Title Page

A PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, 4-ARM STUDY TO INVESTIGATE SYMPTOMS, FUNCTION, HEALTH-RELATED QUALITY OF LIFE AND SAFETY WITH REPEATED SUBCUTANEOUS ADMINISTRATION OF PONSEGROMAB VERSUS PLACEBO IN ADULT PARTICIPANTS WITH HEART FAILURE

Study Intervention Number:	PF-06946860
Study Intervention Name:	Ponsegromab
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ClinicalTrials.gov ID:	NCT05492500
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Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Phase 2 Study of the Effects of Ponsegromab on Health-Related Quality of Life and Safety in Patients With Heart Failure (GARDEN-TIMI 74)

Document History

Document	Version Date
Amendment 2	18 July 2024
Amendment 1	06 June 2023
Original protocol	23 June 2022

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

Protocol Amendment Summary of Changes Table

Amendment 2 (18 July 2024)

Overall Rationale for the Amendment: The overall rationale for this amendment is to incorporate two optional study cohorts (Cohort C and Cohort D, respectively), add an adjudication committee and offer flexible language and clarifications.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Inclusion of optional Cohort C and optional Cohort D, which includes the following unique items: • Study rationale • Study design • Study schema • Inclusion/Exclusion criteria • Study arms and duration • Objectives/endpoints	The addition of optional Cohort C allows for a more comprehensive evaluation of the safety and efficacy of the ponsegromab 100 mg dose level compared to placebo. The addition of optional Cohort D is for a supportive assessment of efficacy and safety endpoints across the spectrum of GDF-15 concentrations in participants with HF.	1 – Protocol Summary 2.3.1 – Risk Assessment 3 – Objectives, Endpoints, and Estimands 4 – Study Design 5 – Study Population 6 – Study Intervention(s) and Concomitant Therapy 7.1 – Discontinuation of Study Intervention 8 – Study Assessments and Procedures 9 – Statistical Considerations
Non-substantial Modification(s)		
Added detailed language for adjudication committee.	Clinical outcomes of all deaths, HF hospitalization and urgent HF visits are tertiary endpoints of this	1.1 – Synopsis 4.1 – Overall Design 8.2.5 – Clinical Outcomes

Description of Change	Brief Rationale	Section # and Name
	protocol. Introduction of a formal adjudication of these events will support and strengthen exploratory analyses planned for these endpoints.	10.1.5 – Committees Structure
Removed "In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately."	Text is not applicable for this study and was inadvertently included in the protocol.	6.4.2 – Blinding of Site Personnel
Added "Deviation(s) from the protocol-specified dosage regimen should be recorded in the CRF. In exceptional circumstances and with agreement from the Sponsor, the study intervention may be administered outside of the window for a given dosing visit with appropriate consideration of timing of any subsequent dosing visit; in such circumstances, the rationale should be recorded in the CRF."	Added text allows for flexibility for case-by-case evaluation to determine whether a missed dose of study intervention can be rescheduled with out-of-window dosing and potential impact to timing of the subsequent dose(s) (eg, pushing to the outer limit of the study visit window).	6.5 – Study Intervention Compliance
Removed reference to the US and Canada regarding sites for the Open-label, PK cohort.	Offer more flexibility with any potential site/country selection.	1.1 – Synopsis 2.1 – Study Rationale 4.2 – Scientific Rationale for Study Design 5.4 – Screen Failures 8.1.1 – Screening Procedures

Description of Change	Brief Rationale	Section # and Name
Added urine sample for CCI [redacted] (Cohorts C & D only)	Explore the effects of ponsegromab on CCI [redacted] in a population with CCI [redacted]	1.3 – Schedule of Activities – Table 1 8.7 – Biomarkers 10.2 Appendix 2 – Clinical Laboratory Tests
Modified contact details for a medically qualified individual.	Clarification: Protocol Administrative Change Letter dated 27 Feb 2024	10.1.11 – Sponsor's Medically Qualified Individual 10.11 – Appendix 11: Abbreviations
Modified language to allow for flexibility to maximize the number of participants who complete follow-up visits.	Clarification: Protocol Administrative Change Letter dated 27 Feb 2024	7.1 – Discontinuation of Study Intervention
Added "…(if this rate is higher, or there is a high rate of non-compliance, more participants may be randomized to ensure the required number of evaluable participants)."	Clarification: Protocol Administrative Change Letter dated 27 Feb 2024	9.5 – Sample Size Determination – Open Label, PK Cohort (Cohort B)
Added "If not previously administered, participants will received 2 SC injections of open-label, placebo (equivalent of highest possible does, 300 mg) during the screening period to assess injection tolerability."	Clarification: Protocol Administrative Change Letter dated 03 Oct 2023	1.1 – Synopsis 6 – Study Intervention(s) and Concomitant Therapy – Study Interventions Administered – Study Arms for Open-label, PK Cohort (Cohort B)
Modified language: Section 8.1.1 – "Of note, a digital wrist device **should** ~~will~~ be dispensed to participants at SV2." Section 8.2.4 – "An activity monitor **should** ~~will~~ be placed on the	Clarification: Protocol Administrative Change Letter dated 03 Oct 2023	8 – Study Assessments and Procedures

Description of Change	Brief Rationale	Section # and Name
participant's non-dominant wrist from SV2 to Day 1 and from Week 20 to Week 22. The participant **should** ~~will~~ be asked to wear the activity monitor continuously during these periods."		
Language added in section headings to maintain consistency with other section headings.	Clarification: Protocol Administrative Change Letter dated 03 Oct 2023	8.6 – Genetics 8.7 – Biomarkers
Updated EU CT Number	EU CT number replaces the EudraCT number (EudraCT Number 2022-001809-50) as we are now using CTIS and run under CTR framework.	Opening page. 1.1 – Synopsis
Provided text clarification and corrections.	Minor clarifications and editorial/typographical changes have been made throughout, including those through new regulatory guidance.	Various sections of the protocol.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 2, Double-blind, Randomized, Placebo-controlled, 4-arm Study to Investigate Symptoms, Function, Health-Related Quality of Life, and Safety, With Repeated Subcutaneous Administration of Ponsegromab Versus Placebo in Adult Participants With Heart Failure.

Brief Title:

A Phase 2 Study of the Effects of Ponsegromab on Health-Related Quality of Life and Safety in Patients With Heart Failure (GARDEN-TIMI 74)

Regulatory Agency Identification Number(s):

US IND Number:	155929
EU CT Number:	2023-509747-27-00
ClinicalTrials.gov ID:	NCT05492500
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C3651011
Phase:	2

Rationale:

The primary purpose of this study is to assess the effect of repeated SC administration of ponsegromab (PF-06946860) on frequency, severity, and burden of symptoms as well as physical limitations in participants with HF and elevated circulating GDF-15 concentrations. The study will also assess the safety, tolerability, PK, PD, and immunogenicity of ponsegromab. A separate, open-label, PK cohort, with more frequent PK and GDF-15 collection after single and multiple SC administration of ponsegromab, will be enrolled at certain participating sites to facilitate a more comprehensive assessment of PK characteristics and PK/PD relationship for GDF-15 in participants with HF.

This study is also known as GDF-15 inhibition in heARt failure: quality of life DiffEreNces (GARDEN-TIMI 74).

Objectives, Endpoints, and Estimands:

Main Cohort (Cohort A), Cohort C and Cohort D

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To compare the effect of ponsegromab 300 mg versus placebo on HF disease-specific health status in participants with HF and serum GDF-15 concentrations CCI pg/mL (Main Cohort [Cohort A] only).	• Change from baseline in KCCQ-23 CSS at Week 22.	• Estimand 1 (similar to "hypothetical") is the difference between ponsegromab and placebo in mean change from baseline in KCCQ-23 CSS at Week 22, in participants with HF and serum GDF-15 concentrations CCI pg/mL, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures or participants' non-compliance with dosing.
Secondary:	**Secondary:**	**Secondary:**
• To compare the effect of ponsegromab versus placebo on HF disease-specific overall health status in participants with HF and serum GDF-15 concentrations CCI pg/mL.	• Change from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22.	• Estimand 2 (similar to "hypothetical") is the difference between ponsegromab and placebo in mean change from baseline in each of KCCQ-23 CSS, OSS, TSS and physical limitation score at Week 22, in participants with HF and serum GDF-15 concentrations CCI pg/mL, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures or participants' non-compliance with dosing.
• To compare the effect of ponsegromab versus placebo on HF disease-specific health status in participants with HF and serum GDF-15 concentrations CCI pg/mL.	• Responses as defined by a ≥5-point increase from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22.	• Estimand 3 (similar to "hypothetical") is the odds ratio between ponsegromab and placebo on the proportion of participants with ≥5-point increase from baseline in each of KCCQ-23 CSS, OSS, TSS, and physical limitation score at Week 22, in participants with HF and serum GDF-15 concentrations CCI pg/mL, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures or participants' non-compliance with dosing.
• To compare the effect of ponsegromab versus placebo on the physical function of participants with HF and serum GDF-15 concentrations CCI pg/mL.	• Change from baseline in 6MWD at Week 22.	• Estimand 4 (similar to "hypothetical") is the difference between ponsegromab and placebo in mean change from baseline in 6MWD at Week 22, in participants with HF and serum GDF-15 concentrations CCI pg/mL, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures or participants' non-compliance with dosing.
• To compare the effect of ponsegromab versus placebo on fatigue reported by participants with HF and serum GDF-15 concentrations CCI pg/mL.	• Change from baseline in PROMIS Fatigue 7a at Week 22.	• Estimand 5 (similar to "hypothetical") is the difference between ponsegromab and placebo in mean change from baseline in PROMIS Fatigue 7a at Week 22 in participants with HF and serum GDF-15 concentrations CCI pg/mL, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures or participants' non-compliance with dosing.

Objectives	Endpoints	Estimands
• To describe the safety and tolerability of ponsegromab in participants with HF.	• Incidence of TEAEs, TESAEs, abnormal laboratory results, and vital signs.	• There are no defined estimands for the incidence of TEAEs, TESAEs, abnormal laboratory results, and vital signs, and these endpoints will be analyzed using Pfizer data standards as applicable.

Open-Label, PK Cohort (Cohort B)

Objectives	Endpoints	Estimands
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the safety and tolerability of ponsegromab in participants with HF and elevated circulating GDF-15 concentrations.	• Incidence of TEAEs, TESAEs, abnormal laboratory results, and vital signs.	• There are no defined estimands for the incidence of TEAEs, TESAEs, abnormal laboratory results, and vital signs, and these endpoints will be analyzed using Pfizer data standards as applicable.

Overall Design:

This is a Phase 2, parallel-group, randomized, double-blind, placebo-controlled study to evaluate the effect of ponsegromab on HRQL, physical activity, safety, and circulating biomarkers in adult participants with HF and elevated circulating GDF-15.

For the Main Cohort (Cohort A), Cohort C, and Cohort D, following the 56-day screening period to confirm eligibility, the study will include a 22-week treatment period (from Day 1 to Week 20, and Week 22 for primary endpoint collection), and a 10-week follow-up period for a total study duration of 32 weeks (not including the screening period).

Approximately 416 participants will be enrolled into the Main Cohort (Cohort A) and randomized to one of 3 doses of ponsegromab (100 mg [n=18], 200 mg [n=18], or 300 mg [n=190]) or to matched placebo (n=190). Participant randomization will be stratified based on CCI [redacted] KCCQ-23 CSS: <45 or ≥45. Approximately 195 additional participants may be enrolled into optional Cohort C and randomized in a 2:1 ratio to either 100 mg ponsegromab (n~130) or to matched placebo (n~65). The additional participants in optional Cohort C will allow for a more comprehensive evaluation of the safety and efficacy of the ponsegromab 100 mg dose level compared to placebo. For each of these cohorts, blinded study drug will be administered SC Q4W for a total of 6 doses during the 22-week treatment period.

The primary endpoint for the study is the change from baseline at Week 22 in KCCQ-23 CSS, an HRQL PRO instrument. CCI [redacted]

Approximately 100 participants (maximum of approximately 150) who meet all eligibility criteria for Cohorts A and C, except the requirement for serum GDF-15 concentration CCI pg/mL, may be enrolled into the optional Cohort D and randomized in a 1:1 ratio to either 300 mg ponsegromab (n~50) or to matched placebo (n~50), administered SC Q4W for a total of 6 doses during the 22-week treatment period. Participant randomization in Cohort D will be stratified by KCCQ-23 CSS: <45 or ≥45. The purpose of this optional cohort is for a supportive assessment of efficacy and safety endpoints across the spectrum of GDF-15 concentrations in participants with HF.

This study will use an unblinded E-DMC to monitor the safety of participants and an unblinded IRC to monitor the efficacy and safety of participants. A blinded Steering Committee will monitor the proportion of study participants with various NYHA classes, left ventricular ejection fractions, GDF-15 concentrations, KCCQ-23 CSS scores, and the relative proportions qualifying under the cachexia, fatigue, and functional impairment criteria and may cap 1 or more to ensure a broad population.

This study will also use a separate blinded adjudication committee consisting of independent external experts who will be responsible for adjudication of all deaths and investigator-reported HF hospitalizations and urgent HF visits.

Open-label, PK Cohort (Cohort B): At certain sites, where permitted, participants who fail to qualify for the Main Cohort may be eligible for participation in a separate open-label, PK cohort. Approximately 20 participants, after confirmation of eligibility, will be randomized to one of 3 dose levels of open-label ponsegromab (100 mg [n=4], 200 mg [n=8], or 300 mg [n=8]) administered SC Q4W for a total of 4 doses, with last dose at Week 12 and follow-up to Week 22.

Number of Participants

Up to approximately 781 participants will be randomized in the study (approximately 416 participants in the Main Cohort [Cohort A], approximately 20 participants in the open-label, PK cohort [Cohort B], approximately 195 participants in Cohort C, and approximately 100 participants [maximum of approximately 150] in Cohort D).

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and randomization. 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.

Study Population: Key inclusion and exclusion criteria are listed below.

Inclusion Criteria

Age and Sex:

1. Participants aged 18 years or older (or the minimum age of consent in accordance with local regulations) at screening.

   - A female participant is eligible to participate if she is not pregnant or breastfeeding.

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

Disease Characteristics:

2. Clinical evidence of HF with each of the following criteria:

   a. LVEF <50% on most recent measurement, within 12 months of screening.

      Note: An assessment of LVEF in the prior 12 months is not required in situations where LVEF has been persistently <50% on prior assessments obtained at least 3 months apart (including the most recent measurement).

   b. NYHA class II-IV at screening.

   c. NT-proBNP ≥400 pg/mL at screening (**Note: Does not apply to open-label, PK cohort [Cohort B]**).

3. Serum GDF-15 concentration CCI pg/mL at screening.

   - **Cohort D only:** Serum GDF-15 concentration CCI pg/mL at screening

4. KCCQ-23 CSS <75 at screening (**Note: Does not apply to open-label, PK cohort [Cohort B]**).

5. Evidence of cachexia or fatigue or functional impairment, as demonstrated by **at least 1** of the following at screening (**Note: Does not apply to open-label, PK cohort [Cohort B]**):

   a. Non-edematous unintentional weight loss ≥5% in the last 6 months or current BMI <20 kg/m^2, associated with subjective fatigue or anorexia; or

   b. Fatigue at least 3 times per week AND at least moderately bothersome fatigue in the past 2 weeks based on the KCCQ-23 administered at screening; or

   c. A score of <60 on the Physical Limitations Domain of the KCCQ-23 administered at screening.

6. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures (including but not limited to subcutaneous injection of study intervention).

Exclusion Criteria

1. Acute decompensated HF within 1 month prior to SV1 or during the screening period.

2. Implantation of a cardiac resynchronization therapy device or valve repair or replacement within 3 months prior to randomization or intent to do so during the trial.

    - **For the open-label, PK cohort only (Cohort B):** implantation of a cardiac resynchronization therapy device more than 1 month prior to randomization is permitted.

3. History of heart transplantation, currently listed for heart transplant, current/planned mechanical circulatory support, or current/planned use of intravenous inotropes (eg, dobutamine, milrinone).

4. Acute coronary syndrome within 1 month prior to randomization.

5. Coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) within 3 months prior to randomization or intent to undergo coronary revascularization during the trial.

    - **For the open-label, PK cohort only (Cohort B):** coronary revascularization more than 1 month prior to randomization is permitted.

6. Untreated indication for an implantable cardiac defibrillator or pacemaker to treat a cardiac rhythm abnormality (ie, tachyarrhythmia or bradyarrhythmia).

7. History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody (IgG protein) or molecules made of components of monoclonal antibody.

8. Other medical (eg, severe, uncorrected aortic stenosis; active malignancy) or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, may limit life expectancy to less than 1 year and/or make the participant inappropriate for the study.

9. Current use of any prohibited concomitant medication(s). Refer to Section 6.9.

10. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention

used in this study (whichever is longer). Treatment with an investigational biotherapeutic agent within 6 months or 5 half-lives (whichever is longer) of Day 1.

11. Previous exposure to ponsegromab in a prior clinical study.

12. Renal disease requiring ongoing dialysis.

13. Cirrhosis with evidence of portal hypertension not due to HF, or the following LFT abnormalities at the time of screening, confirmed by a repeat test if deemed necessary: AST **or** ALT level ≥ 3 x ULN, **or** total bilirubin level ≥ 2 x ULN (unless history of Gilbert's syndrome).

14. 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.

Study Arms and Duration:

Intervention Name	Ponsegromab	Placebo
Arm Name (group of participants receiving a specific treatment or no treatment)	Ponsegromab double-blind treatment	Placebo double-blind treatment
Unit Dose Strength(s)	100 mg/mL	Placebo
Dosage Level(s)	100, 200 or 300 mg Q4W	Placebo Q4W
Route of Administration	SC	SC
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP

	Study Arms for Main Cohort (Cohort A) [a]					
Arm Title	**Ponsegromab or Placebo[b] 100 mg**		**Ponsegromab or Placebo[b] 200 mg**		**Ponsegromab or Placebo[b] 300 mg**	
Arm Type	Experimental n=18	Placebo n=6	Experimental n=18	Placebo n=6	Experimental n=190	Placebo n=178
Arm Description	Participants will receive 100 mg Q4W SC	Participants will receive placebo Q4W SC	Participants will receive 200 mg Q4W SC	Participants will receive placebo Q4W SC	Participants will receive 300 mg Q4W SC	Participants will receive placebo Q4W SC
Associated Intervention Labels	Ponsegromab 100 mg	Placebo	Ponsegromab 200 mg	Placebo	Ponsegromab 300 mg	Placebo

a. A total of 6 doses will be administered from Day 1 to Week 20.

b. As different volumes are required for the different dose levels of ponsegromab, each study arm will have a volume-matched placebo to maintain blinding within each study arm. Each dose will be administered as 2 SC injections of equal volume. In addition, during SV2 all participants will receive 2 SC injections of open-label placebo (equivalent to high dose, 300 mg) to assess injection tolerability.

	Study Arms for Open-label, PK Cohort (Cohort B) [a,b]		
Arm Title	**Ponsegromab 100 mg**	**Ponsegromab 200 mg**	**Ponsegromab 300 mg**
Arm Type	Experimental n=4	Experimental n=8	Experimental n=8
Arm Description	Participants will receive 100 mg Q4W SC	Participants will receive 200 mg Q4W SC	Participants will receive 300 mg Q4W SC
Associated Intervention Labels	Ponsegromab 100 mg	Ponsegromab 200 mg	Ponsegromab 300 mg

a. A total of 4 doses will be administered from Day 1 to Week 12.

b. If not previously administered, participants will receive 2 SC injections of open-label placebo (equivalent of highest possible dose, 300 mg) during the screening period to assess injection tolerability.

	Study Arms for Cohort C [a]	
Arm Title	**Ponsegromab or Placebo[b] 100 mg**	
Arm Type	Experimental n~130	Placebo n~65
Arm Description	Participants will receive 100 mg Q4W SC	Participants will receive placebo Q4W SC
Associated Intervention Labels	Ponsegromab 100 mg	Placebo

a. A total of 6 doses may be administered from Day 1 to Week 20.

b. Each dose will be administered as 2 SC injections of equal volume. In addition, during SV2, all participants will receive 2 SC injections of open-label placebo (equivalent of highest possible dose, 300 mg) to assess injection tolerability.

	Study Arms for Cohort D [a]	
Arm Title	**Ponsegromab or Placebo[b] 300 mg**	
Arm Type	Experimental n~50	Placebo n~50
Arm Description	Participants will receive 300 mg Q4W SC	Participants will receive placebo Q4W SC
Associated Intervention Labels	Ponsegromab 300 mg	Placebo

a. A total of 6 doses may be administered from Day 1 to Week 20.

b. Each dose will be administered as 2 SC injections of equal volume. In addition, during SV2, all participants will receive 2 SC injections of open-label placebo (equivalent of highest possible dose, 300 mg) to assess injection tolerability.

Ethical Considerations:

The results of previous studies of ponsegromab support the investigation of its use for improving symptoms of heart failure, and there is a favorable benefit-risk profile to support the rationale for this study. Taking into account the measures to minimize risk to participants,

the potential risks associated with ponsegromab are justified by the anticipated benefits that may be afforded to participants with heart failure.

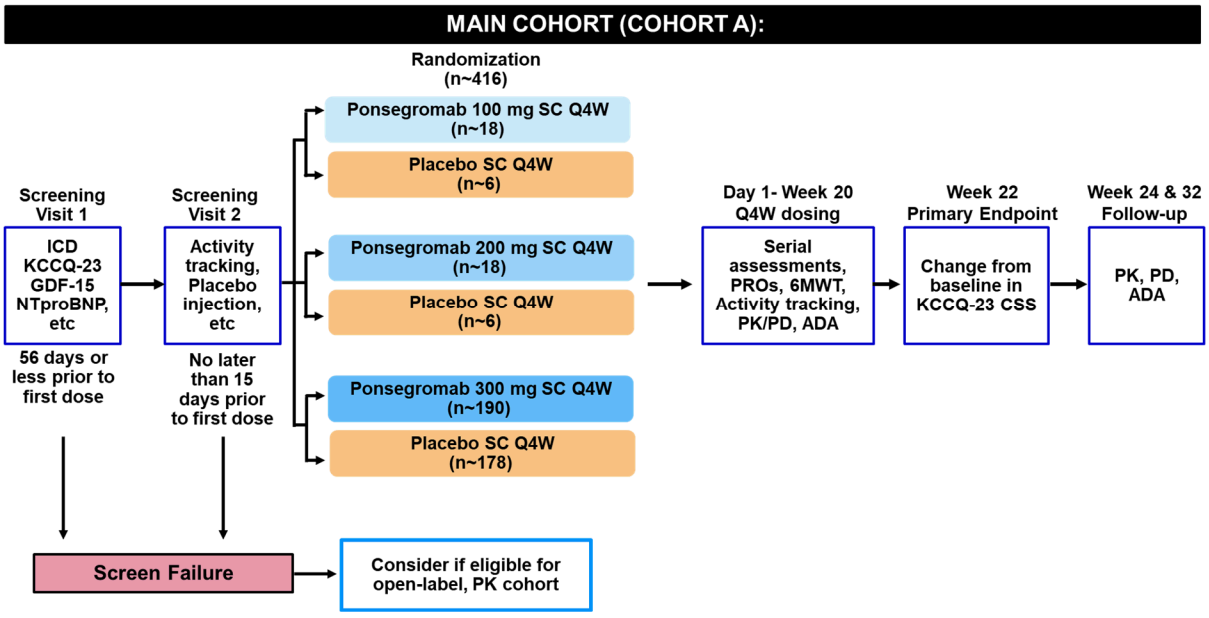
- Participants may benefit, clinically, from more intense monitoring and more frequent assessments compared to usual standard of care. Participants may benefit from contributing to research in heart failure and improving our understanding of the condition.

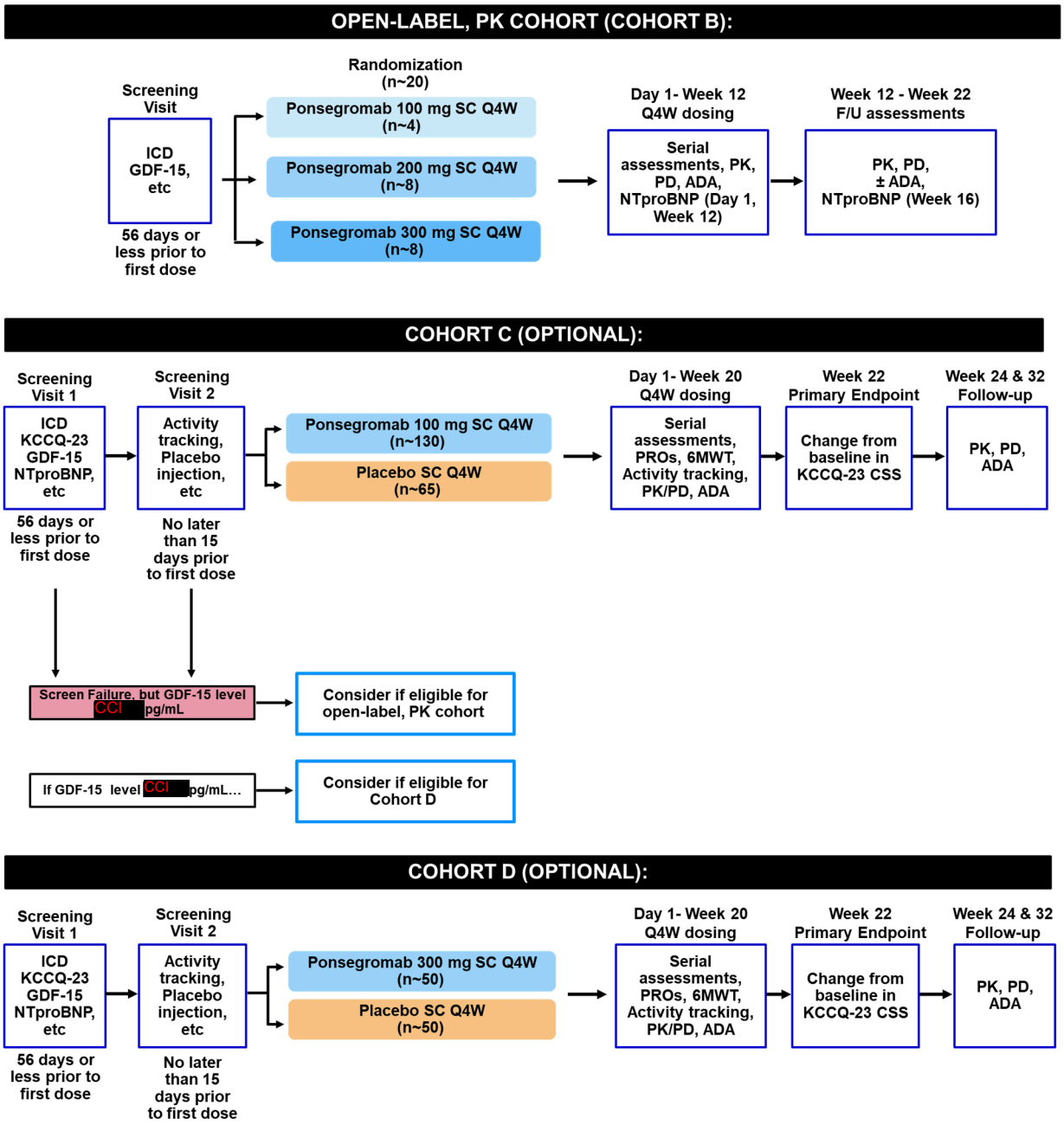
- Based on the experience with ponsegromab, the potential risks for its use in heart failure include discomfort from subcutaneous injections and/or injection site reactions.

- Participants will be expected to commit time and may experience some discomfort while undergoing study assessments. In addition, participants of childbearing potential must agree to use appropriate contraception methods.

1.2. Study Schematic

Figure 1. Schema





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.

All study assessments and procedures conducted on scheduled dosing visits should be completed prior to study intervention administration, unless otherwise specified. 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.

Table 1. Study Schedule of Assessment for the Main Cohort (Cohort A), Cohort C, and Cohort D

Visit Identifier See abbreviations in Appendix 11.	**SV1**	**SV2**	**Week 0**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 22 EoT**	**Week 24 F/U1**	**Week 32 F/U2**	**Flex PK/PD visit***	**Early Term**	**Notes**
Study day	No earlier than -56	No later than -15, when feasible	1	29	57	85	113	141	155	169	225			SV2 may commence following confirmation of eligibility from SV1 assessments. SV2 should commence at a minimum of 15 days prior to first dose, when feasible. Study day relative to start of dosing (Day 1). F/U1 and F/U2 and/or the Flexible PK/PD visit may be conducted by qualified personnel at the participant's home or current residence.
Visit Window (days)	N/A	N/A	N/A	±3	±3	±3	±3	±3	±2	±3	±7			
Informed consent	X													See Section 10.1.3.
Screen for eligibility	X	X												See Section 5.1 and Section 5.2. Screening will be conducted in at least 2 visits (SV1 and SV2). See Section 8.1.1.
Investigator reported assessment of eligibility for Inclusion Criteria #5a	X													See Section 8.1.1. Performed **after** participant completion of KCCQ-23 at SV1.
Demographics	X													
Randomization			X											See Section 6.3.
Medical history	X	X												
Physical examination		X	X						X					See Section 8.3.1. Brief physical examinations to be completed before administration of study intervention.

Table 1. Study Schedule of Assessment for the Main Cohort (Cohort A), Cohort C, and Cohort D

Visit Identifier See abbreviations in Appendix 11.	**SV1**	**SV2**	**Week 0**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 22 EoT**	**Week 24 F/U1**	**Week 32 F/U2**	**Flex PK/PD visit***	**Early Term**	**Notes**
Study day	No earlier than -56	No later than -15, when feasible	1	29	57	85	113	141	155	169	225			SV2 may commence following confirmation of eligibility from SV1 assessments. SV2 should commence at a minimum of 15 days prior to first dose, when feasible. Study day relative to start of dosing (Day 1). F/U1 and F/U2 and/or the Flexible PK/PD visit may be conducted by qualified personnel at the participant's home or current residence.
Visit Window (days)	N/A	N/A	N/A	±3	±3	±3	±3	±3	±2	±3	±7			
Height and Weight	X		X	X	X	X	X	X	X					See Section 8.3.1. Height will be collected at SV1 only.
Vital Signs		X	X	X	X	X	X	X	X	X	X			See Section 8.3.2.
12-Lead ECG			X						X					See Section 8.3.3.
Contraception check	X	X	X	X	X	X	X	X	X	X	X	X	X	Refer to Appendix 4. Contraception through Week 28 will be confirmed at the Week 32 visit.
AE/SAE monitoring	X	→	→	→	→	→	→	→	→	→	X	X	X	See Section 8.4 and Section 8.4.3.
Study Intervention and Other Treatments														See Section 6 for additional information.
Study intervention administration		X	X	X	X	X	X	X						At SV2 only, open-label SC placebo will be administered to assess tolerability (see Section 8.1.1). Also, see Section 6.1.
Prior/concomitant treatment(s)	X	→	→	→	→	→	→	→	→	→	X	X	X	See Section 6.9.
Clinical Outcomes														See Section 8 .
KCCQ-23	X		X	X	X	X	X	X	X				X	SV1 KCCQ-23 CSS required to confirm eligibility. Refer to Section 8.2.1.1.
PROMIS Fatigue 7a			X			X			X				X	Refer to Section 8.2.1.2.
PGI-S			X	X	X	X	X	X	X				X	Refer to Section 8.2.1.3.
PGI-C						X			X				X	Refer to Section 8.2.1.4.
6-Minute Walk Test			X			X			X				X	See Section 8.2.2.
Qualitative Exit Interviews									X				X	Refer to Section 8.2.1.5. Phone interview occurs within 10 BDs of Week 22/early termination visit.
Activity monitoring		X→	X					X →	X					Digital activity wrist monitor placed on participant from SV2 to Day 1 and from Week 20 to Week 22. Refer to Section 8.2.4.

Table 1. Study Schedule of Assessment for the Main Cohort (Cohort A), Cohort C, and Cohort D

Visit Identifier See abbreviations in Appendix 11.	**SV1**	**SV2**	**Week 0**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 22 EoT**	**Week 24 F/U1**	**Week 32 F/U2**	**Flex PK/PD visit***	**Early Term**	**Notes**
Study day	No earlier than -56	No later than -15, when feasible	1	29	57	85	113	141	155	169	225			SV2 may commence following confirmation of eligibility from SV1 assessments. SV2 should commence at a minimum of 15 days prior to first dose, when feasible. Study day relative to start of dosing (Day 1). F/U1 and F/U2 and/or the Flexible PK/PD visit may be conducted by qualified personnel at the participant's home or current residence.
Visit Window (days)	N/A	N/A	N/A	±3	±3	±3	±3	±3	±2	±3	±7			
Laboratory Assessments														Refer to lab manual for collection volumes.
Hematology & chemistry	X		X			X			X				X	See Appendix 2. Samples on dosing days must be collected prior to dosing.
Lipid panel			X						X				X	
Pregnancy test	X		X	X	X	X	X	X	X	X	X		X	Refer to Section 8.3.5. Serum pregnancy only at SV1. Urine or serum pregnancy tests collected and analyzed locally at all other timepoints.
Ponsegromab PK			X	X	X	X	X	X	X	X	X	X*	X	Refer to Section 8.5. PK samples collected on dosing days must be collected prior to dosing. *One flexible PK collection visit to occur 1 week (±2 days) after any IP dosing visit (eg, at W1, or W5, or W9, or W13, or W17, or W21) with the corresponding flexible PD sample.
Immunogenicity (ADA/NAb)			X	X	X		X		X	X	X		X	Refer to Section 8.7.8. Samples collected on dosing visits **must** be collected prior to dosing.
Biomarker Assessments														See laboratory manual.
GDF-15 CCI	X													Required for eligibility. Refer to Section 8.7.1.
CCI [redacted]														
NT-proBNP in plasma	X		X			X			X				X	Day 1 samples collected prior to dosing. Refer to Section 8.7.2.

Table 1. Study Schedule of Assessment for the Main Cohort (Cohort A), Cohort C, and Cohort D

Visit Identifier See abbreviations in Appendix 11.	**SV1**	**SV2**	**Week 0**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 22 EoT**	**Week 24 F/U1**	**Week 32 F/U2**	**Flex PK/PD visit***	**Early Term**	**Notes**
Study day	No earlier than -56	No later than -15, when feasible	1	29	57	85	113	141	155	169	225			SV2 may commence following confirmation of eligibility from SV1 assessments. SV2 should commence at a minimum of 15 days prior to first dose, when feasible. Study day relative to start of dosing (Day 1). F/U1 and F/U2 and/or the Flexible PK/PD visit may be conducted by qualified personnel at the participant's home or current residence.
Visit Window (days)	N/A	N/A	N/A	±3	±3	±3	±3	±3	±2	±3	±7			
hsCRP, albumin, pre-albumin in serum			X						X				X	
CCI (Cohorts C and D only)			X			X			X					Sample collected on Day 1 should be collected prior to dosing. Otherwise, timing of sample collection is random. Refer to Section 8.7.2.
Exploratory Plasma Biomarker			X						X					Refer to Section 8.7.2. Day 1 sample collected prior to dosing. Also, refer to Section 8.7.8.
Retained research samples														
Pfizer Retained Research Samples (Prep D1 K2EDTA whole blood, Prep B1 plasma, Prep B2 serum, Prep R1 PAXgene whole blood)			X						X					See Section 8.6.2 Prep D1 collected at Day 1 visit only, predose. If not collected on Day 1, collect at the next available time point when biospecimens are being collected. Also, refer to Section 8.7.6.
TIMI retained research samples (K2EDTA whole blood, plasma, serum)			X						X					Section 8.6.3 K2EDTA whole blood sample should be collected at Day 1 visit only, predose. Also, refer to Section 8.7.7.

Table 2. Study Schedule of Activities for Open-Label, PK Cohort (Cohort B) Only

Visit Identifier See abbreviations in Appendix 11.	**SV**	**Week 0**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 8**	**Week 12 EoT**	**Week 13**	**Week 14**	**Week 15**	**Week 16 F/U1**	**Week 18**	**Week 22 F/U2**	**Early Term**	**Notes**
Study day	No earlier than -56	1	8	15	22	29	57	85	92	99	106	113	127	155		Study day relative to start of study intervention (Day 1).
Visit Window (days)	N/A	N/A	±2	±2	±2	±2	±3	±2	±1	±2	±2	±3	±3	±3	N/A	
Visit Location	On-site		On-site or at home			On-site			On-site or at home			On-site	On-site or at home		On-site	ne" refers to participant's home or current residence
Informed consent	X															See Section 10.1.3.
Screen for eligibility	X															See Section 5.1 and Section 5.2. Screening will be conducted at SV. See Section 8.1.1.
Demographics	X															
Randomization		X														Randomization occurs following confirmation of eligibility. See Section 6.3.
Medical history	X															
Physical examination	X	X										X				See Section 8.3.1. Brief physical examinations to be completed before administration of study intervention.
Height and Weight	X	X				X	X	X				X				See Section 8.3.1. Height will only be collected at SV.
Vital Signs	X	X				X	X	X				X				See Section 8.3.2.
12-Lead ECG		X										X				See Section 8.3.3.
Contraception check	X	X				X	X	X				X		X	X	Refer Appendix 4. Contraception through Week 20 will be confirmed at the Week 22 visit.
AE/SAE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	X	X	See Section 8.4 and Section 8.4.3.
Study Intervention and Other Treatments																See Section 6.
Open-Label placebo injection	X															At SV only, open-label SC placebo will be administered to assess tolerability (see Section 8.1.1).

Table 2. Study Schedule of Activities for Open-Label, PK Cohort (Cohort B) Only

Visit Identifier See abbreviations in Appendix 11.	**SV**	**Week 0**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 8**	**Week 12 EoT**	**Week 13**	**Week 14**	**Week 15**	**Week 16 F/U1**	**Week 18**	**Week 22 F/U2**	**Early Term**	**Notes**
Study day	No earlier than -56	1	8	15	22	29	57	85	92	99	106	113	127	155		Study day relative to start of study intervention (Day 1).
Visit Window (days)	N/A	N/A	±2	±2	±2	±2	±3	±2	±1	±2	±2	±3	±3	±3	N/A	
Visit Location	On-site		On-site or at home			On-site			On-site or at home			On-site	On-site or at home		On-site	ne" refers to participant's home or current residence
Open-Label, Study intervention administration		X				X	X	X								See Section 6.1.
Prior/concomitant treatment(s)	X	→	→	→	→	→	→	→	→	→	→	→	→	X	X	See Section 6.9.
Laboratory Assessments																Refer to lab manual for collection volumes.
Hematology and blood chemistry	X	X						X				X			X	See Appendix 2. Samples on dosing days must be collected prior to dosing.
Lipid panel		X						X							X	
Pregnancy test	X	X				X	X	X				X		X	X	Refer to Section 8.3.5. Serum pregnancy only at SV. Urine or serum pregnancy tests collected and analyzed locally at all other timepoints.
Ponsegromab PK		X	X	X	X	X	X	X	X	X	X	X	X		X	Refer to Section 8.5. PK samples collected on dosing days **must** be collected prior to dosing.
Immunogenicity (ADA/NAb)		X				X	X	X				X	X		X	Refer to Section 8.7.8. Samples collected on dosing visits **must** be collected prior to dosing.
Biomarker Assessments																See laboratory manual.
GDF-15 CCI	X															Required for eligibility. Refer to Section 8.7.1.
CCI																

Table 2. Study Schedule of Activities for Open-Label, PK Cohort (Cohort B) Only

Visit Identifier See abbreviations in Appendix 11.	**SV**	**Week 0**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 8**	**Week 12 EoT**	**Week 13**	**Week 14**	**Week 15**	**Week 16 F/U1**	**Week 18**	**Week 22 F/U2**	**Early Term**	**Notes**
Study day	No earlier than -56	1	8	15	22	29	57	85	92	99	106	113	127	155		Study day relative to start of study intervention (Day 1).
Visit Window (days)	N/A	N/A	±2	±2	±2	±2	±3	±2	±1	±2	±2	±3	±3	±3	N/A	
Visit Location	On-site		On-site or at home			On-site			On-site or at home			On-site	On-site or at home		On-site	ne" refers to participant's home or current residence
NT-proBNP in plasma	X	X						X				X			X	Day 1 sample collected prior to dosing. Refer to Section 8.7.2.

2. INTRODUCTION

Ponsegromab (PF-06946860) is a humanized mAb which binds to circulating GDF-15. GDF-15 concentrations are elevated in patients with HF. This study investigates the effects of ponsegromab on heart failure symptoms, HRQL, and circulating biomarkers in study participants with HF and elevated concentrations of GDF-15.

2.1. Study Rationale

The primary purpose of this study is to assess the effect of repeated SC administration of ponsegromab on frequency, severity, and burden of symptoms as well as physical limitations in participants with HF and elevated circulating GDF-15 concentrations. The study will also assess the safety, tolerability, PK, PD, and immunogenicity of ponsegromab. A separate, open-label, PK cohort, with more frequent PK and GDF-15 collection after single and multiple SC administration of ponsegromab, will be enrolled at certain participating sites to facilitate a more comprehensive assessment of PK characteristics and PK/PD relationship for GDF-15 in participants with HF.

This study is also known as GDF-15 inhibition in heARt failure: quality of life DiffEreNces (GARDEN-TIMI 74).

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.

2.2.1. Heart Failure

HF is a clinical syndrome in which impaired myocardial contractile function leads to dyspnea or exertional limitations that impair a patient's ability to perform activities of daily life.[1] Based on data collected from the National Health and Nutrition Examination Survey from 2013 to 2016, an estimated 6.2 million American adults have HF and its prevalence is expected to increase to more than 8 million adults by 2030.[2] It is generally a chronic progressive condition, which can be stabilized with medications and/or therapeutic devices, or treated in suitable candidates with heart transplantation. The primary goals of HF care are the prevention of disease progression, the amelioration of symptoms, and the prevention of cardiovascular mortality.

2.2.1.1. GDF-15 and Heart Failure

GDF-15, also known as MIC-1, is a member of the TGF-β superfamily. In healthy individuals, GDF-15 is expressed and secreted at low concentrations by a range of cell types. In response to acute and cellular stressors, such as inflammation, oxidative stress, and cellular senescence, GDF-15 expression increases.[3,4,5,6] As such, circulating GDF-15 concentrations are markedly elevated in several chronic conditions such as cancer, HF, COPD, and CKD, compared to concentrations in healthy individuals.[7,8,9,10,11]

In patients with HF, GDF-15 is a well-established prognostic biomarker of cardiovascular morbidity and mortality.[12] Circulating GDF-15 concentrations are highly associated with HF symptom severity, functional status, and exercise capacity. Moreover, elevated GDF-15 concentrations predict an increased risk of death and adverse HF events in patients with HF.[13] It is hypothesized that ponsegromab may neutralize effects of GDF-15 and thereby improve symptoms in HF patients.

2.2.2. Clinical Overview

To date, the safety of ponsegromab has been assessed in 2 completed Phase 1 clinical studies in healthy adult volunteers (C3651001 and C3651002) and in 2 completed Phase 1b studies in patients with elevated serum GDF-15 levels and cancer cachexia (C3651009) and cancer anorexia (C3651010). A total of 80 participants were exposed to at least one dose of ponsegromab across these studies. A summary of the completed studies is presented in the table below.

Completed Clinical Studies with Ponsegromab

Study Identifier	Study Design and Type of Control	Dosing Regimen, Formulation, Dose	Number of Participants Randomized	Population	Treatment Duration
C3651001	Phase 1, double-blind, randomized, sponsor-open, placebo controlled, single ascending dose study.	Ponsegromab or placebo. Subcutaneously administered solution Dose: 0.1, 0.3, 1, 3, 10, 30, 100 and 300 mg	Total: 63 47 ponsegromab[a], 16 placebo	Eight sequential cohorts of healthy adult participants.	Single dose
C3651002	Phase 1, double-blind, randomized, sponsor-open, placebo controlled, single dose study.	Ponsegromab or placebo. Subcutaneously administered solution Dose: 100 mg	Total: 8 6 ponsegromab, 2 placebo	One cohort of healthy adult Japanese participants.	Single dose
C3651009	Phase 1b, open-label multiple dose study	Ponsegromab Subcutaneously administered solution Dose: 200 mg Q3W	Total: 11 10 ponsegromab[b]	Participants with cancer, cachexia, and serum GDF-15 levels ≥ 1500 pg/ml.	12 weeks

Completed Clinical Studies with Ponsegromab

Study Identifier	Study Design and Type of Control	Dosing Regimen, Formulation, Dose	Number of Participants Randomized	Population	Treatment Duration
C3651010	Phase 1b, double-blind, randomized, placebo controlled followed by open-label extension	Ponsegromab or placebo Subcutaneously administered solution Dose: 200 mg Q3W	Total: 18 Double-blind period 12 ponsegromab 6 placebo Open-label period 14 ponsegromab[c]	Participants with cancer, anorexia, and serum GDF-15 levels ≥ 1500 pg/ml.	6 weeks followed by 18 week open-label extension.

a: n=6 per dose except for the 300 mg dose group where n=5.
b: 1 participant randomized and not dosed.
c: Of these 14, 5 received placebo and 9 received ponsegromab during the preceding double-blind period.

More detailed information for the completed studies may be found in the ponsegromab IB, which is the SRSD for this study.

Of note, the safety and efficacy of ponsegromab is being evaluated in patients with cancer, cachexia, and elevated GDF-15 in an ongoing Phase 2, randomized, double-blind, placebo-controlled, 4-arm, parallel group, multicenter study (C3651003).

2.2.2.1. Summary of Safety Data

Ponsegromab has been administered to a total of 53 healthy participants in the Phase 1 studies. Single doses of ponsegromab were well-tolerated by study participants when administered subcutaneously at 0.1 to 300 mg in these studies. All AEs reported across both studies were mild, and a majority (99 of 103) of events were assessed as not related to study treatment; there were no deaths, and no severe or serious TEAEs. None of the TEAEs reported were associated with discontinuation from the study. No adverse, clinically significant trends were observed in safety parameters including laboratory data, vital signs and ECG parameters. There was no apparent dose-dependent increase in frequency of abnormalities in any the safety parameters assessed.

In the single arm, open-label Phase 1b C3651009 study of patients with cancer, cachexia, and elevated GDF-15 levels, there were 92 TEAEs reported for 10 participants dosed with ponsegromab 200 mg Q3W SC. None of these TEAEs were attributed to study intervention by investigator or sponsor. Of these non-treatment related TEAEs, most were mild or moderate; 5 were serious, of which one was fatal due to neoplasm progression during the follow-up period (131 days after randomization). No deaths occurred during the treatment period.

In the Phase 1b C3651010 study in patients with cancer, anorexia, and elevated GDF-15 levels, there were 58 TEAEs (including 8 SAEs) across 18 participants. Only 1 TEAE (myalgia) was considered treatment-related by the investigator. The incidence and severity of

TEAEs were similar between the two treatment arms. In the double-blind treatment phase there were 3 deaths: one in a participant receiving placebo, due to a cardiac arrest, and 2 in the ponsegromab 200 mg Q3W treatment arm, one due to respiratory failure and one due to acute myocardial infarction. During the open-label extension there were 3 deaths attributed to disease progression. None of these deaths were considered treatment related. Refer to SRSD or IB.

2.2.2.2. Summary of Pharmacokinetics

Following single dose administration of ponsegromab to healthy non-Japanese participants, SC absorption of unbound ponsegromab for the 3 to 300 mg dose groups occurred with median T_{max} ranging from 2.25 to 7.00 days. In general, over the 10 to 300 mg dose range, increases in geometric mean unbound C_{max} in serum were approximately dose-proportional and increases in unbound AUC_{last} and AUC_{inf} in serum appeared to be greater than dose-proportional. The geometric mean CL/F appeared to decrease with increasing dose, and mean terminal $t_{½}$ increased with increasing dose, ranging from 3.52 to 11.1 days across the 10 to 300 mg dose groups.

Following single doses of SC ponsegromab in healthy participants, absorption of total ponsegromab occurred with median T_{max} ranging from 6.00 to 14.0 days across the 1 to 300 mg dose groups. In general, increases in geometric mean total C_{max}, AUC_{last}, and AUC_{inf} in serum appeared to be less than dose-proportional over the 10 to 100 mg dose range, while increases in exposure from 100 to 300 mg doses were largely dose proportional. The mean terminal $t_{½}$ values increased from 20.1 days for the 10 mg group to 30.9 days for the 300 mg group. The long terminal $t_{½}$ of total ponsegromab in serum is driven primarily by the half-life of bound ponsegromab (ponsegromab-GDF-15 complex), as the terminal $t_{½}$ of unbound ponsegromab observed over the same dose range was much shorter. Unbound ponsegromab (not total ponsegromab) is the active moiety that accounts for pharmacological activity of the drug.

CCI [redacted]

2.2.2.3. Summary of GDF-15 Response

In study C3651001, following single SC administration of 1 to 300 mg doses of ponsegromab to healthy non-Japanese adults, CCI [redacted] Following a single SC administration of ponsegromab 100 mg in healthy Japanese adult participants in study

C3651002, serum unbound GDF-15 concentrations were suppressed to below the LLOQ starting CCI , with the median duration of suppression CCI CCI

In study C3651009, following SC administration of ponsegromab at 200 mg Q3W through Week 12 (Day 85) in participants with cancer, cachexia and elevated serum GDF-15 concentrations, median unbound GDF-15 concentrations were suppressed from the baseline concentration of 2269 pg/mL to below the LLOQ at all visits between Day 1 and Week 15 (Day 106).

2.2.2.4. Immunogenicity

Based on the available ADA/Nab data from the Phase 1 C3651001 and C3651002 studies conducted in healthy participants (n=53), none of the 53 participants had pre-existing ADA at baseline and CCI . Overall, there was no apparent effect of ADA observed on the PK, PD and safety profile of ponsegromab.

In C3651009 and C3651010 studies, following SC administration of ponsegromab at 200 mg Q3W through 12 and 24 weeks, respectively, in participants with cancer, cachexia or anorexia, and elevated serum GDF-15 concentrations, the incidence of treatment-induced ADA was very low with overall incidence of treatment-induced ADA of 0 and 9.1% (1/11), respectively, and no incidence of NAb was observed in either study.

2.3. Benefit/Risk Assessment

The available clinical data described in the IB show that no safety concerns have been identified in the four clinical trials completed to date.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of ponsegromab may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) ponsegromab		
SC injection site reactions and hypersensitivity reactions.	Although there were no injection site reactions or delayed hypersensitivity reactions observed in the completed clinical studies, as with all injectable mAbs, there is the potential for injection site reactions or delayed hypersensitivity reactions.	The following exclusion criterion is added: History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody (IgG protein) or molecules made of components of monoclonal antibody. Additionally, injection site reactions will be monitored, and injection sites rotated.
Use of a placebo arm.	Use of a placebo arm represents a risk of lack of benefit for those not receiving active therapy. As there are no data on efficacy yet, this risk cannot be assessed.	Participants will continue to receive standard of care throughout the study for their heart failure.
Study Procedures		
Biologic samples required for this study require invasive procedures (eg, needle insertion), which may lead to bruising or discomfort at insertion site.	HF patients may be sensitive to needle insertions.	Experienced health care providers will deliver a subcutaneous injection during the screening visit so that potential study participants have an opportunity to decline participation if they do not tolerate the procedure.
Challenges in collecting the requisite amount of blood required.	Participants may be anemic or have a concomitant condition that makes it difficult to collect requisite volume of bio-samples.	Effort to streamline bio sample collection in the SoA and reduce volume collected where feasible.
Other		
The COVID-19 pandemic may pose risks to study participation.	Historical precedent.	**Main Cohort (Cohort A), Cohort C, and Cohort D**: Follow-up visits (F/U1 and/or F/U2) and/or the Flexible PK/PD visit may be conducted by qualified personnel at the participant's home or current residence, in order to reduce the risk of exposure at the site.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Open-label, PK Cohort (Cohort B): Scheduled visits, where permitted per SoA, may be conducted by a contracted home health service at the participant's home or current residence, in order to reduce the risk of exposure at the site.

2.3.2. Benefit Assessment

Ponsegromab has not been administered to patients with HF prior to this study. Based upon nonclinical data, it is hypothesized that dosing with ponsegromab will lessen participants' frequency and/or burden of symptoms associated with HF. Participants may benefit, clinically, from more intense monitoring and more frequent assessments compared to usual standard of care. Participants may benefit from contributing to research in heart failure and improving our understanding of the condition.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account all available nonclinical and clinical data regarding the safety 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 participants with HF.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1. Main Cohort (Cohort A), Cohort C and Cohort D

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To compare the effect of ponsegromab 300 mg versus placebo, on HF disease-specific health status in participants with HF and serum GDF-15 concentrations CCI pg/mL (Main Cohort [Cohort A]) only.	• Change from baseline in KCCQ-23 CSS at Week 22.	• Estimand 1 (similar to "hypothetical") is the difference between ponsegromab and placebo in mean change from baseline in KCCQ-23 CSS at Week 22, in study participants with HF and serum GDF-15 concentrations CCI pg/mL, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures or participants' non-compliance with dosing.
Secondary:	**Secondary:**	**Secondary:**
• To compare the effect of ponsegromab versus placebo on HF disease-specific overall health status in participants with HF and serum GDF-15 concentrations CCI pg/mL.	• Change from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22.	• Estimand 2 (similar to "hypothetical") is the difference between ponsegromab and placebo in mean change from baseline in each of KCCQ-23 CSS, OSS, TSS and physical limitation score at Week 22, in participants with HF and serum GDF-15 concentrations CCI pg/mL, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures or

Objectives	Endpoints	Estimands
		participants' non-compliance with dosing.
• To compare the effect of ponsegromab versus placebo on HF disease-specific health status in participants with HF and serum GDF-15 concentrations CCI pg/mL.	• Responses as defined by a ≥5-point increase from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22.	• Estimand 3 (similar to "hypothetical") is the odds ratio between ponsegromab and placebo on the proportion of participants with ≥5-point increases from baseline in each of KCCQ-23 CSS, OSS, TSS, and physical limitation score at Week 22, in participants with HF and serum GDF-15 concentrations CCI pg/mL, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures or participants' non-compliance with dosing.
• To compare the effect of ponsegromab versus placebo on the physical function of participants with HF and serum GDF-15 concentrations CCI pg/mL.	• Change from baseline in 6MWD at Week 22.	• Estimand 4 (similar to "hypothetical") is the difference between ponsegromab and placebo in mean change from baseline in 6MWD at Week 22, in participants with HF and serum GDF-15 concentrations CCI pg/mL, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures or participants' non-compliance with dosing.
• To compare the effect of ponsegromab versus placebo on fatigue reported by participants with HF and serum GDF-15 concentrations CCI pg/mL.	• Change from baseline in PROMIS Fatigue 7a at Week 22.	• Estimand 5 (similar to "hypothetical") is the difference between ponsegromab and placebo in mean change from baseline in PROMIS Fatigue 7a at Week 22 in participants with HF and serum GDF-15 concentrations CCI pg/mL, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures or participants' non-compliance with dosing.
• To describe the safety and tolerability of ponsegromab in participants with HF.	• Incidence of TEAEs, TESAEs, abnormal laboratory results, and vital signs.	• There are no defined estimands for the incidence of TEAEs, TESAEs, abnormal laboratory results, and vital signs, and these endpoints will be analyzed using Pfizer data standards as applicable.

Objectives	Endpoints	Estimands
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
• To compare the effect of ponsegromab 300 mg versus placebo, on HF disease-specific health status in participants with HF and any serum GDF-15 concentration.	• Change from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22. • Responses as defined by a ≥5-point increase from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22.	• Not applicable.
• To compare the effect of ponsegromab 300 mg versus placebo on the physical function of participants with HF and any serum GDF-15 concentration.	• Change from baseline in 6MWD at Week 22.	• Not applicable.
• To compare the effect of ponsegromab 300 mg versus placebo on fatigue reported by participants with HF and any serum GDF-15 concentration.	• Change from baseline in PROMIS Fatigue 7a at Week 22.	• Not applicable.
• To compare the effect of ponsegromab versus placebo on HF disease-specific health status in participants with HF.	• Response as defined by a ≥10-point and ≥15-point increase in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22.	• Not applicable.
• To describe the effect of ponsegromab on impressions of disease severity and change in participants with HF.	• Absolute and change from baseline in PGI-S at Week 22. • Absolute PGI-C at Week 22.	• Not applicable.
• To compare the effect of ponsegromab versus placebo on body weight in participants with HF.	• Change from baseline in body weight at Week 22.	• Not applicable.
• To compare the effect of ponsegromab versus placebo on daily activity measures based on accelerometry in participants with HF.	• Change from baseline in daily activity measures based on accelerometry at Week 22.	• Not applicable.
• To evaluate the PK of ponsegromab in participants with HF.	• Serum unbound and total ponsegromab concentrations on Day 1 (predose) and Weeks 4, 8, 12, 16, 20, 22, 24, and 32.	• Not applicable.
• To compare the effect of ponsegromab versus placebo on GDF-15 concentrations in participants with HF.	• Serum concentrations of GDF-15 on Day 1 and Weeks 4, 8, 12, 16, 20, 22, 24, and 32.	• Not applicable.
• To characterize the immunogenicity of ponsegromab in participants with HF.	• Incidence of anti-ponsegromab antibodies, and neutralizing antibodies.	• Not applicable.
• To compare the effect of ponsegromab versus placebo on markers to check HF risk, acute MI,	• Fold change from baseline in NT-proBNP, hsCRP, albumin and pre-albumin at Week 22.	• Not applicable.

Objectives	Endpoints	Estimands
inflammation, and nutritional status in participants with HF.		
• To compare the effect of ponsegromab versus placebo on CCI in participants with HF.	• Fold change from baseline in CCI at Weeks 12 and 22. • Fold change from baseline in CCI at Weeks 12 and 22 (Cohorts C and D only).	• Not applicable.

• To compare the effect of ponsegromab versus placebo on clinical outcomes of cardiovascular death, hospitalization for HF, or urgent HF visit and on days alive and out of the hospital in participants with HF.	• Hierarchical composite endpoint:
	  • Time to cardiovascular death;
	  • Number of worsening HF events (hospitalization for HF, or urgent HF visit);
	  • Time to first worsening HF event (hospitalization for HF, or urgent heart visit);
	  • Change from baseline in KCCQ-23 CSS at Week 22.
	• Time to first occurrence of the clinical composite of cardiovascular death, hospitalization for HF, or urgent heart visit.
	• Total number of days alive and out of the hospital over 22 weeks.
	• Total number of hospitalizations for HF and urgent HF visits over 22 weeks.
		• Not applicable.

3.2. Open-Label, PK Cohort (Cohort B)

Objectives	Endpoints	Estimands
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the safety and tolerability of ponsegromab in participants with HF and elevated circulating GDF-15 concentrations.	• Incidence of TEAEs, TESAEs, abnormal laboratory results, and vital signs.	• There are no defined estimands for the incidence of TEAEs, TESAEs, abnormal laboratory results, and vital signs, and these endpoints will be analyzed using Pfizer data standards as applicable.
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
• To evaluate the PK of ponsegromab following repeated SC administration in participants with HF and elevated circulating GDF-15 concentrations.	• Serum unbound and total ponsegromab PK parameters after 1st dose on Day 1 and 4th dose on Day 85: AUC_{tau}, C_{max}, T_{max} and as data permit, $t_{½}$, CL/F, Vz/F, PTR after 4th dose.	• There are no defined estimands for PK endpoints.
• To characterize the effect of ponsegromab on circulating GDF-15 concentrations in participants	Serum concentrations of GDF-15 on Day 1 and Weeks 1, 2, 3, 4, 8, 12, 13, 14, 15, 16 and 18.	• Not applicable

Objectives	Endpoints	Estimands
with HF and elevated circulating GDF-15 concentrations.		
• To characterize the immunogenicity of ponsegromab in participants with HF and elevated circulating GDF-15 concentrations.	• Incidence of ADA, and NAb.	• Not applicable.
• To evaluate the effect of ponsegromab on NT-proBNP in participants with HF and elevated circulating GDF-15 concentrations.	• Fold change from baseline in NT-proBNP at Weeks 12 and 16.	• Not applicable.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, parallel-group, randomized, double-blind, placebo-controlled study to evaluate the effect of ponsegromab on HRQL, physical activity, and circulating biomarkers in adult participants with HF and elevated circulating GDF-15.

For the Main Cohort (Cohort A), Cohort C, and Cohort D, following the 56-day screening period to confirm eligibility, the study will include a 22-week treatment period (from Day 1 to Week 20, and Week 22 for primary endpoint collection), and a 10-week follow-up period for a total study duration of 32 weeks not including the screening period.

Approximately 416 participants will be enrolled into the Main Cohort (Cohort A) and randomized to one of 3 doses of ponsegromab (100 mg [n=18], 200 mg [n=18], or 300 mg [n=190]) or to matched placebo (n=190). Approximately 195 additional participants may be enrolled into optional Cohort C and randomized in a 2:1 ratio to either 100 mg ponsegromab (n~130) or to matched placebo (n~65). The participants in optional Cohort C will allow for a more comprehensive evaluation of the safety and efficacy of the ponsegromab 100 mg dose level compared to placebo. For each of these cohorts, blinded study drug will be administered SC Q4W for a total of 6 doses during the 22-week treatment period.

Participant randomization will be stratified based on CCI :

- CCI
- KCCQ-23 CSS: <45 or ≥45.

The primary endpoint for the study is the change from baseline at Week 22 in KCCQ-23 CSS, an HRQL PRO instrument.

Approximately 100 participants (maximum of approximately 150) who meet all eligibility criteria for Cohorts A and C, except the requirement for serum GDF-15 concentration CCI pg/mL, may be enrolled into the optional Cohort D and randomized in a 1:1 ratio to either 300 mg ponsegromab (n~50) or to matched placebo (n~50), administered SC Q4W for a total

of 6 doses during the 22-week treatment period. Participant randomization in Cohort D will be stratified by KCCQ-23 CSS: <45 or ≥45. The purpose of this optional cohort is for a supportive assessment of efficacy and safety endpoints across the spectrum of GDF-15 concentrations in participants with HF.

This study will use an unblinded E-DMC to monitor the safety of participants and an unblinded IRC to monitor the efficacy and safety of participants. A blinded Steering Committee will monitor the proportion of study participants with various NYHA classes, left ventricular ejection fractions, GDF-15 concentrations, KCCQ-23 CSS scores, and the relative proportions qualifying under the cachexia, fatigue, and functional impairment criteria and may cap one or more to ensure a broad population.

This study will also use a separate blinded adjudication committee consisting of independent external experts who will be responsible for adjudication of all deaths and investigator-reported HF hospitalizations and urgent HF visits.

Open-label, PK Cohort (Cohort B): The primary purpose of this open-label, PK cohort is to facilitate a more comprehensive assessment of PK characteristics and PK/PD relationship of ponsegromab following single and repeated SC administration in participants with HF and elevated circulating GDF-15 concentrations.

Approximately 20 participants, after confirmation of eligibility, will be randomized to one of 3 dose levels of open-label ponsegromab (100 mg [n=4], 200 mg [n=8], or 300 mg [n=8]) administered SC Q4W for a total of 4 doses, with last dose at Week 12 and follow-up to Week 22.

4.2. Scientific Rationale for Study Design

The primary purpose of this study is to assess the effect of repeated SC administration of ponsegromab on frequency, severity, and burden of symptoms as well as physical limitations in participants with HF and elevated circulating GDF-15 (CCI pg/mL). The assessments to be performed to achieve these objectives are described in detail in Section 8. The study will also assess the safety, tolerability, PK, PD, and immunogenicity of ponsegromab. A separate, open-label, PK cohort, with more frequent PK and GDF-15 collection after single and multiple SC administration of ponsegromab, will be enrolled at certain participating sites to facilitate a more comprehensive assessment of PK characteristics and PK/PD relationship for GDF-15 in participants with HF. In addition, an optional cohort (Cohort D) will enroll participants with circulating GDF-15 CCI pg/mL to enable a supportive assessment of efficacy and safety endpoints across the spectrum of GDF-15 concentrations in participants with HF.

CCI [redacted] Ponsegromab and GDF-15 concentrations will be measured in this study to (1) assess ponsegromab exposure in this population; (2) understand the range of baseline GDF-15 values and variability in this population; and (3) provide preliminary information on the magnitude of GDF-15 suppression after ponsegromab treatment. As ponsegromab is a monoclonal antibody, immunogenicity samples will be collected for the determination of ADA and NAb.

The rationale for stratification by GDF-15 and KCCQ-23 is an attempt to balance these key parameters across the different treatment groups.

The sample sizes for the ponsegromab 300 mg and placebo dose groups in the Main Cohort (Cohort A) and for the ponsegromab 100 mg dose group in optional Cohort C were chosen to provide acceptable operating characteristics for the primary endpoint for both doses, and thereby support dose-finding efforts for any subsequent clinical studies. The smaller sample size in the ponsegromab 100 mg and 200 mg Q4W arms in the Main Cohort (Cohort A) was chosen empirically to provide sufficient data to gain a preliminary understanding of the PK/PD relationship in this population. The sample size for the open-label, PK cohort (Cohort B) has been chosen empirically to provide sufficient evaluable participants to adequately evaluate the PK of ponsegromab following repeated SC administration to participants with HF and elevated circulating GDF-15 concentrations. The sample size for the optional Cohort D was chosen empirically to provide data on participants with GDF-15 levels CCI [redacted] pg/mL for supportive analyses.

4.2.1. KCCQ-23 Heart Failure Patient Reported Outcome Instrument

The KCCQ-23 is a self-administered questionnaire that quantifies physical limitations, symptoms, self-efficacy, social interference, and quality of life for participants with HF.[14] The KCCQ-23 is sensitive to clinical change, and is a straightforward instrument for participants to complete. The benefit and importance of functional status and PRO data are recognized as key clinical endpoints in HF research.

4.2.2. Patient Input Into Design

Participant input was leveraged based on interviews conducted in patients with various types of cancer. Although this patient population is different from a HF population, the GDF-15-related symptoms overlap in the HF population, including:

- Fatigue/tiredness.
- Physical activity limitations (eg, limited activities of daily living, difficulty walking, reduced physical strength).
- Weight loss/fluctuations.

- Loss of appetite/anorexia.
- Gastric problems (nausea, vomiting).

Twelve patients with cancer (prostate, NSCLC, colorectal, or pancreatic) and their caregivers were interviewed to better understand their burdensome symptoms and resulting impact on clinical trial participation. This targeted patient population emphasized the need to improve appetite and reduce fatigue. Combined with the prognostic associations of circulating GDF-15 with HF morbidity and mortality, the primary objective focusing on KCCQ-23 CSS is appropriate.

Based on feedback from these patients and caregivers, this study incorporated the following elements:

- Including qualitative phone interviews as a holistic assessment so patients may share their overall experiences with the study treatment with the Sponsor.
- Incorporating important aspects of the disease and the potential social and psychological impact in training.

4.2.3. Diversity of Study Population

Reasonable attempts will be made to enroll participants who are representative of the patient population that will be treated with ponsegromab in clinical practice. The team will follow best practices for diverse study population enrollment and retention. The following strategies may be explored in support of diverse recruitment efforts:

- Inclusion of diversity questions into the Feasibility Survey and Pre-Trial Assessment to identify sites with access to diverse patient populations.
- Discussion with investigator sites ahead of selection to assess preparedness, mitigation strategies for reaching diversity goals, and active inclusion.
- Encouragement of investigator sites to complete the Investigator Site Recruitment Plan.
- Provide investigator sites with site kit materials designed for use with diverse patient populations.
- Implement as needed targeted digital outreach to diverse patient groups.
- Have proactive discussions with investigator sites throughout the enrollment period to assess and reevaluate site specific strategies as needed to best position each site for the most diverse representation enrollment outcomes.

- Monitor diverse enrollment to identify potential opportunities to include diverse populations.

4.2.4. Choice of Contraception/Barrier Requirements

Studies to evaluate the developmental toxicity of ponsegromab have not been conducted. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.2.5. Collection of Retained Research Samples

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

4.3. Justification for Dose

In the Main Cohort (Cohort A), ponsegromab will be administered at doses of 100, 200 or 300 mg, or matched placebo, Q4W SC for a total of 6 doses. In Cohort C, ponsegromab will be administered at a dose of 100 mg, or matched placebo, SC Q4W SC for a total of 6 doses. In Cohort D, ponsegromab will be administered at a dose of 300 mg, or matched placebo, SC Q4W for a total of 6 doses. The proposed doses have been determined considering all relevant information obtained from nonclinical safety studies, safety, tolerability, PK and PD data from the 2 completed studies in healthy participants (C3651001 and C3651002, see IB) and CCI [redacted] These doses should facilitate an assessment of the PK/PD relationship between ponsegromab exposure and GDF-15 suppression.

Based on preliminary population PK/PD simulations, the proposed 100 mg Q4W SC dose is expected to suppress the unbound GDF-15 concentration in HF patients with assumed median baseline of 2820 pg/mL in CCI [redacted]% CCI [redacted]% of the patients for CCI [redacted] weeks, respectively. The proposed 200 mg Q4W SC dose is expected to suppress the unbound GDF-15 concentration in CCI [redacted]%, CCI [redacted]% of the patients for CCI [redacted] weeks, respectively. The proposed high dose of 300 mg Q4W SC dose is expected to suppress the unbound GDF-15 concentration in CCI [redacted]% of HF patients for CCI [redacted] weeks.

Based on the $t_{½}$ of the total and unbound ponsegromab and duration of the study, the exposures are expected to have reached steady state after CCI [redacted] doses administered Q4W. Based on these preliminary PK/PD simulations, the predicted steady state total ponsegromab C_{max}, AUC_{tau} and C_{avg}, following Q4W SC doses of 100, 200 and 300 mg, along with the corresponding safety margins calculated using exposure data from the 6-month toxicology study in monkeys (See IB), and exposure multiples calculated using total exposure data following a single 300 mg dose to healthy participants in study C3651001, are summarized in Table 3. The corresponding steady state unbound ponsegromab exposures and exposure multiples calculated using unbound exposure data from study C3651001, are summarized in Table 4.

Table 3. Summary of Predicted Steady State Total Ponsegromab Exposures and Associated Safety Margins and Exposure Multiples Following Q4W SC Doses

SC Dose (mg, Q4W)	C_{max} (µg/mL)	AUC_{tau} (µg•day/mL)	C_{avg} (µg/mL)	Safety Margin[a]		Exposure Multiple[b]	
				C_{max}	C_{avg}	C_{max}	AUC_{tau}
100	CCI						
200							
300							

a. Based on the predicted steady state total C_{max} and C_{avg} following Q4W SC doses of ponsegromab at 100, 200 or 300 mg relative to the NOAEL C_{max} (CCI µg/mL) and C_{avg} CCI µg/mL) observed in the 6-month toxicology study in monkey (IB).

b. Based on the predicted steady state total C_{max} and AUC_{tau} following Q4W SC doses of ponsegromab at 100, 200 or 300 mg relative to the C_{max}, (CCI µg/mL) and AUC_{inf} (CCI µg•day/mL) observed following the 300 mg single dose in C3651001.

Table 4. Summary of Predicted Steady State Unbound Ponsegromab Exposures and Associated Exposure Multiples Following Q4W SC Doses

SC Dose (mg, Q4W)	C_{max} (µg/mL)	AUC_{tau} (µg•day/mL)	C_{avg} (µg/mL)	Exposure Multiple[a]	
				C_{max}	AUC_{tau}
100	CCI				
200					
300					

a. Based on the predicted steady state unbound C_{max} and AUC_{tau} following Q4W SC doses of ponsegromab at 100, 200, and 300 mg relative to the unbound C_{max} (CCI µg/mL) and AUC_{inf} (CCI µg•day /mL) observed following the 300 mg single SC dose in study C3651001.

Given the observed safety data in healthy participants from studies C3651001 and C3651002, and the preliminary safety data from ongoing studies C351009 and C3651010, the proposed 100, 200, and 300 mg Q4W SC doses are expected to have an acceptable safety and tolerability profile.

The same dose levels (100, 200 and 300 mg SC Q4W) as in the Main Cohort (Cohort A) will be studied in the open-label PK cohort (Cohort B). A total of 4 doses will be administered during the 12-week treatment period. Ponsegromab exposures are expected to be close to steady state after 4 doses administered Q4W (>CCI% of steady state).

4.4. End of Study Definition

The end of the study is defined as the date of the last visit in the SoA of the last participant active in either the Main Cohort (Cohort A), open-label, PK cohort (Cohort B), Cohort C, or Cohort D (whichever is the latest).

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

The PCD is the date when the last participant in the Main Cohort (Cohort A), Cohort C (if enrolled) or Cohort D (if enrolled), whichever is latest, has CCI [redacted]

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Participants aged 18 years or older (or the minimum age of consent in accordance with local regulations) at screening.

    a. A female participant is eligible to participate if she is not pregnant or breastfeeding.

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

Disease Characteristics:

2. Clinical evidence of HF with each of the following criteria:

    a. LVEF <50% on most recent measurement, within 12 months of screening.

    Note: An assessment of LVEF in the prior 12 months is not required in situations where LVEF has been persistently <50% on prior assessments obtained at least 3 months apart (including the most recent measurement).

    b. NYHA class II-IV at screening.

    c. NT-proBNP ≥400 pg/mL at screening (**Note: Does not apply to open-label, PK cohort [Cohort B]**).

3. Serum GDF-15 concentration CCI pg/mL at screening.

   - **Cohort D only:** Serum GDF-15 concentration CCI pg/mL at screening.

4. KCCQ-23 CSS <75 at screening (**Note: Does not apply to open-label, PK cohort [Cohort B]**).

5. Evidence of cachexia or fatigue or functional impairment, as demonstrated by **at least one** of the following at screening (**Note: Does not apply to open-label, PK cohort [Cohort B]**):

   a. Non-edematous unintentional weight loss ≥5% in the last 6 months or current BMI <20 kg/m^2, associated with subjective fatigue or anorexia; or

   b. Fatigue at least 3 times per week AND at least moderately bothersome fatigue in the past 2 weeks based on the KCCQ-23 administered at screening; or

   c. A score of <60 on the Physical Limitations Domain of the KCCQ-23 administered at screening.

Other Inclusion Criteria:

6. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures (including but not limited to subcutaneous injection of study intervention).

5.2. Exclusion Criteria

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

Medical Conditions:

1. Acute decompensated HF within 1 month prior to SV1 or during the screening period.

2. Implantation of a cardiac resynchronization therapy device or valve repair or replacement within 3 months prior to randomization or intent to do so during the trial.

   - **For the open-label, PK cohort (Cohort B) only:** implantation of a cardiac resynchronization therapy device more than 1 month prior to randomization is permitted.

3. History of heart transplantation, currently listed for heart transplant, current/planned mechanical circulatory support, or current/planned use of intravenous inotropes (eg, dobutamine, milrinone).

4. Acute coronary syndrome within 1 month prior to randomization.

5. Coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) within 3 months prior to randomization or intent to undergo coronary revascularization during the trial.

    - **For the open-label, PK cohort (Cohort B) only:** coronary revascularization more than 1 month prior to randomization is permitted.

6. Untreated indication for an implantable cardiac defibrillator or pacemaker to treat a cardiac rhythm abnormality (ie, tachyarrhythmia or bradyarrhythmia).

7. History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody (IgG protein) or molecules made of components of monoclonal antibody.

8. Other medical (eg, severe, uncorrected aortic stenosis; active malignancy) or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, may limit life expectancy to less than 1 year and/or make the participant inappropriate for the study.

Prior/Concomitant Therapy:

9. Current use of any prohibited concomitant medication(s). Refer to Section 6.9 Prior and Concomitant Therapy.

Prior/Concurrent Clinical Study Experience:

10. Previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives (whichever is longer) preceding the first dose of study intervention used in this study. Treatment with an investigational biologic agent within 6 months or 5 half-lives (whichever is longer) of Day 1.

11. Previous exposure to ponsegromab in a prior clinical study.

Diagnostic Assessments:

12. Renal disease requiring ongoing dialysis.

13. Cirrhosis with evidence of portal hypertension not due to HF, or the following LFT abnormalities at the time of screening, confirmed by a repeat test if deemed necessary: AST **or** ALT level ≥ 3 x ULN, **or** total bilirubin level ≥ 2 x ULN (unless history of Gilbert's syndrome).

Other Exclusion Criteria:

14. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use 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 and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE.

Main Cohort (Cohort A)/Cohort C/Cohort D: Individuals who qualify for these cohorts but are not randomized for administrative reasons, may be re-screened. Individuals who do not meet the criteria for participation in these cohorts may be re-screened **once** if, in the judgment of the investigator, the reason for initial ineligibility is considered to be resolved, or there has been a change in eligibility status. Individuals who were already screened on two occasions for the Main Cohort (Cohort A), and screen-failed on one or both occasions due to serum GDF-15 concentration CCI pg/mL, may be re-screened on one further occasion for potential eligibility for Cohort D. Given that eligibility criteria are identical for Cohorts C and D (with the exception of the serum GDF-15 concentration requirement), individuals can undergo a common screening period for inclusion in these cohorts, with cohort ultimately determined by the result of the screening GDF-15 assessment. For individuals who are re-

screened for any reason, all screening procedures should be repeated, unless otherwise agreed with the Sponsor in advance, and the participant assigned a new 8-digit SSID.

Open-label, PK cohort (Cohort B): At certain sites, participants may be considered for enrollment in the open-label, PK cohort. This may include participants who screen fail for the Main Cohort (Cohort A) or Cohort C at any time during screening (SV1 or SV2). In such circumstances, screening for the open-label, PK cohort may be performed during the same site visit or on a separate day. Participants will be assigned a new 8-digit SSID. Signed and dated ICD will be required prior to any study-specific activity specified in the SoA for this open-label, PK cohort (Table 2). Screening procedures that were already performed during screening for a different cohort may not need to be repeated for screening for the open-label, PK cohort, if within the screening window. Participants who are screened twice for a different cohort can still be screened for the open-label, PK cohort. However, participants can only be screened once for the open-label, PK cohort, unless randomization is deferred for administrative reasons.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and non-investigational products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to ponsegromab (PF-06946860, IMP), and placebo (IMP).

Study Interventions Administered

Intervention Name	**Ponsegromab (PF-06946860)**	**Placebo**
Arm Name (group of participants receiving a specific treatment or no treatment)	Ponsegromab double-blind treatment	Placebo double-blind treatment
Type	Biologic	Placebo
Dose Formulation	Solution for injection	Solution for injection
Unit Dose Strength(s)	100 mg/mL	Placebo
Dosage Level(s)	100, 200 or 300 mg Q4W	Placebo Q4W
Route of Administration	SC	SC
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in 6-mL glass vial with an up to 1 mL withdrawal volume. Each vial will be labeled as required per country requirement. Each vial is for single use only.	Study intervention will be provided in 6-mL glass vial with an up to 1 mL withdrawal volume. Each vial will be labeled as

Intervention Name	Ponsegromab (PF-06946860)	Placebo
		required per country requirement. Each vial is for single use only.

	Study Arms for Main Cohort (Cohort A) [a]					
Arm Title	**Ponsegromab or Placebo[b] 100 mg**		**Ponsegromab or Placebo[b] 200 mg**		**Ponsegromab or Placebo[b] 300 mg**	
Arm Type	Experimental n=18	Placebo n=6	Experimental n=18	Placebo n=6	Experimental n=190	Placebo n=178
Arm Description	Participants will receive 100 mg Q4W SC	Participants will receive placebo Q4W SC	Participants will receive 200 mg Q4W SC	Participants will receive placebo Q4W SC	Participants will receive 300 mg Q4w SC	Participants will receive placebo Q4W SC
Associated Intervention Labels	Ponsegromab 100 mg	Placebo	Ponsegromab 200 mg	Placebo	Ponsegromab 300 mg	Placebo

a. A total of 6 doses will be administered from Day 1 to Week 20.

b. As different volumes are required for the different dose levels of ponsegromab, each study arm will have a volume-matched placebo to maintain blinding within each study arm. Each dose will be administered as 2 SC injections of equal volume. In addition, during SV2, all participants will receive 2 SC injections of open-label placebo (equivalent of highest possible dose, 300 mg) to assess injection tolerability.

	Study Arms for Open-label, PK Cohort (Cohort B) [a,b]		
Arm Title	**Ponsegromab 100 mg**	**Ponsegromab 200 mg**	**Ponsegromab 300 mg**
Arm Type	Experimental n=4	Experimental n=8	Experimental n=8
Arm Description	Participants will receive 100 mg Q4W SC	Participants will receive 200 mg Q4W SC	Participants will receive 300 mg Q4W SC
Associated Intervention Labels	Ponsegromab 100 mg	Ponsegromab 200 mg	Ponsegromab 300 mg

a. A total of 4 doses will be administered from Day 1 to Week 12.

b. If not previously administered, participants will receive 2 SC injections of open-label placebo (equivalent of highest possible dose, 300 mg) during the screening period to assess injection tolerability.

	Study Arms for Cohort C [a]	
Arm Title	**Ponsegromab or Placebo[b] 100 mg**	
Arm Type	Experimental n~130	Placebo n~65
Arm Description	Participants will receive 100 mg Q4W SC	Participants will receive placebo Q4W SC
Associated Intervention Labels	Ponsegromab 100 mg	Placebo

a. A total of 6 doses may be administered from Day 1 to Week 20.

b. Each dose will be administered as 2 SC injections of equal volume. In addition, during SV2, all participants will receive 2 SC injections of open-label placebo (equivalent of highest possible dose, 300 mg) to assess injection tolerability.

	Study Arms for Cohort D [a]	
Arm Title	**Ponsegromab or Placebo[b] 300 mg**	
Arm Type	Experimental n~50	Placebo n~50
Arm Description	Participants will receive 300 mg Q4W SC	Participants will receive placebo Q4W SC
Associated Intervention Labels	Ponsegromab 300 mg	Placebo

a. A total of 6 doses may be administered from Day 1 to Week 20.

b. Each dose will be administered as 2 SC injections of equal volume. In addition, during SV2, all participants will receive 2 SC injections of open-label placebo (equivalent of highest possible dose, 300 mg) to assess injection tolerability.

6.1. Administration

Each dose of investigational product must be administered by appropriately qualified personnel.

Study intervention will be administered in a divided dose requiring 2 separate SC injections given in rapid succession every 4 weeks. The permitted injection sites are the abdomen, upper arm (right or left) and the thigh (right or left). The following combination of injection sites are provided as examples:

- Two injections in the abdomen (each injection should be administered into a different quadrant and separated by at least 3 cm),
- One injection into each upper arm
- One injection into each thigh

- One injection into the arm (right or left) and one injection in the leg (right or left), or
- One injection in arm or leg (left or right) and one in the abdomen.

The injections can be rotated with each administration for participant comfort. If participants are receiving other, non-study intervention injectable agents, those interventions should be administered in a quadrant different from where the study intervention was administered. Additionally, areas with scarring, redness, tattoos, or other visible marks should be avoided.

Please refer to the IP manual for specific instructions on the handling, preparation, and administration of study intervention.

Premedication is permitted for all participants, consistent with institutional guidelines, and may include an antihistamine, anti-inflammatory agent, or pain reliever.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) 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, prepare, and/or administer study intervention.

3. 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 upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions, 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 excursion definition and information to report for each excursion will be provided to the site in the IP Manual.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

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

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff 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. Returned study intervention must not be re-dispensed to the participants.

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

Investigational Product, ponsegromab (100 mg/mL) and placebo will be prepared in a blinded fashion by qualified personnel according to the IP manual. The study intervention will be administered in a blinded fashion by qualified personnel to the participants. A second staff member will verify the dispensing.

Open-label, PK cohort (Cohort B) only: Open-label ponsegromab will be prepared as per treatment assignment by qualified personnel according to the IPM, and administered by qualified personnel to the participants. A second staff member will verify the dispensing.

6.3. Assignment to Study Intervention

Allocation of participants to treatment groups in Main Cohort (Cohort A), Cohort C and Cohort D will proceed through the use of an IRT system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. Randomization is stratified based on KCCQ-23 CSS score (Main Cohort [Cohort A], Cohort C and Cohort D) and GDF-15 concentrations (Main Cohort [Cohort A] and Cohort C only) from SV1 assessments; these data points will be required to be entered in the IRT system to ensure appropriate randomization allocations.

The site personnel will then be provided with a randomization number corresponding to the assigned treatment group, and DU or container number(s) when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Study intervention will be administered at the study visits summarized in the SoA.

The study-specific IRT reference manual and IPM will provide the contact information and further details on the use of the IRT system.

Open-label, PK cohort (Cohort B): This is an open-label cohort; however, the specific treatment assignment (ie, 100 mg, 200 mg, or 300 mg open-label dose arm) will be assigned using the IRT system. Randomization for this cohort is not stratified.

6.4. Blinding (Main Cohort [Cohort A]/Cohort C/Cohort D)

This is a double-blind study, with blinding of ponsegromab versus placebo for each dose level.

6.4.1. Blinding of Participants (Main Cohort [Cohort A]/Cohort C/Cohort D)

Participants and their caregivers will be blinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel (Main Cohort [Cohort A]/Cohort C/Cohort D)

Investigators and other site staff will be blinded to participants' assigned study intervention, including the site staff assigned to prepare and administer the study intervention. Pharmacists and site personnel will be blinded to study intervention versus placebo within each study arm.

6.4.3. Blinding of the Sponsor (Main Cohort [Cohort A]/Cohort C/Cohort D)

Sponsor staff will be blinded to participants' assigned study intervention, except for sponsor staff involved in the assignment or distribution of study intervention.

Sponsor staff who are not directly involved with the conduct of this study will prepare analyses and documentation containing unblinded data while the study is ongoing to support interactions with the E-DMC and IRC as documented in the respective charters.

6.4.4. Breaking the Blind (Main Cohort [Cohort A]/Cohort C/Cohort D)

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the TIMI Hotline (available 24/7) or the study medical monitor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and the CRF.

The study-specific IRT reference manual and IPM will provide the contact information and further details on the use of the IRT system.

6.5. Study Intervention Compliance

The study intervention will be administered to participants directly by an appropriately qualified individual. In this study, participants are dosed at the site, and they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention if the study intervention is administered at the clinic.

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.

Deviation(s) from the protocol-specified dosage regimen should be recorded in the CRF. In exceptional circumstances and with agreement from the Sponsor, the study intervention may be administered outside of the window for a given dosing visit with appropriate consideration of timing of any subsequent dosing visit; in such circumstances, the rationale should be recorded in the CRF.

A record of the number of vials and syringes dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

6.6. Dose Modification

There is no dose modification of ponsegromab anticipated in this study.

6.7. Continued Access to Study Intervention After the End of the Study

No study intervention will be provided to participants at the end of their study participation. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

6.8. Treatment of Overdose

For this study, any dose of ponsegromab greater than 700 mg within a 4-week period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor or TIMI Hotline within 24 hours.
2. Closely monitor the participant for any AEs/SAEs as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the timeframe (eg, frequency) of overdose(s) in the CRF.
4. Overdose is reportable to Pfizer Safety only when associated with an SAE.
5. Obtain a blood sample for PK, GDF-15, and/or immunogenicity analysis within 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).

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

6.9. Prior and Concomitant Therapy

Participants in this study will be allowed to be on concomitant medications that have been prescribed according to their label. Attempts should be made not to alter the doses and regimens of the background medications after randomization and for the duration of participation in this study, except in circumstances where a change in dose is deemed medically necessary. Any changes must be captured in the CRF. Additionally, many over-the-counter medications are also permitted during this study.

Treatments taken within 56 days in either cohort before the first dose of IP will be documented as prior treatment. Treatments taken after the first dose of IP will be documented as concomitant treatment.

All concomitant treatments, both prescription and over-the-counter 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.

Use of investigational therapies is prohibited during the study. See Appendix 9 for details regarding prohibited concomitant medications due to potential DDI.

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

Background biologics are permitted as indicated by the label (not contra-indicated for combination with an investigational mAb).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

The study intervention **must** be permanently discontinued for the following reasons:

- Severe allergic reaction to study intervention.
- Intent to become pregnant or pregnancy confirmed by β-hCG testing.
- Drug-induced liver injury as described in Section 10.6, Appendix 6, Liver Safety: Suggested Actions and Follow-up Assessments.
- The study participant undergoes heart transplantation or requires mechanical circulatory support.
- The investigator has determined that continuation of the administration of the study intervention is no longer feasible or appropriate.

Other reasons that may prompt consideration for permanent discontinuation of study intervention include the following:

- ECG Findings of potential concern as described in Section 10.8, Appendix 8, ECG Findings of Potential Clinical Concern.
- If a participant experiences serious or severe AEs judged by the Investigator as related to randomized study intervention, the study intervention will be temporarily discontinued until the treatment-related AEs return to a moderate level or less. If the treatment-related AEs return to a moderate level or less, or resolve within 4 weeks, continuation of dosing with study intervention may be considered. If these AEs do not return to moderate within 4 weeks, and after discussion with the TIMI Hotline, the participant will be permanently discontinued from the study intervention.

Any planned or potential discontinuation of study drug should be discussed with the TIMI Hotline (available 24/7). Note that discontinuation of study intervention does not represent withdrawal from the study. If it is confirmed that the participant will permanently discontinue study intervention following discussion with the TIMI Hotline, an Early Termination visit should be performed, which should include assessments of patient-reported outcomes, physical activity (6MWT), and laboratory assessments. In addition, a follow-up visit (F/U1) should be completed approximately 28 days and another follow-up visit (F/U2) should be completed ideally no more than 94 days for the Main Cohort (Cohort A)/Cohort C/Cohort D, and ideally no more than 75 calendar days for the open-label, PK cohort (Cohort B), after discontinuing study intervention primarily for the purpose of assessing resolution of any treatment-related AEs. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

Again, it is important to first contact the TIMI Hotline before classifying a subject as 'Discontinued from Study Intervention' and completing an Early Termination visit.

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

Follow-Up:

At approximately 28 calendar days (F/U1), and again ideally no more than 94 calendar days for the Main Cohort (Cohort A)/Cohort C/Cohort D and ideally no more than 75 calendar days for the open-label, PK cohort (Cohort B) (F/U2) after discontinuation of study intervention, participants should return to undergo review of concomitant treatments, vital signs, and assessment for resolution of any treatment-related AEs. Participants continuing to experience AEs at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. If the unresolved AE is considered by the investigator as possibly related to or associated with ADA formation, the participant will be asked to return for drug concentration and ADA blood sampling at up to 3-month intervals, until the last follow-up of the AE.

7.1.1. COVID-19

If a participant has COVID-19 during the study, this should be reported as an AE or SAE (as appropriate) and appropriate medical intervention provided. Study treatment should continue unless the investigator/treating physician is concerned about the safety of the participant, in which case, temporary or permanent discontinuation may be required.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the TIMI Hotline.

7.2. Discontinuation From the Study

Reasons for discontinuation from the study include the following:

- Participant refused further follow-up (refer to Section 7.2.1);
- Lost to follow-up (refer to Section 7.3);
- 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.

7.2.1. Withdrawal of Consent

Participants who request to discontinue 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 them 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 investigator should inform the TIMI Hotline of any potential withdrawal of consent.

A participant may withdraw from the study at any time at their own request. If a participant withdraws from the study, they 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 consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

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

To prevent participants being lost to follow-up, their contact details, including next of kin contacts should be collected initially, if permitted, and updated regularly by the site staff or representative. The Investigator should educate the participant on the importance of contact with the Investigator throughout the study. Repeated attempts will be made to locate and obtain pertinent medical information for participants who are potentially lost to follow-up.

If a participant fails to return to the clinic for/attend a required study visit, the site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.

Where permissible by local regulations, the ICD will include language to grant the option to employ outside companies to assist in obtaining updated contact information or ascertainment of vital status of lost participants using publicly available source.

A participant will be classified as lost to follow up only if he/she/they has failed to return for the required study visits and his/her/their vital status remains unknown despite multiple attempts to contact him/her/them via telephone, fax, email, certified letter or through patient locator agencies (if allowed by local regulations). These contact attempts should be documented in the participant's medical record. The participant will then be considered lost to follow-up and discontinuation of study will be documented in source data and CRF as the date of last contact.

8. STUDY ASSESSMENTS AND PROCEDURES

All study assessments and procedures conducted on scheduled dosing visits per the SoA should be completed prior to study intervention administration, unless otherwise specified.

8.1. Administrative 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.

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.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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 make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that they have 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.

Laboratory results that have been collected for the purposes of this study and could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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 274 mL for the Main Cohort (Cohort A)/Cohort C/Cohort D (approximately 184 mL for participants enrolled in the open-label, PK cohort [Cohort B]). 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.

8.1.1. Screening Procedures

Screening assessments will be collected in at least two visits, as noted below:

1. SV1: Signed and dated ICD will be collected prior to any study-specific activity. Following consent, the KCCQ-23 PRO will be completed by the participant using an electronic hand-held device. Following KCCQ-23 PRO completion, the Investigator will assess Inclusion Criterion #5a (Section 5.1) through 3 questions about (1) non-edematous unintentional weight loss ≥5% in the last 6 months, (2) current BMI <20 kg/m^2, and (3) associated with subjective fatigue or anorexia, and enter the information into the electronic hand-held device.

   Afterwards, a serum sample will be collected to evaluate GDF-15 concentrations and a plasma sample will be collected to evaluate NT-proBNP concentrations. The GDF-15 [CCI] and NT-proBNP samples should be submitted for analysis immediately, as the results of this lab test will inform eligibility to continue to SV2.

   Additional assessments will be performed as per the SoA for the Main Cohort(Cohort A)/Cohort C/Cohort D (Table 1).

2. SV2: Eligible participants will return to complete remaining screening procedures at a minimum of 15 days prior to first dose, when feasible. SV2 will collect all remaining Screening assessments, including activity monitoring (see below), placebo injection to assess tolerability and other assessments. Please refer to the SoA for the Main Cohort (Cohort A)/Cohort C/Cohort D (Table 1) for additional details.

   - Of note, a digital wrist device should be dispensed to participants at SV2. A minimum of 14 days of activity monitoring should be collected prior to Day 1, which should be taken into consideration when scheduling SV2.

Open-label, PK Cohort (Cohort B) Only: At certain sites, where permitted, participants may be considered for enrollment in the open-label, PK cohort. This may include participants who screen fail for the Main Cohort (Cohort A) or Cohort C at any time during screening (SV1 or SV2). In such circumstances, participants will be eligible during that same visit or on a separate day to undergo screening to enroll in the open-label, PK cohort (Section 5.4). Signed and dated ICD for this cohort will be collected prior to any study-specific activity. Please refer to the SoA for this open-label, PK cohort (Table 2). Screening procedures that were already performed during screening for a different cohort may not need to be repeated for screening for the open-label, PK cohort, if within the screening window.

8.1.2. Contracted Home Health Visits (Open-Label, PK Cohort [Cohort B] Only)

A home health care service may be contracted and utilized to facilitate only the open-label, PK cohort at specified visits. Home visits may include a home healthcare service conducting an in-person study visit at the participant's home or current residence rather than an in-person study visit at the site. The following may be performed during a home visit (see the open-label, PK cohort SoA [Table 2]):

- PK, PD and/or ADA sample collection.

8.2. Efficacy Assessments (Main Cohort [Cohort A]/Cohort C/Cohort D)

8.2.1. Patient Reported Outcomes

All PRO assessments are completed electronically by study participants at the clinic as per the SoA and Table 5. Every effort should be made to have the study participant complete all PRO assessments before any other clinical assessments that take place at the clinical site. There are no PRO assessments in the open-label, PK cohort.

Additional details are provided in the PRO/eCOA Training Manual.

Table 5. PRO Assessments

PRO Measure	Assessment schedule	Number of Questions	Completion Time
KCCQ-23	SV1, W0 (baseline), W4, W8, W12, W16, W20, W22, or early term.	23	~6 minutes
PROMIS Fatigue 7a ("Past 7 days" recall version)	W0 (baseline), W12, W22, or early term.	7	~2 minutes
PGI-S	W0 (baseline), W4, W8, W12, W16, W20, W22, or early term.	4	~1 minute
PGI-C	W12, W22, or early term.	4	~1 minute

8.2.1.1. Kansas City Cardiomyopathy Questionnaire

The KCCQ is a self-reported 23-item questionnaire that assesses HRQL in participants with HF. Items assess physical limitations, symptoms (frequency, severity, and recent change over time), QoL, social interference, and self-efficacy. Response options vary by question. There

are 10 summary scores within KCCQ-23: physical limitation, symptom stability, symptom frequency, symptom burden, total symptom score, self-efficacy, quality of life, social limitation, overall summary score, and clinical summary score. Raw summary scores are transformed to a 0-100 scale where higher scores indicate better health.[15]

8.2.1.2. PROMIS Fatigue (Version 7a)

The PROMIS Fatigue 7a is a self-reported measure that assesses a range of symptoms in the past 7 days from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles.[16]

The short form 7A consists of 7 items that study participants will rate from 1: "Never" to 5: "Always". A global raw score ranging from 7 to 35 is calculated and can be translated into a T-score (Mean = 50, SD = 10) using the applicable score conversion table provided in the PROMIS User's Manual.

8.2.1.3. Patient's Global Impression of Severity

The PGI-S is a measure consisting of 4 questions that ask the study participants to evaluate the severity of their fatigue, shortness of breath, overall symptoms of HF, and daily activity limitations over the past 14 days on a 5-point verbal response scale that ranges from "None" to "Very severe".

The PGI-S is recommended by the FDA for use as an anchor measure to generate an appropriate threshold that represents meaningful within-individual change in the target patient population.[17]

8.2.1.4. Patient's Global Impression of Change

The PGI-C is a measure consisting of 4 questions that ask study participants to rate the overall change in their fatigue, shortness of breath, overall symptoms of HF, and ability to do daily activities on a 5-point verbal rating scale ranging from "Much better" to Much worse".

The PGI-C is recommended by FDA for use as an anchor measure to generate an appropriate threshold that represents meaningful within-individual change in the target patient population.[17]

8.2.1.5. Qualitative Exit Interviews

Qualitative exit interviews with a select group of US English-speaking participants (up to 50) at selected sites will be conducted by telephone, as indicated in the SoA. The interviews will be conducted by trained moderators, that are not part of study site staff, will be audio recorded and transcribed, and are anticipated to be approximately 60 minutes in duration.

The transcripts and interviewer field notes will be used to examine changes in symptoms and impacts experienced over the period of study duration, to describe treatment experience, and

the importance of any improvement reported by the study participants. Following the analysis of the qualitative data, a summary report that describes the study objectives, methods, participants, and results of the qualitative interviews will be reported separately from the CSR.

8.2.2. 6MWT

The 6MWT is a submaximal exercise test that entails measurement of distance walked over a span of 6 minutes.[18] The 6MWD (distance traveled in meters) provides a measure for integrated global response of multiple cardiopulmonary and musculoskeletal systems involved in exercise. Additional training information will be provided in Firecrest regarding the appropriate methodology for observation and data collection.

8.2.3. Body Weight

Weight will be recorded using a calibrated scale (with the same scale used if possible for the duration of the study) reporting weight in either lb or kg, and accuracy to the nearest 0.2 lb. (or 0.1 kg); that is, the device must be able to distinguish a difference between 150.4 lb. (68.4 kg) versus 150.2 lb. (68.3 kg). The scale must be placed on a stable, flat surface.

Weight measurement should be taken under the following conditions:

- After void of urine;
- After removal of shoes, bulky layers of clothing and jackets so that only light clothing remains;
- While remaining still during the measurement.

Body weight is not considered an efficacy assessment for the open-label, PK cohort.

8.2.4. Activity Monitoring (Main Cohort [Cohort A]/Cohort C/Cohort D)

An activity monitor should be placed on the participant's non-dominant wrist from SV2 to Day 1 and from Week 20 to Week 22. The participant should be asked to wear the activity monitor continuously during these periods. Please refer to the activity monitoring guide for detailed instructions.

Activity monitoring data will capture real-life activities and movement patterns.

8.2.5. Clinical Outcomes

Details of deaths occurring during trial follow-up will be collected in the CRF and/or separate adjudication packages. Investigators will classify deaths as cardiovascular or non-cardiovascular according to the primary cause of death, which is the underlying disease or injury that initiated the train of events resulting in death. In addition, all deaths will be

adjudicated by a blinded adjudication committee consisting of independent external experts. Cardiovascular death includes:

- Death resulting from an acute myocardial infarction
- Sudden cardiac death
- Death due to heart failure or cardiogenic shock
- Death due to stroke
- Death due to cardiovascular hemorrhage
- Death due to other cardiovascular cause (eg, pulmonary embolism, peripheral artery disease)

Worsening heart failure events occurring during the trial (after randomization) will be collected in the eCRF and/or separate adjudication packages. Worsening heart failure events include both heart failure hospitalizations and urgent heart failure visits. Please refer to the eCRF completion requirements for the clinical criteria needed to classify an event as a heart failure hospitalization or urgent heart failure visit. All investigator-reported worsening heart failure events will be adjudicated by a blinded adjudication committee consisting of independent external experts.

The occurrence of potential clinical outcome will trigger the compilation of a dossier that includes anonymized supporting medical record information that will be sent to the adjudication committee.

8.3. Safety Assessments

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

Although not observed so far with ponsegromab, injection site reactions and delayed hypersensitivity reactions are theoretically possible in response to injected monoclonal antibodies. Participants should be monitored after receiving injections for clinical signs of systemic immune reactions, and any such reactions assessed and reported as part of standard safety/AE monitoring, including adverse events that are manifestations of injection site reactions. Additional assessments may be conducted at investigator discretion and/or until any symptoms resolve. 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. As part of the safety analysis, any cases of potential anaphylaxis will be assessed by the sponsor against the Sampson criteria.[19]

8.3.1. Physical Examinations

A brief physical examination will include, at a minimum, assessments of the lungs, cardiovascular system, and abdomen. Height and weight will also be measured and recorded. Height will only be captured once, at the initial screening assessment. Please refer to Section 8.2.3 for details regarding collection of body weight.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

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 8.4.1 to 8.4.3.

8.3.2. Vital Signs

Any untoward vital sign 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 8.4.1 to 8.4.3.

8.3.2.1. Blood Pressure and Pulse Rate

BP and PR measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

BP and PR measurements should be preceded by at least 5 minutes of rest with the participant in a supine position, before the collection of laboratory tests, in a quiet setting without distraction (eg, television, cell phones) and the results recorded in the CRF. It would not be considered a protocol deviation if BP and PR measurements are collected after laboratory tests.

8.3.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex.

If the site does not have an ECG machine that performs automated interval calculations, the investigator is permitted to calculate the standard intervals.

8.3.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that 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 significant and abnormal during participation in the study or up to the time of the final planned follow-up visit 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 study medical monitor.

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

See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

8.3.5. Pregnancy Testing

A serum pregnancy test is required at the initial screening visit and will be sent to the central lab. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. Pregnancy test results must be reviewed and confirmed as negative, in order to continue dosing with study intervention (see also Section 7.1).

8.3.5.1. At-Home Pregnancy Testing

If a participant requiring pregnancy testing cannot visit the study site for a follow-up visit (F/U1 and/or F/U2), a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home or current residence, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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

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

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

During the active collection period as described in Section 8.4.1, 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.

8.4.1. 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 undergoing any study-related procedure and/or receiving study intervention, through and including the time of the final planned follow-up visit, except as indicated below, after the last administration of the study intervention.

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

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 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 its being available.

8.4.1.2. 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 8.4.1, 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.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.4.2. 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.

8.4.3. 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 provided in Appendix 3.

8.4.4. 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.

8.4.5. 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 EDP, EDB, and occupational exposure.

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.

- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of 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 eg, skin contact.

    - A male family member or healthcare provider who has been exposed to the study intervention by eg, skin contact then inseminates 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 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 final planned 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.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female nonparticipant 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 EDB 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 EDB 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 EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.4.5.3. 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.

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

This section is not applicable because efficacy of the underlying disease (HF) is not expected in the study population with the study intervention.

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. 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.

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	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.

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.

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

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

8.5. Pharmacokinetics

Blood samples of approximately 4 mL, to provide a minimum of 1.5 mL serum, will be collected for measurement of serum unbound and total concentrations of ponsegromab as specified in the respective SoA (ie, Table 1 for the Main Cohort (Cohort A)/Cohort C/Cohort D and Table 2 for the open-label, PK cohort).

In addition, in the Main Cohort (Cohort A)/Cohort C/Cohort D, if the participant consents to the extra sample collection, a flexible PK sample may be collected at 1 week (±2 days) post any dose (ie, collect a sample at Week 1, Week 5, Week 9, Week 13, Week 17, or Week 21 for a dose administered on Day 1, Week 4, Week 8, Week 12, Week 16 or Week 20, respectively), in conjunction with the flexible PD sample collection (see Section 8.7.1). It will not be considered a protocol deviation if the participant chooses not to have this additional visit.

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. In some instances, as specified in the respective SoAs, the samples from the participant may be collected at their home or current residence.

The actual times may change, but the number of samples will remain the same. Collection of samples within the protocol-allowed visit window, as defined in SoA or noted above 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 ponsegromab. Samples collected for analyses of ponsegromab serum concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

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

Samples collected for measurement of serum concentrations of ponsegromab (unbound and total) will be analyzed using a validated analytical method(s) in compliance with applicable SOPs.

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

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

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

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics (Main Cohort [Cohort A]/Cohort C/Cohort D)

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected on Day 1 prior to first dose, as local regulations and IRBs/ECs allow.

Retained Research Samples may be used for research related to the study intervention(s) and HF. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

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

8.6.3. Retained Research Samples for Future Genetic Research by TIMI (Main Cohort [Cohort A]/Cohort C/Cohort D)

A 4-mL blood sample optimized for DNA isolation in K2EDTA will be collected on Day 1, as local regulations and IRBs/ECs allow.

These samples may be used for research related to the study intervention(s), and HF by the TIMI Study Group. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the stored samples.

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

8.7. Biomarkers

Collection of samples for biomarker research is also part of this study.

The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- Serum GDF-15 (Section 8.7.1);
- NT-proBNP, hsCRP, albumin and pre-albumin (Section 8.7.2).
- CCI [redacted] ratio for Cohorts C and D only (Section 8.7.2)

8.7.1. GDF-15

Blood samples of approximately 6 mL, to provide a minimum of 2 mL serum, will be collected for measurement of serum concentrations of CCI [redacted] GDF-15 at time points specified in the respective SoA (ie, Table 1 for the Main Cohort (Cohort A)/Cohort C/Cohort D and Table 2 for the open-label, PK cohort).

In addition, in the Main Cohort (Cohort A)/Cohort C/Cohort D, if the participant consents to the extra sample collection, a CCI [redacted], in conjunction with the flexible PK sample collection (see Section 8.5). It will not be considered a protocol deviation if the participant chooses not to have this additional visit.

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. In some instances, as specified in the respective SoAs, samples from the participant may be collected at their home or current residence.

At the initial screening visit, CCI GDF-15 (CCI) sample will be analyzed using the IUO CCI GDF-15 assay, for determination of enrollment eligibility. In addition, this sample may be used to help support development of a potential companion diagnostic test for ponsegromab. This screening assay will be validated in a CLIA accredited central laboratory. CCI

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. Collection of samples within the protocol-allowed visit window, as defined in SoA or above 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 PD of ponsegromab. Samples collected for PD analyses may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, and/or evaluation of bioanalytical methods, or for other internal exploratory purposes.

The PD samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PD 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.

GDF-15 concentration information that may unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

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

8.7.2. Exploratory Biomarkers

These analytes will be used for exploratory research to measure the effect of ponsegromab on biomarkers of hemodynamic stress (NT-proBNP), inflammation (hsCRP), CCI CCI for Cohorts C and D only, and nutritional status (albumin and pre-albumin). Samples will be collected according to the SoA. All samples collected on Day 1 must be collected prior to study intervention administration.

Laboratory/analyte results from albumin, pre-albumin, NT-proBNP, and hsCRP samples collected after the first dose of study intervention through EOT that could unblind the study will not be reported to investigator sites or other blinded personnel until the study has been unblinded.

Other exploratory plasma biomarkers may also be analyzed.

8.7.3. Specified Gene Expression (RNA) Research

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

8.7.4. Specified Protein Research

Specified protein research is not included in this study.

8.7.5. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.6. Retained Research Samples for Biomarkers (Main Cohort [Cohort A]/Cohort C/Cohort D)

These Retained Research Samples will be collected in this study:

- 2.5-mL whole blood (Prep R1 optimized for RNA);
- 10-mL whole blood (Prep B2 optimized for serum);
- 10-mL whole blood (Prep B1 optimized for plasma).

Retained Research Samples will be collected as local regulations and IRB/ECs allow according to the SoA.

Retained Research Samples may be used for research related to the study intervention and HF. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

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

8.7.7. Retained Research Samples for Future Biomarker Research by TIMI (Main Cohort [Cohort A]/Cohort C/Cohort D)

The following samples will be collected in this study for future research by TIMI group:

- One 10-mL whole blood will be collected and isolated plasma retained in K2EDTA.

- One 10-mL whole blood will be collected and isolated serum retained with no additive.

Samples will be collected as local regulations and IRB/ECs allow according to the SoA.

These samples may be used for research related to the study intervention(s) and HF by the TIMI Study Group. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the stored samples.

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

8.7.8. Samples for Exploratory Plasma Biomarker Research by Pfizer (Main Cohort [Cohort A]/Cohort C/Cohort D)

One 4-ml whole blood sample will be collected and isolated plasma retained in lithium heparin.

Samples will be collected according to the SoA, as local regulations and IRBs/ECs allow.

These samples may be used for research related to the study intervention(s), and HF disease by Pfizer.

8.8. Immunogenicity Assessments

Blood samples of approximately 4 mL, to provide a minimum of 1.5 mL serum, will be collected for determination of ADA and NAb as specified in the SoA. Participants found to have anti-ponsegromab antibodies still present at the end of study may be requested to provide additional immunogenicity samples (either at the site or at home/current residence) at approximately 90-day intervals until ADA titers return to baseline levels or up to approximately 12 months from the last dose administered if no safety concerns associated with the ADA.

Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for determination of ADA and NAb may also be used for additional characterization of the immune response and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. These data will be used for internal exploratory purposes.

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

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

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

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

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

8.9. 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 the 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

The null hypothesis of no difference between ponsegromab and placebo will be tested for each primary and selected secondary and tertiary endpoints. The alternative hypothesis is that ponsegromab is superior to placebo. There is no hypothesis testing planned for the open-label, PK cohort.

9.1.1. Estimands

Details of all the estimands and analyses will be presented in the SAP.

9.1.1.1. Primary Estimands

The primary estimand is applied to the comparison between ponsegromab 300 mg and placebo only.

Estimand related to the **HF disease-specific health status** primary objective (Main Cohort [Cohort A] only):

Estimand 1 (similar to "hypothetical") is intended to provide a population level estimate of the treatment effect on the change from baseline in KCCQ-23 CSS for ponsegromab compared with placebo in all evaluable participants in the Main Cohort, under the scenario of no discontinuation of study intervention and without the potential confounding effect of prohibited procedures or participants' non-compliance with dosing (ie, using the censored analysis set for the Main Cohort as defined in Section 9.1.1.3).

- Population: Participants with HF, elevated circulating GDF-15 concentrations and KCCQ-23 CSS <75.
- Endpoint: Change from baseline in KCCQ-23 CSS at Week 22.
- Intercurrent Events:
  a. Discontinuation of study intervention: Data collected after a participant has discontinued study intervention will be censored and treated as missing data.
  b. Prohibited procedures: Data collected after a participant has undergone prohibited procedures, that would modulate the primary endpoint will be censored and treated as missing data. Any procedures will be reviewed prior to database lock to determine which would be classed as "prohibited" for this estimand.
  c. Inadequate compliance: Data collected after a participant has missed a dose will be censored and treated as missing data. For participants who resume dosing, their subsequent data may be included in the analysis following a review of their compliance prior to database lock. Details will be provided in the SAP.

     Missing data due to censoring, study withdrawal or other reasons, are assumed to be missing at random in the analysis.
- Population-level summary: Difference in mean change from baseline for the KCCQ-23 CSS at Week 22 between ponsegromab and placebo.

Alternative estimands (eg, one similar to "treatment policy", using a complete analysis set where all observations post-discontinuation, prohibited procedure or inadequate compliance, will be included) for the primary objective may be used in order to examine the robustness of the results and will be detailed in the SAP.

9.1.1.2. Secondary Estimands

The secondary estimands are applied to the comparisons between each ponsegromab dose and placebo. Data from the Main Cohort (Cohort A) will be used for comparisons between ponsegromab 300 mg and placebo. Data from the Main Cohort (Cohort A) and Cohort C,

combined (ie, Cohort A + Cohort C), will be used for comparisons between ponsegromab 100, 200 and 300 mg (as appropriate) and placebo. See Section 9.3.1 for more details.

Estimand related to the **HF disease-specific health status** secondary objective (Main Cohort [Cohort A] ± Cohort C):

Estimand 2 will be similar to Estimand 1, except for the following:

- Endpoint: Change from baseline in each of KCCQ-23 CSS*, OSS, TSS and physical limitation score at Week 22.
- Population-level summary: Difference in mean change from baseline for the KCCQ-23 CSS, OSS, TSS, or physical limitation score at Week 22 between ponsegromab and placebo.

* Note: For KCCQ-23 CSS, comparisons between ponsegromab 100 or 200 mg and placebo are based on data from the Main Cohort (Cohort A) and Cohort C combined, only.

Estimand related to the **HF disease-specific health status (responses as defined by a ≥ 5-point increase from baseline)** secondary objective (Main Cohort [Cohort A] ± Cohort C):

Estimand 3 will be similar to Estimand 1, except for the following:

- Endpoint: Responses as defined by a ≥5-point increase in each of KCCQ-23 CSS, OSS, TSS, and physical limitation score at Week 22.
- Population-level summary: Odds ratio for the proportions of study participants with ≥5-point increase in KCCQ-23 CSS, OSS, TSS, and physical limitation score at Week 22 between ponsegromab and placebo.

Estimand related to the **physical function** secondary objective (Main Cohort [Cohort A] ± Cohort C):

Estimand 4 will be similar to Estimand 1, except for the following:

- Endpoint: Change from baseline in the 6MWD at Week 22.
- Population-level summary: Difference in mean change from baseline for the 6MWD at Week 22 between ponsegromab and placebo.

Estimand related to the **Fatigue** secondary objective (Main Cohort [Cohort A] ± Cohort C):

Estimand 5 will be similar to Estimand 1, except for the following:

- Endpoint: Change from baseline in PROMIS Fatigue 7a at Week 22.

- Population-level summary: Difference in mean change from baseline for PROMIS Fatigue 7a at Week 22 between ponsegromab and placebo.

Estimands related to the **safety and tolerability** secondary objective (All Cohorts):

There are no defined estimands for the incidence of treatment-emergent adverse events and treatment-emergent serious adverse events, abnormal laboratory results and vital signs, and these endpoints will be reported using Pfizer data standards as applicable. The Main Cohort (Cohort A) and Cohort C will be reported combined; the open-label, PK cohort (Cohort B) will be reported separately; Cohort D will be reported separately.

9.1.1.3. Tertiary/Exploratory Estimands

Tertiary/exploratory endpoints may be analyzed using similar estimands or analyzed in a descriptive manner without reference to an estimand. Other supporting estimands may be used for some of the primary and secondary endpoints as a means to examine the robustness of results, compare to available literature and/or be used for future study planning as needed.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and randomization. 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.
Evaluable	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention, for the given part of the study (Main Cohort [Cohort A], open-label, PK cohort [Cohort B], Cohort C or Cohort D). Participants will be analyzed according to the randomized intervention.
Safety Analysis Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention, for the given part of the study (Main Cohort [Cohort A], open-label, PK cohort [Cohort B], Cohort C or Cohort D). Participants will be analyzed according to the product they actually received.

Defined Analysis Set	Description
Censored	All evaluable participants. For participants who discontinue study intervention or receive a prohibited procedure, all observations post-discontinuation, or post-procedure, will be censored and treated as missing data. For participants who miss a dose, all observations post-missed dose will be censored. For participants who resume dosing, their subsequent data may be included in the analysis following a review of their compliance prior to database lock. Details will be provided in the SAP.
PK concentration	All participants randomly assigned to study intervention and who take at least 1 dose of ponsegromab and in whom at least 1 PK concentration value is reported, for the given part of the study (Main Cohort [Cohort A], open-label, PK cohort [Cohort B], Cohort C or Cohort D).
PK parameter (open-label, PK cohort [Cohort B] only)	All participants randomly assigned to study intervention and who take at least 1 dose of ponsegromab and have at least 1 of the PK parameters of interest calculated.
PD	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 PD (GDF-15) concentration value is reported for any PD endpoint, for the given part of the study (Main Cohort [Cohort A], open-label, PK cohort [Cohort B], Cohort C or Cohort D).
Immunogenicity	All participants randomly assigned to study intervention and who take at least 1 dose of ponsegromab and in whom at least 1 ADA result is reported, for the given part of the study (Main Cohort [Cohort A], open-label, PK cohort [Cohort B], Cohort C or Cohort D).

9.3. Statistical Analyses

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

9.3.1. General Considerations

The open-label, PK cohort (Cohort B) will be presented separately from the Main Cohort (Cohort A), Cohort C and Cohort D.

Following PCD, the data will be analyzed and reported in a CSR. The results for the open-label, PK cohort (Cohort B) may be reported separately.

The main efficacy analyses for the 300 mg ponsegromab treatment group will be performed using data from the Main Cohort (Cohort A) only; statistical models will include data from the 300 mg ponsegromab treatment group and placebo only. The main statistical analyses for the 100 mg and 200 mg ponsegromab treatment groups will be performed using combined data from the Main Cohort (Cohort A) and Cohort C; statistical models will include data from all three ponsegromab treatment groups and placebo, with these analyses also providing sensitivity analyses for the 300 mg ponsegromab treatment group.

For safety analyses, the Main Cohort (Cohort A) and Cohort C will be reported combined; the open-label, PK cohort (Cohort B) will be reported separately; Cohort D will be reported separately.

9.3.1.1. Analyses for Continuous Endpoints

The MMRM model will include participant as a random term, and baseline, time (as a factor), baseline-by-time interaction, treatment and treatment-by-time interaction as fixed terms in the model. An unstructured covariance matrix will be fitted to the repeated times within subject (other covariance matrices will be considered if necessary), and the Kenward-Roger approximation will be used for estimating degrees of freedom. Additional terms may be fitted in the model (eg, cohort, LVEF, log GDF-15 concentrations, log NT-proBNP), as appropriate.

9.3.1.2. Analyses for Binary Endpoints

The logistic regression model will include baseline and treatment as fixed terms in the model. Additional terms may be fitted in the model (eg, cohort, LVEF, log GDF-15 concentrations, log NT-proBNP), as appropriate.

9.3.2. Primary Endpoints Analysis

Main Cohort (Cohort A): KCCQ-23 CSS at Week 22

Change from baseline in KCCQ-23 CSS at Week 22 will be analyzed using Estimand 1 and an MMRM model (as per Section 9.3.1.1). The MMRM model will be fitted to the change from baseline at all post-treatment timepoints up to Week 22 using the Censored analysis set for the Main Cohort (Cohort A). The analysis will include data from the 300 mg ponsegromab treatment group and placebo only. Additional terms for LVEF, GDF-15 concentrations and NT-proBNP will be fitted in the model. Least squares means (and 90%

CIs) and mean differences versus placebo (and 90% CIs and p-values) will be provided. No adjustments will be made for multiplicity.

9.3.3. Secondary Endpoints Analysis

Endpoint	Statistical Analysis Methods
Main Cohort (Cohort A)/Cohort C/Cohort D	
Change from baseline in KCCQ-23 CSS, OSS, TSS and physical limitation score at Week 22	Change from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation scores will be analyzed separately using Estimand 2 and an MMRM model (as per Section 9.3.1.1). The MMRM model will be fitted to the change from baseline at all post-treatment timepoints up to Week 22 using the Censored analysis set for the Main Cohort (Cohort A) ± Cohort C. Least squares means (and 90% CIs) and mean differences versus placebo (and 90% CIs and p-values) will be provided. No adjustments will be made for multiplicity.
Responses as defined by a ≥5-point increase from baseline in KCCQ-23 CSS, OSS, TSS and physical limitation score at Week 22.	Responses as defined by a ≥5-point increase in KCCQ-23 CSS, OSS, TSS, and physical limitation score will be analyzed separately using Estimand 3 and a logistic regression model (as per Section 9.3.1.2). The model will be fitted to the data at Week 22 using the Censored analysis set for the Main Cohort (Cohort A) ± Cohort C. Proportions (and 90% CIs), odds (and 90% CIs) and odds ratios versus placebo (and 90% CIs and p-values) will be provided. No adjustments will be made for multiplicity.
Change from baseline in 6MWD at Week 22.	Change from baseline in 6MWD will be analyzed using Estimand 4 and an MMRM model (as per Section 9.3.1.1). The MMRM model will be fitted to the change from baseline at all post-treatment timepoints up to Week 22 using the Censored analysis set for the Main Cohort (Cohort A) ± Cohort C. Least squares means (and 90% CIs) and mean differences versus placebo (and 90% CIs and p-values) will be provided. No adjustments will be made for multiplicity.

Endpoint	Statistical Analysis Methods
Main Cohort (Cohort A)/Cohort C/Cohort D	
Change from baseline in PROMIS Fatigue 7a at Week 22.	Change from baseline in PROMIS Fatigue 7a will be analyzed using Estimand 5 and an MMRM model (as per Section 9.3.1.1). The MMRM model will be fitted to the change from baseline at all post-treatment timepoints up to Week 22 using the Censored analysis set for the Main Cohort (Cohort A) ± Cohort C. Least squares means (and 90% CIs) and mean differences versus placebo (and 90% CIs and p-values) will be provided. No adjustments will be made for multiplicity.
Incidence of TEAEs, TESAEs, abnormal laboratory results, and vital signs.	All safety analyses will be performed on the safety population for the Main Cohort (Cohort A), Cohort C and Cohort D. The safety data will be summarized in accordance with Pfizer Data Standards. All safety data will be summarized descriptively through appropriate data tabulation, descriptive statistics, categorical summaries, and graphical presentations, as appropriate. The Main Cohort (Cohort A) and Cohort C will be reported combined; Cohort D will be reported separately.
Open-Label, PK Cohort (Cohort B)	
Incidence of TEAEs, TESAEs, abnormal laboratory results, and vital signs.	All safety analyses will be performed on the safety population for the open-label, PK cohort (Cohort B). The safety data will be summarized in accordance with Pfizer Data Standards. All safety data will be summarized descriptively through appropriate data tabulation, descriptive statistics, categorical summaries, and graphical presentations, as appropriate.

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

Details on the analyses of Tertiary/Exploratory endpoints will be described in the SAP.

9.3.5. Other Safety Analyses

All safety analyses will be performed on the corresponding safety population.

9.3.6. Other Analyses

Selected data collected at Screening may be reported. These data include demographic data, prior and concomitant medications, LVEF, NYHA classification, GDF-15 concentrations, height, weight, BMI and KCCQ-23 scores. In addition, a subset of medical history data will be reported; this may include time since diagnosis, time since last HF hospitalization, body weight history (eg, evidence of cachexia), where feasible. Other data collected at screening

that are used for inclusion/exclusion criteria, such as laboratory data, will be considered source data, and will not be required to be reported, unless otherwise noted.

As permitted by data, and determined by the sponsor, the PK/PD relationship between serum ponsegromab concentration and the effect on primary, secondary and/or tertiary endpoints may be explored using a population PK/PD approach. The population PK/PD analysis, if conducted, will be reported in a separate report.

Qualitative exit interviews with a selected group of participants (up to 50) at selected sites will be conducted by telephone at the end of the Main Cohort (Cohort A), Cohort C and Cohort D, after Week 22, as indicated in the SoA. Interviews will be conducted by trained moderators and are anticipated to be approximately 60 minutes in duration. Using the transcripts and interviewer field notes, dominant trends will be identified in each interview and compared across all the interviews to describe the participant experience with a focus on the themes or patterns in the way the treatment experience is described, and the importance of any improvements reported. These results will be reported in a separate report.

Pharmacogenomic or biomarker data from Retained Research Samples or other exploratory plasma biomarker data may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.4. Interim Analyses

Interim analyses will be performed at least once while the study is ongoing to assess efficacy and/or safety after at least approximately 25% of the planned participants in the ponsegromab 300 mg and placebo arms in the Main Cohort (Cohort A), ie, approximately 80 participants, complete their study participation through at least Week 12 of the Main Cohort (Cohort A).

Interim analysis results may be used for internal business decisions including, but not limited to, future study planning, stopping for futility, stopping for early success, conducting a sample size re-estimation, or adapting the study after the interim analysis. Participants may be discontinued from the study intervention/study as a result of the interim analysis, as described in Section 9.3.2.

Before any interim analysis is performed, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind (if applicable) as per Pfizer's SOPs will be documented and approved in an IRC charter and/or data access plan. In addition, the analysis details will be documented and approved in the SAP or an additional interim analysis SAP.

In addition, ongoing monitoring of the safety of participants will be performed by an E-DMC. Further details are provided in Section 10.1.5.2 and will be further documented in an E-DMC charter.

9.4.1. PK/PD Unblinding Plan

If needed, a PK/PD unblinding plan will be developed for the Main Cohort (Cohort A), Cohort C and Cohort D, to safeguard the study blind for members of the study team. These procedures will be in accordance with applicable Pfizer SOPs for releasing randomization codes and breaking the study blind. Under this plan, a limited number of individuals, not on the study team, will be unblinded, with the purpose of composing PK/PD and/or immunogenicity analysis sets and conducting PK/PD analysis that will not be made available to the study team until after database lock.

9.5. Sample Size Determination

The planned total sample size for the study is up to approximately 781 randomized participants.

Main Cohort (Cohort A)

A sufficient number of participants will be screened to achieve a total of approximately 416 randomized participants, with 380 participants randomly assigned to ponsegromab 300 mg Q4W and placebo Q4W in approximately a 1:1 ratio, plus an additional 36 participants randomly assigned to ponsegromab 100 mg Q4W and 200 mg Q4W in approximately a 1:1 ratio. Participants will be randomized initially in a 1:1:1:1 ratio to all four treatment arms (until approximately 72 participants are randomized), followed by a 1:1 ratio to the 300 mg Q4W and placebo arms only. This planned number of randomized participants is expected to ensure completion of the Main Cohort (Cohort A) of approximately 161 evaluable participants in the 300 mg Q4W and placebo Q4W treatment arms and approximately 15 evaluable participants in the 100 mg and 200 mg Q4W treatment arms, assuming a discontinuation rate of 15% (if this rate is higher, or there is a high rate of non-compliance, more participants may be randomized to ensure the required number of evaluable participants).

The sample size in the ponsegromab 300 mg Q4W and placebo arms is based CCI

CCI

The sample size in the ponsegromab 100 mg and 200 mg Q4W arms has been chosen empirically to provide sufficient data to gain a preliminary understanding of the PK/PD relationship in this population, and is not based on the primary endpoint.

Open-Label, PK Cohort (Cohort B)

Approximately 20 additional participants will be randomly assigned to open-label ponsegromab 100 mg, 200 mg and 300 mg Q4W in approximately a 1:2:2 ratio. This sample size has been chosen empirically to provide sufficient evaluable participants (approximately 15) to adequately evaluate the PK of ponsegromab following repeated SC administration to participants with HF and elevated circulating GDF-15 concentrations, assuming a 15% discontinuation rate (if this rate is higher, or there is a high rate of non-compliance, more participants may be randomized to ensure the required number of evaluable participants).

Cohort C (optional)

A sufficient number of participants will be screened to achieve a total of approximately 195 randomized participants, with 130 participants randomly assigned to ponsegromab 100 mg Q4W and 65 to placebo Q4W in approximately a 2:1 ratio. This planned number of randomized participants is expected to ensure completion in Cohort C of approximately 110 evaluable participants in the 100 mg Q4W and 55 in the placebo Q4W treatment arms, assuming a discontinuation rate of 15% (if this rate is higher, or there is a high rate of non-compliance, more participants may be randomized to ensure the required number of evaluable participants). This sample size of 165 completers is based on the primary efficacy endpoint and, when combined with the completing 100 mg Q4W and placebo Q4W participants in the Main Cohort (Cohort A), gives similar acceptable Operating Characteristics to those for the 300 mg Q4W arm in the Main Cohort.

CCI [redacted]

Cohort D (optional)

Approximately 100 participants will be randomly assigned to ponsegromab 300 mg Q4W or placebo in approximately a 1:1 ratio in Cohort D. This sample size has been estimated based on the number of participants being screened for Cohort C and the anticipated screen-fail rate. The actual sample size may be lower or higher than estimated, with a maximum of approximately 150 total participants in this cohort. Enrollment into Cohort D will stop approximately when enrollment into Cohort C stops.

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, European Medical Device Regulation 2017/745 for clinical device research, 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 sub-investigators 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 their 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 their 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 their 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 their right to access and correct their 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.

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

10.1.4. Data Protection

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

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

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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Steering Committee

A steering committee chaired by the TIMI Study Group and consisting of physicians from Pfizer and the National Lead Investigators for participating countries will provide academic leadership, will monitor the proportion of study participants with various NYHA classes, left ventricular ejection fractions, GDF-15 concentrations, KCCQ-23 CSS scores, and the relative proportions qualifying under the cachexia, fatigue, and functional impairment criteria and

may cap one or more to ensure a broad population. Additional details will be provided in the charter.

10.1.5.2. Data Monitoring Committee

This study will use an E-DMC. The E-DMC is independent of the study team and includes external members with expertise in the disease state and clinical trials. The E-DMC charter describes the role of the E-DMC in more detail.

The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The E-DMC will review blinded and unblinded safety data prepared by an independent statistician who is not part of the study team. The recommendations made by the E-DMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities and investigators, as appropriate.

10.1.5.3. Internal Review Committee

This study will also use an IRC. The IRC is independent of the study team and may include a mix of external and internal members. The IRC charter describes the role of the IRC in more detail.

The IRC will be responsible for ongoing monitoring of the efficacy and safety of participants in the study according to the charter. The IRC will review blinded and unblinded efficacy and safety data prepared by an independent statistician who is not part of the study team. The recommendations made by the IRC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data to regulatory authorities and investigators, as appropriate.

10.1.5.4. Use of Adjudication Committee(s)

This protocol will use an independent adjudication committee to determine whether certain investigator-reported events meet standardized definitions for the clinical outcomes described in Section 8.2.5. Further information about this endpoint adjudication committee is provided in a charter, including a description of the scope of the committee's responsibilities, the process and definitions to be utilized by the committee for adjudication, and communication plan including timelines.

The occurrence of potential clinical outcome events as defined in Section 8.2.5 will trigger the compilation of a dossier that includes anonymized supporting medical record information that will be sent to the adjudication committee.

The results of the adjudication committees' decisions will be databased and be used for the statistical analyses of these endpoints. The details of these analyses will be described in the SAP.

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/CTIS, and/or www.pfizer.com, and other public registries and websites 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/CTIS

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

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-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 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and 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 non-compliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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

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

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

10.1.8. Source Documents

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

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

Definition of what constitutes source data and its origin can be found in the Source Document Locator, 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.

The sponsor or designee will perform monitoring 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 of the first participant's first visit.

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, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. 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

For multicenter trials, the primary publication will be a joint publication developed by the academic leadership and Pfizer reporting the primary endpoint(s) of the study covering all study sites. An analogous approach will be taken for secondary analyses covering data from all study sites.

Individual study site investigators agree to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Individual site investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is

submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer 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-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

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 Medically Qualified Individual

The sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the Investigator Site File or equivalent.

Participants are provided with a Pfizer study information card at the time of informed consent which includes contact information for their investigator in case of study-related medical questions. The study information card contains, at a minimum, (a) study number, (b) participant's study identification number, and (c) principal investigator contact information.

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.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count	Urea and creatinine CCI CystatinC (at baseline only) Sodium Potassium AST, ALT Total bilirubin Alkaline phosphatase Total protein Glucose (non-fasting) Lipid panel: • Total cholesterol • HDL-cholesterol • Non-HDL-cholesterol • Calculated LDL-cholesterol • Triglycerides.	CCI [c] At screening: • FSH[a] Per SoA or as needed: Pregnancy test (β-hCG, or urine test)[b]

a. For confirmation of postmenopausal status only.

b. Serum β-hCG will be collected at screening for female participants of childbearing potential. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC.

c. Only for Cohort C and Cohort D.

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

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

10.3.1. Definition of AE

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

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

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either 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.

Events NOT Meeting the AE Definition

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

10.3.2. Definition of 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

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.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs or SAEs associated with EDP or EDB 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 nonparticipant (not involving EDP or EDB)	None. Exposure to a study nonparticipant 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 the 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: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or VERY SEVERE to describe the maximum intensity of the AE. The severity of the AE should be determined using the Toxicity Grading Scale:

MILD	Does not interfere with participant's usual function.
MODERATE	Interferes to some extent with participant's usual function.

SEVERE	Interferes significantly with participant's usual function.
VERY SEVERE	Unacceptable and intolerable events or events which are irreversible or cause the participant to be in imminent danger of death.

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 their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have 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 their 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 DCT

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT.
- If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT 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 DCT 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 the 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, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, 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

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

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

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

  OR

- Is a WOCBP and agrees to use a highly effective contraceptive method (failure rate of <1% per year) during the intervention period and for at least 8 weeks after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective, user-dependent method is chosen, she agrees to concurrently use an effective barrier method of contraception. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for reviewing the woman's medical history, menstrual history, and recent sexual activity in order to decrease the risk of enrolling 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 a 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 of age 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 highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she 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.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

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

5. Vasectomized partner.

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

Highly Effective Methods That Are User Dependent

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

    - Oral + barrier*;
    - Intravaginal + barrier*;
    - Transdermal + barrier*.

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

    - Oral + barrier*;
    - Injectable + barrier*.

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.

* Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following:

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

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

- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to ponsegromab or study interventions of this class to understand treatments for the disease under study or the disease itself.

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

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

- The samples will be retained as indicated:

    - Retained samples will be stored indefinitely or for another period as per local requirements.

    - Retained samples for TIMI will be stored indefinitely, or for another period as per local requirements.

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

    - Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

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

Potential Cases of Drug-Induced Liver Injury

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

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili 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 T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

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

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

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

Rises in AST/ALT and T bili 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 T bili 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 T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

10.7. Appendix 7: Kidney Safety Monitoring Guidelines

10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to eGFR [Scr-based eGFR] or [eCrCl]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

2021 CKD-EPI Scr Only	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if >0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if >0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Scr-Scys Combined	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤0.7	if ≤0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤0.7	if >0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if >0.7	if ≤0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if >0.7	if >0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤0.9	if ≤0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤0.9	if >0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if >0.9	if ≤0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if >0.9	if >0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

Inker LA et al. N Engl J Med. 2021;385:1737-49.

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

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

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

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <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.

10.9. Appendix 9: Prohibited Concomitant Medications

Ponsegromab, a humanized mAb directed against GDF-15, is not expected to affect the PK of small molecule drugs either via cytokine-mediated effects on CYP enzymes or transporters.

The below investigational products are not permitted:

- Investigational products (drug or vaccine) are not permitted within 30 days (or as determined by the local requirement) or 5 half-lives (whichever is longer) of Day 1 through Week 32.

- Investigational biologic agents are not permitted within 6 months or 5 half-lives (whichever is longer) of Day 1 through Week 32.

The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgment on the ongoing participation of any participant with prohibited medication use during the study.

10.10. Appendix 10: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the TOC. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 1 (06 June 2023)

Overall Rationale for the Amendment: The overall rationale for this amendment is to incorporate an open-label, PK cohort, clarifications to eligibility criteria and other sections, remove the Heart Failure Daily Diary, and simplify approach to activity monitoring.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Inclusion of Open-label, PK Cohort, which includes the following unique items separate from the main cohort: • Study rationale • Study design • Study schema • SoA • Inclusion/Exclusion criteria • Study arms and duration • Objectives/endpoints • Contracted Home Health Visits	Open-label, PK cohort added to facilitate a more comprehensive assessment of PK characteristics and PK/PD relationship at each ponsegromab dose level in participants with heart failure and elevated GDF-15 levels, in response to a regulatory request.	1 – Protocol Summary 2 – Introduction 3.2 – Objectives, Endpoints, and Estimands (Open-label, PK cohort) 4 – Study Design 5 – Study Population 6 – Study Intervention(s) and Concomitant Therapy 7 – Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal 8 – Study Assessments and Procedures 9 – Statistical Considerations
Removal of HF Daily Diary	Early feedback from sites/investigators that this ePRO was an excessive burden on participants and sites. Strategic reassessment concluded that this ePRO did not provide incremental value	1 – Protocol Summary 3.1 – Objectives, Endpoints, and Estimands (Main cohort) 8.1.1 – Screening Procedures

Description of Change	Brief Rationale	Section # and Name
	beyond other ePROs included in the protocol.	8.2.1 – Patient Reported Outcomes (Main Cohort Only) 9 – Statistical Considerations
Exclusion Criteria #3: Excluded current/planned use of intravenous inotropes (eg, dobutamine, milrinone) #8: Specified the exclusion of severe, uncorrected aortic stenosis; active malignancy and reduced life expectancy to less than 1 year. #11: Excluded participants with "Previous exposure to ponsegromab in a prior clinical study." #13: Excluded participants with the following LFT abnormalities at the time of screening, confirmed by a repeat test if deemed necessary: AST **or** ALT level ≥ 3 x ULN, **or** total bilirubin level ≥ 2 x ULN (unless history of Gilbert's syndrome).	Clarifications offered to existing exclusion criteria to reduce likelihood of enrolling participants who would not be appropriate for study.	1 – Protocol Summary 5.2 – Exclusion Criteria
Inclusion Criteria #2: Added note that 12-month window is not required if LVEF has been persistently <50% on prior assessments.	Clarifications offered to existing inclusion criteria to ensure likelihood of enrolling participants who would be appropriate for study.	1 – Protocol Summary 5.1 – Inclusion Criteria
Reduced frequency of activity monitoring to the following periods: from	Feedback provided from sites and participants that original requirement for continuous wear through	1.3 – Schedule of Activities 3.1 – Objectives, Endpoints, and Estimands (Main cohort)

Description of Change	Brief Rationale	Section # and Name
SV2 to Day 1 and from Week 20 to Week 22	Week 22 was an excessive burden. Strategic reassessment favored reduced frequency.	8.1.1 – Screening Procedures 8.2.4 – Activity Monitoring (Main Cohort Only)
Main cohort SoA: Added Early Termination Hematology & Chemistry Panel Added Week 24 contraception check.	Additional safety measurement.	1.3 – Schedule of Activities
Main cohort SoA: Added Lipid panel assessment	Requested safety measurement from a regulatory authority.	1.3 – Schedule of Activities 10.2 – Appendix 2: Clinical Laboratory Tests
Main cohort SoA: Added NT-proBNP in plasma assessment at Week 12	Align with Week 12 assessment of other efficacy endpoints.	1.3 – Schedule of Activities
Updated clinical overview, including summary of safety data, pharmacokinetics, GDF-15 response and immunogenicity from completed clinical studies.	Updates in line with updates to the IB.	2.2.2 – Clinical Overview 2.3 – Benefit/Risk Assessment
Revised discontinuation criteria to clarify scenarios when study intervention must be permanently discontinued and considerations for permanent discontinuation.	Updates requested by regulatory authority.	7.1 – Discontinuation of Study Intervention
Removed legal guardian and legally authorized representative	Legal guardians and legally authorized representatives not permitted to act on behalf of participants.	8.4 – Adverse Events, Serious Adverse Events, and Other Safety Reporting 9.2 – Analysis Set 10.1.3 – Informed Consent Process

Description of Change	Brief Rationale	Section # and Name
10.4.2 – Modified contraception intervention period from at least 22 weeks to at least 8 weeks after the last dose of study intervention. 8.4.5.1 – Modified follow-up time period for pregnancy from at least 5 terminal half-lives after the last dose to up to the time of the final planned follow-up visit.	Updated to clarify intention to collect data on pregnancy through the duration of follow-up which incorporates the 5 half-lives window (11.1 days) of unbound ponsegromab noted in Section 2.2.2.2 – Summary of Pharmacokinetics.	10.4.2 – Female Participant Reproductive Inclusion Criteria 8.4.5.1 – Exposure During Pregnancy
Updated inclusion criteria for female participation.	Update reflects current recommendation based on nonclinical and clinical data.	10.4.2 – Female Participant Reproductive Inclusion Criteria
Non-substantial Modification(s)		
Streamlined text to emphasize that no injection site reactions or delayed hypersensitivity reactions have been observed in the completed clinical studies.	Clarification	2.3.1– Risk Assessment
Inclusion Criterion #2a: Modified text to state, "LVEF <50% on most recent measurement, within 12 months **of screening**."	Clarification	1 – Protocol Summary 5.1 – Inclusion Criteria
Inclusion Criterion #5: Clarified that all criteria should be met **at screening.** #5b: Specified that criteria is **based on the KCCQ-23 administered at screening.**	Clarification	1 – Protocol Summary 5.1 – Inclusion Criteria
Exclusion Criterion #1: Modified text to state,	Clarification	1 – Protocol Summary

Description of Change	Brief Rationale	Section # and Name
"Acute decompensated HF within 1 month prior to **SV1 or during the screening period**."		5.2 – Exclusion Criteria
Exclusion Criterion #12: Modified text to state, "Renal disease requiring **ongoing** dialysis."	Clarification	1 – Protocol Summary 5.2 – Exclusion Criteria
Modified text to emphasize that SV2 should commence at a minimum of 15 days prior to Day 1, when feasible.	Clarification	1.3 – Schedule of Activities
Extended the time period for use of prior treatments from 28 to 56 days.	Time period reflects screening period and ensures consistency with other language throughout protocol.	6.9 – Prior and Concomitant Therapy
Clarified Early Termination and Follow-up Visits requirements following discontinuation of study intervention.	Clarification to align with CRF completion requirements	7.1 – Discontinuation of Study Intervention
Added instructional language for COVID-19 safety reporting	Clarification	7.1.1 – COVID-19
Updated measures for participants lost to follow-up	Clarified text to minimize loss to follow up, and procedures in event of loss to follow-up.	7.3 – Lost to Follow-up
Total blood sampling updated to 274 mL (main cohort) and 184 mL (open-label, PK cohort)	Updates reflective of changes in protocol amendment	8.1 – Administrative Procedures
Added language for home health care services for the open-label, PK cohort	Contracting outside vendor to perform blood sampling at participant home or	8.1.2 – Contracted Home Health Visits (Open-Label, PK Cohort Only)

Description of Change	Brief Rationale	Section # and Name
	current residence as per SoA	
Added language specific to classification of deaths as cardiovascular or non-cardiovascular according to the primary cause of death	Clarification to align with CRF completion requirements	8.2.5 – Clinical Outcomes
Added "The investigator should inform the TIMI Hotline of any potential withdrawal of consent."	Clarification to align with CRF completion requirements	7.2.1 – Withdrawal of Consent
Added "If the site does not have an ECG machine that performs automated calculations, the investigator is permitted to calculate the standard intervals."	Clarification	8.3.3 – Electrocardiograms
Added language specific to male participants who inseminate a female partner	Language inadvertently omitted in initial protocol.	8.4.5.1 – Exposure During Pregnancy
Updated blood sample volume to 4 mL.	Volume consistent with laboratory manual.	8.6.3 – Retained Research Samples for Future Genetic Research by TIMI
Added "Participants who are rescreened are required to sign a new ICD."	Clarification	10.1.3 – Informed Consent Process
Removed "eg, implantation of a pacemaker, coronary revascularization and heart transplant."	Language aligns with SAP	9.1.1.1 – Primary Estimands
Updated model language to state **log** GDF-15 concentrations and **log** NT-proBNP	Language aligns with SAP	9.3.1 – General Considerations
Removed "…and their partner(s)…" in the first sentence.	Language inadvertently included. No contraception is required for male partner(s) of female study	5.3.1 – Contraception

Description of Change	Brief Rationale	Section # and Name
	participants that are WOCBP.	
Added text "A second staff member will verify the dispensing."	Clarification to coincide with language in IP manual.	6.2.1 – Preparation and Dispensing
Modified details of the PK/PD unblinding plan.	Clarification of the specifics of the PK/PD unblinding plan.	9.4.1 – PK/PD Unblinding Plan
Modified to "Response as defined by a ≥10-point and ≥15-point increase in... "	Correction: Protocol Administrative Change Letter dated 03 Aug 2022	3 – Objectives, Endpoints, and Estimands
Modifications to language to reflect steady state exposures, not exposures after 6 Q4W SC doses.	Clarification: Protocol Administrative Change Letter dated 03 Aug 2022	4.3 – Justification for Dose
Language modified for clarification.	Clarification: Protocol Administrative Change Letter dated 03 Aug 2022	6.1– Administration
Modified follow-up time period for laboratory test values considered clinically significant and abnormal from 28 days to up to the time of the final planned follow-up visit	Clarification: Protocol Administrative Change Letter dated 03 Aug 2022	8.3.4 – Clinical Safety Laboratory Assessments
Revised text to emphasize that only follow-up visits (F/U1, F/U2), the flexible PK/PD visit, and any additional immunogenicity sampling may be conducted at the participant's home or current residence by qualified personnel.	Clarification; Protocol Administrative Change Letter dated 11 Oct 2022	1.3 – Schedule of Activities – Table 1, Study Schedule of Assessment for the Main Cohort 2.3.1 – Risk Assessment 8.3.5.1 – At-Home Pregnancy Testing 8.5 – Pharmacokinetics 8.7.1 – GDF-15 8.8 – Immunogenicity Assessments

Description of Change	Brief Rationale	Section # and Name
Added the following text in bold, "**In addition, this sample may be used to help support development of a potential companion diagnostic test for ponsegromab.** This **screening** assay will be validated in a CLIA accredited central laboratory."	Additional details: Protocol Administrative Change Letter dated 11 Oct 2022	8.7.1 – GDF-15
Added the following text in bold, "Samples will be collected according to the SoA, **as local regulations and IRB/ECs allow**."	Clarification: Protocol Administrative Change Letter dated 11 Oct 2022	8.7.8 – Samples for Exploratory Plasma Biomarker Research by Pfizer
Modified language to emphasize that glucose sampling is non-fasting	Clarification: Protocol Administrative Change Letter dated 11 Oct 2022	10.2 – Appendix 2: Clinical Laboratory Tests
Modified active collection period from 28 days to up to the time of the final planned follow-up visit.	Clarification; Protocol Administrative Change Letter dated 27 Jan 2023	8.4.1 – Time Period and Frequency for Collecting AE and SAE Information
Provided text clarification and corrections.	Minor clarifications and editorial/typographical changes have been made throughout, including those through new regulatory guidance.	Various sections of the protocol

10.11. Appendix 11: Abbreviations

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

Abbreviation	Term
6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
ADA	anti-drug antibodies
ADL	activity/activities of daily living
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{inf}	area under the serum concentration time profile from time zero extrapolated to infinite time
AUC_{last}	area under the serum concentration time profile from time zero to the time of the last quantifiable concentration
AUC_{tau}	area under the serum concentration-time curve over the dosing interval tau
AV	atrioventricular
β-hCG	β-human chorionic gonadotropin
BD	business day
BP	blood pressure
bpm	beats per minute
C_{avg}	average concentration
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CL/F	apparent clearance
CLIA	Clinical Laboratory Improvements Amendments
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	Clinical Study Report
CSS	Clinical Summary Score
CT	computed tomography;clinical trial
CTIS	Clinical Trial Information System
CTR	Clinical Trials Regulation
CYP	cytochrome P450

Abbreviation	Term
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram or electrocardiography
eCOA	electronic clinical outcome assessment
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
E_{max}	maximal effect
EOT	end of treatment
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
F/U1	follow-up visit 1
F/U2	follow-up visit 2
GCP	Good Clinical Practice
GDF-15	growth differentiation factor 15
GGT	gamma-glutamyl transferase
HDL	high-density lipoprotein
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HR	heart rate
HRQL	health-related quality of life
HRT	hormone replacement therapy
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IgG	immunoglobulin g
IMP	investigational medicinal product
IND	Investigational New Drug

Abbreviation	Term
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
IRC	internal review committee
IRT	Interactive Response Technology
KCCQ-23	Kansas City Cardiomyopathy Questionnaire
KDIGO	Kidney Disease: Improving Global Outcomes
LBBB	left bundle branch block
LDL	low-density lipoprotein
LFT	liver function test
LLOQ	lower limit of quantitation
LVEF	left ventricular ejection fraction
mAbs	monoclonal antibodies
MI	myocardial infarction
MIC-1	Macrophage Inhibitory Cytokine 1
MMRM	mixed models repeated measures
MQI	medically qualified individual
N/A	Not Applicable
NAb	neutralizing antibodies
NIMP	noninvestigational medicinal product
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
NT-proBNP	N-terminal pro-B type natriuretic peptide
NYHA	New York Heart Association
OSS	Overall Summary Score
PAX	paired box
PCD	primary completion date
PD	pharmacodynamic(s)
PGI-C	Patient Global Impression of Severity
PGI-S	Patient Global Impression of Change
PK	pharmacokinetic(s)
PR	pulse rate
PRO	patient reported outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PTR	peak-to-trough ratio
PVC	premature ventricular contraction
Q3W	every three weeks
Q4W	every four weeks

Abbreviation	Term
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
QTL	quality tolerance limit
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
Scr	serum creatinine
SD	standard deviation
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single-reference safety document
SSID	single subject identifier
SUSAR	Suspected Unexpected Serious Adverse Reaction
SV1	Screening visit 1
SV2	Screening visit 2
$t_{½}$	terminal elimination half-life
T bili	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TGF-β	transforming growth factor beta
TIMI	TIMI Study Group, an academic research organization
T_{max}	time for C
TSS	Total Symptom Score
ULN	upper limit of normal
CCI [redacted]	
US	United States
WBC	white blood cell
WOCBP	woman/women of childbearing potential

11. REFERENCES

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