



**A PHASE 1, RANDOMIZED, DOUBLE-BLIND, THIRD-PARTY OPEN,  
PLACEBO-CONTROLLED, STUDY TO EVALUATE THE PHARMACOKINETICS,  
SAFETY, AND TOLERABILITY FOLLOWING A SINGLE DOSE OF PF-06823859  
IN HEALTHY CHINESE PARTICIPANTS**

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

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## Document History

Document	Version Date
Amendment 1	10 May 2022
Original protocol	25 Jun 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 (10 May 2022)

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1. Synopsis, Subsection “Number of Participants”; Section 4.1. Overall Design, Subsection “Number of Participants”; Section 4.2. Scientific Rationale for Study Design	<p>The following statement was updated:</p> <p>Original statement:            If more than 2 participants discontinue or withdraw before completing at least the follow-up visit at Day 100, participants may be replaced at the discretion of the investigator upon alignment with the sponsor.</p> <p>Updated statement:            If more than 2 participants discontinue or withdraw before completing at least the follow-up visit at Day 100, or if there are participants whose PK samples are considered to be non-evaluable with respect to the primary PK objective, additional</p>	<p>To allow additional participants to enroll in the study in the event of participants whose PK samples are considered to be non-evaluable with respect to the primary PK objective or if more than 2 participants discontinue or withdraw before completing at least the follow-up visit at Day 100, to ensure approximate 10 participants could provide evaluable PK samples for no less than Day 100 follow-up visit.</p>	Substantial

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>	<b>Substantial or Nonsubstantial</b>
	<p>participants may be enrolled upon alignment between the sponsor and the investigator such that approximate 10 participants could provide evaluable PK samples for no less than Day 100 follow-up visit. For participants whose PK samples are considered to be non-evaluable with respect to the primary PK objective, their PK sample collection will stop for ethic consideration.</p>		
<p>Section 9.5. Sample Size Determination</p>	<p>The following statement was added:</p> <p>If more than 2 participants discontinue or withdraw before completing at least the follow-up visit at Day 100, or if there are participants whose PK samples are considered to be non-evaluable with respect to the primary PK objective, additional participants may be enrolled upon alignment between the sponsor and the investigator such that approximate 10 participants could provide evaluable PK samples for no less than Day 100 follow-up visit.</p>	<p>To allow additional participants to enroll in the study in the event of participants whose PK samples are considered to be non-evaluable with respect to the primary PK objective or if more than 2 participants discontinue or withdraw before completing at least the follow-up visit at Day 100, to ensure approximate 10 participants could provide evaluable PK samples for no less than Day 100 follow-up visit.</p>	<p>Substantial</p>

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>	<b>Substantial or Nonsubstantial</b>
Section 1.3. Schedule of Activities	ECG was updated to be measured on Day -1 instead of Day 1.	To keep consistent with Exclusion Criteria #18 evaluation (Day -1/baseline) and to align with site practice.	Nonsubstantial
Section 1.3. Schedule of Activities	In the footnote “h”, the statement of “at least 48 hours before and” was removed for COVID-19 questionnaire.	To align with site practice.	Nonsubstantial
Section 5.2. Exclusion Criteria #2	The word “syphilis” was added to statement, the updated statement being: History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, <b>syphilis</b> , HBsAg, or HCVAb.	To keep consistent with assessment requirement listed in Section 1.3 Schedule of Activities.	Nonsubstantial
Section 5.2. Exclusion Criteria #17	Update “≤50 bpm” to “<50 bpm”.	To correct a typo.	Nonsubstantial
Section 8.2.4. Electrocardiogram	The original statement of “Appendix 7” was updated to “Appendix 6”:  ECG values of potential clinical concern are listed in <b>Appendix 6</b> .	To correct a typo.	Nonsubstantial
Section 8.2.5. Clinical Safety Laboratory Assessments	The original statement of “Appendix 6” was updated to “Appendix 5”:  See <b>Appendix 5</b> for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.	To correct a typo.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 9.4. Interim Analyses	<p>In the second sentence of the paragraph, the word “However” was deleted and “agency communication” was added, the updated sentence being:</p> <p><b>As</b> this is an 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, <b>agency communication</b>, and/or supporting clinical development.</p>	<p>The word “However” was deleted to align with mandatory template text.</p> <p>The wording “agency communication” was added to reflect updated purpose of potential unblinded data review.</p>	Nonsubstantial
Section 10.2. Appendix 2: Clinical Laboratory Tests	Syphilis test was added to “Other” safety laboratory assessment.	To keep consistent with assessment requirement listed in Section 1.3 Schedule of Activities.	Nonsubstantial
Section 10.4.4. Contraception Methods	The word “Injectable” was removed from “6. Combined [estrogen- and progestogen-containing] hormonal contraception associated with inhibition of ovulation”.	To align with protocol template updates.	Nonsubstantial

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## 1. PROTOCOL SUMMARY

### 1.1. Synopsis

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

#### Rationale

The purpose of this study is to evaluate the single-dose PK, safety, and tolerability of PF-06823859 after single IV administration to healthy adult Chinese participants. The information of PK, safety, and tolerability in healthy Chinese participants is being collected to support future PF-06823859 clinical development as well as drug registration in China.

#### Objectives and Endpoints

Objectives	Endpoints
<b>Primary:</b>	<b>Primary:</b>
<ul style="list-style-type: none"><li>To evaluate the PK profile of single IV dose of 900 mg PF-06823859 in healthy Chinese participants.</li><li>To determine the safety and tolerability of single IV dose of 900 mg PF-06823859 in healthy Chinese participants.</li></ul>	<ul style="list-style-type: none"><li>Serum PF-06823859 primary PK parameters, as permitted by data: <math>C_{max}</math>, <math>T_{max}</math>, <math>AUC_{14day}</math>, <math>AUC_{28day}</math>, <math>AUC_{inf}</math>, and <math>t_{1/2}</math>.</li><li>Assessments of AEs/SAEs including infusion site reactions and viral infections, vital signs, ECGs and laboratory tests.</li></ul>
<b>Secondary:</b>	<b>Secondary:</b>
<ul style="list-style-type: none"><li>To further evaluate the PK of PF-06823859</li><li>To evaluate the immunogenicity of PF-06823859.</li></ul>	<ul style="list-style-type: none"><li>Serum PF-06823859 PK parameters, as permitted by data: <math>C_{max}</math> (dn), <math>AUC_{last}</math>, <math>AUC_{last}</math> (dn), <math>AUC_{inf}</math> (dn), CL, <math>V_z</math>, and MRT.</li><li>Incidence of the development of ADA and Nab.</li></ul>

#### Overall Design

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

#### Number of Participants

Approximately 12 participants will be enrolled into the study. Approximately 10 participants will be randomized to PF-06823859 and approximately 2 participants will be randomized to placebo.

If more than 2 participants discontinue or withdraw before completing at least the follow-up visit at Day 100, or if there are participants whose PK samples are considered to be non-evaluable with respect to the primary PK objective, additional participants may be enrolled upon alignment between the sponsor and the investigator such that approximate 10 participants could provide evaluable PK samples for no less than Day 100 follow-up visit. For participants whose PK samples are considered to be non-evaluable with respect to the primary PK objective, their PK sample collection will stop for ethic consideration.

### **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. Participants will be admitted into the CRU approximately 1 day prior to dosing and are required to remain 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**

Statistical objective is exploratory. Only descriptive analyses will be performed.

#### **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 <sup>a</sup> Abbreviations used in this table may be found in <a href="#">Appendix 7</a> .	Screening	CRU Confinement										Follow-Up							ET			
		-28 to -2	-1	1					2	3	4	5	8	15	29	43	57	71		100	127	157
Days Relative to Day 1	-	-	-					-	-	-	-	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	-
Visit Window (days)	-	-	-					-	-	-	-	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	-
Hours After Dose			0 <sup>b</sup>	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	X	
Inclusion/exclusion criteria	X	X																				
Medical/medication history (update)	X	X																				
History of illicit drug, alcohol and tobacco use	X	X																				
Report prior or concomitant treatments	X	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 and weight at screening, only) <sup>c</sup>	X	X																			X	
Single 12-Lead ECG	X	X								X			X		X		X	X	X	X	X	
Supine blood pressure, pulse rate and temperature	X		X							X			X		X		X	X	X	X	X	
Chest radiograph <sup>d</sup>	X																				X	
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	X	X	X	X	X	X	X	X	X	X	X	
Study intervention administration			X <sup>e</sup>																			
Safety laboratory (after ≥4-hour fast) including PT, INR, aPTT	X	X						X			X	X	X		X		X	X	X	X	X	
Viral surveillance (CMV, VZV, EBV, HHV6, HSV-1, HSV-2)	X										X		X		X					X	X	

Visit Identifier <sup>a</sup> Abbreviations used in this table may be found in <a href="#">Appendix 7</a> .	Screening	CRU Confinement										Follow-Up							ET		
		-28 to -2	-1	1					2	3	4	5	8	15	29	43	57	71		100	127
Days Relative to Day 1	-28 to -2	-1	1					2	3	4	5	8	15	29	43	57	71	100	127	157	-
Visit Window (days)	-	-	-					-	-	-	-	±1	±1	±1	±3	±3	±3	±3	±3	±3	-
Hours After Dose		0 <sup>b</sup>	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 <sup>f</sup>	X														X				X	X	
Interferon Gamma Release Assay <sup>g</sup>	X																				
COVID-19 questionnaire <sup>h</sup>	X	X									X	X	X	X	X	X	X	X	X	X	
COVID-19 testing <sup>i</sup>	X								X												
COVID-19 check temperature <sup>j</sup>	X	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetic blood sampling		X	X <sup>k</sup>	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	
Immunogenicity (ADA, NAb) <sup>l</sup>		X									X	X		X	X	X	X	X	X		
Urine drug testing	X	X																			
Urinalysis (after ≥4-hour fast)	X	X					X			X	X	X	X	X		X	X	X	X		

- a. Day relative to start of study intervention (Day 1).
- b. Pre-dose (except for study intervention administration).
- c. A full physical examination may be done at screening or Day -1. Brief physical examination to follow-up open AEs after Day -1 may be done.
- d. Chest X-ray or other appropriate diagnostic image (ie, CT or MRI) results within 12 weeks 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 continuously monitored for infusion related reactions from start of study intervention administration until the end of infusion.
- f. Participants who are HBsAg negative but HBcAb negative and HBsAb positive without unequivocal documentation of prior HBV vaccination or who are HBsAg negative but 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 in screening and the participant is enrolled in the study, HBV DNA testing must be performed on. If HBV DNA is undetectable in the HBV DNA reflex testing in screening and the participant is enrolled in the study, HBV DNA testing must be performed on Day 71, 157 and ET. See [Section 8.2.5.1](#).
- g. Acceptable IGRA assays are QuantiFERON<sup>®</sup>-TB Gold In-Tube (QFT-GIT) test and T-SPOT<sup>®</sup>-TB test. A documented TB test performed within 12 weeks prior to Day 1 is acceptable. Participants with a history of tuberculosis may not require TB testing as per the protocol exclusion criteria in [Section 5.2](#).
- h. Check exposure to positive participant, residence or travel in area of high incidence and COVID-19 related signs and symptoms. To be done at each visit.
- i. The testing for COVID-19 pathogen by PCR will be performed within 72 hours prior to admission on Day -1. In addition, a subsequent COVID-19 test will be performed after 4 days (ie, upon completion of 4 × 24 hours in house), or 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).

Visit Identifier <sup>a</sup> Abbreviations used in this table may be found in <a href="#">Appendix 7</a> .	Screening	CRU Confinement											Follow-Up							ET
		-28 to -2	-1	1				2	3	4	5	8	15	29	43	57	71	100	127	
<b>Days Relative to Day 1</b>	-28 to -2	-1	1				2	3	4	5	8	15	29	43	57	71	100	127	157	-
<b>Visit Window (days)</b>	-	-	-				-	-	-	-	±1	±1	±1	±3	±3	±3	±3	±3	±3	-
<b>Hours After Dose</b>			0 <sup>b</sup>	1	2	6	12	24	48	72	96	-	-	-	-	-	-	-	-	-

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

## 2. INTRODUCTION

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

### 2.1. Study Rationale

The purpose of this study is to evaluate the single-dose PK, safety, and tolerability of PF-06823859 after single IV administration to healthy adult Chinese participants. The information of PK, safety, and tolerability in healthy Chinese participants is being collected to support future PF-06823859 clinical development as well as registration in China.

### 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.<sup>1,2</sup>

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.<sup>3</sup> 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

In vitro assessments indicate that PF-06823859 is a potent inhibitor of IFN- $\beta$ /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. In addition, the nonclinical PK profiles of PF-06823859 in the cynomolgus monkey were typical for a human IgG mAb in monkeys. 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.



Detailed information concerning the nonclinical studies conducted with PF-06823859 can be found in the IB.

### 2.2.2. Clinical Overview

As of the protocol date, the Phase 1, randomized, double-blind, third-party open, placebo-controlled, dose escalating study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple intravenous and subcutaneous doses of PF-06823859 in healthy participants (C0251001) has been completed. In addition, the 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 IB.

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

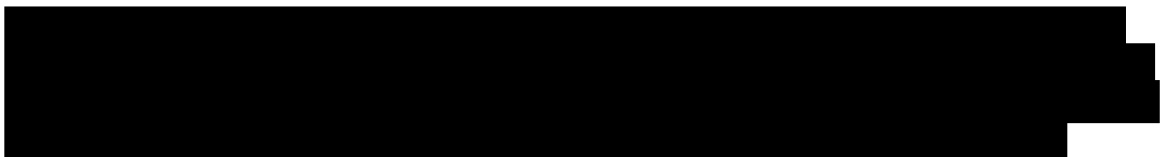
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CCI



### 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, and PK data for further clinical development.

Nonclinical data to date ([Section 2.2](#)) 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 IFN- $\beta$ .<sup>4</sup> 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 planned 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 IFN- $\beta$  blockade as with any antagonist of Type 1 interferon signaling (eg, anti-IFNAR1, anti-IFN- $\alpha$ , 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](#).

The clinical impact of these potential risks will be minimized through the proposed standard, intensive, inpatient monitoring of the participants following administration of single, IV dose of the study intervention.

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
<b>Primary:</b>	<b>Primary:</b>
<ul style="list-style-type: none"> <li>To evaluate the PK profile of single IV dose of 900 mg PF-06823859 in healthy Chinese participants.</li> <li>To determine the safety and tolerability of single IV dose of 900 mg PF-06823859 in healthy Chinese participants.</li> </ul>	<ul style="list-style-type: none"> <li>Serum PF-06823859 primary PK parameters, as permitted by data: <math>C_{max}</math>, <math>T_{max}</math>, <math>AUC_{14day}</math>, <math>AUC_{28day}</math>, <math>AUC_{inf}</math>, and <math>t_{1/2}</math>,</li> <li>Assessments of AEs/SAEs including infusion site reactions and viral infections, vital signs, ECGs and laboratory tests.</li> </ul>
<b>Secondary:</b>	<b>Secondary:</b>
<ul style="list-style-type: none"> <li>To further evaluate the PK of PF-06823859</li> <li>To evaluate the immunogenicity of PF-06823859.</li> </ul>	<ul style="list-style-type: none"> <li>Serum PF-06823859 PK parameters, as permitted by data: <math>C_{max}</math> (dn), <math>AUC_{last}</math>, <math>AUC_{last}</math> (dn), <math>AUC_{inf}</math> (dn), CL, <math>V_z</math>, and MRT.</li> <li>Incidence of the development of ADA and Nab.</li> </ul>

### 4. STUDY DESIGN

#### 4.1. Overall Design

This is a Phase 1, randomized, double-blind, sponsor-open, placebo-controlled, single arm study to evaluate the PK, safety, and tolerability following a single dose of PF-06823859 (900 mg) in healthy Chinese participants.

#### Number of Participants

Approximately 12 participants will be enrolled into the study. Approximately 10 participants will be randomized to PF-06823859 and approximately 2 participants will be randomized to placebo.

If more than 2 participants discontinue or withdraw before completing at least the follow-up visit at Day 100, or if there are participants whose PK samples are considered to be non-evaluable with respect to the primary PK objective, additional participants may be enrolled upon alignment between the sponsor and the investigator such that approximate 10 participants could provide evaluable PK samples for no less than Day 100 follow-up visit. For participants whose PK samples are considered to be non-evaluable with respect to the primary PK objective, their PK sample collection will stop for ethic consideration.

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. Participants will be admitted into the CRU approximately 1 day prior to dosing and are required to remain in the CRU through completion of Day 5 evaluations. Participants will return to the CRU for outpatient follow-up visits through Day 157.

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.

No formal interim analysis will be conducted for this study. As this is a sponsor-open study, the sponsor will conduct unblinded reviews of the safety, PK, and immunogenicity data through Day 28 after treatment administration to preliminarily assess any ethnic differences between Chinese and non-Chinese to support China joining future global PF-06823859 clinical development.

#### **4.2. Scientific Rationale for Study Design**

This study is designed to characterize the PK, safety, and tolerability of PF-06823859 after single IV dose administration in healthy Chinese participants.

To date, no PK or safety data of PF-06823859 in Chinese are available. Although there is no expected relevant PK difference between Chinese and non-Chinese because monoclonal antibodies are generally known for the absence of ethnic differences in their distribution and elimination, similar to that of endogenous IgG,<sup>5</sup> it is still important to characterize PK and establish safety in Chinese participants to support future PF-06823859 clinical development as well as drug registration in China. Information collected from this study allows comparison of PK and safety profiles of PF-06823859 in Chinese and non-Chinese participants.

Single-dose rather than repeated dosing is planned in the study due to the long PF-06823859 terminal half-life as well as the steady-state PK can be well predicted from single dose data based on information of Study C0251001. The study duration and frequency of each assessment were decided based on information of Study C0251001.

In order to sufficiently evaluate PK, safety, and tolerability of PF-06823859 in Chinese participants while at the same time considering the clinical practice and minimal necessity for PK evaluation, if more than 2 participants discontinue or withdraw before completing at least the follow-up visit at Day 100, or if there are participants whose PK samples are considered to be non-evaluable with respect to the primary PK objective, additional participants may be enrolled upon alignment between the sponsor and the investigator such that approximate 10 participants could provide evaluable PK samples for no less than Day 100 follow-up visit. For participants whose PK samples are considered to be non-evaluable with respect to the primary PK objective, their PK sample collection will stop for ethic consideration.

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 IFN- $\beta$  blockade as with any antagonist of Type 1 interferon signaling (eg,

anti-IFNAR1, anti-IFN- $\alpha$ , 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](#)).

#### 4.3. Justification for Dose

The proposed single IV dose level is 900 mg. The dose is selected based on the safety and tolerability in Study C0251001 and the doses of the Phase 2 study (Study C0251002) that is ongoing in patients with DM, to compare safety and PK among Chinese and non-Chinese.

PF-06823859 dose of 900 mg has been selected to evaluate the PK, safety, and tolerability of PF-06823859 in healthy Chinese 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. In the ongoing Phase 2 study (C0251002), PF-06823859 doses of CCI Q4W and CCI Q4W are being evaluated with the primary objective being to characterize the effect of PF-06823859 in DM patients.

CCI



Based on the above data, 900 mg is selected to evaluate PK, safety, and tolerability of PF-06823859 in healthy Chinese participants.

#### 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 18 to 45 years of age, inclusive, at the time of signing the ICD.
  - Refer to [Appendix 4](#) for reproductive criteria for male ([Section 10.4.1](#)) and female ([Section 10.4.2](#)) participants.

#### Type of Participant and Disease Characteristics:

2. Male and female Chinese participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and 12-lead ECG.
3. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

#### Weight:

4. BMI of 19 to 27 kg/m<sup>2</sup> (inclusive); and a total body weight >50 kg (110 lb).

#### Informed Consent:

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

## 5.2. Exclusion Criteria

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

### Medical Conditions:

1. 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 B, or hepatitis C; positive testing for HIV, syphilis, HBsAg, or HCVAb. Hepatitis B vaccination is allowed.

For hepatitis B, all participants must undergo testing for HBsAg, HBcAb, and HBsAb.

- Participants who are HBsAg positive will be excluded.
  - Participants who are negative for all 3 serology tests may be eligible.
  - HBsAg negative, HBcAb positive, and HBsAb negative participants are to be excluded from the study.
  - Participants who are HBsAg negative, HBcAb negative and HBsAb positive and provide documentation of prior HBV vaccination, may be eligible for the study and will not require HBV DNA monitoring during the study.
  - Participants who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND participants who are HBsAg negative, HBcAb positive, and HBsAb positive, will have HBV DNA assessed at screening.
    - If HBV DNA is detectable, participants will be excluded.
    - If HBV DNA is not detectable, participants may be eligible. If the participant is included in the study, for subsequent visits HBV DNA testing must be performed according to the [SoA](#).
3. History of autoimmune disorders.
  4. History of allergic or anaphylactic reaction to a therapeutic drug.
  5. History of recent active infections within 28 days prior to the screening visit.
  6. Participants with a fever within 7 days prior to dosing.



7. Infected with *Mycobacterium TB* as defined by any of the following:
  - A positive IGRA test performed at or within the 12 weeks prior to Day 1 is exclusionary; a negative test is required for eligibility. The following are acceptable IGRA assays: T-SPOT® TB test, QuantiFERON®-TB Gold In-Tube test (QFT-GIT), QuantiFERON®-TB Gold test (QFT-G) or QuantiFERON®-TB Gold Plus test (QFT-G Plus). In participants with a history of BCG vaccination, the IGRA test is strongly recommended since the Mantoux test (tuberculin, PPD skin test) may be positive due to vaccination.
  - If the results of the IGRA are indeterminate, the test may be repeated 1 time, and if a negative result is obtained, enrollment may proceed. A positive test on repeat is exclusionary.
  - A chest radiograph should be obtained if not done within the 3 months prior to screening. To be considered eligible for the study, the chest radiograph must be negative for active TB infection
  - History of either untreated or inadequately treated latent or active TB infection.
  - A participant who is currently being treated for active TB infection must be excluded from the study.
  - A participant who is being treated for latent TB infection can only be enrolled with exclusion of close contacts of multi-drug resistant TB, documentation of an adequate treatment regimen, and prior approval of the sponsor.
8. Contact with positive case of COVID-19 or travel to an area defined as high risk by relevant authority in the past 14 days.
9. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

**Prior/Concomitant Therapy:**

10. 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).
11. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s). Refer to [Section 6.8](#) for additional details.

12. Recent exposure to any live or attenuated live virus vaccines within 6 weeks of Day 1.
  - The use of COVID-19 vaccines are allowed. Any live or live attenuated COVID-19 vaccine will require a 6-week time period before admission to CRU. If the participant receives a COVID-19 vaccine during the study period, this should be recorded as a concomitant medication, and standard AE collection and reporting processes should be followed in the event of any AEs to the vaccination

**Prior/Concurrent Clinical Study Experience:**

13. Previous administration with an investigational drug within 30 days (or as determined by the local requirement. 180 days for biologics) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).
14. Participants that have received PF-06823859 or any other interferon alpha or interferon beta therapy at any time in the past.

**Diagnostic Assessments:**

15. A positive urine drug test.
16. Screening supine BP  $\geq 140$  mm Hg (systolic) or  $\geq 90$  mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is  $\geq 140$  mm Hg (systolic) or  $\geq 90$  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 or  $< 50$  bpm. If the PR is greater than 100 bpm or less than 50 bpm, the PR should be repeated 2 more times and the average of the three pulse rate 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 QTcF interval  $> 450$  msec, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is  $> 450$  msec, this interval should be rate-corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

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  $\geq 1.5 \times \text{ULN}$ ;
- Total bilirubin level  $\geq 1.5 \times \text{ULN}$ ; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is  $\leq \text{ULN}$ .
- Hemoglobin level  $\leq 120 \text{ g/L}$  ( $12.0 \text{ g/dL}$ );
- Platelet count  $\leq 150 \times 10^9/\text{L}$  ( $150,000 \text{ cells/mm}^3$ );
- WBC count of  $\leq 3.0 \times 10^9/\text{L}$  ( $3000 \text{ cells/mm}^3$ );
- ANC  $< 1500 \text{ cells/mm}^3$ ;
- ALC  $< 800 \text{ cells/mm}^3$ ;
- eGFR  $< 90 \text{ mL/min/1.73 m}^2$  based on the CKD-EPI 2009 equation<sup>6</sup>;
- In the opinion of the investigator or Pfizer (or designee), have any clinically significant laboratory abnormality that may affect participant's safety or interpretation of study data.

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 1 pint (500 mL) or more within 60 days prior to dosing.
23. History of sensitivity to heparin or heparin -induced thrombocytopenia.
24. Pregnant and/or breastfeeding females.
25. Unwilling or unable to comply with the criteria in the [Lifestyle Considerations](#) section of this protocol.

26. 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 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 confinement in the CRU.

#### **5.3.3. Activity**

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

#### **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 schedule of activities ([SoA](#)), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception) 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 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

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

	labeled as required per country requirement.	be labeled as required per country requirement.
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Participants will receive study intervention at approximately 0800 hours on Day 1 (plus or minus 2 hours). Study intervention does not require fasting, but it should be noted that the safety laboratory test at Day -1 prior to the study intervention need a fast of at least 4 hours. Investigator site personnel will administer study intervention as a 60-minute intravenous infusion 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 drug 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 drug administration should be discontinued immediately and permanently.
- If a participant experiences symptoms typical of infusion related reactions (eg, lightheadedness, nausea, chills, fever), the study drug 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 drug administration should be discontinued immediately and permanently.
- In the event that there is an infusion interruption, the entire duration of drug 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 investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.
8. Further guidance and information for the final disposition of unused study interventions are provided in the 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 allocated manually and 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.

This is an investigator- and participant-blind (sponsor open) placebo-controlled study. 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. 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  $\leq 1$  g/day.

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

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.

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

### **7.2.1. Withdrawal of Consent**

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

### **7.3. Lost to Follow-up**

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. 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, but some laboratory items may need to be retested if the screening period exceeds more than 30 days.

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, but some laboratory items may need to be retested if previous results are more than 30 days ago. 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.

The PK results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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

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

The total blood sampling volume for individual participants in this study is approximately 335 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 complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

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

Physical examinations may be conducted by a physician.

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 at other times specified in the [SoA](#) 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. Additional chest X-ray will be performed based on clinical needs when AEs occur.

### **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 intravenous 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 pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

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

#### **8.2.3.1. Temperature**

Temperature will be measured per local practice. The method chosen by the CRU should be used consistently throughout the study. 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 heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

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

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

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

ECG values of potential clinical concern are listed in [Appendix 6](#).

### **8.2.5. 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 Day 157 ( $\pm 3$  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 5](#) for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

All protocol required laboratory assessments, as defined in [Appendix 2](#), must be conducted in accordance with the laboratory manual and the [SoA](#).

If laboratory values from non protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the source data, and in the CRF AE narrative.

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



### 8.2.5.1. 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 is tested viral load positive for HBV at screening will be excluded from the study. If there is any positive for viral load of HBV after screening, the participant should be discontinued from study treatment and referred to a hepatologist/specialist caring for HBV infection for appropriate evaluation and treatment.

### 8.2.6. Tuberculosis Test

Participants should be screened for TB using an IGRA per local guidelines. 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-GIT) test, T-SPOT®TB test, QuantiFERON®-TB Gold test (QFT-G) or QuantiFERON®-TB Gold Plus test (QFT-G Plus).. If T-SPOT test was completed within 12 weeks prior to Day 1, this is acceptable, however this test type cannot be offered for participants requiring the test during screening. 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.

#### **8.2.7. 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, a blood sample for viral surveillance sample may also be taken at the time of an AE, as clinically appropriate.

#### **8.2.8. COVID-19 Specific Assessments**

Participants will be tested for SARS-COVID-19 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 a central or local laboratory. 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.

#### **8.2.9. Pregnancy Testing**

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the [SoA](#). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit

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

#### **8.2.10. Infusion Site Assessment**

Infusion site reactions will be assessed according to the [SoA](#). Infusion site reactions may include but are not limited to: erythema, induration, ecchymosis, pain, and pruritus.

Any signs or symptoms related to either an infusion site reaction should be treated according to the investigator's standard of care and reported as adverse events.

### **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 157 calendar days ( $\pm 3$  days) 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.

#### **8.3.2. Method of Detecting AEs and SAEs**

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

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

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

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

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

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

#### **8.3.4. Regulatory Reporting Requirements for SAEs**

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

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

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

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

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

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

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

##### **8.3.5.1. Exposure During Pregnancy**

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.

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

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 157 days ( $\pm 3$  days) after last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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

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

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

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

#### **8.3.5.2. Exposure During Breastfeeding**

An exposure during breastfeeding occurs if:

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

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

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with

authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

### **8.3.5.3. Occupational Exposure**

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

### **8.3.6. Cardiovascular and Death Events**

Not applicable.

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

Not applicable

### **8.3.8. Adverse Events of Special Interest**

Not applicable.

#### **8.3.8.1. Lack of Efficacy**

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

### **8.3.9. Medical Device Deficiencies**

Not applicable.

### **8.3.10. Medication Errors**

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

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

<b>Safety Event</b>	<b>Recorded on the CRF</b>	<b>Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness</b>
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 a minimum of 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 data collection tool (eg, CRF). Collection of samples more than 10 hours after dose administration that are obtained  $\leq 1$  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 data collection tool (eg, CRF). This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples will be used to evaluate the PK of 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, or for other internal **CCI** purposes.

**CCI**

Samples collected for measurement of serum concentrations of PF-06823859 will be analyzed using a validated analytical method in compliance with applicable SOPs.

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 may 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.

### **8.5. Genetics**

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

### **8.6. Biomarkers**

Biomarkers are not evaluated in this study.

### **8.7. Immunogenicity Assessments**

Blood samples of approximately 6 mL, to provide a minimum of 2 mL of 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.

CCI [REDACTED]

[REDACTED]

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples determined to be positive for ADA may be further characterized for NAb.

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 may 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**

Not applicable.

### **9.2. Analysis Sets**

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

<b>Participant Analysis Set</b>	<b>Description</b>
Safety Analysis Set	All randomized participants who received at least 1 dose of the study intervention
PK Concentration Set	All randomized participants who received at least 1 dose of study intervention and at least 1 concentration value is reported
PK Parameter Set	All randomized participants who received at least 1 dose of study intervention and at least 1 of the PK parameters is calculated
Immunogenicity Analysis Set	All randomized participants who received at least 1 dose of study intervention with at least 1 post-treatment anti-drug 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 endpoints.

#### 9.3.1. General Considerations

No formal statistical tests will be performed. Descriptive summaries will be provided for all endpoints by treatment group.

#### 9.3.2. Pharmacokinetic Analyses of PF-06823859

The PK parameters for PF-06823859 following single dose administration will be derived from the concentration-time profiles by noncompartmental analysis as detailed in Table 1. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling times will be used in the derivation of PK parameters.

**Table 1. Definition of Serum PK Parameters for PF-06823859**

Parameter	Definition	Method of determination
$C_{max}$	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
$AUC_{inf}^a$	Area under the serum concentration-time profile from time zero 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
$AUC_{inf} (dn)^a$	Dose normalized $AUC_{inf}$	$AUC_{inf}/Dose$
$AUC_{last}$	Area under the serum concentration-time profile from time zero to the time of the last quantifiable concentration ( $C_{last}$ )	Linear/Log trapezoidal method
$AUC_{last} (dn)$	Dose normalized $AUC_{last}$	$AUC_{last}/Dose$
$AUC_{14day}$	Area under the concentration-time profile from time zero to 14 days post-dose (336 hours)	Linear/Log trapezoidal method
$AUC_{28day}$	Area under the concentration-time profile from time zero to 28 days post-dose (672 hours)	Linear/Log trapezoidal method
$t_{1/2}^a$	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	$Dose/AUC_{inf}$
$V_z$	Volume of distribution	$Dose/(AUC_{inf}*k_{el})$

**Table 1. Definition of Serum PK Parameters for PF-06823859**

<b>Parameter</b>	<b>Definition</b>	<b>Method of determination</b>
MRT <sup>a</sup>	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

The serum PK parameters for PF-06823859 will be summarized descriptively by treatment group, as applicable. Serum concentration of PF-06823859 will be summarized descriptively and plotted by study day.

### 9.3.3. 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

All safety analyses will be performed on the safety set.

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

Incidence of viral infections or change in baseline of viral loads (CMV, VZV, EBV, HHV6, and HSV-1/2) if they occur, will be summarized by treatment group.

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

#### 9.3.4.1. Electrocardiogram Analyses

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

The number (%) of participants with maximum post dose 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

### 9.4. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an 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, agency communication, and/or supporting clinical development.

### 9.5. Sample Size Determination

The total sample size of approximately 12 participants (10 active, 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.

If more than 2 participants discontinue or withdraw before completing at least the follow-up visit at Day 100, or if there are participants whose PK samples are considered to be non-evaluable with respect to the primary PK objective, additional participants may be enrolled upon alignment between the sponsor and the investigator such that approximate 10 participants could provide evaluable PK samples for no less than Day 100 follow-up visit.

## **10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS**

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

#### **10.1.1. Regulatory and Ethical Considerations**

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

### **10.1.2. Financial Disclosure**

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

### **10.1.3. Informed Consent Process**

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative 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 or their legally authorized representative 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 or his or her legally authorized representative 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 or his or her legally authorized representative 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 or his or her legally authorized representative.

The participant or his or her legally authorized representative 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 or his or her legally authorized representative 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 or his or her legally authorized representative must be re-consented 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 or the participant's legally authorized representative.

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

#### **10.1.4. Data Protection**

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

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

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

#### **10.1.5. Committees Structure**

##### **10.1.5.1. Data Monitoring Committee**

This study will not use a DMC.

#### **10.1.6. Dissemination of Clinical Study Data**

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (ClinicalTrials.gov), the EudraCT, and/or [www.pfizer.com](http://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](http://www.clinicaltrials.gov)

Pfizer posts clinical trial results on [www.clinicaltrials.gov](http://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](http://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](http://www.pfizer.com) for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

Documents within marketing authorization packages/submissions

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

Data sharing

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

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not

be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

#### **10.1.7. Data Quality Assurance**

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

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

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

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

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

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

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

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

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow

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

#### **10.1.8. Source Documents**

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

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

Definition of what constitutes source data and its origin can be found in source data agreement, 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.

#### **10.1.9. Study and Site Start and Closure**

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

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

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

The investigator may initiate study-site closure at any time upon notification to the sponsor 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.

#### **10.1.10. Publication Policy**

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

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

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

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

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

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

#### **10.1.11. Sponsor's Qualified Medical Personnel**

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Investigator Site Master File.

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 2. Protocol-Required Safety Laboratory Assessments**

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN/urea and creatinine	<u>Local Dipstick:</u>	<u>As per SoA:</u>
Hematocrit	Glucose (fasting)	pH	<ul style="list-style-type: none"> <li>• COVID-19 testing</li> </ul>
RBC count	Calcium	Glucose (qual)	<ul style="list-style-type: none"> <li>• Pregnancy test (b-hCG)<sup>b</sup></li> </ul>
MCV	Sodium	Protein (qual)	<ul style="list-style-type: none"> <li>• Urine drug screening<sup>c</sup></li> </ul>
MCH	Potassium	Blood (qual)	<ul style="list-style-type: none"> <li>• Viral surveillance: CMV, VZV, EBV,</li> </ul>
MCHC	Chloride	Ketones	<ul style="list-style-type: none"> <li>• HHV6, HSV-1/2</li> </ul>
Platelet count	Total CO <sub>2</sub> (bicarbonate)	Nitrites	<ul style="list-style-type: none"> <li>• PT</li> </ul>
WBC count	AST, ALT	Leukocyte	<ul style="list-style-type: none"> <li>• INR</li> </ul>
Total neutrophils	Total bilirubin	esterase/WBC	<ul style="list-style-type: none"> <li>• aPTT</li> </ul>
(Abs)	Alkaline phosphatase		<ul style="list-style-type: none"> <li>• HBV DNA<sup>d</sup>, if applicable</li> </ul>
Eosinophils (Abs)	Uric acid	<u>Laboratory:</u>	
Monocytes (Abs)	Albumin	Microscopy and	
Basophils (Abs)	Total protein	Culture <sup>a</sup>	
Lymphocytes (Abs)			<u>At screening only:</u>
			<ul style="list-style-type: none"> <li>• FSH<sup>e</sup></li> <li>• HIV</li> <li>• HBsAg</li> <li>• HBsAb</li> <li>• HBcAb</li> <li>• HCVAb</li> <li>• syphilis</li> </ul>

- Urine Microscopy was routinely done in site. Urine or blood Culture will be done under investigator's judgement.
- Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine  $\beta$ -hCG for female participants of childbearing potential.
- The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
- HBV DNA testing will be performed according to [Section 8.2.5.1](#).
- For confirmation of postmenopausal status only.

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

<b>AE Definition</b>
<ul style="list-style-type: none"><li>• 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.</li><li>• 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.</li></ul>

<b>Events Meeting the AE Definition</b>
<ul style="list-style-type: none"><li>• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:<ul style="list-style-type: none"><li>• Is associated with accompanying symptoms;</li><li>• Requires additional diagnostic testing or medical/surgical intervention;</li><li>• 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.</li></ul></li><li>• Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.</li><li>• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.</li><li>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.</li><li>• 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.</li></ul>



<b>Events <u>NOT</u> Meeting the AE Definition</b>
<ul style="list-style-type: none"><li>• 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.</li><li>• 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.</li><li>• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.</li><li>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).</li><li>• 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.</li></ul>

**10.3.2. Definition of an SAE**

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

<p><b>d. Results in persistent or significant disability/incapacity</b></p> <ul style="list-style-type: none"><li>• The term disability means a substantial disruption of a person’s ability to conduct normal life functions.</li><li>• 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.</li></ul>
<p><b>e. Is a congenital anomaly/birth defect</b></p>
<p><b>f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious.</b></p> <p>The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.</p>
<p><b>g. Other situations:</b></p> <ul style="list-style-type: none"><li>• 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.</li><li>• 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.</li></ul>

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

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

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  <b>Note:</b> Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF.	All instances of EDP are reported (whether or not there is an associated SAE)*  All instances of EDB are reported (whether or not there is an associated SAE). **
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB).	None. Exposure to a study non-participant is not collected on the CRF.	The exposure (whether or not there is an associated AE or SAE) must be reported.***

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

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

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

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

<ul style="list-style-type: none"><li>• It is <b>not</b> 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.</li><li>• 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.</li><li>• 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.</li></ul>
<b>Assessment of Intensity</b>
<p>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:</p> <ul style="list-style-type: none"><li>• Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</li><li>• 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.</li><li>• 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.</li></ul> <p>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.</p>

<b>Assessment of Causality</b>
<ul style="list-style-type: none"><li>• 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.</li><li>• 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.</li></ul>

- 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

- | <b>SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool</b>   |
|--|
| <ul style="list-style-type: none"><li>• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.</li><li>• 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.</li><li>• The site will enter the SAE data into the electronic system as soon as the data become available.</li><li>• 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.</li><li>• 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.</li></ul> |

- | <b>SAE Reporting to Pfizer Safety via CT SAE Report Form</b>  |
|---|
| <ul style="list-style-type: none"><li>• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.</li><li>• 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.</li><li>• 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.</li></ul> |

## 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 157 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s) (*eg, 5 terminal half-lives*):

- Refrain from donating sperm.

PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent;

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in [Section 10.4.4](#)).

### 10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below during the intervention period and for at least 157 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) (*5 terminal half-lives*). 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 157 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) (*5 terminal half-lives*). 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.

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

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

#### **10.4.3. 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;
7. Progestogen-only hormone contraception associated with inhibition of ovulation.
  - Oral;
  - Injectable.
8. Sexual abstinence.

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

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

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

## 10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-Up Assessments

### Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

## 10.6. Appendix 6: ECG Findings of Potential Clinical Concern

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

- 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.

## 10.7. Appendix 7: 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
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
AUC <sub>14day</sub>	AUC from time 0 to 14 days post-dose
AUC <sub>28day</sub>	AUC from time 0 to 28 days post-dose
AUC <sub>inf</sub>	AUC from time 0 extrapolated to infinite time
AUC <sub>last</sub>	AUC from time 0 to the time of the last quantifiable concentration
AUC <sub>τ</sub>	AUC from time 0 to time τ, the dosing interval
AUMC <sub>inf</sub>	area under the moment curve from time 0 extrapolated to infinity
AV	atrioventricular
BCG	Bacillus Calmette-Guérin
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
C <sub>av</sub>	concentration average
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatinine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
C <sub>max</sub>	maximum observed concentration
CMV	cytomegalovirus
CO <sub>2</sub>	carbon dioxide
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CT	clinical trial; computed tomography

<b>Abbreviation</b>	<b>Term</b>
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
DOF	duration of the IV infusion
DU	dispensable unit
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
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ePPND	enhanced pre and postnatal development
ET	early termination
EU	European Union
EudraCT	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
HBV DNA	hepatitis B virus DNA
HCVAb	hepatitis C antibody
HHV6	Human Herpes Virus 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



<b>Abbreviation</b>	<b>Term</b>
IFN	interferon
IFN- $\alpha$	interferon- $\alpha$
IFN- $\beta$	interferon- $\beta$
IFNAR	interferon-a/b 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
IPAL	Investigational Product Accountability Log
IRB	institutional review board
ISR	injection site reaction
IV	intravenous
JAK	Janus kinase
$k_{el}$	terminal phase rate constant
LBBB	left bundle branch block
LFT	liver function test
Log <sub>e</sub>	natural logarithm
mAb	monoclonal antibody
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	medical device regulation
MRI	magnetic resonance imaging
MRT	mean residence time
N/A	not applicable
NAb	neutralizing antibodies
NIMP	noninvestigational medicinal product
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
PPD	purified protein derivative
PR	pulse rate
PT	prothrombin time
PVC	premature ventricular contraction/complex
Q2W	once every 2 weeks
Q4W	once every 4 weeks
QFT-GIT	QuantiFERON <sup>®</sup> -TB Gold In Tube

<b>Abbreviation</b>	<b>Term</b>
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
$R_{ac}$ , $AUC_{\tau}$	accumulation ratio for $AUC_{\tau}$
$R_{ac}$ , $C_{max}$	accumulation ratio for $C_{max}$
RBC	red blood cell
SAD	single ascending dose
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
SLE	systemic lupus erythematosus
SoA	schedule of activities
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
$t_{1/2}$	terminal phase half-life
THC	tetrahydrocannabinol
$T_{max}$	time to reach $C_{max}$
T-Spot	T-spot <sup>®</sup> TB
ULN	upper limit of normal
US	United States
$V_{ss}$	volume at steady state
$V_z$	volume at distribution
VZV	varicella-zoster virus
WBC	white blood cell
WOCBP	woman of childbearing potential

## 11. REFERENCES

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- <sup>1</sup> National Organization of Rare Disease, NORD 2015. Available from: <http://rarediseases.org/rare-diseases/dermatomyositis/>. Accessed: 16 June 2021.
- <sup>2</sup> Myositis Support and Understanding Association Inc. 2010-2017. Available from: <https://understandingmyositis.org/types-of-myositis/dermatomyositis/?gclid=CIXP-fLSns8CFYM9gQodSZID1A>. Accessed: 16 June 2021.
- <sup>3</sup> Fasano S, Alves SC, Isenberg DA. Current pharmacological treatment of idiopathic inflammatory myopathies. *Expert Rev Clin Pharmacol*. 2015. DOI: 10.1586/17512433.2016.1136561.
- <sup>4</sup> Takayanagi H, Kim S, Matsuo K, et al. RANKL maintains bone homeostasis through c-FOS-dependent induction of interferon- $\beta$ . *Nature*. 2002;416 (6882): 744.
- <sup>5</sup> Chiba K, Yoshitsugu H, Kyosaka Y, et al. A comprehensive review of the pharmacokinetics of approved therapeutic monoclonal antibodies in Japan: Are Japanese phase I studies still needed? *J Clin Pharmacol*. 2014;54(5):483-94.
- <sup>6</sup> Levey AS, Stevens LA, Schmid CH, et al. CKD-EPI . A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-12. DOI: 10.7326/0003-4819-150-9-200905050-00006. Erratum in: *Ann Intern Med*. 2011 ;155(6):408. PMID: 19414839; PMCID: PMC2763564.