Title Page

A PHASE 1, RANDOMIZED, FIXED SEQUENCE, MULTIPLE-DOSE, OPEN-LABEL STUDY TO ESTIMATE THE EFFECT OF NIRMATRELVIR (PF-07321332)/RITONAVIR ON ROSUVASTATIN PHARMACOKINETICS IN HEALTHY ADULT PARTICIPANTS

Study Intervention Number:	PF-07321332
Study Intervention Name:	Nirmatrelvir
US IND Number:	153517
EUCT Number:	2023-503570-20-00
ClinicalTrials.gov ID:	Not Available
Pediatric Investigational Plan Number:	Not Applicable
Protocol Number:	C4671052
Phase:	1
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Study to Learn About the Study Medicine Called Nirmatrelvir/Ritonavir in People Who are Healthy Volunteers Co-administered the Medicine Rosuvastatin

Document History

Document	Version Date
Amendment 1	10 May 2023
Original protocol	03 April 2023

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any global protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 1 (10 May 2023)

Overall Rationale for the Amendment: The protocol was amended to include additional risks and risk mitigation measures for ritonavir and rosuvastatin dosing, as well as to add additional safety laboratory testing and physical examinations.

Description of Change	Brief Rationale	Section # and Name
Addition of haematological abnormalities as a risk of ritonavir dosing, along with risk mitigation measures.	Risk and risk mitigation measures added to align with ritonavir prescribing information (Norvir® SmPC).	Section 2.3.1 Risk Assessment
Addition of severe cutaneous adverse reactions as a risk of rosuvastatin dosing, along with risk mitigation measures.	Risk and risk mitigation added to align with rosuvastatin prescribing information (Crestor® SmPC).	Section 2.3.1 Risk Assessment
Safety laboratory testing added on Day 3, Period 1; Day 5, Period 1; and Day 3, Period 2.	Additional safety laboratory testing timepoints were included as additional risk mitigation to monitor for haematological abnormalities following ritonavir dosing as well as liver enzyme abnormalities and skeletal muscle effects following rosuvastatin dosing. Day 5, Period 1 timepoint added as a mitigation prior to initiating Period 2 dosing.	Sections 1.3 Schedule of Activities, Section 2.3.1 Risk Assessment and Section 8.1 Administrative and Baseline Procedures

Description of Change	Brief Rationale	Section # and Name
Brief physical examinations added on Day 5, Period 1; Day 2, Period 2; and Day 5, Period 2.	Additional physical examinations were included as additional risk mitigation to monitor for rashes following ritonavir dosing as well as skeletal muscle effects and severe cutaneous adverse reactions following rosuvastatin dosing. Day 5, Period 1 timepoint added as a mitigation prior to initiating Period 2 dosing.	Sections 1.3 Schedule of Activities and Section 2.3.1 Risk Assessment
Skin and skeletal muscle assessment added to brief physical exams.	To monitor for rashes and skeletal muscle effects following ritonavir and rosuvastatin dosing.	Section 8.3.1 Physical Examinations

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1. PROTOCOL SUMMARY

1.1. Synopsis

This is a Phase 1, randomized, fixed sequence, multiple-dose, open-label study of the effect of nirmatrelvir (PF-07321332)/ritonavir on rosuvastatin pharmacokinetics (PK) in healthy adult participants. The study will also assess the safety and tolerability of a single dose of rosuvastatin when coadministered with nirmatrelvir/ritonavir.

Protocol Title: A Phase 1, Randomized, Fixed Sequence, Multiple-Dose, Open-Label Study to Estimate the Effect of Nirmatrelvir (PF-07321332)/Ritonavir on Rosuvastatin Pharmacokinetics in Healthy Adult Participants

Brief Title: A Study to Learn About the Study Medicine Called Nirmatrelvir/Ritonavir in People Who are Healthy Volunteers Co-administered the Medicine Rosuvastatin

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US IND Number:	153517
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ClinicalTrials.gov ID:	Not available
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C4671052
Phase:	1

Rationale:

Nirmatrelvir is a potent and selective inhibitor of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease (M^{pro}) that was developed as an oral treatment of coronavirus disease 2019 (COVID-19). Ritonavir is a strong cytochrome P450 (CYP)3A4 inhibitor being used to inhibit the metabolism of nirmatrelvir (PF-07321332) in order to increase plasma concentrations of nirmatrelvir to values that are efficacious. The clinical development program for nirmatrelvir/ritonavir includes 16 completed clinical studies: 11 Phase 1 studies in healthy participants (C4671001, C4671008, C4671012, C4671013, C4671014, C4671015, C4671016, C4671019, C4671023, C4671024, and C4671036), one Phase 1 study in renal impairment participants (C4671011), one Phase 1 study in hepatic impairment participants (C4671010) and 3 Phase 2/3 pivotal studies in COVID-19 patients (C4671002, C4671005, and C4671006).

Both nirmatrelvir and ritonavir have the potential to inhibit OATP1B1. Rosuvastatin is a well-known sensitive substrate of OATP1B1 and is likely to be a concomitant medication in patients who have COVID-19 and are prescribed nirmatrelvir/ritonavir. Therefore, this study will assess the impact of nirmatrelvir/ritonavir on the pharmacokinetics of rosuvastatin.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To assess the effect of multiple doses of nirmatrelvir/ritonavir on the plasma pharmacokinetics of a single, oral dose of rosuvastatin in healthy participants.	• AUC_{inf} and C_{max} of rosuvastatin.
Secondary:	**Secondary:**
• To further characterize the plasma pharmacokinetics of a single, oral dose of rosuvastatin administered with nirmatrelvir/ritonavir. • To evaluate the safety and tolerability of a single oral dose of rosuvastatin when coadministered with nirmatrelvir/ritonavir.	• AUC_{last}, T_{max}, $t_{½}$, CL/F, and V_z/F of rosuvastatin. • Vital signs, laboratory tests and adverse events.

Overall Design:

This is a Phase 1, randomized, fixed sequence, multiple-dose, open-label study of the effect of nirmatrelvir/ritonavir on rosuvastatin PK in healthy adult participants. Participants will receive 2 treatments across 2 periods, as described below:

Sequence	Period 1	Washout	Period 2
Sequence 1 (N = 12)	Treatment A	At least 5 days between the 2 rosuvastatin dosing events	Treatment B

Abbreviation: N = number of enrolled participants.

- Treatment A (rosuvastatin, Reference): Single oral administration of rosuvastatin 10 mg tablet on Day 1 in the morning (AM dose).
- Treatment B (rosuvastatin + nirmatrelvir/ritonavir, Test): nirmatrelvir/ritonavir 300 mg (2×150 mg)/100 mg tablets q12h (BID) for 2 days (Day 1 morning [AM] and evening [PM] and Day 2 morning [AM], 3 doses total) with a single oral administration of rosuvastatin 10 mg tablet on Day 2 in the morning (AM dose). Nirmatrelvir and ritonavir will be dosed within no more than 5 minutes of each other. Rosuvastatin single dose will be dosed within 5 minutes after the Day 2 morning (AM) nirmatrelvir/ritonavir dose.

The expected duration of participation from Screening to the follow-up telephone contact will be approximately 11 weeks.

A total of approximately 12 healthy male and/or female participants will be enrolled in the study. Participants who discontinue from the study may be replaced at the sponsor's discretion.

Participants will report to the clinical research unit (CRU) the day prior to Day 1 dosing (ie, Day -1) in Period 1. Participants will remain in the CRU for a total of 11 days and 10 nights (including Period 1 and Period 2). To adequately remove any drug effects of rosuvastatin from Period 1 to Period 2, there will be a minimum 5-day washout period between the 2 rosuvastatin dosing events. The total rosuvastatin PK will then be assessed over 72 hours.

If a participant has any clinically significant, study related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the participant may be asked to remain in the CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up.

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

Number of Participants:

Approximately 12 participants will be enrolled in the study.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

1. Male and female participants aged 18 years (or the minimum age to consent in accordance with local regulations) or older at Screening who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, vital signs, and standard 12-lead electrocardiogram (ECG).

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

3. Female participants must have a negative pregnancy test.

4. Body mass index (BMI) of 16-32 kg/m^2 and a total body weight >50 kg (110 lb).

5. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

1. Positive test result for SARS-CoV-2 infection on Day -1 or who have received a COVID-19 vaccine within 7 days before screening or admission, or who are to be vaccinated with a COVID-19 vaccine at any time during the study confinement.

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).

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

    - History of human immunodeficiency virus (HIV) infection, hepatitis B, or hepatitis C; positive testing for HIV, hepatitis B surface antigen (HBsAg), or hepatitis C antibody (HCVAb). Hepatitis B vaccination is allowed.

3. Clinically relevant abnormalities requiring treatment (eg, acute myocardial infarction, unstable ischemic conditions, evidence of ventricular dysfunction, serious tachy- or brady-arrhythmias) or indicating serious underlying heart disease (eg, prolonged PR interval, cardiomyopathy, heart failure greater than New York Heart Association Functioncal Classification 1 (NYHA 1), underlying structural heart disease, Wolff Parkinson-White syndrome).

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

5. Participants, who according to the product label for rosuvastatin, would be at increased risk if dosed with rosuvastatin.

Study Arms and Duration:

Study Intervention(s)			
Intervention Name	PF-07321332 (nirmatrelvir) tablets	Ritonavir tablets	Rosuvastatin tablets
Use	Test	Test	Reference, Test
IMP or NIMP/AxMP	IMP	NIMP/AxMP	NIMP/AxMP
Dose Formulation	Tablet	Tablet	Tablet
Unit Dose Strength(s)	150 mg	100 mg	10 mg

Study Intervention(s)			
Route of Administration	Oral	Oral	Oral

Study Arm/Period(s)		
Arm/Period Title	Treatment A (rosuvastatin, Reference)	Treatment B (rosuvastatin + nirmatrelvir/ritonavir, Test)
Arm/Period Description	Single oral dose of rosuvastatin 10 mg tablet on Day 1 in the morning (AM dose).	Nirmatrelvir/ritonavir 300 mg (2 x 150 mg)/100 mg tablets q12h (BID) for 2 days (Day 1 morning [AM] and evening [PM] and Day 2 morning [AM], 3 doses total) with a single oral dose of rosuvastatin 10 mg tablet on Day 2 in the morning (AM dose). Nirmatrelvir and ritonavir will be dosed within no more than 5 minutes of each other. Rosuvastatin single dose will be dosed within 5 minutes after the first Day 2 morning (AM) nirmatrelvir/ritonavir dose.

Statistical Methods:

Natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals (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. Treatment A (rosuvastatin) will be the Reference treatment while Treatment B (rosuvastatin + nirmatrelvir/ritonavir) will be the Test treatment.

The PK concentration analysis set is defined as all participants who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported. The PK parameter analysis set is defined as all participants who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of primary interest are reported. Plasma PK parameters of rosuvastatin will be derived (as data permits) from the concentration-time data using standard noncompartmental methods. Actual PK sampling times will be used in the derivation of rosuvastatin PK parameters when available, otherwise nominal times will be used.

PK parameters, including plasma AUC_{inf}, AUC_{last}, C_{max}, T_{max} , $t_{½}$, CL/F, and V_z/F of rosuvastatin will be summarized descriptively by treatment. For AUC_{inf}, AUC_{last} and C_{max}, a listing of the individual participant ratios (Test/Reference) will be provided. Box and whisker plots for AUC_{inf}, AUC_{last} and C_{max} will be plotted by treatment.

Adverse events (AEs), ECGs, blood pressure (BP), pulse rate, 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 PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Ethical Considerations:

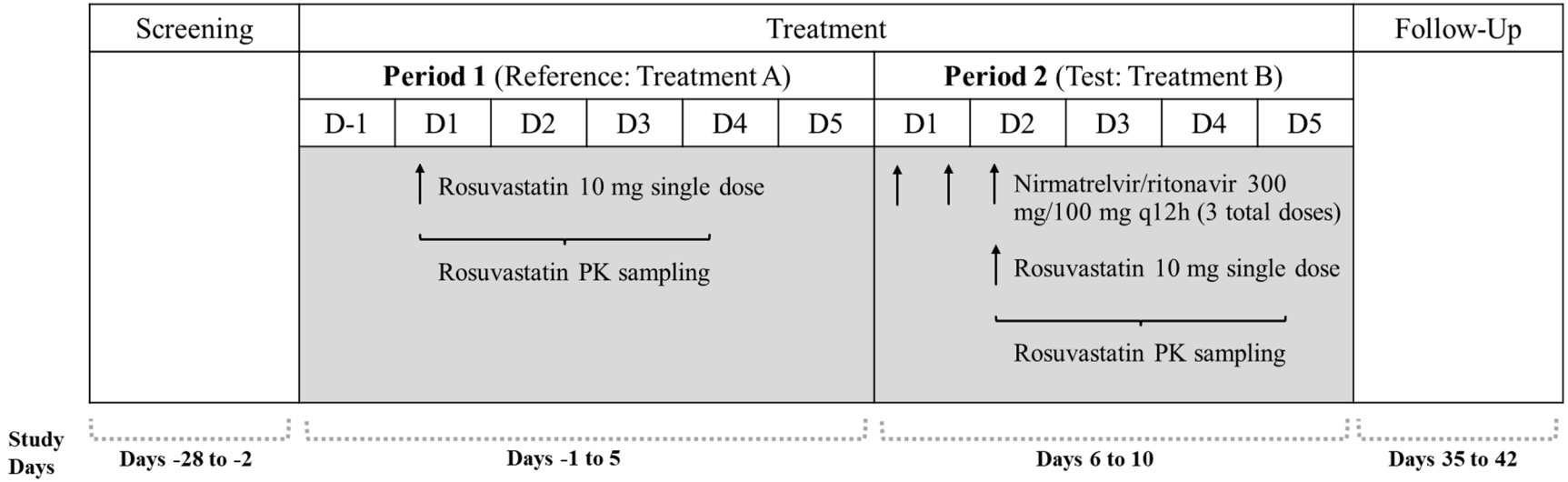
Neither nirmatrelvir/ritonavir nor rosuvastatin are expected to provide any clinical benefit to healthy participants in this study. This study is designed primarily to further the understanding of human PK, metabolism, and elimination of nirmatrelvir/ritonavir.

Based on data from Study C4671001, the clinical safety profile of nirmatrelvir appears to be acceptable at single doses up to 1500 mg alone and up to 2250 mg administered with ritonavir (100 mg at -12h, 0h, 12h), split dosing administration (2250 mg, administered as 3 doses of 750 mg) at short intervals (approximately 2 hours from the previous dose), and at repeated daily doses administered orally for 10 days of up to 500 mg nirmatrelvir q12h with 100 mg ritonavir q12h.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of nirmatrelvir/ritonavir may be found in the Investigator's Brochure (IB), which is the Single Reference Safety Document (SRSD) for this study.

1.2. Schema

Figure 1. Study Schema



1.3. Schedule of Activities

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

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

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 8	**Screening[a]**	**Period 1[b] Treatment A**						**Period 2 Treatment B**					**F/U**	**Early Discontinuation**
Days Relative to Day 1	**-28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**28-35 Days[c]**	
Informed consent	X													
CRU confinement[d]		X	X	X	X	X	X	X	X	X	X	X		
Inclusion/exclusion criteria	X	X												
Medical/medication history (update)[e]	X	X												
Demography[f]	X													
Physical examination[g]	X	X					X		X			X		
Safety laboratory[h]	X	X			X		X			X		X		X
FSH[i]	X													
Urine drug testing[j]	X	X												
Serology: HBsAg, HBsAb, HBcAb, HCVAb, and HIV	X													
Pregnancy test (WOCBP only)	X	X										X		X
Contraception check[k]	X	X											X	
12-lead ECG (triplicate)[l]	X													X
Vital signs (BP/PR)[m]	X		X		X			X		X				X

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 8	Screening[a]	Period 1[b] Treatment A						Period 2 Treatment B					F/U	Early Discontinuation
Days Relative to Day 1	**-28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**28-35 Days[c]**	
COVID-19 testing[n]		X												
COVID-19 temperature check[n]		X												
Nirmatrelvir/ritonavir administration[o]								X	X					
Rosuvastatin administration[p]			X						X					
PK blood sampling for rosuvastatin[q]			X	X	X	X			X	X	X	X		X
PK blood sampling for nirmatrelvir/ritonavir[r]									X					
Blood sampling for CP-1[s]			X						X					
Serious and non-serious AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant treatment(s)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Discharge from CRU[t]												X		

a. Screening will be performed within 28 days prior to the first dose of nirmatrelvir/ritonavir.
b. Participants will report to the CRU the day prior to Day 1 dosing (ie, Day -1) in Period 1. Participants will remain in the CRU for a total of 11 days and 10 nights (including Period 1 and Period 2).
c. Follow-up contact will occur via telephone contact and must occur between 28 to 35 days from administration of the final dose of rosuvastatin.
d. Participants will be admitted to the CRU on Day -1. Participants will be discharged on Day 5, Period 2 following the final assessments.
e. 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.
f. Demographics will include participant race, ethnicity, age, and gender during the Screening visit.
g. A complete physical examination will be performed by trained medical personnel at the investigator site at Screening or Day -1 of Period 1 only (height and weight must be obtained at Screening to obtain BMI for eligibility criteria). A brief physical examination will be performed on Day 5 of Period 1, Day 2 of Period 2, and Day 5 of Period 2. Additional physical examination(s) may be performed at other time points at the discretion of the investigator.
h. Safety laboratory assessments including urinalysis, hematology, and chemistry 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.
i. For confirmation of postmenopausal status only in females <60 years old and not using hormonal or HRT 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. The investigator or their designee will inform the participant the need to use highly effective contraception consistently and correctly according to contraception guidelines.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 8	Screening[a]	Period 1[b] Treatment A						Period 2 Treatment B					F/U	Early Discontinuation
Days Relative to Day 1	**-28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**28-35 Days[c]**	

l. Triplicate 12-lead ECG readings approximately 2-4 minutes apart will be taken at specified times. All ECG assessments will be made after at least a 5-minute rest in a supine position and prior to any blood draws or vital sign measurements.

m. Single supine BP and PR will be performed following approximately 5 minutes of rest in a supine position. BP and pulse rate assessments will be performed after collection of ECGs and prior to collection of blood draws if scheduled at the same time.

n. COVID-19 assessments will be performed according to local procedures.

o. Nirmatrelvir/ritonavir will be administered orally, q12h for 2 days (Day 1 morning [AM] and evening [PM] and Day 2 morning [AM], total of 3 doses) in the Treatment B (Test) arm only. Nirmatrelvir and ritonavir will be dosed within no more than 5 minutes of each other.

p. Rosuvastatin will be administered orally as a single dose in both the Treatment A (Reference) and Treatment B (Test) arms. In the Treatment B (Test) arm, rosuvastatin will be dosed within 5 minutes after the Day 2 morning (AM) nirmatrelvir/ritonavir dose.

q. One (approximately 4 mL) blood sample for PK analysis of rosuvastatin will be taken at the following timepoints post-dose in each period: 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours.

r. One pre-dose blood sample (approximately 4 mL) for PK analysis of nirmatrelvir/ritonavir will be taken prior to the Day 2 morning (AM) dose of nirmatrelvir/ritonavir in the Treatment B (Test) arm only to ensure achievement of steady-state trough concentration.

s. Blood samples (approximately 2 mL) for analysis of CP-1 biomarker will be collected. CP-1 sampling will occur immediately following (i.e., within 5 minutes) the 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours rosuvastatin PK samples during both Treatment A and Treatment B dosing.

t. Participants will be eligible for discharge in Period 2, Day 5 at the discretion of the investigator following PK sampling at 72 hours post the last dose of rosuvastatin.

Table 2. Rosuvastatin Pharmacokinetic Sampling Times

Visit Identifier	**Period 1 (Treatment A) and Period 2 (Treatment B)**																**Notes**
Day Relative to Rosuvastatin Dose	**1**												**2**		**3**	**4**	
Hours After Dose	**0**	**0.5**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**16**	**24**	**36**	**48**	**72**	Hour 0 = predose sample collection
Rosuvastatin treatment administration	X																
Rosuvastatin PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CP-1 blood sampling	X	X	X	X	X	X	X	X	X	X	X						

2. INTRODUCTION

Nirmatrelvir is a potent and selective inhibitor of the SARS-CoV-2 M^{pro} that was developed for the treatment of COVID-19. Ritonavir is a strong CYP3A4 inhibitor being used to inhibit the metabolism of nirmatrelvir in order to increase plasma concentrations of nirmatrelvir to values that are efficacious.

2.1. Study Rationale

The purpose of the study is to assess the effect of nirmatrelvir/ritonavir on the plasma PK of rosuvastatin, a sensitive OATP1B1 substrate. Both nirmatrelvir and ritonavir have the potential to inhibit OATP1B1.[1,2] Rosuvastatin is considered a well-known sensitive substrate of OATP1B1 and is likely to be a concomitant medication in patients who have COVID-19 and are prescribed nirmatrelvir/ritonavir. Therefore, this study will assess the impact of nirmatrelvir/ritonavir on the pharmacokinetics of rosuvastatin.

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 30 January 2020 and further characterized the disease outbreak as a pandemic on 11 March 2020.[2]

Nirmatrelvir is an orally bioavailable $3CL^{pro}$ inhibitor shown to be effective against SARS-CoV-2 $3CL^{pro}$ (K_i = 0.00311 μM) in a biochemical enzymatic assay. Nirmatrelvir was developed as an oral treatment in patients with COVID-19 infection.

Ritonavir is a strong CYP3A4 inhibitor being used to inhibit the metabolism of nirmatrelvir in order to increase plasma concentrations of nirmatrelvir to values that are efficacious. Ritonavir is not expected to have any pharmacological impact on the SARS-CoV-2 virus and its elimination. Ritonavir is being used only as a PK boosting agent.

The clinical development program for nirmatrelvir/ritonavir includes 16 completed clinical studies: 11 Phase 1 studies in healthy participants (C4671001, C4671008, C4671012, C4671013, C4671014, C4671015, C4671016, C4671019, C4671023, C4671024, and C4671036), one Phase 1 study in renal impairment participants (C4671011), one Phase 1 study in hepatic impairment participants (C4671010) and three Phase 2/3 pivotal study in COVID-19 patients (C4671002, C4671005, and C4671006).

2.2.1. Nonclinical Pharmacology

Details of the nonclinical pharmacology of nirmatrelvir/ritonavir can be found in the current IB.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

Hepatic CYP3A enzymes were identified as the main pathway for clearance of nirmatrelvir in vitro in liver microsomes (mouse, rat, hamster, rabbit, monkey, and human), hepatocytes (rat, monkey, and human), and in vivo in rat and monkey after repeat oral dosing. In a

reaction phenotyping study using human liver microsomes in the presence of selective CYP inhibitors, CYP3A4 was predicted to be the major contributor (f_m = 0.99) to the in vitro oxidative metabolism of nirmatrelvir. No significant CYP3A5 contribution is expected to the metabolism of nirmatrelvir.

Due to the predominant role of CYP3A4 in the metabolic clearance of nirmatrelvir, ritonavir (a CYP3A4 inhibitor) is administered in clinical use in order to increase the plasma concentrations of nirmatrelvir. Upon coadministration with ritonavir, the primary clearance mechanism of nirmatrelvir is renal elimination of unchanged drug.

Nirmatrelvir has low potential to inhibit a majority of various efflux and uptake transporters as investigated using stably transfected HEK293 cells or vesicle-based systems. At the proposed therapeutic dose, there is a potential for pharmacokinetic interactions arising from the inhibition of MDR1 (P-gp) and OATP1B1 by nirmatrelvir. Additionally, ritonavir has the potential to inhibit OATP1B1 (see Section 4.2). Additional information of the nonclinical PK and metabolism of nirmatrelvir and nirmatrelvir/ritonavir 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 600 mg/kg in the rat and monkey studies, respectively). Nirmatrelvir-related nonadverse, test article-related clinical findings included sporadic occurrence of emesis with slight body weight decreases in monkeys in the 1-month study. In rats, monitorable and reversible clinical pathology findings included those possibly suggestive of low-grade inflammation or alterations in the coagulation pathways without clinical or microscopic correlates. In monkeys, monitorable and reversible clinical pathology findings included increase in ALT and/or AST and increase in fibrinogen at the high dose in 1-month study without clinical or microscopic correlates. In rats administered 1000 mg/kg/day, lower mean absolute and relative heart weights (females) and higher mean 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, nonadverse microscopic findings of minimal to mild severity in the liver and thyroid gland consistent with adaptive changes related to microsomal enzyme induction.

Nirmatrelvir 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 nirmatrelvir 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 PK of nirmatrelvir has been assessed in studies in healthy adult participants (C4671001, C4671008, C4671013, C4671014, C4671015, C4671016,

C4671019, C4671023, C4671024, and C4671036), as well as in renal impairment participants (C4671011) and hepatic impairment participants (C4671010). The relative bioavailability and food effect were evaluated in two phase 1 studies (C4671001 and C4671019) in healthy participants. Efficacy and safety of nirmatrelvir were evaluated in interventional Phase 2/3 Studies (C4671002, C4671005, C4671006).

Included in this Clinical Overview are summaries of the results of Study C4671001 and C4671005.

Study C4671001 was a 5-part study consisting of SAD (PART-1), MAD (PART-2), relative bioavailability/food effect (PART-3), metabolism and excretion study (PART-4) and supratherapeutic exposure cohort (PART-5). 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 nirmatrelvir, respectively. PART-3 was randomized and open-label to evaluate relative bioavailability and food effect of an oral tablet formulation. PART-4 was an open-label, nonrandomized, single-period to evaluate the metabolism and excretion of nirmatrelvir. PART-5 was a double-blind, sponsor-open, randomized, crossover study to evaluate safety and tolerability at supratherapeutic exposures.

C4671005 evaluated the efficacy and safety of nirmatrelvir in an interventional Phase 2/3 Study (C4671005). C4671005 was a Phase 2/3 randomized, placebo-controlled trial in nonhospitalized adult participants with a laboratory-confirmed diagnosis of SARS-CoV-2 infection.

2.2.4.1. Safety Overview

In the completed Phase 1 studies in healthy participants and Phase 2/3 study in participants with a laboratory-confirmed diagnosis of SARS-CoV-2 infection, nirmatrelvir/ritonavir was generally safe and well tolerated.

Safety data from Study C4671001 indicate that nirmatrelvir was safe and well tolerated in healthy adult participants at all the exposures tested including supratherapeutic exposure. Current evidence indicates that the clinical safety profile of nirmatrelvir is acceptable at single doses up to a 2250 mg dose administered as 3 split doses of 750 mg administered with ritonavir, and at repeated daily doses administered orally for 10 days of up to 500 mg nirmatrelvir BID with 100 mg ritonavir BID. In all 5-parts of the study, there were no deaths, severe AEs, or SAEs. nirmatrelvir alone or nirmatrelvir/ritonavir was generally safe and well tolerated in healthy participants in all parts including SAD, MAD, and SE cohorts. No notable safety findings were observed. All TEAEs were mild in severity, except for one AE which was moderate in severity, and not considered treatment related. Overall, there were no clinically meaningful laboratory changes, no clinically significant findings in vital sign measurements or 12-lead ECG assessments throughout this study. The safety data, including AEs, laboratory abnormalities, vital signs, and 12-lead ECGs indicate that nirmatrelvir has an acceptable safety and tolerability profile in healthy adult participants.

C4671005 is a Phase 2/3 randomized, placebo-controlled trial in nonhospitalized adult participants with a laboratory-confirmed diagnosis of SARS-CoV-2 infection. A total of

2224 symptomatic adult participants 18 years of age and older at high risk of developing severe disease received at least 1 dose of either nirmatrelvir/ritonavir (n=1,109) or placebo (n=1,115). Adverse events (all grades regardless of causality) in the nirmatrelvir/ritonavir group (≥1%) that occurred at a greater frequency (≥5 participant difference) than in the placebo group were dysgeusia (6% and <1%, respectively), diarrhea (3% and 2%), hypertension (1% and <1%), and myalgia (1% and <1%).

Further details on the clinical safety information with nirmatrelvir are provided in the current IB.

2.2.4.2. Summary of Nirmatrelvir/Ritonavir Pharmacokinetics in Human

Study 1001 - FIH

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

PK data on Day 1, Day 5 and Day 10 following multiple oral administration of nirmatrelvir/ritonavir 75/100 mg, 250/100 mg, and 500/100 mg q12h suggest a less than dose proportional increase in exposure at steady state. Following multiple dosing over 10 days, steady state was achieved on Day 2 with approximately 2-fold accumulation. Day 5 and Day 10 exposure was similar at all doses. The absorption of nirmatrelvir/ritonavir in fasted state occurred with the median T_{max} ranging between 0.75 hours to 2.75 hours across all doses upon single or repeat dosing.

Nirmatrelvir plasma exposure for the tablet treatment was lower compared to the suspension, with approximately 19% and 44% lower geometric mean AUC_{last} and C_{max} values, respectively.

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

2.3. Benefit/Risk Assessment

Neither nirmatrelvir/ritonavir nor rosuvastatin are expected to provide any clinical benefit to healthy participants in this study. This study is designed primarily to further the understanding of human PK, metabolism, and elimination of nirmatrelvir/ritonavir.

Based on data from Study C4671001, the clinical safety profile of nirmatrelvir/ritonavir appears to be acceptable at single doses up to 1500 mg alone and up to 2250 mg administered with ritonavir (100 mg at -12h, 0h, 12h), split dosing administration (3 doses of 750 mg) at short intervals (approximately 2 hours from the previous dose), and at repeated daily doses administered orally for 10 days of up to 500 mg nirmatrelvir q12h with 100 mg ritonavir q12h.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of nirmatrelvir/ritonavir may be found in the IB, which is the SRSD for this study. Refer to the Study Intervention(s) table in Section 6.1 for a complete description of SRSDs, including SRSDs for required NIMPs/AxMPs, for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Nirmatrelvir		
Dysgeusia	When co-administered with ritonavir in Study C4671005, dysgeusia was recorded as an AE by 6% of participants receiving nirmatrelvir/ritonavir compared to <1% of participants receiving placebo	Participants may utilize recommendations to alleviate symptoms of dysgeusia while taking treatment such as peppermint post-dose. Dosing recommendations will be provided to the participant.
Emesis	Sporadic emesis was observed at ≥100 mg/kg/day of nirmatrelvir in the 15-day NHP toxicology study.	AEs will be monitored and participants may receive antiemetics.
Hypertension	Transient increases in systolic, diastolic and mean BP were observed in pre-clinical studies. When co-administered with ritonavir in Study C4671005 (adults at high risk for severe disease) a small imbalance in hypertension AEs (1% vs < 1%) was reported.	Vital signs and all AEs will be monitored in the study.
Study Intervention: Ritonavir		
Gastrointestinal disturbances (including diarrhea, nausea, vomiting, and abdominal pain)	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose of 100 mg q12h is used in this study. There is a short duration of treatment (three periods with a single dose each). There will be close observation of AEs.
Neurological disturbances (eg, paresthesia, including oral paresthesia, dysgeusia, and dizziness)	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose of 100 mg 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 patients who are HIV-positive at 600 mg BID.	Lower dose of 100 mg used in this study. There will be close observation of AEs and monitoring through physical exams. A full physical exam will be conducted at

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		screening or Day -1, Period 1. Brief physical exams will be conducted at Day 5, Period 1; Day 2, Period 2; and Day 5, Period 2, with additional exam(s) at the discretion of the investigator. Brief physical exams include skin assessment, and may be updated based on AEs if appropriate. If needed therapeutic interventions per standard of care may be provided.
Fatigue/Asthenia	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose of 100 mg used in this study. There will be close observation of AEs. Fatigue (low energy or tiredness) will be assessed through collection of daily signs and symptoms and will also be assessed through targeted physical examinations when performed during the study visits.
Haematological abnormalities	Adverse reactions in clinical studies and post-marketing in adult patients include decreased white blood cells, decreased haemoglobin, decreased neutrophils, increased eosinophils, and thrombocytopenia (common), as well as increased neutrophils (uncommon).	Lower dose of 100 mg used in this study. There will be close observation of AEs and monitoring through lab testing. Safety lab tests will be conducted at screening and on Day -1, Period 1; Day 3, Period 1; Day 5, Period 1; Day 3, Period 2; and Day 5, Period 2, with additional test(s) at the discretion of the investigator.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Rosuvastatin		
Skeletal muscle effects (eg, myopathy and rhabdomyolysis)	Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. These risks can occur at any dose level, but are increased at the highest dose (40 mg).	Only single dosing of 10 mg will be used in this study (one single dose per period). There will be close observation of AEs and monitoring through targeted physical exams and lab testing, including monitoring of creatinine kinase levels. A full physical exam will be conducted at screening or Day -1, Period 1. Brief physical exams will be conducted at Day 5, Period 1; Day 2, Period 2; and Day 5, Period 2, with additional exam(s) at the discretion of the investigator. Brief physical exams include skeletal muscle assessment, and may be updated based on AEs if appropriate. Safety lab tests will be conducted at screening and on Day -1, Period 1; Day 3, Period 1; Day 5, Period 1; Day 3, Period 2; and Day 5, Period 2, with additional test(s) at the discretion of the investigator.
Liver enzyme abnormalities	Increases in serum transaminases have been reported. In most cases, elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to rosuvastatin therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials.	Only single dosing of 10 mg will be used in this study (one single dose per period). Liver enzyme tests will be performed before dosing, after dosing, and prior to discharge, or at any point if signs or symptoms of liver injury occur. Safety lab tests will be conducted at screening and on Day -1, Period 1; Day 3,

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Period 1; Day 5, Period 1; Day 3, Period 2; and Day 5, Period 2, with additional test(s) at the discretion of the investigator.
Severe cutaneous adverse reactions	Severe cutaneous adverse reactions including Stevens-Johnson syndrome and drug reaction with eosinophilia and systemic symptoms, which could be life-threatening or fatal, have been reported with rosuvastatin.	Only single dosing of 10 mg will be used in this study (one single dose per period). There will be close observation of AEs and monitoring through targeted physical exams. A full physical exam will be conducted at screening or Day -1, Period 1. Brief physical exams will be conducted at Day 5, Period 1; Day 2, Period 2; and Day 5, Period 2, with additional exam(s) at the discretion of the investigator. Brief physical exams include skin assessment, and may be updated based on AEs if appropriate.
Study Procedures		
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel will obtain the blood draw.

2.3.2. Benefit Assessment

Neither nirmatrelvir/ritonavir nor rosuvastatin are expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, and PK data for further clinical development. Rosuvastatin is contraindicated according to the SmPC[3] in patients with hypersensitivity to rosuvastatin or to any of the excipients, in patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 times the ULN, in patients with severe renal impairment (creatinine clearance <30 mL/min), in patients with myopathy, in patients receiving concomitant ciclosporin, and during pregnancy and lactation and in WOCBP not using appropriate contraceptive measures. All such patients are excluded from participating in this study as listed in Section 5.2.

2.3.3. Overall Benefit/Risk Conclusion

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

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To assess the effect of multiple doses of nirmatrelvir/ritonavir on the plasma pharmacokinetics of a single, oral dose of rosuvastatin in healthy participants.	• AUC_{inf}, C_{max}, of rosuvastatin.
Secondary:	**Secondary:**
• To further characterize the plasma pharmacokinetics of a single, oral dose of rosuvastatin administered with nirmatrelvir/ritonavir. • To evaluate the safety and tolerability of a single oral dose of rosuvastatin when co-administered with nirmatrelvir/ritonavir.	• AUC_{last}, T_{max}, $t_{½}$, CL/F, and V_z/F of rosuvastatin. • Vital signs, laboratory tests and adverse events.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, randomized, fixed sequence, multiple-dose, open-label study of the effect of nirmatrelvir/ritonavir on rosuvastatin PK in healthy adult participants.

A total of approximately 12 healthy male and/or female participants will be enrolled in the study. Participants who discontinue from the study may be replaced at the sponsor's discretion.

Participants will be screened within 28 days prior to the first dose of investigational product. Participants will report to the CRU the day prior to Day 1 dosing (ie, Day -1) in Period 1. Participants will remain in the CRU for a total of 11 days and 10 nights (including Period 1 and Period 2). To adequately remove any drug effects of rosuvastatin from Period 1 to Period 2, there will be a minimum 5-day washout period between the 2 rosuvastatin dosing events. The total rosuvastatin PK will then be assessed over 72 hours.

Participants will receive 2 treatments across 2 periods, as outlined in Table 3 below:

Table 3. Treatment Sequence

Sequence	Period 1	Washout	Period 2
Sequence 1 (N = 12)	Treatment A	At least 5 days between the 2 rosuvastatin dosing events	Treatment B

N = number of enrolled participants.

- Treatment A (rosuvastatin, Reference): Single oral administration of rosuvastatin 10 mg tablet on Day 1 in the morning (AM dose).

- Treatment B (rosuvastatin + nirmatrelvir/ritonavir, Test): Nirmatrelvir/ritonavir 300 mg (2 × 150 mg)/100 mg tablets q12h (BID) for 2 days (Day 1 morning [AM] and evening [PM] and Day 2 morning [AM], 3 doses total) with a single oral administration of rosuvastatin 10 mg tablet on Day 2 in the morning (AM dose). Nirmatrelvir and ritonavir will be dosed within no more than 5 minutes of each other. Rosuvastatin single dose will be dosed within 5 minutes after the Day 2 morning (AM) nirmatrelvir/ritonavir dose.

The expected duration of participation from Screening to the follow-up telephone contact will be approximately 11 weeks.

If a participant has any clinically significant, study related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the participant may be asked to remain in the CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up.

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

An in vitro DDI risk analysis for nirmatrelvir in accordance with the EMA 2012 DDI guidance was conducted using data reported in the Population Modeling Analysis Report (PMAR-1323[4]). Nirmatrelvir showed potential for OATP1B1 inhibition (Table 4).

Table 4. Assessment of Risk for in Vivo DDIs Between Nirmatrelvir and Co-administered Substrates of OATP1B1 Transporter, Based on the 2012 EMA Drug Interactions Guideline

Transporter	IC_{50} (µM)	K_i[a] (µM)	$C_{max,u}$ (µM)	50 × $C_{max,u}$ (µM)	$I_{in,max,u}$[b] (µM)	25 × $I_{in,max,u}$	Criteria for Potential DDI	$R_{h(\geq 0.04)}$	$R_{r(\geq 0.02)}$	DDI Risk (Yes/No)
OATP1B1	44.4	44.4	NA	NA	3.88	97	$K_i \leq (25 \times I_{in,max,u})$	0.087	NA	Yes
BCRP	>1000	>1000	NA	NA	NA	NA	$K_i \leq (0.1 \times$ Dose/250 mL)	NA	NA	No
OAT3	520.6	520.6	1.96	98	NA	NA	$K_i \leq (50 \times C_{max,u})$	NA	0.004	No

$C_{max,u}$ = Maximum unbound inhibitor concentration (clinical oral dose of 300 mg nirmatrelvir + 100 mg ritonavir BID - mean steady state. total $C_{max} \times f_{u,p}$ = 1.96 µM, from PMAR-1323[4].

$f_{u,p}$ = Fraction unbound in human plasma = 0.31; IC_{50} = 50% inhibitory concentration.

$I_{in,max,u}$ = Maximal unbound inhibitor concentration in the hepatic inlet; NA= not applicable; K_i = concentration at half-maximal rate of inhibition; R_B = Blood-to-plasma ratio (0.6); $R_h = I_{in,max,u}/K_i$; $R_r = C_{max,u}/K_i$.

a. The estimated Ki values were assumed to be equal to the IC_{50} values for all transporter inhibition assays, based on the respective probe substrate concentration-to-K_m ratio.

b. $I_{in,max,u} = f_{u,b} \times I_{in,max,b} = f_{u,b} \times [C_{max,b} + (F_a F_g \times k_a \times \text{Dose})/Q_h] = f_{u,p}/R_B \times [C_{max} \times R_B + (F_a F_g \times k_a \times \text{Dose})/Q_h]$.

Nirmatrelvir shows an R_h of 0.087, which is above the EMA cutoff criteria of 0.04. Therfore, a clinical interaction study with an OATP1B1 substrate is needed to assess the effect of nirmatrelvir/ritonavir on this transporter. Rosuvastatin is used in DDI studies as a substrate to assess changes in activity of OATP1B1.[5]

Several in vitro studies suggest that ritonavir is also an inhibitor of OATP1B1, with reported IC_{50} values ranging from 0.497 to 6.1 µM.[6,7,8] Clinical studies evaluating the impact of ritonavir on substrates of OATP1B1 are few and confounded by 1) simultaneous administration with another protease inhibitor that is also an OATP inhibitor, and 2) coadministration with an OATP substrate that is also a CYP3A4 substrate. In one clinical study of 200 mg ritonavir co-administered with mebrofenin, a substrate of OATPs for uptake and MRP2 for efflux, mebrofenin AUC increased 1.3× with a 22% corresponding decrease in biliary excretion.[9]

Rosuvastatin is also a subtrate for BCRP and OAT3 transport in addition to OATP1B1. Nirmatrelvir did not show potential for BCRP or OAT3 inhibition using the EMA guidance Table 5). In vitro studies suggest that ritonavir might inhibit BCRP (IC_{50} = 19.5-33.9 µM), but not OAT3.[6,10,11,12] Therefore, inhibitory effects by nirmatrelvir on BCRP and OAT3 are not anticipated to confound the assessment of nirmatrelvir's impact on rosuvastatin PK. In order to mitigate the risk of BCRP inhibition by ritonavir, CP-1 (an endogenous biomarker of OATP1B1 inhibition, see Section 8.7) will be collected to deconvolute the mechanism of rosuvastatin DDI by nirmatrelvir/ritonavir.

Rosuvastatin has a $t_{½}$ of ~20 hours, hence the requirement of 5-day washout between the 2 rosuvastatin dosing events.[13] Plasma PK samples of rosuvastatin will be collected over 3 days post dosing to ensure that the majority of rosuvastatin is recovered.

Nirmatrelvir/ritonavir has been shown to reach steady-state exposure by Day 2 following q12h dosing of 300 mg/100 mg. Thus, nirmatrelvir/ritonavir will be dosed over 2 days (3 doses) in the Treatment arm to ensure steady-state is reached prior to administering rosuvastatin.

Additional information for nirmatrelvir/ritonavir may be found in the IB. The information for rosuvastatin may be found in the approved Belgian SmPC (Crestor®).

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data are limited for nirmatrelvir/ritonavir, 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).

4.3. Justification for Dose

This study is designed to estimate the effect of steady-state nirmatrelvir/ritonavir 300 mg/100 mg q12h dosing on the pharmacokinetics of a 10 mg single dose of rosuvastatin.

The dose of nirmatrelvir/ritonavir 300/100 mg BID for 5 days is the approved therapeutic dose and treatment duration under emergency use authorization. This dose is lower than the

highest dose evaluated in the Phase 1 C4671001 study and is safe and well-tolerated. Nirmatrelvir/ritonavir reaches steady-state by Day 2 of dosing.

Rosuvastatin is a synthetic statin that has been developed for the treatment of patients with dyslipidemia. Rosuvastatin is administered orally and approximately 50% of the drug is absorbed resulting in 20% absolute bioavailability.[14] The C_{max} is reached 3 to 5 hours after administration of a 10 mg to 80 mg oral dose. Both the C_{max} and AUC increase in proportion to the dose from 10 mg to 80 mg dose range.[15] Rosuvastatin mostly goes through biliary and renal excretion with minimal metabolism. The $t_{½}$ is ~20 hours.[13] After 20 mg oral dose, 90% of the dose is recovered from feces and 10% is recovered from the urine, mostly as unchanged drug.[13] Active secretion accounts for more than 90% of renal clearance.[14]

In a single dose escalation study, rosuvastatin was safe and well tolerated at doses up to 80 mg.[15] The most common AEs reported were headache and rash. There was no evidence of a relationship between the frequency of AEs and rosuvastatin dose. No SAEs were reported.[14] Most DDI studies involving rosuvastatin as a substrate are conducted at 10 mg or 20 mg dose level.[16,17,18]

In previous drug interaction studies of protease inhibitors boosted with 100 mg ritonavir co-administered with 10 mg rosuvastatin, rosuvastatin AUC increased 1.48 – 3.13-fold relative to rosuvastatin dosed alone.[19,20] Given this level of previously observed AUC increase, a 10mg dose would be comparable to a ~20-30 mg dose, which is still below the maximum observed tolerable dose of 80 mg.[21] This level of increased systemic exposure is still considered safe and well tolerated in both Western and Asian populations. In these previous protease inhibitor/rosuvastatin DDI studies, study drugs were well-tolerated, with no SAEs attributed to rosuvastatin dosing.[19,20]

Rosuvastatin is not expected to significantly affect the exposures of nirmatrelvir/ritonavir. Thus, the combination of 300 mg/100 mg nirmatrelvir/ritonavir and 10 mg rosuvastatin is expected to be tolerated by healthy participants.

4.4. End of Study Definition

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

A participant is considered to have completed the study if they have completed all periods 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, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered

appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male and female participants aged 18 years (or the minimum age of consent in accordance with local regulations) or older at screening who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, vital signs and standard 12-lead ECG.

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

Other Inclusion Criteria:

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

3. Female participants must have a negative pregnancy test.

4. BMI of 16-32 kg/m^2; and a total body weight >50 kg (110 lb).

5. 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 on 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).

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

- History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, or HCVAb. Hepatitis B vaccination is allowed.

3. Clinically relevant abnormalities requiring treatment (eg, acute myocardial infarction, unstable ischemic conditions, evidence of ventricular dysfunction, serious tachy or bradyarrhythmias) or indicating serious underlying heart disease (eg, prolonged PR interval, cardiomyopathy, heart failure greater than NYHA 1, underlying structural heart disease, Wolff Parkinson-White syndrome).

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

5. Participants, who according to the product label for rosuvastatin, would be at increased risk if dosed with rosuvastatin, including participants with myopathy and with hypersensitivity to rosuvastatin or any of its excipients.

Prior/Concomitant Therapy:

6. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. (Refer to Section 6.9 Prior and Concomitant Therapy for additional details).

7. Current use of any prohibited concomitant medication(s) or participant unwilling or unable to use a required concomitant medication(s). Refer to Section 6.9 Prior and Concomitant Therapy.

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

Prior/Concurrent Clinical Study Experience:

9. Previous administration with an investigational product (drug or vaccine) 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). Participation in other studies involving study intervention within 30 days prior to study entry. A participant may be eligible even if they are in the follow-up phase of an investigational study as long as they have not received treatment in that study for at least 1 month.

Diagnostic Assessments:

10. A positive urine drug test. A single repeat for positive drug screen may be allowed.

11. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic) for participants <60 years; and ≥150/90 mm/Hg for participants ≥60 years old, following at least 5 minutes of supine rest. If systolic BP is ≥ 140 or 150 mm Hg (based on age) or diastolic ≥90 mm Hg, 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.

12. Renal impairment as defined by an eGFR in adults of <60 mL/min/1.73m^2. Based upon participant age at screening, eGFR is calculated using the CKD-EPI formula in Section 10.6.2 to determine eligibility and to provide a baseline to quantify any subsequent kidney safety events.

    For eligibility assessment based upon estimated renal function, the higher of the screening and baseline eGFR values may be used.

13. Standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms, complete LBBB, signs of an acute or indeterminate age myocardial infarction, STT interval changes suggestive of myocardial ischemia, second or third degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

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

    - ALT, AST, Bili >1.0 × ULN.

Other Exclusion Criteria:

15. 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).

16. Use of tobacco or nicotine containing products in excess of the equivalents of 5 cigarettes per day or 2 chews of tobacco per day.

17. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

18. History of sensitivity reactions to ritonavir or rosuvastatin, or any of the formulation components of nirmatrelvir, ritonavir, or rosuvastatin.

19. Pregnant or breastfeeding women.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their 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. The investigator or designee will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

At time points indicated in 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 and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the predose PK sample.

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

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

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

- An evening snack may be permitted.

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

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

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

- Participants will abstain from the use of tobacco- or nicotine- containing products for 24 hours prior to dosing 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;

- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down (except when required for BP and pulse rate measurements), eating, and drinking beverages other than water during the first 4 hours after the morning (AM) dose on PK sampling days.

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 interventions are all prespecified investigational and noninvestigational medicinal products/auxiliary medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to nirmatrelvir 150 mg tablet, ritonavir 100 mg tablet and rosuvastatin 10 mg tablet.

6.1. Study Intervention(s) Administered

Study Intervention(s)			
Intervention Name	PF-07321332 (nirmatrelvir) tablets	Ritonavir tablets	Rosuvastatin tablets
Type	Drug	Drug	Drug
Use	Test	Test	Reference, Test
IMP or NIMP/AxMP	IMP	NIMP/AxMP	NIMP/AxMP
Dose Formulation	Tablet	Tablet	Tablet
Unit Dose Strength(s)	150 mg	100 mg	10 mg
Dosage Level(s)	300 mg q12h for 2 days (Day 1 morning [AM] and evening [PM] and Day 2 morning [AM], 3 doses total)	100 mg q12h for 2 days (Day 1 morning [AM] and evening [PM] and Day 2 morning [AM], 3 doses total)	10 mg single dose (for both Treatment A and Treatment B)
Route of Administration	Oral	Oral	Oral
Sourcing	Provided centrally by the sponsor.	Provided locally by the CRU.	Provided locally by the CRU.
Packaging and Labeling	Study intervention will be provided in a bulk container (HDPE). Each bottle will be labeled as required per country requirement.	Study intervention will be provided in the commercial presentation as sourced by site. Each container will be labeled as required per country requirement.	Study intervention will be provided in the commercial presentation as sourced by site. Each container will be labeled as required per country requirement.
SRSD	IB	IB	SmPC
Current/Former Name(s) or Alias(es)	Nirmatrelvir (PF-07321332)	As available locally	As available locally

Study Arm/Period(s)		
Arm/Period Title	Treatment A (rosuvastatin, Reference)	Treatment B (rosuvastatin + nirmatrelvir/ritonavir, Test)
Arm/Period Description	Single oral dose of rosuvastatin 10 mg tablet on Day 1 in the morning (AM dose).	Nirmatrelvir/ritonavir 300 mg (2 × 150 mg)/ 100 mg tablets q12h (BID) for 2 days (Day 1 morning [AM] and evening [PM] and Day 2 morning [AM], total of 3 doses) with a single oral dose of rosuvastatin 10 mg tablet on Day 2 in the morning (AM dose). Nirmatrelvir and ritonavir will be dosed within no more than 5 minutes of each other. Rosuvastatin single dose will be dosed within 5 minutes after the Day 2 morning (AM) nirmatrelvir/ritonavir dose.

Nirmatrelvir 150 mg tablets will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

Ritonavir (Norvir® or other local commercialized product) 100 mg tablets will be supplied locally by the CRU.

Rosuvastatin (Crestor® or other local commercialized product) 10 mg tablets will be supplied locally by the CRU.

6.1.1. Administration

For Treatment A, following an overnight fast of at least 10 hours, participants will receive on Day 1 in the morning (AM dose) a single 10 mg (1 × 10 mg tablet) dose of rosuvastatin at approximately 0800 hours (plus or minus 2 hours).

For Treatment B, participants will receive 300 mg (2 × 150 mg tablet) nirmatrelvir administered orally with 100 mg (1 × 100 mg tablet) ritonavir q12h for 2 days (Day 1 morning [AM] and evening [PM] and Day 2 morning [AM], 3 doses total) starting at approximately 0800 hours (plus or minus 2 hours). On Day 1, the nirmatrelvir/ritonavir doses will be administered after at least a 2 hour fast. On Day 2, following an overnight fast of at least 10 hours, the final (third) nirmatrelvir/ritonavir dose will be co-administered with a single 10 mg (1 × 10 mg tablet) dose of rosuvastatin in the morning (AM dose). Nirmatrelvir and ritonavir will be dosed within no more than 5 minutes of each other. Rosuvastatin single dose will be dosed within 5 minutes after the Day 2 morning (AM) nirmatrelvir/ritonavir dose.

Investigator site personnel will administer study intervention during each period with ambient temperature water to a total volume of approximately 240 mL. For Treatment B, when nirmatrelvir/ritonavir is co-administered with rosuvastatin for the Day 2 morning (AM) dose, participants may receive additional ambient temperature water up to 100 mL, if needed. This will be documented by the site. Participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing.

Administration of study intervention(s) will be performed by an appropriately qualified and trained member of the study staff as allowed by local, state, and institutional guidance.

Following administration of study intervention(s), participants will be observed for the time of residence within the CRU by an appropriately qualified and trained member of the study staff. Appropriate medication and other supportive measures for management of a medical emergency will be available in accordance with local guidelines and institutional guidelines.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) 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, prepare, and/or administer study intervention.

3. 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 upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to the labeled storage conditions, 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 excursion definition and information to report for each excursion will be provided to the site in the CRU local/site procedures.

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

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

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

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

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

6.2.1. Preparation and Dispensing

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

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

6.3. Assignment 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. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

6.4. Blinding

This is an open-label study.

6.4.1. Blinding of Participants

Participants will be unblinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be unblinded to participants' assigned study intervention.

6.4.3. Blinding of the Sponsor

Sponsor staff will be unblinded to participants' assigned study intervention.

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.

6.5. 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.

6.6. Dose Modification

No dose modification is anticipated.

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

No study intervention will be provided to participants at the end of their study participation. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

6.8. Treatment of Overdose

For this study, any dose of nirmatrelvir greater than 600 mg, ritonavir greater than 200 mg, or rosuvastatin greater than 20 mg within a 24-hour time period [±2 hours] will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).
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 day from the date of the last dose of study intervention if requested by the study 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 study medical monitor as needed based on the clinical evaluation of the participant.

6.9. Prior and Concomitant Therapy

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

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

As nirmatrelvir and ritonavir are both primarily metabolized by CYP3A4, concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 14 days plus 5 half-lives prior to dosing of study intervention. Additionally, ritonavir and nirmatrelvir are inhibitors of CYP3A4. Therefore, medications highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events are not permitted during dosing of nirmatrelvir/ritonavir, through 4 days after the last dose of nirmatrelvir/ritonavir.

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.

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 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.

7.1.1. Potential Cases of Acute Kidney Injury

Participants exposed to IMP demonstrating transient or sustained increase in Screat (with decrease in Screat-based eGFR or eCrCL) require expedited evaluation to differentiate AKI from DICI. DICI is defined as transporter-mediated effect related to altered renal tubular creatinine handling without histological injury.

Differentiating Acute Kidney Injury from DICI:
AKI may be due to one or more types of injury, including DIKI. Differentiation of DIKI from other causes of AKI and from DICI may require clinical, radiographic, histopathologic, and laboratory assessments, as well as nephrology consultation.

Both AKI (including DIKI) and DICI are associated with (i) confirmed Screat increase ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours OR (ii) confirmed Screat increase ≥1.5 times baseline (known or suspected to have occurred within the prior 7 days).

Only AKI (including DIKI) is associated with

- For ADULT and PEDIATRIC participants, (i) simultaneous, confirmed serum cystatin C (Scys) increase and confirmed Screat increase OR (ii) confirmed albuminuria increase (see Appendix 6 for Grades A1 to A3 quantitation) OR (iii) urine volume <0.5 mL/kg/h for 6 consecutive hours.

- For ADULTS only, AKI is associated with decrease in Screat-based eGFR and combined Screat-Scys-based eGFR (when available).

Regardless of the presence or absence of increase in Screat, DIKI and other causes of AKI may be suspected if either there is (i) new-onset or worsening albuminuria or proteinuria are detected or (ii) urine volume (if measured) is <0.5 mL/kg/h for 6 consecutive hours.

Only DICI is associated with:

- For ADULT participants only, confirmed Screat increase without confirmed increase in reflex Scys AND confirmed Screat-based eGFR decrease without confirmed combined Screat-Scys-based eGFR decrease.

The participant should return to the site for evaluation as soon as possible, preferably within 48 hours of awareness of the abnormal results. Evaluation should include physical examination, laboratory tests, detailed medical and surgical history, review of all medications (including recreational drugs and supplements [herbal]), family history, sexual history, travel history, blood transfusion, and potential occupational exposure to chemicals. If appropriate,

nephrology consultation may be recommended to facilitate differentiation of renal parenchymal disease, pre-renal azotemia, and post-renal obstruction. All confirmed cases of clinically relevant decrease in kidney function should be considered potential cases of DIKI if no other reason for the kidney function abnormalities has been found.

7.1.2. 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 ms.
- Change from baseline: QTcF >60 ms and QTcF >450 ms.

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.

7.1.3. Stopping Rules

Dosing will be halted at any time if 1 of the following circumstances occurs and it is determined by the investigator that the occurrence is at least possibly related to the administration of study intervention:

- A SAE (eg, a serious AE considered at least possibly related to study intervention administration) in 1 participant.
- Severe NSAE (eg, severe NSAEs considered at least possibly related to study intervention administration) in 2 participants, independent of whether it is within or not within the same SOC.

When stopping rules are met, a data review will be conducted by the sponsor and investigator. If integrated analysis of available data leads to the conclusion that further dosing is justified, an amendment to the protocol may be required if additional safety monitoring is warranted.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their 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's decision;
- Pregnancy.

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

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

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

If a participant withdraws from the study, they 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 will be performed and no additional data will 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 them 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 the participant 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 attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline 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.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

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

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

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

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In

addition, other clinical assessments or specimen collections may not need to be repeated, as appropriate.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that 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 they have 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 255 mL (for both Periods 1 and 2). 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 56 consecutive days.

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

Medical history collected will include a history of prior illegal drug, alcohol, and tobacco use, as well as blood donation with prior 60 days. Demographics collected will include participant's race, ethnicity, age, and gender.

8.2. Efficacy Assessments

Efficacy parameters are not evaluated in this study.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

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

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

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

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

Physical examination findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

8.3.2.1. Blood Pressure and Pulse Rate

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.

BP and pulse rate assessments will be performed after collection of ECGs and prior to collection of blood draws if scheduled at the same time.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2.2. Temperature

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

8.3.3. Electrocardiograms

Standard 12-lead ECGs will be collected at times specified in the SoA section of this protocol using an ECG system that automatically calculates the HR and measures PR, QT, QTcF, and QRS intervals. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position and prior to any blood draws or vital sign measurements.

Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected will be recorded.

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

If a) a post dose QTcF interval remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF value get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF values 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.

8.3.4. 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 significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that 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 significant and 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 study medical monitor.

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

See Appendix 5 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 6 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

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

8.3.5. COVID-19 Specific Assessments

Participants will be tested for COVID-19 infection per local procedures. Additional testing may be required by local regulations or by the PI.

8.3.6. Pregnancy Testing

A urine or serum pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and 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 to starting the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.4. 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 8.4.1, 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.

8.4.1. 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 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 the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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

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

If a participant 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 they consider 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/PSSA.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form/PSSA 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 its being available.

8.4.1.2. 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 8.4.1, 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.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

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

8.4.2. 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.

8.4.3. 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 provided in Appendix 3.

8.4.4. 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.

8.4.5. 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 EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. 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 inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of 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 inseminates 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/participant's partner, the investigator must report this information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form *or* via PSSA 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 or via PSSA. 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 report 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 report. 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 pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

- 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.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB 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 EDB 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 *or* via PSSA. When EDB 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 report is maintained in the investigator site file.

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

8.4.5.3. 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 or via PSSA 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 report is maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. 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.

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form/PSSA to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	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.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, such medication errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s), are recorded on the AE page of the CRF.

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

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

8.5. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of rosuvastatin, nirmatrelvir, and ritonavir as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will

not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples will be used to evaluate the PK of rosuvastatin and confirm achievement of target steady-state trough concentration of nirmatrelvir and ritonavir. Samples collected for analyses of rosuvastatin and nirmatrelvir/ritonavir concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

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

Samples collected for measurement of plasma concentrations of rosuvastatin and nirmatrelvir/ritonavir will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

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

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

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

Retained research samples for genetics are not collected in this study.

8.7. Biomarkers

Collection of samples for biomarker research is also part of this study.

The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- CP-1 biomarker plasma samples.

Blood samples will be collected for measurement of plasma concentrations of CP-1 as specified in the SoA. CP-1 will be collected during both Treatment A (Reference) and Treatment B (Test) arms. Samples collected for measurement of plasma concentrations of CP-1 will be kept in amber vials covered with tin foil, stored at -80°C, and analyzed using a validated analytical method. 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.

CP-1 samples will be collected for exploratory research of CP-1 as an endogenous biomarker for OATP1B1 inhibition. CP-1 is a porphyrin metabolite from heme synthesis and relatively selective substrate for OATP1B1. Changes in CP-1 have been successfully applied as a biomarker for OATP1B1 modulation in vivo.[22,23] For a statin that is not a substrate for CYP3A, such as pitavastatin and rosuvastatin, there is an approximately 1:1 relationship between changes in CP-1 and changes in statin AUC ratios upon treatment with OATP inhibitors (Table 5).

Table 5. Changes in CP-1 and Statin AUC ratios

Precipitant Drug / Dose	CP-1 AUCR	Pitavastain AUCR	Rosuvastatin AUCR	Reference
Rifampicin 600 mg	4.0	ND	5.0	Lai et al, 2016[24]
Rifampicin 600 mg	3.5	2.8	2.4	Takehara et al, 2018[25]
Rifampicin 600 mg	3.7	4.0	2.5	Mori et al, 2020[26]
Rifampicin 300 mg	2.4	3.4	2.3	Mori et al, 2020[26]
Rifampicin 300 mg	2.3	2.3	2.2	Takehara et al, 2018[25]
Rifampicin 150 mg	1.5	2.5	1.6	Mori et al, 2020[26]
Pimodivir 600 mg	1.4	1.5	ND	Kunze et al, 2018[27]
Itraconazole 200 mg	0.9	0.77	1.4	Shen et al, 2018[28] Pitavastatin label[29]
Diltiazem 240 mg	1.0	1.1	ND	Shen et al, 2018[28]; Pitavastatin label[29]
RO7049389 800 mg	3.0	1.9	ND	Feng et al, 2021[30]
SLCO1B1*15/*15 vs WT	2.2	1.7	1.6	Mori et al, 2019[31]

AUCR = AUC ratio = AUC in presence of Precipitant Drug/AUC in absence of Precipitant Drug.

8.7.1. Pharmacodynamic Biomarkers

Pharmacodynamic biomarkers are not collected in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. 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

Not applicable. This is an estimation study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening.
Safety Analysis Set	All participants who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
PK Concentration Set	All participants who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported.
PK Parameter Set	All participants who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of primary interest are reported.

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. General Considerations

9.3.2. Primary Endpoint(s) Analysis

Natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effect model with treatment as a fixed effect and participant 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. Treatment A (rosuvastatin) will be the Reference treatment while Treatment B (rosuvastatin + nirmatrelvir/ritonavir) will be the Test treatment.

PK parameters, including plasma AUC_{inf}, AUC_{last}, C_{max}, and T_{max}, $t_{½}$, CL/F and V_z/F of rosuvastatin will be summarized descriptively by treatment. For AUC_{inf}, AUC_{last} and C_{max}, a listing of the individual participant ratios (Test/Reference) will be provided. Box and whisker plots for AUC_{inf}, AUC_{last} and C_{max}, will be plotted by treatment.

The plasma concentrations of rosuvastatin 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 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.

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

9.3.2.1. Definition of Endpoint(s)

Derivation of Pharmacokinetic Parameters

Plasma PK parameters of rosuvastatin will be derived (as data permit) from the concentration-time data using standard noncompartmental methods as outlined in the Table 6. Actual PK sampling times will be used in the derivation of rosuvastatin PK parameters when available. 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 6. Plasma Rosuvastatin PK Parameters Definitions

Parameter	Definition	Method of Determination
AUC_{inf}*	Area under the concentration-time curve from time 0 extrapolated to infinity.	$AUC_{last} + (C_{last}*/k_{el})$, where C_{last}* is the predicted plasma concentration at the last quantifiable time point from the log-linear regression analysis.
AUC_{last}**	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}).	Linear/Log trapezoidal method.
C_{max}	Maximum observed concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence

Table 6. Plasma Rosuvastatin PK Parameters Definitions

Parameter	Definition	Method of Determination
$t_{½}$*	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the loglinear concentration-time curve. Only those data points judged to describe the terminal loglinear decline will be used in the regression.
CL/F*	Apparent clearance	$Dose/AUC_{inf}$
V_z/F*	Apparent volume of distribution	$Dose/(AUC_{inf} \bullet k_{el})$

*If data permit.
**T_{last} will also be included in order to provide additional context for AUC_{last}. T_{last} will only be listed, not summarized.

9.3.3. Other Safety Analyses

All safety analyses will be performed on the safety population.

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

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

9.3.4. Other Analyses

9.3.4.1. Biomarker Assessment

CP-1 biomarker data will be listed and descriptively summarized by nominal sampling time and by treatment.

9.4. Interim Analyses

No interim analysis will be conducted for this study.

9.5. Sample Size Determination

A sample size of 12 participants will provide adequate precision to estimate the relative bioavailability of rosuvastatin. The width of 90% CI for different estimated effects, with 80% coverage probability, is presented in the Table 7.

Table 7. Expected Width of 90% Confidence Interval for Different Possible Estimated Effects and Parameters of Interest

Parameter	Estimated Effect (100*Test/Reference)	90% CI		CI Width
AUC	100%	84.94%	117.73%	32.78%
	120%	101.93%	141.27%	39.34%
	140%	118.92%	164.82%	45.90%
	150%	127.41%	176.59%	49.18%
	160%	135.91%	188.36%	52.45%
	180%	152.90%	211.9%	59.01%
	200%	169.89%	235.45%	65.57%
C_{max}	100%	85.23%	117.33%	32.10%
	120%	102.28%	140.79%	38.52%
	140%	119.32%	164.26%	44.94%
	150%	127.85%	175.99%	48.15%
	160%	136.37%	187.73%	51.36%
	180%	153.41%	211.19%	57.78%
	200%	170.46%	234.66%	64.20%

These estimates are based on the assumption that within-participant standard deviations are 0.193 and 0.189 for $\ln AUC_{inf}$ and $\ln C_{max}$, respectively, as obtained from Study B7981024.

Participants who discontinue from the study may be replaced at the sponsor's discretion.

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, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

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

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

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

10.1.2. Financial Disclosure

Not applicable.

10.1.3. Informed Consent Process

The investigator or the investigator'srepresentative 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 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 their 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 their 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 their right to access and correct their personal data and to withdraw consent for the processing of their 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 IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

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

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

10.1.4. Data Protection

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

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

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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites 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/CTIS

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

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-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 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is

responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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

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

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

10.1.8. Source Documents

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

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

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes a source document and its origin can be found in the Source Document Locator, which is maintained by the sponsor's designee (Pfizer CRU).

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor's designee (Pfizer CRU).

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

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

10.1.9. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

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, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. 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 ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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

10.1.10. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer 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-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.11. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the CTMS.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from non-study healthcare professionals, 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.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant.

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; for example: calculation of estimated kidney function (ie, 2021 CKD-EPI eGFR). 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 8. Protocol-Required Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Urea Creatinine Cystatin C[a] eGFR, eCrCl[b] Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein Creatinine kinase	Local dipstick: pH[c] Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy[d] and culture[e]	At screening: • FSH[f] • Urine drug screening[g] • Hepatitis B surface antigen • Hepatitis B surface antibody • Hepatits B core antibody • Hepatitis C antibody • Pregnancy test (β-hCG)[h] • Human immunodeficiency virus At admission: • Urine drug screening[g] • Pregnancy test (β-hCG)[h]

a. Cystatin C (Scys): Screening or Baseline Scys is recommended to help differentiate post-baseline DIKI from DICI. Post-baseline, Scys is measured if and only if serum creatinine increase post-baseline is observed (see Section 7.1.1).
b. Screening and Baseline eGFR or eCrCl is measured with Screat-based formula. Age-specific kidney function calculation (see Section 10.6.2) is recommended to assess presence or absence of post-baseline change in kidney function.
c. Can be performed on dipstick or pH meter device.
d. Only if dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
e. Urinary culture only if deemed appropriate by the investigator.
f. For confirmation of postmenopausal status only in females <60 years old and not using hormonal or HRT only.
g. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
h. Local urine or serum testing will be used. See SoA for collection times and Section 8.3.6 for more details.

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. Upon completion of the study, these retained safety

samples may be used for the assessment of exploratory safety biomarkers or unexpected safety findings. These data will not be included in the CSR. Samples to be used for this purpose will be shipped to either a Pfizer-approved BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

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

10.3.1. Definition of AE

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

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

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal 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 an increase in either 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.

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
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 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 using the CT SAE Report Form *or* via PSSA 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/PSSA 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/PSSA for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form/PSSA 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 EDP or EDB **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 nonparticipant (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 SAE): is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form *or* via PSSA.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form or PSSA, 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 or via PSSA.

- 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: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.

- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

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.

Assessment of Causality

- 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 their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have 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 their 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/PSSA 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.

Follow-Up of AEs and SAEs
• 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 DCT
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT (eg, eSAE or PSSA). • If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available. • After the study is completed at a given site, the electronic DCT 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 DCT 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 the CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is one of the methods to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.

SAE Reporting to Pfizer Safety via the CT SAE Report Form
• 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 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 WOCBP 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

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

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 definition in Section 10.4.3).

  OR

- Is a WOCBP and agrees to use a highly effective contraceptive method (failure rate of <1% per year) during the intervention period and for at least 28 days/weeks after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective, user-dependent method is chosen, she agrees to concurrently use an effective barrier

method of contraception. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

Because ritonavir may reduce the effect of estradiol-containing contraceptives when agents are co-administered, a barrier method or other nonhormonal method of contraception must also be used if the participant is using estradiol-containing contraceptives during the study treatment and until one menstrual cycle after stopping 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 or oligomenorrhea) 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 a 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 highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she 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.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral + barrier*
    - Intravaginal + barrier*
    - Transdermal + barrier*
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral + barrier*
    - Injectable + barrier*

Sexual Abstinence

8. 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

* Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following:

- 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).

10.5. Appendix 5: 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 T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili 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 T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili 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** T bili 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 T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili 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 T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, eosinophils (%), 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, total bile acids, 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 T bili 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.

10.6. Appendix 6: Kidney Safety: Monitoring Guidelines

10.6.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline Screat measurement to estimate kidney function [Screat-based eGFR] or creatinine clearance [eCrCl]). Obtaining Screening or Baseline Scys and postbaseline reflex Scys (if confirmed Screat increase ≥0.3 mg/dL) makes it feasible to distinguish AKI from DICI. If Screat increase is confirmed after baseline, then reflex measurement of Scys is indicated (for adult and for pediatric participants):

ADULTS: Currently, 2021 CKD-EPI eGFR equations (Screat only-based and combined Screat plus Scys-based) are valid for use in adults only. At baseline Screat and Scys values are needed to calculate 2021 CKD-EPI eGFR by Screat only-based equation (see Table 10.6.2.1) and by combined Screat plus Scys-based equation. When post-baseline Screat increase ≥0.3 mg/dL is confirmed, then reflex Scys measurement is needed to enable post-baseline comparison of eGFR changes (Screat only-based eGFR and combined Screat plus Scys eGFR).

PEDIATRICS: Currently, no Screat plus Scys eGFR equations have been universally adopted for pediatrics. Therefore, comparison of baseline Screat and Scys to post-baseline Screat and reflex Scys are utilized to support differentiation of AKI from DIKI. Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.6.2. Age-Specific Kidney Function Calculation Recommendations

10.6.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

eGFR (mL/min/1.73m²)[32]

2021 CKD-EPI Screat Only	**Screat** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	NA	$eGFR = 143 \times (Screat/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	NA	$eGFR = 143 \times (Screat/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤ 0.9	NA	$eGFR = 142 \times (Screat/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	NA	$eGFR = 142 \times (Screat/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Screat-Scys Combined	**Screat** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	if ≤ 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤ 0.7	if > 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ≤ 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if ≤ 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if > 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ≤ 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$

Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

10.6.3. Kidney Function Calculation Tools

The sponsor has provided the following resources to investigational sites when required to calculate age-specific kidney function at Screening, Baseline, and post-Baseline visits. Site calculations of kidney function can be performed manually, using the age appropriate formulae (see Section 10.6.2) and can use recommended online kidney function calculators to reduce the likelihood of a calculation error.

The United States National Kidney Foundation Online Calculators.

- Adults (18 years and above) - 2021 CKD-EPI Creatinine Online Calculator (eGFR): https://www.kidney.org/professionals/KDOQI/gfr_calculator

Investigational sites are responsible to ensure that the accurate age-specific equation is selected and that the correct units for serum creatinine (mg/dL only), serum cystatin C (mg/L only), total body weight (kg only), and age (years). Investigators are expected to (i) review and confirm correctness of the kidney function calculation results and (ii) evaluate the calculated value within the context of historical information available to them in the participant's medical record. Investigators are responsible for the clinical oversight of the participant eligibility process, kidney function calculation, and dose selection and adjustments per study protocol. Investigators are encouraged to direct questions or uncertainties regarding kidney function and dosing to the Pfizer Clinical Team and Medical Monitor, if needed.

10.6.4. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AEgrading for decline in kidney function (ie, eGFR or eCrCl) will be according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

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 ms. • New prolongation of QTcF to >480 ms (absolute). • New prolongation of QTcF by >60 ms 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-second 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 ms.
• Absolute value of QTcF > 450 ms AND QTcF change from baseline >60 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex>120 ms).
• New-onset right bundle branch block (QRS complex>120 ms).
• Symptomatic bradycardia.
• Asystole
  • In awake, symptom-free participants in sinus rhythm, with documented asystolic pauses ≥3 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 asystolic 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 (HR <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 major events of potential clinical concern listed above 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 is to reported as AEs/SAEs.

10.8. Appendix 8: Abbreviations

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

Abbreviation	Term
A1 to A3	albuminuria (KDIGO albuminuria severity standardization)
Abs	absolute
ADL	activity/activities of daily living
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{inf}	area under the concentration-time curve from time 0 extrapolated to infinity
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})
AUCR	AUC in presence of Precipitant Drug/AUC in absence of Precipitant Drug
AV	atrioventricular
AxMP	auxiliary medicinal product
BBS	Biospecimen Banking System
BCRP	breast cancer resistance protein
β-hCG	β-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CL/F	apparent clearance
C_{max}	maximum observed concentration
$C_{max,u}$	maximum unbound inhibitor concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
$3CL^{pro}$	3C-like protease
CP-1	coproporphyrin I
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial

Abbreviation	Term
CTIS	Clinical Trial Information System
CYP	cytochrome P450
DCT	data collection tool
DDI	drug-drug interaction
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
^{19}F-NMR	fluorine-19 nuclear magnetic resonance spectroscopy
F/U	follow-up
FIH	first in human
f_m	fraction metabolized
FSH	follicle-stimulating hormone
$f_{u,p}$	fraction unbound in human plasma
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
HCVAb	hepatitis C antibody
HDPE	high density polyethylene
HEK293	human embryonic kidney 293 cells
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICD	informed consent document

Abbreviation	Term
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
$I_{in,max,u}$	maximal unbound inhibitor concentration in the hepatic inlet
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IV	Intravenous(ly)
KDIGO	Kidney Disease Improving Global Outcomes
K_{el}	elimination constant
K_i	inhibitor constant
LBBB	left bundle branch block
LFT	liver function test
MAD	multiple ascending dose
MDR	medical device regulation
M^{pro}	main protease
MQI	medically qualified individual
MRP2	multi-drug resistance protein 2
NA	not applicable
ND	not determined
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
NSAE	non-serious adverse event
NYHA 1	New York Heart Association Functioncal Classification 1
OAT3	organic anion transporter 3
OATP	organic anion transporting polypeptide
OATP1B1	organic anion transporting polypeptide 1B1
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PVC	premature ventricular contraction/complex
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia’s formula
qual	qualitative
R_B	blood-to-plasma ratio
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Scys	serum cystatin C

Abbreviation	Term
Screat	serum creatinine
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOC	System Organ Class
SOP	standard operating procedure
SRSD	Single Reference Safety Document
STT	ST and T wave
SUSAR	Suspected Unexpected Serious Adverse Reaction
T bili	total bilirubin
$t_{½}$	terminal half-life
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
T_{last}	time of the last quantifiable concentration
T_{max}	time for C_{max}
ULN	upper limit of normal
US	United States
vs	versus
V_z/F	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WT	wildtype

11. REFERENCE

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