



**A PHASE I, MULTIPLE DOSE, OPEN-LABEL
PHARMACOKINETIC STUDY OF
NIRMATRELVIR/RITONAVIR IN HEALTHY LACTATING
WOMEN**

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Brief Title: A Phase 1 Multiple Dose Open-Label Pharmacokinetic Study of
Nirmatrelvir/Ritonavir in Healthy Lactating Women

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1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: A Phase 1 Multiple Dose Open-Label Pharmacokinetic Study of Nirmatrelvir/Ritonavir in Healthy Lactating Women

Rationale

Paxlovid® (nirmatrelvir/ritonavir), would likely be widely used in lactating women resulting in exposure to infants through the breast milk. The purpose of the study is to determine the amount of nirmatrelvir and ritonavir that distributes into breast milk following multiple oral doses of nirmatrelvir/ritonavir in healthy lactating women. This would allow assessment of potential risk from drug exposure during breastfeeding.

Objectives and Endpoints

Objectives	Endpoints
Primary:	Primary:
<ul style="list-style-type: none"> To evaluate the amount of nirmatrelvir secreted in human breast milk following multiple oral BID dosing with nirmatrelvir/ritonavir 	<ul style="list-style-type: none"> Breast milk nirmatrelvir PK parameters: C_{max}, T_{max}, AUC_{τ}, $t_{1/2}$, C_{av}, Ae_{τ}, $Ae_{\tau}\%$, and CL_{bm}
Secondary:	Secondary:
<ul style="list-style-type: none"> To determine the ritonavir concentrations in human breast milk following multiple oral BID dosing with nirmatrelvir/ritonavir To characterize the plasma PK parameters of nirmatrelvir and ritonavir following multiple oral BID doses with nirmatrelvir/ritonavir in lactating women Estimate the infant daily dose that would result from nirmatrelvir and ritonavir secretion in breast milk following multiple oral BID doses with nirmatrelvir/ritonavir. To characterize the safety and tolerability of nirmatrelvir/ritonavir in lactating women. 	<ul style="list-style-type: none"> Breast milk ritonavir PK Parameters: C_{max}, T_{max}, AUC_{τ}, $t_{1/2}$, C_{av}, Ae_{τ}, $Ae_{\tau}\%$, and CL_{bm} Plasma nirmatrelvir and ritonavir PK parameters: C_{max}, C_{av}, C_{trough}, T_{max}, AUC_{τ}, $t_{1/2}$, CL/F and V_z/F. For both nirmatrelvir and ritonavir: Ae_{24bm}, $MPAUC_{\tau}$ and MPC_{max} during the dosing interval τ; CL_{bm}, M/P, $BWNID$, $BWNMD$, $BWNIDPCM$. Safety: TEAEs, clinical laboratory tests, vital signs, PE, and ECGs.

Overall Design

Brief Summary

This is an open-label, PK study to determine the amount of nirmatrelvir and ritonavir secreted in breast milk following multiple BID oral dosing in lactating women.

Approximately 8 healthy lactating women, who are documented PCR negative for COVID-19, will be enrolled. In the event that participants withdraw or are unable to express breast milk during a collection interval, additional participants may be recruited.

Participants will not be permitted to breastfeed their infant from the evening of the day prior to the first dose and for 72 hours (3 days) after the Day 2 dose. Participants must have a plan for feeding the infant during the time when the infant cannot breastfeed. Though not a study requirement, participants may wish to express sufficient breast milk in advance of the study to cover the duration when breastfeeding is not permitted (ie, when nursing is restricted during study participation).

If a participant has any clinically significant, study related abnormalities at the conclusion of a scheduled inhouse 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 8 participants will be enrolled to study intervention.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and screening. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration

Each participant will be screened to determine eligibility within 28 days prior to study treatment. Eligible participants will report to the CRU on Day -1 and participants will be admitted to the CRU at a time convenient to the participant and the CRU. A safety follow-up call will be made to participants approximately 28 to 35 days from administration of the final dose of study intervention.

Each enrolled participant on Day 1 will receive 1 dose of nirmatrelvir/ritonavir in the morning and 1 dose in the evening and finally 1 dose of nirmatrelvir/ritonavir in the morning of Day 2. There will not be any dietary restrictions associated with dosing. Starting Day 2 there will be collections of breast milk and blood over 48 hours to characterize the PK of nirmatrelvir and ritonavir in this population.³

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

Pharmacokinetics Analysis

The PK concentration population is defined as all participants randomly assigned to study intervention and who take at least 1 dose of nirmatrelvir/ritonavir and in whom at least 1 concentration value is reported.

The PK parameter analysis population is defined as all participants assigned to study intervention and who take at least 1 dose of nirmatrelvir/ritonavir and in whom at least one of the PK parameters of interest are reported.

PK parameters for nirmatrelvir and ritonavir in maternal breast milk and plasma will be analyzed using standard noncompartmental methods. Actual PK sampling times will be used in the derivation of nirmatrelvir and ritonavir PK parameters when available, otherwise nominal times will be used. The nirmatrelvir and ritonavir concentrations for breast milk and plasma will be listed and summarized descriptively by actual and nominal PK sampling times, respectively. PK parameters for breast milk and plasma will be listed and summarized using descriptive statistics utilizing all participants for whom a valid PK parameter can be calculated and reported. Individual participant and summary profiles (mean and median plots) concentration time data will be plotted by analyte using actual and nominal times respectively with breast milk and plasma data on the same plot. Plots of AUC, C_{max} , and C_{av} will be presented for each analyte comparing the PK parameters in breast milk versus those in plasma.

No formal hypothesis testing will be performed on the PK parameters.

Safety Analysis

All safety analyses will be performed on the safety analysis set, which is defined as all participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

1.2. Schema

Not applicable

1.3. Schedule of Activities

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

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

Visit Identifier Abbreviations used in this table may be found in Appendix 9	Screening ^a		Multiple Dose Period																			28-35 days (Follo w-Up)	Early Terminatio n/ Discontinu ation	
Days Relative to Day 1	Days -28 to -2	Day -1	Day 1			Day 2												Day 3				Day 4	Day 28-35 ^u	
<i>Hours post dose</i>			Pre dose	0	12	Pre dose	0	0.5	1	2	3	4	6	8	10	12	18	24	32	40	48			
Admission to CRU		X																						
Informed consent	X																							
Inclusion/exclusion criteria	X	X																						
Medical/medication history (update) ^b	X	X																						
Demography ^c	X																							
Physical examination ^d	X	X																						
Safety laboratory (including aPTT, PT-INR, Fibrinogen, and eGFR) ^e	X	X																			X		X	
Urine drug testing ^f	X	X																						
Serology: HBsAg, HBsAb, HBcAb, HCVAb, and HIV ^g	X																							
Pregnancy Test	X	X																			X		X	
Contraception check ^h	X	X																			X	X	X	
Single supine 12-Lead ECG ⁱ	X																							

Visit Identifier Abbreviations used in this table may be found in Appendix 9	Screening ^a		Multiple Dose Period																			28-35 days (Follo w-Up)	Early Terminatio n/ Discontinu ation	
Days Relative to Day 1	Days -28 to -2	Day -1	Day 1			Day 2												Day 3				Day 4	Day 28-35 ^u	
<i>Hours post dose</i>			Pre dose	0	12	Pre dose	0	0.5	1	2	3	4	6	8	10	12	18	24	32	40	48			
Vital signs (BP/PR/temperature) ^j	X		X ^r		X ^r	X ^r															X		X	
COVID-19 questionnaire ^k	X	X																						
COVID-19 testing ^l	X	X																						
Nirmatrelvir /ritonavir administration				X ^s	X ^s		X ^t																	
PK Blood Sampling for nirmatrelvir /ritonavir ^m							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Breast Pump Trial ⁿ	X	X																						
Breast Milk Collection ^o		X	X				X	→	→	X	→	X	→	X	→	X	→	X	X	X	X		X	
Retained Research Sample for Genetics (Prep D1) ^p			X																					
Retained Research Samples for Biomarkers (Prep B2) ^p			X																					
Nursing Mother Questionnaire	X																							
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	
Prior/Concomitant Medication	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	
CRU discharge ^q																					X			

Visit Identifier Abbreviations used in this table may be found in Appendix 9	Screening ^a		Multiple Dose Period																		28-35 days (Follo w-Up)	Early Terminatio n/ Discontinu ation	
Days Relative to Day 1	Days -28 to -2	Day -1	Day 1			Day 2											Day 3				Day 4	Day 28-35 ^u	
<i>Hours post dose</i>			Pre dose	0	12	Pre dose	0	0.5	1	2	3	4	6	8	10	12	18	24	32	40	48		

- Screening will be performed within 28 days prior to the first dose of nirmatrelvir/ritonavir.
- 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.
- Demographics will include participant race, ethnicity, age, and gender during the screening visit.
- Physical examination may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation, at the investigator site at screening or Day -1 (height and weight must be obtained at screening to obtain BMI for eligibility criteria). A brief PE may be performed at other designated time points at the discretion of the investigator.
- Safety laboratory assessments including urinalysis, hematology, chemistry, eGFR and coagulation will be performed at the indicated time-points. All the safety laboratory samples must be collected following at least a 4-hour fast. Additional safety laboratory assessments may be performed at any time at the discretion of the investigator.
- 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.
- HBsAb may be routinely tested or only if HBsAg and/or HBeAb are positive. HBsAb due to vaccination is permissible.
- The investigator or his/her designee will discuss with the participant the need to use highly effective contraception consistently and correctly according to contraception guidelines.
- 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.
- Single supine BP, and PR will be performed following approximately a 5-minute rest in a supine position. BP, and PR assessments will be performed after collection of ECGs and prior to collection of blood draws if scheduled at the same time. Temperature will be measured orally as per CRU standard practice.
- Check exposure to positive case, residence or travel in area of high incidence and COVID-19 related signs and symptoms.
- A subsequent COVID-19 test may be performed if they develop COVID-19 like symptoms.
- One (approximately 4 mL) blood sample for PK analysis nirmatrelvir and ritonavir will be taken at the designated time points.
- Participants must try using the electric breast pump either at Screening or Day -1.
- Breast milk to be collected over a 2-hour interval on Day -1. Breast milk to be collected over a 2-hour interval prior to Day 1 dose and for 48 hours after Day 2 dosing over the following time intervals: 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 32, 32 to 40 and 40 to 48 hours. At least 14 mL of breast milk must be expressed over a 2-hour period prior to the dose on Day 1 using the electric breast pump for a participant to be eligible for enrollment.
- Retained Research Samples Prep D1 for Genetics and Prep B2 for Biomarkers: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.
- Participants will be discharged after collection of the 48-hour PK and breast milk sample on Day 4
- Prior to, and 1 hour after, the AM and PM dose.
- Two tablets of 150 mg of nirmatrelvir and one 100 mg of ritonavir tablet will be administered in the morning and in the evening. Doses will be separated by 12 hours.
- Two tablets of 150 mg of nirmatrelvir and one 100 mg of ritonavir tablet will be administered in the morning (AM).
- Contact may occur via telephone and must occur 28 to 35 days from administration of the final dose of study intervention.

2. INTRODUCTION

PF-07321332 (also referred as nirmatrelvir) is a potent and selective inhibitor of the SARS-CoV-2 3CL protease that is approved for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Ritonavir is a strong CYP3A4 inhibitor used to inhibit the metabolism of PF-07321332 in order to increase plasma concentrations of PF-07321332. In a phase 3 randomized, controlled trial, nirmatrelvir/ritonavir (300 mg/100 mg BID for 5 days) administered to unvaccinated outpatients infected with SARS-CoV-2 showed an 89.1% relative risk reduction in Covid-19–related hospitalization or death.¹

2.1. Study Rationale

Paxlovid® (nirmatrelvir/ritonavir), would likely be used in lactating women resulting in exposure to infants through the breast milk. The purpose of the study is to determine the amount of nirmatrelvir and ritonavir that distributes into breast milk following multiple oral doses of nirmatrelvir/ritonavir in healthy lactating women. This would allow assessment of potential risk to infants from drug exposure during breastfeeding.

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

PF-07321332 is an orally bioavailable 3CL^{pro} inhibitor shown to be effective against SARS-CoV-2 3CL^{pro} ($K_i = 0.00311 \mu\text{M}$) in a biochemical enzymatic assay. Since the 3CL^{pro} from human coronaviruses are structurally similar and share a high degree of conservation at the active site of the enzyme, the ability of PF-07321332 to inhibit the 3CL^{pro} of other coronaviruses (SARS-CoV-1 and HCoV-229E, MERS, HCoV-OC43, HCoV-HKU1, and HCoV-NL63) was also confirmed, indicating a potential for broad spectrum anti-coronavirus activity. The coronavirus 3CL protease is a virally encoded enzyme that is critical to the SARS-CoV-2 replication cycle, analogous to other obligatory virally encoded proteases (eg, HIV Protease, HCV Protease).³ PF-07321332 is being developed as an oral treatment in patients with COVID-19 infection.

Ritonavir is a strong CYP3A4 inhibitor being used to inhibit the metabolism of PF-07321332 in order to increase plasma concentrations of PF-07321332 to values that are 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. Further details for the ritonavir can be found in Paxlovid SmPC.⁴

The clinical development program for PF-07321332 includes 7 completed clinical studies: 5 Phase 1 studies in healthy participants (C4671001, C4671012, C4671013, C4671014 and

C4671015), 1 Phase 1 study in renal impairment participants (C4671011) and 1 Phase 1 study in hepatic impairment participants (C4671010).

As the lactating women were not included in previous studies, the excretion of nirmatrelvir in breast milk is not known.

However, ritonavir excretion in the breast milk was reported in literature. Earlier studies in HIV infected nursing mothers showed limited exposure of ritonavir in breastfed infants. In a study by Corbett AH et al.,⁵ ritonavir was administered 100 mg twice daily in HIV infected mothers, after delivery until cessation of breastfeeding for a maximum of 28 weeks. 30 mother/infant pairs (10 each at 6, 12, and 24 weeks postpartum) were enrolled. At a median of 14.9 hours after the previous evening's dose, BM and MP samples were obtained prior to the morning dose and 2, 4 and 6 hours after the dose. 112 of 121 BM samples and 111 of 115 MP samples contained detectable concentrations of ritonavir, with a median concentration of 0.079 µg/ml and 0.364 µg/ml respectively. Median ritonavir AUC_{0-6hr} in BM and MP were 0.490 µg.h/ml and 2.30 µg.h/ml respectively. Median BM/MP ratio of all BM and MP concentrations was found to be 0.195 (range 0.159, 0.243).

In another study by Palombi L et al.,⁶ HIV-positive pregnant women were dosed with lopinavir 400 mg and ritonavir 100 mg twice daily as a prophylaxis from gestational week 25 until 6 months after delivery. In 66 women studied, blood and breast milk samples were collected at delivery, and at months 1, 3 and 6 postpartum. Samples were collected at a median of 4.5 hours after the last dose administration and a median of 30 minutes after the last breastfeeding. Median ritonavir concentration in BM and MP were 79 ng/ml and 422 ng/ml respectively. Median BM/MP ratio was found to be 0.20 (range 0.12-0.78). The infant's median ritonavir concentration was 7 ng/ml (range 0-138).

2.2.1. Nonclinical Pharmacology

Details of the nonclinical pharmacology of PF-07321332 can be found in the current IB.⁷

2.2.2. Nonclinical Pharmacokinetics and Metabolism

Hepatic CYP3A enzymes were identified as the main pathway for clearance of PF-07321332 in vitro in liver microsomes (mouse, rat, hamster, rabbit, monkey, and human), hepatocytes (rat, monkey, and human), and in vivo in rat and monkey after repeat oral dosing. In a reaction phenotyping study using human liver microsomes in the presence of selective CYP inhibitors, CYP3A4 was predicted to be the major contributor ($f_m = 0.99$) to the in vitro oxidative metabolism of PF-07321332. No significant CYP3A5 contribution is expected to the metabolism of PF-07321332.

Additional information of the nonclinical PK and metabolism of PF-07321332 is available in the current IB.⁷

2.2.3. Nonclinical Safety

There were no adverse findings observed in repeat-dose toxicity studies in rats and monkeys up to 2 weeks duration and the NOAELs were the highest dose administered (1000 mg/kg

and 600 mg/kg in the rat and monkey studies, respectively). PF-07321332-related non-adverse, test article-related clinical findings included sporadic occurrence of emesis with slight body weight decreases in monkeys 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, non-adverse microscopic findings of minimal to mild severity in the liver and thyroid gland consistent with adaptive changes related to microsomal enzyme induction.

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

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

Further details of the nonclinical safety program are provided in the current IB.⁷

2.2.4. Clinical Overview

Safety, tolerability and PK of PF-07321332 in healthy adult participants was explored in Phase 1 FIH Study (C4671001). 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 PF-07321332, 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 PF-07321332. PART-5 was a double-blind, sponsor-open, randomized, crossover study to evaluate safety and tolerability at supratherapeutic exposures.

Efficacy and safety of PF-07321332 was evaluated in interventional Phase 2/3 Study (C4671005). C4671005 was a Phase 2/3 randomized, placebo-controlled trial in non-hospitalized adult participants with a laboratory-confirmed diagnosis of SARS-CoV-2 infection. Included in this Clinical Overview are summaries of the results of Study C4671001 and C4671005.

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, PF-07321332/ritonavir was generally safe and well tolerated.

Safety data from Study C4671001 indicate that PF-07321332 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 PF-07321332 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 PF-07321332 BID with 100 mg ritonavir BID. In all 5-parts of the study, there were no deaths, severe AEs, or SAEs. PF-07321332 alone or PF-07321332/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 1 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 ECGs indicate that PF-07321332 has an acceptable safety and tolerability profile in healthy adult participants.

C4671005 is a Phase 2/3 randomized, placebo-controlled trial in non-hospitalized 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 ($\geq 1\%$) that occurred at a greater frequency (≥ 5 participant difference) than in the placebo group were dysgeusia (5.6% and 0.3%, respectively), diarrhoea (3.1% and 1.6%), vomiting (1.1% and 0.8%), and headache (1.4% and 1.3%).

Further details on the clinical safety information with PF-07321332 are provided in the current IB⁷.

2.2.4.2. Summary of PF-07321332 Pharmacokinetics in Human

Single dose PK data from Study C4671001 at PF-07321332 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 PF-07321332 was absorbed rapidly with median T_{max} of 1 hour or less when administered alone and 2.75 hours or less when administered with ritonavir. Since PF-07321332 is primarily metabolized by CYP3A4 and ritonavir is a CYP3A4 inhibitor, dosing with ritonavir increased the exposure of PF-07321332. Highest observed mean C_{max} and AUC_{last} was 5.09 $\mu\text{g/mL}$ and 64.26 $\mu\text{g}\cdot\text{h/mL}$, respectively, at 750 mg PF-07321332 dosed with ritonavir. The mean half-life of PF-07321332 was approximately 2 hours when administered alone and increased to approximately 6-13 hours when co-administered with ritonavir. Dosing with a high-fat meal modestly increased the exposure of PF-07321332 (approximately 15% increase in mean C_{max} and 1.5% increase in mean AUC_{last}).

PK data on Day 1, Day 5 and Day 10 following multiple oral administration of PF-07321332/ritonavir 75/100 mg, 250/100 mg, and 500/100 mg 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 PF-07321332/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.

PF-07321332 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 effect of food (eg, high-fat high-calorie meal) on exposures of PF-07321332 after oral administration of a suspension of PF-07321332, enhanced with 100 mg ritonavir, resulted in approximately 1.5% increase in AUC_{inf} and 15% increase in C_{max} of PF-07321332.

The primary route of elimination of PF-07321332 when administered with ritonavir was renal excretion of intact drug. A total of 49.6% and 35.3% of the administered dose of PF-07321332 300 mg was recovered in urine and feces, respectively. PF-07321332 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 PF-07321332 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 PF-07321332.

Further details on the clinical PK of PF-07321332 are provided in the current IB.⁷

2.3. Benefit/Risk Assessment

Nirmatrelvir/ritonavir is not expected to provide any clinical benefit to healthy lactating women in this study. This study is designed primarily to generate safety, tolerability, and PK data for further clinical development.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of nirmatrelvir/ritonavir may be found in the nirmatrelvir IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) nirmatrelvir		
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 blood pressure were observed in pre-clinical studies. 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(s) 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 BID is used in this study. There will be close observation of AEs and ongoing review of AEs by the sponsor. Taking study intervention with food may improve tolerability.
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 used in this study. There will be close observation of AEs and ongoing review of AEs by the sponsor.
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 used in this study. There will be close observation of AEs and monitoring through brief physical exams. If needed, therapeutic interventions per SoC may be provided.
Fatigue/Asthenia	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs. Fatigue (low energy or tiredness) will be assessed through collection of signs and symptoms and will also be assessed through brief physical examinations when performed during the study visits.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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

Nirmatrelvir/ritonavir will not provide any clinical benefit to participants in this study. Any anticipated benefit to participants would be in terms of contribution to the process of developing a new therapy in an area of unmet medical need.

2.3.3. Overall Benefit/Risk Conclusion

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

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	Primary:
<ul style="list-style-type: none"> To evaluate amount of nirmatrelvir secreted in human breast milk following multiple oral BID dosing with nirmatrelvir/ritonavir 	<ul style="list-style-type: none"> Breast milk nirmatrelvir PK parameters: C_{max}, T_{max}, AUC_{τ}, $t_{1/2}$, C_{av}, Ae_{τ}, $Ae_{\tau}\%$, and CL_{bm} (breast milk clearance)
Secondary:	Secondary:
<ul style="list-style-type: none"> To determine ritonavir concentrations in human breast milk following multiple oral BID dosing with nirmatrelvir/ritonavir To characterize plasma PK parameters of nirmatrelvir and ritonavir following multiple oral BID doses with nirmatrelvir/ritonavir in lactating women Estimate the infant daily dose that would result from nirmatrelvir and ritonavir secretion in breast milk following multiple oral BID doses with nirmatrelvir/ritonavir. To characterize the safety and tolerability of nirmatrelvir and ritonavir in lactating women. 	<ul style="list-style-type: none"> Breast milk ritonavir PK Parameters: C_{max}, T_{max}, AUC_{τ}, $t_{1/2}$, C_{av}, Ae_{τ}, $Ae_{\tau}\%$, and CL_{bm} Plasma nirmatrelvir and ritonavir PK parameters: C_{max}, C_{av}, C_{trough}, T_{max}, AUC_{τ}, C_{av}, C_{min}, $t_{1/2}$, CL/F and VzF. For both nirmatrelvir and ritonavir: Ae_{24bm}, $MPAUC_{\tau}$ and MPC_{max} during the dosing interval τ; CL_{bm}, M/P, $BWNID$, $BWNMD$, $BWNIDPCM$. Safety: TEAEs, clinical laboratory tests, vital signs, PE, and ECGs.

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, PK, multiple-dose study in 8 healthy lactating females who are actively breastfeeding and are documented PCR negative for COVID-19 infection at the time of enrollment to determine the amount of nirmatrelvir and ritonavir secreted in breast milk following multiple BID oral dosing in lactating women. In the event that participants

withdraw or are unable to express breast milk during a collection interval, additional participants may be recruited.

Participants will not be permitted to breastfeed their infant from the evening of the day prior to the first dose and for 72 hours (3 days) after the Day 2 dose. Participants must have a plan for feeding the infant during the time when the infant cannot breast feed. Though not a study requirement, participants may wish to express sufficient breast milk in advance of the study to cover the duration when breast feeding is not permitted (ie, when nursing is restricted during study participation).

Participants on Day 1 will receive one dose of nirmatrelvir/ritonavir in the morning and 1 dose in the evening and finally 1 dose of nirmatrelvir/ritonavir in the morning of Day 2. There will not be any dietary restrictions associated with dosing. After the Day 2 dose there will be collections of breast milk and plasma over 48 hours to characterize the PK of nirmatrelvir and ritonavir in this population.

Potential participants will be screened within 28 days prior to study treatment (Days -28 to Day -2). All participants who meet the eligibility criteria check into the CRU on Day -1 at a time convenient to the participant and the CRU and receive the Day 1 and Day 2 doses every 12 hours and reside at the CRU until the morning of Day 4 (ie, 48 hours after the Day 2, morning dose).

Participants will be discharged from the CRU on the morning of Day 4 (48 hours after the Day 2 dose) and may begin to breast feed their infant 72 hours (3 days) after the Day 2 dose. Participants will be given a note card reminding them when they can resume breast feeding. Study treatment and sample collection are displayed in Table 1. Administration of the study medication is further described in [Section 6.1.1](#).

Participants must confirm that they will not breastfeed their infant from the evening of the day prior to the first dose and for 72 hours after the last dose and conform to the study protocol.

Table 1. Study Treatment and sample collection

Day 1:	Two tablets of 150 mg nirmatrelvir and 1 tablet of 100 mg ritonavir q12h for 2 doses. Collect pre dose blood and breast milk.
Day 2:	Two tablets of 150 mg nirmatrelvir and 1 tablet of 100 mg ritonavir in the morning. Collect blood and breast milk for 12 hours as outlined in SoA .
Day 3:	Collect 12 to 24, 24 to 32 and 32-to-40-hour breast milk samples. Collect 18, 24, 32, 40-hour blood samples.
Day 4	Collect 40-to-48-hour breast milk samples. Participants may begin to breast feed their infant 72 hours (3 days) after the last nirmatrelvir/ritonavir dose on Day 2. At this time, more than 7 half-lives will have elapsed in the average participant, and >99% of nirmatrelvir and ritonavir would have been eliminated from the average participant's body and breast milk. Collect 48-hour plasma sample.

Following the Day 2 dose, plasma and breast milk will be collected for 48 hours to characterize the nirmatrelvir and ritonavir PK. Safety and tolerability will be assessed by

clinical monitoring and includes adverse event monitoring, clinical safety laboratory assessments, and supine vital sign measurements.

If a participant has any clinically significant, study related abnormalities at the conclusion of a scheduled inhouse 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

Breastfeeding women were not included in the nirmatrelvir/ritonavir clinical development program. So, there is no data available to assess the effects of nirmatrelvir/ritonavir on the breastfed infant or on breast milk excretion. The purpose of this study is to assess penetration of nirmatrelvir and ritonavir in human breast milk. The objective is to measure the concentration of nirmatrelvir and ritonavir breast milk in healthy women.

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data are limited for nirmatrelvir, 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](#)).

4.2.2. Collection of Retained Research Samples

Retained Research Samples will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.3. Justification for Dose

The dose of 300 mg nirmatrelvir/100 mg ritonavir BID will be given based on efficacy demonstrated in Phase 3 clinical trials. Nirmatrelvir/ritonavir is given over 5 days for treating the COVID-19, to this end excretion of nirmatrelvir/ritonavir in breast milk at steady state is being assessed.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the [SoA](#) for the last participant in the trial globally.

A participant is considered to have completed the study if she has completed the study, including the last scheduled procedure shown in the [SoA](#).

5. STUDY POPULATION

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

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Healthy lactating females who are actively breast-feeding or expressing breast milk, who are at least 12 weeks post-partum and not currently pregnant, and must be 18 to 55 years of age, inclusive, at the time of signing the ICD.
 - Refer to [Appendix 4](#) for reproductive criteria ([Section 10.4.2](#)).

Type of Participant and Disease Characteristics:

2. Female participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, vital signs and 12-lead ECGs.
3. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
4. Female participants of childbearing potential must have a negative pregnancy test.

Weight:

5. BMI of minimum 17.5 kg/m²; and a total body weight >50 kg (110 lb).

Informed Consent:

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

Other Inclusions:

7. Participants must have determined a plan for feeding the infant during the time when the infant cannot breastfeed. Though not a study requirement, participants may wish to express sufficient breast milk in advance of the study to cover the duration when breastfeeding is not permitted (ie, when nursing is restricted during study participation).

8. Infants of women enrolled in the study must be able to feed successfully from a bottle or other age-appropriate alternative feeding method (eg, cup, syringe, finger-feeder, paladai, etc.) prior to the start of the study and must be able to tolerate infant formula if the participant does not have a supply of stored breast milk sufficient to cover the duration of the study (ie, when nursing is restricted during study participation).
9. Participants must be willing to temporarily discontinue breastfeeding their infants for a total of 4.5 days (approximately 108 hours), ie, from the evening of the day before Day 1 through to 72 hours after the last dose (approximately 8 AM the morning of Day 5). Participants must be willing to regularly pump breasts throughout the study and express breast milk according to a schedule designed to maintain lactation throughout the study period.
10. Participants must agree that breast milk expressed following nirmatrelvir/ritonavir administration through 72 hours after the last nirmatrelvir/ritonavir dose will not be fed to any infant.
11. Participants must be able to express at least 14 mL of breast milk over a 2-hour interval prior to the dose on Day 1.
12. Participants must be willing to use an electric breast pump.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Positive test result (RT-PCR) for SARS-CoV-2 infection at the time of screening or Day -1.
2. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).
3. 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, underlying structural heart disease, Wolff Parkinson-White syndrome).
4. Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).
5. History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, or HCVAb. Hepatitis B vaccination is allowed.

6. History of febrile illness or mastitis within 5 days prior to the first dose of study medication.
7. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality, or other conditions or situations related to COVID-19 pandemic (eg, contact with positive case, residence, or travel to an area with high incidence) that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

8. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Refer to [Section 6.8 Concomitant Therapy](#) for additional details.
 - Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of nirmatrelvir/ritonavir and during study treatment.
9. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s). Refer to [Section 6.8 Concomitant Therapy](#).

Prior/Concurrent Clinical Study Experience:

10. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s). Refer to [Section 6.8 Concomitant Therapy](#).
11. Participants who have received a COVID-19 vaccine within 7 days before screening or admission, or who are to be vaccinated with a COVID-19 vaccine at any time during the study confinement period.

Diagnostic Assessments:

12. A positive urine drug test.
13. Screening supine BP ≥ 140 mm Hg (systolic) or ≥ 90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥ 140 mm Hg (systolic) or ≥ 90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.
14. Baseline standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTcF interval >450 msec, complete LBBB, signs of an acute or -indeterminate age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia,

second or -third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >450 msec, this interval should be -rate corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility. -Computer interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

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

- AST **or** ALT level $\geq 1.25 \times \text{ULN}$;
- Total bilirubin level $\geq 1.5 \times \text{ULN}$; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is $\leq \text{ULN}$.

Other Exclusions:

16. 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 4 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).
17. Use of tobacco or nicotine containing products in excess of the equivalents of 5 cigarettes per day or 2 chews of tobacco per day.
18. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.
19. History of sensitivity to heparin or -heparin induced thrombocytopenia.
20. Unwilling or unable to comply with the criteria in the [Lifestyle Considerations](#) section of this protocol.
21. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.
22. History of sensitivity reactions to nirmatrelvir or ritonavir, or any of the formulation components of nirmatrelvir or ritonavir.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the pre dose PK sample.
- Water is permitted until 1 hour prior to study intervention administration. Water may be consumed without restriction beginning 1 hour after dosing except water consumed during breakfast if administration of the morning dose will occur at fed state for Days 1 & 2. 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 dosing.
- Dinner will be provided approximately 9 to 10 hours after 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.
- No meal restriction on dosing days on Days 1 & 2.

5.3.2. 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 study PK sample.
- Participants will abstain from alcohol for 24 hours prior (except as stated above for red wine) to admission to the CRU and continue abstaining from alcohol until collection of the final study PK sample. 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.

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.
- In order to standardize the conditions on PK sampling days on Days 2, participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements) during the first 4 hours after the morning dose on Day 2.

5.3.4. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and her partner from the permitted list of contraception methods (see [Appendix 4 Section 10.4.2](#)) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the [SoA](#), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception) considering that their risk for pregnancy may have changed since the last visit. In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Screen failure data are collected and remain as source and are not reported on the CRF.

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

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to nirmatrelvir and ritonavir.

6.1. Study Intervention(s) Administered

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

Commercially available 100 mg ritonavir tablets will be supplied by the CRU.

6.1.1. Administration

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

Participants should take study medication at approximately 08:00 and 20:00 hours (plus or minus 2 hours).

Nirmatrelvir and ritonavir will be dosed simultaneously (within no more than 5 minutes of each other, starting with nirmatrelvir). Investigator site personnel will administer study intervention with ambient temperature water to a total volume of approximately 240 mL. Additional water (50 mL) may be given to participants, as needed, to help ingestion of study interventions. Participants will swallow all tablet formulations whole and will not manipulate or chew the study intervention prior to swallowing.

In order to standardize the conditions on PK sampling days on Days 2, all participants will be required to refrain from lying down (except when required for BP, PR, and ECG measurements) during the first 4 hours after the morning dose on Day 2.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.
3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the PCRU local/site procedures.
4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.
5. Study interventions should be stored in their original containers.

6. Site staff will instruct participants on the proper storage requirements for take-home study intervention.
7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.
8. Further guidance and information for the final disposition of unused study interventions are provided in the PCRU's 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, participant in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

Nirmatrelvir 150 mg and ritonavir 100 mg 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. Measures to Minimize Bias:

6.3.1. Allocation to Study Intervention

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

The investigator will assign participant numbers to the participants as they are screened for the study. 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. Study Intervention Compliance

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

6.5. Dose Modification

No dose modification is anticipated.

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

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

6.7. Treatment of Overdose

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

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of nirmatrelvir/ritonavir (whichever is longer).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE**.
5. Obtain a blood sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

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

6.8. Concomitant Therapy

Participants will abstain from all concomitant treatments, except for the treatment of adverse events and hormonal contraceptives that meet the requirements of this study in participants who are WOCBP (see [Appendix 4](#)).

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.

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 28 days prior to dosing of investigational product. 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 as per the [SoA](#).

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

6.8.1. Rescue Medicine

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- 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

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

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

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

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include serum BUN, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If ≥ 2 healthy participants are noted to have 2 consecutive SCr results of ≥ 0.3 mg/dL (or ≥ 26.5 $\mu\text{mol/L}$), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

7.2. Participant Discontinuation/Withdrawal From the Study

- A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:
- Refused further 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, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow up

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

Study procedures and their timing are summarized in the [SoA](#). Protocol waivers or exemptions are not allowed.

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

Adherence to the study design requirements, including those specified in the [SoA](#), is essential and required for study conduct.

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

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

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

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (PR 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 112 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 30 consecutive days.

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

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

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

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

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

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

8.2.2. Vital Signs

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

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

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

8.2.2.1. Temperature

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

8.2.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the [SoA](#) section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

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

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

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

ECG values of potential clinical concern are listed in [Appendix 7](#).

8.2.4. Clinical Safety Laboratory Assessments

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

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

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

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

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

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

8.2.5. COVID-19 specific assessments

Participants will be checked for recent exposure to positive case, COVID-19 related signs and symptoms. Participants will be tested for SARS-COV-2 infection by PCR prior to being admitted to the clinic for confinement and a subsequent COVID-19 test may be performed if they develop COVID-19 like symptoms. Additional testing may be required by local regulations or by the Principal Investigator.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the [SoA](#). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.2.7. Nursing Mother Questionnaire

The Nursing Mother Questionnaire should be conducted at Screening and can be found in [Appendix 8](#).

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

The definitions of an AE and an SAE can be found in [Appendix 3](#).

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

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

During the active collection period as described in Section 8.3.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

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

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

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

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-Up of AEs and SAEs

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

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

Further information on follow-up procedures is given in [Appendix 3](#).

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.3.5.1. Exposure During Pregnancy

- An EDP occurs if:
- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:
 - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion.

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

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

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures

for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- The participant is found to be breastfeeding while receiving or less than 72 hours after discontinuing study intervention.
- The participant is found to be breastfeeding while being exposed or having been exposed to study intervention within 72 hours (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion.

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

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

8.3.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form regardless of

whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form must be maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

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

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

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

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

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

Medication errors include:

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

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

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

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

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

8.4. Pharmacokinetics

8.4.1. Breast Milk for Analysis of nirmatrelvir and ritonavir

Breast milk samples will be collected for measurement of breast milk concentrations of nirmatrelvir and ritonavir as specified in the [SoA](#). Instructions for the collection and handling of biological samples will be provided in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.

Breast milk samples will be used to evaluate the PK of nirmatrelvir and ritonavir. Samples collected for analyses of nirmatrelvir and 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 breast milk samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples collected for measurement of breast milk concentrations of nirmatrelvir and 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 amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.4.2. Plasma for Analysis of nirmatrelvir and ritonavir

Blood samples of approximately 4 mL, to provide approximately 1.5 mL plasma, will be collected for measurement of plasma concentrations of 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.

Samples will be used to evaluate the PK of nirmatrelvir and ritonavir. Samples collected for analyses of nirmatrelvir and 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 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 nirmatrelvir and 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 amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.5. Genetics

8.5.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.5.2. Retained Research Samples for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected according to the [SoA](#), as local regulations and IRBs/ECs allow.

Retained Research Samples may be used for research related to the study intervention(s) and safety biomarkers. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

See [Appendix 5](#) for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual and other supporting documents.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.6.1. Specified Gene Expression (RNA) Research

Specified gene expression (RNA) research is not included in this study.

8.6.2. Specified Protein Research

Specified protein research is not included in this study.

8.6.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.6.4. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study:

- 10 mL whole blood (Prep B2 optimized for serum;).

Retained Research Samples will be collected as local regulations and IRB/ECs allow according to the [SoA](#).

Retained Research Samples may be used for research related to the study intervention(s) and safety biomarkers. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

See [Appendix 5](#) for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual and other supporting documents.

8.7. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.8. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

There are no statistical hypotheses for this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
PK Concentration	The PK concentration population is defined as all participants randomly assigned to study intervention and who take at least 1 dose of nirmatrelvir/ritonavir and in whom at least 1 concentration value is reported.
PK Parameter	The PK parameter analysis population is defined as all participants assigned to study intervention and who take at least 1 dose of nirmatrelvir/ritonavir and in whom at least 1 of the PK parameters of interest is reported
Safety Analysis Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

9.3. Statistical Analyses

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

9.3.1. Derivation of Pharmacokinetic Parameters

Breast milk and plasma PK parameters of nirmatrelvir and ritonavir will be derived (as data permit) from the concentration-time data using standard noncompartmental methods as

outlined in Table 2. Actual PK sampling times will be used in the derivation of PK parameters when available, otherwise nominal times will be used. For the breast milk data, the midpoint (ie, 1 hour for a 0–2-hour collection) of each breast milk collection interval will be used as the time variable.

In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

The PK parameters for nirmatrelvir and ritonavir will be derived from the concentration time profiles (plasma and breast milk) as detailed in Table 2. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters. The maternal breast milk PK parameters shown in Table 3 will be calculated for each participant where possible. For breast milk, the concentration-time profile consists of the observed concentrations and the midpoints for each collection interval.

Table 2. Plasma and Breast Milk Nirmatrelvir and Ritonavir PK Parameters Definitions

Parameter	Definition	Method of Determination
Plasma and Breast Milk		
AUC_{τ}^a	Area under the concentration-time curve at steady state over the dosing interval	Linear trapezoidal method
AUC_{last}	Area under the concentration-time curve from 0 to time of last measurable concentration	Linear/Log trapezoidal method
C_{max}	Maximum observed concentration	Observed directly from data
T_{max}	Time to reach C_{max}	Observed directly from data as time of first occurrence
$t_{1/2}^a$	Terminal phase half-life	$\log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
Plasma Only		
C_{min}	Minimum observed concentration	Observed directly from data
C_{av}	Average concentration	AUC_{τ}/τ
CL/F	Apparent clearance of drug from eg, plasma	$Dose/AUC_{\tau}$
V_z/F	Apparent volume of distribution	$Dose/(AUC_{\tau} \cdot k_{el})$
Breast Milk Only		
Ae_{rbm}	Amount excreted in breast milk over the dosing interval τ (12 hours)	Sum of (breast milk concentration * sample volume ^c) for each collection interval from 0 to 12 hours postdose.
$Ae_{rbm}\%$	Percent of dose excreted in breast milk during the dosing interval τ	$100 \cdot (Ae_{\tau}/Dose)$
CL_{bm}	Breast milk clearance	$Ae_{rbm}/\text{plasma } AUC_{\tau}$

a. If data permit

Table 3. Parameters for Estimation of Absolute and Relative Infant Dose

Parameter	Definition	Method of Determination
Ae_{24bm}	Daily (24 hour) amount of nirmatrelvir excreted in breast milk	$2 * Ae_{rbm}$
$MPAUC_{\tau}$	Breast milk to plasma ratio for AUC_{τ}	$AUC_{\tau} \text{ (breast milk)}/AUC_{\tau} \text{ (plasma)}$
MPC_{max}	Breast milk to plasma ratio for C_{max}	$C_{max} \text{ (breast milk)}/C_{max} \text{ (plasma)}$
BWNID ^a	Body weight normalized infant dose in $\mu\text{g/kg/day}$	$MPAUC_{\tau} * C_{av} * 150 \text{ mL/kg/day}$, where 150 mL/kg/day is the standardized milk consumption for an infant
BWNMD	Body weight normalized maternal dose in $\mu\text{g/kg/day}$	Maternal dose in $\mu\text{g/day}$ (150 mg BID = 300000 $\mu\text{g/day}$)/maternal weight in kg at Screening
BWNIDPCM ^b	Infant dose expressed as % of body weight normalized maternal dose	$100 * BWNID/BWNMD$

a. The absolute infant dose

b. The relative infant dose

9.3.2. Statistical Methods for Pharmacokinetic Data

Concentrations for nirmatrelvir and ritonavir in plasma and breast milk will be listed. Plasma and breast milk concentrations will be listed and summarized descriptively by nominal PK sampling time, respectively. PK parameters for breast milk and plasma will be listed and summarized using descriptive statistics utilizing all participants for whom a valid PK parameter can be calculated and reported.

Individual participant and summary profiles (mean and median plots) concentration time data will be plotted by analyte using actual (for individual) and nominal (for mean and median) times respectively. Mean and median profiles will be presented on both linear and semi-log scales. Plots of AUC_{τ} , C_{max} , and C_{av} will be presented for each analyte comparing the PK parameters in breast milk versus those in plasma. Additional specifications about the tables, listings, and figures will be outlined in the SAP.

For comparison AUC_{τ} , C_{max} , and C_{av} plots of these parameters will be plotted by body fluid for each analyte (plasma and breast milk PK parameters on 1 plot). Additional specifications about the tables, listings, and figures will be outlined in the SAP.

9.3.3. Other Safety Analyses

All safety analyses will be performed on the safety population.

Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history (prior illegal drug, alcohol, and tobacco use, as well as blood donation within prior 60 days) 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 including participant race, ethnicity, age, and gender collected at screening will be reported.

9.3.4. Other Analyse(s)

Pharmacogenomic or biomarker data from Retained Research Samples may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.4. Interim Analyses

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

9.5. Sample Size Determination

The study has not been powered for any formal hypothesis testing. The sample size of 8 participants at minimum is expected to provide adequate PK data to characterize nirmatrelvir and ritonavir concentrations in breast milk. In the event that participants withdraw or are unable to express breast milk during a collection interval, additional participants may be recruited. Based on descriptive statistics for nirmatrelvir from a previous study (C4671019), 8 participants would provide expected 90% confidence intervals for AUC_{inf} and C_{max} of (10613, 63006) and (481, 6910), respectively. This is based on a means (%CVs) of AUC_{inf} 36810 ng.hr/mL (36%) and 3696 ng.hr/mL (44%), respectively.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

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

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

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

10.1.2. Financial Disclosure

Not applicable.

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

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

10.1.4. Data Protection

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use a DMC.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data sharing

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

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

10.1.7. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.8. 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 source data and its origin can be found in the Source Document Locator, which is maintained by the sponsor's designee (Pfizer Clinical Research Unit).

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

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

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

10.1.9. Study and Site Start and Closure

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

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

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

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

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

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

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

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

10.1.10. Publication Policy

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

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

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

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

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

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

10.1.11. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (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 investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant.

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 4. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN and creatinine	<u>Local Dipstick:</u>	<ul style="list-style-type: none"> • SARS-CoV-2 RT-PCR • Urine drug screening^b • Pregnancy test (β-hCG)^c • eGFR (CKD-EPI 2021)
Hematocrit	Glucose (fasting)	pH ^d	
RBC count	Calcium	Glucose (qual)	
MCV	Sodium	Protein (qual)	
MCH	Potassium	Blood (qual)	
MCHC	Chloride	Ketones	<u>Coagulation:</u>
Platelet count	Total CO ₂ (bicarbonate)	Nitrites	<ul style="list-style-type: none"> • aPTT • PT-INR • Fibrinogen
WBC count	AST, ALT	Leukocyte esterase	
Total neutrophils (Abs)	Total bilirubin		
Eosinophils (Abs)	Alkaline phosphatase	<u>Laboratory:</u>	<u>At screening only:</u>
Monocytes (Abs)	Uric acid	Microscopy ^a	<ul style="list-style-type: none"> • HBsAg • HbsAb^e • HBcAb • HCVAb • HIV
Basophils (Abs)	Albumin		
Lymphocytes (Abs)	Total protein		

- Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
- The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
- Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-hCG for female participants of childbearing potential.
- Can be performed on dipstick or pH-meter device.
- HBsAb may be routinely tested or only if HBsAg and/or HBcAb are positive. HBsAb due to vaccination is permissible.

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
<ul style="list-style-type: none">• 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
<ul style="list-style-type: none">• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:<ul style="list-style-type: none">• Is associated with accompanying symptoms;• Requires additional diagnostic testing or medical/surgical intervention;• Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.• Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
<ul style="list-style-type: none"> 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 1 or more of the criteria listed below:
a. Results in death
<p>b. Is life-threatening</p> <p>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.</p>
<p>c. Requires inpatient hospitalization or prolongation of existing hospitalization</p> <p>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.</p> <p>Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.</p>

<p>d. Results in persistent or significant disability/incapacity</p> <ul style="list-style-type: none"> 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.
<p>e. Is a congenital anomaly/birth defect</p>
<p>f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious.</p> <p>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.</p>
<p>g. Other situations:</p> <ul style="list-style-type: none"> 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
<p>The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2)</p>

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

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

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF.	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE). **
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB).	None. Exposure to a study non-participant is not collected on the CRF.	The exposure (whether or not there is an associated AE or SAE) must be reported.***

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

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

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

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

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

Assessment of Intensity

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

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as “related to study intervention” for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

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

- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Female Participant Reproductive Inclusion Criteria

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

- Is not a WOCBP (surgically sterilized or ovarian failure).

OR

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

A WOCBP agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.2. Contraception Methods

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

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
 2. Intrauterine device.
 3. Intrauterine hormone-releasing system.
 4. Bilateral tubal occlusion (eg, bilateral tubal ligation).
 5. Vasectomized partner.
- A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has

been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.
 - Oral;
 - Intravaginal;
 - Transdermal;
 - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation.
 - Oral;
 - Injectable.
8. Sexual abstinence.
 - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to study intervention or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in the CSR or in a separate study summary or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
 - Retained samples will be stored indefinitely or for another period as per local requirements.
- Participants may withdraw their consent for the storage and/or use of their Retained Research Samples at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.
- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values $>3 \times \text{ULN}$ AND a TBili value $>2 \times \text{ULN}$ with no evidence of hemolysis and an alkaline phosphatase value $<2 \times \text{ULN}$ or not available.
- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
- Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND $>3 \times \text{ULN}$; or $>8 \times \text{ULN}$ (whichever is smaller).
- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least $1 \times \text{ULN}$ **or** if the value reaches $>3 \times \text{ULN}$ (whichever is smaller).

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

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

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

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
<ul style="list-style-type: none"> Marked sinus bradycardia (rate <40 bpm) lasting minutes. New PR interval prolongation >280 msec. New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs
<ul style="list-style-type: none"> QTcF prolongation >500 msec. New ST-T changes suggestive of myocardial ischemia. New-onset left bundle branch block (QRS >120 msec). New-onset right bundle branch block (QRS >120 msec). Symptomatic bradycardia. Asystole: <ul style="list-style-type: none"> In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node. In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer. Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm. Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

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

10.8. Appendix 8: Nursing Mother Questionnaire

1. Number of pregnancies:
2. Number of live births including the current child:
3. Date of last childbirth delivery (dd-MMM-yyyy):
4. Duration of current lactation:
5. Have you breastfed in the past?
 - (1) Yes
 - (2) No
6. If yes to question 5, please list the length of time in (weeks) that you breastfed each child.

Child 1: weeks

Child 2: weeks

Child 3: weeks

Child 4: weeks

Child 5: weeks

Child 6: weeks

Child 7: weeks

Child 8: weeks

Child 9: weeks

Child 10: weeks
7. Number of days since weaning your current child: days

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
3CL	3C-like protein
Abs	absolute
ADL	activities of daily living
AE	adverse event
Ae_{24bm}	daily (24 hour) amount of nirmatrelvir excreted in breast milk
$Ae_{\tau bm}$	amount excreted in breast milk over the dosing interval τ (12 hours)
$Ae_{\tau bm\%}$	percent of amount excreted in breast milk over the dosing interval τ (12 hours)
Ae_{τ}	dose excreted in breast milk during the dosing interval τ
$Ae_{\tau\%}$	percent of dose excreted in breast milk during the dosing interval τ
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\tau}$	area under the curve to the end of the dosing period
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from 0 to time of last measurable concentration
AUC_{τ}	area under the concentration-time curve at steady state over the dosing interval τ
β -hCG	β -human chorionic gonadotropin
BID	twice a day
BM	breast milk
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
BWNID	body weight normalized infant dose in $\mu\text{g/kg/day}$
BWNIDPCM	infant dose expressed as % of body weight normalized maternal dose
BWNMD	body weight normalized maternal dose in $\mu\text{g/kg/day}$
C_{av}	average concentration
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	total clearance of drug from eg, plasma
C_{last}	last quantifiable concentration

Abbreviation	Term
CL _{bm}	breast milk clearance
CL/F	Apparent clearance of drug from eg, plasma
C _{max}	maximum observed concentration
C _{min}	minimum observed concentration
CO ₂	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial
C _{trough}	pre dose concentration
CYP	cytochrome P450
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FIH	first-in-human
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IQMP	Integrated Quality Management Plan
IRB	institutional review board
IV	intravenous(ly)

Abbreviation	Term
LBBB	left bundle branch block
LFT	liver function test
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MERS	Middle East respiratory syndrome
MP	maternal plasma
M/P	milk to plasma ratio
MPAUC _t	milk to plasma ratio for AUC _t
MPC _{max}	milk to plasma ratio for C _{max}
M ^{pro}	main protease
N/A	not applicable
NHP	non-human primate
NOAEL	no-observed-adverse-effect-level
PCR	polymerase chain reaction
PCRU	Pfizer Clinical Research Unit
PD	pharmacodynamic(s)
PE	physical examination
PK	pharmacokinetic(s)
PR	pulse rate
PT	prothrombin time
q12h	every 12 hours
QTc	corrected QT interval
QTcF	the corrected QT interval by Fridericia
QTL	quality tolerance limit
RBC	red blood cell
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCr	serum creatinine
SE	supratherapeutic exposure
SmPC	summary of product characteristics
SoA	schedule of activities
SoC	standard of care
SOP	standard operating procedure
SRSD	single-reference safety document
SUSAR	Suspected Unexpected Serious Adverse Reaction
t _{1/2}	terminal phase half-life
TBili	total bilirubin

Abbreviation	Term
TEAE	treatment-emergent adverse event
T _{max}	time to reach C _{max}
ULN	upper limit of normal
US	United States
V _z /F	apparent volume of distribution for extravascular dosing
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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