# A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY AND PHARMACOKINETICS FOLLOWING SINGLE INTRAVENOUS DOSE OF PF-06823859 IN JAPANESE HEALTHY PARTICIPANTS

| | |
|---|---|
| **Study Intervention Number:** | PF-06823859 |
| **Study Intervention Name:** | N/A |
| **US IND Number:** | N/A |
| **EudraCT Number:** | N/A |
| **ClinicalTrials.gov ID:** | N/A |
| **Protocol Number:** | C0251005 |
| **Phase:** | 1 |

**Brief Title:** A Phase 1 Study to Evaluate the Safety, Tolerability, Immunogenicity and Pharmacokinetics of Single-Dose of PF-06823859 in Japanese Healthy Participants

## Document History

| Document | Version Date |
|---|---|
| Amendment 1 | 09 Jul 2021 |
| Original protocol | 26 May 2021 |

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

## Protocol Amendment Summary of Changes Table

## Amendment 1 (09-Jul-2021)

## Overall Rationale for the Amendment:

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 5.2 Exclusion Criteria 6 | Added descriptions that history of allergic or anaphylactic reaction to any components in the study intervention is also excluded. | To ensure participant's safety. |

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# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

**Brief Title:** A Phase 1 Study to Evaluate the Safety, Tolerability, Immunogenicity and Pharmacokinetics of Single-Dose of PF-06823859 in Japanese Healthy Participants.

### Rationale

The purpose of this study is to evaluate the safety, tolerability, immunogenicity and PK of PF-06823859 after single IV administration to Japanese healthy adult participants. The information of safety, tolerability, immunogenicity and PK in Japanese healthy participants is being collected to support the development of PF-06823859 in Japan.

### Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| **Primary:** | **Primary:** |
| • To evaluate the safety and tolerability of single IV dose of 300 and 900 mg PF-06823859 in Japanese healthy participants. | • Assessments of AEs/SAEs including IRR, infusion sites and viral infections, vital signs, ECGs and laboratory tests. |
| **Secondary:** | **Secondary:** |
| • To evaluate the PK profile of single IV dose of 300 and 900 mg PF-06823859 in Japanese healthy participants.<br>• To evaluate the immunogenicity of PF-06823859. | • Serum PF-06823859 PK parameters, as permitted by data: $C_{max}$, $C_{max}$ (dn), $T_{max}$, $AUC_{inf}$, $AUC_{inf}$ (dn), $AUC_{last}$, $AUC_{last}$ (dn), $AUC_{14day}$, $AUC_{28day}$, $t_{½}$, CL, $V_{ss}$ and MRT.<br>• Incidence of the development of ADA and NAb. |

**Overall Design**

This is a Phase 1, randomized, double-blind, sponsor-open, placebo-controlled study to evaluate the safety, tolerability, immunogenicity and PK of PF-06823859 following a single intravenous dose of PF-06823859 300 and 900 mg in Japanese healthy adult participants.

**Number of Participants**

Approximately 12 participants are planned to be enrolled into the study. The study consists of 2 cohorts, and approximately 5 participants will be randomized to PF-06823859 and approximately 1 participant will be randomized to placebo in each cohort (Section 9.5).

Participants who discontinue prior to completion of the study for non-safety related reasons may be replaced at the discretion of the investigator upon consultation with the sponsor.

**Intervention Groups and Duration**

Within 28 days of successful completion of the screening process, eligible participants will be enrolled and randomized to receive a single IV infusion of PF-06823859 or placebo. The participants in Cohort 2 should be dosed following at least 96 hours safety pause after the participants in Cohort 1 has been dosed. Participants will be admitted into the CRU approximately 1 day prior to dosing and are required to stay overnight in the CRU through completion of Day 5 evaluations. Participants will return to the CRU for outpatient follow-up visits through Day 157.

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

**Statistical Methods**

Safety and tolerability data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and/or graphical presentations.

Serum concentrations and serum PK parameters of PF-06823859 will be summarized descriptively.

## 1.2. Schema

Not applicable.

## 1.3. Schedule of Activities

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

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

| **Visit Identifier**[a] Abbreviations used in this table may be found in Appendix 8. | **Screening** | **CRU Confinement** | | | | | | | | | | **Follow-Up** | | | | | | | | | **ET** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Days Relative to Day 1** | **-28 to -2** | **-1** | **1** | | | | | **2** | **3** | **4** | **5** | **8** | **15** | **29** | **43** | **57** | **71** | **99** | **127** | **157** | **-** |
| **Visit Window (days)** | - | - | - | | | | | - | - | - | - | ±1 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | - |
| **Hours After Dose** | | | 0[b] | 1 | 2 | 6 | 12 | 24 | 48 | 72 | 96 | - | - | - | - | - | - | - | - | - | - |
| Informed consent | X | | | | | | | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | | | | | | | |
| CRU confinement | | X | → | → | → | → | → | → | → | → | X | | | | | | | | | | |
| Visit to the CRU | X | X | | | | | | | | | | X | X | X | X | X | X | X | X | X | X |
| Inclusion/exclusion criteria | X | X | | | | | | | | | | | | | | | | | | | |
| Medical/medication history (update) | X | X | | | | | | | | | | | | | | | | | | | |
| History of illegal drug & alcohol and tobacco use | X | X | | | | | | | | | | | | | | | | | | | |
| Report prior or concomitant treatments | X | X | → | → | → | → | → | → | → | → | → | X | X | X | X | X | X | X | X | X | X |
| Contraception check | X | X | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X |
| Physical exam (including height & body weight at screening, only)[c] | X | X | | | | | | | | | | | | | | | | | | | X |
| Single 12-Lead ECG | X | | X | | | | | | | | X | | | X | | X | | X | X | X | X |
| Supine BP, PR and oral or axillary temperature | X | | X | | | | | | | | X | | | X | | X | | X | X | X | X |
| Chest X-ray[d] | X | | | | | | | | | | | | | | | | | | | | |
| Serious and nonserious AE monitoring | X | → | → | → | → | → | → | → | → | → | X | X | X | X | X | X | X | X | X | X | X |
| Study intervention administration | | | X[e] | | | | | | | | | | | | | | | | | | |
| Safety laboratory (after ≥4 hour fasting) including PT, INR, aPTT | X | X | | | | | | X | | | X | X | X | X | | X | | X | X | X | X |
| Viral surveillance (CMV, VZV, EBV, HHV6, HSV-1/2) | X | | | | | | | | | | | X | X | X | | X | | | | X | X |

| **Visit Identifier**[a] Abbreviations used in this table may be found in Appendix 8. | **Screening** | **CRU Confinement** | | | | | | | | | **Follow-Up** | | | | | | | | | **ET** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Days Relative to Day 1** | **-28 to -2** | **-1** | **1** | | | | | **2** | **3** | **4** | **5** | **8** | **15** | **29** | **43** | **57** | **71** | **99** | **127** | **157** | **-** |
| **Visit Window (days)** | - | - | - | | | | | - | - | - | - | ±1 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | - |
| **Hours After Dose** | | | 0[b] | 1 | 2 | 6 | 12 | 24 | 48 | 72 | 96 | - | - | - | - | - | - | - | - | - | - |
| FSH in females amenorrheic ≥12 months, only | X | | | | | | | | | | | | | | | | | | | | |
| Pregnancy test (WOCBP only) | X | X | | | | | | | | | | X | | X | | X | X | X | X | X | X |
| HIV, HBsAg, HBsAb, HBcAb, HCVAb, syphilis | X | | | | | | | | | | | | | | | | | | | | |
| HBV DNA, *if applicable*[f] | X | | | | | | | | | | | | | | | | X | | | X | X |
| Interferon Gamma Release Assay[g] | X | | | | | | | | | | | | | | | | | | | | |
| COVID-19 questionnaire[h] | X | X | | | | | | | | | | X | X | X | X | X | X | X | X | X | X |
| COVID-19 testing[i] | X | | | | | | | | | X | | | | | | | | | | | |
| COVID-19 check temperature[j] | X | X | X | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PK blood sampling | | | X | X[k] | X | X | X | X | X | | X | | X | X | X | X | X | X | X | X | X |
| Immunogenicity (ADA, NAb)[l] | | | X | | | | | | | | | | X | X | | X | X | X | X | X | X |
| CCI [redacted] | | | | | | | | | | | | | | | | | | | | | |
| Urine drug testing | X | X | | | | | | | | | | | | | | | | | | | |
| Urinalysis (after ≥4 hour fasting) | X | X | | | | | | X | | | X | X | X | X | | X | | X | X | X | X |

| Visit Identifier[a] Abbreviations used in this table may be found in Appendix 8. | Screening | CRU Confinement | | | | | | | | | Follow-Up | | | | | | | | | ET |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Days Relative to Day 1** | **-28 to -2** | **-1** | **1** | | | | | **2** | **3** | **4** | **5** | **8** | **15** | **29** | **43** | **57** | **71** | **99** | **127** | **157** | **-** |
| **Visit Window (days)** | - | - | - | | | | | - | - | - | - | ±1 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | - |
| **Hours After Dose** | | | 0[b] | 1 | 2 | 6 | 12 | 24 | 48 | 72 | 96 | - | - | - | - | - | - | - | - | - | - |

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

b. Pre-dose (except for study intervention administration)

c. Physical examination may be performed at non-specified timings if there are findings during the previous examination or new/open AEs, if appropriate and at the discretion of the investigator.

d. Chest X-ray or other appropriate diagnostic image (ie, CT or MRI) results within 12 weeks prior of the screening visit, otherwise a chest X-ray must be performed and results obtained prior to dosing in the study. See Section 8.2.2.

e. Participants should be monitored from start of study intervention infusion until the end of infusion to assess the infusion site. See Section 8.2.5.

f. Participants who are HBsAg negative, HBcAb negative and HBsAb positive without unequivocal documentation of prior HBV vaccination or who are HBsAg negative, HBcAb positive and HBsAb positive are required to undergo HBV DNA reflex testing at screening. If HBV DNA is undetectable in the HBV DNA reflex testing at screening and the participant is enrolled the study, HBV DNA testing must be performed on Day 71, 157 and ET. See Section 8.2.6.1.

g. Additional TB testing is allowed at any time if requested by the investigator and/or if there is a suspicion of TB reactivation or new TB infection. See Section 8.2.7.

h. Check exposure to positive subject, residence or travel in area of high incidence and COVID-19 related signs and symptoms. To be done at least 2 days before and at each visit.

i. The testing for COVID-19 pathogen by PCR will be performed between Day -5 and Day -3 to permit availability of test result prior to admission on Day -1. A subsequent COVID-19 test will be performed if they develop COVID-19 like symptom.

j. To be done at least daily during residence and at every follow-up visit after discharge from the CRU.

k. End of infusion (ie, 1 hour post-dose)

l. Participants with positive results may be requested to return for additional follow-up for up to approximately 3 months after final visit.

CCI [redacted]

# 2. INTRODUCTION

PF-06823859 is a potent, selective, humanized IgG1 neutralizing antibody directed against the human soluble cytokine IFNβ, a member of the type I IFN family of cytokines that is currently being developed for the treatment of SLE with added potential for therapeutic benefit in DM.

## 2.1. Study Rationale

The purpose of the study is to investigate the safety, tolerability, immunogenicity and PK of PF-06823859 in Japanese healthy adult participants. The information of safety, tolerability, immunogenicity and PK in Japanese healthy participants is being collected to support the development of PF-06823859 in Japan.

## 2.2. Background

DM is an acquired rare inflammatory disease classified as both a neuromuscular disease and an autoimmune disease. DM is characterized by a distinctive skin rash and muscle weakness or inflamed muscles. Symptoms can come on suddenly or gradually over time. It is thought that the inflammation resulting in cell damage is created when the immune system attacks healthy muscle tissue and blood vessels under the skin. DM is idiopathic; however, some individuals may have a genetic predisposition that is triggered by medications, viruses, bacteria, trauma, toxins, cancer or other illness. DM symptoms often wax and wane for no apparent reason and females are affected twice as often as males.[1,2]

DM has no known cure and there are no widely approved treatments. Patients typically use a combination of drugs to seek relief for their inflammatory symptoms. Typically, the first line of treatment for the muscle disease is corticosteroids to address the inflammation as well as suppress the immune system. Other immunosuppressive drugs, notably azathioprine, methotrexate, mycophenolate mofetil and cyclophosphamide are used as subsequent lines of therapies in refractory cases or as steroid-sparing agents. However, complications of long-term steroid and immunosuppressive therapies are well documented. Other novel approaches have emerged as potential treatment, including tacrolimus (broadly immunosuppressive drug developed for transplant use), intravenous immunoglobulin, and rituximab, following positive outcomes in some case studies. However, additional randomized controlled trials with these treatments are needed to guide clinical practice.[3] Consequently, DM remains a disease with very high unmet medical need, and development of safe and effective therapies is warranted.

### 2.2.1. Nonclinical Overview

Detailed information concerning the nonclinical studies conducted with PF-06823859 can be found in the SRSD, which for this study is the IB. Overall, these assessments indicate that PF-06823859 is a potent inhibitor of IFNβ/IFNAR signaling in human and cynomolgus monkey cells, and the data support the use of the cynomolgus monkey as a pharmacologically relevant species for nonclinical toxicity studies. Furthermore, the nonclinical safety profile of PF-06823859 has been adequately characterized in vitro and in

vivo in cynomolgus monkey to support progression into clinical trials up to 3 months in duration.

### 2.2.2. Clinical Overview

As of the protocol date, Phase 1, randomized, double-blind, third-party open, placebo-controlled, dose escalating study to evaluate the safety, tolerability, PK and PD of single and multiple IV and SC doses of PF-06823859 in healthy participants (C0251001) has been completed. In addition, Phase 2a, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of PF-06823859 in adult participants with DM (C0251002) is ongoing with no data available at this time.

Detailed information concerning the clinical studies conducted with PF-06823859 can be found in the SRSD, which for this study is the IB.

#### 2.2.2.1. Safety

Data from Study C0251001 suggests that PF-06823859 was generally well tolerated and safe when given up to 2000 mg as single IV dose and up to 1800 mg given 600 mg IV Q2W × 3. The most common AE was upper respiratory tract infection, likely due to viral infection. No serious AE or death occurred during the study.

During the SAD period, all TEAEs reported were mild in severity. During the MAD period, while the majority of the TEAEs were mild in severity, 4 TEAEs were moderate in severity: 2 TEAEs (abdominal pain upper and headache) in the placebo SC × 3 doses treatment group, 1 TEAE (upper respiratory tract infection) in the PF-06823859 300 mg SC × 3 doses treatment group and 1 TEAE (sinusitis) in the PF-06823859 600 mg IV (Q4W) × 2 doses treatment group, none of which were considered by the investigator as treatment related.

One participant experienced a mild localized erythema with induration and tenderness after each of the 100 mg SC dosing with PF-06823859 administered Q2W for a total of 3 doses, but no signs or symptoms of a systemic reaction. These local reactions resolved without further intervention within a few days. This participant also had treatment-induced ADA, which had returned to baseline at the time of discharge (Section 2.2.2.3).

Overall, there was no apparent difference in the total rate of AEs between the participants treated with PF-06823859 compared to placebo and no apparent dose relationship with the doses of PF-06823859. However, the rate of mild upper respiratory tract infection appears to be higher in participants treated with PF-06823859.

There were no clinically significant observations in ECG, vital signs or laboratory abnormalities.

#### 2.2.2.2. Pharmacokinetics

Following single IV administration of 30 mg to 2000 mg doses, PF-06823859 demonstrated a bi-phasic PK profile with a terminal half-life ranging from 22.73 to 29.08 days, slow CL (0.005953 to 0.006817 L/h) and small volume of distribution (4.828 to 6.013 L), all attributes

of a typical IgG1 molecule. Further, $T_{max}$ occurred around 1 hour after the end of the IV infusion, $C_{max}$ ranged from 10.81 to 708.3 µg/mL, and $AUC_{inf}$ ranged from 5042 to 322,100 µg.h/mL. Both $C_{max}$ and $AUC_{inf}$ showed dose proportional increases across the 30 mg to 2000 mg dose range.

Following multiple IV administration of PF-06823859 at either 600 mg dosing Q2W for a total of 3 doses or 600 mg dosing Q4W for a total of 2 doses, $C_{max}$ and $C_{av}$ after last dose were 284.9 µg/mL and 181.6 µg/mL for 600 mg IV Q2W and 259.5 µg/mL and 109.6 µg/mL for 600 mg IV Q4W. $R_{ac}$ (based on $AUC_{\tau}$) following 600 mg IV Q2W and 600 mg IV Q4W dosing on Day 29 were 1.893 and 1.407, respectively. $R_{ac}$, $C_{max}$ (based on $C_{max}$) was similar with a mean ratio of 1.079 for 600 mg IV Q2W dosing regimen and 1.298 for 600 mg IV Q4W dosing regimen.

Following multiple SC administration of PF-06823859 at either 100 mg or 300 mg dosing Q2W for a total of 3 doses, $C_{max}$ was reached moderately slow with median $T_{max}$ of 96 hours following the first SC dose on Day 1, and slightly earlier at 48 hours after the second dose (Day 15) and the third dose (Day 29), respectively. In addition, $C_{max}$ and $C_{av}$ after last dose were 19.49 µg/mL and 18.11 µg/mL for 100 mg SC and 62.92 µg/mL and 54.26 µg/mL for 300 mg SC. $R_{ac}$ (based on $AUC_{\tau}$) following 100 mg SC Q2W and 300 mg SC Q2W dosing on Day 29 were 2.376 and 2.499, respectively. $R_{ac}$, $C_{max}$ (based on $C_{max}$) was similar with a mean ratio of 2.063 for 100 mg SC Q2W dosing regimen and 2.294 for 300 mg SC Q2W dosing regimen.

#### 2.2.2.3. Immunogenicity

Among all 48 participants treated with PF-06823859 in Study C0251001, 6 participants tested positive for ADA (SAD: 2 participants at 30 mg IV and 1 participant at 900 mg IV; MAD: 1 participant each at 100 mg SC Q2W, 300 mg SC Q2W and 600 mg IV Q2W). Of these 6 participants, 1 participant at 100 mg SC developed treatment induced NAb.

### 2.3. Benefit/Risk Assessment

A single-dose of PF-06823859 is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, immunogenicity and PK data for further clinical development.

Nonclinical data to date (Section 2.2.1) has not identified any risk to reproductive organs in sexually mature cynomolgus monkeys, the pharmacologically relevant species. Given that an ePPND study will be conducted later in development, this protocol that allows enrollment of WOCBP has requirements for pregnancy testing (WOCBP only) and use of contraceptives to mitigate unintended exposures.

There is a theoretical risk that alterations in bone may occur based on published observations of osteopenia in mice genetically deficient in IFNβ.[4] The potential for bone effects was assessed in the 3-month GLP toxicity study in sexually mature cynomolgus monkeys, and there were no microscopic findings in bone, nor alterations in circulating bone-related biomarkers. However, the potential for bone effects in developing/growing bones has not

been specifically assessed in growing animals. This risk is considered to be low given the lack of observed effects in the GLP toxicity study as well as the limited duration of total exposure to PF-06823859 in this study. While appropriate risk mitigation has been employed, possible risks will be communicated to study participants in the ICD.

There is a potential risk of increased susceptibility to viral infections with IFNβ blockade as with any antagonist of Type 1 interferon signaling (eg, anti-IFNAR1, anti-IFNα, JAK inhibitors). Viral monitoring will be conducted as a precautionary measure to ensure participant safety. Furthermore, during the pandemic, study participants could be infected with the SARS-CoV-2 during study participation. This could lead to increased health risk for this participant and others in the study. Thus, participants must undergo COVID-19 specific assessments according to the SoA.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-06823859 may be found in the IB, which is the SRSD for this study.

## 3. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| **Primary:** | **Primary:** |
| • To evaluate the safety and tolerability of single IV dose of 300 and 900 mg PF-06823859 in Japanese healthy participants. | • Assessments of AEs/SAEs including IRR, infusion sites and viral infections, vital signs, ECGs and laboratory tests. |
| **Secondary:** | **Secondary:** |
| • To evaluate the PK profile of single IV dose of 300 and 900 mg PF-06823859 in Japanese healthy participants.<br>• To evaluate the immunogenicity of PF-06823859. | • Serum PF-06823859 PK parameters, as permitted by data: $C_{max}$, $C_{max}$ (dn), $T_{max}$, $AUC_{inf}$, $AUC_{inf}$ (dn), $AUC_{last}$, $AUC_{last}$ (dn), $AUC_{14day}$, $AUC_{28day}$, $t_{½}$, CL, $V_{ss}$ and MRT<br>• Incidence of the development of ADA and NAb. |

## 4. STUDY DESIGN

### 4.1. Overall Design

This is a Phase 1, randomized, double-blind, sponsor-open, placebo-controlled study to evaluate the safety, tolerability, immunogenicity and PK of PF-06823859 in Japanese healthy adult participants.

Approximately 12 participants are planned to be enrolled into the study. The study consists of 2 cohorts, and approximately 5 participants will be randomized to PF-06823859 and approximately 1 participant will be randomized to placebo in each cohort. Participants who discontinue prior to completion of the study for non-safety related reasons may be replaced at

the discretion of the investigator upon consultation with the sponsor. Each participant will receive PF-06823859 or placebo per the scheme summarized in Table 1.

**Table 1. Randomization Scheme**

| Cohort | Treatment | Number of participants |
|---|---|---|
| 1 | PF-06823859 300 mg | 5 |
| | Placebo | 1 |
| 2 | PF-06823859 900 mg | 5 |
| | Placebo | 1 |

Within 28 days of successful completion of the screening process, eligible participants will be enrolled and randomized to receive a single IV infusion of PF-06823859 or placebo. The participants in Cohort 2 should be dosed following at least 96 hours safety pause after the participants in Cohort 1 has been dosed. Participants will be admitted into the CRU approximately 1 day prior to dosing and are required to stay overnight in the CRU through completion of Day 5 evaluations. Participants will return to the CRU for outpatient follow-up visits per SoA through Day 157. Participants may be asked to return for additional follow-up visits beyond the anticipated end of study visit for safety reasons and/or at the discretion of the investigator.

ADA levels will be monitored from samples collected at the times specified in the SoA. Samples found to be positive will be further evaluated for NAb. Participants with positive results may be requested to return for additional follow-up for up to approximately 3 months after the last scheduled follow-up visit.

### 4.2. Scientific Rationale for Study Design

The purpose of this study is to evaluate the safety, tolerability, immunogenicity and PK of PF-06823859 after single IV administration to Japanese healthy adult participants. This study will be randomized, placebo-controlled, double-blinded to treatment assignment in each cohort to permit an unbiased assessment of safety and tolerability.

To date, no safety, immunogenicity and PK data of PF-06823859 in Japanese are available. Although there is no expected relevant PK difference between Japanese and Westerners because monoclonal antibodies are generally known that the absence of ethnic differences in their distribution and elimination, similar to that of endogenous IgG,[5] it is still important to evaluate safety and characterize PK in Japanese participants before initiating studies in the targeted Japanese patient population.

Single-dose rather than repeated dosing is planned in the study as the steady-state PK can be well predicted from single-dose data. The study duration and frequency of each assessment were decided based on information of Study C0251001.

Assessment of clinical safety laboratory tests (Appendix 2), vital signs, 12-lead ECG, physical examinations, and AE monitoring will provide essential data to evaluate the safety and tolerability of PF-06823859. There is a potential risk of increased susceptibility to viral infections with IFNβ blockade as with any antagonist of Type 1 interferon signaling (eg, anti-IFNAR1, anti-IFNα, JAK inhibitors). Viral monitoring will be conducted as a precautionary measure to ensure participant safety.

COVID-19 specific assessments have been incorporated to minimize the risks of COVID-19 related complications to participants and the study site personnel.

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

Human reproductive safety data are not available for PF-06823859, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

#### 4.2.2. Collection of Retained Research Samples

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

### 4.3. Justification for Dose

The proposed single IV dose levels are 300 mg and 900 mg. These doses are selected based on the safety and tolerability in Study C0251001, CCI [redacted]

PF-06823859 doses of 300 mg and 900 mg have been selected to evaluate the safety, tolerability, immunogenicity and PK of PF-06823859 in Japanese healthy adult participants so that safety and tolerability can be examined in the dose range including the maximum potential dose in the planned global late phase studies. CCI [redacted]

As described in Section 2.2.2, PF-06823859 repeated IV dose of 600 mg IV Q4W for a total of 2 doses was generally safe and well tolerated in non-Japanese healthy participants in Study C0251001. In addition, $R_{ac}$ (based on $AUC_{\tau}$) and $R_{ac}$, $C_{max}$ (based on $C_{max}$) following 600 mg IV Q4W dosing on Day 29 were 1.4 and 1.3, respectively. Considering these results from Study C0251001, exposure following a single 900 mg IV dose is expected to be comparable to steady-state exposure following repeated IV dose of 600 mg IV Q4W.

Based on the above, 300 mg and 900 mg, which CCI [redacted] allow the direct comparison of PK with Cohort 3 (300 mg single IV dose) and Cohort 4 (900 mg single IV dose) in Study C0251001 respectively, has been selected as the proposed dose level in the current study.

### 4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all periods of the study, including the last visit.

## 5. STUDY POPULATION

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

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

### 5.1. Inclusion Criteria

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

**Age and Sex:**

1. Male and female participants must be 20 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. Participants must have 4 biologically Japanese grandparents born in Japan.

3. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and 12-lead ECG.

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 25 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).

2. History of HIV infection, hepatitis C or syphilis; positive testing for HIV, HCVAb or syphilis at screening.

3. Infection with HBV as defined in Section 8.2.6.1.

4. Clinically significant abnormality, including but not limited to current, active TB or previous inactive TB, general infections, heart failure or malignancy, on chest X-ray performed at screening or within 12 weeks of screening.

5. History of autoimmune disorders.

6. History of allergic or anaphylactic reaction to a therapeutic drug or any components in the study intervention.

7. Participants with clinically significant infections, based on which the investigator judges that the participant should not be enrolled in the study, within 28 days prior to the screening visit.

8. Participants with a fever, based on which the investigator judges that the participant should not be enrolled in the study, within the last 7 days prior to dosing.

9. Participants who have evidence of TB infection as defined in Section 8.2.7.

    - Participants who have been treated or are currently being treated for active or latent TB infection are to be excluded.

    - Participants with a history of either untreated or inadequately treated latent or active TB infection are to be excluded.

10. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic (eg, Contact with positive case, residence, or travel to an area with high incidence) that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

**Prior/Concomitant Therapy:**

11. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. (Refer to Section 6.8 for additional details).

12. Recent exposure to any live or attenuated live virus vaccines within 6 weeks of admission to CRU.

    - The use of COVID-19 vaccines (except for live or attenuated live virus vaccines) are allowed before 14 days prior to Day 1 or after discharge from CRU.

**Prior/Concurrent Clinical Study Experience:**

13. Participants who have received PF-06823859 or any other IFNα or IFNβ therapy at any time in the past.

14. Previous administration with an investigational drug within 4 months (180 days for biologics) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

**Diagnostic Assessments:**

15. A positive urine drug test.

16. 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.

17. Screening PR >100 bpm. If the PR is greater than 100 bpm, the PR should be repeated 2 more times and the average of the 3 PR values should be used to determine the participant's eligibility.

18. Baseline standard 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 a participant.

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

    - AST **or** ALT level ≥1.5 × 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.

20. A positive COVID-19 test by PCR at screening.

**Other Exclusions:**

21. 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).

22. Blood donation (excluding plasma donations) of approximately ≥400 mL within 3 months or ≥200 mL within a month prior to dosing. Additionally, approximately ≥400 mL within 4 months for female participants.

23. History of sensitivity to heparin or heparin-induced thrombocytopenia ***only if*** heparin is planned to flush intravenous catheters.

24. History of substance abuse within 12 months of the screening visit.

25. Pregnant females; breastfeeding females.

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

27. 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 4 hours prior to any safety laboratory evaluations.

- 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 in the CRU and during clinical confinement at the CRU.

- Participants will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol during clinical confinement at the CRU. 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 clinical confinement at 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.

### 5.3.4. Contraception

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

### 5.4. Screen Failures

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

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

## 6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to PF-06823859 and placebo.

### 6.1. Study Intervention(s) Administered

PF-06823859 100 mg/mL Solution for Injection will be supplied by Pfizer and packaged in a single-use carton containing a 6 mL glass vial sealed with a stopper and aluminum flip off cap. Each vial contains PF-06823859 in 1.35 mL of solution. Placebo for PF-06823859 100 mg/mL Solution for Injection will also be provided.

These products will be supplied to the CRU as open label packaged supplies and must be received at the site by unblinded site staff. The site will take all necessary precautions to maintain the investigator and site personnel blind.

#### 6.1.1. Administration

| **Intervention Name** | PF-06823859 100 mg/mL | Placebo for PF-06823859 |
|---|---|---|
| **ARM Name (group of patients receiving a specific treatment, or no treatment)** | Active | Placebo |
| **Type** | Biologic | Biologic |
| **Dose Formulation** | Solution for injection | Solution for injection |
| **Unit Dose Strength(s)** | 100 mg/mL | 0 mg/mL |
| **Dosage Level(s)** | 300 mg, 900 mg | Placebo |
| **Route of Administration** | Intravenous | Intravenous |
| **Use** | Experimental | Placebo |
| **IMP or NIMP** | IMP | IMP |
| **Sourcing** | Provided by the sponsor. | Provided by the sponsor. |
| **Packaging and Labeling** | Study intervention will be provided in vials packaged in individual cartons. Each vial and carton will be labeled as required per country requirement. | Study intervention will be provided in vials packaged in individual cartons. Each vial and carton will be labeled as required per country requirement. |

Participants will receive study intervention at approximately 0800 hours on Day 1 (plus or

minus 4 hours). Study intervention does not require fasting, but it should be noted that the safety laboratory tests at Day -1 prior to the dose of study intervention need a fast of at least 4 hours. Investigator site personnel will administer study intervention as a 60-minute IV using a calibrated infusion pump. Study medication must not be administered as an IV push or bolus. The infusion rate, amount of volume infused, start and stop time of the infusion will be recorded. Time 0 is the time when the study intervention infusion begins. The infusion will be on the opposite arm from PK sampling.

Administer study intervention according to the IP Manual.

#### 6.1.1.1. Intravenous Infusion Discontinuation

- If a participant experiences symptoms typical of an allergic reaction, the study intervention infusion should be discontinued immediately and permanently.

- If a participant experiences symptoms typical of IRR (eg, lightheadedness, nausea, chills, fever), the study intervention infusion should be stopped. At the discretion of the investigator, the infusion can be restarted at a slower rate if symptoms are resolved within 1 hour after the stop of infusion. If symptoms return, then the study intervention infusion should be discontinued immediately and permanently.

- In the event that there is an infusion interruption, the entire duration of study intervention infusion, from the initial start of infusion to the completion of infusion, should not exceed 3 hours. Participants will receive appropriate treatment at the discretion of the investigator.

### 6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission

to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

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

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

6. See the IP manual for storage conditions of the study intervention.

7. The head of the medical institution (where applicable) or study intervention administrator 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 IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

### 6.2.1. Preparation and Dispensing

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

PF-06823859 and placebo will be prepared by qualified unblinded site personnel according to the IP manual. Blinded study intervention will be administered in a blinded fashion to the participant.

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

### 6.3.1. Allocation to Study Intervention

Participants will be randomly assigned to receive study intervention from a central randomization scheme. Investigators 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. A sealed envelope that contains the study intervention assignment(s) for each participant will be provided to the investigator. The sealed envelope will be retained by the investigator (or representative) in a secured area. 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 and entered on the CRF.

Once the study is complete, all envelopes (sealed and opened) must be inventoried and retained until authorization for destruction has been provided.

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. Other Pfizer personnel will be unblinded to participant treatments in order to permit real-time interpretation of the safety and PK data. 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 dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The site will complete the required dosage Preparation Record located in the IP manual. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

### 6.5. Dose Modification

Not applicable.

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

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

### 6.7. Treatment of Overdose

For this study, any dose of PF-06823859 greater than 2000 mg within a month will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-06823859 (whichever is longer).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

### 6.8. Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day. Ibuprofen may be used at doses of ≤1.6 g/day.

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

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

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

### 6.8.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-06823859; standard medical supportive care must be provided to manage the AEs.

## 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

### 7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

### 7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;

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

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

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

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

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

### 7.2.1. Withdrawal of Consent

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

## 7.3. Lost to Follow up

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

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

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

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

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

# 8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

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

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 (PR and BP) should be collected prior to the insertion of the catheter.

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

The total blood sampling volume for individual participants in this study is approximately 290 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

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

### 8.1. Efficacy Assessments

Not applicable.

### 8.2. Safety Assessments

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

#### 8.2.1. Physical Examinations

A 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.

Physical examinations may be conducted by a physician.

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

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

#### 8.2.2. Chest X-ray

Chest radiograph (posterior-anterior and lateral views are recommended, however, local guidelines should be followed) or other appropriate diagnostic image (ie, CT or MRI) should be taken at screening visit or within 12 weeks prior to screening visit and read by a qualified radiologist and must show no evidence of abnormalities including but not limited to current, active TB or previous inactive TB, general infections, heart failure or malignancy. Documentation of the official reading must be located and available in the source documentation.

#### 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. BP should not be taken

from the arm with an IV infusion. Participants should be instructed not to speak during measurements.

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

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

#### 8.2.3.1. Temperature

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

### 8.2.4. 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 HR and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a postdose QTc interval is increased by ≥45 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTc values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTc interval remains ≥45 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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

qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 7.

### 8.2.5. Infusion Site Assessment

Participants should be monitored from start of study intervention infusion until the end of infusion to assess the infusion sites. The infusion sites will be assessed for erythema, induration, ecchymosis, pain, and pruritus, or other observed characteristics after study intervention.

Any observed abnormality at the infusion site should be treated according to the investigator's standard of care and reported as AEs.

### 8.2.6. 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 150 calendar 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.

#### 8.2.6.1. HBV testing

Participant's eligibility should be determined according to the following criteria based on the results of positive testing for HBsAg, HBcAb and HBsAb at screening.

- If all 3 tests are negative, the participant is eligible for study inclusion.
- If HBsAg is positive, the participant must be excluded from participation in the study.
- If HBsAg is negative, HBcAb is positive, and HBsAb is negative, the participant must be excluded from participation in the study.
- If HBsAg is negative, HBcAb is negative, HBsAb is positive, and prior HBV vaccination is unequivocally documented, the participant is eligible for the study and does not require HBV DNA monitoring during the study.
- If HBsAg is negative, HBcAb is negative, HBsAb is positive, and no unequivocal documentation of prior HBV vaccination is available, the participant is required to undergo HBV DNA reflex testing. If HBV DNA is detected, the participant must be excluded from participation in the study; If HBV DNA is undetectable, the participant is eligible for study inclusion but required to HBV DNA testing for the subsequent visits according to the SoA.
- If HBsAg is negative, HBcAb is positive, and HBsAb is positive, the participant is required to undergo HBV DNA reflex testing. If HBV DNA is detected, the participant must be excluded from participation in the study; If HBV DNA is undetectable, the participant is eligible for study inclusion but required to HBV DNA testing for the subsequent visits according to the SoA.

A participant who tested viral load positive for HBV at any time during the study should consider starting nucleoside antagonist immediately in parallel with consultation with hepatologist in accordance with the Japan Society of Hepatology Guidelines for the management of HBV infection.[6]

### 8.2.7. Tuberculosis test

Participants should be screened for TB using an IGRA. IGRA will be tested during screening or within 12 weeks prior to Day 1. The following are acceptable assays: QuantiFERON®-TB Gold In Tube (QFT-G) test and T-spot®TB (T-Spot) test. If at any time the participant has signs or symptoms associated with TB, additional TB testing will be performed.

Participant's eligibility should be determined according to the following criteria based on the results of IGRA during screening or within 12 weeks prior to Day 1.

- Participants who test negative for IGRA is eligible for study inclusion.
- Participants who test positive for IGRA must be excluded from participation in the study.

- If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. A positive test on repeat is exclusionary. Participants with repeat indeterminate IGRA results may be enrolled after consultation with an infectious disease and/or pulmonary specialist who determines that the risk of infection is low (ie, participant would be acceptable for immunosuppressant treatment without additional action).

Site personnel should follow the processing and analyses steps based on the assay chosen. Ensure incubation steps are followed as appropriate. Documentation of IGRA product used and the test result must be in the participant's source documentation.

### 8.2.8. Viral Surveillance

Blood samples for possible analysis of CMV, EBV, HSV-1, HSV-2, VZV and HHV6 will be collected according to the times outlined in the SoA.

*Note: Due to long turnaround time, the retrospective nature of these labs might make their reporting time quite delayed.*

In addition to time points specified in the SoA, a blood sample for viral surveillance sample may also be taken at the time of an AE, as clinically appropriate.

### 8.2.9. COVID-19 Specific Assessments

Participants will be tested for SARS-CoV-2 infection by PCR at the timepoints specified in the SoA, or if they develop COVID-19 like symptoms. Additional testing may be required by local regulations or by the Principal Investigator. The test result must be negative in order for a participant to proceed with admission on Day -1. COVID-19 tests may be conducted at central or local labs. COVID-19 specific assessments data will be considered source data. If the participant has a positive COVID-19 test result, the concerned participant may be isolated and withdrawn from the study at the discretion of the investigator upon consultation with the sponsor. The positive COVID-19 test result should be recorded in the AE section of the CRF.

### 8.2.10. Pregnancy Testing

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

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

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

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

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

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

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

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 150 calendar days, except as indicated below, after the last administration of the study intervention.

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

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

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

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

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she

considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

#### 8.3.1.1. Reporting SAEs to Pfizer Safety

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

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

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

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

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

### 8.3.2. Method of Detecting AEs and SAEs

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

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

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

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

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

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

### 8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

#### 8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

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

- A male family member or healthcare provider who has been exposed to the study intervention by ingestion 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 150 calendar days.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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

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

- Spontaneous abortion including miscarriage and missed abortion;

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

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

#### 8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion 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 during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE.

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

### 8.3.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

### 8.3.8. Adverse Events of Special Interest

Not applicable.

#### 8.3.8.1. Lack of Efficacy

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

### 8.3.9. Medical Device Deficiencies

Not applicable.

### 8.3.10. Medication Errors

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

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

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

Medication errors include:

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

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

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

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

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

### 8.4. Pharmacokinetics

Blood samples of approximately 3 mL, to provide approximately 1 mL serum, will be collected for measurement of serum concentrations of PF-06823859 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration and during confinement in the CRU that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. During follow-up period (after Day 5), collection of samples that are obtained within 3 days of planned visit will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

Samples will be used to evaluate the PK of PF-06823859. Samples collected for analyses of PF-06823859 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, CCI [redacted]

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

Samples collected for measurement of serum concentrations of PF-06823859 will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor.

On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Drug concentration information that would unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

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

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[redacted]

### 8.7. Immunogenicity Assessments

Blood samples of approximately 6 mL, to provide approximately 2 mL serum, will be collected for determination of ADA and NAb as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for determination of ADA and NAb may also be used for additional characterization of the immune response and/or evaluation of the bioanalytical method, CCI [redacted]

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

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples tested as ADA positive (not just confirmed positive, but also with a titer positive result) will be further tested for NAb using validated NAb assays.

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

Immunogenicity information that would unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

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

### 8.8. Health Economics

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

## 9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in 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 statistical hypotheses will be tested in this study.

### 9.2. Analysis Sets

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

| Participant Analysis Set | Description |
|---|---|
| Enrolled/Randomly assigned to study intervention | "Enrolled" means a participant's, 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. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. |
| Safety Analysis Set | All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received. |
| PK concentration | All participants randomly assigned to study intervention who received at least 1 dose of study intervention and in whom at least 1 serum sample concentration value of PF-06823859 is reported. |
| PK parameter | All participants randomly assigned to study intervention who received at least 1 dose of study intervention and who have at least 1 of the PK parameters of PF-06823859 of interest calculated. |
| Immunogenicity | All participants randomly assigned to study intervention who received at least 1 dose of study intervention with at least one post-treatment anti-drug (PF-06823859) antibody determination. |

### 9.3. Statistical Analyses

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

#### 9.3.1. General Considerations

All analyses described below will be conducted by treatment. In addition, data from placebo in Cohort 1 and Cohort 2 will be pooled.

#### 9.3.2. Primary Endpoint(s)

All safety analyses will be performed on the safety analysis set.

The primary endpoints of this study are assessments of AEs/SAEs including IRR, viral infections, vital signs, ECGs and laboratory tests.

The primary endpoints will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and/or graphical presentations in order to evaluate the safety and tolerability of PF-06823859.

#### 9.3.2.1. Electrocardiogram (ECG) Analysis

Changes from baseline for the ECG parameters (QT interval, HR, QTc interval, PR interval, and QRS interval) will be summarized by treatment and time.

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

**Safety QTc 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 corrected and uncorrected QT values ≥500 msec will be summarized.

### 9.3.3. Secondary Endpoint(s)

#### 9.3.3.1. Pharmacokinetic Analyses

PK parameters for PF-06823859 following single-dose administration will be derived from the serum concentration-time profiles using noncompartmental methods, as data permit.

The PK parameters to be assessed in this study, their definition, and method of determination are listed in analysis as described in Table 2. Actual PK sampling times will be used in the derivation of PK parameters.

The serum PK parameters in Table 2 will be summarized descriptively by treatment group in accordance with Pfizer data standards, as data permit. The plot will include individual participant values and the geometric means for each dose. These plots will be used to help understand the relationship between the PK parameters and dose.

**Table 2. Serum PF-06823859 PK Parameters**

| Parameter | Definition | Method of Determination |
|---|---|---|
| $AUC_{14day}$ | Area under the serum concentration-time profile from time 0 to 14 days post-dose (336 hours) | Linear/Log trapezoidal method |
| $AUC_{28day}$ | Area under the serum concentration-time profile from time 0 to 28 days post-dose (672 hours) | Linear/Log trapezoidal method |
| $AUC_{last}$ | Area under the serum concentration-time profile from time 0 to the time of the last quantifiable concentration ($C_{last}$) | Linear/Log trapezoidal method |
| $AUC_{last}$ (dn) | Dose normalized $AUC_{last}$ | $AUC_{last}$/Dose |
| $AUC_{inf}$[a] | Area under the serum concentration-time profile from time 0 extrapolated to infinite time | $AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis |
| $AUC_{inf}$ (dn) | Dose normalized $AUC_{inf}$ | $AUC_{inf}$/Dose |
| $C_{max}$ | Maximum serum concentration | Observed directly from data |
| $C_{max}$ (dn) | Dose normalized $C_{max}$ | $C_{max}$/Dose |
| $T_{max}$ | Time at which $C_{max}$ occurs | Observed directly from data as time of first occurrence |
| $t_{1/2}$ [a] | 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 |
| CL [a] | Clearance | Dose/$AUC_{inf}$ |
| $V_{ss}$ [a] | Volume of distribution at steady state | CL*MRT |
| MRT | Mean residence time | $AUMC_{inf}/AUC_{inf}$ – DOF/2, where $AUMC_{inf}$ is the area under the moment curve from time 0 extrapolated to infinity and DOF is the duration of the IV infusion. |

a. If data permitted.

### 9.3.3.2. Immunogenicity Analyses

Overall incidence of development of ADA, NAb will be calculated and summarized by treatment and time points specified in the SoA. Participants level immune response will also be summarized by treatment. Effect of positive ADA and neutralizing immune response on safety and PK may be assessed, if appropriate.

### 9.3.4. Other Safety Analyses

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

Medical history and 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.

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[redacted]

### 9.4. Interim Analyses

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

### 9.5. Sample Size Determination

A sufficient number of participants will be screened to achieve 6 participants randomly assigned to study intervention per cohort and 12 evaluable participants for an estimated total of 5 evaluable participants in PF-06823859 300 mg, 5 evaluable participants in PF-06823859 900 mg, or 2 evaluable participants in placebo. Approximately 12 participants will be randomly assigned to study intervention such that approximately 12 evaluable participants complete the study.

A total sample size of 12 participants (including 10 active and 2 placebo) is not based on any statistical considerations. The sample size was based on the clinical consideration to provide safety and tolerability information and pharmacological considerations and on the need to minimize exposure to healthy participants. No formal inferential statistics will be applied to the safety or PK data.

Participants who discontinue prior to completion of the study for non-safety related reasons may be replaced at the discretion of the investigator upon consultation with the sponsor.

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

### 10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new

information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

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

### 10.1.2. Informed Consent Process

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

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

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

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

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

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

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

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

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

### 10.1.3. Data Protection

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

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

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

### 10.1.4. Committees Structure

#### 10.1.4.1. Data Monitoring Committee

This study will not use a DMC.

### 10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 24 months after study completion. 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.

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

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

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

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

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

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator or authorized site personnel 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 or authorized site personnel 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 or authorized site personnel will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

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

### 10.1.7. Source Documents

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

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

Definition of what constitutes source data and its origin can be found in the study monitoring plan, which is maintained by the sponsor.

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

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

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

### 10.1.8. 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 or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

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

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

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

### 10.1.9. 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 supporting study documentation .

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an Emergency Contact Card (ECC) at

the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she will be directed back to the investigator site.

## 10.2. Appendix 2: Clinical Laboratory Tests

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

**Table 3. Protocol-Required Safety Laboratory Assessments**

| Hematology | Chemistry | Urinalysis | Other |
|---|---|---|---|
| Hemoglobin<br>Hematocrit<br>RBC count<br>MCV<br>MCH<br>MCHC<br>Platelet count<br>WBC count<br>Total neutrophils (%)<br>Eosinophils (%)<br>Monocytes (%)<br>Basophils (%)<br>Lymphocytes (%) | BUN and creatinine<br>Glucose (fasting)<br>Calcium<br>Sodium<br>Potassium<br>Chloride<br>AST, ALT<br>Total bilirubin<br>Alkaline phosphatase<br>Uric acid<br>Albumin<br>Total protein | pH<br>Glucose (qual)<br>Protein (qual)<br>Blood (qual)<br>Ketones<br>Nitrites<br>Leukocyte esterase<br>Urobilinogen<br>Urine bilirubin<br>Microscopy[a] | At screening only:<br>• FSH[b]<br>• HIV<br>• HBsAg<br>• HBsAb<br>• HBcAb<br>• HCVAb<br>• Syphilis<br>• IGRA[c]<br><br>As per SoA:<br>• Urine drug screening[d]<br>• Pregnancy test (β-hCG)[e]<br>• Viral surveillance: CMV, VZV, EBV, HHV6, HSV-1, HSV-2<br>• PT<br>• INR<br>• aPTT<br>• HBV DNA[f], *if applicable*<br>• COVID-19 testing |

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. For confirmation of postmenopausal status only.
c. IGRA will be performed according to Section 8.2.7.
d. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
e. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-hCG for female participants of childbearing potential.
f. HBV DNA testing will be performed according to Section 8.2.6.1.

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.

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

### 10.3.1. Definition of AE

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

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

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

### 10.3.2. Definition of an SAE

| **An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:** |
|---|
| **a. Results in death** |
| **b. Is life-threatening**<br><br>The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. |
| **c. Requires inpatient hospitalization or prolongation of existing hospitalization**<br><br>In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.<br><br>Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE. |

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

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

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

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

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

**g. Other situations:**

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

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

**AE and SAE Recording/Reporting**

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2)

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

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

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

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

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

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

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

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

**Assessment of Intensity**

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

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

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

**Assessment of Causality**

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

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

**Follow-Up of AEs and SAEs**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.

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

### 10.3.4. Reporting of SAEs

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

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

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

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

## 10.4. Appendix 4: Contraceptive and Barrier Guidance

### 10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 150 calendar days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

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

  OR

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

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

### 10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below during the intervention period and for at least 150 calendar days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with high user dependency, as described below during the intervention period and for at least 150 calendar days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition, a second effective method of

contraception, as described below, must be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

### 10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female.

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

if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

### 10.4.4. Contraception Methods

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

**Highly Effective Methods That Have Low User Dependency**

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

**Highly Effective Methods That Are User Dependent**

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.
    - Oral;
    - Intravaginal;*
    - Transdermal;*
    - Injectable.*
7. Progestogen-only hormone contraception associated with inhibition of ovulation.
    - Oral;*
    - Injectable.*
8. Sexual abstinence.

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

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

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

*) Not approved in Japan

CCI

[redacted]

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

### Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**ECG Findings That Qualify as SAEs**

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

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

## 10.8. Appendix 8: Abbreviations

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

| Abbreviation | Term |
|---|---|
| Abs | absolute |
| ADA | antidrug antibodies |
| ADL | activities of daily living |
| AE | adverse event |
| ALT | alanine aminotransferase |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| $AUC_{14day}$ | AUC from time 0 to 14 days post-dose |
| $AUC_{28day}$ | AUC from time 0 to 28 days post-dose |
| $AUC_{inf}$ | AUC from time 0 extrapolated to infinite time |
| $AUC_{last}$ | AUC from time 0 to the time of the last quantifiable concentration |
| $AUC_{\tau}$ | AUC from time 0 to time $\tau$, the dosing interval |
| AV | atrioventricular |
| β-hCG | beta-human chorionic gonadotropin |
| BMI | body mass index |
| BP | blood pressure |
| bpm | beats per minute |
| BUN | blood urea nitrogen |
| $C_{av}$ | concentration average |
| CFR | Code of Federal Regulations |
| CIOMS | Council for International Organizations of Medical Sciences |
| CK | creatine kinase |
| CL | clearance |
| $C_{max}$ | maximum observed concentration |
| CMV | cytomegalovirus |
| COVID-19 | coronavirus disease 2019 |
| CRF | case report form |
| CRO | contract research organization |
| CRU | clinical research unit |
| CSR | Clinical Study Report |
| CT | computed tomography |
| CT SAE | clinical trial serious adverse event (report form) |
| DILI | drug-induced liver injury |
| DM | dermatomyositis |
| DMC | Data Monitoring Committee |
| dn | dose normalized |
| DNA | deoxyribonucleic acid |

| Abbreviation | Term |
|---|---|
| EBV | Epstein-Barr virus |
| EC | Ethics Committee |
| ECC | emergency contact card |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDB | exposure during breastfeeding |
| EDP | exposure during pregnancy |
| EMA | European Medicines Agency |
| ePPND | enhanced pre and postnatal development |
| ET | early termination |
| EU | European Union |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database) |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| GLP | Good Laboratory Practice |
| HBcAb | hepatitis B core antibody |
| HBsAb | hepatitis B surface antibody |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HBV DNA | hepatitis B virus DNA |
| HCVAb | hepatitis C antibody |
| HHV6 | human herpesvirus 6 |
| HIV | human immunodeficiency virus |
| HR | heart rate |
| HRT | hormone replacement therapy |
| HSV-1 | herpes simplex virus type 1 |
| HSV-2 | herpes simplex virus type 2 |
| IB | Investigator's Brochure |
| ICD | informed consent document |
| ICH | International Council for Harmonisation |
| ID | identification |
| IFN | interferon |
| IFNAR | Type 1 interferon α/β receptor |
| IgG | immunoglobulin G |
| IGRA | Interferon-Gamma Release Assays |
| IMP | investigational medicinal product |
| IND | Investigational New Drug |
| INR | international normalized ratio |
| IP manual | investigational product manual |

| Abbreviation | Term |
|---|---|
| IPAL | Investigational Product Accountability Log |
| IRB | Institutional Review Board |
| IRR | infusion related reaction |
| IV | intravenous(ly) |
| JAK | Janus kinase |
| $k_{el}$ | terminal phase rate constant |
| LBBB | left bundle branch block |
| LFT | liver function test |
| MAD | multiple ascending dose |
| MCH | mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| MCV | mean corpuscular volume |
| MRI | magnetic resonance imaging |
| MRT | mean residence time |
| msec | millisecond |
| N/A | not applicable |
| NAb | neutralizing antibodies |
| NIMP | noninvestigational medicinal product |
| PCR | polymerase chain reaction |
| PD | pharmacodynamic(s) |
| PK | pharmacokinetic(s) |
| PR | pulse rate |
| PT | prothrombin time |
| PVC | premature ventricular contraction/complex |
| Q2W | once every 2 weeks |
| Q4W | once every 4 weeks |
| QFT-G | QuantiFERON®-TB Gold In Tube |
| QTc | corrected QT |
| QTcF | corrected QT (Fridericia method) |
| qual | qualitative |
| $R_{ac}$ | accumulation ratio for $AUC_{\tau}$ |
| $R_{ac}$, $C_{max}$ | accumulation ratio for $C_{max}$ |
| RBC | red blood cell |
| CCI | [redacted] |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SC | subcutaneous(ly) |
| SLE | systemic lupus erythematous |
| SoA | schedule of activities |

| Abbreviation | Term |
|---|---|
| SOP | standard operating procedure |
| SRSD | single reference safety document |
| SUSAR | suspected unexpected serious adverse reaction |
| TB | tuberculosis |
| TBili | total bilirubin |
| TEAE | treatment emergent adverse event |
| $t_{½}$ | terminal phase half-life |
| THC | tetrahydrocannabinol |
| $T_{max}$ | time to reach $C_{max}$ |
| T-Spot | T-spot®TB |
| ULN | upper limit of normal |
| US | United States |
| $V_{ss}$ | volume at steady state |
| VZV | varicella-zoster virus |
| WBC | white blood cell |
| WOCBP | woman of childbearing potential |

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