A PHASE 1, OPEN-LABEL, 3-TREATMENT, 6-SEQUENCE, 3-PERIOD CROSSOVER STUDY TO ESTIMATE THE EFFECT OF PF-07321332/RITONAVIR AND RITONAVIR ON THE PHARMACOKINETICS OF DABIGATRAN IN HEALTHY PARTICIPANTS

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Brief Title: A Phase 1 Study to Estimate the Effect of PF-07321332/Ritonavir and Ritonavir on the PK of Dabigatran in Healthy Participants

Document History

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1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: A Phase 1 Study to Estimate the Effect of PF-07321332/Ritonavir and Ritonavir on the PK of Dabigatran in Healthy Participants

Rationale

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.

In vitro and in vivo metabolite profiling suggests that the primary clearance mechanism for PF-07321332 is CYP3A4 mediated oxidation. 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. As such, in the FIH study, C4671001, the CYP3A4 inhibitor ritonavir was used to enhance the exposure of PF-07321332 in order to achieve plasma levels that are anticipated to be efficacious. Preliminary PK data following multiple oral administrations of PF-07321332/ritonavir at doses of 75/100 mg, 250/100 mg, and 500/100 mg q12h suggest that the renal pathway may also play a significant role in PF-07321332 excretion when co-administered with ritonavir, with approximately 32.5% (PF-07321332/ritonavir 500/100 mg) to 64.6% (PF-07321332/ritonavir 75/100 mg) of the drug excreted unchanged in urine across doses at steady-state, and renal clearance ranging between 3.5 to 4.4 L/h across doses. Ritonavir is extensively metabolized, primarily by CYP3A4.[1]

The DDI potential of PF-07321332 was further evaluated using a static mechanistic model using the projected C_{max} for reversible inhibition or C_{av} time-dependent inhibition in plasma, intestinal lumen, enterocytes, liver, and portal inlet (incorporating $k_{p,uu}$ and k_a). Based on this model, PF-07321332 has minimal risk to inhibit CYPs other than 3A4, UGTs and transport proteins; however, the potential remains to reversibly and time-dependently inhibit CYP3A4 and inhibit P-gp in humans at the proposed therapeutic dose.

Dabigatran etexilate (herein referred to as dabigatran) is a sensitive probe substrate of the efflux transporter P-gp that experiences a ≥2 fold increase in exposure upon coadministration with P-gp inhibitors verapamil or quinidine.[2] Additionally, dabigatran is primarily renally eliminated by glomerular filtration (approximately 80%).[2]

Ritonavir is classified as a P-gp inhibitor. Although limited clinical data exist on drug-drug interactions with ritonavir and P-gp probe substrates like dabigatran, results from a study assessing the concomitant administration of dabigatran etexilate and ritonavir did not result in statistically significant changes in any of the PK parameters of dabigatran or changes in thrombin time measures as compared to dabigatran administered alone. However, there was statistically significant and similar decreases in the dabigatran AUC and C_{max} when dabigatran and ritonavir were administered separately by 2 hours compared to values

obtained when dabigatran was administered alone, suggesting there may be the potential of ritonavir to induce P-gp. Even though dabigatran is primarily renally eliminated, results suggested that whether dabigatran and ritonavir were administered simultaneously or separated by 2 hours, there was no change in dabigatran $t_{½}$ or K_{el} compared to dabigatran administered alone.[2]

Based on available data to date, it is possible that administration of a P-gp substrate, dabigatran with PF-07321332/ritonavir may lead to changes in exposures of dabigatran.[3] Therefore, results of this study will provide guidance for dosing with substrates of P-gp.

The purpose of this study is to estimate the effect of PF-07321332/ritonavir and ritonavir on the PK of dabigatran in healthy participants.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the effect of the multiple doses of PF-07321332/ritonavir co-administered with dabigatran orally (test) compared to dabigatran administered orally as a single dose (reference).	• Plasma dabigatran (total) PK parameters: C_{max}, AUC_{inf} (or AUC_{last} if AUC_{inf} cannot be reliably estimated).
Secondary:	**Secondary:**
• To estimate the effect of the multiple doses of ritonavir co-administered with dabigatran orally (test) compared to dabigatran administered orally as a single dose (reference).	• Plasma dabigatran (total) PK parameters: C_{max}, AUC_{inf} (or AUC_{last} if AUC_{inf} cannot be reliably estimated).
• To evaluate the safety and tolerability of dabigatran alone and following co-administration with multiple dosing of PF-07321332/ritonavir or ritonavir	• Safety: TEAEs, clinical laboratory tests, vital signs, PE, and ECGs.
• To characterize the PK of dabigatran and PF-07321332 in study treatments.	• Dabigatran (total): T_{max}, $t_{½}$, as data permit • PF-07321332: C_{max}, AUC_{tau}, T_{max}, $t_{½}$, CL/F, V_z/F.
CCI [redacted]	[redacted]

Overall Design

Brief Summary

This is a Phase 1, open-label, randomized, 3-treatment, 6-sequence, 3-way crossover design to estimate the effect of PF-07321332/ritonavir and ritonavir on the PK of dabigatran in healthy participants. A total of approximately 24 healthy male and/or female participants will

be enrolled into the study. The purpose of this study is to estimate the effect of PF-07321332/ritonavir and ritonavir on the PK of dabigatran in healthy participants. Safety and tolerability will also be assessed throughout the duration of the study. This study will consist of 3 treatments. Treatment 1 (T1) will include administration of dabigatran administered as a 75 mg single oral dose on Day 1 followed by a 3-day washout. Treatment 2 (T2) will include multiple dose administration of PF-07321332/ritonavir 300 mg/100 mg q12h for 2 days (Days 1 and 2). On the second day of T2 (Day 2) in the morning, a single oral dose of dabigatran 75 mg will be administered, followed by a 3-day washout. Treatment 3 (T3) will include multiple dose administration of ritonavir 100 mg q12h for 2 days (Days 1 and 2). On the second day (Day 2) in the morning, dabigatran will be administered as a single oral 75 mg dose. PK sampling over 48 hours will be included in all 3 treatments to determine PK parameters. Each washout period will begin after the first dose of study treatment in that treatment period.

Each participant will be screened to determine eligibility within 28 days prior to study treatment. Eligible participants will report to the CRU at least 12 hours prior to Day 1 dosing in Period 1 and will be required to stay in the CRU for 13 days and 12 nights.

The following describes the study design as an example for Sequence 1 (T1-T2-T3):

Participants in T1 (Day 1) will receive dabigatran orally administered as a 75 mg dose followed by a 3-day washout. Serial PK samples will be collected up to 48 hours after single dose administration to determine PK parameters.

T2 will begin on Study Day 5 (referred to as T2 Day 1). Participants in T2 (Day 1) will receive multiple doses of PF-07321332/ritonavir 300 mg/100 mg q12h on Days 1 and 2 followed by a single dose of 75 mg dabigatran administered orally on Day 2, followed by a 3-day washout. Serial PK samples will be collected up to 48 hours following the administration of PF-07321332/ritonavir co-administered with a single oral dose of 75 mg dabigatran.

T3 will begin on Study Day 10 (referred to as T3 Day 1). Participants in T3 (Day 1) will receive multiple dose administration of ritonavir 100 mg q12h on Days 1 and 2. On Day 2, participants will be administered a single oral 75 mg dose of dabigatran. Serial PK samples will be collected up to 48 hours following the administration of ritonavir 100 mg q12h co-administered with a single oral dose of 75 mg dabigatran.

Eligible participants will be admitted to the CRU on Day -1 (at least 12 hours prior to Day 1 dosing of dabigatran dosing on Day 1) and will be confined in the CRU for 13 days and 12 nights. On the morning of Day 1 (T1), the participants will receive a single oral dose of 75 mg of dabigatran administered orally, followed by a 3-day washout. Serial blood samples at specified intervals will be collected up to 48 hours post-dose for PK assessments. On the morning of Day 1 and Day 2 in T2, PF-07321332/ritonavir 300 mg/100 mg will be administered as multiple doses q12h. Dabigatran 75 mg will be administered orally, as a single dose on Day 2. On the morning of Day 1 and Day 2 in T3 participants will receive multiple dosing of ritonavir 100 mg q12h. On Day 2 of T3, participants will receive

administration of a single oral dose of 75 mg dabigatran. Serial blood samples at specified intervals will be collected up to 48 hours post-dose for PK assessments of both ritonavir and dabigatran. Each washout period will begin after the first dose of study treatment in that treatment period.

All study treatments, regardless of dosing regimen should be administered in the fasting condition. Specifically, morning doses should be followed by an overnight fast of approximately 8-10 hours. When PK is performed after the morning dose, a 4-hour fast should occur. Evening dose will be administered 1 hour before or 2 hours after a meal.

Safety assessments will be performed during Screening, on Day -1 prior to dosing, and at specified time points. PEs, 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 13 days/12 nights (excluding screening and follow-up contact).

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

Number of Participants

Approximately 24 participants may be enrolled to study intervention.

Note: "Enrolled" means a participant, 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 participant will be screened to determine eligibility within 28 days prior to study treatment. Eligible participants will report to the CRU at least 12 hours prior to Day -1 and will be required to stay in the CRU for 13 days and 12 nights. A safety follow-up call will be made to participants approximately 28 to 35 days from administration of the final dose of study intervention.

Each enrolled participant will participate in 3 treatments and each washout period will begin after the first dose of study treatment:

- Treatment 1: In Treatment 1, dabigatran will be administered orally as a 75 mg single dose in the morning followed by a 3-day washout.

- Treatment 2: In Treatment 2, PF-07321332/ritonavir 300 mg/100 mg q12h will be administered as multiple doses over a period of 2 days. Morning and evening doses will be administered on Day 1, but only the morning dose will be administered on Day 2. In the morning on Day 2, 75 mg of dabigatran will be administered orally as a single dose. Treatment 2 will be followed by a 3-day washout.

- Treatment 3: In Treatment 3, ritonavir 100 mg q12h will be administered as multiple doses over a period of 2 days. Morning and evening doses will be administered on Day 1, but only the morning dose will be administered on Day 2. In the morning on Day 2, 75 mg of dabigatran will be administered orally as a single dose.

Participants will randomly be assigned to 1 of 6 sequences as follows:

	Period 1	**Period 2**	**Period 3**
Sequence 1	Treatment 1	Treatment 2	Treatment 3
Sequence 2	Treatment 3	Treatment 1	Treatment 2
Sequence 3	Treatment 2	Treatment 3	Treatment 1
Sequence 4	Treatment 3	Treatment 2	Treatment 1
Sequence 5	Treatment 2	Treatment 1	Treatment 3
Sequence 6	Treatment 1	Treatment 3	Treatment 2

Participants will be discharged in T3, Study Day 13 following completion of all assessments.

The total planned duration of participation, from the Screening visit to the last Follow-up phone call, is approximately 11 weeks.

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

A sample size of approximately 24 participants will provide adequate precision to estimate the effects of multiple dose PF-07321332/ritonavir on the PK of single dose dabigatran. The expected widths of the 90% CIs with 80% coverage probability are shown in the following table for a range of possible effects.

Parameter	**Estimated Effect (100*Test/Reference)**	**90% CI**	**CI Width**
AUC_{inf}	80%	63.09%, 101.45%	38.36%
	100%	78.86%, 126.81%	47.95%
	120%	94.63%, 152.17%	57.54%
	140%	110.40%, 177.53%	67.13%

Parameter	Estimated Effect (100*Test/Reference)	90% CI	CI Width
	160%	126.17%, 202.89%	76.72%
	180%	141.95%, 228.26%	86.31%
C_{max}	80%	60.49%, 105.80%	45.31%
	100%	75.61%, 132.25%	56.64%
	120%	90.74%, 158.70%	67.97%
	140%	105.86%, 185.15%	79.30%
	160%	120.98%, 211.60%	90.62%
	180%	136.10%, 238.06%	101.95%

These estimates are based on the assumption that within-participant standard deviations are 0.452 and 0.532 for $lnAUC_{inf}$ and lnC_{max}, respectively, as obtained from the mean of 2 clinical studies (B1871043 and B7451026) and literature[4] in healthy participants.

Participants who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

Pharmacokinetics Analysis

The PK concentration population is defined as all participants assigned to investigational product and treated who have at least 1 concentration measured.

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.

Pharmacokinetic parameters for PF-07321332, ritonavir and dabigatran (total) will be analyzed by standard noncompartmental method of analysis. Actual PK sampling times will be used in the derivation of PF-07321332, ritonavir and dabigatran PK parameters. The PF-07321332, ritonavir and dabigatran plasma PK parameters will be summarized descriptively by treatment. Plasma concentrations will be listed and summarized descriptively by treatment and nominal PK sampling time. Individual participant and summary profiles (mean and median plots) of the plasma concentration time data will be plotted using actual and nominal times, respectively. Box and whisker plots of AUC_{inf}, AUC_{tau} and C_{max} will be plotted by treatment.

Drug-Drug Interaction

Natural log transformed parameters (AUC_{inf} [if data permit], AUC_{last} and $C_{max)}$ of dabigatran will be analyzed using a mixed effect model with treatment, period and sequence as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for

the ratios. Dabigatran administered alone will be the reference treatment and PF-07321332/ritonavir co-administered with dabigatran and ritonavir co-administered with dabigatran will be the test treatments.

Safety Analysis

AEs, ECGs, vital signs (BP, pulse rate, RR and temperature) 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.

1.2. Schema

The following schematic represents the study design as an example for Sequence 1.

Sequence 1	**Period 1**		**Period 2**		**Period 3**	
Screening **Days -28 to -2**	**Treatment 1** **(Days 1 and 2)**	**3-Day washout[a]**	**Treatment 2** **(Days 1 and 2)**	**3-Day washout[a]**	**Treatment 3** **(Days 1 and 2)**	**Follow-up** **Days 28-35**
	(Reference) 75 mg single oral dose of dabigatran		(Test) PF-07321332 /ritonavir 300/100 mg q12h multiple doses on Days 1 and 2.[b] On Day 2, a single oral 75 mg dose of dabigatran		(Test) Ritonavir 100 mg q12h on Days 1 and 2.[b] On Day 2, a single oral dose of 75 mg dose of dabigatran	

a. The 3-day washout will begin after the first dose of study medication.

b. Morning and evening doses will be administered on Day 1, but only the morning dose will be administered on Day 2.

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.

All SoA/PK sampling schedules below do not include days of washout.

Visit Identifier Abbreviations used in this table may be found in Appendix 9.	**Screening**[a]	**Treatment (See Detailed SoAs Below for Each Treatment)**									**Follow-Up**	**Early Termination/ Discontinuation**
Days Relative to Day 1 of Period 1	**Day -28 to Day -2**	**Day -1**								**Day 13**	**28-35 Days**[b]	
Hours After Dose												
Informed consent	X											
CRU confinement[c]		X	→	→	→	→	→	→	→	X		
Inclusion/exclusion criteria	X	X										
Medical/medication history (update)[d]	X	X										
Physical examination[e]	X	X										X
Safety laboratory[f]	X	X										X
TSH & Free T4	X	X										
Demography[g]	X											
Pregnancy test (WOCBP only)	X	X								X		X
Contraception check[h]	X	X								X	X	X
FSH[i]	X											
Urine drug testing[j]	X	X										
12-Lead ECG[k]	X	X										X
Vital signs (BP/PR/RR/temperature)[l]	X	X										X
HIV, HBsAg, HBsAb, HBcAb, HCVAb	X											

Visit Identifier Abbreviations used in this table may be found in Appendix 9.	**Screening[a]**	**Treatment (See Detailed SoAs Below for Each Treatment)**									**Follow-Up**	**Early Termination/ Discontinuation**
Days Relative to Day 1 of Period 1	**Day -28 to Day -2**	**Day -1**								**Day 13**	**28-35 Days[b]**	
Hours After Dose												
COVID-19 questionnaire[m]	X	X										
COVID-19 testing[n]	X	X										
COVID-19 check temperature[o]	X	X								X	X	X
Study intervention administration[p]												
PK blood sampling[q]												X
Blood/Plasma ratio sample[r]												
CCI [redacted]			[redacted]									
CRU discharge										X		
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→

a. Screening will be performed within 28 days prior to the first dose of study intervention.
b. Contact may occur via telephone contact and must occur 28 to 35 days from administration of the final dose of study intervention.
c. Participants will be admitted to the CRU on Day -1. Participants will be discharged on Day 13 following the final assessments.
d. Medical history will include a history of prior illegal drug, alcohol, and tobacco use, as well as blood donation within prior 60 days. Medical history will be recorded at Screening and updated on Day -1 of Period 1.
e. A PE will be performed by trained medical personnel at the investigator site at Screening and Day -1 of Period 1 only (height and weight must be obtained at Screening to obtain BMI for eligibility criteria) and at Early Termination/Discontinuation. A brief PE may be performed at other designated time points at the discretion of the investigator.
f. Safety laboratory assessments including urinalysis, hematology, chemistry and coagulation will be performed at the indicated time points. All the safety laboratory samples must be collected following at least a 4-hour fast. Additional safety laboratory assessments may be performed at any time at the discretion of the investigator.
g. Demographics will include participant race, ethnicity, age, and gender during the Screening visit.
h. The investigator or his/her designee will discuss with the participant the need to use highly effective contraception consistently and correctly according to contraception guidelines.
i. For postmenopausal (amenorrheic for at least 12 consecutive months) female participants only.
j. Urine drug (mandatory) and alcohol breath test (at discretion of investigator) will be performed at Screening and on Day -1. These tests may be performed at any other time at the discretion of the investigator.
k. Triplicate 12-lead ECG readings will be taken at specified times. All ECG assessments will be made after at least a 10-minute rest in a supine position and prior to any blood draws or vital sign measurements. ECG assessment should be taken in the morning with vitals.

Visit Identifier Abbreviations used in this table may be found in Appendix 9.	**Screening**[a]	**Treatment (See Detailed SoAs Below for Each Treatment)**									**Follow-Up**	**Early Termination/ Discontinuation**
Days Relative to Day 1 of Period 1	**Day -28 to Day -2**	**Day -1**								**Day 13**	**28-35 Days**[b]	
Hours After Dose												

l. Single supine BP, RR and PR will be performed following at least a 5-minute rest in a supine position. BP, RR and PR assessments will be performed after collection of ECGs and prior to collection of blood draws if scheduled at the same time.
m. Check exposure to positive participant, residence or travel in area of high incidence and COVID-19 related signs and symptoms. To be done at Screening and no more than 48 hours before confinement to the CRU.
n. The testing for COVID-19 pathogen by RT-PCR will be performed at specified times while the participant is admitted for residence. For participants, a COVID-19 test will be performed after 4 days (ie, upon completion of 4 × 24 hours in house), or if they develop COVID-19 like symptoms.
o. To be done at least daily during residence.
p. Please see the treatment tables below.
q. Please see the PK sampling schedule tables below. PK samples should be collected at time of early termination/discontinuation
r. Please see the Treatment 2 table below.
[redacted]

A. Treatment 1 (Single oral dose of dabigatran): Screening – Day 3

Visit Identifier Abbreviations used in this table may be found in Appendix 9.	Schedule for Treatment 1		
Days Relative to Day 1	**Day 1**	**Day 2**	**Day 3**
Safety laboratory (including Fibrinogen)[a]	X		X
aPTT, PT-INR	X	X	X
TSH & Free T4	X		X
12-lead ECG[b]	X	X	
Vital signs (BP/PR/RR/temperature)[c]	X	X	
COVID-19 questionnaire[d]			
COVID-19 testing[e]			X
COVID-19 check temperature[f]	X	X	X
Dabigatran administration[g]	X		
PK blood sampling for dabigatran (total)[h]	X	X	X

a. Safety laboratory assessments including urinalysis, hematology, and chemistry will be performed at the indicated timepoints. All the safety laboratory samples must be collected following at least a 4 hour fast. Additional safety laboratory assessments may be performed at any time at the discretion of the investigator.

b. All ECG assessments (triplicate) will be made after at least a 10-minute rest in a supine position and prior to any blood draws or vital sign measurements. ECG assessment should be taken in the morning with vitals.

c. Single supine blood pressure and pulse rate will be performed following at least a 5-minute rest in a supine position. BP and PR assessments will be performed after collection of ECGs and prior to collection of blood draws if scheduled at the same time. RR will also be evaluated. Vitals should be taken in the morning with ECG assessments.

d. Check exposure to positive participant, residence or travel in area of high incidence and COVID-19 related signs and symptoms. To be done at Screening and no more than 48 hours before confinement to the CRU.

e. The testing for COVID-19 pathogen by RT-PCR or rapid testing via Abbott ID will be performed at specified times while the participant is admitted for residence. For participants, a COVID-19 test will be performed after 4 days (ie, upon completion of 4 × 24 hours in house), or if they develop COVID-19 like symptoms.

f. To be done at least daily during residence.

g. Dabigatran will be administered orally as a single dose. Dabigatran should be administered in the fasting condition (no food or drink except water).

h. One (approximately 4 mL) blood sample for PK analysis of dabigatran (total) will be taken at the following timepoints: Day 1 pre-dose, and at 1, 2, 4, 6, 8, 12, 16, 24, 36 and 48 hours post-dose.

Treatment 1 (Single oral dose of dabigatran): PK Sampling Schedule (Days 1-3)

Visit Identifier	Treatment 1 on PK Days										
Study Day	Day 1								Day 2		Day 3
Planned Hours Post Morning Dose	0[a]	1	2	4	6	8	12	16	24	36	48
Study intervention administration	X										
PK blood sampling for dabigatran (total)	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X					X			X		
Vital Signs (BP/PR/RR/Temperature)	X					X			X		

a. Predose sample collection.

B. Treatment 2 (PF-07321332/ritonavir with dabigatran): Days 1-4

Visit Identifier Abbreviations used in this table may be found in Appendix 9.	Schedule for Treatment 2			
Days Relative to Day 1	**Day 1**	**Day 2**	**Day 3**	**Day 4**
Safety laboratory (including Fibrinogen)[a]	X		X	
TSH & Free T4	X		X	
aPTT, PT-INR	X	X	X	
12-lead ECG[b]	X		X	
Vital signs (BP/PR/RR/temperature)	X		X	
COVID-19 testing[c]				X
COVID-19 check temperature[d]	X	X	X	X
Dabigatran administration[e]		X		
PF-07321332/ritonavir administration[e]	X (am/pm)	X (am only)		
PK Blood Sampling for dabigatran (total)[f]		X	X	X
PK Blood Sampling for PF-07321332 and ritonavir[g]		X		
CCI [redacted]		[redacted]		
Blood/plasma ratio sample[i]		X		

a. Safety laboratory assessments including urinalysis, hematology, and chemistry will be performed at the indicated timepoints. All the safety laboratory samples must be collected following at least a 4 hour fast. Additional safety laboratory assessments may be performed at any time at the discretion of the investigator.
b. All ECG assessments (triplicate) will be made after at least a 10-minute rest in a supine position and prior to any blood draws or vital sign measurements. ECG assessments should be taken in the morning with vital signs.
c. The testing for COVID-19 pathogen by RT-PCR or rapid testing via Abbott ID will be performed at specified times while the participant is admitted for residence. For participants, a COVID-19 test will be performed after 4 days (ie, upon completion of 4 × 24 hours in house), or if they develop COVID-19 like symptoms.
d. To be done at least daily during residence.
e. On the morning of Day 2 (T2), dabigatran will be administered orally as a single dose. Dabigatran should be administered in the fasting condition (no food or drink except water). On T2 Day 1 and Day 2 following an approximately 8-10-hour fasting period, PF-07321332/ritonavir 300 mg/ 100 mg will be co-administered q12h as multiple doses in the fasting condition.
f. One (approximately 4 mL) blood sample for PK analysis of dabigatran (total) will be taken at the following timepoints: Treatment 2 Day 2 (Study Day 6) pre-dose, and at 1, 2, 4, 6, 8, 12, 16, 24, 36 and 48 hours post-dose.
g. One (approximately 4 mL) blood sample for PK analysis of PF-07321332 and ritonavir will be taken at the following timepoints: Treatment 2 Day 2 (Study Day 6) pre-dose, and at 1, 2, 4, 6, 8, 12 hours post-dose.
C [redacted]
i. Whole blood sample/aliquot (approximately 150 µL) for in vivo blood/plasma ratio assessment.

Treatment 2 (PF-07321332/ritonavir with dabigatran): PK Sampling Schedule (Days 1-4)

Visit Identifier	Treatment 2 on PK Days																		
	Day 1								Day 2								Day 3		Day 4
Planned Hours Post Morning Dose	**0[a]**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**0[a]**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**24**	**36**	**48**
PF-07321332/ritonavir administration	X						X		X										
Dabigatran administration									X										
PK blood sampling for PF-07321332/ritonavir									X	X	X	X	X	X	X				
PK blood sampling for dabigatran (total)									X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X			X								X					X		
Vital Signs (BP/PR/RR/Temperature)	X			X								X					X		
CCI [redacted]										[redacted]									
Blood/Plasma ratio sample[c]												X							

a. Pre-dose sample

CCI [redacted]

c. Whole blood sample/aliquot (approximately 150 µL) for in vivo blood/plasma ratio assessment.

C. Treatment 3 (Ritonavir with dabigatran): Days 1-4

Visit Identifier Abbreviations used in this table may be found in Appendix 9.	Schedule for Treatment 3			
Days Relative to Day 1	**Day 1**	**Day 2**	**Day 3**	**Day 4**
Safety laboratory (including Fibrinogen)[a]	X		X	
aPTT, PT-INR	X	X	X	X
TS4 & Free T4	X		X	
12-lead ECG[b]	X		X	
Vital signs (BP/PR/RR/temperature)[c]	X		X	X
COVID-19 testing[d]				X
COVID-19 check temperature[e]	X	X	X	X
Dabigatran administration[f]		X		
Ritonavir administration[g]	X (am/pm)	X (am only)		
PK blood sampling for dabigatran (total)[h]		X	X	X

a. Safety laboratory assessments including urinalysis, hematology, and chemistry will be performed at the indicated timepoints. All the safety laboratory samples must be collected following at least a 4 hour fast. Additional safety laboratory assessments may be performed at any time at the discretion of the investigator.
b. All ECG assessments (triplicate) will be made after at least a 10-minute rest in a supine position and prior to any blood draws or vital sign measurements. ECG assessments should be taken in the morning with vitals.
c. Single supine BP and PR will be performed following at least a 5-minute rest in a supine position. BP and PR assessments will be performed after collection of ECGs and prior to collection of blood draws if scheduled at the same time. RR will also be evaluated. Vitals should be taken in the morning with ECG assessments.
d. The testing for COVID-19 pathogen by RT-PCR or rapid testing via Abbott ID will be performed at specified times while the participant is admitted for residence. For participants, a COVID-19 test will be performed after 4 days (ie, upon completion of 4 × 24 hours in house), or if they develop COVID-19 like symptoms.
e. To be done at least daily during residence.
f. Dabigatran will be administered orally as a single dose. Dabigatran should be administered in the fasting condition (no food or drink except water).
g. In T3 Day 1 and Day 2, participants will receive multiple dosing of ritonavir 100 mg q12h the fasting condition over a period of 2 days.
h. One (approximately 4 mL) blood sample for PK analysis of dabigatran (total) will be taken at the following timepoints in T3: Day 2 pre-dose, and at 1, 2, 4, 6, 8, 12, 16, 24, 36 and 48 hours post-dose.

Treatment 3 (Ritonavir with dabigatran): PK Sampling Schedule (Days 1-4)

Visit Identifier	Treatment 3 on PK Days																		
	Day 1								Day 2								Day 3		Day 4
Planned Hours Post Morning Dose	**0[a]**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**0[a]**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**24**	**36**	**48**
Ritonavir administration	X						X		X										
Dabigatran administration									X										
PK blood sampling for dabigatran (total)									X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X			X								X					X		
Vital Signs (BP/PR/RR/temperature)	X			X								X					X		

a. Pre-dose sample.

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

In vitro and in vivo metabolite profiling suggests that the primary clearance mechanism for PF-07321332 is CYP3A4 mediated oxidation. 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. As such, in the FIH study, C4671001, the CYP3A4 inhibitor ritonavir was used to enhance the exposure of PF-07321332 in order to achieve plasma levels that are anticipated to be efficacious. Preliminary PK data following multiple oral administrations of PF-07321332/ritonavir at doses of 75/100 mg, 250/100 mg, and 500/100 mg q12h suggest that the renal pathway may also play a significant role in PF-07321332 excretion when co-administered with ritonavir, with approximately 32.5% (PF-07321332/ritonavir 500/100 mg) to 64.6% (PF-07321332/ritonavir 75/100 mg) of the drug excreted unchanged in urine across doses at steady-state, and renal clearance ranging between 3.5 to 4.4 L/h across doses. Ritonavir is extensively metabolized, primarily by CYP3A4.[1]

The DDI potential of PF-07321332 was further evaluated using a static mechanistic model using the projected C_{max} for reversible inhibition or C_{av} time-dependent inhibition in plasma, intestinal lumen, enterocytes, liver, and portal inlet (incorporating $k_{p,uu}$ and k_a). Based on this model, PF-07321332 has minimal risk to inhibit CYPs other than 3A4, UGTs and transport proteins: however, the potential remains to reversibly and time-dependently inhibit CYP3A4 and inhibit P-gp in humans at the proposed therapeutic dose.

Dabigatran etexilate (herein referred to as dabigatran) is a sensitive probe substrate of the efflux transporter P-gp that experiences a ≥2-fold increase in exposure upon coadministration with P-gp inhibitors verapamil or quinidine.[2] Additionally, dabigatran is primarily renally eliminated by glomerular filtration (approximately 80%).[2]

Ritonavir is classified as a P-gp inhibitor. Although limited clinical data exists on drug-drug interactions with ritonavir and P-gp probe substrates like dabigatran, results from one study assessing the concomitant administration of dabigatran etexilate and ritonavir did not result in statistically significant changes in any of the PK parameters of dabigatran or changes in thrombin time measures as compared to dabigatran administered alone. However, there was statistically significant and similar decreases in the dabigatran AUC and C_{max} when dabigatran and ritonavir were administered separately by 2 hours compared to values obtained when dabigatran was administered alone, suggesting there may be the potential of ritonavir to induce P-gp. Even though dabigatran is primarily renally eliminated, results suggested that whether dabigatran and ritonavir were administered simultaneously or separated by 2 hours, there was no change in dabigatran $t_{½}$ or K_{el} compared to dabigatran administered alone.[2]

Based on available data to date, it is possible that administration of a P-gp substrate, dabigatran with PF-07321332/ritonavir may lead to further changes in exposures of dabigatran.[3] Therefore, results of this study will provide guidance for dosing with substrates of P-gp.

The purpose of this study is to estimate the effect of PF-07321332/ritonavir and ritonavir on the PK of dabigatran in healthy participants.

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.[5]

PF-07321332 is an orally bioavailable $3CL^{pro}$ inhibitor shown to be effective against SARS-CoV-2 $3CL^{pro}$ (Ki = 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).[6] 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 is not expected to have any pharmacological impact on the SARS-CoV-2 virus. Ritonavir 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.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

Hepatic CYP3450 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 (Study PF-07321332_09Nov20_084546). 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. (Study PF-07321332_21Nov20_072016). 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.

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

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 75 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.

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). Prior to Amendment 3, Study C4671001 is a 4-part study consisting of SAD (PART-1), MAD (PART-2), relative bioavailability/food effect (PART3), and metabolism and excretion study (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. Included in this Clinical Overview are summaries of the preliminary results from PART-1 and PART-2.

2.2.4.1. Safety Overview

Preliminary safety and tolerability data from Study C4671001 as of 07 April 2021 in PART-1 and 14 April 2021 in PART-2 (data snapshot taken) demonstrated PF-07321332 was generally safe and well-tolerated in healthy participants at single doses of PF-07321332 ranging from 150 mg to 1500 mg alone and at 250 mg and 750 mg with ritonavir (100 mg at -12h, 0h, 12h) in the PART-1: SAD, and 10 days of dosing from 75 mg BID to 500 mg BID with 100 mg ritonavir BID in the PART-2: MAD of the study.

Following single doses of PF-07321332 with and without ritonavir, all AEs were mild and none was considered treatment related. There were no obvious trends in, or association of, TEAEs with any dose level of PF-07321332. Following multiple doses, the most commonly observed AEs by system organ class were gastrointestinal disorders and nervous system disorders. Diarrhea was the most common reported AE, occurring in 4 participants across treatment groups. A total of 5 treatment related TEAEs were observed in Part-2: MAD. Across treatment groups, blood TSH increased in 3 participants, and 2 participants reported dysgeusia. The 3 participants with elevated TSH results did not experience related clinical symptoms and the free T4 results remained within reference range.

Based on review of preliminary (unaudited) data, all reported adverse events have been of mild intensity. There have been no deaths, serious adverse events, or SUSARs reported. There were no clinically meaningful findings in vital signs, ECG, or potential Hy's Law cases reported during this study.

Further details on the clinical safety information with PF-07321332 are provided in the current IB.

2.2.4.2. Summary of PF-07321332 Pharmacokinetics in Human

Preliminary single dose PK data from Study C4671001 at doses of PF-07321332 of 150 mg, 500 mg, and 1500 mg alone and at 250 mg and 750 mg with ritonavir 100 mg (dosed at -12h, 0h, and 12h) show that PF-07321332 was absorbed rapidly with median T_{max} of 1 hour or less when administered alone and 2.75 hours or less when administered with ritonavir. Since PF-07321332 is primarily metabolized by CYP3A4 and ritonavir is a CYP3A4 inhibitor, dosing with ritonavir increased the exposure of PF-07321332. Highest observed mean C_{max} and AUC_{last} was 5.09 µg/mL and 64.26 µg.h/mL, respectively, at 750 mg PF-07321332 dosed with ritonavir. The mean half-life of PF-07321332 was approximately 2 hours when administered alone and increased to approximately 6-13 hours when co-administered with ritonavir. Dosing with a high-fat meal modestly increased the exposure of PF-07321332 (approximately 15% increase in mean C_{max} and 1.6% in mean AUC_{last}).

Preliminary PK data on Day 1, Day 5 and Day 10 following multiple oral administration of PF-07321332/ritonavir 75/100 mg, 250/100 mg, and 500/100 mg BID suggest less than proportional increase in exposures at steady state. Multiple dosing over 10 days achieved steady state on Day 2 with approximately 2-fold accumulation. Day 5 and Day 10 exposure was similar at all doses. Approximately 32.5% to 64.6% of the drug was excreted unchanged

in urine across different doses at steady-state. The renal clearance ranged between 3.5 to 4.4 L/h across doses.

Further details on the clinical PK of PF-07321332 are provided in the current IB.

2.3. Benefit/Risk Assessment

- PF-07321332/ritonavir alone or in combination with dabigatran is not expected to provide any clinical benefit to healthy participants in this study. This study is designed primarily to generate safety, tolerability, and pharmacokinetic data for further clinical development.

- 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 AEs of PF-07321332 may be found in the IB, which is the SRSD for this study. The SRSDs for ritonavir[7] and dabigatran[8] are the corresponding USPIs.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): PF-07321332		
Emesis	Sporadic emesis was observed at ≥100 mg/kg/day of PF-07321332 in the 15-day NHP- toxicology study (See IB). Based on preliminary data, no emesis was observed in the FIH Study C4671001 at single doses of PF-07321332 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.	As this is an investigational agent, there is some risk that is mitigated by close observation of AEs, etc. If needed, palliative care or antiemetics may be provided.
Neuronal and pulmonary effects	Transient effect in rat neuronal and pulmonary endpoints were observed in rat toxicology study at the high dose level (1000 mg/kg as single dose; See IB). Based on preliminary data, no AEs suggestive of neuronal or pulmonary effects were observed in the FIH Study C4671001 at single doses of PF-07321332 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.	Vital signs, including respiratory rate, will be monitored for pulmonary effect. There will be close observation of AEs for any signs of neuronal effect.
Hemodynamic effects	Low level inflammation (increase in fibrinogen) in 15-day NHP toxicology study and changes in platelets, globulin and albumin/globulin ratio and coagulation system (increase in PT and aPTT) in 14-day rat toxicology study (See IB). No relevant laboratory changes in inflammatory markers have been observed in the FIH Study C4671001 at single doses of PF-07321332 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.	Fibrinogen, platelets, PT-INR and aPTT, albumin and total proteins will be monitored.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Thyroid function studies	In 14-day rat toxicology study at high dose of PF-07321332 (1000 mg/kg/day) thyroid gland changes observed were of low severity and without evidence of tissue damage. In the FIH Study C4671001, 3 participants had TEAEs of elevated TSH levels across treatment groups (PF-07321332 or placebo with ritonavir 100 mg BID) in the MAD part of the study. There was no clinical correlation with these TSH changes and free T4 remained within reference range at all times.	TSH and free T4 will be evaluated to monitor thyroid function
Study Intervention(s): Ritonavir		
Gastrointestinal disturbances (including diarrhea, nausea, vomiting and abdominal pain).	Frequently reported adverse reaction in HIV patients at 600 mg BID.	Lower dose of 100 mg twice daily is used in this study. There will be close observation of AEs. If needed, anti-emetics may be provided.
Neurological disturbances (eg, paresthesia, including oral paresthesia, dysgeusia and dizziness).	Frequently reported adverse reaction in HIV patients at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs.
Rash (most commonly reported as erythematous and maculopapular, followed by pruritic).	Frequently reported adverse reaction in HIV patients at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs and monitoring through targeted physical exams. If needed, palliative care may be provided.
Fatigue/Asthenia	Frequently reported adverse reaction in HIV patients at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs and monitoring through targeted physical exams.
Limited case reports of renal toxicity	Although ritonavir therapy is not generally considered nephrotoxic, a limited number of cases of acute kidney injury secondary to ritonavir have been reported post-marketing in HIV patients.	Lower dose used in this study. There will be close observation of AEs and renal function.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention (s): Dabigatran		
Spinal/Epidural hematoma:	When spinal/epidural anesthesia or spinal puncture is employed patients treated with anticoagulant agents are at risk of developing an epidural or spinal hematoma.	Participants are excluded who have had neuraxial anesthesia or have undergone spinal puncture
Bleeding which can be serious, and sometimes lead to death. This is because PRADAXA® is a blood thinner medicine that lowers the chance of blood clots forming in your body.	Dabigatran increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Promptly evaluate any signs or symptoms of blood loss (eg, a drop in hemoglobin and/or hematocrit or hypotension).	Measurement of PT, aPTT, INR throughout all 3 treatments in the study. In addition, CBC to monitor platelets, Hgb, HCT, etc. as well as hemodynamic monitoring such as BP and PR are also being evaluated in the study.

2.3.2. Benefit Assessment

PF-07321332/ritonavir and dabigatran will not provide any clinical benefit to healthy participants 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

PF-07321332/ritonavir and dabigatran are not expected to provide any clinical benefit to healthy participants in this study. Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with administration of PF-07321332/ritonavir and dabigatran are justified by the anticipated benefit, in terms of contribution to the process of developing a new therapy in an area of unmet medical need.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the effect of the multiple doses of PF-07321332/ritonavir co-administered with dabigatran orally (test) compared to dabigatran administered orally as a single dose (reference).	• Plasma dabigatran (total) PK parameters: C_{max}, AUC_{inf} (or AUC_{last} if AUC_{inf} cannot be reliably estimated).
Secondary:	**Secondary:**
• To estimate the effect of the multiple doses of ritonavir co-administered with dabigatran orally (test) compared to dabigatran administered orally as a single dose (reference). • To evaluate the safety and tolerability of dabigatran alone and following co-administration with multiple dosing of PF-07321332/ritonavir or ritonavir • To characterize the PK of dabigatran and PF-07321332 in study treatments.	• Plasma dabigatran (total) PK parameters: C_{max}, AUC_{inf} (or AUC_{last} if AUC_{inf} cannot be reliably estimated). • Safety: TEAEs, clinical laboratory tests, vital signs, PE, and ECGs. • Dabigatran (total): T_{max}, $t_{½}$, as data permit • PF-07321332: C_{max}, AUC_{tau}, T_{max}, $t_{½}$, CL/F, V_z/F.
CCI [redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, randomized, 3-treatment, 6-sequence, 3-way crossover design to estimate the effect of PF-07321332/ritonavir or ritonavir on the PK of a P-gp substrate, dabigatran in healthy participants.

This study will consist of 3 treatments. In T1, dabigatran will be administered orally as a 75 mg single dose followed by a 3-day washout. In T2, PF-07321332/ritonavir 300 mg/100 mg q12h will be administered as a multiple dose over a period of 2 days. In the morning on Day 2, 75 mg of dabigatran will be administered orally as a single dose. Treatment 2 will be followed by a 3-day washout. In T3, ritonavir 100 mg q12h will be administered as a multiple dose over a period of 2 days. In the morning on Day 2, 75 mg of dabigatran will be administered orally as a single dose. Each washout period will begin after the first dose of study treatment. A total of approximately 24 healthy male and/or female participants will be enrolled into the study. Participants who discontinue from the study may be replaced at the sponsor's discretion in collaboration with the Investigator.

The purpose of this study is to estimate the effect of PF-07321332/ritonavir and ritonavir on the PK of dabigatran in healthy participants.

Healthy participants (approximately n=24) will be screened to determine eligibility within 28 days prior to study treatment. Medical history and results of PE, physical measurements, vital signs, 12-lead ECGs, and clinical laboratory evaluations will determine eligibility. Participants will report to the CRU at least 12 hours prior to Day 1 dosing in T1 and will be required to stay in the CRU for 13 days and 12 nights. Each washout period will begin after the first dose of study treatment.

Participants will randomly be assigned to 1 of 6 sequences as follows:

	Period 1	**Period 2**	**Period 3**
Sequence 1	Treatment 1	Treatment 2	Treatment 3
Sequence 2	Treatment 3	Treatment 1	Treatment 2
Sequence 3	Treatment 2	Treatment 3	Treatment 1
Sequence 4	Treatment 3	Treatment 2	Treatment 1
Sequence 5	Treatment 2	Treatment 1	Treatment 3
Sequence 6	Treatment 1	Treatment 3	Treatment 2

The following describes the study design as an example for Sequence 1 (T1-T2-T3):

Participants in T1 (Day 1) will receive dabigatran orally administered as a 75 mg dose followed by a 3-day washout. Serial PK samples will be collected up to 48 hours after single dose administration to determine PK parameters.

T2 will begin on Study Day 5 (referred to as T2 Day 1). Participants in T2 (Day 1) will receive multiple doses of PF-07321332/ritonavir 300 mg/100 mg q12h on Days 1 and 2 followed by a single dose of 75 mg dabigatran administered orally on Day 2. A 3-day washout will ensue the co-administration of PF-07321332/ritonavir and dabigatran. Serial PK

samples will be collected up to 48 hours following the administration of PF-07321332/ritonavir co-administered with a single oral dose of 75 mg dabigatran.

T3 will begin on Study Day 10 (referred to as T3 Day 1). Participants in T3 (Day 1) will receive multiple dose administration of ritonavir 100 mg q12h on Days 1 and 2. In the morning on Day 2, participants will be administered a single oral 75 mg dose of dabigatran. Serial PK samples will be collected up to 48 hours following multiple dose administration of ritonavir 100 mg co-administered with a single oral dose of 75 mg dabigatran.

The total planned duration of participation, from the Screening visit to the last Follow-up phone call, is approximately 11 weeks.

Eligible participants will be admitted to the CRU on Day -1 (at least 12 hours prior to Day 1 dosing of dabigatran dosing on Day 1) and will be confined in the CRU for 13 days and 12 nights. On the morning of Day 1 (T1), the participants will receive a single oral dose of 75 mg of dabigatran administered orally, followed by a 3-day washout. Serial blood samples at specified intervals will be collected up to 48 hours post-dose for PK assessments. On the morning of Day 1 and Day 2 in T2, PF-07321332/ritonavir 300 mg/100 mg will be administered as multiple doses q12h. Dabigatran 75 mg will be administered orally, as a single dose on Day 2. On the morning of Day 1 and Day 2 in T3 participants will receive multiple dosing of ritonavir 100 mg q12h. On Day 2 of T3, participants will receive administration of a single oral dose of 75 mg dabigatran. Serial blood samples at specified intervals will be collected up to 48 hours post-dose for PK assessments of both ritonavir and dabigatran. Each washout period will begin after the first dose of study treatment.

All study treatments, regardless of dosing regimen should be administered in the fasting condition. Specifically, morning doses should be followed by an overnight fast of approximately 8-10 hours. When PK is performed after the morning dose, a 4-hour fast should occur. Evening dose will be administered 1 hour before or 2 hours after a meal.

Safety assessments will be performed during Screening, on Day -1 prior to dosing, and at specified time points. PEs, 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 13 days/12 nights (excluding screening and follow-up contact). Participants will be discharged in T3, Study Day 13 following completion of all assessments.

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

4.2. Scientific Rationale for Study Design

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.

In vitro and in vivo metabolite profiling suggests that the primary clearance mechanism for PF-07321332 is CYP3A4 mediated oxidation. 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. As such, in the FIH study, C4671001, the CYP3A4 inhibitor ritonavir was used to enhance the exposure of PF-07321332 in order to achieve plasma levels that are anticipated to be efficacious. Preliminary PK data following multiple oral administrations of PF-07321332/ritonavir at doses of 75/100 mg, 250/100 mg, and 500/100 mg q12h suggest that the renal pathway may also play a significant role in PF-07321332 excretion when co-administered with ritonavir, with approximately 32.5% (PF-07321332/ritonavir 500/100 mg) to 64.6% (PF-07321332/ritonavir 75/100 mg) of the drug excreted unchanged in urine across doses at steady-state, and renal clearance ranging between 3.5 to 4.4 L/h across doses. Ritonavir is extensively metabolized, primarily by CYP3A4.[1]

The DDI potential of PF-07321332 was further evaluated using a static mechanistic model using the projected C_{max} for reversible inhibition or C_{av} time-dependent inhibition in plasma, intestinal lumen, enterocytes, liver, and portal inlet (incorporating $k_{p,uu}$ and k_a). Based on this model, PF-07321332 has minimal risk to inhibit CYPs other than 3A4, UGTs and transport proteins; however, the potential remains to reversibly and time-dependently inhibit CYP3A4 and inhibit P-gp in humans at the proposed therapeutic dose.

Dabigatran is a sensitive probe substrate of the efflux transporter P-gp that experiences a ≥ 2-fold increase in exposure upon coadministration with P-gp inhibitors verapamil or quinidine.[2] Additionally, dabigatran is primarily renally eliminated by glomerular filtration (approximately 80%).[2]

Ritonavir is classified as a P-gp inhibitor. Although limited clinical data exists on drug-drug interactions with ritonavir and P-gp probe substrates like dabigatran, results from one study assessing the concomitant administration of dabigatran etexilate and ritonavir did not result in statistically significant changes in any of the PK parameters of dabigatran or changes in thrombin time measures as compared to dabigatran administered alone. However, there was statistically significant and similar decreases in the dabigatran AUC and C_{max} when dabigatran and ritonavir were administered separately by 2 hours compared to values obtained when dabigatran was administered alone, suggesting there may be the potential of ritonavir to induce P-gp. Even though dabigatran is primarily renally eliminated, results suggested that whether dabigatran and ritonavir were administered simultaneously or separated by 2 hours, there was no change in dabigatran $t_{½}$ or K_{el} compared to dabigatran administered alone.[2]

Based on available data to date, it is possible that administration of a P-gp substrate, dabigatran with PF-07321332/ritonavir may lead to changes in exposures of dabigatran.[3] Therefore, results of this study will provide guidance for dosing with substrates of P-gp. Lastly, the rationale to study the effect of ritonavir on dabigatran is for labeling purposes. Pfizer is pursuing the goal of a label similar to ritonavir with respect to DDIs. If the results from this study suggest that there is no influence of ritonavir on dabigatran concentrations as

compared to PF-07321332/ritonavir, this may be a convincing argument to not pursue additional DDI studies and accept the ritonavir label.

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).

CCI

[redacted]

4.3. Justification for Dose

A dose of 300 mg PF-07321332, pharmacokinetically enhanced with 100 mg ritonavir, to be administered as a single dose is planned in this study. This is the anticipated Phase 2/3 dose of PF-07321332/ritonavir of 300/100 mg.

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 form 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.

The dose of ritonavir to be used in this study is 100 mg administered in combination with PF-07321332. This dose is the typical dose of ritonavir when used as a PK enhancer.

Little research is available to date utilizing dabigatran as a P-gp substrate. Some DDI studies available in the published literature utilize a 150 mg single oral dose when using dabigatran as a P-gp probe.[3] As increases in dabigatran exposure may occur when co-administered with PF-07321332/ritonavir or ritonavir alone a single oral dose of 75 mg of dabigatran was chosen for this study.

4.4. End of Study Definition

The end of the study is defined as the date of last scheduled procedure shown in the SoA for the last participant in the trial.

A participant is considered to have completed the study if he/she has completed all parts of the study, including the last scheduled procedure shown in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be

taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants must be 18 to 60 years of age, inclusive, at the time of signing the ICD.

Type of Participant and Disease Characteristics:

2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, PE, laboratory tests, and cardiac monitoring.

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

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

4. Female participates of childbearing potential must have a negative pregnancy test.

Weight:

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

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

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

2. 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).

3. Any history of malignancy (with the exception of adequately treated or excised non-metastatic basal cell or squamous cell carcinoma of the skin or cervical carcinoma in situ).

4. 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).

5. Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy)

6. History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HbsAb, HbsAg, HbcAb, or HCVAb. Hepatitis B vaccination is allowed.

7. Any conduction abnormality (including but not specific to left or right complete bundle branch block, or AV block [2_{nd} degree or higher]).

8. Having undergone neuraxial intervention or undergoing spinal puncture 12 weeks prior to study start or planned neuraxial intervention or spinal puncture within 12 weeks after the end of the study.

9. Active pathological bleeding or risk of bleeding including prior personal or familiar history of abnormal bleeding, hereditary or acquired coagulation or platelet disorder or abnormal coagulation test (PT/INR or PTT/aPTT greater than upper limit of normal) result at screening.

10. Mechanical prosthetic heart valve surgery.

11. 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:

12. 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).

13. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s). Refer to Section 10.8 (Appendix 8) Concomitant Therapy.

14. Participants who have been vaccinated with COVID-19 vaccines within the past week (7 days) of dosing or are to be vaccinated with these vaccines at any time during the study confinement period.

Prior/Concurrent Clinical Study Experience:

15. 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). Participants who have participated in previous clinical trials with PF-07321332 may be eligible to participate in this study as long as they meet all other criteria.

Diagnostic Assessments:

16. A positive urine drug test.

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

18. Baseline 12-lead ECG (triplicate) that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTcF interval >450 msec, complete LBBB, signs of an acute or indeterminate age- myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >450 msec, this interval should be rate corrected- using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility. Computer interpreted- ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

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

    - AST **or** ALT level >1.0 × ULN;

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

- eGFR <90 mL/min/1.73m^2 (-10%) based on the CKD-EPI equation.

Other Exclusions:

20. Active acute or chronic infection requiring treatment with oral/parenteral antibiotics, antivirals (including biologic treatments), antiparasitics, antiprotozoals, or antifungals.

21. Participants considered in imminent need for surgery or with elective surgery scheduled to occur during the study.

22. 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).

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

24. History of sensitivity to heparin or heparin–induced thrombocytopenia.

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

26. 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.

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

28. Women who are pregnant or breastfeeding or planning to become pregnant during the study period.

29. For any of the diagnostic tests/assessments, if a result is outside the normal limit, the principal investigator can make a decision in consult with the Pfizer medical monitor.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Vaccine and Exposure to Infections Guidelines

Participant-Specific Recommendations:

It is recommended that all participants should be up-to-date with respect to standard of care vaccinations as defined by their country health ministry.

Guidance on Vaccinations:

Vaccination with live attenuated vaccine is prohibited within the 6 weeks prior to Day 1 (Baseline), during the study, and until the last Follow up visit. Similarly, current routine household contact with individuals who have been vaccinated with live-attenuated vaccines should be avoided in the same period. This is due to the potential for virus to be shed in bodily fluids (including stool) following vaccination with live vaccines, leading to a potential risk that the virus may be transmitted. General guidelines for immunosuppressed subjects suggest that exposure (through routine contact) should be avoided following vaccination (of others) with these vaccines for the stated time period:

a. Varicella or attenuated typhoid fever vaccination for 4 weeks following vaccination.

b. Oral polio vaccination for 6 weeks following vaccination.

c. Attenuated rotavirus vaccine for 10 days following vaccination.

d. FluMist (intranasal flu vaccine) for 1 week following vaccination.

Participants should avoid exposure to vaccinated or infected persons and contact the investigator promptly if they develop signs or symptoms of any infections.

If a participant is offered, in accordance with the prevailing local guidelines, a non-live COVID-19 vaccine, it is permitted during this study and should be reported as a concomitant medication.

5.3.2. Meals and Dietary Restrictions

- All study treatments, regardless of dosing regimen should be administered in the fasting condition (no food and drink except water). Specifically, morning doses should be followed by an overnight fast of approximately 8-10 hours. When PK is performed after the morning dose, a 4-hour fast should occur. Evening dose will be administered 1 hour before or 2 hours after a meal.

- On days where no PK sampling is required, participants can resume normal intake of both food and water.

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

- Lunch can be provided approximately 4 hours after dosing the last dose of the morning of either dabigatran or PF-07321332/ritonavir.

- Dinner can be provided approximately 2 hours after dosing the last dose in the evening of either PF-07321332/ritonavir or ritonavir.

- An evening snack may be permitted.

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

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

5.3.3. Caffeine, Alcohol, and Tobacco

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

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

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

5.3.4. 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.

5.3.5. 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 on the CRF.

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

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/ritonavir and dabigatran.

6.1. Study Intervention(s) Administered

PF-07321332 100 mg tablets will be supplied by Pfizer. Ritonavir 100 mg tablets and dabigatran 75 mg capsules will be supplied by the CRU.

6.1.1. Administration

Investigational products will be administered orally and according to the conditions described in the SoA section and Protocol Section 5.3.2 Meals and Dietary Restrictions.

In T1, Day 1 participants will receive a single 75 mg dose of dabigatran administered orally in the morning starting at approximately 0800 hours (plus or minus 2 hours).

In T2, on Days 1 and 2, participants will receive 300 mg PF-07321332 administered orally with 100 mg ritonavir at approximately 0800 hours (plus or minus 2 hours). PF-07321332 and ritonavir should be administered no more than 5 minutes of each other. PF-07321332 and ritonavir will be administered q12h on Days 1 (am and pm) and 2 (am only). On the morning of Day 2, a single oral dose of dabigatran 75 mg will be administered in combination with PF-07321332/ritonavir. Administration of dabigatran should occur at approximately 0815 to 0830 hours (plus or minus 10 minutes) after administration of PF-07321332/ritonavir.

In T3, on Days 1 and 2, participants will receive 100 mg ritonavir q12h at approximately 0800 hours (plus or minus 2 hours). Ritonavir will be administered q12h on Days 1 (am and pm) and 2 (am only). On the morning of Day 2, a single oral dose of 75 mg dabigatran will

be administered in combination with ritonavir. Administration of dabigatran should occur at approximately 0815 to 0830 hours (plus or minus 10 minutes) after administration of ritonavir.

Each washout period will begin after the first dose of study treatment.

Investigator site personnel can administer water at ambient temperature in all Treatment periods. Study intervention will be administered according to the IMP and the protocol.

All study treatments, regardless of dosing regimen should be administered in the fasting condition (no food and drink except water). Specifically, morning doses should be followed by an overnight fast of approximately 8-10 hours. When PK is performed after the morning dose, a 4-hour fast should occur. Evening dose will be administered 1 hour before or 2 hours after a meal.

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.

The tablets/capsules will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

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

No dose modification is anticipated.

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 600 mg or ritonavir greater than 200 mg within a 24-hour time period (±2 hours) will be considered an overdose.

An accidental overdose of dabigatran may lead to hemorrhagic complications. In the event of hemorrhagic complications, initiate appropriate clinical support, discontinue treatment, and investigate the source of bleeding. For dabigatran, a specific reversal agent (idarucizumab) is available.[9]

There is no specific treatment for an overdose of either PF-07321332 or ritonavir.

In the event of an overdose, the investigator should:

1. Contact the Pfizer 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 1 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

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

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.

Herbal supplements and hormonal methods of contraception (including oral and transdermal contraceptives, injectable progesterone, vaginal ring, and postcoital contraceptive methods) and hormone replacement therapy must have been discontinued at least 28 days prior to the first dose of investigational product.

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. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07321332 or ritonavir. For dabigatran, the specific reversal agent (idarucizumab) is available.[9] 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:

- AE requiring discontinuation in investigator's view,
- Pregnancy,
- Positive COVID-19 test.

If a positive COVID-19 test is confirmed during study conduct, and if in the opinion of the Principal Investigator, in consultation with the sponsor, it is in the best interest of either the participant or the investigational site to discontinue, then the participant should be discontinued from the study.

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

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further

receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

If a participant uses prohibited medication, guidance in Appendix 8 should be followed.

7.1.1. ECG Changes

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

- QTcF >500 msec.
- Change from baseline: QTcF >60 msec and QTcF >450 msec.

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

7.1.2. Potential Cases of Acute Kidney Injury

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

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

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

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include serum BUN, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If ≥2 healthy participants are noted to have 2 consecutive SCr results of

≥0.3 mg/dL (or ≥26.5 µmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

7.1.3. Liver Injury

Reasons for permanent discontinuation of study intervention due to potential liver injury are described in Appendix 6.

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;
- Investigator decision.

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.

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 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 470 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 Protocol Section 5.3 Lifestyle Considerations and Section 6.8 Concomitant Therapy.

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 PE will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems. A medical history will also be collected including smoking status and alcohol use.

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

PEs 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.

PE findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward PE 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 Section 8.3.1 to Section 8.3.3.

8.2.2. Vital Signs

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

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

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

8.2.2.1. Respiratory Rate

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

8.2.2.2. Temperature

Temperature will be measured orally (other body locations, eg, tympanic, are acceptable provided the same method is used and documented throughout the study). No eating, drinking, or smoking is allowed for 15 minutes prior to the measurement.

8.2.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) 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 approximately 10 minutes in a supine position.

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

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 post-dose QTcF interval is increased by ≥60 msec from the baseline and is >450 msec for participants with normal renal function and >470 msec for participants with impaired renal 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 ≥60 msec from the baseline **and** is >450 msec for participants with normal renal function and >470 msec for participants with impaired renal 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 48 hours 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.

For any of the clinical safety laboratory assessments, if a result is outside the normal limit, the principal investigator in consult with the Pfizer medical monitor can make a decision regarding clinical significance.

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

Urine drug (mandatory) and alcohol breath test (at discretion of investigator) will be performed at Screening and on Day -1. These tests may be performed at any other time at the discretion of the investigator.

8.2.5. COVID-19 Specific Assessments

Participants will be tested for SARS-COV-2 infection by RT-PCR prior to being admitted to the clinic for confinement and a subsequent SARS-CoV-2 test or rapid testing assessment (eg, Abbot) will be performed after 4 days (ie, upon completion of 4 × 24 hours in house), or 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.

The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. The investigator, or his or her designee, will confirm that the participant is adhering to the contraception method(s) required in the protocol. The required frequency of pregnancy testing for this study is described in the SoA.

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 intervention (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, except as indicated below, 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 intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek 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, inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation or skin contact then exposes his female partner prior to or around the time of conception.

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

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

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

preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a liveborn 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, inhalation, or skin contact.

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

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

8.3.5.3. Occupational Exposure

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

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes.

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

8.3.8.1. Lack of Efficacy

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

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

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

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

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

Medication errors include:

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

For further clarification, a medication error is:

- Any preventable event causing or leading to inappropriate medication use or participant harm;
- When a participant misunderstood, could not read, was not aware of, or not given dosing instructions

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, Ritonavir, and Dabigatran

Blood samples of approximately 4 mL, to provide a minimum of 1.5 mL of plasma will be collected for measurement concentrations of dabigatran (total), PF-07321332 and ritonavir as specified in the SoA. CCI [redacted] Instructions for the collection

and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

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

CCI [redacted]

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

CCI [redacted]

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.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

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 the 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.

Participant Analysis Set	Description
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.

9.3.1. Pharmacokinetic Analyses

9.3.1.1. Derivation of Pharmacokinetic Parameters Prior to Analysis

The plasma PK parameters for PF-07321332, ritonavir, and dabigatran (total) will be derived from the concentration time profiles as detailed in Table 1 for each analyte and treatment. 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 1. Plasma PK Parameters

Parameter	Analyte	Definition	Method of Determination
AUC_{last}	dabigatran	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration ($C_{last)}$	Linear/Log trapezoidal method.
AUC_{inf}	dabigatran	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.
AUC_{tau}	PF-07321332 and ritonavir	Area under the plasma concentration-time profile from time 0 to time tau (τ) the dosing interval, where tau=12 hours for BID dosing.	Linear/Log trapezoidal method.

Table 1. Plasma PK Parameters

Parameter	Analyte	Definition	Method of Determination
C_{max}	PF-07321332, ritonavir, dabigatran	Maximum plasma concentration	Observed directly from data.
T_{max}	PF-07321332, ritonavir, dabigatran	Time for C_{max}	Observed directly from data as time of first occurrence.
$t_{½}$[a]	PF-07321332, ritonavir, dabigatran	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL/F[a]	PF-07321332, ritonavir, dabigatran	Apparent clearance	Dabigatran (SD): Dose/AUC_{inf} PF-07321332 and ritonavir (MD): Dose/AUC_{tau}
V_z/F[a]	PF-07321332, ritonavir, dabigatran	Apparent volume of distribution	Dabigatran (SD): Dose/(AUC_{inf}•k_{el}) PF-07321332 and ritonavir (MD): Dose/(AUC_{tau}•k_{el})

a. If data permit.

9.3.2. Statistical Methods for PK Data

The plasma concentrations of PF-07321332, ritonavir and dabigatran will be listed and descriptively summarized by nominal PK sampling time and treatment. Individual participant, as well as mean and median profiles of the plasma concentration time data will be plotted by treatment for each analyte using actual (for individual) and nominal (for mean and median) times respectively. Mean and median profiles will be presented on both linear and semi-log scales. For comparison of AUC_{inf} and C_{max} with and without dabigatran, box and whisker plots of these parameters will be plotted by treatment for each analyte.

Natural log transformed parameters (AUC_{inf} [if data permit)], AUC_{last}, and C_{max}) of dabigatran will be analyzed using a mixed effect model with treatment, period and sequence as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Dabigatran administered alone will be the reference treatment and PF-07321332/ritonavir co-administered with dabigatran and ritonavir co-administered with dabigatran will be the test treatments.

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

9.3.3. Other Safety Analyses

All safety analyses will be performed on the safety population.

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

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

All safety analyses will be summarized in accordance with Pfizer implemented CDISC Standards. All participants who receive IP (safety population) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations.

The incidence of the primary safety endpoints of TEAEs and SAEs, as well as SAEs and AEs leading to discontinuation will be summarized for each dose group.

CCI

[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.

9.5. Sample Size Determination

A sample size of approximately 24 participants will provide adequate precision to estimate the effects of multiple dose PF-07321332/ritonavir on the PK of single dose dabigatran. The expected widths of the 90% CIs with 80% coverage probability are shown in the following table for a range of possible effects.

Parameter	Estimated Effect (100*Test/Reference)	90% CI	CI Width
AUC_{inf}	80%	63.09%, 101.45%	38.36%
	100%	78.86%, 126.81%	47.95%
	120%	94.63%, 152.17%	57.54%
	140%	110.40%, 177.53%	67.13%
	160%	126.17%, 202.89%	76.72%
	180%	141.95%, 228.26%	86.31%
C_{max}	80%	60.49%, 105.80%	45.31%
	100%	75.61%, 132.25%	56.64%
	120%	90.74%, 158.70%	67.97%
	140%	105.86%, 185.15%	79.30%
	160%	120.98%, 211.60%	90.62%
	180%	136.10%, 238.06%	101.95%

These estimates are based on the assumption that within-participant standard deviations are 0.452 and 0.532 for $lnAUC_{inf}$ and lnC_{max}, respectively, as obtained from the mean of 2 clinical studies (B1871043 and B7451026) and literature[4] in healthy participants.

Participants who withdraw from the study may be replaced at the discretion of the Principal investigator upon consultation with the sponsor.

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. 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.

10.1.3. Data Protection

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

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

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

10.1.4. Committees Structure

10.1.4.1. Data Monitoring Committee

This study will not use a DMC.

10.1.5. 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. Participant 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.

10.1.6. 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 and/or paper form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the clinical study report.

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 IQMP 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.

10.1.7. 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 Source Document Locator, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Source Document Locator, 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.

10.1.8. Study and Site Start and Closure

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

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

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or 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 IRB/ECs, 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.

10.1.9. 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.

10.1.10. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an 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, and (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 2. 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 (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Creatine kinase Uric acid Albumin Total protein	Local Dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy and culture[a]	• SARS-CoV-2 RT-PCR • TSH • Free T4 • Urine drug screening[b] • Pregnancy test (β-hCG)[c] • aPTT • PT-INR • Fibrinogen At screening only • FSH[d] • HIV • HBsAg • HBcAb • HCVAb • HBsAb[e]

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase and culture only if bacteriuria.
b. 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).
c. 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.
d. For confirmation of postmenopausal status only.
e. HBsAb will be performed as reflex testing for any participant who is HBsAg and HBcAb positive.

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 Meeting 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.

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), preferably with low user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

A WOCBP agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. 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 non-estrogen 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).

CCI

[redacted]

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

Potential Cases of Drug Induced- Liver Injury

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

10.8. Appendix 8: Prohibited and Precautionary Concomitant Medications That May Result in DDI

The prohibited concomitant medications listed below should not be taken with PF-07321332, ritonavir or dabigatran during dosing and up to 4 days after the final dose of ritonavir.

The Pfizer study team is to be notified of any prohibited medications taken during the study.

This list of drugs prohibited or precautionary for potential DDI concerns with the IMP may be revised during the course of the study with written notification from sponsor, to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs).

This is not an all-inclusive list. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Prohibited Medications		
Medications that are Strong Inducers of CYP3A4[a]		
Drug Class	**Specific Medication**	**Clinical Comments**
Anticoagulant	Dabigatran	Potential to impact the PK of PF-07321332 and ritonavir
Anti-epileptic	Phenytoin, carbamazepine	
Herbal Products	St. John's wort	
Medications Dependent on CYP3A4 for Clearance, with Drug Interactions with PF-07321332/ritonavir[a]		
Alpha 1-Adrenoreceptor Antagonist	Alfuzosin	Risk of hypotension, syncope
Antianginal	Ranolazine	Risk of cardiac arrhythmias
Antiarrhythmics	Amiodarone, Bepridil, Flecainide, Propafenone, Quinidine, Dronedarone, Encainide	Risk of cardiac arrhythmias
Antihistamines	Astemizole, Terfenadine	Risk of cardiac arrhythmias
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine	Risk of acute ergot toxicity (peripheral vasospasm and ischemia of the extremities)
HMG CoA Reductase Inhibitors	Lovastatin, Simvastatin	Risk of rhabdomyolysis; consider alternative agent: pravastatin
Neuroleptic	Pimozide	Risk of cardiac arrhythmias
PDE-5 inhibitors	Sildenafil (Revatio) - PAH	Risk of visual disturbances, hypotension, prolonged erection, and syncope
Sedatives/hypnotics	Oral Midazolam, Triazolam	Risk of prolonged sedation or respiratory depression

a. If a drug is not listed, it should not automatically be assumed it is safe to co-administer.

Precautionary Medications		
Medications to be Used with Caution when Co-administered with PF-07321332/ritonavir[a]		
Drug Class	**Specific Drugs**	**Clinical Comments**
Anticonvulsants	Lamotrigine, Valproate Phenytoin Carbamazepine	Coadministration may decrease lamotrigine, valproate, and phenytoin concentrations. Coadministration may increase carbamazepine concentrations. Careful monitoring of adverse effects. Alternative agents: Gabapentin Topiramate
Anticoagulants	Rivaroxaban	Increased risk of bleeding, subject should not be enrolled if on blood thinners.
Antidepressant	Trazadone, Desipramine, Fluoxetine Paroxetine, Sertraline	May increase antidepressant concentration.
Anti-infective	Erythromycin	Coadministration may increase erythromycin concentration.
Antifungals	Itraconazole Voriconazole	Coadministration may increase itraconazole concentration. Monitor for adverse effects. Coadministration may decrease voriconazole concentration.
Calcium Channel Blockers	Diltiazem, Verapamil, Felodipine, Nicardipine, Nisoldipine, Amlodipine	Coadministration may increase concentrations. The impact on the PR interval of co-administration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration is indicated, consider a dose reduction (amlodipine recommended dose reduction of 50%). Close monitoring is recommended.
Cardiac Glycosides	Digoxin	Coadministration increases digoxin concentration.
Hepatitis C direct acting antivirals	Boceprevir, Glecaprevir/Pibrentasvir Simeprevir, Sofosbuvir/Velpatasvir/Voxilaprevir Ombitasvir/Paritaprevir/Ritonavir, Dasabuvir	Coadministration is not recommended as it resulted in increased plasma concentrations of Hep C antiviral; Caution or not recommended.
HIV Protease Inhibitors **NNRTs, Fusion Inhibitors**	Lopinavir, Amprenavir, Indinavir, Nelfinavir, Saquinavir Abacavir, Didanosine, Zidovudine	Coadministration may increase HIV protease inhibitor concentrations; coadministration with caution.
HMG CoA reductase inhibitors	Atorvastatin, Rosuvastatin	Use with caution; risk of myopathy including rhabdomyolysis. Use lowest dose of statin. Alternative agents: Pravastatin.

Precautionary Medications		
Hypoglycemics	Glipizide, Tolbutamide Repaglinide	Potentially decrease glipizide and tolbutamide concentrations. Potentially increase repaglinide concentrations.
Immunosuppressants	Cyclosporine, Tacrolimus, Sirolimus	Coadministration may increase immunosuppressant concentrations.
Narcotic Analgesics	Methadone, Fentanyl	Moderate to weak decreases in methadone AUC have been observed Fentanyl concentration may increase.

a. If a drug is not listed, it should not automatically be assumed it is safe to co-administer.

Prohibited Medications		
Medications that are Strong Inducers of P-gp		
Drug Class	**Specific Medication**	**Clinical Comments**
Antibiotic	Rifampin	Reduction to exposure of dabigatran
Medications that are Strong inhibitors of P-gp		
Antiarrhythmics	amiodarone	Increase exposures of dabigatran
Alpha/Beta Blocker	carvedilol	Increase exposures of dabigatran
Antibiotic	clarithromycin	Increase exposures of dabigatran
Calcium Channel Blocker	verapamil	Increase exposures of dabigatran
Protease Inhibitor	ritonavir	Increase exposures of dabigatran
Antifungal	itraconazole	Increase exposures of dabigatran

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
→	ongoing/continuous event
%CI	confidence interval (%)
3CL	3C-like
$3CL^{pro}$	3C-like protein
Ab	antibody
Abs	absolute
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{inf}	area under the plasma concentration-time curve from time 0 extrapolated to infinity
AUC_{last}	area under the plasma concentration time curve from time 0 to the time of the last measurable concentration
AUC_{tau}	area under the plasma concentration-time profile from time zero to time tau (τ) the dosing interval, where tau=12 hours for BID dosing
AV	atrioventricular
BBS	Biospecimen Banking System
β-hCG	beta-human chorionic gonadotropin
BID	twice a day
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
C_{av}	average concentration during a dosing interval
CBC	complete blood count
CDISC	clinical data interchange standard consortium
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
CL/F	apparent clearance of drug from eg, plasma
C_{last}	last observed (quantifiable) plasma concentration
C_{max}	maximum observed plasma concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit

Abbreviation	Term
CSR	Clinical Study Report
CT	clinical trial
CTMS	clinical trial management system
CYP	cytochrome P450
CYP3A	cytochrome P450 3A
CYP3A4	cytochrome P450 3A4
CYP3A5	cytochrome P450 3A5
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
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
EOT	end of treatment
EU	European Union
EudraCT	European Clinical Trials Database
FIH	first-in-human
f_m	fraction metabolized
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HcoV	human coronavirus
HcoV-229E	human coronavirus 229E
HcoV-HKU1	human coronavirus HKU1
HcoV-NL63	human coronavirus NL63
HcoV-OC43	human coronavirus OC43
HCT	hematocrit
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
Hep C	hepatitis C
HgB	hemoglobin
HIV	human immunodeficiency virus
HMG CoA	3-hydroxy-3-methyl-glutaryl-CoA
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document

Abbreviation	Term
ICH	International Council for Harmonisation
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IQMP	Independent Qualified Medical Practitioners
IRB	Institutional Review Board
IV	intravenous
k_a	absorption rate constant
k_{el}	terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.
K_i	inhibition constant
$k_{p, uu}$	unbound partition coefficient
LBBB	left bundle branch block
LFT	liver function test
$lnAUC_{inf}$	log-transformed AUC_{inf}
lnC_{max}	log-transformed C_{max}
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MD	multiple dose
MERS	Middle East respiratory syndrome
msec	millisecond
N/A	not applicable
NHP	non-human primate
NNRT	non-nucleoside reverse transcriptase
NOAEL	no observed adverse effect level
PAH	pulmonary arterial hypertension
PD	pharmacodynamic(s)
PDE	phosphodiesterase
PE	physical examination
P-gp	P-glycoprotein
pH	potential of hydrogen
PI	principle investigator
PK	pharmacokinetic(s)
PR	pulse rate
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)

Abbreviation	Term
qual	qualitative
QTL	quality tolerance limits
RBC	red blood cell
RR	respiratory rate
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 2
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCr	serum creatinine
SD	single dose
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single-reference safety document
SUSAR	suspected unexpected serious adverse reaction
T1	Treatment 1
$t_{½}$	terminal half-life
T2	Treatment 2
T3	Treatment 3
T4	thyroxine
Tbili	total bilirubin
TEAE	treatment emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time to first occurrence of C_{max}
TSH	thyroid stimulating hormone
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
V_z/F	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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