# A PHASE 1, OPEN-LABEL, RANDOMIZED, SINGLE-DOSE, CROSSOVER STUDY TO ESTIMATE THE RELATIVE BIOAVAILABILITY OF PF-07321332/RITONAVIR ORAL POWDER IN 3 DIFFERENT DELIVERY VEHICLES RELATIVE TO THE COMMERCIAL PF-07321332/RITONAVIR TABLETS IN HEALTHY ADULT PARTICIPANTS UNDER FASTED CONDITIONS

| | |
|---|---|
| **Study Intervention Number:** | PF-07321332 |
| **Study Intervention Name:** | NA |
| **US IND Number:** | CCI |
| **EudraCT Number:** | NA |
| **ClinicalTrials.gov ID:** | NA |
| **Protocol Number:** | C4671024 |
| **Phase:** | 1 |

**Brief Title:** A Phase 1 Relative Bioavailability Study of PF-07321332/Ritonavir Oral Powder Relative to the Commercial Tablets in Healthy Participants

## Document History

| Document | Version Date |
|---|---|
| Original protocol | 09 February 2022 |

## TABLE OF CONTENTS

CCI [redacted]

CCI [redacted]

## LIST OF TABLES

# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

**Brief Title:** A Phase 1 Relative Bioavailability Study of PF-07321332/Ritonavir Oral Powder Relative to the Commercial Tablets in Healthy Participants.

### Rationale

PF-07321332 is a potent and selective inhibitor of the SARS-CoV-2 $M^{pro}$ that is currently being developed as an oral treatment of COVID-19. Ritonavir is a strong CYP3A4 inhibitor being used to inhibit the metabolism of PF-07321332 in order to increase plasma concentrations of PF-07321332 to values that are efficacious. The clinical development program for PF-07321332 includes 8 completed clinical studies: five Phase 1 studies in healthy participants (C4671001, C4671012, C4671013, C4671014 and C4671015), one Phase 1 study in renal impairment participants (C4671011), one Phase 1 study in hepatic impairment participants (C4671010) and one Phase 2/3 pivotal study in COVID-19 patients (C4671005).

The purpose of this study is to estimate the rBA of PF-07321332/ritonavir oral powder relative to the commercial tablet formulation under fasted condition in healthy adult participants. The study will also assess the effect of 3 different food vehicles on the rBA of the PF-07321332/ritonavir oral powder formulation as well as the safety, tolerability, and palatability of PF-07321332/ritonavir oral powder in healthy adult participants.

## Objectives and Endpoints

| Primary Objective: | Primary Endpoint: |
|---|---|
| • To estimate the rBA of the PF-07321332/ritonavir 300 mg/100 mg oral powder mixed with water compared to the PF-07321332/ritonavir commercial tablets under fasted conditions.<br>• To estimate the rBA of the PF-07321332/ritonavir 300 mg/100 mg oral powder mixed with applesauce compared to the PF-07321332/ritonavir commercial tablets under fasted conditions.<br>• To estimate the rBA of the PF-07321332/ritonavir 300 mg/100 mg oral powder mixed with vanilla pudding compared to the PF-07321332/ritonavir commercial tablets under fasted conditions. | • The ratio of $AUC_{last}$, $AUC_{inf}$ (if data permits) and $C_{max}$ of PF-07321332 and ritonavir. |
| **Secondary Objective:** | **Secondary Endpoints:** |
| • To evaluate the safety and tolerability of PF-07321332/ritonavir in healthy participants.<br>• To assess the palatability of PF-07321332/ritonavir oral powder mixed with water/applesauce/vanilla pudding. | • Assessment of TEAEs, clinical laboratory abnormalities, vital signs, PEs, and 12-lead ECGs.<br>• Assessment of palatability using via questionnaire: mouth feel, bitterness, tongue/mouth burn, throat burn and overall liking. |
| CCI [redacted] | [redacted] |
| [redacted] | [redacted] |

## Overall Design

### Brief Summary

This is a Phase 1, open-label, single-dose, randomized, crossover study in healthy adult participants to estimate rBA of PF-07321332/ritonavir 300 mg/100 mg oral powder mixed with 3 different delivery vehicles (Test formulations) compared to the PF-07321332/ritonavir commercial tablets (Reference formulation) under fasted conditions. The study will also assess the safety, tolerability, and palatability of PF-07321332/ritonavir oral powder in healthy adult participants.

The study will consist of 4 treatments: a single oral dose of PF-07321332/ritonavir 300 (2 × 150 mg)/100 mg tablets (Treatment A), a single oral dose of PF-07321332/ritonavir 300 mg/100 mg oral powder mixed in water (Treatment B), a single oral dose of PF-07321332/ritonavir 300 mg/100 mg oral powder mixed in applesauce (Treatment C) and a single oral dose of PF-07321332/ritonavir 300 mg/100 mg oral powder mixed in vanilla pudding (Treatment D). All treatments will be administered under fasted condition. Between each treatment, a minimum of 4 days washout is proposed to minimize any residual PF-07321332 and ritonavir concentrations prior to start of the next treatment.

Approximately 12 healthy male and/or female participants will be randomized to ensure at least 10 participants will complete the study. Participants who discontinue from the study for non-safety reasons may be replaced at the sponsor's discretion in collaboration with the investigator.

Healthy participants will be screened to determine eligibility within 28 days prior to study treatment. Medical history and results of PEs, vital signs, 12-lead ECGs, and clinical laboratory evaluations will determine eligibility. Eligible participants will be admitted to the PCRU on Day -1 and will be confined in the PCRU until discharge which is Day 4 of Period 4.

On Day 1 of each period, participants will receive a single oral dose of study interventions PF-07321332/ritonavir 300 mg/100 mg as per the randomization schedule. Study treatments will be administered with approximately 240 mL of ambient temperature water under fasted conditions (overnight fast and no food until 4 hours after dosing). Serial PK samples will be collected up to 72 hours post dose. Participants will be discharged from the PCRU on Period 4, Day 4 following completion of all assessments.

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

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

**Number of Participants**

Approximately 12 participants will be randomly assigned to study intervention such that approximately 3 participants will be enrolled into 1 of 4 sequences.

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 enrolled participant will participate in 4 study periods to receive 4 different treatments according to the sequence determined by randomization:

- Treatment A: Single oral dose of PF-07321332/ritonavir 300 mg (2 × 150 mg)/100 mg commercial tablets under fasted conditions (Reference)
- Treatment B: Single oral dose of PF-07321332/ritonavir 300 mg/100 mg oral powder mixed with water under fasted conditions (Test 1)
- Treatment C: Single oral dose of PF-07321332/ritonavir 300 mg/100 mg oral powder mixed with applesauce under fasted conditions (Test 2)
- Treatment D: Single oral dose of PF-07321332/ritonavir 300 mg/100 mg oral powder mixed with vanilla pudding under fasted conditions (Test 3)

Participants will be randomly assigned to 1 of 4 sequences as below:

| Treatment | Period 1 | Period 2 | Period 3 | Period 4 |
|---|---|---|---|---|
| **Sequence 1 (N =3)** | Treatment A | Treatment B | Treatment C | Treatment D |
| **Sequence 2 (N =3)** | Treatment B | Treatment D | Treatment A | Treatment C |
| **Sequence 3 (N =3)** | Treatment C | Treatment A | Treatment D | Treatment B |
| **Sequence 4 (N =3)** | Treatment D | Treatment C | Treatment B | Treatment A |

Between each treatment, a minimum of 4 days washout is proposed to minimize any residual PF-07321332 and ritonavir concentrations prior to start of the next treatment. Participants will be discharged on Day 4 of Period 4, following completion of all assessments.

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

**Data Monitoring Committee or Other Independent Oversight Committee:** No

**Statistical Methods**

Natural log transformed $AUC_{inf}$ (if data permits), $AUC_{last}$ and $C_{max}$ will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within a sequence as a random effect.

**Sample Size Determination**

A sample size of 12 participants will be sufficient to provide a reliable estimate of rBA and intrasubject variability of PF-07321332 and ritonavir. Participants who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

**Pharmacokinetics Analysis**

The PK concentration analysis set is defined as all participants who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported.

The PK parameter analysis set is defined as all participants who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of primary interest are reported.

PK parameters for PF-07321332 and ritonavir will be analyzed using standard noncompartmental method of analysis. Actual PK sampling times will be used in the derivation of PF-07321332 and ritonavir PK parameters when available, otherwise nominal times will be used. The PF-07321332 and ritonavir plasma PK parameters will be summarized descriptively by treatment and Day. Plasma concentrations will be listed and summarized descriptively by treatment, and nominal PK sampling time. Individual participant and summary profiles (mean and median plots) of the plasma concentration time data will be plotted using actual and nominal times, respectively.

To estimate relative bioavailability, natural log transformed $AUC_{inf}$ (if data permits), $AUC_{last}$ and $C_{max}$ values of PF-07321332 and ritonavir will be analyzed using a mixed effect model with sequence, period and treatment as fixed effect and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios.

**Palatability Assesment**

Participants will be asked to fill out the Palatability Questionnaire after administration for Treatments B, C and D. The Palatability Questionnaire will be administered at 1 (immediately after dosing), 5, 10, and 20 minutes after administration. Details about the Palatability Questionnaire are provided in Appendix 8 (Section 10.8).

**Safety Analysis**

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

## 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.

**SoA:**

| **Visit Identifier** Abbreviations used in this table may be found in Appendix 9 | **Screening[a]** | **Period 1** | | | | | **Period 2 and 3** | | | | **Period 4** | | | | **Follow-Up** | **Early Termination/ Discontinuation** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Days Relative to Day 1** | **Days -28 to -2** | **Day -1** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** | **28-35 Days[b]** | |
| Informed consent | X | | | | | | | | | | | | | | | |
| CRU Confinement[c] | | X | ® | ® | ® | ® | ® | ® | ® | ® | ® | ® | ® | X | | X |
| Inclusion/exclusion criteria | X | X | | | | | | | | | | | | | | |
| Medical/medication history (update)[d] | X | X | | | | | | | | | | | | | | |
| Demography[e] | X | | | | | | | | | | | | | | | |
| PE[f] | X | X | | | | | | | | | | | | | | |
| Safety laboratory[g] | X | X | | | | | | | | | | | | X | | X |
| FSH[h] | X | | | | | | | | | | | | | | | |
| Urine drug testing[i] | X | X | | | | | | | | | | | | | | |
| Serology: HBsAg, HBsAb, HBcAb, HCVAb, and HIV[j] | X | | | | | | | | | | | | | | | |
| Pregnancy test (WOCBP only) | X | X | | | | | | | | | | | | X | | X |
| Contraception check[k] | X | X | | | | | | | | | | | | | X | |
| 12-lead ECG (single)[l] | X | | X[m] | | | | | | | | | | | X | | X |
| Vital signs (BP/PR)[n] | X | | X | | | | X | | | | X | | | X | | X |
| COVID-19 questionnaire[o] | X | X | | | | | | | | | | | | | | |
| COVID-19 testing[p] | X | X | | | | X | | | | | | | | | | |
| COVID-19 check temperature[q] | X | X | | | | | | | | | | | | | | |

| **Visit Identifier** Abbreviations used in this table may be found in Appendix 9 | **Screening[a]** | **Period 1** | | | | | **Period 2 and 3** | | | | **Period 4** | | | | **Follow-Up** | **Early Termination/ Discontinuation** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Days Relative to Day 1** | **Days -28 to -2** | **Day -1** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** | **28-35 Days[b]** | |
| PF-07321332/ritonavir dosing[r] | | | X | | | | X | | | | X | | | | | |
| Palatability Questionnaire[s] | | | X | | | | X | | | | X | | | | | |
| PK Blood Sampling for PF-07321332/ ritonavir[t] | | | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| CCI [redacted] | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| Serious and nonserious AE monitoring | X | ® | ® | ® | ® | ® | ® | ® | ® | ® | ® | ® | ® | ® | X | X |
| Concomitant treatments | X | X | X | ® | ® | ® | ® | ® | ® | ® | ® | ® | ® | X | | X |
| CRU discharge | | | | | | | | | | | | | | X | | |

a. Screening will be performed within 28 days prior to the first dose of PF-07321332/ritonavir.
b. Follow-up contact may occur via telephone contact and must occur 28 to 35 days from administration of the final dose of study intervention.
c. Participants will be admitted to the CRU on Day -1. Participants will be discharged on Period 4 Day 4 following the final assessments.
d. Medical history will include a history of prior illegal drug, alcohol, and tobacco use, as well as blood donation within prior 60 days. Medical history will be recorded at Screening and updated on Period 1 Day -1.
e. Demographics will include participant race, ethnicity, age, and gender during the Screening visit.
f. PE will be performed by trained medical personnel at the investigator site at Screening or Period 1 Day -1 only (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.
g. Safety laboratory assessments including urinalysis, hematology, chemistry and coagulation will be performed at Screening, Period 1 Day -1, Period 4 Day 4, and early termination/discontinuation if applicable. 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.
h. For confirmation of postmenopausal (amenorrheic for at least 12 consecutive months) female participants.
i. Urine drug (mandatory) and alcohol breath test (at discretion of investigator) will be performed at Screening and on Period 1 Day -1. These tests may be performed at any other time at the discretion of the investigator.
j. HBsAb will be tested if HBsAg and/or HBcAb are positive.
k. 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.
l. Single 12-lead ECG readings approximately will be taken at specified time point. All ECG assessments will be made after at least a 5-minute rest in a supine position and prior to any blood draws or vital sign measurements.
m. This will be done predose of Period 1 Day 1.

| Visit Identifier<br>Abbreviations used in this table may be found in Appendix 9 | Screening[a] | Period 1 | | | | | Period 2 and 3 | | | | Period 4 | | | | Follow-Up | Early Termination/ Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Days Relative to Day 1** | **Days -28 to -2** | **Day -1** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** | **28-35 Days[b]** | |

n. Single supine BP and PR will be performed following at least a 5-minute rest in a supine position, at specified time point. BP, and PR assessments will be performed after collection of ECGs and prior to collection of blood draws if scheduled at the same time. Vital signs will be done predose of Period 1 Day 1, and 2 hours and 6 hours post dose on Day1 of each treatment period and also on Day 4 of Period 4.
o. Check exposure to positive participant, residence or travel in area of high incidence and COVID-19 related signs and symptoms.
p. The testing for COVID-19 pathogen by RT-PCR will be performed at the specified time points and an additional SARS-CoV-2 test will also be performed after 4 days (ie, upon completion of 4 × 24 hours in the PCRU), ie, Period 1 Day 4. Additional testing for COVID-19 pathogen will also be done as per local requirements or by the principle investigator.
q. Temperature measurements may be done more frequently as clinically warranted.
r. PF-07321332/ritonavir will be administered orally after overnight fasting on Day 1 of each treatment period. There will be at least a 4-day washout between each dose.
s. Review taste questionnaire and instructions with participants prior to the first taste assessment to Treatment B, C, D, on Period 1, Day 1. Each participant will record the sensory attributes at timed intervals of 1 (immediately after dosing), 5, 10 and 20 minutes after swallowing the suspension, using a Taste Assessment Questionnaire (see Appendix 8)
t. One (approximately 4 mL) blood sample for PK analysis of PF-07321332 and ritonavir will be taken at the designated time points. See PK sampling schema in table below.

[redacted]

## Pharmacokinetic Sampling Schema

| Visit Identifier | Treatment Period 1 to 4 | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **Day 1** | | | | | | | | | | | | **Day 2** | **Day 3** | **Day 4** |
| **Planned Hours Post Dose on That Day** | **0** | **0.5** | **1** | **1.5** | **2** | **2.5** | **3** | **4** | **6** | **8** | **12** | **16** | **24** | **48** | **72** |
| PK blood sampling for PF-07321332/ritonavir | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| CCI [redacted] | | | [redacted] | | [redacted] | | [redacted] | [redacted] | | [redacted] | [redacted] | | | | |
| [redacted] | | | | | [redacted] | | | | | | | | | | |

CCI [redacted]

# 2. INTRODUCTION

PF-07321332 is a potent and selective inhibitor of the SARS-CoV-2 $M^{pro}$ that is currently being developed as an oral treatment of COVID-19. Ritonavir is a strong CYP3A4 inhibitor being used to inhibit the metabolism of PF-07321332 in order to increase plasma concentrations of PF-07321332 to values that are efficacious.

## 2.1. Study Rationale

The purpose of this study is to estimate the rBA of PF-07321332/ritonavir oral powder in 3 different delivery vehicle relative to the commercial tablet formulation under fasted condition in healthy adult participants. The study will also assess the safety, tolerability, and palatability of PF-07321332/ritonavir oral powder in healthy adult participants. The study will be used to assess the microsampling technique and if acceptable, the technique can be used in future clinical trials to reduce patient burden.

## 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.[1]

PF-07321332 is an orally bioavailable $3CL^{pro}$ inhibitor shown to be effective against SARS-CoV-2 $3CL^{pro}$ ($K_i$ = 0.00311 μM) in a biochemical enzymatic assay. 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.

The clinical development program for PF-07321332 includes 8 completed clinical studies: five Phase 1 studies in healthy participants (C4671001, C4671012, C4671013, C4671014 and C4671015), one Phase 1 study in renal impairment participants (C4671011), one Phase 1 study in hepatic impairment participants (C4671010) and one Phase 2/3 study in COVID-19 patients (C4671005).

### 2.2.1. Nonclinical Pharmacology

Details of the nonclinical pharmacology of PF-07321332 can be found in the current IB[2].

### 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[2].

### 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 nonadverse, test article-related clinical findings included sporadic occurrence of emesis with slight body weight decreases in monkeys in the 1-month study. In rats, monitorable and reversible clinical pathology findings included those possibly suggestive of low-grade inflammation or alterations in the coagulation pathways without clinical or microscopic correlates. In monkeys, monitorable and reversible clinical pathology findings included increase in ALT and/or AST and increase in fibrinogen at the high dose in 1-month study without clinical or microscopic correlates. In rats administered 1000 mg/kg/day, lower mean absolute and relative heart weights (females) and higher mean liver weights (both sexes) were observed relative to controls. The lower heart weights had no microscopic correlates and were fully reversed at the end of the 2-week recovery period. Higher liver weights correlated with reversible, nonadverse microscopic findings of minimal to mild severity in the liver and thyroid gland consistent with adaptive changes related to microsomal enzyme induction.

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

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

Further details of the nonclinical safety program are provided in the current IB[2].

### 2.2.4. 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 nonhospitalized 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 one AE which was moderate in severity, and not considered treatment related. Overall, there were no clinically meaningful laboratory changes, no clinically significant findings in vital sign measurements or 12-lead ECG assessments throughout this study. The safety data, including AEs, laboratory abnormalities, vital signs, and 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 nonhospitalized adult participants with a laboratory-confirmed diagnosis of SARS-CoV-2 infection. A total of 2224 symptomatic adult participants 18 years of age and older at high risk of developing severe disease received at least 1 dose of either nirmatrelvir/ritonavir (n=1,109) or placebo (n=1,115). Adverse events (all grades regardless of causality) in the nirmatrelvir/ritonavir group (≥1%) that occurred at a greater frequency (≥5 participant difference) than in the placebo group were dysgeusia (6% and <1%, respectively), diarrhea (3% and 2%), hypertension (1% and <1%), and myalgia (1% and <1%).

Further details on the clinical safety information with PF-07321332 are provided in the current IB[2].

### 2.2.4.2. Summary of PF-07321332 Pharmacokinetics in Human

CCI [redacted]

CCI [redacted] Since PF-07321332 is primarily metabolized by CYP3A4 and ritonavir is a CYP3A4 inhibitor, dosing with ritonavir increased the exposure of PF-07321332. Highest observed mean $C_{max}$ and $AUC_{last}$ was 5.09 µg/mL and 64.26 µg•h/mL, respectively, at 750 mg PF-07321332 dosed with ritonavir. The mean half-life of PF-07321332 was approximately 2 hours when administered alone and increased to approximately 6-13 hours when coadministered with ritonavir. Dosing with a high-fat meal modestly increased the exposure of PF-07321332 (approximately 15% increase in mean $C_{max}$ and 1.6% 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. CCI [redacted]

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[2].

### 2.3. Benefit/Risk Assessment

PF-07321332 is not expected to provide any clinical benefit to healthy participants in this study. This study is designed primarily to further the understanding of human PK, metabolism, and elimination of PF-07321332.

Based on data from Study C4671001 and C4671005, the clinical safety profile of PF-07321332 appears to be acceptable at single doses up to 1500 mg alone and up to 2250 mg administered with ritonavir (100 mg at -12h, 0h, 12h), split dosing administration (3 doses of 750 mg) at short intervals (approximately 2 hours from the previous dose), and at

repeated daily doses administered orally for 10 days of up to 500 mg PF-07321332 q12h with 100 mg ritonavir q12h.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-07321332 and ritonavir may be found in the IB[2], which is the SRSD for this study.

## 3. OBJECTIVES AND ENDPOINTS

| Primary Objective: | Primary Endpoint: |
|---|---|
| • To estimate the rBA of the PF-07321332/ritonavir 300 mg/100 mg oral powder mixed with water compared to the PF-07321332/ritonavir commercial tablets under fasted conditions.<br><br>• To estimate the rBA of the PF-07321332/ritonavir 300 mg/100 mg oral powder mixed with applesauce compared to the PF-07321332/ritonavir commercial tablets under fasted conditions.<br><br>• To estimate the rBA of the PF-07321332/ritonavir 300 mg/100 mg oral powder mixed with vanilla pudding compared to the PF-07321332/ritonavir commercial tablets under fasted conditions. | • The ratio of $AUC_{last}$, $AUC_{inf}$ (if data permits) and $C_{max}$ of PF-07321332 and ritonavir. |
| **Secondary Objective:** | **Secondary Endpoints:** |
| • To evaluate the safety and tolerability of PF-07321332/ritonavir in healthy participants.<br><br>• To assess the palatability of PF-07321332/ritonavir oral powder mixed with water/applesauce/vanilla pudding. | • Assessment of TEAEs, clinical laboratory abnormalities, vital signs, PEs, and 12-lead ECGs.<br><br>• Assessment of palatability using via questionnaire: mouth feel, bitterness, tongue/mouth burn, throat burn and overall liking. |
| CCI [redacted] | [redacted] |
| [redacted] | [redacted] |

# 4. STUDY DESIGN

## 4.1. Overall Design

This is a Phase 1, open-label, single-dose, randomized, crossover study in healthy adult participants to estimate rBA of PF-07321332/ritonavir 300 mg/100 mg oral powder formulation mixed with 3 different delivery vehicles (Test formulations) compared to the PF-07321332/ritonavir commercial tablet formulation (Reference formulation) under fasted condition. The study will also assess the safety, tolerability, and palatability of PF-07321332/ritonavir oral powder in healthy adult participants.

Approximately 12 healthy male and/or female participants will be enrolled and randomized to 1 of 4 possible treatment sequences to ensure at least 10 participants will complete the study. Participants who discontinue from the study for nonsafety reasons may be replaced at the sponsor's discretion in collaboration with the investigator. The replacement participant will receive the same treatment sequences as the participant who discontinued.

Each enrolled participant will participate in 4 study periods to receive 4 different treatments according to the sequence determined by randomization:

- Treatment A: Single oral dose of PF-07321332/ritonavir 300 mg (2 × 150 mg)/100 mg commercial tablets under fasted conditions (Reference)
- Treatment B: Single oral dose of PF-07321332/ritonavir 300 mg/100 mg oral powder mixed with water under fasted conditions (Test 1)
- Treatment C: Single oral dose of PF-07321332/ritonavir 300 mg/100 mg oral powder mixed with applesauce under fasted conditions (Test 2)
- Treatment D: Single oral dose of PF-07321332/ritonavir 300 mg/100 mg oral powder mixed with vanilla pudding under fasted conditions (Test 3)

Participants will be randomly assigned to 1 of 4 sequences as shown below in Table 1. Participants will be discharged on Day 4 of Period 4, following completion of all assessments. Between each treatment, a minimum of 4 days washout is proposed to minimize any residual PF-07321332 concentrations prior to start of the next treatment. The total planned duration of participation from the Screening visit to the last follow-up phone call, is approximately 11 weeks.

**Table 1. Randomized Treatment Sequences**

| Treatment Sequence | Period 1 | Period 2 | Period 3 | Period 4 |
|---|---|---|---|---|
| **Sequence 1 (N =3)** | Treatment A | Treatment B | Treatment C | Treatment D |
| **Sequence 2 (N =3)** | Treatment B | Treatment D | Treatment A | Treatment C |
| **Sequence 3 (N =3)** | Treatment C | Treatment A | Treatment D | Treatment B |

**Table 1. Randomized Treatment Sequences**

| Treatment Sequence | Period 1 | Period 2 | Period 3 | Period 4 |
|---|---|---|---|---|
| **Sequence 4 (N =3)** | Treatment D | Treatment C | Treatment B | Treatment A |

Healthy participants will be screened to determine eligibility within 28 days prior to study treatment. Medical history and results of PEs, vital signs, 12-lead ECGs, and clinical laboratory evaluations will determine eligibility. Eligible participants will be admitted to the PCRU on Day -1 and will be confined in the PCRU until discharge which is Day 4 of Period 4.

On Day 1 of each period, participants will receive a single dose of study intervention PF-07321332/ritonavir 300 mg/100 mg as per the randomization schedule. Study treatments will be administered with approximately 240 mL of ambient temperature water under fasted conditions (overnight fast and no food until 4 hours after dosing). Serial PK samples will be collected up to 72 hours post dose. Participants will be discharged from the PCRU on Period 4, Day 4 following completion of all assessments.

If a participant has any clinically significant, study related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the participant may be asked to remain in the PCRU 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

PF-07321332/ritonavir oral powder is an alternative formulation for pediatric patients who are not able to swallow PF-07321332/ritonavir commercial tablets. The objective of the study is to estimate the rBA of PF-07321332/ritonavir oral powder mixed with 3 different delivery vehicles (Test formulations) compared to PF-07321332/ritonavir commercial tablet formulation (Reference formulation). The study will also assess the safety, tolerability, and palatability of PF-07321332/ritonavir oral powder in healthy adult participants.

The study is being designed as a crossover study to account for any period effect. Between each treatment, a minimum of 4 days washout is proposed to minimize any residual PF-07321332 and ritonavir concentrations prior to start of the next treatment, as PF-07321332 has a half-life of approximately 6 to13 hours when co-administered with ritonavir.

#### 4.2.1. Choice of Contraception/Barrier Requirements

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

### 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 PF-07321332/ritonavir 300 mg/100 mg BID for 5 days is the approved therapeutic dose and treatment duration under emergency use authorization. This dose is lower than the highest dose evaluated in the Phase 1 C4671001 study and is safe and well tolerated.

This study is designed to evaluate rBA of PF-07321332/ritonavir oral powder mixed with 3 different delivery vehicles compared to PF-07321332/ritonavir commercial tablet formulation in healthy adult participants at the approved therapeutic dose. Therefore, a single oral dose PF-07321332 /ritonavir 300/100 mg will be used in this relative bioavailability study.

### 4.4. End of Study Definition

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

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

## 5. STUDY POPULATION

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

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

### 5.1. Inclusion Criteria

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

**Age and Sex:**

1. Male and/or female participants must be ≥18 years of age, inclusive, at the time of signing the ICD.

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

**Type of Participant and Disease Characteristics:**

2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, PE, laboratory tests, vital signs and standard 12-lead ECGs.

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

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

**Weight:**

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

**Informed Consent: .**

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

### 5.2. Exclusion Criteria

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

**Medical Conditions:**

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

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

3. Clinically relevant abnormalities requiring treatment (eg, acute myocardial infarction, unstable ischemic conditions, evidence of ventricular dysfunction, serious tachy- or brady-arrhythmias) or indicating serious underlying heart disease (eg, prolonged PR interval, cardiomyopathy, heart failure greater than NYHA 1, 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, HBcAb or HCVAb. Hepatitis B vaccination is allowed.

6. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or

situations related to COVID-19 pandemic (eg, contact with positive case) that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

**Prior/Concomitant Therapy:**

7. 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 PF-07321332/ritonavir and during study treatment.

   - Concomitant use of any medications or substances that are inhibitors of CYP3A4 are prohibited during study treatment and 4 days after the last dose of study intervention.

8. 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.

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

**Prior/Concurrent Clinical Study Experience:**

10. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer). Participants who have participated in previous clinical trials with PF-07321332 may be eligible to participate in this study as long as they meet all other criteria.

**Diagnostic Assessments:**

11. A positive urine drug test.

12. 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.

13. Baseline 12-lead ECG (single) 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, old or age indeterminate

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.

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

    - AST **or** ALT level >1.5 × ULN;
    - TBili level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ULN.
    - eGFR <60 mL/min/1.73 $m^2$ based on the CKD-EPI equation.

**Other Exclusions:**

15. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit or 3 ounces (90 mL) of wine).

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

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

18. History of sensitivity to heparin or heparin-induced thrombocytopenia.

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

20. 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.

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

22. Pregnant or breastfeeding women.

## 5.3. Lifestyle Considerations

### 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 predose PK sample on Day 1 of each Period.

- Water is permitted until 1 hour prior to study intervention administration. Water may be consumed without restriction beginning 1 hour after PF-07321332/ritonavir dosing. Noncaffeinated drinks (except red wine, 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 PF-07321332/ritonavir dosing.

- Dinner will be provided approximately 9 to 10 hours after PF-07321332/ritonavir dosing.

- An evening snack may be permitted.

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

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

### 5.3.2. 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 PK sample of each study period.

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

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

### 5.3.3. Activity

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

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

- Participants will be confined to the procedure room for the first 4 hours after dosing on Day 1, except to use the bathroom. After this, participants may be ambulatory but should not engage in strenuous activities.

### 5.3.4. Contraception

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

## 5.4. Screen Failures

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

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

# 6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to PF-07321332 and ritonavir.

### 6.1. Study Intervention(s) Administered

PF-07321332 150 mg tablets and PF-07321332 oral powder will be supplied by the sponsor.

Commercially available ritonavir oral powder 100 mg will either be supplied by the sponsor or will be sourced by the PCRU.

Commercially available ritonavir 100 mg tablets will be sourced by the PCRU.

Vehicles (water, applesauce, vanilla pudding) for PF-07321332 and ritonavir oral powder administration will be sourced by the PCRU.

#### 6.1.1. Administration

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

On Day 1 of each treatment period, following an overnight fast of at least 10 hours, participants will receive PF-07321332 300 mg (as 2 × 150 mg tablets) with ritonavir 100 mg (as 1 × 100 mg tablet) with approximately 240 mL ambient temperature water or PF-07321332/ritonavir 300 mg/100 mg oral powder mixed with either water or applesauce or vanilla pudding with approximately 240 mL ambient temperature water administered orally starting at approximately 0800 hours (plus or minus 2 hours). PF-07321332 and ritonavir will be dosed simultaneously (within no more than 5 minutes of each other). Participants will swallow all tablet formulations whole and will not manipulate or chew the tablets prior to swallowing.

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

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

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

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

### 6.2.1. Preparation and Dispensing

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

PF-07321332 150 mg tablets will be prepared at the PCRU 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.

Commercial ritonavir (Norvir® or other local commercialized product) oral tablets will be dispensed at the PCRU into individual dosing containers using the package insert as

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

PF-07321332/ritonavir oral powder will be prepared at the PCRU 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). Details of dose preparations, volume/amount of food vehicle, will be given in the EDR. Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator site's labeling requirements.

## 6.3. Measures to Minimize Bias: Randomization and Blinding

### 6.3.1. Allocation to Study Intervention

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

The investigator will assign participant numbers to the participants as they are screened for the study. 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 PCRU will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

## 6.5. Dose Modification

No dose modification is anticipated.

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

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

## 6.7. Treatment of Overdose

For this study, any dose of PF-07321332 greater than 300 mg or ritonavir 100 mg within a 24-hour time period [±2 hours] will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-07321332/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 PF-07321332 and ritonavir are both primarily metabolized by CYP3A4, concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to dosing of study intervention. Additionally, ritonavir and PF-07321332 are inhibitors of CYP3A4. Therefore, medications highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events are not permitted during dosing of PF-07321332/ritonavir, through 4 days after the last dose of PF-07321332/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 site visit.

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

### 6.8.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07321332 or ritonavir; 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. ECG Changes

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

- QTcF >500 msec;
- Change from baseline: QTcF >60 msec.

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

### 7.1.2. Potential Cases of Acute Kidney Injury

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

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

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

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

### 7.1.3. Stopping Rules

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

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

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

## 7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at 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 attend a required study visit:

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

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

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

## 8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

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

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

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (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 300 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 56 consecutive days.

To prepare for study participation, participants will be instructed on the information Section 5.3 Lifestyle Considerations and Section 6.8 Concomitant Therapy 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 PE will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

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

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

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

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

### 8.2.2. Vital Signs

Supine BP, PR 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 PR is acceptable; however, when done manually, PR 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 PR should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and PR 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, or smoking is allowed for 15 minutes prior to the measurement.

### 8.2.3. Electrocardiograms

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

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

### 8.2.5. COVID-19 Specific Assessments

Participants will be tested for SARS-CoV-2 infection by RT-PCR prior to being admitted to the PCRU for confinement and a subsequent SARS-CoV-2 test will be performed after 4 days (ie, upon completion of 4 × 24 hours in house), or if they develop COVID-19 like symptoms. Additional testing may be required by local regulations or by the principal investigator.

### 8.2.6. Pregnancy Testing

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

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

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

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

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

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

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

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

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

minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

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

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

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

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

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

#### 8.3.1.1. Reporting SAEs to Pfizer Safety

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

#### 8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

### 8.3.2. Method of Detecting AEs and SAEs

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

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

### 8.3.3. Follow-Up of AEs and SAEs

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

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

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

### 8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

#### 8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

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

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

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

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural

integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

### 8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

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

#### 8.3.5.3. Occupational Exposure

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

### 8.3.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

### 8.3.8. Adverse Events of Special Interest

Not applicable.

#### 8.3.8.1. Lack of Efficacy

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

### 8.3.9. Medical Device Deficiencies

Not applicable.

### 8.3.10. Medication Errors

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

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

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

Medication errors include:

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

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

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

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

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

### 8.4. Pharmacokinetics

#### 8.4.1. Plasma for Analysis of PF-07321332 and Ritonavir

Blood samples of approximately 4 mL, to provide approximately 1.5 mL plasma, will be collected for measurement of plasma concentrations of PF-07321332 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 PF-07321332 and ritonavir. CCI

Samples collected for measurement of plasma concentrations of PF-07321332 and ritonavir will be analyzed using a validated analytical method in compliance with applicable SOPs. CCI

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.

CCI

CCI

CCI

[redacted]

## 8.7. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

### 8.8. Health Economics

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

### 8.9. Taste Assessment of PF-07321332 Suspension

The sensory attributes of PF-07321332/ritonavir oral powder will be evaluated by the participant using a Taste Assessment Questionnaire (Appendix 8) in the period when suspension may be administered. Partcipants will review the taste questionnaire and instructions prior to the first taste assessment to Treatment B, C, D, on Period 1 Day 1. Each participant will complete the Taste Assessment Survey immediately following dosing (within 1 min) and at 5, 10, and 20 minutes post oral administration of PF-07321332/ritonavir oral powder.

## 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 |
|---|---|
| Enrolled/Randomly assigned to study intervention | "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and 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. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. |
| Safety Analysis Set | All participants who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received. |
| PK Concentration Set | All participants who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported. |

| Participant Analysis Set | Description |
|---|---|
| PK Parameter Set | All participants who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of primary interest are reported. |

## 9.3. Statistical Analyses

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

### 9.3.1. Pharmacokinetic Analyses

#### 9.3.1.1. Derivation of Pharmacokinetic Parameters

Plasma PK parameters of PF-07321332 and ritonavir will be derived (as data permits) 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. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

**Table 2. Plasma PF-07321332 and Ritonavir PK Parameters Definitions**

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

*If data permits.

### 9.3.2. Statistical Methods for PK Data

For the primary objective, natural log transformed $AUC_{inf}$ (if data permits), $AUC_{last}$ and $C_{max}$ will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within a sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. Treatment A will be the Reference treatment while Treatments B, C, and D will be the Test treatments.

CCI [redacted]

PK parameters, including plasma $AUC_{inf}$ (if data permits), $AUC_{last}$, $C_{max}$, and CCI [redacted] (if data permits) of PF-07321332 and ritonavir will be summarized descriptively by treatment. For $AUC_{inf}$ (if data permits), $AUC_{last}$, and $C_{max}$, a listing of the individual participant ratios (Test/Reference) will be provided. Box and whisker plots for $AUC_{inf}$ (if data permits), $AUC_{last}$, and $C_{max}$, will be plotted by treatment.

The plasma concentrations of PF-07321332 and ritonavir will be listed and descriptively summarized by nominal PK sampling time and treatment. Individual participant, as well as mean and median profiles of the plasma concentration time data will be plotted by treatment using actual (for individual) and nominal (for mean and median) times respectively. Mean and median profiles will be presented on both linear and semi-log scales.

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

### 9.3.3. Other Safety Analyses

All safety analyses will be performed on the safety population.

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

Medical history and PE and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical

and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at Screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at Screening will be reported.

### 9.3.4. Other Analyse(s)

#### 9.3.4.1. Taste Assessment

The data collected for taste assessment using the sponsor-provided taste questionnaire will be numerically derived by measuring length (using a scale with gradations of at least 0.1 cm) of the "x" marked by the participant relative to the "good trait". The taste attributes (bitterness, and tongue/mouth burn sensation) from the taste questionnaires (Appendix 8) will be listed and descriptively summarized and appropriate plots may be generated.

CCI [redacted]

[redacted]

## 9.4. Interim Analyses

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

## 9.5. Sample Size Determination

A sample size of 12 participants will provide adequate precision to estimate the relative bioavailability and intrasubject variability PF-07321332. The following table presents the width of 90% CI for different estimated effects, with 80% coverage probability.

| Parameter | Estimated Effect (100*Test/Reference) | 90% CI | | CI Width |
|---|---|---|---|---|
| AUC | 85% | 75.19% | 96.09% | 20.90% |
| | 90% | 79.61% | 101.74% | 22.13% |
| | 95% | 84.04% | 107.39% | 23.36% |
| | 100% | 88.46% | 113.05% | 24.59% |
| | 105% | 92.88% | 118.7% | 25.82% |
| | 110% | 97.31% | 124.35% | 27.05% |
| | 115% | 101.73% | 130% | 28.28% |
| $C_{max}$ | 85% | 78.47% | 92.08% | 13.61% |
| | 90% | 83.08% | 97.49% | 14.41% |
| | 95% | 87.7% | 102.91% | 15.21% |
| | 100% | 92.31% | 108.33% | 16.01% |
| | 105% | 96.93% | 113.74% | 16.81% |
| | 110% | 101.55% | 119.16% | 17.61% |
| | 115% | 106.16% | 124.57% | 18.41% |

These estimates are based on the assumption that within-participant standard deviations are 0.161and 0.105 for $lnC_{max}$ and $lnAUC_{inf}$ , respectively, as obtained from clinical Studies C4671001 and C4671014 in healthy participants.

In addition, a sample size of 12 participants will provide adequate precision to estimate the relative bioavailability and intrasubject variability ritonavir. The following table presents the width of 90% CI for different estimated effects, with 80% coverage probability.

| Parameter | Estimated Effect (100*Test/Reference) | 90% CI | | CI Width |
|---|---|---|---|---|
| AUC | 85% | 71.18% | 101.50% | 30.32% |
| | 90% | 75.37% | 107.47% | 32.10% |
| | 95% | 79.56% | 113.44% | 33.89% |
| | 100% | 83.74% | 119.41% | 35.67% |
| | 105% | 87.93% | 125.38% | 37.45% |
| | 110% | 92.12% | 131.35% | 39.24% |
| | 115% | 96.30% | 137.32% | 41.02% |
| $C_{max}$ | 85% | 63.39% | 113.99% | 50.60% |
| | 90% | 67.11% | 120.69% | 53.58% |
| | 95% | 70.84% | 127.40% | 56.55% |
| | 100% | 74.57% | 134.10% | 59.53% |
| | 105% | 78.30% | 140.81% | 62.51% |
| | 110% | 82.03% | 147.51% | 65.48% |
| | 115% | 85.76% | 154.22% | 68.46% |

These estimates are based on the assumption that within-participant standard deviations are 0.234 and 0.387 for $lnAUC_{inf}$ and $lnC_{max}$, respectively, as obtained from clinical Study C4671014 in healthy participants.

Participants who withdraw from the study or discontinue treatment, or whose PK samples are considered to be nonevaluable with respect to the primary PK objective may be replaced at the discretion of the investigator upon consultation with the sponsor.

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

### 10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

### 10.1.2. 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.

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

### 10.1.4. Data Protection

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

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

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

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 [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.

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

Description of the use of the computerized system is documented in the Source Document Locator, which is maintained by the sponsor's designee (Pfizer Clinical Research Unit).

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 CTMS

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

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 3. Protocol-Required Safety Laboratory Assessments**

| Hematology | Chemistry | Urinalysis | Other |
|---|---|---|---|
| Hemoglobin<br>Hematocrit<br>RBC count<br>MCV<br>MCH<br>MCHC<br>Platelet count<br>WBC count<br>Total neutrophils (Abs)<br>Eosinophils (Abs)<br>Monocytes (Abs)<br>Basophils (Abs)<br>Lymphocytes (Abs) | BUN and creatinine<br>Glucose (fasted)<br>Calcium<br>Sodium<br>Potassium<br>Chloride<br>Total $CO_2$ (bicarbonate)<br>AST, ALT<br>Total bilirubin<br>Alkaline phosphatase<br>Uric acid<br>Albumin<br>Total protein | <u>Local Dipstick:</u><br>pH<br>Glucose (qual)<br>Protein (qual)<br>Blood (qual)<br>Ketones<br>Nitrites<br>Leukocyte esterase<br><br><u>Laboratory:</u><br>Microscopy and Culture[a] | • SARS-CoV-2 RT-PCR<br>• Urine drug screening[b]<br>• Pregnancy test (β-hCG)[c]<br>• eGFR [CKD-EPI]<br>• aPTT<br>• PT-INR<br>• Fibrinogen<br><br><u>At Screening only:</u><br>• FSH[d]<br>• HBsAg<br>• HBsAb[e]<br>• HBcAb<br>• HCVAb<br>• HIV |

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

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. CCI [redacted] These data will not be included in the CSR. Samples to be used for this purpose will be shipped to either a Pfizer-approved BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

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

### 10.3.1. Definition of AE

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

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

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

### 10.3.2. Definition of an SAE

| **An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:** |
|---|
| **a. Results in death** |
| **b. Is life-threatening**<br><br>The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. |
| **c. Requires inpatient hospitalization or prolongation of existing hospitalization**<br><br>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.<br><br>Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE. |

**d. Results in persistent or significant disability/incapacity**

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

**e. Is a congenital anomaly/birth defect**

**f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious.**

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

**g. Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

**AE and SAE Recording/Reporting**

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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

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

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

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

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

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

**Assessment of Intensity**

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

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

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

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

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

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

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

**Follow-Up of AEs and SAEs**

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

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

### 10.3.4. Reporting of SAEs

**SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool**

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

**SAE Reporting to Pfizer Safety via CT SAE Report Form**

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

## 10.4. Appendix 4: Contraceptive and Barrier Guidance

### 10.4.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either**:**

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

  OR

- Must agree to use contraception/barrier as detailed below:

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

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

### 10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), 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). If a highly effective method that is user dependent is chosen, a second effective method of contraception, as described below, must also be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

### 10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female.

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

### 10.4.4. Contraception Methods

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

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 woman of childbearing potential 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.

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

    - Oral;

    - Intravaginal;

    - Transdermal.

7. Progestogen only hormone contraception associated with inhibition of ovulation.

    - Oral;

    - Injectable.

8. Sexual abstinence.

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

**In addition, one of the following effective barrier methods must also be used when option 6 or 7 are chosen above:**

- 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).

Because ritonavir may reduce the effect of estradiol-containing contraceptives when agents are coadministered, a barrier method or other nonhormonal method of contraception must also be used if the participant is using estradiol-containing contraceptives.

CCI [redacted]

[redacted]

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

### Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT may precede TBili elevations (>2 × ULN) by several days or weeks. Any substantial elevaton in ALT, AST or bilirubin above baseline may be a potential DILI. The treating physician can determine what is an elevation of concern—in many cases, elevation in ALT, AST 3 × ULN or TBili value 1.5 × ULN prompts treating physicians to consider evaluation for hepatic injury. Hepatic injury may be from the study druy, a co-administerd study drug or the disease under study or other medical conditions.

The threshold of laboratory abnormalities for causality assessment and a potential DILI case depends on the participant's individual baseline values and underlying conditions based on treating physicians' opinion and declared attribution. Participants who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

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

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

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

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

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment by the treating physician and their health care team;

any case where uncertainty remains as to whether it represents a potential DILI and also potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated for causality 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 at time and dose of last dose of study intervention. 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 LT abnormalities has yet been found. The treating physician is encouraged to consult with any other speciality that may assit in interprepation of the lab result or patient care management (eg, gastroenterologist, clinical pathologist, pharmacy, etc)**. Such potential DILI cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LT abnormalities.**

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

## 10.7. Appendix 7: ECG Findings of Potential Clinical Concern

**ECG Findings That <u>May</u> Qualify as AEs**

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

**ECG Findings That <u>May</u> Qualify as SAEs**

- QTcF prolongation >500 msec.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset left bundle branch block (QRS >120 msec).
- New-onset right bundle branch block (QRS >120 msec).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  - In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

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

**ECG Findings That Qualify as SAEs**

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

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

## 10.8. Appendix 8: Palatability Questionnaire

### PF-07321332/Ritonavir Oral Powder Palatability Questionnaire

1. Questionnaire should be administered to adult subjects, preferably by the clinician or the nurse.

2. Use **colored copy** of the Palatability Questionnaire.

3. **Do not alter (reduce or enlarge) the original size of the Palatability Questionnaire**.

4. Please collect the following background information:

### Background Information

| | |
|---|---|
| Study #/Study Site | |
| Period and Day | |
| Subject ID (Rand ID) | |
| Treatment | |
| Collect Date | |
| Questionnaire Fully Completed (circle one) | Yes/No |

**Please answer the following questions and provide a mark (✕) on the color bar at 1 (immediately), 5, 10 and 20 minutes after dosing. Please ensure subject has access to these descriptions when completing the questionnaire.**

**Q1: Mouth feel – Please tell us about the mouth feel (such as grittiness, stickiness, waxiness) of the product you tasted.**

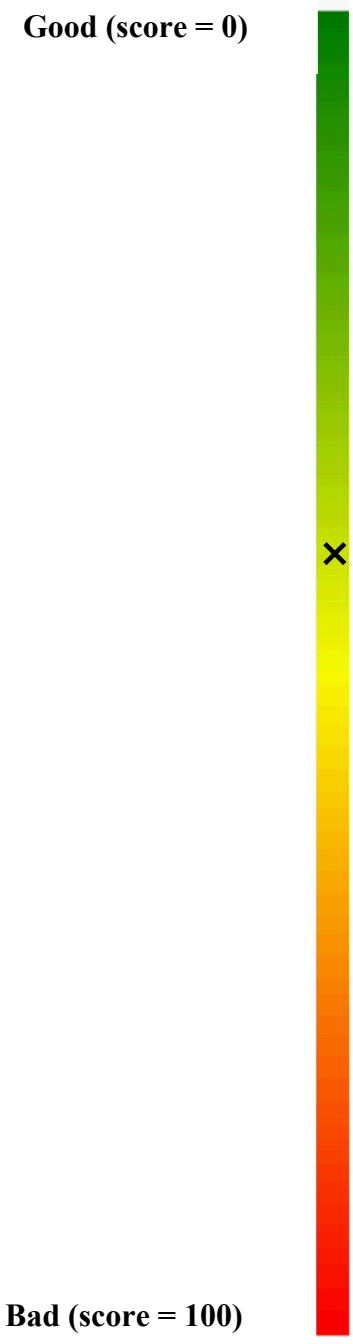
**Q2: Bitterness – Please tell us about the degree of bitterness of the product you tasted.**

**Q3: Tongue/mouth burn – Please tell us about the degree of tongue/mouth burn of the product you tasted.**

**Q4: Throat burn – Please tell us about the degree of throat burn of the product you tasted.**

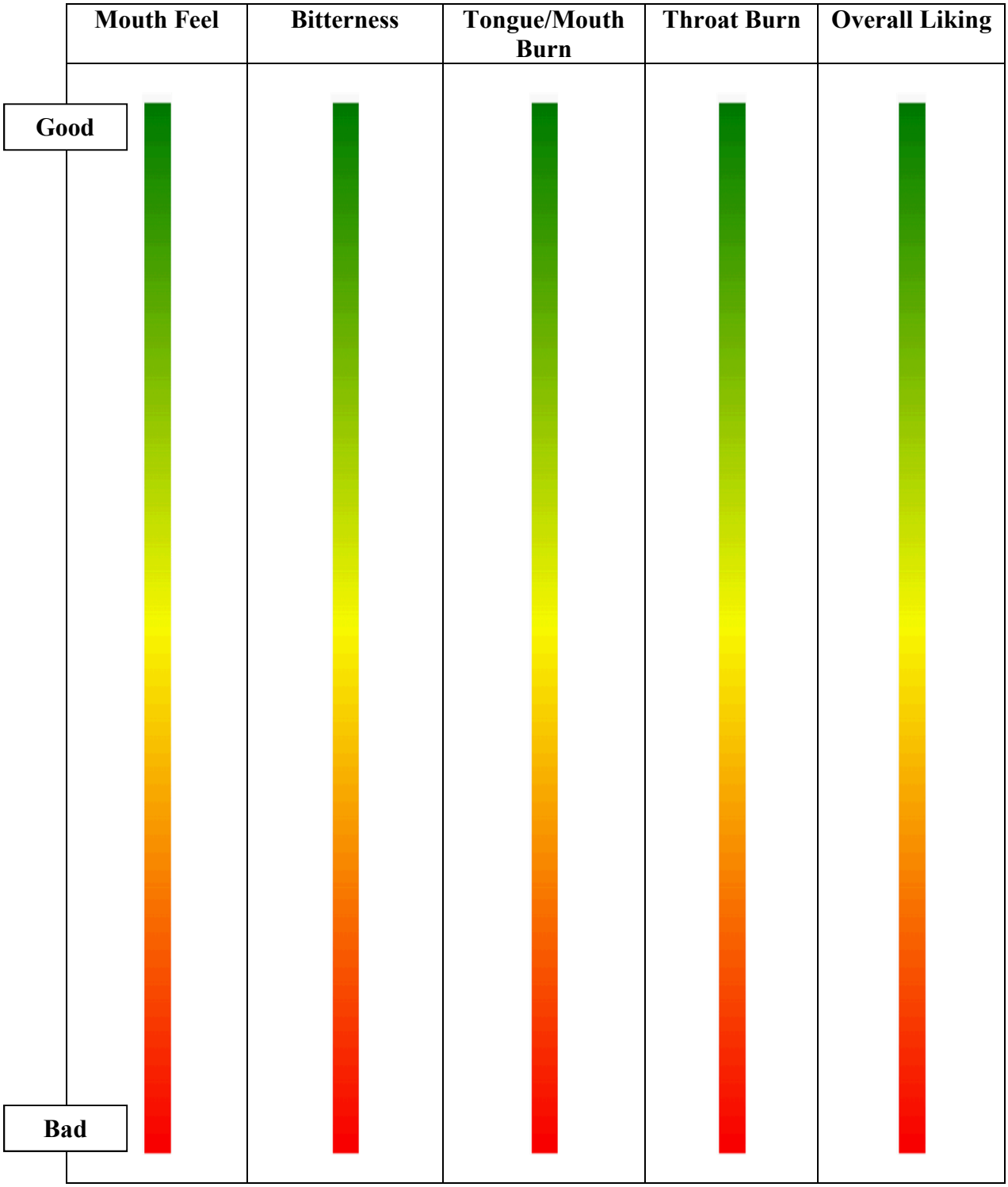
**Q5: Overall liking – Please indicate how much you like or dislike the product you tasted.**

**Example: How to provide a mark (✕) on the color bar.**



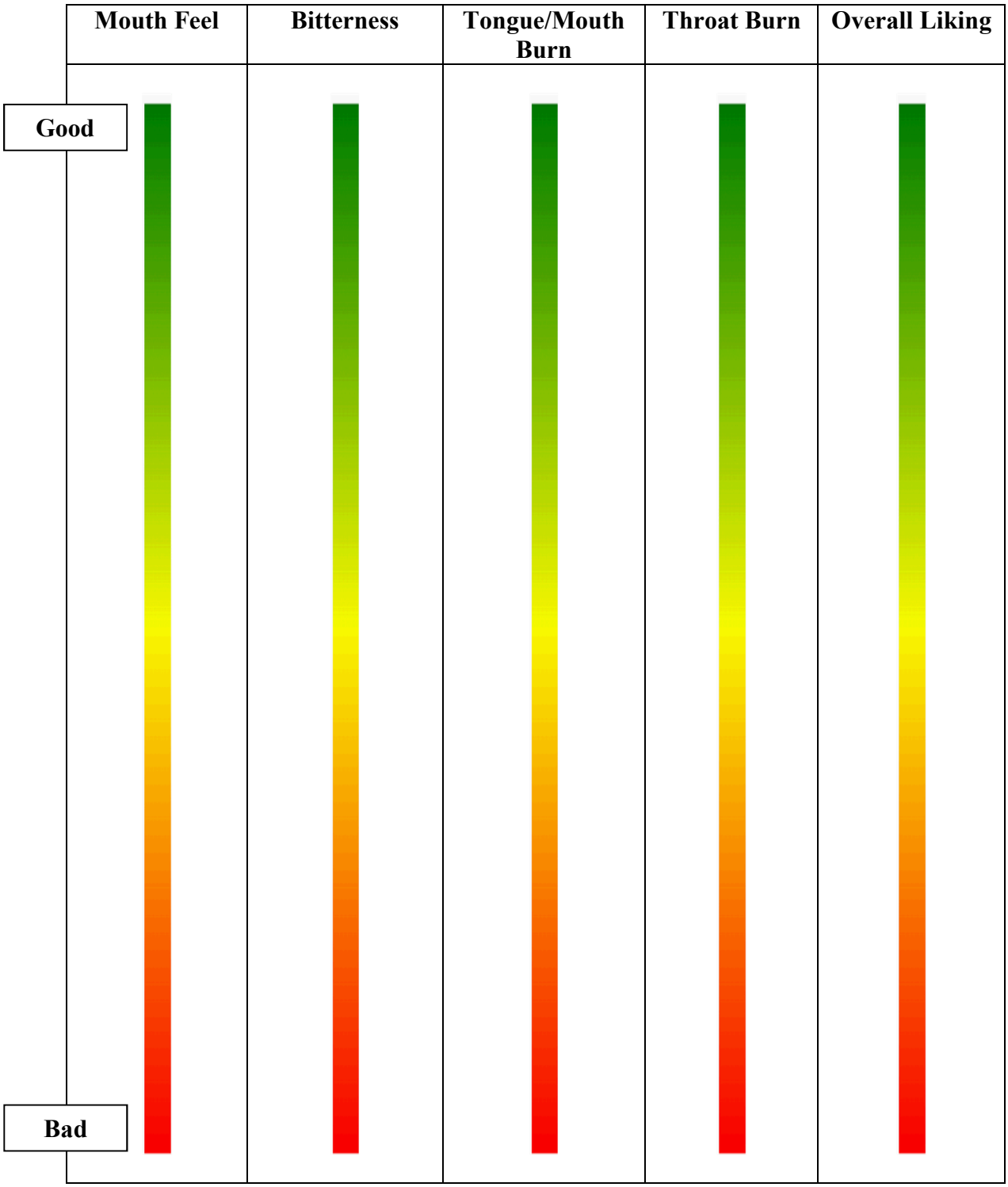
**Within 1 minute (immediately) after dosing**

**Provide a mark ( × ) <u>on the color bar</u>.**



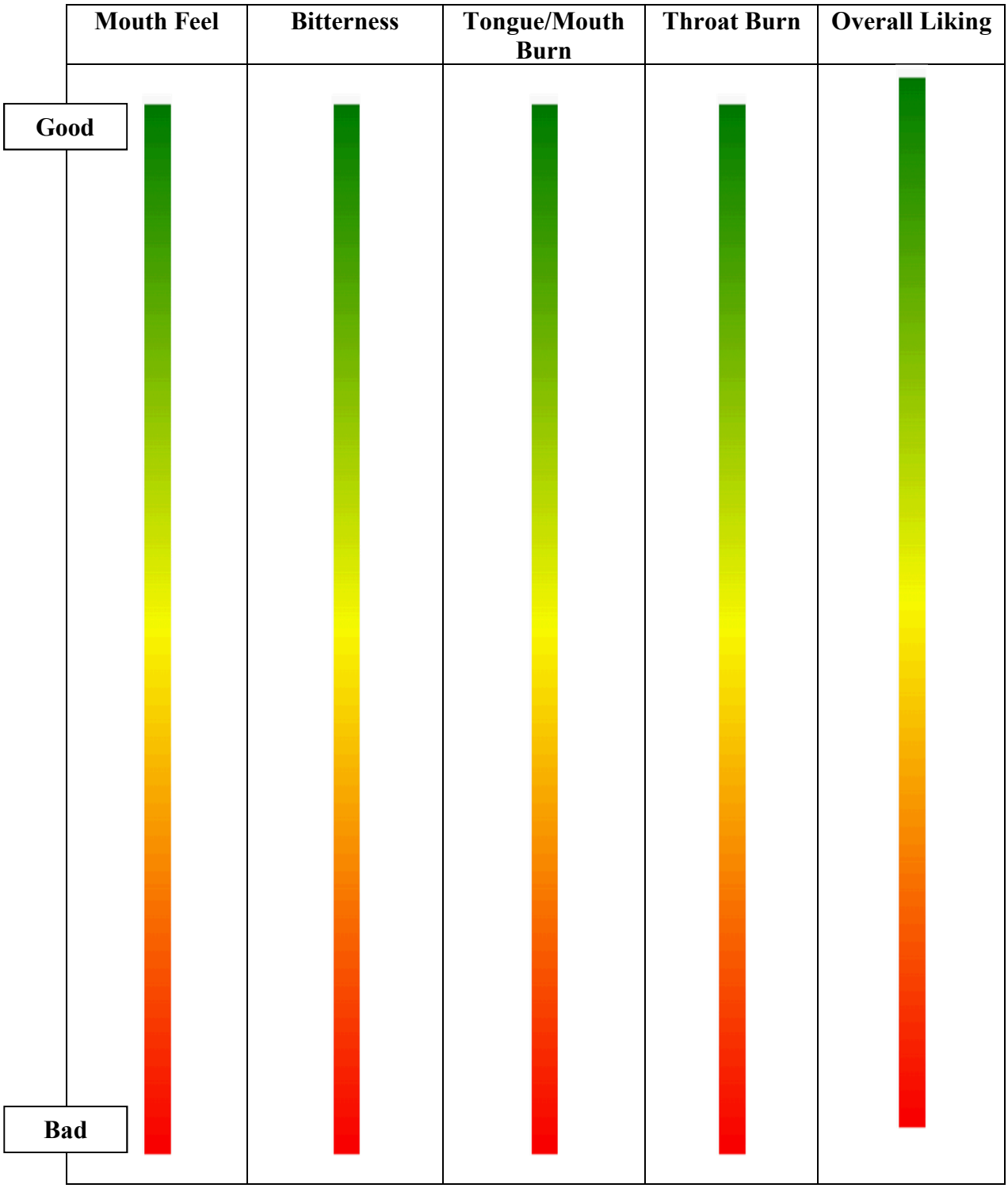
**5 minutes after dosing**

**Provide a mark ( × ) <u>on the color bar</u>.**



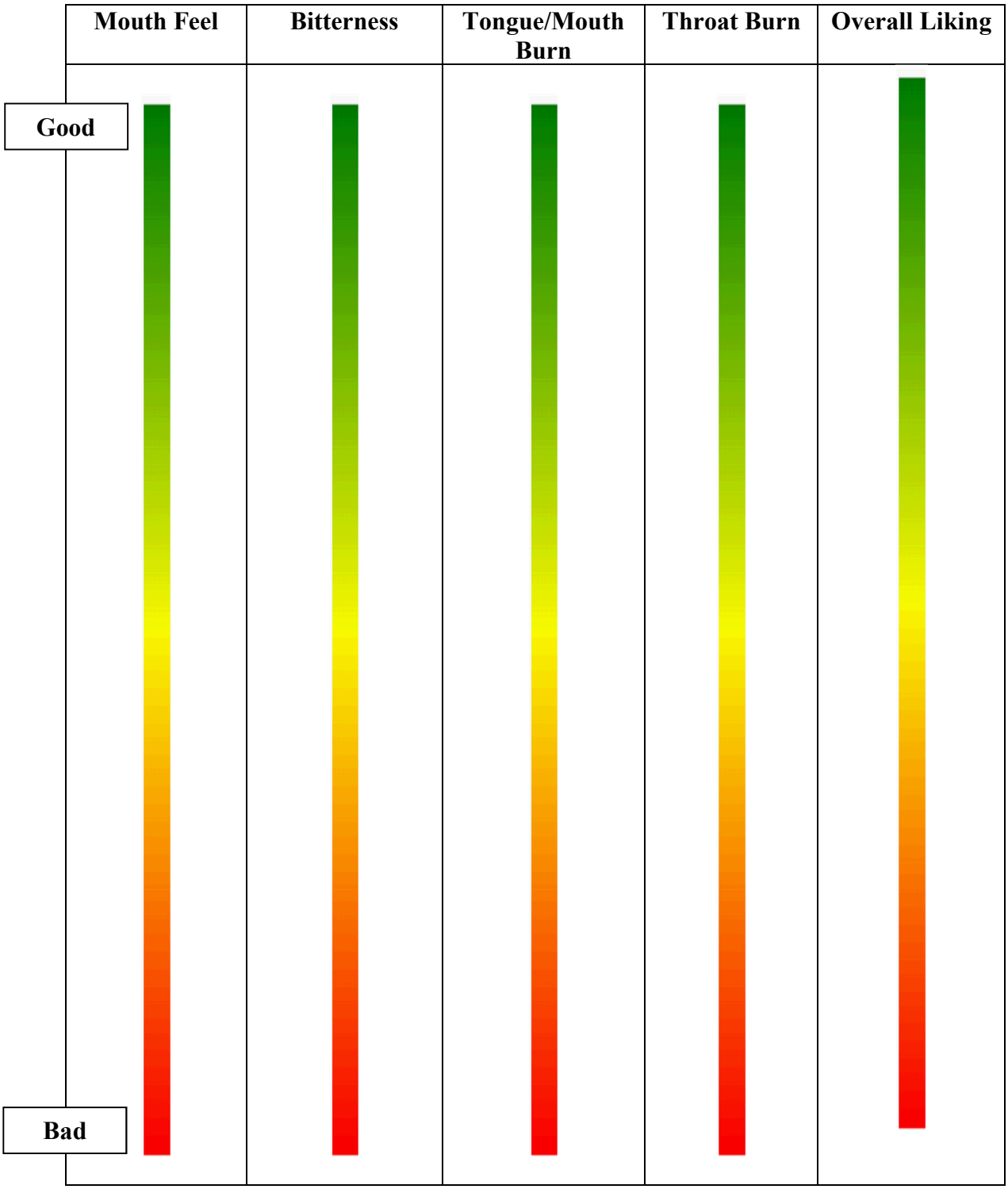
**10 minutes after dosing**

**Provide a mark ( × ) <u>on the color bar</u>.**

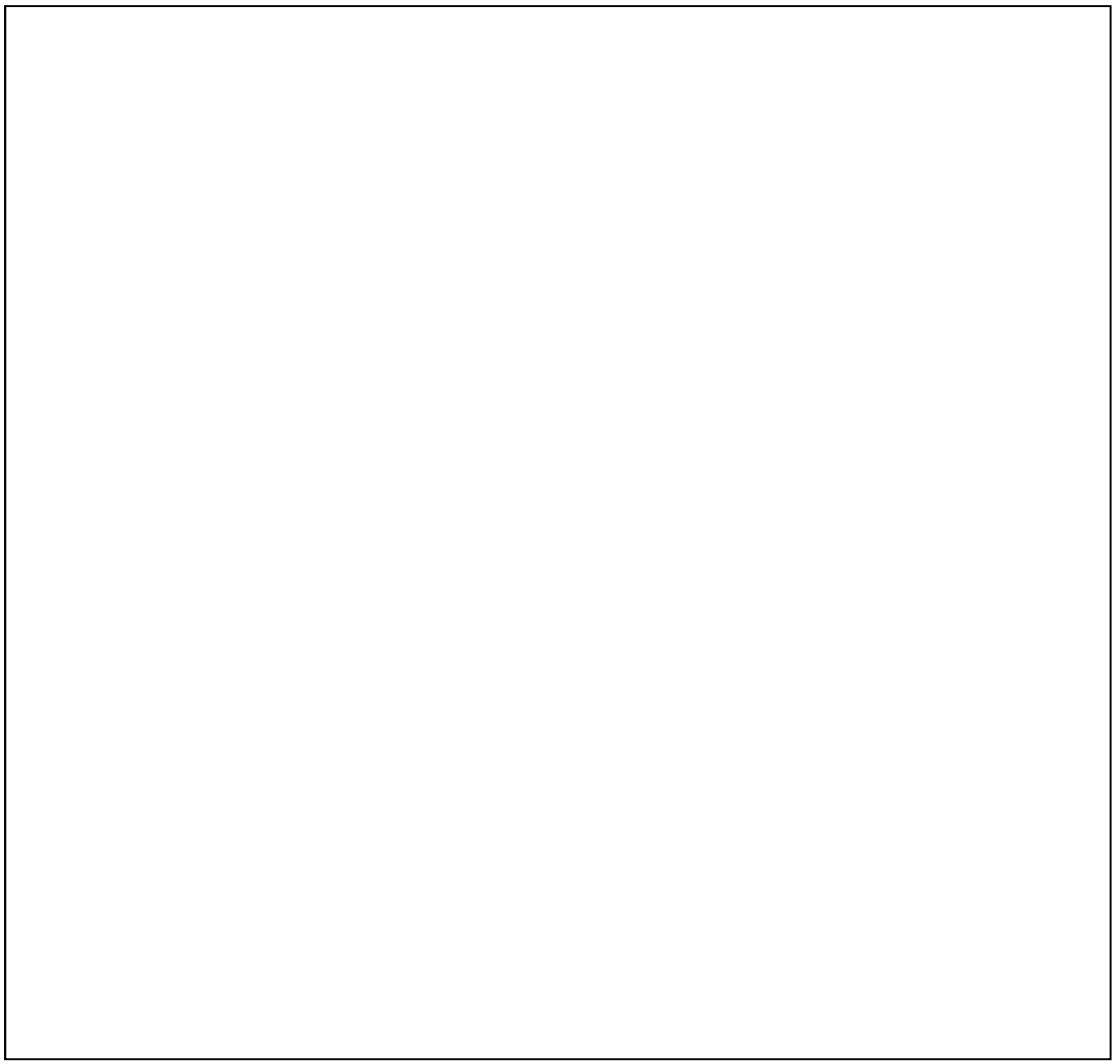


**20 minutes after dosing**

**Provide a mark ( × ) <u>on the color bar.</u>**



**Additional Feedback** – After completing the "20 minute after dosing" palatability questions, please provide any additional descriptive feedback in the box below regarding the taste or odor of the drug.



## 10.9. Appendix 9: Abbreviations

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

| Abbreviation | Term |
|---|---|
| | ongoing/continuous event |
| $^{19}$F-NMR | $^{19}$F nuclear magnetic resonance |
| 3CL$^{pro}$ | 3C-like protein |
| Abs | absolute |
| ADL | activities of daily living |
| AE | adverse event |
| ALT | alanine aminotransferase |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| $AUC_{inf}$ | area under the concentration-time curve from time zero 0 extrapolated to infinity |
| $AUC_{last}$ | area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration |
| CCI | [redacted] |
| AV | atrioventricular |
| BBS | Biospecimen Banking System |
| β-hCG | β-human chorionic gonadotropin |
| BID | twice a day |
| BMI | body mass index |
| BP | blood pressure |
| bpm | beats per minute |
| BUN | blood urea nitrogen |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| CK | creatine kinase |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CCI | [redacted] |
| $C_{last}$ | last quantifiable concentration |
| $C_{max}$ | maximum 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 |

| Abbreviation | Term |
|---|---|
| CT | clinical trial |
| CTMS | Clinical Trial Management System |
| CYP | cytochrome P450 |
| CYP3A | cytochrome P450, family 3, subfamily A |
| CYP3A4 | cytochrome P450 3A4 |
| CYP3A5 | cytochrome P450 3A5 |
| DILI | drug-induced liver injury |
| DMC | Data Monitoring Committee |
| EC | ethics committee |
| ECC | emergency contact card |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDB | exposure during breastfeeding |
| EDP | exposure during pregnancy |
| EDR | extemporaneous dispensing record |
| eGFR | estimated glomerular filtration rate |
| EMA | European Medicines Agency |
| EU | European Union |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials (European European Clinical Trials Database) |
| FIH | first in human |
| $f_m$ | fraction metabolized |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| GLP | Good Laboratory Practice |
| HBcAb | hepatitis B core antibody |
| HBsAb | hepatitis B surface antibody |
| HBsAg | hepatitis B surface antigen |
| HCVAb | hepatitis C antibody |
| HR | heart rate |
| HRT | hormone replacement therapy |
| IB | Investigator's Brochure |
| ICD | informed consent document |
| ICH | International Council for Harmonisation for Techinical Requirements for Pharmaceuticals for Human Use |
| ID | identification |
| $lnAUC_{inf}$ | log-transformed $AUC_{inf}$ |
| $lnC_{max}$ | log-transformed $C_{max}$ |
| IND | Investigational New Drug |
| IPAL | Investigational Product Accountability Log |
| IQMP | Integrated Quality Management Plan |

| Abbreviation | Term |
|---|---|
| IRB | Institutional Review Board |
| IV | Intravenous(ly) |
| $K_{el}$ | first order elimination rate constant |
| $K_i$ | inhibition constant |
| LBBB | left bundle branch block |
| LFT | liver function test |
| $lnAUC_{inf}$ | log-transformed $AUC_{inf}$ |
| $lnC_{max}$ | log-transformed $C_{max}$ |
| $Log_e$ | natural logarithm |
| LFT | liver function test |
| MAD | multiple ascending dose |
| MCH | mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| MCV | mean corpuscular volume |
| $M^{pro}$ | main protease |
| msec | millisecond |
| N/A | Not Applicable |
| NOAEL | No observed adverse effect level |
| NSAE | non-serious adverse event |
| NYHA | New York Heart Association |
| PCRU | Pfizer Clinical Research Unit |
| PD | pharmacodynamic(s) |
| PE | physical examination |
| PK | pharmacokinetic(s) |
| PR | pulse rate |
| PT-INR | prothrombin time-international normalized ratio |
| q12h | every 12 hours |
| QTc | corrected QT interval |
| QTcF | QT corrected using Fridericia's formula |
| qual | qualitative |
| rBA | relative bioavailablity |
| RBC | red blood cell |
| RT-PCR | reverse-transcriptase 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 |
| SD | standard deviation |
| SE | supratherapeutic exposure |
| SoA | schedule of activities |
| SOC | System Organ Class |

| Abbreviation | Term |
|---|---|
| SOP | standard operating procedure |
| SRSD | single reference safety document |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| [redacted] | [redacted] |
| TBili | total bilirubin |
| TEAE | treatment-emergent adverse event |
| THC | tetrahydrocannabinol |
| [redacted] | [redacted] |
| ULN | upper limit of normal |
| US | United States |
| [redacted] | [redacted] |
| WBC | white blood cell |
| WHO | World Health Organization |
| WOCBP | woman/women of childbearing potential |

## 11. REFERENCES

1 World Health Organization. WHO Situation Report –51 Coronavirus disease 2019 (COVID-19). 11 March 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed: 29 March 2020.

2 Investigator's Brochure, PF-07321332. (Version 4.0)

# Document Approval Record

| | |
|---|---|
| **Document Name:** | C4671024 Protocol Relative BA Pediatric 09 Feb 2022 |
| **Document Title:** | C4671024 Protocol Relative BA Pediatric 09 Feb 2022 |

| Signed By: | Date(GMT) | Signing Capacity |
|---|---|---|
| PPD | 11-Feb-2022 11:30:55 | Final Approval |
| PPD | 14-Feb-2022 14:56:40 | Final Approval |