



**A PHASE 1, OPEN-LABEL, SINGLE DOSE STUDY TO INVESTIGATE THE
PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY, AND
TOLERABILITY OF PONSEGROMAB ADMINISTERED SUBCUTANEOUSLY IN
HEALTHY ADULT CHINESE PARTICIPANTS**

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Phase:	1

Brief Title: A Phase 1 PK, PD, Safety, and Tolerability Study With Ponsegromab
Single-Dose Subcutaneously Administered in Healthy Adult Chinese Participants

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 1, Open-Label, Single Dose Study to Investigate the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Ponsegromab Administered Subcutaneously in Healthy Adult Chinese Participants

Brief Title: A Phase 1 PK, PD, Safety and Tolerability Study With Ponsegromab Single-Dose Subcutaneously Administered in Healthy Adult Chinese Participants

Rationale

The purpose of this study is to evaluate the PK, PD, safety, and tolerability of ponsegromab following 100 mg and 400 mg single SC dose in healthy adult Chinese participants. Results from this study will be used to inform clinical development of ponsegromab in China, to facilitate China's participation in global pivotal studies, and to support China registration of ponsegromab.

Objectives and Endpoints

Objectives	Endpoints
Primary:	Primary:
<ul style="list-style-type: none">To characterize the serum PK of ponsegromab following a single SC administered dose in healthy adult Chinese participants.	<ul style="list-style-type: none">Ponsegromab serum PK parameters (unbound and total), as data permit: AUC_{inf}, AUC_{last}, C_{max}, T_{max}, and t_{1/2}.
Secondary:	Secondary:
<ul style="list-style-type: none">To evaluate the safety and tolerability of ponsegromab following a single SC administered dose in healthy adult Chinese participants.	<ul style="list-style-type: none">AEs, clinical safety laboratory tests, vital signs (blood pressure, pulse rate), physical examinations, and 12-lead ECGs for approximately 18 weeks post single dose.
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Overall Design

Brief Summary

This is an open-label, single dose study to characterize the PK, PD, safety, and tolerability of ponsegromab following 100 mg or 400 mg single SC dose in healthy adult Chinese participants.

Number of Participants

Approximately 18 participants will be enrolled in this study (N=9 for each cohort) with the goal of attaining approximately 16 participants (N=8 for each cohort) evaluable for the primary endpoints.

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

Intervention Groups and Duration

Participants who meet eligibility criteria at baseline will receive a single SC dose of ponsegromab at 100 mg (Cohort 1) or 400 mg (Cohort 2) on Day 1. Participants in the 100 mg cohort will be dosed firstly, and will be kept under safety monitoring for 8 days at the CRU. Progression to 400 mg will occur only if 100 mg is well tolerated after reviewing the safety data up to 8 days post-dose as judged by the investigator. Sentinel dosing may be implemented in the 400 mg cohort as judged by the investigator: eg, 2 participants may be dosed prior to the remaining participants in Cohort 2. If the dose level is determined to have an acceptable safety and tolerability profile up to 8 days post-dose, as judged by the investigator for the first 2 sentinel participants, the remaining 7 participants in that cohort will be dosed. The total duration of each participation in this study is approximately 22 weeks, including a screening period of up to 4 weeks to confirm eligibility and a follow-up period of approximately 18 weeks after the single SC dose.

Participants who discontinue prior to completion of the study for non-safety related reasons may be replaced, at the discretion of the investigator and sponsor study team.

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

All data analyses will be descriptive. The serum PK parameters of ponsegromab (unbound and total) will be listed and descriptively summarized by cohort. CCI [REDACTED]
[REDACTED] For each cohort,

the serum concentrations of ponsegromab (unbound and total) will be listed and descriptively summarized by nominal sampling time and cohort. Within each cohort, individual participant and summary profiles (mean and median plots) of the serum concentration-time

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Safety data (AEs, ECGs, BP, PR, and safety laboratory data) will be presented in tabular and/or graphical format and summarized descriptively by cohort, where appropriate.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

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

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

	Screening		Inpatient stay at CRU								Outpatient FU								ET/DC
Day relative to Day 1 For abbreviations, refer to Appendix 7	Day -28 to Day -2	Admit to CRU ^a (Day -1)	Day 1		Day 2	Day 3	Day 4	Day 6	Day 8	Day 10 ±1	Day 15 ±1	Day 29 ±1	Day 50 ±2	Day 71 ±3	Day 93 ±7	Day 106 ±7	Day 127 ^b ±7		
Hours After Dose (for inpatient portion)			0	12 ±1	24 ±2	48 ±2	72 ±4	120 ±4	168 ±4										
Informed consent	X																		
Inpatient stay at CRU		X	→	→	→	→	→	→	X										
Outpatient visit to CRU										X	→	→	→	→	→	→	X		
Assessment of eligibility, medical/medication history ^c	X	X																	
Physical exam and weight (plus height at Screening, only) ^d	X	X							X	X	X	X	X	X	X	X	X	X	
Review alcohol/caffeine/tobacco, as applicable	X	X							X	X	X	X	X	X	X	X	X	X	
Review prior or concomitant treatments, as applicable	X	X	→		→	→	→	→	→	→	→	→	→	→	→	→	X	X	
Demography	X																		
Review contraception use	X	X							X	X	X	X	X	X	X	X	X	X	
Serious and non-serious AEs monitoring	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	
Injection site assessment ^e			X	→	X														
Supine 12-lead ECG (triplicate)	X		X ^f		X		X		X	X			X	X			X	X	
Single, supine BP and PR (triplicate pre-dose Day 1, only)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Eligibility overview for study enrollment ^g		X	X																
Study intervention administration			X																

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	Screening		Inpatient stay at CRU							Outpatient FU							ET/DC
Day relative to Day 1 For abbreviations, refer to Appendix 7	Day -28 to Day -2	Admit to CRU ^a (Day -1)	Day 1	Day 2	Day 3	Day 4	Day 6	Day 8	Day 10 ±1	Day 15 ±1	Day 29 ±1	Day 50 ±2	Day 71 ±3	Day 93 ±7	Day 106 ±7	Day 127 ^b ±7	
Hours After Dose (for inpatient portion)			0	12 ±1	24 ±2	48 ±2	72 ±4	120 ±4	168 ±4								
Blood samples: serum FSH (females amenorrheic ≥12 months, only), HIV, HBsAg, HBcAb, HCVAb, Syphilis test	X																
Safety laboratory tests ^h	X	X			X		X		X		X	X	X	X		X	X
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Blood Sample (s): serum ponsegromab (PK)			X ⁱ	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine drug test	X	X															
COVID-19 test(s) ^j	X																

- Participants will admit to CRU at least 12 hours prior to dosing. Admission procedures to be conducted once, unless deemed necessary by investigator or sponsor.
- FU to approximately 18 weeks postdose planned; FU visits may be adjusted at investigator/sponsor discretion, including to monitor open AE, or based on emerging data (see Section 4.4).
- Medication history will be updated at each visit.
- Full PE at Screening or admission; at all other timepoints, limited PE performed for findings during previous exam or new/open AEs, at investigator discretion. PE may be conducted at final FU visit, at investigator discretion. Body weight to be measured at all indicated timepoints.
- Injection site assessment at predose (-30 min to 0 h), and 1 h (±10 min), 6 h (±0.5 h), 12 h (±1 h) and 24 h (±2 h) postdose. Additional assessments at investigator discretion and/or until any symptoms resolve. Additional requirements see Section 8.2.2.
- Baseline ECGs should be triplicate collections at 60 min (±5 min) predose, 30 min (±5 min) predose, and 15 min (±5 min) predose (nine measurements in total). Additional requirements on ECGs see Section 8.2.4.
- Eligibility overview for study enrollment could be performed after all procedures are completed on Day -1, or before all procedures on Day 1, according to site operating practices.
- See [Appendix 2](#) for safety laboratory tests in the study.
- Predose sample collection may be conducted between CRU admission and dose administration on Day 1.
- The timing and methods of COVID-19 test(s) should follow the requirements from local regulations or the investigator (CRU).

2. INTRODUCTION

Cachexia is a metabolic disorder and comorbidity that occurs with several chronic diseases including cancer, heart failure, COPD, and CKD. Cachexia manifests as marked involuntary body weight loss, muscle atrophy, and reduced appetite, progressing to significant functional impairment and increased risk of death.

GDF-15 is a stress responsive cytokine secreted by tumor cells, macrophages and damaged cells.¹⁻⁵ In several chronic conditions such as cancer, COPD, and CKD, circulating GDF-15 concentrations are markedly elevated compared to healthy individuals.⁶⁻⁹ Elevated GDF-15 is associated with weight loss/cachexia in cancer¹⁰⁻¹³ and also heart failure^{14,15} patients. In addition, elevated circulating GDF-15 levels are associated with poor survival in many cancers, heart failure, CKD and COPD.¹⁶⁻²² In rodents and non-human primates, GDF-15 induces anorexia and weight loss²³⁻²⁷ by acting through the GFRAL. Furthermore, increased GDF-15 levels are associated with cachexia in mouse tumor models, and neutralization of GDF-15 reverses weight loss and improves survival.¹²

Ponsegromab is a humanized mAb which binds to the GDF-15 protein and prevents its interaction with GFRAL and is currently being developed for the treatment of cachexia in cancer patients. Its potential to mitigate muscle mass loss, improve anorexia, and reduce fatigue in patients with cancer cachexia is being investigated. In addition to cancer cachexia, it has the potential to improve the symptoms and function of patients with heart failure who have elevated levels of GDF-15.

2.1. Study Rationale

This study is the first clinical study with ponsegromab in the Chinese population. The purpose of this study is to evaluate the PK, PD, safety, and tolerability of ponsegromab following 100 mg and 400 mg single subcutaneous dose in healthy adult Chinese participants. Ponsegromab exhibits target mediated disposition, in addition to non-specific catabolism, which is considered to be less susceptible to ethnic factors. Results from this study will be used to preliminarily support the ethnic sensitivity assessment between Chinese and Westerners, to inform clinical development of ponsegromab in China, to facilitate China's participation in global pivotal studies, and to support China registration of ponsegromab.

2.2. Background

A summary of relevant, currently available data is provided in this protocol. Additional details and further information for this compound may be found in the [IB](#).

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[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]		
[REDACTED]	[REDACTED]	[REDACTED]

2.3.2. Benefit Assessment

Ponsegromab is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, PK, and PD data for further clinical development.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account all available nonclinical and clinical data regarding the reassuring safety

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and tolerability of ponsegromab to date, and measures to monitor and minimize risk to study participants, the overall benefit/risk profile supports further clinical development of ponsegromab in healthy adult Chinese participants.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	Primary:
<ul style="list-style-type: none"> To characterize the serum PK of ponsegromab following a single SC administered dose in healthy adult Chinese participants. 	<ul style="list-style-type: none"> Ponsegromab serum PK parameters (unbound and total), as data permit: AUC_{inf}, AUC_{last}, C_{max}, T_{max}, and t_{1/2}.
Secondary:	Secondary:
<ul style="list-style-type: none"> To evaluate the safety and tolerability of ponsegromab following a single SC administered dose in healthy adult Chinese participants. 	<ul style="list-style-type: none"> AEs, clinical safety laboratory tests, vital signs (blood pressure, pulse rate), physical examinations, and 12-lead ECGs for approximately 18 weeks post single dose.
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4. STUDY DESIGN

4.1. Overall Design

This study is an open-label, single dose study to characterize the PK, PD, safety, and tolerability of ponsegromab.

The study will enroll 2 cohorts of approximately 18 healthy adult Chinese participants (N=9 for each cohort). Participants will receive ponsegromab 100 mg (Cohort 1) or ponsegromab 400 mg (Cohort 2) on Day 1.

The total duration of each participation in this study is approximately 22 weeks, including a screening period of up to 4 weeks to confirm eligibility, and a follow-up period of approximately 18 weeks after the single SC dose. Participants will be admitted to the CRU at least 12 hours prior to their planned dose administration time, and will be required to remain in the CRU until completion of procedures on Day 8 as described in the [SoA](#). Admission procedures are to be conducted once, unless deemed necessary by investigator or sponsor. Inpatient stay at CRU can be prolonged for safety monitoring purpose, at the discretion of the investigator and sponsor.

Each participant will receive 1 single SC dose of ponsegromab 100 mg or ponsegromab 400 mg on Day 1. Participants in 100 mg cohort will be dosed firstly, and will be kept under safety monitoring for 8 days at the CRU. Progression to 400 mg will occur if 100 mg is well

tolerated after reviewing the safety data up to 8 days post-dose. Sentinel dosing may be implemented in the 400 mg cohort as judged by the investigator: eg, 2 participants may be dosed prior to the remaining participants in Cohort 2. If the dose level is determined to have an acceptable safety and tolerability profile up to 8 days post-dose, as judged by the investigator for the first 2 sentinel participants, the remaining 7 participants in that cohort will be dosed.

Participants will return for outpatient visits per the [SoA](#). Participants who experience AE will continue to be followed to resolution or stabilization of the event as agreed upon by the investigator and sponsor.

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

4.2. Scientific Rationale for Study Design

This study is the first clinical study with ponsegromab in the Chinese population. The study is designed as open-label, with PK in healthy adult Chinese participants as the primary objective. The safety and tolerability **CCI**

CCI will be investigated as secondary **CCI**

The intended route of administration of ponsegromab to patients is SC; the same route will be tested in this study.

As is typical for early development studies, and to allow better comparisons in PK, PD, safety, and tolerability of ponsegromab between Chinese and non-Chinese, the population envisioned for this China Phase 1 study will be similar to that in studies C3651001 and C3651002, ie, healthy male and female participants. Female participants will be confirmed to be categorized as women of non-childbearing potential as, at the present time, embryo-fetal developmental toxicology studies with ponsegromab have not been conducted. In male participants, appropriate measures to minimize potential transfer of ponsegromab via semen to partners are expected to be followed (see [Appendix 4](#)).

Risks to study participants will be minimized by dose administration in an inpatient setting, with careful assessment and on-going review of safety data. After single-dose SC administration, there will be a follow-up period of approximately 18 weeks. This duration has been chosen based on the PK half-life of ponsegromab observed in the completed clinical trials **CCI** Clinical safety laboratory tests (see Section [8.2.5](#)), thorough assessments of vital signs, ECGs, physical examinations, and AE monitoring will provide essential data to evaluate the safety and tolerability of ponsegromab.

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populations including global Phase 1 study (C3651001), Japan Phase 1 study (C3651002), and the current China Phase 1 study (C3651012) are all designed as single dose. Serial PK samples will be collected following single dosing to generate PK parameters which allows comparison among different ethnic populations.

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4.3. Justification for Dose

Participants enrolled will receive a single 100 mg or 400 mg SC dose of ponsegromab on

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Specifically, the 400 mg is expected to cover the potential highest clinical dose in subsequent

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direct comparison of ponsegromab exposure cross three different populations (Chinese, Westerners, and Japanese).

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 procedures at their last follow-up visit. Follow-up visits in addition to those in the [SoA](#) may be scheduled at investigator discretion, including to monitor open AE, or based on emerging data.

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

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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. Participants must be 18 to 55 years of age, inclusive, at the time of signing the ICD.
 - Female participants must be of non childbearing potential (see Section 10.4.3).
 - 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, BP and PR measurement, 12-lead ECG, and laboratory tests. Chinese participants are defined as individuals currently residing in mainland China who were born in China and have both parents of Chinese descent.
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 17.5 to 30.5 kg/m²; 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, syphilis, hepatitis B, or hepatitis C; positive testing for HIV, syphilis, HBsAg, or HCVAb. Hepatitis B vaccination is allowed.
 3. History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody or molecules made of components of monoclonal antibodies.
 4. History of recurrent infections or active infection within 28 days of screening.
 5. History of sensitivity to heparin or heparin-induced thrombocytopenia.
 6. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic (eg, contact with positive case, residence, or travel to an area with high incidence) that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

7. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. (Refer to Section 6.8 Concomitant Therapy for additional details).
8. Exposure to live vaccines within 28 days of screening.

Prior/Concurrent Clinical Study Experience:

9. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or marketed or investigational monoclonal antibodies within 3 months or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

10. A positive urine drug test.
11. Screening supine BP ≥ 140 mm Hg (systolic) or ≥ 90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥ 140 mm Hg (systolic) or ≥ 90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.
12. Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTcF interval > 450 msec, or QRS interval > 120 msec). If the baseline uncorrected QT interval is

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>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.

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

- AST **or** ALT level $\geq 1.5 \times \text{ULN}$;
- 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 $\leq \text{ULN}$.

14. COVID-19 positive.

Other Exclusions:

15. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 240 mL beer, 30 mL of 40% spirit or 90 mL of wine).
16. Blood donation (excluding plasma donations) of approximately 400 mL or more within 60 days prior to dosing.
17. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.
18. 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 (no water restriction) at least 4 hours prior to any safety laboratory evaluations.
- An evening snack may be permitted.

- 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 must abstain from alcohol for 24 hours prior to screening, at least 24 hours prior to admission to the CRU, and 24 hours prior to all outpatient visits. Participants are suggested to abstain from alcohol until completion of the final FU visit. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.
- Participants will abstain from caffeine-containing products for 24 hours prior to all outpatient visits (including screening and FU visits), at least 24 hours prior to admission and during confinement in the CRU.
- 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 did not pass the "Eligibility overview for study enrollment" (as shown in the [SoA](#)). Screen failure data are collected and remain as source and are not reported on the CRF.

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

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to ponsegromab.

6.1. Study Intervention(s) Administered

Ponsegromab will be provided by Pfizer as liquids in sterile single-use, open-labeled vials at the CRU.

Participants will receive study intervention administered as a subcutaneous injection. All dose administration will occur at the study site.

Ponsegromab will be supplied as individual, single-use vials which are labeled according to local regulatory requirements.

Ponsegromab 100 mg/mL Solution for Injection will be presented as a sterile solution for SC administration. Each vial will contain a nominal volume of 1 mL with 100 mg/mL of ponsegromab.

6.1.1. Administration

Participants will receive study intervention at approximately 0800 hours (± 2 hours). The administration of SC study intervention must be performed by qualified and trained investigator site personnel according to the IP manual. The number of injections and injection sites will be recorded. The SC injection(s) area can be the front of the middle thigh, anterolateral thigh, abdomen, or outer area of the upper arm. If an arm is used for the SC injection, the opposite arm should be used for blood sample collections and BP measurements. Multiple injections at the same nominal time should use a unique site for each injection, to limit each injection site volume to 1 mL.

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.

Ponsegromab will be handled and prepared according to the IP manual that will be provided to the site.

See the IP manual for instructions on how to prepare the study intervention for SC administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, and institutional guidance. A second staff member will verify the dispensing.

All vials will be presented as single-use vials.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

This is an open-label study including 2 independent dose cohorts. Randomization and blinding are not applicable. The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide an allocation schedule to the investigator. The participant will receive the study intervention in compliance with the [SoA](#) and the protocol instruction.

6.4. Study Intervention Compliance

Participants will be dosed at the site. They will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the CRU 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

By design, this study only includes administration of single, SC dose of ponsegromab at 2 fixed dosage levels (100 mg and 400 mg). As such, dose modifications will not be made during the study.

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

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The definition of overdose for this trial is based on the operational aspects of the protocol design. Given the nature of this study (ie, SC dose administered in the clinic), and the allowed visit window, an overdose will be defined as more than 4 doses of ponsegromab SC administered.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of ponsegromab (whichever is longer).
3. Document the quantity of the excess dose as well as the time 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, CCI analysis approximately 5-7 days from the date of the last dose of study intervention if requested by the study 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.

Use of marketed or investigational monoclonal antibodies are prohibited within 3 months or 5 half-lives (whichever is longer) prior to the first dose of study medication.

Participants will abstain from all concomitant treatments, except for the treatment of AEs. 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.

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.

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.

7.1.1. Potential Cases of Acute Kidney Injury

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

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

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

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further study procedures;
- Lost to follow-up;

- Death;
- Study terminated by sponsor.

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 and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

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

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and

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well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

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

The total blood sampling volume for individual participants in this study is approximately 300 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

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

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

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

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

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

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. Injection Site Assessment

Injection site reactions will be assessed according to the [SoA](#). Additional assessments may be conducted at investigator discretion and/or until any symptoms resolve. Injection site reactions may include but are not limited to: erythema, induration, ecchymosis, pain, and pruritus. The size and severity of injection site reactions will be assessed and documented. If deemed appropriate by the investigator, a consultation with a dermatologist may be performed. Documentation of a reaction may include items such as investigator notes, photographs, dermatologist report, and/or clinic notes.

8.2.3. Vital Signs

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

When triplicate BP and PR are required (on Day 1), they will be obtained approximately 2 to 4 minutes apart; the average of the triplicate BP and PR measurements collected prior to dosing on Day 1 will serve as each participant's baseline value.

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

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 QTcF intervals and QRS complex. The timing of the PK samples should drive the timing of the ECGs. Note that ECGs do not need to be recorded at every time a PK sample is collected, but whenever an ECG is recorded, a PK sample should be collected at approximately the same time (preferably immediately after). 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.

Triplicate standard 12-lead ECGs will be obtained approximately within 5 minutes. The average of the triplicate ECG measurements collected prior to dosing on Day 1 will serve as each participant's baseline value.

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

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

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

ECG values of potential clinical concern are listed in [Appendix 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 the time frame before the final planned follow-up visit

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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.

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

8.2.6. COVID-19 specific assessments

Participants will be tested for SARS-COVID-19 infection prior to being admitted to the clinic for confinement or site visit in compliance with the requirements from local regulations or the investigator. Additional testing for COVID-19 (e.g. chest radiograph) may be required by local regulations or by the investigator.

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 the time of the final planned follow-up visit after the administration of the study intervention.

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

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-Up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A male participant who has been exposed to 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 inhalation or skin contact.
 - A male family member or healthcare provider who has been exposed to the study intervention by 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 the time of the last follow-up visit.
- 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 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.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

Not applicable.

8.3.9.2. Follow-Up of Medical Device Deficiencies

Not applicable.

8.3.9.3. Prompt Reporting of Device Deficiencies to the Sponsor

Not applicable.

8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

Not applicable.

8.3.10. Medication Errors

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

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

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

Medication errors include:

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

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

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

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

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

8.4. Pharmacokinetics

Blood samples of approximately 4 mL, to provide approximately 1.5 mL serum, will be collected for measurement of serum concentrations of ponsegromab, 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 within the protocol-allowed visit window, as defined in the [SoA](#), will not be

captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

Samples will be used to evaluate the PK of serum unbound and total ponsegromab at all times specified in the [SoA](#) and will be reported in the CSR, as data permit (see Section [9.3.1](#)). Samples collected for analyses of ponsegromab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, or for evaluation of the bioanalytical method.

Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Samples collected for measurement of serum unbound and total concentrations of ponsegromab will be analyzed using validated analytical methods 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.

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

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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CCI [REDACTED]

8.6. Genetics

8.6.1. Specified Genetics

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

8.7. Biomarkers

Biomarkers are not evaluated in this study.

CCI [REDACTED]

CCI

8.9. 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

There are no statistical hypotheses for this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	“Enrolled” means a participant’s agreement to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.
Safety Analysis Set	All enrolled participants who receive a dose of ponsegromab. Participants will be analyzed according to the product they actually received.
PK Concentration Analysis Set	All enrolled participants who receive a dose of ponsegromab and in whom at least 1 serum concentration value is reported.
PK Parameter Analysis Set	All enrolled participants who receive a dose of ponsegromab and who have at least 1 of the serum PK parameters of interest calculated.

Participant Analysis Set	Description
CCI	

9.3. Statistical Analyses

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

9.3.1. Pharmacokinetic Analyses

9.3.1.1. Derivation of PK Parameters

Ponsegromab serum PK parameters (total and unbound) will be derived from the concentration-time profiles using noncompartmental methods 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. Serum PK Parameters

Parameter	Definition	Method of Determination
CCI		
$C_{max}(dn)$	Dose-normalized C_{max}	$C_{max}/Dose$
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{1/2}^a$	Terminal half-life	$\log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve
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
CCI		
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
CCI		

a. As data permit.

9.3.1.2. Statistical Methods for Pharmacokinetic Data

The serum concentration of ponsegromab (unbound and total) will be listed and descriptively summarized by nominal sampling time and cohort. Individual participant and summary profiles (mean and median plots) of the serum concentration-time data will be plotted by cohort using actual and nominal sampling times respectively.

The serum PK parameters of ponsegromab (unbound and total) will be listed and summarized descriptively by cohort, as data permit. CCI

The PK parameter analysis set will be used.

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

9.3.2. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. The safety analyses will be presented by cohort.

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

Medical history and physical examination 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.

9.3.2.1. Electrocardiogram Analyses

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

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

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

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single

observation at that time point. If any of the 3 individual ECG tracings has a QTc value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec. Changes from baseline will be defined as the change between the postdose QTc value and the average of the predose triplicate values on Day 1.

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

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9.4. Interim Analyses

Interim analysis may be conducted for regulatory communication. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK/PD modeling, and/or supporting regulatory communication and clinical development.

9.5. Sample Size Determination

There is no statistical hypothesis for this study, therefore, the study sample size is not based on statistical decision rule.

Approximately 18 participants will be enrolled in this study (N=9 for each cohort) with the goal of attaining approximately 16 participants (N=8 for each cohort) evaluable for the primary endpoints.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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 and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

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

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

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

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

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

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

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

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

10.1.4. Data Protection

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use a DMC.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data sharing

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

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

10.1.7. Data Quality Assurance

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

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

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

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

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

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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 the study monitoring plan, which is maintained by the sponsor.

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

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

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

10.1.9. 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 SToD system.

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 Hematocrit RBC count MCV MCH MCHC Platelet count MPV WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO ₂ (bicarbonate) AST ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy ^a	Urine drug screening ^b COVID-19 test ^c At screening only: FSH ^d HBsAg HBcAb HCVAb HIV Syphilis test (TPPA)
	Additional Tests (Needed for Hy's Law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels		

- Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase
- The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
- The timing and methods of COVID-19 test(s) should follow the requirements from local regulations or investigator (CRU).
- 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

AE Definition
<ul style="list-style-type: none">• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.• Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

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

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Events <u>NOT</u> Meeting the AE Definition
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| <ul style="list-style-type: none">• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).• Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen. |
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10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
--

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization
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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.
--

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
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<p>d. Results in persistent or significant disability/incapacity</p> <ul style="list-style-type: none"> • The term disability means a substantial disruption of a person’s ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
<p>e. Is a congenital anomaly/birth defect</p>
<p>f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious.</p> <p>The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.</p>
<p>g. Other situations:</p> <ul style="list-style-type: none"> • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

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

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

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

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

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

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

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

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

Assessment of Intensity

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

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

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

Assessment of Causality

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

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

Follow-Up of AEs and SAEs

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

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

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

SAE Reporting to Pfizer Safety via CT SAE Report Form

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. 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 18 weeks after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either:

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

OR

- Must agree to use contraception/barrier as detailed below:
 - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.
 - In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in [Section 10.4.4](#)).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not a WOCBP (see definitions below in Section 10.4.3).

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female.

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

10.4.4. Contraception Methods

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

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion (eg, bilateral tubal ligation).

5. Vasectomized partner:

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

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

- Oral;
- Intravaginal;
- Transdermal;

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

- Oral;
- Injectable.

8. Sexual abstinence:

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

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

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

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

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

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

ECG Findings That Qualify as SAEs

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

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

10.7. Appendix 7: Abbreviations

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

Abbreviation	Term
Abs	absolute
ADA	antidrug antibodies
ADCC	antibody dependent cell-mediated cytotoxicity
ADL	activity of daily living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC _{168H}	area under the curve from the time of dose administration up to 168 hours
AUC _{inf}	area under the serum concentration time profile from time zero extrapolated to infinite time
CCI	
AUC _{last}	area under the serum concentration time profile from time zero to the time of the last quantifiable concentration (C _{last})
CCI	
AV	atrioventricular
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
C1q	complement component 1q
C _{av}	average concentration
CDC	complement-dependent cytotoxicity
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD	chronic kidney disease
CL	clearance
CCI	
C _{last}	last quantifiable concentration
C _{max}	maximum observed concentration
CCI	
CO ₂	carbon dioxide (bicarbonate)
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit

Abbreviation	Term
CSR	clinical study report
CT	clinical trial
CYP	Cytochrome P450
DC	discontinuation
DILI	drug-induced liver injury
DMC	data monitoring committee
CCI	
DNA	deoxyribonucleic acid
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EMA	European Medicines Agency
E _{max}	maximum effect
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
Fcγ	fragment crystallizable gamma
FIH	first in human
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GDF-15	growth differentiation factor 15
GDNF	glial cell-derived neurotrophic factor
GFRAL	glial cell-derived neurotrophic factor (GDNF) family receptor α like
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	investigator brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IgG1	immunoglobulin G1
IND	investigational new drug application

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Abbreviation	Term
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IV	intravenous
k_{el}	terminal phase rate constant
LFT	liver function test
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MPV	mean platelet volume
N	number
N/A	not applicable
NAb	neutralizing antibodies
NOAEL	no observed adverse effect level
PD	pharmacodynamic(s)
PE	physical exam
pH	potential of hydrogen
PK	pharmacokinetic(s)
POC	proof of concept
PR	pulse rate
PT	prothrombin time
PVC	premature ventricular contraction
Q	distributive clearance
Q3W	administered every 3 weeks
QT	Q wave interval
QTcF	corrected QT (Fridericia method)
qual	qualitative
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SARS	Severe Acute Respiratory Syndrome
SC	subcutaneous
SCr	serum creatinine
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SToD	Study Team on Demand
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TBili	total bilirubin

Abbreviation	Term
TEAE	treatment-emergent adverse event
TGFβ	transforming growth factor beta
THC	tetrahydrocannabinol
T _{max}	time for C _{max}
TPPA	Treponema pallidum particle agglutination test
ULN	upper limit of normal
US	United States
CCI	
WBC	white blood cell
WOCBP	women of childbearing potential

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