Ritonavir administration[k]		X	X	X			
Plasma PK for PF-07321332 [redacted][l]			X	X	X	X	
[redacted]			[redacted]	[redacted]			
[redacted]		[redacted]					
Prior/concomitant treatments	X	X	→	→	X	X	X
COVID-19 testing[o]	X	X					
COVID-19 check temperature[p]	X	X	X	X	X		
COVID-19 questionnaire[q]	X	X					
CRU discharge					X		
Serious and nonserious adverse event monitoring	X	X	→	→	X	X	X
Standard meals		X	X[r]	X	X		

a. Day relative to start of PF-07321332 dosing (Day 1).
b. Contact may occur via telephone contact and must occur 28 to 35 days from administration of PF-07321332 or from the time of early termination/discontinuation.
c. Demographics will include race, age, and gender.
d. Complete physical examination will be performed at screening; and limited PE will be conducted on Day -1, Day 3, early termination, and at any time point as deemed necessary by the investigator.
e. Safety laboratory assessments include chemistry, hematology, and urinalysis (and microscopy, if needed) and must be collected following at least a 4 hour fast.
f. The Child-Pugh classification (Appendix 9) will be used to define the participants of Cohort 2 with moderate hepatic impairment (Child-Pugh Class B) at Screening.
g. Confirmation of the correct use of appropriate contraceptive method.
h. Single 12-lead ECG readings will be taken pre-dose on Day 1 and at specified times. All ECG assessments will be made prior to any blood draws or vital sign measurements.
i. Single seated BP and PR will be performed pre-dose on Day 1 and at specified times. All BP and PR will be measured prior to collection of blood draws if scheduled at the same time, after collection of ECGs.
j. Testing will be performed as described in Appendix 2.

Visit Identifier[a]	Screening	Day -1	Day 1	Day 2	Day 3	Early Termination/ DC	Follow-up Contact
Days Relative to Day 1 Abbreviations used in this table can be found in Appendix 10	**Day -28 to Day -2**						**28-35 Days[b]**

k. Ritonavir will be administered on Day -1 at -12 hours, Day 1 at 0 hours and 12 hours, and Day 2 at 24 hours, relative to PF-07321332 dosing.
l. Blood samples are to be collected for plasma PK assessment of PF-07321332 CCI on Day 1 at 0 (pre-dose for PF-07321332), 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours, Day 2 at 24 and 36 hours, and Day 3 at 48 hours, relative to PF-07321332 dosing, and at early termination/DC (if before 48 hours post-dose for PF-07321332), if needed.
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o. Testing for COVID-19 pathogen will be performed prior to being admitted to the clinic for confinement, on Day -1, and if participant develops COVID-19 like symptoms.
p. To be done at least daily during residence.
q. Check exposure to positive case, residence or travel in area of high incidence and COVID-19 related signs and symptoms.
r. Meals/snacks to be served at clock times matching approximately 0H, 4H, 7H, 10H, and 14H (optional) relative to dosing on Day 1 (while inpatient).

2. INTRODUCTION

PF-07321332 is a potent and selective inhibitor of the SARS-CoV-2 3CL protease that is currently being developed as an oral treatment of COVID-19. Ritonavir is a strong CYP3A4 inhibitor being used to inhibit the metabolism of PF-07321332 in order to increase plasma concentrations of PF-07321332 to values that are anticipated to be efficacious.

2.1. Study Rationale

PF-07321332/ritonavir is intended for short term (eg, 5 day) use, in patients with COVID-19, some of whom may have some degree of impaired hepatic function. Therefore, the purpose of this study is to characterize the effect of hepatic impairment on the plasma PK of PF-07321332/ritonavir. Findings from this study will be used to develop dosing recommendations so that the dose and/or dosing interval may be adjusted appropriately in the presence of hepatic disease.

2.2. Background

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]

PF-07321332 is an orally bioavailable $3CL^{pro}$ inhibitor shown to be effective against SARS-CoV-2 $3CL^{pro}$ (K_i = 0.00311 µM) in a biochemical enzymatic assay. Since the $3CL^{pro}$ from human coronaviruses are structurally similar and share a high degree of conservation at the active site of the enzyme, the ability of PF-07321332 to inhibit the $3CL^{pro}$ of other coronaviruses (SARS-CoV-1 and HCoV-229E, MERS, HCoV-OC43, HCoV-HKU1, and HCoV-NL63) was also confirmed, indicating a potential for broad spectrum anti-coronavirus activity. 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).[2] PF-07321332 is being developed as an oral treatment in patients with COVID-19 infection.

Ritonavir is a strong CYP3A4 inhibitor being used to inhibit the metabolism of PF-07321332 in order to increase plasma concentrations of PF-07321332 to values that are anticipated to be efficacious. Ritonavir did not show SARS-CoV-2 antiviral activity in vitro up to 3 µM ritonavir and is being used only as a pharmacokinetic boosting agent.

2.2.1. Nonclinical Pharmacology

Details of the nonclinical pharmacology of PF-07321332 can be found in the current IB.[3]

2.2.2. Nonclinical Pharmacokinetics and Metabolism

Hepatic CYP450 enzymes were identified as the main pathway for clearance of PF-07321332 in vitro in liver microsomes (mouse, rat, hamster, rabbit, monkey, and human), hepatocytes (rat, monkey, and human), and in vivo in rat and monkey after repeat oral dosing. In a reaction phenotyping study using human liver microsomes in the presence of selective CYP inhibitors, CYP3A4 was predicted to be the major contributor (f_m = 0.99) to the in vitro

oxidative metabolism of PF-07321332. No significant CYP3A5 contribution is expected to the metabolism of PF-07321332. Urinary excretion of PF-07321332 following single IV or oral doses in rats was approximately 11%, suggesting minor urinary contributions to the overall elimination of PF-07321332.

PF-07321332 is not extensively bound to human plasma proteins, with f_u of 0.31 observed in the in vitro protein binding study.

Additional information of the nonclinical PK and metabolism of PF-07321332 is available in the current IB.[3]

2.2.3. Nonclinical Safety

There were no adverse findings observed in repeat-dose toxicity studies in rats and monkeys up to 2 weeks duration and the NOAELs were the highest dose administered (1000 mg/kg and 600 mg/kg in the rat and monkey studies, respectively). PF-07321332-related non-adverse, test article-related clinical findings included sporadic occurrence of emesis with slight body weight decreases in monkeys. Monitorable and reversible clinical pathology findings included those possibly suggestive of low-grade inflammation (in rats and monkeys) or alterations in the coagulation pathways (in rats only) without clinical or microscopic correlates. Other non-adverse clinical pathology findings were likely due to the emesis and subsequent dehydration in monkeys. In rats administered 1000 mg/kg/day, lower mean absolute and relative heart weights (females) and higher absolute and relative liver weights (both sexes) were observed relative to controls. The lower heart weights had no microscopic correlates and were fully reversed at the end of the 2-week recovery period. Higher liver weights correlated with reversible, non-adverse microscopic findings of minimal to mild severity in the liver and thyroid gland consistent with adaptive changes related to microsomal enzyme induction.

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

The nonclinical studies performed adequately support the oral administration of PF-07321332 in the clinic for up to 14 days.

Further details of the nonclinical safety program are provided in the current IB.[3]

2.2.4. Clinical Overview

Safety, tolerability and pharmacokinetics of PF-07321332 in healthy adult participants is currently being explored in an ongoing Phase 1 FIH study (C4671001). Study C4671001 is a 4-part study consisting of SAD (PART-1), MAD (PART-2), relative bioavailability/food effect (PART-3) evaluations, and evaluation for metabolism and excretion (PART-4). PART-1 and -2 are randomized, double-blind, sponsor-open, and placebo-controlled to evaluate safety, tolerability, and PK of single and multiple escalating oral doses of PF-07321332, respectively. PART-3 is randomized and open-label to evaluate relative bioavailability and food effect of an oral tablet formulation. PART-4 is an open-label,

non-randomized, single period to evaluate the metabolism and excretion of PF-07321332.

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2.3. Benefit/Risk Assessment

PF-07321332/ritonavir is not expected to provide any clinical benefit to healthy participants or participants with hepatic impairment in this study. This study is designed primarily to characterize the effect of hepatic impairment on the plasma PK of a single dose of PF-07321332 pharmacokinetically enhanced with ritonavir. The data from this study are expected to provide the basis for development of dosing recommendations for target patient populations who may have hepatic impairment.

Based on preliminary data from the ongoing Phase 1 study (C4671001) collected as of 07 April 2021 in PART-1 and 14 April 2021 in PART-2 (data snapshot taken), the clinical safety profile of PF-07321332 appears to be acceptable at single doses up to 1500 mg alone and up to 750 mg administered with ritonavir (100 mg at -12h, 0h, 12h), and at repeated daily doses administered orally for 10 days of up to 500 mg PF-07321332 BID with 100 mg ritonavir BID.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-07321332 with ritonavir may be found in the IB and ritonavir USPI[4], which are the SRSDs for this study.

CCI

	CCI [redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

2.3.2. Benefit Assessment

PF-07321332/ritonavir will not provide any clinical benefit to healthy participants or participants with hepatic impairment in this study. Any anticipated benefit to participants would be in terms of contribution to the process of developing a new therapy in an area of unmet medical need.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with PF-07321332/ritonavir are justified by the anticipated benefits that may be afforded to participants with COVID-19.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To compare the PK of PF-07321332, following a single oral dose administration of PF-07321332 pharmacokinetically boosted with ritonavir in adult participants with moderate hepatic impairment and age and body weight-matched participants without hepatic impairment.	• Plasma PF-07321332 PK parameters: C_{max}, AUC_{last}, AUC_{inf} (if data permit)
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of PF-07321332 and ritonavir, following a single oral dose administration of PF-07321332 pharmacokinetically boosted with ritonavir, in participants with moderate hepatic impairment and in healthy participants with normal hepatic function.	• Incidence of TEAEs, abnormal ECGs, vital signs, and laboratory values
CCI [redacted]	[redacted]
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, non-randomized, open-label, single-dose study to compare the pharmacokinetics of PF-07321332, given in combination with PK boosting agent, ritonavir, in adult participants with moderate hepatic impairment relative to participants without hepatic impairment.

The study will have 2 cohorts: participants without hepatic impairment (Cohort 1) and participants with moderate hepatic impairment (Cohort 2).

Enrollment will be in a staged manner such that participants with hepatic impairment (Cohorts 2) will be enrolled first. Participants without hepatic impairment (Cohort 1) will begin recruitment towards the end of Cohort 2 or earlier, at the sponsor's discretion, such that the enrollment in both cohorts may overlap. Participants in Cohort 1 will match the average demographics (at a minimum, age and weight; and gender as much as practically possible) of participants in Cohort 2. Approval from the sponsor must be obtained before proceeding with recruitment for participants in Cohort 1.

Table 1. Hepatic Function Categories Based on Child-Pugh Score

Cohort	Description	Child-Pugh Score	Number of Participants
1	Without hepatic impairment	Not Applicable	8
2	Moderate hepatic impairment	Class B (7 to 9 points)	8

The Child-Pugh classification (CPC; Appendix 9) will be used to define the participants of Cohort 2 with moderate hepatic impairment (Child-Pugh Class B).

All participants will be required to provide their own consent to participate in this study, hence participants with clinically active Grade 3 or Grade 4 encephalopathy will be excluded. However, participants who have a previous history of Grade 3 or Grade 4 encephalopathy but are currently receiving an intervention [for example: lactulose or lactitol, alone or in combination with rifaximin, and/or neomycin] to control their encephalopathy related signs and symptoms are eligible provided the on-treatment encephalopathy grading at the Screening visit is Grade 2 or lower thereby permitting them to provide their own informed consent.

Eligible participants will be admitted to the CRU on Day -1 (at least 12 hours prior to the dosing of PF-07321332 on Day 1) and will be confined in the CRU until Day 3. On the evening of Day -1, participants will receive a single 100 mg dose of ritonavir (-12 hour relative to PF-07321332 dosing). On the morning of Day 1, the participants will receive a single dose of 100 mg PF-07321332 with a 100 mg dose of ritonavir after an overnight (or a minimum 6 hour) fast. Ritonavir, 100 mg, will continue to be dosed at 12 and 24 hours post PF-07321332 dosing to ensure maintenance of the PK boosting effect. Serial blood [redacted] samples at specified intervals will be collected for PK assessments as per SoA. Safety assessments will be performed during Screening, on Day -1 prior to dosing, and on Day 3.

Physical examinations and clinical laboratory tests will be conducted, and AEs will be monitored to assess safety. Vital signs and ECG measurements will be done on Day 1, prior to dosing. The total participation time (eg, CRU confinement time for study procedures) for each participant in this study is approximately 3 nights/4 days (excluding Screening & Follow-Up contact).

A safety follow-up call will be made to participants 28 to 35 days from administration of the dose of study intervention.

Participants who prematurely discontinue for non-safety related reasons may be replaced, at the discretion of the PI and sponsor study team.

The overall study design is summarized in Figure 1. For individual participants, the total duration of participation from the Screening visit to the Follow-Up visit will range from 5 weeks (minimum) to 9 weeks (maximum).

4.2. Scientific Rationale for Study Design

This study is a Phase 1, non-randomized, open-label study of PF-07321332 in participants with moderate hepatic impairment and participants with normal hepatic function, matched for age, body weight and, to the extent possible, for gender composition. Details on age and body weight matching criteria are specified in Section 5.1.

PF-07321332 alone is primarily eliminated through a CYP450 mediated oxidation with CYP3A4 as the major contributor (f_m = 0.99). However, in the presence of the CYP3A4 inhibitor ritonavir, preliminary data suggests renal excretion may play a significant role in PF-07321332 excretion. In FIH study, approximately 64.6% to 32.5% of the administered dose was excreted unchanged in urine and remaining drug may get eliminated via metabolism. Preliminary PBPK modeling suggests < 2 × increase in AUC in mild hepatic impaired participants (Child-Pugh A) and < 3 × increase in moderate (Child-Pugh B) hepatic impaired participants. Therefore, the PK will only be evaluated in moderately hepatic impaired participants. Ritonavir has not been studied in severe hepatic impaired patients and currently prohibited to be used in those population. Therefore, this study does not plan to evaluate PK in severely hepatically impaired participants.

A single dose of PF-07321332 was selected and 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. As ritonavir is not eliminated renally, multiple doses of 100 mg ritonavir will be administered at -12, 0, 12, and 24 hours relative to PF-07321332 dosing to ensure adequate PK boosting effect over the duration of PF-07321332 exposure.

PF-07321332 is not extensively bound to human plasma proteins, with f_u of 0.31 observed in the in vitro protein binding study. Thus, no additional blood samples will be collected in this study for ex vivo protein binding analysis.

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data are limited for PF-07321332, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

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4.3. Justification for Dose

A single oral dose of 100 mg PF-07321332, pharmacokinetically enhanced with ritonavir (100 mg at -12, 0, 12, and 24 hours relative to PF-07321332), is planned in this study. This is anticipated to be at the lower end of the clinically effective dose range, and below the anticipated Phase 2/3 dose of PF-07321332/ritonavir of 300/100 mg. Although single doses up to 750 mg PF-07321332 with ritonavir have been evaluated, exposure increased less than dose proportional within the 250 mg to 750 mg dose range evaluated. Therefore, 100 mg PF-07321332 is appropriate considering systemic exposures of PF-07321332 may be increased when administered in hepatic impairment.

When co-administered with ritonavir, doses of PF-07321332 up to 750 mg single dose and 500 mg q12h for 10 days were generally safe and well tolerated based on preliminary data from the Phase 1 Study C4671001. There have been no deaths or serious adverse events or SUSARs reported. Based on review of preliminary (unaudited) data, all reported adverse events have been of mild intensity. There were no clinically meaningful findings in vital signs, ECG, or potential Hy's Law cases reported during the study.

Using preliminary PBPK model, the projected AUC and C_{max} at the proposed dose are CCI [redacted] which are below the highest observed exposures at safe and tolerate dose in study C4671001 and are approximately 19 × and 25 × below NOAEL exposures observed in toxicity studies in rats, respectively.

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

4.4. End of Study Definition

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

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

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. Participants must be 18 to 75 years of age, inclusive, at the time of signing the ICD.

    - [***For Cohort 1 only***] Each participant's age is within ±10 years of the mean age of the hepatic impairment group. Attempts will be made to ensure that the male-to-female distribution in Cohort 1 is comparable to that in hepatic impairment cohort, Cohort 2.

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

3. [***For Cohort 1 only***] Male and female participants who are classically healthy having no clinically relevant abnormalities as determined by medical evaluation including medical history, physical examination including blood pressure and pulse rate measurement, 12-lead ECG, and laboratory tests. No known or suspected hepatic impairment.

4. [***for Cohort 2 only***] Stable hepatic impairment that meets the criteria for Class B of the CPC (refer to Appendix 9) with no clinically significant change in disease status within the 28 days prior to the Screening visit, as documented by the participant's recent medical history (for example: no worsening clinical signs of hepatic impairment, no worsening of total bilirubin or PT by more than 50%).

Weight:

5. BMI of 17.5 to 40 kg/m^2; and a total body weight >50 kg (110 lb).

    - [***For Cohort 1 only***] Each participant's body weight within ±15 kg of the mean body weight of hepatic impairment group.

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, prior bariatric surgery, gastrectomy, ileal resection).

   NOTE: Participants who have undergone cholecystectomy and/or appendectomy are eligible for this study so long as the surgery occurred more than 6 months prior to Screening.

3. At screening, participants with a positive result for HIV antibodies.

4. [***For Cohort 1 only***] Participants with chronic liver disease including history of hepatitis, hepatitis B, or hepatitis C or evidence of active disease, at screening.

   *NOTE: P*articipants with a previously positive hepatitis B surface antibody result due to vaccination are deemed eligible.

5. [***For Cohort 2 only***]

   - Hepatic carcinoma ***or*** hepatorenal syndrome ***or*** limited predicted life expectancy (defined as less than 1 year).

   - A diagnosis of hepatic dysfunction secondary to any acute ongoing hepatocellular process that is documented by medical history, physical examination, liver biopsy, hepatic ultrasound, computerized tomography scan, or MRI.

   - Signs of clinically active Grade 3 or Grade 4 hepatic encephalopathy (ie, > Grade 2 Portal Systemic Encephalopathy score; refer to Appendix 9).

   - Severe ascites and/or pleural effusion.

   - History of kidney, liver, or heart transplantation.

6. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic (eg, Contact with positive case, residence, or travel to an area with high incidence) that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

7. Participants who have been vaccinated with COVID-19 vaccines within the past 1 week of dosing.

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 investigational product used in this study (whichever is longer).

9. 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 6.8 Concomitant Therapy for additional details). 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.

   For participants with hepatic impairment, stable concomitant medications (including herbal supplements) may be given following **approval by the sponsor** if they are considered necessary for the welfare of the study participants (eg, standard therapy for underlying diseases), are not contraindicated with the IP, and are unlikely to interfere with the PK of the IP.

10. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s) (Refer to Section 6.8 Concomitant Therapy for additional details).

Prior/Concurrent Clinical Study Experience:

11. 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).

12. Participants with known prior participation (ie, randomized and received at least 1 dose of investigational product) in a study involving PF-07321332.

Diagnostic Assessments:

13. A positive urine drug test at Screening or on Day -1.

NOTE: Participants in Cohort 2 who have been medically prescribed opiates/opioids or benzodiazepines and report the use of these drugs to the investigator at Screening may be allowed to participate if approved by the sponsor.

14. In females of childbearing potential, a positive urine pregnancy test at Screening or Day -1.

15. Vital sign measurements at Screening that demonstrates:

    [***For Cohort 1 only***] Screening seated BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of rest.

    [***For Cohort 2 only***]

    - Screening seated BP ≥180 mm Hg and/or ≥100 mm Hg (diastolic) following at least 5 minutes of rest.

      NOTE: If SBP is ≥140 mm Hg (for Cohort 1) ***or*** ≥180 mm Hg (for Cohort 2) or if DBP ≥90 mm Hg (for Cohort 1) or ≥100 mm Hg (for Cohort 2), 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.

    - For participants with SBP ≥160 (and <180) mm Hg ***or*** DBP ≥95 (and <100) mm Hg, the period between Screening and Day -1 must be used to refine the doses of the agents used for management of BP with the aim to have stable BP by Day -1. Participants must have measurement on Day 1 of SBP ≤160 mm Hg ***and*** DBP <95 mm Hg.

16. Screening standard 12-lead ECG that demonstrates:

    - Clinically relevant abnormalities requiring treatment (eg, acute myocardial infarction, serious tachy- or brady-arrhythmias) or indicating serious underlying heart disease (eg, prolonged PR interval, cardiomyopathy, underlying structural heart disease, Wolff Parkinson-White syndrome);

      [***For Cohort 1 only***] Screening supine 12-lead ECG demonstrating QTcF interval >450 msec or a QRS interval >120 msec;

      [***For Cohort 2 only***] Screening supine 12-lead ECG demonstrating a QTcF interval >470 msec or a QRS interval >120 msec;

      NOTE: If QTcF exceeds 450 msec (for Cohort 1) or 480 msec (for Cohort 2), ***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 eligibility.

17. 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:

    - eGFR <60 mL/min/1.73m^2 based on the CKD-EPI equation, with single repeat allowed.

    - [***For Cohort 1 only***]

        - AST ***or*** ALT level ≥ ULN;

        - Albumin > ULN;

        - Prothrombin time > ULN;

        - Total bilirubin level ≥1.5 × ULN;

          NOTE: Participants with a history of Gilbert syndrome (and hence elevated total bilirubin) are eligible provided direct bilirubin level is ≤ ULN;

    - [***For Cohort 2 only***] ALT ***or*** AST >5 × ULN

18. In the opinion of the investigator or Pfizer (or designee), have any clinically significant laboratory abnormality that that could affect interpretation of study data or the participant's participation in the study.

Other Exclusions:

19. 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).

    - At Screening or Day -1, a positive breath alcohol test or urine test.

20. Female participants of childbearing potential who are unwilling or unable to use highly effective methods of contraception as outlined in Section 5.3.4 for the duration of the study and for at least 28 days after the administration of investigational product, pregnant female participants, female participants planning to become pregnant during the duration of the study until 28 days after the administration of investigational product, breastfeeding female participants.

21. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.

22. History of sensitivity reactions to ritonavir, or any of the formulation components of PF-07321332 or ritonavir.

23. History of sensitivity to heparin or heparin induced thrombocytopenia, only if heparin is used to flush intravenous catheters used during serial blood collections.

24. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

25. 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.

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 any safety laboratory evaluations and overnight (at least 6 hours) prior to the collection of the predose PK sample and PF-07321332 administration on Day 1. There will be no restriction to breakfast on the other days provided other restrictions are followed.

- Water is permitted until 1 hour prior to study intervention administration. Water may be consumed without restriction beginning 1 hour after dosing. Noncaffeinated drinks (except grapefruit or grapefruit related citrus fruit juices - see below) may be consumed with meals and the evening snack.

- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos) 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.

5.3.2. Caffeine, Alcohol, and Tobacco

- Consumption of caffeinated drinks and tobacco (or nicotine containing products) is permitted during participation in the study; however, there may be a need for brief interruption while at the site, depending on local site policy.

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, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing of PF-07321332 (does not apply to ritonavir dosing).

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 schedule of activities (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) considering that their risk for pregnancy may have changed since the last visit. 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 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 if prior reason for not meeting the eligibility criteria has been resolved. Rescreening may only occur with sponsor approval. In the event that the participation of a participant in the study is delayed, outdated screening procedures can be repeated. Rescreened participants should be assigned the same participant number as for the initial screening.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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 PF-07321332 and ritonavir.

6.1. Study Intervention(s) Administered

For this study, the investigational products are PF-07321332 (provided as 100 mg tablets) and ritonavir (provided as 100 mg tablets).

PF-07321332 100 mg tablets and ritonavir 100 mg tablets will be supplied by Pfizer to the CRU in bulk along with individual dosing containers for unit dosing.

6.1.1. Administration

Investigational products will be administered orally and according to the conditions described in the SoA section and Protocol Section 5.3.1 Meals and Dietary Restrictions.

On Day -1, 12 hours prior to dosing of PF-07321332, participants will receive a 100 mg ritonavir tablet (as 1 × 100 mg) with approximately 240 mL ambient temperature water. On Day 1, following an overnight fast of at least 6 hours, participants will receive 100 mg PF-07321332 (as 1 × 100 mg tablet) at approximately 0800 hours (plus or minus 2 hours) and 100 mg ritonavir (as 1 × 100 mg tablet). Participants will receive 2 additional doses of 100 mg ritonavir (as 1 × 100 mg tablet) at 12 and 24 hours after receiving PF-07321332. Investigator site personnel will administer study intervention with ambient temperature water to a total volume of approximately 240 mL. Participants will swallow the study intervention whole and will not manipulate or chew the study intervention prior to swallowing.

In order to standardize the conditions of PK sampling, all participants will be required to refrain from lying down (except when required for ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing of PF-07321332.

6.2. Preparation, Handling, Storage, and 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 IP manual.

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. 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.

7. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. 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 as described in the IP manual.

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 ritonavir tablets will be prepared 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 to the participant 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's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

The investigator will assign participant numbers to the participants as they are screened for the study. All participants enrolled will receive treatment according to the dose/schedule.

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. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the

study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Dose Modification

Dose modifications for PF-07321332 and ritonavir are not allowed.

6.6. Continued Access to Study Intervention After the End of the Study

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

6.7. Treatment of Overdose

For this study, any dose of PF-07321332 greater than 100 mg or ritonavir greater than 200 mg within a 24-hour time period will be considered an overdose.

There is no 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 PF-07321332 or ritonavir (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 Pfizer 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).

6.8. 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.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

As PF-07321332 and ritonavir are both primarily metabolized by CYP3A4, concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to dosing of investigational product. Additionally, ritonavir and PF-07321332

are inhibitors of CYP3A4. Therefore, medications highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events are not permitted during dosing of PF-07321332/ritonavir. A non-exhaustive list of prohibited and precautionary medications is provided in Appendix 8. If a medication is not listed, it should not automatically be assumed it is safe to co-administer.

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.

6.8.1. Participants with Healthy Liver Function (Cohort 1)

In general, participants will abstain from all concomitant treatments (prescription or over the counter) as described in Section 6.8, except for the treatment of AEs. Of note, the following restrictions apply:

- 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 ***after*** approval by the sponsor.

6.8.2. Participants with Impaired Liver Function (Cohort 2)

Participants are permitted to be on stable doses (at least up to 5 half-lives) of background medications if they are considered necessary for the welfare of the study participants (eg, standard therapy for the underlying disease), are not contraindicated with the investigational product, and are unlikely to interfere with the PK of the investigational product. ***Whenever possible***, attempts must be made to ***not*** alter the doses and regimens of the concomitant medications after Day 1 and until the end of study on Day 3.

- Approved concomitant medications should be administered to hepatically impaired participants at least 2 hours prior to dosing or withheld until 4 hours after PF-07321332 dosing.

6.8.3. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07321332 or ritonavir; standard medical supportive care must be provided to manage the AEs.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following.

- AEs requiring discontinuation in investigator's view;
- Pregnancy;
- Positive COVID-19 test.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and PK, if possible. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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.

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 study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;

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 from the study intervention and 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.

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. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether 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.

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 is approximately 90 mL. 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 Section 5.3 Lifestyle Considerations and Section 6.8 Concomitant Therapy sections of the protocol.

8.1. Efficacy Assessments

Not Applicable.

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.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to 8.3.3.

8.2.2. Vital Signs

Seated 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.

8.2.3. 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) should not be used 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 5 minutes in a supine position.

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 QTcF interval is increased by ≥30 msec from the baseline **and** is >450 msec for participants with normal hepatic function and >470 msec for participants with impaired hepatic function; or b) an absolute QT 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 QTcF interval remains ≥30 msec from the baseline **and** is >450 msec for participants with normal hepatic function and >470 msec for participants with impaired hepatic function; or b) an absolute QT value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring.

A cardiologist should be consulted if QTcF intervals do not return to less than the criteria 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 QTcF values are in the acceptable range.

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

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 28 calendar days 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.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

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. COVID-19 specific assessments

Participants will be tested for SARS-CoV-2 infection as per site-specific regulations prior to being admitted to the clinic for confinement and a subsequent COVID-19 test will be performed if they develop COVID-19 like symptoms. Additional testing may be required by local regulations or by the Principal Investigator.

8.2.6. 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 intervention. 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 the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the Investigator or other healthcare providers (clinical signs, test results, etc.).

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 (see Section 7.1).

During the active collection period as described in Section 8.3.1, 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.

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 permanently discontinues or temporarily discontinues study 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 information on AEs or SAEs 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.

Reporting of AEs and SAEs for participants who fail screening are subject to the CRF requirements as described in Section 5.4.

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 or 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 toward 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. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

Any such exposure to the study intervention under study 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 EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion 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 participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- 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.

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

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form regardless of whether there is an associated SAE. Since the information about the occupational exposure 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 must be 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

Not applicable.

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. Pharmacokinetics

8.4.1. Plasma for Analysis of PF-07321332 CCI

Blood samples of approximately 4 mL, to provide a minimum of 1.5 mL plasma, will be collected for measurement of concentrations of PF-07321332 CCI 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 data collection tool (eg, CRF/DCT). 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 data collection tool (eg, CRF/DCT). This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples will be used to evaluate the PK of PF-07321332 CCI . Each plasma sample will be divided into 2 aliquots. Samples collected for analyses of PF-07321332 CCI plasma 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, CCI .

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of PF-07321332 CCI 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.

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8.7. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.8. Health Economics

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

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

No statistical hypothesis will be tested in this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
PK Concentration	The PK concentration population is defined as all participants assigned to investigational product and treated who have at least 1 concentration measured.
PK Parameter	The PK parameter analysis population is defined as all participants assigned to investigational product and treated who have at least 1 of the PK parameters of primary interest measured.
Safety Analysis Set	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.

9.3. 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.

One-way ANOVA will be used to compare the natural log transformed AUC_{last}, AUC_{inf} (if data permit) and C_{max} for PF-07321332 between Cohort 2 with moderate hepatic impairment

(Test) and Cohort 1 with normal hepatic function (Reference). 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 the adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

Box and whisker plots for individual participant parameters (AUC_{inf} and C_{max}) will be constructed by cohort and overlaid with geometric means.

For summary statistics and median/mean 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.

9.3.1. Other Safety Analyses

All safety analyses will be performed on the safety population.

AEs, 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 physical examination 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.

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9.3.2.1. Pharmacokinetic Analyses

9.3.2.1.1. Analysis Population

The PK concentration population will be defined as all participants treated in whom at least 1 plasma concentration value is reported.

The PK parameter analysis population is defined as all participants dosed who have at least 1 of the PK parameters of primary interest.

9.3.2.1.2. Derivation of Pharmacokinetic Parameters Prior to Analysis

The plasma PK parameters for PF-07321332 will be derived from the concentration time profiles as detailed in Table 2. 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 2. Plasma PK Parameters

Parameter	Analyte	Definition	Method of Determination
AUC_{last}	PF-07321332	Area under the plasma concentration-time profile from time 0 to the time of C_{last}	Linear/Log trapezoidal method.
CCI	[redacted]	[redacted]	[redacted]
AUC_{inf}*	PF-07321332	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, Where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis.
C_{max}	PF-07321332, ritonavir	Maximum plasma concentration	Observed directly from data.
CCI	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

* As data permit.

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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK/PD modeling, and/or supporting clinical development.

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[redacted]	[redacted]	[redacted]	[redacted]
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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, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (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 the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, 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, privacy and data protection 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 on which 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.

Participants who are rescreened are required to sign a new ICD.

10.1.4. 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 form and will be password-protected 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 ID. 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.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use a DMC.

10.1.6. 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 data from these trials available 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.

10.1.7. 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.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic form and are password-protected 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, including definition of study critical data items and processes (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, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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.

10.1.8. 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 and its origin can be found in the clinical monitoring plan, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

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

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 guidelines, and all applicable regulatory requirements.

10.1.9. 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 or designee/CRO 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 the ICH 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.

10.1.10. 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.

10.1.11. 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 SToD system.

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an Emergency Contact Card (ECC) at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, 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 4. 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/urea and creatinine Glucose Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Alkaline phosphatase Total bilirubin Direct bilirubin[a] Indirect bilirubin[a] Uric acid Albumin Total protein	Local Dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Laboratory: Microscopy[b]	• SARS-CoV-2 RT-PCR[c] • Urine drug screening[d] • Breath or urine alcohol test[e] • Pregnancy test (β-hCG)[f] At Screening Only[g]: • PT • aPTT • PT-INR • HIV • HbsAg • HbcAb[h] • HCVAb[i] • FSH[j]

a. Direct and indirect bilirubin assessed when total bilirubin is > ULN, ***only***.
b. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
c. Testing for COVID-19 pathogen will be performed prior to being admitted to the clinic for confinement, on Day -1, and if participant develops COVID-19 like symptoms.
d. At Screening and Day -1; The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
e. At Screening and Day -1.
f. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-hCG for female participants of childbearing potential.
g. Tests will only be performed at Screening.
h. HBsAb will be performed as reflex testing for any participant who is HBsAg negative and HBcAb positive.
i. HCV RNA will be performed as reflex testing for any participant who is HCV Ab positive.
j. At Screening for confirmation of postmenopausal status only.

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.

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] Samples to be used for this purpose will be shipped to either a Pfizer-approved BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

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 condition 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 or 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 that 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 an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
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 admitted (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 or significant 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), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a 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 participant 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.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. 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	All AEs/SAEs associated with exposure during pregnancy or breastfeeding **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF.	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE). **
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB).	None. Exposure to a study non-participant is not collected on the CRF.	The exposure (whether or not there is an associated AE or SAE) must be reported.***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or Occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or 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 or 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 or 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 or 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: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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.

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or VERY SEVERE to describe the maximum intensity of the AE. The severity of the AE should be determined using the Toxicity Grading Scale:

MILD	Does not interfere with participant's usual function.
MODERATE	Interferes to some extent with participant's usual function.
SEVERE	Interferes significantly with participant's usual function.

VERY SEVERE	Unacceptable and intolerable events or events which are irreversible or cause the participant to be in imminent danger of death.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- 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.
- 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 or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or 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 submitted documents. • 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) 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 and Barrier 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 contraception/barrier as detailed below:

  - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

- 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), as described below during the intervention period and for at least 28 days after the last dose of PF-07321332, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention. If a highly effective method that is user dependent is chosen, a second effective method of contraception, as described below (except options 5 and 6), must also be used. 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.
   - A 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 (eg, bilateral tubal ligation).
5. Vasectomized partner.
    - A 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

6. Combined (estrogen- and progestogen -containing) hormonal contraception associated with inhibition of ovulation.
    - Oral;
    - Intravaginal;
    - Transdermal.
7. Progestogen-only hormone contraception associated with inhibition of ovulation.
    - Oral;
    - Injectable.
8. 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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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 “adaptors” 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 Hy's law cases, 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, or 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, 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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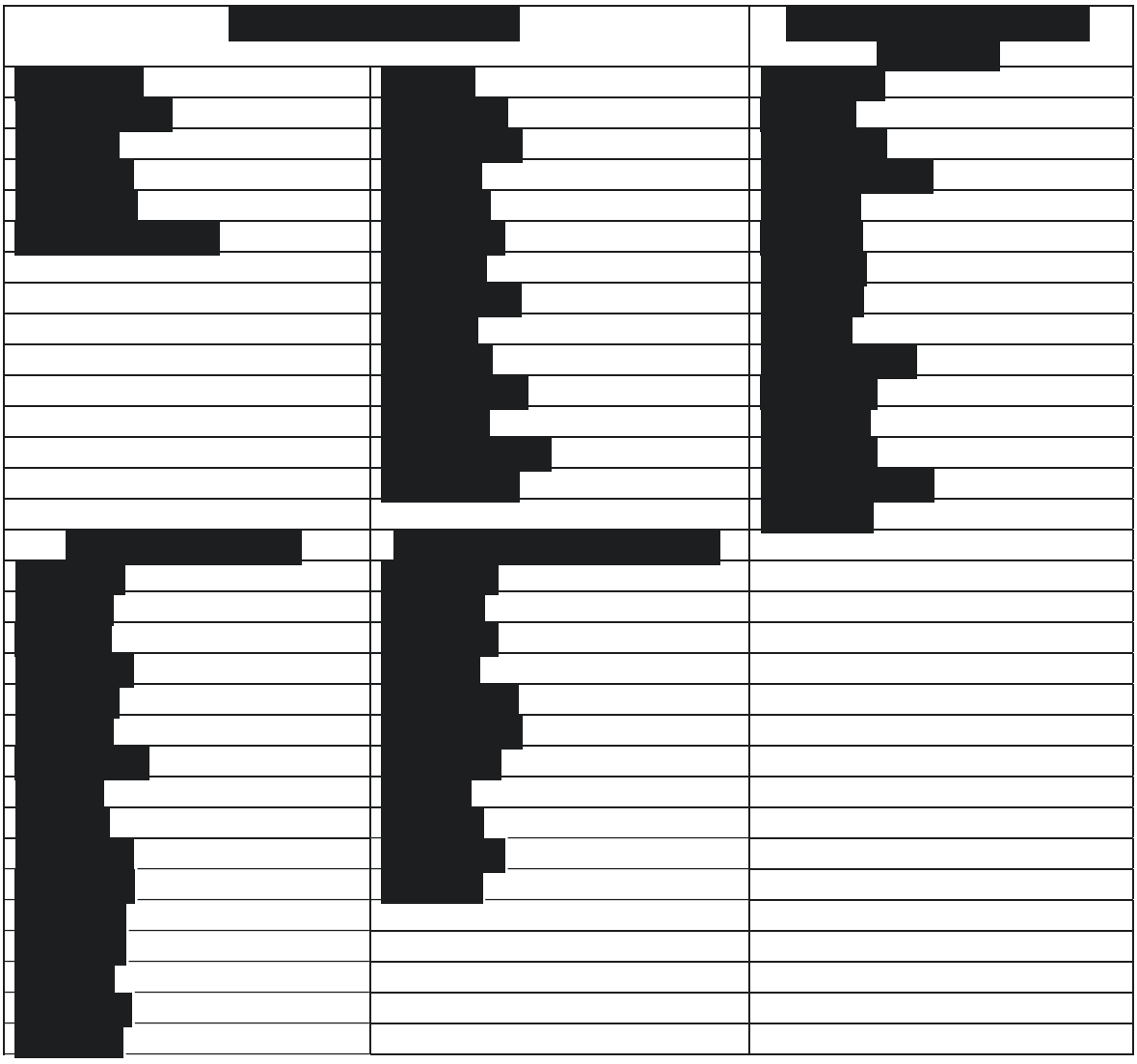

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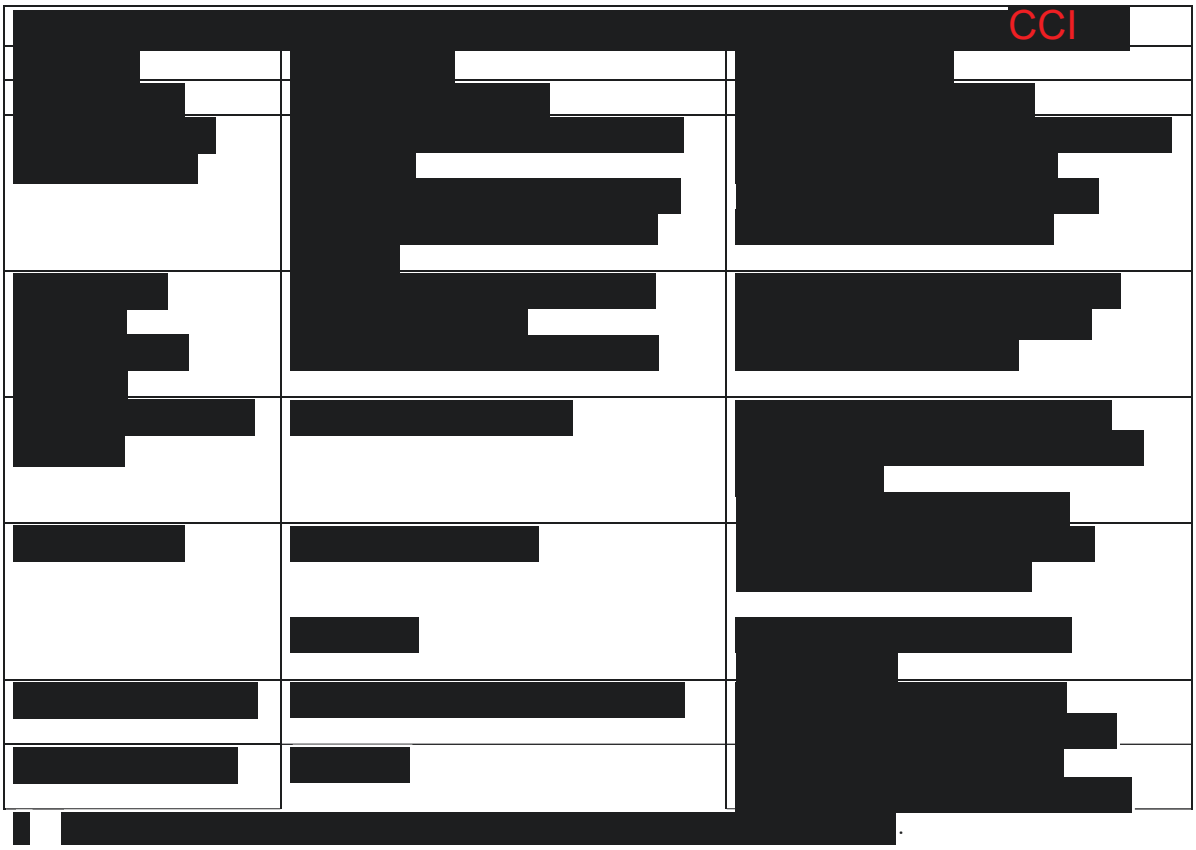
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10.9. Appendix 9: Child-Pugh Classification (CPC) of Liver Dysfunction

Table 5. Scoring for Child-Pugh Classification

Cohort	CPC	Level of dysfunction	Total Score (tally based on assessment of parameters in Table 6)
1	Not Applicable	Without hepatic impairment	Not Applicable
NA	A	Mild	5-6
2	B	Moderate	7-9
NA	C	Severe	≥10

Table 6. Derivation of Child-Pugh Classification Score

Assessment Parameters	Assigned score for observed findings		
	1 point	2 points	3 points
Encephalopathy grade[a] (refer to Table 7 below)	0	1 or 2	3 or 4[a]
Ascites	Absent	Asymptomatic	Requiring intervention
Serum total bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
Prothrombin time, sec prolonged[b]	<4	4 to 6	>6

a. Participants with a prior history of Grade 3 or Grade 4 encephalopathy who are *currently* receiving an intervention [*for example*: lactulose or lactitol, alone or in combination with rifaximin, and/or neomycin] to manage encephalopathy-related signs and symptoms should be scored for encephalopathy grading *based on their presentation while on intervention at the Screening visit* and can be included in this study as long as they do ***not*** have clinically active Grade 3 or Grade 4 encephalopathy.
b. As assessed relative to PT control (***or*** upper limit of normal).

Table 7. Determination of Encephalopathy Grade

Encephalopathy Grade	Definition
0	Normal consciousness, personality, neurological exam
1	Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting
2	Lethargic, time disoriented, inappropriate, asterixis, ataxia
3[a]	Somnolent, stuporous, place disoriented, hyperactive reflexes, rigidity
4[a]	Unrousable coma, no personality/behavior, decerebrate

a. Participants with clinically active Grade 3 or 4 encephalopathy are excluded.

CPC should be assessed *at Screening* to determine the classification of a given participant.

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
→	ongoing/continuous event
$3CL^{pro}$	3C-like protein
Ab	antibody
Abs	absolute
ADL	activities of daily living
CCI [redacted]	[redacted]
AE	adverse event
CCI [redacted]	[redacted]
[redacted]	[redacted]
ALT	alanine aminotransferase
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
CCI [redacted]	[redacted]
[redacted]	[redacted]
AUC_{inf}	area under the plasma concentration-time profile from time 0 extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of C_{last}
AV	atrioventricular
β-hCG	beta-human chorionic gonadotropin
BBS	Biospecimen Banking System
BID	twice a day
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
CCI [redacted]	[redacted]
C_{last}	predicted plasma concentration at the last quantifiable time point

Abbreviation	Term
CCI	[redacted]
C_{max}	maximum plasma concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CPC	Child-Pugh score
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
DBP	diastolic blood pressure
DC	discontinuation
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EC	ethics committee
ECC	Emergency Contact Card
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FIH	first-in-human
f_m	fraction metabolized
FSH	follicle stimulating hormone
f_u	fraction unbound
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
H	hour
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCoV-OC43	human coronavirus OC43
HCoV-229E	human coronavirus 229E

Abbreviation	Term
HCoV-HKU1	human coronavirus HKU1
HCoV-NL63	human coronavirus NL63
HCVAb	hepatitis C antibody
HCV	hepatitis C virus
hep C	hepatitis C
HI	hepatic impairment
HIV	human immunodeficiency virus
HMG CoA reductase	3-hydroxy-3-methyl-glutaryl-CoA reductase
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IV	intravenous
k_{el}	elimination rate constant
K_i	inhibition constant
LFT	liver function test
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MERS	Middle East respiratory syndrome
MRI	magnetic resonance imaging
N/A	not applicable
NHP	non-human primate
NNRT	non-nucleoside reverse transcriptase
NOAEL	no observed adverse effect level
NTI	narrow therapeutic index
PAH	pulmonary arterial hypertension
PBPK	physiologically based pharmacokinetic
PD	pharmacodynamic(s)
PE	physical examination
pH	potential of hydrogen
PI	principle investigator
PK	pharmacokinetic(s)
PR	pulse rate

Abbreviation	Term
PT	prothrombin time
PT-INR	prothrombin time-international normalized ratio
PVC	premature ventricular contraction/complex
q12h	every 12 hours
QT	time from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT interval
QTcF	corrected QT (Fridericia method)
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
RT-PCR	reverse-transcriptase polymerase chain reaction
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single-reference safety document
SToD	Study Team on Demand
SUSAR	suspected unexpected serious adverse reaction
[redacted]	[redacted]
T4	thyroxine
TBili	total bilirubin
TEAE	treatment emergent adverse event
THC	tetrahydrocannabinol
TIPS	transjugular intrahepatic portosystemic shunt
CCI	[redacted]
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
CCI	[redacted]
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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