A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED, FIRST-IN-HUMAN STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SINGLE ASCENDING ORAL DOSES OF PF-07258669 ADMINISTERED TO HEALTHY ADULT PARTICIPANTS

Study Intervention Number:	PF-07258669
Study Intervention Name:	N/A
US IND Number:	CCI [redacted]
EudraCT Number:	2020-004280-42
Protocol Number:	C4541001
Phase:	1

Short Title: A Phase 1 Study of Single Ascending Doses of PF-07258669 in Healthy Adult Participants

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 1	09 November 2020	• Precautionary sentinel dosing will be used in each period of each cohort. The rationale for, and description of, sentinel dosing was added to Section 1.1 (Synopsis), Section 1.2 (Schema), Section 1.3 (Schedule of Activities), Section 2.3 (Benefit/Risk Assessment), Section 2.3.1 (Risk Assessment), Section 4.1 (Overall Design), Section 4.2 (Scientific Rationale for Study Design), and Section 6.6.1 (Dose Escalation and Stopping Rules). • The starting dose level for this study was reduced from 0.3 mg to 0.1 mg [redacted] • [redacted]
Original protocol	07 October 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1 Study of Single Ascending Doses of PF-07258669 in Healthy Adult Participants

Rationale: This study is the first clinical study with PF-07258669. The safety, tolerability, and plasma PK of PF-07258669 after administration of escalating, single, oral doses will be evaluated.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety and tolerability of single ascending doses of PF-07258669 administered orally to healthy adult participants.	• Assessment of adverse events, clinical safety laboratory tests, vital signs, continuous cardiac monitoring, 12-lead electrocardiograms, respiratory rate, oral body temperature, physical examinations, and neurological examinations.
Secondary:	**Secondary:**
• To evaluate the pharmacokinetics of PF-07258669 following single doses of PF-07258669 administered orally to healthy adult participants.	• PK parameters derived from plasma PF-07258669 concentrations: C_{max}, AUC_{last}, AUC_{inf}, T_{max}, and $t_{½}$, if data permit.
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Overall Design: This study is a randomized, investigator- and participant-blind, sponsor-open, placebo-controlled, first-in-human, single ascending oral dose study of PF-07258669 administered to healthy adult participants. Precautionary sentinel dosing will be used in each period of each cohort. Two participants (1 receiving PF-07258669 and

1 receiving placebo) within a period will be dosed initially before the remaining participants of that period are dosed. Safety and tolerability data through at least 24 hours post-dose for the sentinel participants will be reviewed prior to dosing the remaining participants of that period.

Number of Participants: A maximum of approximately 24 participants will be randomized in this study (8 per cohort).

Intervention Groups and Duration: The study interventions include PF-07258669 and placebo. Both will be administered as extemporaneously-prepared solutions or suspensions for oral administration. Participants will receive single doses in each period of the study.

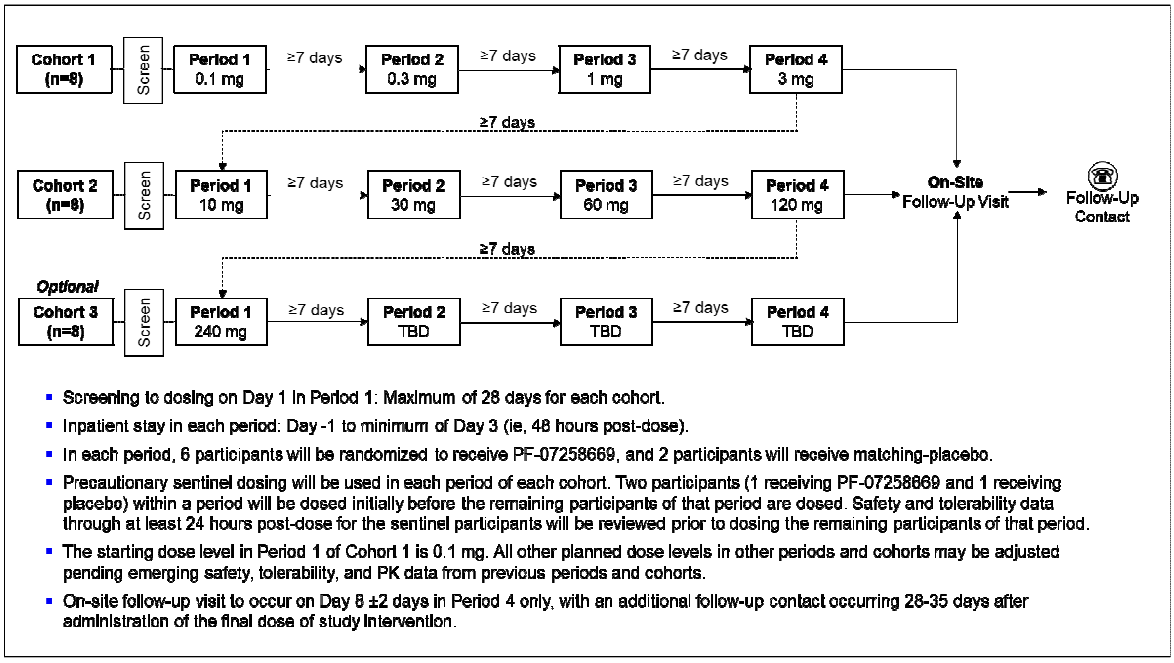
Data Monitoring Committee or Other Independent Oversight Committee: No.

Statistical Methods: The sample size has been chosen based on the need to minimize first exposure to humans of a new chemical entity and the requirement to conduct adequate safety, toleration, and PK assessments at each dose level.

All safety analyses will be performed on the safety analysis set, which is defined as all participants randomly assigned to study intervention and who receive a dose of study intervention. Participants will be analyzed according to the product they actually received. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

The PK parameters for PF-07258669 following oral dose administration will be derived from the plasma concentration-time profiles. PK parameters and concentrations of PF-07258669 will be descriptively summarized by dose and nominal time, as appropriate.

1.2. Schema



- Screening to dosing on Day 1 in Period 1: Maximum of 28 days for each cohort.
- Inpatient stay in each period: Day -1 to minimum of Day 3 (ie, 48 hours post-dose).
- In each period, 6 participants will be randomized to receive PF-07258669, and 2 participants will receive matching-placebo.
- Precautionary sentinel dosing will be used in each period of each cohort. Two participants (1 receiving PF-07258669 and 1 receiving placebo) within a period will be dosed initially before the remaining participants of that period are dosed. Safety and tolerability data through at least 24 hours post-dose for the sentinel participants will be reviewed prior to dosing the remaining participants of that period.
- The starting dose level in Period 1 of Cohort 1 is 0.1 mg. All other planned dose levels in other periods and cohorts may be adjusted pending emerging safety, tolerability, and PK data from previous periods and cohorts.
- On-site follow-up visit to occur on Day 8 ±2 days in Period 4 only, with an additional follow-up contact occurring 28-35 days after administration of the final dose of study intervention.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Identifier[a]	Screening	Period 1 to Period 4[b]															Follow-Up		ET/DC
	Day -28 to Day -2	Day -1	Day 1											Day 2		Day 3	Visit: Day 8±2[c]	Contact: 28-35 Days[c]	
Hours After Dose			0[d]	0.17	0.5	1	1.5	2	4	6	8	10	12	16	24	36	48			
Informed consent and demography	X																		
Outpatient visit	X																X		
Inpatient stay at CRU		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X[e]			
Review inclusion/exclusion criteria	X	X[f]																	
Medical/medication history	X	X[f]																	
History of alcohol, tobacco, and illegal drug use	X	X[f]																	
Contraception check[g]	X	X														X	X	X	X
COVID-19 questionnaire[h]	X	X																	
COVID-19 test[i]	X	X															X		
COVID-19 body temperature check	X	X	X										X		X	X	X	X	X
Physical exam (height and weight at Screening only)[j]	X	X																	
Neurological examination		X	X					X	X		X						X		X
Review concomitant treatments	X	X															X	X	X
Respiratory rate			X		X		X		X		X		X		X				X
Oral body temperature			X		X		X		X		X		X		X				
12-Lead ECG[k]	X		X		X	X	X	X	X	X	X		X		X		X	X		X
Supine BP and PR	X				X	X		X	X		X		X		X		X	X		X
Orthostatic (supine and standing) BP and PR			X				X			X										
Continuous cardiac telemetry[l]			X	→	→	→	→	→	→	→	X									
CCI [redacted]			[redacted]				[redacted]		[redacted]			[redacted]			[redacted]					
Serious/nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Blinded study intervention administration[o]			X[p]																	
Blood Samples for:																				
Clinical safety laboratory tests, including lipid panel[q]	X	X													X		X	X		X

Visit Identifier[a]	Screening	Period 1 to Period 4[b]															Follow-Up		ET/DC
	Day -28 to Day -2	Day -1	Day 1											Day 2		Day 3	Visit: Day 8±2[c]	Contact: 28-35 Days[c]	
Hours After Dose			0[d]	0.17	0.5	1	1.5	2	4	6	8	10	12	16	24	36	48			
Serum FSH[r]	X																			
HBcAb, HBsAg, HBsAb, HCVAb, HIV testing	X																			
Pfizer Prep B2 banked sample[s]			X																	
Pfizer Prep D1.5 banked sample[s]			X																	
PF-07258669 plasma pharmacokinetics			X	X	X	X	X	X	X	X	X		X	X	X	X	X			X
CCI																				
Urine Samples for:																				
Urine drug test	X	X																		
Clinical safety laboratory tests[q]	X	X													X		X	X		X

Abbreviations: → = ongoing/continuous event; AE = adverse event; BP = blood pressure; CRU = clinical research unit; DC = discontinuation; ECG = electrocardiogram; ET = early termination; FSH = follicle stimulating hormone; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B antibody; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C antibody; HIV = human immunodeficiency virus; PR = pulse rate.

a. Day relative to start of study treatment (Day 1).

b. There will be a washout interval of ≥7 days between doses within an individual participant.

c. Onsite follow-up visit to occur on Day 8 ±2 days in Period 4 only. Follow-up contact may occur via telephone contact and must occur 28-35 days after administration of the final dose of study intervention.

d. Day 1 activities at time=0 hours are prior to the dose, except for study treatment administration.

e. Participants may be confined to the CRU after completion of Day 3 activities at the discretion of the investigator or if safety, tolerability, or PK data dictate the need to prolong confinement in the CRU.

f. Period 1 only. Review any changes from Screening.

g. Contraception only required for male study participants and is recommended for partners of male study participants who are WOCBP.

h. COVID-19 questionnaire includes check for suspected contact, risk zone, and COVID-19 related symptoms.

i. Testing for active COVID-19 infection via testing for SARS-CoV-2 viral dosing (using PCR). To meet PCRU practice, testing for active COVID-19 infection will be performed at screening, admission, and follow-up visit.

j. Complete physical examination must either be conducted at Screening or upon admission in Period 1 only. Limited physical examination may be performed at admission on Day -1 in Period 1 if a complete physical examination is performed at Screening. Limited physical examinations may be performed as appropriate at other times at the investigator's discretion if there are findings during the previous examination or new/open adverse events.

k. Single 12-lead ECG at Screening. Triplicate 12-lead ECGs at all other timepoints.

l. Baseline telemetry to be recorded for at least 2 hours prior to the first dose in Period 1 only. This may be done immediately prior to dosing or at some 2 hour continuous interval in the 24 hours prior to dosing, as long as the participant is awake. Post-dose telemetry will continue for 8 hours after dosing.

CCI

c [redacted]

o. Precautionary sentinel dosing will be used in each period of each cohort. Two participants (1 receiving PF-07258669 and 1 receiving placebo) within a period will be dosed initially before the remaining participants of that period are dosed. Safety and tolerability data through at least 24 hours post-dose for the sentinel participants will be reviewed prior to dosing the remaining participants of that period.

p. Participants should fast for at least 10 hours prior to dosing.

q. Participants should fast for at least 12 hours prior to sample collection.

r. Females who have been amenorrheic for at least 12 months.

s. Period 1 only. If not collected on the designated collection day, collect at the next available time when biospecimens are being collected in conjunction with a participant visit.

c [redacted]

2. INTRODUCTION

PF-07258669 is an MC4R antagonist [redacted]

2.1. Study Rationale

This study will be the first time PF-07258669 is administered to humans. The purpose of the study is to evaluate the safety, tolerability, and PK of PF-07258669 following administration of single oral doses to healthy adult participants.

2.2. Background

2.2.1. MC4R [redacted]

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2.2.5. Nonclinical Safety

PF-07258669 was evaluated in a series of safety pharmacology and toxicity studies in rats and dogs up to 1 month in duration, as well as in a battery of genetic toxicity studies. CCI [redacted] The NOAELs in the pivotal 1-month toxicity studies were 100 mg/kg/day in rats (total C_{max} of 25,000 ng/mL and AUC of 224,000 ng•h/mL in males) and 30/60 mg/kg/day in male/female dogs (total C_{max} of 13,200 ng/mL and AUC of 159,000 ng•h/mL in males). PF-07258669 is not genotoxic CCI [redacted] Details of the nonclinical safety program are provided in the investigator's brochure.

2.3. Benefit/Risk Assessment

This study is the first time that PF-07258669 will be administered to humans and is designed primarily to generate safety, tolerability, and PK data for further clinical development. PF-07258669 is not expected to provide any clinical benefit to healthy participants. The purpose of the study is to provide the basis for further clinical development of PF-07258669 CCI [redacted] As of October 2020, no specific human risks have been identified; CCI [redacted] The clinical impact of these potential risks will be minimized through the proposed cautious dose-escalation process wherein higher doses of PF-07258669 will be administered only after lower doses have been found to be well tolerated with an acceptable safety profile. In addition, this study will use sentinel dosing and includes standard, intensive, inpatient monitoring of all participants following administration of single, oral doses of the study intervention.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-07258669 may be found in the investigator's brochure, which is the SRSD for this study.

CCI

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

2.3.2. Benefit Assessment

The participants in this study are not expected to obtain any specific benefit beyond contributing to the process of developing new therapies in an area of unmet need. They will receive close monitoring of their safety via study procedures undertaken (eg, physical examinations, 12-lead ECGs, vital signs) which will occur as outlined in this protocol.

2.3.3. Overall Benefit/Risk Conclusion

Based on the totality of available nonclinical data, and taking into account the measures taken to minimize risk to participants participating in this study, the overall benefit/risk profile supports clinical testing of PF-07258669.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety and tolerability of single ascending doses of PF-07258669 administered orally to healthy adult participants.	• Assessment of adverse events, clinical safety laboratory tests, vital signs, continuous cardiac monitoring, 12-lead electrocardiograms, respiratory rate, oral body temperature, physical examinations, and neurological examinations.
Secondary:	**Secondary:**
• To evaluate the pharmacokinetics of PF-07258669 following single doses of PF-07258669 administered orally to healthy adult participants.	• PK parameters derived from plasma PF-07258669 concentrations: C_{max}, AUC_{last}, AUC_{inf}, T_{max}, and $t_{½}$, if data permit.
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This study is a randomized, investigator- and participant-blind, sponsor-open, placebo-controlled, first-in-human, single ascending oral dose study of PF-07258669 administered to healthy adult participants. Up to approximately 24 healthy adult participants (up to 3 cohorts of approximately 8 participants each) will be enrolled in this study. Each participant is planned to undergo 4 treatment periods receiving 3 doses of PF-07258669 and 1 dose of placebo.

Precautionary sentinel dosing will be used in each period of each cohort. Two participants (1 receiving PF-07258669 and 1 receiving placebo) within a period will be dosed initially before the remaining participants of that period are dosed. Safety and tolerability data through at least 24 hours post-dose for the sentinel participants will be reviewed prior to dosing the remaining participants of that period.

Dose levels will be escalated to bracket the expected clinical dose range, but projected exposures will not exceed the pre-defined human exposure limits. The optional third cohort will only be used if the objectives of the study are not fulfilled in Cohort 1 and Cohort 2. The total duration of participation from the screening visit to the telephone follow-up contact will be approximately 14 weeks.

If a participant drops out before completing all study periods within a cohort, or withdraws for reasons unrelated to the safety of the study intervention, the participant may be replaced at the discretion of the investigator and sponsor. The replacement participant(s) may or may not be required to complete all periods of the cohort in which they are participating at the discretion of the investigator and sponsor.

4.2. Scientific Rationale for Study Design

The population planned for this study will be healthy males and females of nonchildbearing potential. Female participants will be confirmed not to be of childbearing potential because embryo-fetal developmental toxicity studies with PF-07258669 have not been conducted. In male participants, appropriate measures are expected to be followed to minimize potential transfer of PF-07258669 via semen to partners (see Appendix 4).

Because this is the first time PF-07258669 will be administered to humans, an escalating single oral dose design is planned with careful assessment and ongoing review of safety, tolerability, and PK data of PF-07258669. Sentinel dosing will also be utilized in each period to ensure that safety and tolerability data in a subset of 2 participants within each period supports testing additional participants.

At each dose level, 6 participants are planned to receive PF-07258669 and 2 participants are planned to receive placebo with all participants at the end of the study having received 1 dose of placebo and 3 doses of PF-07258669. In addition, the highest anticipated C_{max} and AUC_{24} PF-07258669 will not exceed the pre-identified human exposure stopping limits nor exceed the highest feasible total daily dose of 2000 mg.

The design permits both within- and between-participant assessments of safety, tolerability, and PK. Furthermore, to permit an unbiased assessment of safety, the administration of both PF-07258669 and placebo in each period will be double-blinded to both site staff (except those involved in preparation of doses) as well as the participants.

PK samples are planned to be collected over 48 hours post-dose. However, sampling times, duration of sampling, and/or the length of the washout period may be modified and/or extended if data generated in previous periods indicate that the half-life is longer than predicted.

There will be a washout interval of ≥7 days between doses within an individual participant, which is deemed sufficient based on the predicted PF-07258669 effective half-life [redacted]. In addition, this interval accounts for the required time for review of the safety, tolerability, and PK data from each dosing period before making a decision on the subsequent PF-07258669 dose to be evaluated. The planned doses in the escalation sequence (Table 1 and Section 1.2) may be modified or repeated, as guided by emerging safety, tolerability, and PK data but will follow the dose-escalation rules defined in Section 6.6.1.

[redacted]

[redacted]

[redacted]

Although there is no suspicion of human teratogenicity based on the expected pharmacology of PF-07258669, human reproductive safety data are not available for PF-07258669. Therefore, the use of a highly effective method of contraception is required for male study participants and is recommended for partners of male study participants who are WOCBP (see Appendix 4).

Banked Biospecimens 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 proposed dose levels of PF-07258669 were derived based on cumulative nonclinical data including in vitro and in vivo pharmacology and PK data and the completed nonclinical toxicity studies. Dose levels have been selected to bracket the expected clinical dose and exposure range, while considering uncertainty in the projected clinically efficacious dose. Dose levels beyond the starting dose may be modified based on emerging human safety, tolerability, and PK data in the current study.

CCI [redacted]

CCI [redacted]

CCI [redacted]

4.3.2. Human Exposure Stopping Limits

The human exposure stopping limits are based on exposures observed in dogs in nonclinical toxicology studies and are corrected for species-dependent plasma protein binding between dog and human CCI [redacted].

CCI [redacted]

The human AUC_{24} stopping limit is based on the NOAEL in male dogs (30 mg/kg/day) in 4-week GLP toxicology study. The total AUC_{24} in male dogs was 159,000 ng·h/mL, which is the lowest AUC_{24} observed at the NOAEL across all toxicology studies in rats and dogs. After correcting for protein binding differences between dog and human, the human AUC_{24} stopping limit is a total AUC_{24} of 212,000 ng·h/mL.

4.3.3. Rationale for Dose Selection

The safety, tolerability, and plasma PK of PF-07258669, after administration of single escalating oral doses across a wide dose/exposure range, will be evaluated in this study. Dosing will occur in the fasted state. The doses presented in Table 1 are projected based on nonclinical data and may be modified based on emerging human safety, tolerability, and PK data. Human PK parameter estimates, toxicokinetic data, and projected effective concentrations were used to establish the initial range of planned doses in this study. The projected human exposures assume dose-proportional increases in exposure within the planned dose range.

CCI [redacted]

CCI [redacted]

Due to the CCI projected $t_{½}$ of PF-07258669, plasma concentrations are expected to decrease rapidly upon attainment of C_{max}. CCI [redacted] Therefore, given that the predicted exposure following a dose of 0.1 mg is not expected to result in any biological activity and affords large margins over the human C_{max} stopping limit, it is deemed an appropriate starting dose level for this study.

The dose range to be studied was selected to account for uncertainties in the projected C_{eff} and the projected therapeutic dose, while also bracketing the expected clinically effective dose range in humans CCI [redacted] and providing safety coverage for a wide range of PF-07258669 doses.

Assessment of the safety, tolerability, and PK after each single dose level will be conducted before escalating to the next dose level. The dose/exposure-escalation increments are planned to be up to approximately semi-logarithmic increases in exposure from the previous highest dose. The actual dose levels, target exposures, and/or dose level increments may be adjusted (higher or lower) during the study based on emerging human safety, tolerability, and PK data, but projected exposures will not exceed the predefined human exposure limits. If C_{max}-related adverse events are observed, split dosing may be used to potentially increase AUC without increasing C_{max}. Dose levels may also be repeated if warranted.

4.4. End of Study Definition

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

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.

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. Female participants of nonchildbearing potential and males must be 18 to 55 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. Female participants of non-child bearing potential and male participants and who are overtly healthy as determined by medical evaluation including medical history, physical examination, neurological examination, laboratory tests, and cardiac monitoring.

3. Participants who are willing to avoid direct sunlight exposure or any high intensity ultraviolet light exposure from admission to the follow-up contact and to apply sunscreen/lotion with a high sun protection factor, as appropriate.

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

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. 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), as well as presence of lipid panel abnormalities (eg, hypercholesterolemia, hypertriglyceridemia).

2. Evidence of history of orthostatic hypotension or symptomatic bradycardia.

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

4. History of phototoxicity or photosensitivity.

5. History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) or hepatitis C antibody (HCVAb). Hepatitis B vaccination is allowed. As an exception a positive HBsAb test due to hepatitis B vaccination is permissible.

6. Other medical or psychiatric condition including recent (within the past year), or active suicidal ideation/behavior, or laboratory abnormality, or other condition or situation related to the COVID-19 pandemic 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 6.5 for additional details).

Prior/Concurrent Clinical Study Experience:

8. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

9. A positive urine drug test at screening or admission and confirmed by a single repeat test, if deemed necessary.

10. 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.

11. Current findings or documented past history of blood pressure values <90 mmHg systolic or <50 mmHg diastolic.

12. 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTc interval >450 msec, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the

baseline uncorrected QT interval is >450 msec, this interval should be rate-corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc 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 participants.

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

    - AST **or** ALT level ≥1.0× ULN;
    - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ULN;
    - Any lipid panel parameter (ie, total cholesterol, triglycerides, HDL, and/or LDL) ≥1.25× ULN.

14. A positive COVID-19 test.

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 equivalent of 5 cigarettes/day or 2 chews of tobacco/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.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 12 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the predose PK sample.
- Water is permitted until 1 hour prior to study intervention administration. Water may be consumed without restriction beginning 1 hour after dosing. Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices—see below) may be consumed with meals and the evening snack.
- Lunch will be provided approximately 4 hours after dosing.
- Dinner will be provided approximately 9 to 10 hours after dosing.
- An evening snack may be permitted.
- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.
- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

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

5.3.3. Activity

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

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

- Participants will be confined to the procedure room for the first 4 hours after dosing on Day 1 during continuous cardiac monitoring, except to use the bathroom. After this, if the equipment setup allows, participants may be ambulatory during the ECG monitoring period, but should not engage in strenuous activities. If equipment does not allow ambulation, appropriate accommodations will be made by the investigator site to facilitate continuous monitoring (eg, bedside urinals should be provided to accommodate participants' excretory needs).

- Participants will be advised to avoid direct sunlight exposure or any high intensity UV light exposure, from admission in Period 1 through the follow-up contact. In addition, participants will be instructed to apply sun cream/lotion with a sun protection factor (SPF) of ≥50, as appropriate.

5.3.4. Contraception

Contraception is only required for male study participants and is recommended for partners of male study participants who are WOCBP.

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the schedule of activities (SoA), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). 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 randomly assigned to study intervention/enrolled in the study. Screen failure data are collected and remain as source and are not reported to the clinical database.

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

6. STUDY INTERVENTION

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 all of the following:

- PF-07258669;
- Placebo for PF-07258669.

6.1. Study Intervention(s) Administered

PF-07258669 and placebo will be provided by Pfizer as bulk powders for extemporaneous preparation of oral solutions and suspensions at the CRU.

PF-07258669 and placebo will be presented to the participants in individual dosing containers.

6.1.1. Administration

Following an overnight fast of at least 10 hours, participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours) without breakfast on Day 1.

Investigator site personnel will administer a single oral dose of study intervention on Day 1 of each period with ambient temperature water to a total volume of approximately 240 mL. Study intervention will be administered according to the EDR.

6.2. Preparation/Handling/Storage/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 CRU 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. See the EDR for storage conditions of the study intervention once prepared.

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

8. Further guidance and information for the final disposition of unused study interventions are provided in the CRU 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-07258669 and placebo oral dosing solutions and suspensions will be prepared in the CRU by 2 operators, 1 of whom is a pharmacist. Details of dose preparation will be given in a separate 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 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.

Participants will be randomly assigned to receive study intervention from a central randomization scheme. Investigators and participants will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third party (for example, pharmacist) will be responsible for the preparation and dispensing of all study intervention according to the randomization schedule and assigned treatment for the individual participant.

6.3.2. Breaking the Blind

The method for breaking the blind in this study will be manual. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. When the blinding code is broken, the reason must be fully documented in the CRF.

Blood specimens will be obtained from all participants for PK analysis to maintain the study blind at the investigator site. Only the investigator site staff and blinded study monitor, if assigned, will be blinded to study treatment. A limited number of Pfizer study team personnel will be unblinded to participant treatments in order to permit real-time interpretation of the safety and PK data and provide information necessary to potentially alter the dose-escalation sequence. The blinded study monitor, if assigned, will remain blinded to treatment until all monitoring for the study has been completed. Specimens from participants randomized to placebo will not be routinely analyzed. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer unblinded personnel and will not be released to the blinded investigator or blinded investigator site personnel until the study database has been locked or the investigator requests unblinding for safety reasons.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff.

6.5. Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention through the follow-up contact. 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.

Females taking hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

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

6.5.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07258669; standard medical supportive care must be provided to manage the AEs.

6.6. Dose Modification

The decision to proceed to the next dose level of PF-07258669 (eg, an increase, decrease, or repeat of a previous dose level) will be made by the study team and the investigator based on safety, tolerability, and preliminary PK data at the prior dose level. At least 6 participants (including at least 1 placebo participant) must complete the prior dose level. PK data through at least 24 hours post-dose will be reviewed.

The dosing schedule may also be adjusted to add cohorts (8 participants/cohort) to evaluate additional dose levels. The study procedures for these additional participant(s)/cohort(s) will be the same as that described for other study participants/cohorts.

6.6.1. Dose Escalation and Stopping Rules

Precautionary sentinel dosing will be used in each period of each cohort. Two participants (1 receiving PF-07258669 and 1 receiving placebo) within a period will be dosed initially before the remaining participants of that period are dosed. Safety and tolerability data through at least 24 hours post-dose for the sentinel participants will be reviewed prior to dosing the remaining participants of that period.

Dose escalation stopping rules will be used to determine whether the maximal tolerated dose has been attained. Dose escalation may be stopped if it is determined that the limits of safety and/or tolerability have been reached. This decision will be made after a discussion takes place between the sponsor study team and the investigator. The sponsor study team may not overrule the investigator's decision to stop dose escalation. If dose escalation is stopped because of any of these criteria, additional cohorts may receive the same or lower doses of the study intervention.

The dose escalation will be terminated based on the following criteria:

- If 50% or more of the participants receiving active drug at a given dose level (but not participants receiving placebo) develop similar clinically significant laboratory, ECG, or vital sign abnormalities, in the same organ class, indicating dose-limiting intolerance.

- Severe nonserious AEs, considered as, at least, possibly related to study intervention administration, in 2 participants at a given dose level (but not participants receiving placebo), independent of within or not within the same system organ class, indicating dose-limiting intolerance.

- Dosing will be paused for any SAE that occurs in a participant receiving active treatment until causality is fully assessed by the PI and sponsor. Dosing may resume if the SAE is determined to be not drug-related by the PI and sponsor. If the SAE is determined to be either drug-related or unknown, either dosing will cease or the SAE will be evaluated by the sponsor's protocol review committee (or similar review group), which is independent of the study team and investigators. If the protocol review committee determines that dosing may resume, a plan that mitigates risks to participants with the resumption of dosing will be implemented. Such a plan could include a revision of inclusion/exclusion criteria, repeating or reducing the dose, or adding appropriate safety monitoring.

- It is determined that the limit of safety and/or tolerability has been reached. This decision will be made following discussions between the study team and the investigator.

- Other findings that, at the discretion of the study team and investigator, indicate that dose escalation should be halted.

- CCI [redacted]

- If, based on the observed data, the group mean C_{max} or AUC (based on total plasma concentration) of the next planned dose is projected to exceed the escalation limits, that dose will not be explored. Modified doses may be explored if they are not expected to exceed PK stopping criteria.

Progression to the next dose level will occur if the last dose was well tolerated and after satisfactory review of the available safety and PK data.

At a minimum, review of safety and tolerability data through 48 hours post-dose, and PK data through 24 hours post-dose, is required in order to escalate to the next dose level. The safety and tolerability assessments are outlined in the study endpoints and include assessment of adverse events, clinical safety laboratory tests, vital signs, continuous cardiac monitoring, 12-lead electrocardiograms, respiratory rate, oral body temperature, physical examinations, and neurological examinations.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following: adverse event, or some other (administrative) reason.

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

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

ECG Changes

A participant who meets either of the following bulleted criteria 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.

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 in a given period 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.

7.2. 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 follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the participant to comply with the protocol required schedule of study visits or procedures.

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 received at least 1 dose of the study intervention and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued both from the study intervention and from 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.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not 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.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical assessments or specimen collections, eg, banked biospecimens, may be used without repeat collection, as appropriate.

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

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 475 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

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

8.1. Efficacy Assessments

No efficacy assessments are being conducted in this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

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

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

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

8.2.2. Neurological Examinations

Neurological examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. The neurological exam will consist of assessment of higher cortical function, the cranial nerves, motor function, deep tendon reflexes, sensory exam, and coordination and gait. The exam should be done to the extent needed to assess the participant for any potential changes in neurological status, as determined by the investigator (or designee).

8.2.3. Vital Signs

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

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

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

The procedure for collecting postural or orthostatic data will be:

- Assess BP after the participant is in the supine position for a minimum of 5 minutes;
- Have the participant stand up for 2 minutes;
- Assess BP after the participant is in the standing position for approximately 2 minutes.

Orthostatic hypotension is defined as a decrease of ≥20 mm Hg for systolic BP or ≥10 mm Hg for diastolic BP 2 minutes after standing from a supine position. Orthostatic hypotension may be symptomatic or asymptomatic. Symptoms of orthostatic hypotension are those that develop upon assuming the erect posture from a supine position and may include: lightheadedness, dizziness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, and/or neck ache.

If a participant has symptoms suggestive of orthostasis, but not documented orthostatic hypotension, repeated measurements of supine/standing BP (triplicate supine/1 standing and further monitoring based on investigator/medical judgement) should be obtained. Lesser degrees of BP reduction may still be considered clinically significant if the participant becomes symptomatic upon standing, especially in the presence of a significant increase in pulse rate (≥30 beats per minute [bpm]).

8.2.4. Respiratory Rate

Respiratory rate will be measured at times specified in the SoA. After approximately 5 minutes rest in supine position, respiratory rate will be measured by observing and counting the respirations of the subject for 30 seconds and multiplied by 2. When blood pressure is to be taken at the same time, respiration measurement will be done during the 5 minutes of rest and before blood pressure measurement.

8.2.5. Oral Body Temperature

Body temperature will be measured orally. No eating or drinking is allowed for 15 minutes prior to the measurement.

8.2.6. 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 QTcF intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) is not permitted 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 10 minutes in a supine position.

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

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

If a) a postdose QTcF interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTcF 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 criterion 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 QTcF 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.

8.2.6.1. Continuous Cardiac Monitoring by Telemetry

All abnormal rhythms will be recorded and reviewed by the study physician for the presence of rhythms of potential clinical concern. The time, duration, and description of the clinically significant event will be recorded in the CRF. In addition, a printed record of the tracing(s) of the clinically significant rhythm(s) will be made and retained with other source documents.

Telemetry should be collected using a centralized system that also allows for the storage and advanced analysis of all recorded data in order to preserve important events for future evaluations. Holter monitoring should not be used in parallel with continuous telemetry, unless it is the only means of data storage available at the investigator site, or verifiable arrhythmia quantification is required. To establish a baseline, telemetry should be recorded for at least 2 hours before dosing in Period 1. This may be done immediately prior to dosing or at some 2-hour continuous interval in the 24 hours prior to dosing, as long as the recording is performed when the participant is awake. Telemetry may be stopped within a reasonably short period of time prior to dosing, in order to avoid interference with study operations conducted immediately before dosing. However, it is expected that the telemetry leads will be in place and the system connected prior to dosing.

8.2.7. 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 14 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

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

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.

8.2.8. COVID-19 Specific Assessments

Participants will be tested for SARS-COVID-19 infection by PCR prior to being admitted to the clinic. Subsequent COVID-19 tests will be performed if they develop COVID-19 like symptoms. Additional testing may be required by local regulations or by the investigator.

8.3. Adverse Events and Serious Adverse Events

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

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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).

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 and Pfizer concurs with that assessment.

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

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

If a participant definitively 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 AE or SAE 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.

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/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 towards 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. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- 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 exposure during pregnancy:

    - 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 at least 28 days after the last dose of the study intervention.

- 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 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 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

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information 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 is 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, at the wrong dosage strength, or inadvert exposure.

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. Treatment of Overdose

CCI [redacted]

The sponsor does not recommend 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-07258669 (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 Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within 5 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

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

[redacted]

8.7. Genetics

8.7.1. Specified Genetics

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

8.7.2. Banked Biospecimens for Genetics

A 2-mL blood sample optimized for DNA isolation Prep D1.5 will be collected as local regulations and IRBs/ECs allow.

Banked Biospecimens may be used for research related to the study intervention(s). Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the lab manual and other supporting documentation.

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8.8.2. Banked Biospecimens for Biomarkers

Additional Banked Biospecimens in this study are:

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

Banked Biospecimens will be collected as local regulations and IRB/ECs allow. Banked Biospecimens may be used for research related to the study intervention(s) and safety biomarkers. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples. See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the lab manual and other supporting documentation.

8.8.3. Specified Gene Expression (RNA) Research

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

8.8.4. Specified Protein Research

Specified protein research is not included in this study.

8.8.5. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

No formal hypothesis tests are planned for this study.

9.2. Sample Size Determination

A sample size of up to approximately 8 participants per cohort (approximately 6 participants receiving PF-07258669 and up to 2 participants receiving placebo within each period) has been chosen based on the need to minimize first exposure to humans of a new chemical entity and the requirement to provide adequate safety, tolerability, and PK assessment at each dose level. There are 2 planned cohorts and an additional optional third cohort which will only be used if the objectives of the study are not fulfilled in Cohort 1 and Cohort 2.

Participants who discontinue prior to completion of the study may be replaced, at the discretion of the investigator and sponsor.

9.3. Analysis Sets

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

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

9.4. 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. Analysis of the tertiary/exploratory endpoints will be documented in the SAP.

9.4.1. Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, pulse rate, respiratory rate, oral body temperature, continuous cardiac monitoring, 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, pulse rate, and respiratory rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

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

9.4.1.1. Electrocardiogram Interval Analyses

Changes from baseline for the ECG parameters (ie, QT interval, heart rate, QTcF interval, PR interval, and QRS complex) will be summarized by treatment and time.

The number (%) of participants with maximum postdose QTcF values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTcF Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

When more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec. Changes

from baseline will be defined as the change between the postdose QTcF value and the average of the predose triplicate values on Day 1.

In addition, an attempt may be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of participant factors (covariates) on the relationship may be examined. The results of such analyses will not be included in the CSR.

9.4.2. PK Analyses

The analysis populations are defined as in Section 9.3.

9.4.2.1. Derivation of PK Parameters

The PK parameters for PF-07258669, following oral dose administration, will be derived from the plasma concentration-time profiles as detailed in Table 2, as data permit. In all cases, actual PK sampling times will be used in the derivation of PK parameters.

Table 2. Plasma PK Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}*	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where C_{last}* is the predicted plasma concentration at the last quantifiable timepoint estimated from the log-linear regression analysis
C_{max}	Maximum observed concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{1/2}$*	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve • Only those data points judged to describe the terminal log-linear decline will be used in the regression
CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

*As data permit.

9.4.2.2. Statistical Methods for PK Data

Plasma concentrations of PF-07258669 will be summarized descriptively by dose and nominal PK sampling time. Individual participant and median profiles of the plasma concentration-time data will be plotted by dose using actual (for individual) and nominal (for median) times respectively. Median profiles will be presented on both linear and log scales.

The plasma PK parameters will be summarized descriptively by dose in accordance with Pfizer data standards, as data permit. CCI [redacted]

Additional PK analyses may be performed if deemed appropriate, and may not be included in the CSR.

9.4.3. Other Analyses

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

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is a sponsor-open study, a limited number of the sponsor's team members (excluding site staff) may conduct unblinded reviews of the data during the course of the study for the purpose of safety and tolerability assessments, facilitating dose-escalation decisions, facilitating PK modeling, and/or supporting clinical development.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a DMC.

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 and 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.

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 guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (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 ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study 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, HIPAA 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 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.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

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 identification. 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. 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 available data from these trials 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.

10.1.6. Data Quality Assurance

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

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

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 (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, remote, or on-site monitoring), are provided in the IQMP.

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

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, and all applicable regulatory requirements.

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

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

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

10.1.7. Source Documents

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

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

Definition of what constitutes source data can be found in the Source Document Locator.

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

10.1.8. Study and Site Start and Closure

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

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

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

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

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

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

10.1.9. Publication Policy

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

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

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

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

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

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

10.1.10. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 3. Protocol Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN (urea) and creatinine eGFR (CKD-EPI) Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein Lipid panel: • Total cholesterol • Triglycerides • HDL • LDL (calculated)	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	• Urine drug screening[b] • COVID-19 testing At screening only: • FSH[c] • Hepatitis B surface antigen • Hepatitis B surface antibody • Hepatitis B core antibody • Hepatitis C antibody • Human immunodeficiency virus

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
c. For confirmation of postmenopausal status only.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigator sites or other blinded personnel until the study has been unblinded.

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]

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

10.3.1. Definition of AE

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

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

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/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 which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from

baseline is not considered an AE.

d. Results in persistent 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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but 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.
- 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 patient 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.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. 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, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding. Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/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/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/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/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: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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/SAE.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- 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/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/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 completed CRF.
- 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) in order 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 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 a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception is recommended for 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 a WOCBP (see definitions below in Section 10.4.3.

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.
     - 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

The following contraception methods are to be used by women of childbearing potential who are partners of male participants in this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner.

- Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

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

   - Oral;
   - Intravaginal;
   - Transdermal;
   - Injectable.

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

   - Oral;
   - Injectable.

8. Sexual abstinence.

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

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

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

- The scope of the genetic research may be narrow ((eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-07258669/placebo or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

    - Samples for banking will be stored indefinitely or for another period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Banked Biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Banked Biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, 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, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

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

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and

monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

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

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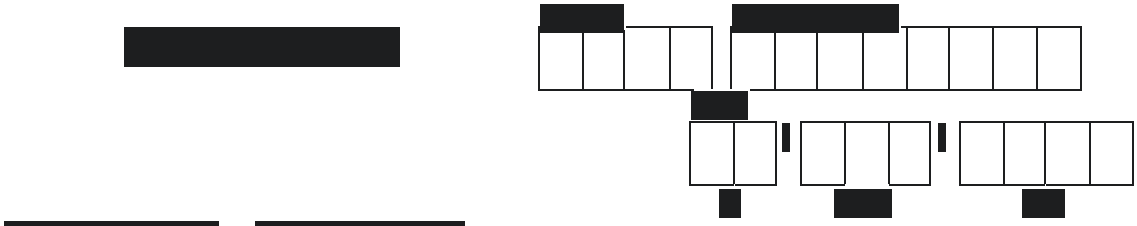

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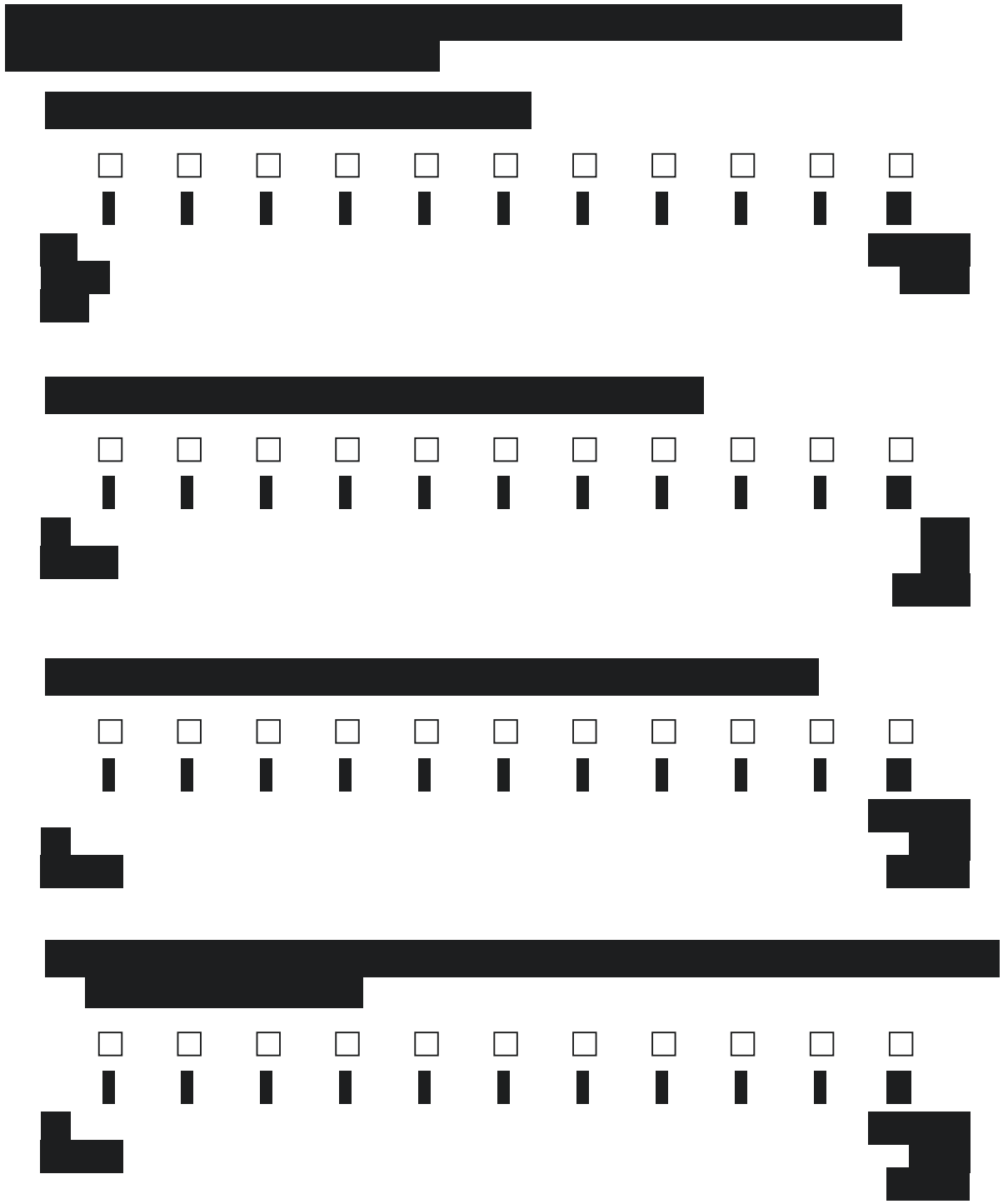

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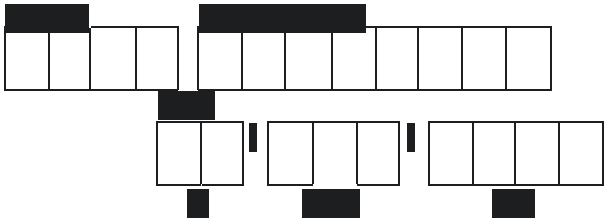

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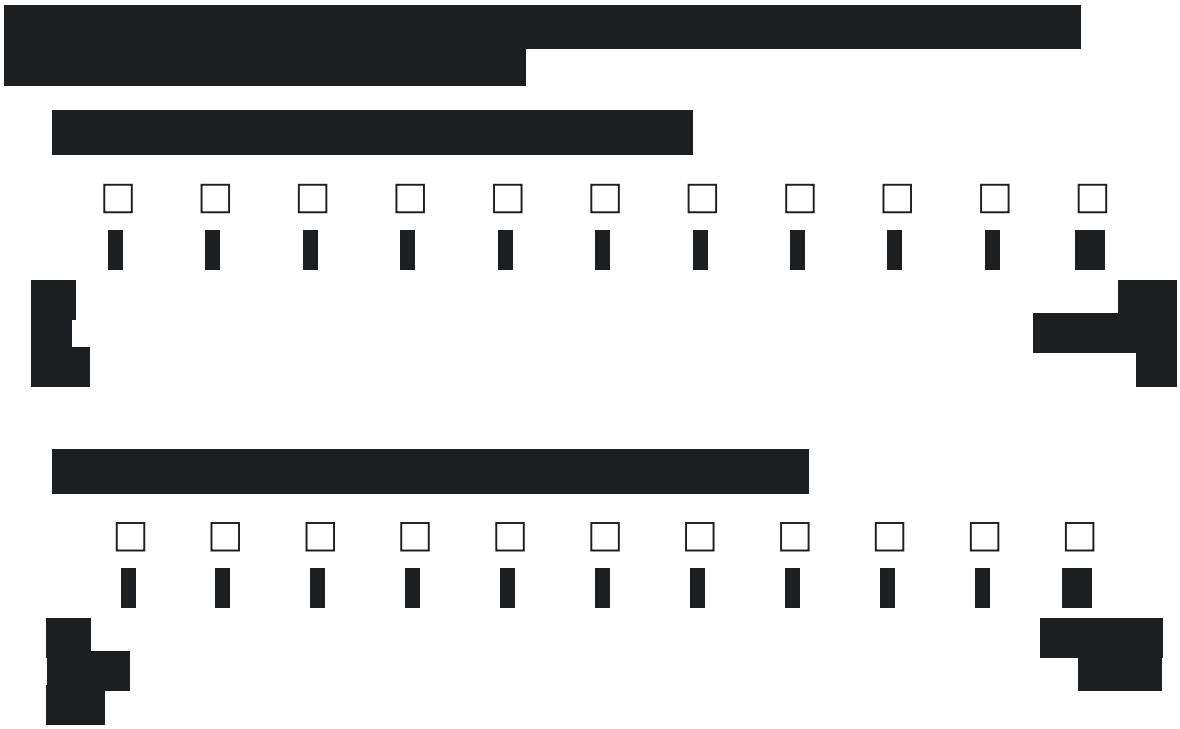

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
Abs	absolute
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
CCI	[redacted]
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the curve from time=0 to time=24 hours post dose
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration
AUC_{inf}	area under the plasma concentration-time profile from time 0 extrapolated to infinite time
CCI	[redacted]
AV	atrioventricular
CCI	[redacted]
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CCI	[redacted]
C_{eff}	efficacious concentration
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{last}	last quantifiable concentration
CCI	[redacted]
C_{max}	maximum observed concentration
CCI	[redacted]
CO_2	carbon dioxide (bicarbonate)
COVID-19	Coronavirus Disease 2019
CCI	[redacted]
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CCI	[redacted]

Abbreviation	Term
CSR	clinical study report
CT	clinical trial
CTMS	clinical trial management system
CCI	[redacted]
DC	discontinuation
CCI	[redacted]
DILI	drug-induced liver injury
DMC	data monitoring committee
CCI	[redacted]
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
CCI	[redacted]
FSH	follicle-stimulating hormone
CCI	[redacted]
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GPCR	G-protein coupled receptor
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification

Abbreviation	Term
IND	investigational new drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IQMP	integrated quality management plan
IRB	institutional review board
IV	intravenous
[redacted]	[redacted]
k_{el}	elimination rate constant
[redacted]	[redacted]
LBBB	left bundle branch block
LFT	liver function test
LDL	low-density lipoprotein
[redacted]	[redacted]
MC1R	melanocortin-1 receptor
MC2R	melanocortin-2 receptor
MC3R	melanocortin-3 receptor
MC4R	melanocortin-4 receptor
MC5R	melanocortin-5 receptor
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
[redacted]	[redacted]
msec	millisecond
N/A	not applicable
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect-level
PCR	polymerase chain reaction
PCRU	Pfizer clinical research unit
PD	pharmacodynamic(s)
[redacted]	[redacted]
PI	principal investigator
PIMS	Phase 1 Management System
PK	pharmacokinetic(s)
[redacted]	[redacted]
PR	pulse rate
PT	prothrombin time
PVC	premature ventricular contraction/complex
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
RBC	red blood cell

Abbreviation	Term
CCI [redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SoA	schedule of activities
SOP	standard operating procedure
SPF	sun protection factor
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal half-life
TBili	total bilirubin
THC	tetrahydrocannabinol
T_{max}	time for C_{max}
CCI [redacted]	[redacted]
ULN	upper limit of normal
US	United States
UV	ultraviolet
CCI [redacted]	[redacted]
WBC	white blood cell
WOCBP	woman of childbearing potential

11. REFERENCES

[redacted]

CCI

CCI

CCI

CCI