Protocol C3651011

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

Statistical Analysis Plan (SAP)

Version: 2

Date: 18 Oct 2024

NOTE: *Italicized* text within this document has been taken verbatim from the Protocol.

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 21 Oct 2022	Original 23 Jun 2022	N/A	N/A
2 18 Oct 2024	Amendment 1 06 Jun 2023 Amendment 2 18 Jul 2024	Open-label, PK cohort added in response to regulatory request. Additional cohorts C and D added for lower dose and lower GDF-15 Daily diary removed. Frequency of activity monitoring reduced. Additional NT-proBNP timepoint added. [redacted] endpoints/objectives added AE outputs updated based on current guidance. Interim Analysis details added.	• Throughout: Protocol language updated; General updates to clarify relevant part of the study; Daily diary removed; total GDF-15 removed • 2.2: Objectives updated to match protocol; clarification on definition of inadequate compliance; Additional protocol estimand wording added for safety and tertiary endpoints • 2.3: Updated study description and schema added • 3: Clarification of baseline definition • 3.2.2: Further clarification of censoring • 3.2.5.1/6.2.5.1: Medical evaluation of I-AEs updated • 3.2.5.2: CFB in lipid panel endpoints added • 3.2.5.3: Maximum changes in vitals signs added • 3.3: Additional endpoints added; PGI-S and PGI-C clarified; %CFB in body weight removed; activity timepoints reduced and endpoints updated; definition of "compliant day" updated; healthy volunteer GDF-15 level corrected; method for dealing with BLQ values added; [redacted] added; clarification of clini calculations; sections added for open-label, PK cohort endpoints • 3.4: Modified BMI added • 3.5: Maximum changes in QTcF added • 4: Further clarification of analysis set definitions and details • 5.1: Additional hypothesis testing wording added for open-label, PK cohort • 5.2: General approach for analysis added; cohort added into analyses; Addition of ANCOVA, logistic regression without imputation, Cumulative incidence plots, Cox proportional hazards

			• 5.3: Additional wording added for managing BLQ concentrations and missing data for PK parameters and screening data for PK Cohort participants • 6.1.1: Clarification of cohort approach; Box and whisker plots removed; clarification of model terms; additional sensitivity analysis added • 6.2/6.6: Clarification of cohort approach; sensitivity analysis added; Addition of a ponsegromab combined group in safety outputs (including ECGs); Summaries of injection site reactions added; Additional summaries for lipid panel endpoints • 6.3: Additional endpoints added; sensitivity analysis added; Activity timepoints reduced and analysis changed to ANCOVA; Clarification of cohort approach; hsCRP, albumin and pre-albumin timepoints reduced and analysis changed to ANCOVA; total GDF-15 endpoint removed; CCI [redacted] added; clarification that clinical outcomes are adjudicated; additional analysis for individual components of clinical composite; sections added for open-label, PK cohort endpoints • 6.4: Subset analyses added • 6.5: Baseline summaries updated; Additional detail added for participant discontinuations, prior/concomitation medications/procedures, and compliance • 7: Details added for interim analyses • 8: Reference added • Appendix 4: Clarified when cohort is included in model; Example SAS code for ANCOVA, logistic regression without imputation, cumulative incidence plots and proportional hazards added • Appendix 7: Abbreviations updated

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3651011 (the main cohort [Cohort A], the open-label, PK cohort [Cohort B], optional Cohort C, and optional Cohort D). This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives, Endpoints, and Estimands

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

Type	Objectives	Endpoints	Estimands
Primary:	*Primary:*	*Primary:*	*Primary:*
Efficacy	• *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 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:*	*Secondary:*
Efficacy	• *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.*
Efficacy	• *To compare the effect of ponsegromab versus placebo on HF disease-specific health status in participants with HF*	• *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,*

	and serum GDF-15 concentrations CCI CCI *pg/mL.*		*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.*
Efficacy	• *To compare the effect of ponsegromab versus placebo on the physical function of participants with HF and serum GDF-15 concentrations* CCI 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.*
Efficacy	• *To compare the effect of ponsegromab versus placebo on fatigue reported by participants with HF and serum GDF-15 concentrations* CCI 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 changes 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.*
Safety	• *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.*
Tertiary/Exploratory:	*Tertiary/Exploratory:*	*Tertiary/Exploratory:*	*Tertiary/Exploratory:*
Efficacy	• *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.*
Efficacy	• *To compare the effect of ponsegromab 300*	• *Change from baseline in 6MWD at Week 22.*	• *Not applicable.*

	mg versus placebo on the physical function of participants with HF and any serum GDF-15 concentration.		
Efficacy	• *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.*
Efficacy	• *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.*
Efficacy	• *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.*
Efficacy	• *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.*
Efficacy	• *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.*
Pharmacokinetics	• *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.*
Biomarkers	• *To compare the effect of ponsegromab versus placebo on GDF-15 concentrations in participants with HF.*	• *Serum concentrations of GDF-15 on* CCI [redacted]	• *Not applicable.*
Immunogenicity	• *To characterize the immunogenicity of ponsegromab in participants with HF.*	• *Incidence of anti-ponsegromab antibodies, and neutralizing antibodies.*	• *Not applicable.*
Biomarkers	• *To compare the effect of ponsegromab versus placebo on markers to check HF*	• *Fold change from baseline in NT-proBNP, hsCRP, albumin and pre-albumin at Week 22.*	• *Not applicable.*

	risk, acute MI, inflammation, and nutritional status in participants with HF.		
Efficacy	• *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.*

Efficacy	• *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.*

2.2.2. Open-label, PK Cohort (Cohort B)

Type	Objectives	Endpoints	Estimands
Secondary:	*Secondary:*	*Secondary:*	*Secondary:*
Safety	• *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:*	*Tertiary/Exploratory:*
Pharmacokinetics	• *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.*

Biomarkers	• *To characterize the effect of ponsegromab on circulating GDF-15 concentrations in participants with HF and elevated circulating GDF-15 concentrations.*	• *Serum concentrations of GDF-15 on* CCI [redacted]	• *Not applicable*
Immunogenicity	• To characterize the immunogenicity of ponsegromab in participants with HF and elevated circulating GDF-15 concentrations.	• *Incidence of ADA, and NAb.*	• *Not applicable.*
Biomarkers	• *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.*

2.2.3. Primary Estimand(s)

*Estimands 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* (Cohort A)*, 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* (Cohort A) *as defined in* Section 4).

- *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*, or has received an incomplete dose, *will be censored and treated as missing data. For participants who resume (*complete) *dosing, their subsequent data may be included in the analysis following a review of their compliance prior to database lock.*

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.*

Estimand 1b (similar to "treatment policy") 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 (Cohort A), regardless of discontinuation of study intervention, dosing compliance or prohibited procedures (ie, using the complete analysis set for the Main Cohort (Cohort A) as defined in Section 4).

- Population: Participants with HF, elevated circulating GDF-15 levels and KCCQ-23 CSS <75
- Endpoint: Change from baseline in KCCQ-23 CSS at Week 22
- Intercurrent Events: There are no changes made based on intercurrent events. For participants who discontinue study intervention, receive a prohibited procedure and/or miss a dose or receive an incomplete dose, all observations post-discontinuation, post-procedure or post-missed/incomplete dose will be included in the analysis set.
- Population-level summary: Difference in mean change from baseline for the KCCQ-23 CSS at Week 22 between ponsegromab and placebo

2.2.4. Secondary Estimand(s)

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 and placebo.

*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: Response 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 proportion 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.

2.2.5. 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.

2.3. Study Design

This is a Phase 2, parallel-group, randomized, double-blind, placebo-controlled study to evaluate the effect of ponsegromab (PF-06946860) *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 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 [redacted]:

- CCI [redacted]
- [redacted] *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.

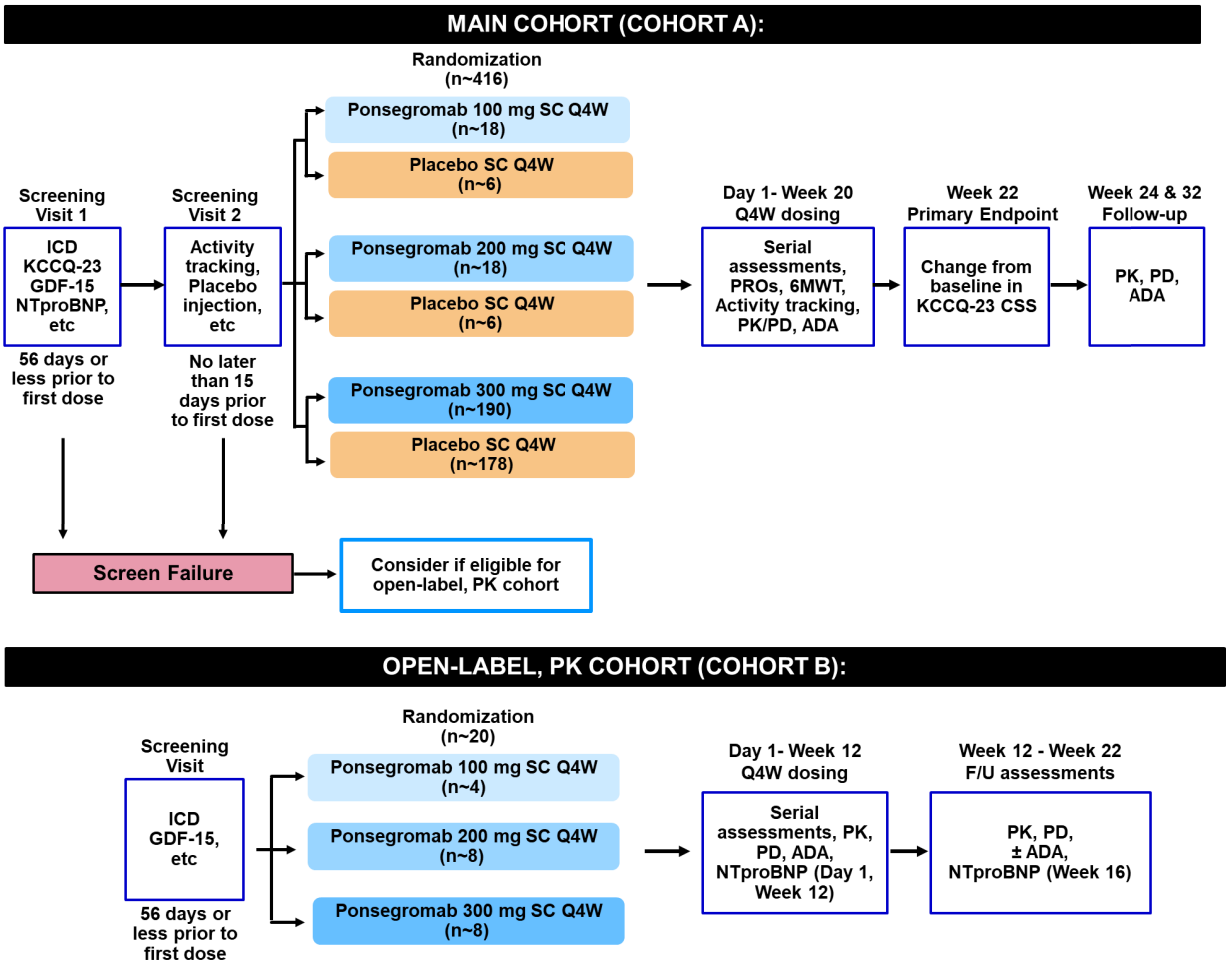
Approximately 100 participants (maximum of approximately 150) who meet all eligibility criteria for Cohorts A and C, except the requirement for serum GDF-15 concentration CCI [redacted] CCI [redacted] *pg/mL, may be enrolled into the optional Cohort D and randomized in a 1:1 ratio to*

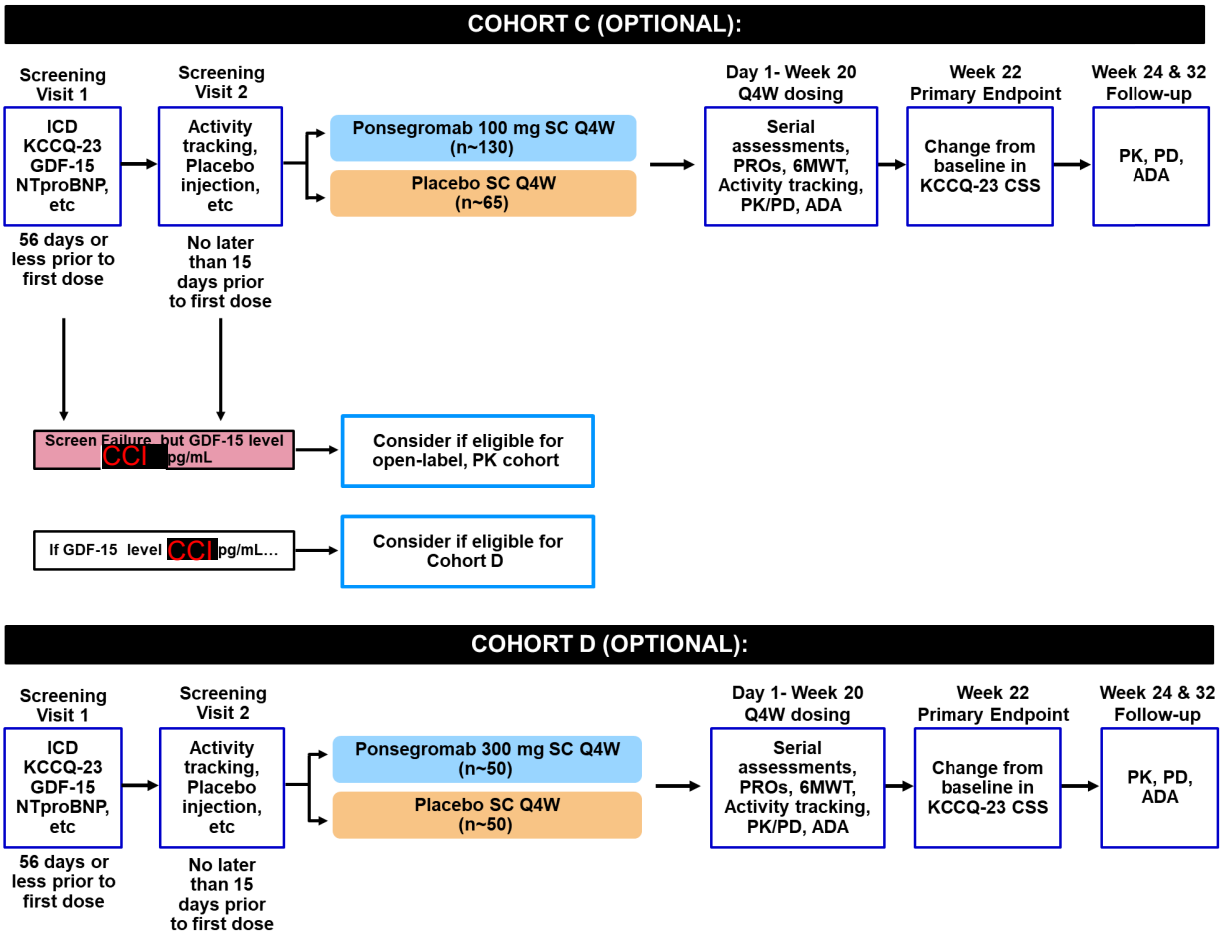
either 300 mg ponsegromab (n~50) or to matched placebo (n~50), administered SC Q4W for a total of 6 doses during the 22 week treatment period. Participant randomization in Cohort D will be stratified by KCCQ-23 CSS: <45 or ≥45. The purpose of this optional cohort is for a supportive assessment of efficacy and safety endpoints across the spectrum of GDF-15 concentrations in participants with HF.

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.

Figure 1. Study Design





3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

For all safety endpoints, unless otherwise stated, baseline is defined as the last pre-dose measurement. For all efficacy endpoints, unless otherwise stated, baseline is defined as the last measurement on study day 1.

3.1. Primary Endpoint(s)

3.1.1. Change from baseline in KCCQ-23 CSS at Week 22 (Cohort A only)

The KCCQ is a self-reported 23-item questionnaire that assesses HRQL in participants with HF over the past 2 weeks. *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: physical limitation, symptom stability, symptom frequency, symptom burden, total symptom score* (TSS)*, self-efficacy, quality of life, social limitation, overall summary score* (OSS)*, and clinical summary score* (CSS)*. Raw summary scores are transformed to a 0-100 scale where higher scores indicate better health.* The KCCQ-23 questionnaire and full scoring instructions are provided in Appendix 1.

The change from baseline in KCCQ-23 CSS will be calculated for all post-baseline timepoints.

3.2. Secondary Endpoint(s)

3.2.1. Change from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22 (Cohorts A and C)

See Section 3.1.1.

The change from baseline in KCCQ-23 CSS, OSS, TSS and physical limitation will be calculated for all post-baseline timepoints.

3.2.2. Responses as defined by a ≥5-point increase from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22 (Cohorts A and C)

See Section 3.1.1.

Each of these endpoints will have two levels: 'Response' and 'Non-response'. The former will be based on participants having a ≥5-point increase from baseline in KCCQ-23 CSS, OSS, TSS, or physical limitation, respectively, at Week 22. Otherwise, participants will be classed as having a 'Non-response'. Participants with an intercurrent event of premature discontinuation of IP, prohibited procedure or inadequate compliance prior to Week 22 will have their Week 22 value censored (if not missing). Missing or censored values at Week 22 will be imputed as described in Section 5.3. Participants who die during the study will be classed as having a 'Non-response' after imputation.

These endpoints will be calculated similarly for all other post-baseline timepoints.

3.2.3. Change from baseline in 6MWD at Week 22 (Cohorts A and C)

The 6MWT is a submaximal exercise test that entails measurement of distance walked over a span of 6 minutes. The 6MWD (distance traveled in meters) provides a measure for integrated global response of multiple cardiopulmonary and musculoskeletal systems involved in exercise.

The change from baseline in 6MWD will be calculated for all post-baseline timepoints with a valid test result.

3.2.4. Change from baseline in PROMIS Fatigue 7a at Week 22 (Cohorts A and C)

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.

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 Appendix 2.

The change from baseline in PROMIS-Fatigue T-score will be calculated for all post-baseline timepoints.

3.2.5. Incidence of TEAEs, TESAEs, abnormal laboratory results, and vital signs (All Cohorts [A, B, C and D])

3.2.5.1. Adverse Events

An adverse event is considered a Treatment-Emergent Adverse Event (TEAE) if the event started during the effective duration of treatment. All events that start on or after the first dosing day and time/start time, if collected, but before the last dose plus the lag time will be flagged as TEAEs. The lag time is defined by the Pfizer standard of 365 days post last dose of IP. The algorithm will not consider any events that started prior to the first dose date.

A Treatment-Emergent Serious Adverse Event (TESAE) is a TEAE which also meets the definition of a Serious Adverse Event (SAE).

A 3-tier approach will be used to summarize TEAEs. Under this approach, TEAEs are classified into 1 of 3 tiers: -

> Tier 1 events: These are prespecified events of clinical importance and are maintained in a list in the product's Safety Review Plan (or similar, e.g. Safety Surveillance Review Plan).
>
> Tier 2 events: These are events that are not tier 1 but are "common." A Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) is defined as a Tier 2 event if there are at least 5% of participants reporting the event in either the placebo group or combined over the ponsegromab treatment groups.
>
> Tier 3 events: These are events that are neither Tier 1 nor Tier 2 events.

Potential immunogenic AEs including potential cases of angioedema, anaphylaxis, hypersensitivity, delayed hypersensitivity reactions and events potentially meeting the Sampson criteria (as defined in Appendix 3) will be medically evaluated in a blinded manner throughout the study to determine whether or not they are immune reactions and possibly related to study drug and categorized as per guidance as: 1) Hypersensitivity, 2) Anaphylaxis, 3) Angioedema, 4) Delayed immune response and / or 5) Cytokine Release syndrome.

3.2.5.2. Injection site reactions will include the signs and symptoms reported along with the AE of injection site reaction. Laboratory Results

To determine if there are any clinically significant laboratory abnormalities, the safety laboratory tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each participant's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

Change from baseline will be calculated for each of the lipid panel endpoints (total cholesterol, HDL-cholesterol, non-HDL-cholesterol, calculated LDL cholesterol and triglycerides) at the Week 22 timepoint.

3.2.5.3. Vital Signs

The change from baseline for vital signs (supine systolic and diastolic blood pressure and pulse rate) will be calculated for all post baseline timepoints.

The maximum increase/decrease from baseline over all measurements taken post-dose will be calculated for supine systolic and diastolic blood pressures and pulse rate. The maximum increase from baseline will be calculated as the maximum change from baseline for a participant, except in the case where a participant does not show an increase. In such an instance, the minimum decrease should be taken. Similarly, the maximum decrease from baseline will be determined by selecting the minimum value of the changes from baseline. In cases where a participant does not show a decrease, the minimum increase should be taken.

3.3. Other Endpoint(s)

3.3.1. Change from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22 (Cohorts A and D combined)

See Section 3.2.1.

3.3.2. Responses as defined by a ≥5-point increase from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22 (Cohorts A and D combined)

See Section 3.2.2.

3.3.3. Change from baseline in 6MWD at Week 22 (Cohorts A and D combined)

See Section 3.2.3.

3.3.4. Change from baseline in PROMIS Fatigue 7a at Week 22 (Cohorts A and D combined)

See Section 3.2.4.

3.3.5. Response as defined by a ≥10-point and ≥15-point increase in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22 (Cohorts A, C and D)

See Section 3.1.1.

Each of these endpoints will have two levels: 'Response' and 'Non-response'. The former will be based on participants having a ≥10-point or 15-point increase from baseline in KCCQ-23 CSS, OSS, TSS, or physical limitation, respectively. Otherwise, participants will be classed as having a 'Non-response'. Participants with an intercurrent event of premature discontinuation of IP prior to Week 22 will have their Week 22 value censored (if not missing). Missing or censored values at Week 22 will be imputed as described in Section 5.3. Note that data for participants who die during the study will be included in the imputation but will then be classed as having a 'Non-response' after imputation.

These endpoints will be calculated for all post-baseline timepoints.

3.3.6. Absolute and change from baseline in PGI-S at Week 22 and PGI-C at Week 22 (Cohorts A, C and D)

3.3.6.1. PGI-S

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 symptomsof 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.

The change from baseline in PGI-S will be calculated for all post-baseline timepoints.

3.3.6.2. PGI-C

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.

3.3.7. Change from baseline in body weight at Week 22 (Cohorts A, C and D)

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).

Absolute change from baseline in body weight will be calculated for all post-baseline timepoints.

3.3.8. Change from baseline in daily activity measures based on accelerometry at Week 22 (Cohorts A, C and 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.

The following daily endpoints will be provided from the activity monitor:

- *Moderate to Vigorous Physical Activity Time (MVPA; mins/day)
- *Total vector magnitude (counts/1000/day)
- *Non-sedentary Physical Activity (mins/day)

- *Number of Steps per Day (steps/day)
- *Max 6 mins of activity level (M6mins; counts/day)
- Sedentary Activity Time (mins/day)
- Light Activity Time (mins/day)
- Moderate Activity Time (mins/day)
- Vigorous Activity Time (mins/day)
- Max 15/60 mins of activity level (M15mins, M60mins; counts/day)
- Average activity counts for the most active 10 hours of the day (M10hr; counts/day)
- Average activity counts for the least active 5 hours of the day (L5hr; counts/day)
- Total Activity Count for Axis X (counts/1000/day)
- Total Activity Count for Axis Y (counts/1000/day)
- Total Activity Count for Axis Z (counts/1000/day)
- Wear Time (mins/day)
- Wear Awake Time (mins/day)

Note: * Priority endpoints

Fortnightly averages (on Day 1 and at Week 22) will be calculated as the mean taken over the 14 days immediately prior (e.g. if the Week 22 visit occurs on Day 155, the Week 22 average will be taken over Days 141 to 154). These fortnightly averages will not overlap a dosing visit, i.e. if the Week 20 visit occurs on Day 143, the Week 22 average will only be taken over Days 143 to 154. If fewer than 4 compliant days of scores are recorded, the mean should be treated as missing (a day is defined as compliant if at least 10 hours of awake wear and/or 18 hours of total wear time are present).

Baseline is defined as the mean taken over the 14 days prior to Day 1 (e.g. Days -14 to -1). Change from baseline will be calculated for the Week 22 timepoint.

3.3.9. Serum unbound and total ponsegromab concentrations on Day 1 (predose) and Weeks 4, 8, 12, 16, 20, 22, 24 and 32 (Cohorts A, C and D)

Blood samples will be collected for measurement of serum unbound and total concentrations of ponsegromab as specified in the protocol.

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).

Trough concentrations (C_{trough}) are defined as the samples measured pre-dose at Weeks 4, 8, 12, 16, and 20.

3.3.10. Serum concentrations of GDF-15 on CCI [redacted] (Cohorts A, C and D)

Blood samples will be collected for measurement of serum concentrations of CCI [redacted] *GDF-15 at time points specified in the* protocol.

In addition, in the Main Cohort (Cohort A)/Cohort C/Cohort D, if the participant consents to the extra sample collection, a CCI [redacted]

Change from baseline and fold change from baseline (i.e. post-dose / baseline), for CCI [redacted] GDF-15, will be calculated for all post-baseline timepoints.

Additionally, the CCI [redacted] GDF-15 will be compared to the median healthy volunteer level, at all timepoints, to create an endpoint with two levels ('Yes' and 'No') indicating whether the concentration is below the estimated healthy volunteer median level CCI [redacted].

3.3.11. Incidence of anti-ponsegromab antibodies, and neutralizing antibodies (Cohorts A, C and D)

Blood samples will be collected for determination of ADA and NAb as specified in the protocol. *Participants found to have anti-ponsegromab antibodies still present at the end of study may be requested to provide additional immunogenicity samples.* See Appendix 6 for immunogenicity terms and definitions.

3.3.12. Fold change from baseline in NT-proBNP, hsCRP, albumin and pre-albumin at Week 22 (Cohorts A, C and D)

The fold change from baseline (i.e. post-dose / baseline) in each analyte will be calculated for all post-baseline timepoints. Note: concentrations below the limit of quantification (BLQ) will be set to the lower limit of quantification (LLQ) prior to calculation of the ratio.

3.3.13. Fold change from baseline in CCI [redacted] (Cohorts A, C and D) and CCI [redacted] (Cohorts C and D only) at Weeks 12 and 22

The fold change from baseline (i.e. post-dose / baseline) in each endpoint will be calculated for all post-baseline timepoints.

Additionally, the % reduction in CCI [redacted] will be calculated at Weeks 12 and 22, where

% reduction at Week X = 100 * (baseline – Week X) / baseline.

3.3.14. Clinical outcomes (Cohorts A, C and D)

Both investigator-reported and adjudicated events will be recorded.

3.3.14.1. Hierarchical composite endpoint of time to cardiovascular death, number of worsening HF events (hospitalization for HF, or urgent HF visit), time to first worsening HF event and change from baseline in KCCQ-23 CSS at Week 22

The time (days) to cardiovascular death will be calculated for each participant.

The number of hospitalizations for HF and the number of urgent HF visits, over the 22 weeks, will be calculated for each participant. The total number of these worsening heart failure events will also be calculated for each participant, as well as the total number divided by the number of days of study participation (up to Week 22), where 'number of days of study participation' = time from randomization to Week 22, or to time lost-to-follow-up, withdrawal from study, or death. This total will then be multiplied by 154 days in order to provide a 22-week estimate. Similarly, the total number of combined cardiovascular deaths and worsening heart failure events will be calculated.

The composite HF outcome (cardiovascular death, hospitalization for HF or urgent HF visits) will be determined for each participant as well as each individual component as a first event.

The time (days) to first hospitalization for HF and the time (days) to first urgent HF visit will be calculated for each participant. The time to the first of these worsening HF events (hospitalization for HF or urgent HF visit) will also be calculated for each participant.

The change from baseline in KCCQ-23 CSS at Week 22 will be calculated (see Section 3.1.1).

3.3.14.2. Time to first occurrence of the clinical composite of cardiovascular death, hospitalization for HF, or urgent HF visit

The time (days) to the first occurrence of cardiovascular death or worsening HF events will be calculated.

3.3.14.3. Total number of days alive and out of the hospital over 22 weeks

The total number of days each participant is alive and out of the hospital (DAOH) over the 22 weeks will be calculated:

- For participants alive, lost to follow-up or withdrawal, at Week 22:
  - 'time on study' = time from randomization to Week 22, or to time lost-to-follow-up or withdrawal
  - 'hospitalization time' = sum of all the durations in hospital during the participant's 'time on study'
  - DAOH = 'time on study' – 'hospitalization time'
- For participants who die before Week 22:
  - 'time on study' = time from randomization to Week 22 (Day 155)
  - 'hospitalization time' = sum of all the durations in hospital during the participant's 'time on study'
  - DAOH = 'time on study' – 'hospitalization time' – number of days from the date of death to Week 22

Additionally, the number of days alive and out of the hospital divided by the number of days of study participation (%DAOH) will be calculated:

% DAOH = 100 * (DAOH / 'time on study').

3.3.14.4. Total number of hospitalizations for HF and urgent HF visits over 22 weeks

See Section 3.3.14.1.

3.3.15. Serum unbound and total ponsegromab PK parameters (Cohort B only)

Blood samples will be collected for measurement of serum unbound and total concentrations of ponsegromab as specified in the protocol.

The following PK parameters for unbound and total ponsegromab after 1st dose on Day 1 and 4th dose on Day 85, will be derived, using the PK concentration analysis set for the open-label, PK cohort, from the concentration-time profiles using noncompartment methods, as data permit.

Table 2. Derivation of Ponsegromab PK Parameters

Parameter	Day(s)	Definition	Method of Determination
AUC_{tau}	1, 85	Area under the plasma concentration-time profile from time zero to time tau, the dosing interval, where tau = 28 days for Q4W dosing.	Linear/Log trapezoidal method
C_{max}	1, 85	Maximum plasma concentration during the dosing interval	Observed directly from data
T_{max}	1, 85	Time for C_{max}	Observed directly from data as time of first occurrence
AUC_{tau} (dn)	1, 85	Dose normalized AUC_{tau}	AUC_{tau}/Dose
C_{max} (dn)	1, 85	Dose normalized C_{max}	C_{max}/Dose
C_{min}	1, 85	Minimum plasma concentration during the dosing interval	Observed directly from data
CL/F	85	Apparent clearance for oral dosing	Dose/AUC_{tau}
R_{ac}	85	Observed accumulation ratio	Day 85 AUC_{tau}/Day 1 AUC_{tau}
$R_{ac,Cmax}$	85	Observed accumulation ratio for C_{max}	Day 85 C_{max}/Day 1 C_{max}
PTR	85	Peak-to-trough ratio	C_{max}/C_{min}
$t_{½}$*	85	Terminal half-life	Loge(2)/kel, where kel is the terminal phase elimination rate constant calculated by a linear regression of the log-linear concentration-time curve
V_Z/F*	85	Apparent volume of distribution for oral dosing	Dose/(AUC_{tau} * kel)
*As data permits.			

3.3.16. Serum concentrations of GDF-15 on CCI [redacted] (Cohort B only)

See Section 3.3.10.

3.3.17. Incidence of ADA, and NAb (Cohort B only)

See Section 3.3.11.

3.3.18. Fold change from baseline in NT-proBNP at Weeks 12 and 16 (Cohort B only)

See Section 3.3.12.

3.4. Baseline Variables

Modified BMI (mBMI) will be calculated at baseline as:

$$\frac{weight\ at\ Day\ 1\ [kg]}{height\ at\ screening\ [m]^2} \times\ serum\ albumin\ at\ Day\ 1\ [g/L]$$

3.5. Safety Endpoints

The change from baseline for ECGs (heart rate, QT, QTcF, PR and QRS interval) will be calculated for all post baseline timepoints. The maximum increase from baseline over all measurements taken post-dose will be calculated for QTcF. The maximum increase from baseline will be calculated as the maximum change from baseline for a participant, except in the case where a participant does not show an increase. In such an instance, the minimum decrease should be taken.

Other safety endpoints are covered in Section 3.2.5.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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* (not including the open-label placebo administered in screening), *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* (not including

	the open-label placebo administered in screening), *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.* This will be the study intervention received by the participant for the majority of the timepoints during the study (not including the open-label placebo administered in screening). If a participant receives an equal number of different doses, then the lowest of those doses will be used. If a participant receives an equal number of placebo and a given dose of ponsegromab, the ponsegromab dose will be used.

Defined Analysis Set	**Description**
Censored	*All evaluable participants. For participants who discontinue study intervention or receive a prohibited procedure, all observations post-discontinuation* (i.e. last dose of IP +31 days)*, or post-procedure, will be censored and treated as missing data. For participants who miss a dose*, or receive an incomplete dose, *all observations post-missed*/incomplete *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.*
Complete	All evaluable participants. For participants who discontinue study intervention, receive a prohibited procedure and/or miss a dose, or receive an incomplete dose, all observations post-discontinuation, post-procedure or post-missed/incomplete dose will be included in the analysis set.
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], or open-label, PK cohort [Cohort B], Cohort C or Cohort D).*
PK parameter (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 [redacted]) concentration*

	value is reported, for any PD endpoint, for the given part of the study (Main Cohort [Cohort A], or 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], or open-label, PK cohort [Cohort B], Cohort C or Cohort D).*

4.1. Prohibited Procedures

Listings of non-drug treatment(s)/procedure(s) will be provided (see Section 6.5.5). These will be blinded tables and will be reviewed prior to database lock to determine which procedures would be classed as "prohibited".

4.2. Treatment Compliance

Treatment dosing will be reviewed prior to database lock to determine, for participants who miss a dose, or receive an incomplete dose, and resume (complete) dosing, whether their subsequent data may be included in the analysis. Subsequent data will be included immediately after (complete) IP dosing is resumed.

4.3. Incorrect Randomization

Participants who are randomized to the wrong stratum, in error, will have the incorrect stratum assignment remain in IMPALA but the clinical database will include the correct stratum. The latter will subsequently be used for all relevant analyses, if appropriate.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

Primary statistical inference will be based on the primary endpoint, change from baseline in KCCQ-23 CSS at Week 22. *The null hypothesis of no difference between ponsegromab and placebo will be tested* for the 300 mg dose group from Cohort A only. *The alternative hypothesis is that ponsegromab is superior to placebo.* The Type I error rate (α-level) used for the statistical inference will be 5% (1-sided). Each dose of ponsegromab will be compared separately with placebo. No adjustment for multiple comparisons will be made.

Similar hypotheses will be applied to the secondary efficacy endpoints (and selected exploratory efficacy endpoints), where the type I error rate will also be 5% (1-sided). Note the alternative hypothesis for the response endpoint is that ponsegromab is superior to placebo as shown by an odds ratio > 1. Note also that these additional inferences for the 300 mg ponsegromab treatment group will also be based on data from Cohort A only. Inference for the 100 and 200 mg ponsegromab treatment groups will be based on data from Cohorts A and C combined.

For all other endpoints, the results of any statistical analyses are for exploratory purposes only and there is no formal hypothesis testing.

There is no hypothesis testing planned for the open-label, PK cohort.

5.2. General Methods

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 in a separate CSR.

*For **safety analyses and PK/PD/immunogenicity analyses**, the Main Cohort (Cohort A) and Cohort C will be reported combined*, with data from the same treatment group combined across cohorts*; the open-label, PK cohort (Cohort B) will be reported separately; Cohort D will be reported separately.*

Efficacy analyses will be produced using 4 different approaches:

1. Main Cohort (Cohort A) only: *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.* Summaries will include data from all treatment groups.

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

3. Main Cohort (Cohort A) and Cohort C combined: *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.* Summaries will include data from all treatment groups. Data from the same treatment group will be combined across cohorts, and cohort will be added as a term in the statistical models.

4. Main Cohort (Cohort A) and Cohort D combined: These analyses will provide sensitivity analyses for the 300 mg ponsegromab treatment group, in participants with any serum GDF-15 concentration. Both summaries and statistical models will include data from the 300 mg ponsegromab treatment group and placebo only. Data from the same treatment group will be combined across cohorts, and cohort will be added as a term in the statistical models.

The analyses related to the primary, secondary and exploratory endpoints will be based on the appropriate population for analysis (see Section 4).

Unless otherwise stated, all summaries and plots will be presented by treatment group. The following treatment group labels (or similar) will be used:

Placebo
Ponsegromab 100 mg
Ponsegromab 200 mg
Ponsegromab 300 mg

A ponsegromab combined treatment group (combined over the ponsegromab doses, either within a single cohort or within combined cohorts) and an overall treatment group will also be presented for safety analyses.

5.2.1. Summaries for Continuous Endpoints

Unless otherwise stated, continuous variables will be presented using summary statistics: number of observations, arithmetic mean, standard deviation (SD), median, 25th and 75th percentiles, and range (minimum and maximum) values. For endpoints to be analyzed on the natural log scale ($\log_e$), the geometric mean and geometric coefficient of variation (CV) will additionally be presented.

5.2.2. Summaries for Categorical Endpoints

Categorical variables will be presented using summary statistics: number of observations and percentages.

5.2.3. Mixed Models Repeated Measures (MMRM) Analysis

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, baseline *LVEF, log GDF-15 concentration* from SV1, baseline *log NT-proBNP), as appropriate. Least squares means (and 90% CIs) and mean differences versus placebo (and 90% CIs and p-values*, for primary, secondary, and selected exploratory endpoints*) will be provided. No adjustments will be made for multiplicity.* In addition, the following plots will be produced:

- Profile plots of the LS means (and 90% CIs) over time, with a separate line for each treatment group
- Profile plots of the LS mean differences to placebo (and 90% CIs) over time, with a separate line for each dose of ponsegromab.

Standard SAS output will be provided to support the statistical summary table for the analysis model, but will not be included in the CSR.

Example SAS code is provided in Appendix 4.

Statistical Model Diagnostics

The presence of outliers will be investigated for this model. An outlier will be defined as any response data value with a studentized (conditional) residual greater than 3, or less than -3. A listing will be presented of any participants meeting these criteria and will be included with standard SAS output. The assumptions of normality will be verified graphically using residual plots. For each fitted model, a set of conditional studentized residual plots will be produced, including residual plot, histogram of normality, quantile-quantile (QQ) plot and summary of fit statistics. The residual plots will not be included in the CSR.

If there are outliers or major deviations from normality, then the effect of these on the conclusions may be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

5.2.4. Logistic Regression with multiple imputation

The logistic regression model will include baseline score *and treatment as fixed terms in the model. Additional terms may be fitted in the model (eg, cohort,* baseline *LVEF, log GDF-15 concentration* from SV1, baseline *log NT-proBNP), as appropriate*. Missing values (e.g. due to censoring) will be imputed for missing data using a multiple imputation method as described in Section 5.3. O*dds (and 90% CIs) and odds ratios versus placebo (and 90% CIs* [and p-values, for secondary endpoints]) *will be provided. No adjustments will be made for multiplicity.*

Standard SAS output will be provided to support the statistical summary table for the analysis model and multiple imputation approach, but will not be included in the CSR.

Example SAS code is provided in Appendix 4.

5.2.5. Analysis of Covariance (ANCOVA)

The ANCOVA model will include baseline and treatment as fixed terms in the model. Additional terms may be fitted in the model (eg, cohort, baseline LVEF, log GDF-15 concentration from SV1, baseline log NT-proBNP), as appropriate. Least squares means (and 90% CIs) and mean differences versus placebo (and 90% CIs) will be provided. No adjustments will be made for multiplicity. In addition, plots of LS means and differences (including 90% CIs for both) will be produced.

Standard SAS output will be provided to support the statistical summary table for the analysis model, but will not be included in the CSR.

Example SAS code is provided in Appendix 4.

Statistical Model Diagnostics

The presence of outliers will be investigated for this model. An outlier will be defined as any response data value with a studentized (conditional) residual greater than 3, or less than -3. A

listing will be presented of any participants meeting these criteria and will be included with standard SAS output. The assumptions of normality will be verified graphically using residual plots. For each fitted model, a set of conditional studentized residual plots will be produced, including residual plot, histogram of normality, quantile-quantile (QQ) plot and summary of fit statistics. The residual plots will not be included in the CSR.

If there are outliers or major deviations from normality, then the effect of these on the conclusions may be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

5.2.6. Logistic Regression without multiple imputation

The logistic regression model will include treatment as a fixed term in the model. Additional terms may be fitted in the model (eg, cohort, baseline LVEF, log GDF-15 concentration from SV1, baseline log NT-proBNP), as appropriate. Missing values (e.g. due to censoring) will not be imputed. Odds (and 90% CIs) and odds ratios versus placebo (and 90% CIs [and p-values, for selected endpoints]) will be provided. No adjustments will be made for multiplicity.

Standard SAS output will be provided to support the statistical summary table for the analysis model, but will not be included in the CSR.

Example SAS code is provided in Appendix 4.

5.2.7. Cumulative Incidence Plots

Cumulative incidence plots will be produced based on the time to the event of interest (starting from the time of start of dosing on Day 1; finishing at Week 22) for the treatment groups separately, on the same plot. This will be based on plotting the cumulative incidence function (with no competing risks), which will be presented as a percentage on the y-axis. Participants who discontinue from the study or from study intervention will be censored at the associated discontinuation date (i.e. date of death, study withdrawal, lost-to-follow-up, or last dose of IP +31 days). Number of participants at risk at each timepoint will be included in the plot.

Example SAS code is provided in Appendix 4.

5.2.8. Cox Proportional Hazards Model

The Cox proportional hazards model will include treatment as a fixed term in the model. Additional terms may be fitted in the model (eg, cohort, baseline LVEF, log GDF-15 concentration from SV1, baseline log NT-proBNP, baseline KCCQ-23 CSS), as appropriate. Hazard ratios versus placebo (and 90% CIs) will be provided. No adjustments will be made for multiplicity.

Standard SAS output will be provided to support the statistical summary table for the analysis model.

Example SAS code and further details of the statistical methodology is provided in Appendix 4.

5.2.9. Win-Ratio Approach

The unmatched win-ratio approach is a method for analysing hierarchical compositive endpoints, applying the following principle to all possible patient pairs between the treatment group and the control group (i.e. each patient in the treatment group is compared with every patient in the control group): -

- For any pair, the result for the most important outcome determines the "winner" (e.g. the one who dies later, if time to death is the most important outcome). If the winner cannot be determined, the second-most important outcome is considered, and so forth until the winner can be determined; otherwise the pair is tied.
- The win ratio is the ratio of winners to losers for the treatment group.

The unmatched win-ratio approach will only include the 300 mg ponsegromab and placebo treatment groups. The number of 'winners' and the number of 'losers' for ponsegromab 300 mg versus placebo will be provided, as well as the win-ratio (and 90% CI) versus placebo.

Example SAS code is provided in Appendix 4.

5.3. Methods to Manage Missing Data

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

5.3.1. Concentrations Below the Limit of Quantification

In all PD data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to the lower limit of quantification (LLQ).

In all PK data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero.

In listings, BLQ values (for PK, PD, and hsCRP) will be reported as "<LLQ", where LLQ will be replaced with the value for the LLQ, and BLQ values will be set to LLQ for certain analyses.

5.3.2. Deviations, Missing Concentrations and Anomalous Values

For PK and PD summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if one of the following cases is true:

1. A concentration has been collected as ND (i.e. not done) or NS (i.e. no sample),
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist/statistician.

5.3.3. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK and PD parameters.

If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (ie not calculated). (Note that NC values will not be generated beyond the day that a participant discontinues.)

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular dose with ≥3 evaluable measurements.

If an individual participant has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses. For PK parameter calculations, the sponsor standard rules will be applied.

5.3.4. Multiple Imputation

For summarizing the proportion of responses (e.g. in KCCQ-23 CSS), all change from baseline data from the censored analysis set will be included (i.e. all timepoints up to and including Week 22). A multiple imputation method will be implemented, using a multivariate imputation method by chained equations, which is still valid with an arbitrary missing data pattern. The model will include baseline score and treatment. Additional terms may also be included (eg, cohort, baseline LVEF, log GDF-15 concentration at SV1, baseline log NT-proBNP), as appropriate. Twenty sets of imputations of each missing value will be constructed from the multiple imputation method and the proportion of responses by treatment will be determined with associated standard errors utilizing a normal approximation and will be combined using standard multiple imputation techniques proposed by Rubin[1] to yield overall estimates and CIs. If there is more missing data in the study than anticipated, the number of imputation sets may be increased as required. Note that data for participants who die during the study will be included in the imputation but will then be classed as having a 'Non-response' after imputation.

For logistic regression, all change from baseline data from the censored analysis set will be included (i.e. all timepoints up to and including Week 22). The same imputed datasets as produced for the proportion of responses above will be utilized, where a Logistic Regression model (as described in Section 5.2.4) will be applied to each of the 20 imputed datasets separately. Parameter estimates, of the log odds for each treatment and log odds ratios for each dose relative to placebo, will be combined using standard multiple imputation techniques proposed by Rubin[1] to yield overall estimates of the log odds and log odds ratios and their associated standard errors and will be used to create 90% CIs on the log-odds scale. The log odds (and CIs) and log odds ratios (and CIs) will be back transformed into odds and odds ratios (and CIs) for final reporting.

5.3.5. PK Cohort (Cohort B) Participants

For participants in the PK cohort who previously screenfailed from the main cohort, their original screening data (CCI GDF-15, hematology, clinical chemistry, pregnancy test and OL placebo injection for tolerability) will be used if these tests are not repeated at time of rescreening and if rescreening is within 28 days of the original screening.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Change from baseline in KCCQ-23 CSS at Week 22 (Cohort A only)

Summaries and analyses will use efficacy approach 1, as described in Section 5.2.

6.1.1.1. Main Analysis

This analysis will be performed on the censored analysis set, as defined in Section 4.

Absolute values and changes from baseline in the KCCQ-23 CSS score will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.1. Tables will include baseline and all post-baseline timepoints.

Change from baseline in KCCQ-23 CSS at Week 22 will be analyzed using Estimand 1 and an MMRM model, as described in Section 5.2.3. *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* (as defined in Section 4) from Cohort A participants only. *Additional terms for* baseline *LVEF,* log CCI *GDF-15 concentrations* from SV1 *and* baseline log *NT-proBNP will be fitted in the model.*

Additional plots of LS means and differences (including 90% CIs for both), for Week 22 only, will be produced over treatment (for the primary endpoint only).

6.1.1.2. Sensitivity/Supplementary Analyses

A sensitivity analysis will be performed on the complete analysis set, as defined in Section 4. The analysis will mirror the main analysis as laid out in Section 6.1.1.1, but will use Estimand 1b (as described in Section 2.2.3).

Additionally, a supplementary analysis will be performed on the censored analysis set, as defined in Section 4. The summaries and analysis will mirror the main analysis as laid out in Section 6.1.1.1, but will be restricted to participants with a KCCQ-23 CSS score at baseline < 75.

6.2. Secondary Endpoint(s)

The efficacy analyses will be performed on the censored analysis sets, as defined in Section 4, and using efficacy approaches 1 and 3, as described in Section 5.2.

6.2.1. Change from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22 (Cohorts A and C)

Summaries and analyses will use efficacy approach 3 for all endpoints, as described in Section 5.2 and efficacy approach 1 for all endpoints other than CSS (which has already been detailed in Section 6.1).

KCCQ-23 CSS, OSS, TSS and physical limitation will each be summarized and analyzed across all timepoints, in a similar manner to the main analysis of the primary endpoint, as outlined in Section 6.1.1.1. This analysis will estimate the treatment effect related to Estimand 2 (as described in Section 2.2.4). Note that for efficacy approach 3, cohort will be included as a term in the statistical model.

For KCCQ-23 CSS score, a supplementary analysis will also be performed. The summaries and analysis will mirror that described above, but will be restricted to participants with a KCCQ-23 CSS score at baseline < 75.

6.2.2. Response as defined by a ≥5-point increase from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22 (Cohorts A and C)

Summaries and analyses will use efficacy approaches 1 and 3 for all endpoints, as described in Section 5.2.

Responses as defined by a ≥5-point increase in KCCQ-23 CSS, OSS, TSS, and physical limitation score will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.2, with no imputation for missing data. Tables will include all post-baseline timepoints. Plots of the percentages over time will also be produced, with all treatments on the same plot for each score.

The percentage of responses (and 90% CIs) at Week 22 will also be reported by treatment after multiple imputation for missing values as per Section 5.3.4. These responses *will* also *be analyzed separately using Estimand 3 and a logistic regression model* with multiple imputation (as described in Section 5.2.4), where missing values will be imputed using multiple imputation as per Section 5.3.4. *The* logistic regression *model will be fitted to the data at Week 22* only. Note that for efficacy approach 3, cohort will be included as a term in the statistical model.

For KCCQ-23 CSS score, a supplementary analysis will also be performed. The summaries and analysis will mirror that described above, but will be restricted to participants with a KCCQ-23 CSS score at baseline < 75.

6.2.3. Change from baseline in 6MWD at Week 22 (Cohorts A and C)

Summaries and analyses will use efficacy approaches 1 and 3, as described in Section 5.2.

6MWD will be summarized and analyzed across all timepoints, in a similar manner to the main analysis of the primary endpoint, as outlined in Section 6.1.1.1. This analysis will

estimate the treatment effect related to Estimand 4 (as described in Section 2.2.4). Note that for efficacy approach 3, cohort will be included as a term in the statistical model.

6.2.4. Change from baseline in PROMIS Fatigue 7a at Week 22 (Cohorts A and C)

Summaries and analyses will use efficacy approaches 1 and 3, as described in Section 5.2.

PROMIS Fatigue 7a will be summarized and analyzed across all timepoints, in a similar manner to the main analysis of the primary endpoint, as outlined in Section 6.1.1.1. This analysis will estimate the treatment effect related to Estimand 5 (as described in Section 2.2.4). Note that for efficacy approach 3, cohort will be included as a term in the statistical model.

6.2.5. Incidence of TEAEs, TESAEs, abnormal laboratory results and vital signs (All Cohorts [A, B, C and D])

For analysis of adverse events (AEs), laboratory abnormalities and vitals signs *the Main Cohort (Cohort A) and Cohort C will be reported combined*, with data from the same treatment group combined across cohorts*; the open-label, PK cohort (Cohort B) will be reported separately; Cohort D will be reported separately.* The safety analyses will use the corresponding safety analysis sets, defined in Section 4.

6.2.5.1. Adverse Events

Adverse events (Tier 1, 2 and 3 AEs as described in Section 3.2.5.1) will be summarized by treatment group (including ponsegromab combined) and overall, in accordance with sponsor reporting standards. The adverse events will be sorted in descending frequency within a system organ class. If applicable, subject discontinuations due to adverse events will be detailed and summarized.

Incidence and severity of TEAE and TESAE tables will additionally be produced ('All causality' and 'Treatment related', separately) to summarise the total number of adverse events by preferred term, which will be reported by treatment group (including ponsegromab combined) and overall.

TEAEs classed as Tier 2 events (except for the PK cohort) will each be tabulated by treatment group (including ponsegromab combined). The number and percentage of participants will be presented, along with the risk difference (and 95% confidence interval) between each dose of ponsegromab and placebo. No adjustment for multiplicity will be used.

Tier 2 TEAEs (except for the PK cohort) will also be presented graphically in two-panel plots; the left panel will present the proportions of TEAEs observed in a dose group of ponsegromab (including ponsegromab combined) and separately placebo, while the right panel will display the 95% confidence interval for the risk differences for each TEAE. A vertical line corresponding to the value of 0 will be added to the right-hand plot. Each panel will be paged by treatment group of ponsegromab.

Tier 2 TEAE outputs will be ordered in descending point estimate of risk difference within System Organ Class. If two or more events have the same frequency they will be sorted alphabetically by preferred term. Footnotes will be included on the tables to provide proper interpretation of confidence intervals and to describe how the comparison was conducted, e.g. "Confidence intervals are not adjusted for multiplicity and should be used for screening purposes only. 95% Confidence intervals are provided to help gauge the precision of the estimates for Risk Difference. Risk Difference is computed as ponsegromab versus placebo."

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

TEAE classed as Tier 1 events (except for the PK cohort) will be tabulated by treatment group. The number and percentage of participants, reporting events listed in the pre-specified Tier 1 list, will be tabulated by treatment group (with ponsegromab treatment groups combined only) and overall, and by severity. Note that Tier 1 events are not planned to be presented graphically due to the small number of expected events.

Note that Tier 1 and 2 events will not be presented for the open-label, PK cohort (Cohort B).

Injection site reactions (ISR) will also be summarized by treatment group (including ponsegromab combined) and overall, in accordance with sponsor reporting standards. The ISRs will be sorted in descending frequency within a system organ class. Incidence and severity of ISR tables will additionally be produced ('All causality' and 'Treatment related', separately) to summarise the total number of ISR by preferred term, which will be reported by treatment group (including ponsegromab combined) and overall.

Potential immunogenic AEs will be summarized by medical evaluation category (see Section 3.2.5.1) and treatment groups (including ponsegromab combined) and overall.

6.2.5.2. Laboratory Results

Laboratory data will be listed and summarized by treatment group (including ponsegromab combined) and overall, in accordance with the sponsor reporting standards.

Absolute values and change from baseline at Week 22 in lipid panel endpoints (total cholesterol, HDL-cholesterol, non-HDL-cholesterol, calculated LDL cholesterol and triglycerides) will be summarized by treatment group (including ponsegromab combined) and overall.

6.2.5.3. Vital Signs

Absolute values and changes from baseline in vital signs (supine systolic and diastolic blood pressure and pulse rate) will be summarized by treatment group (including ponsegromab combined) and overall, and timepoint, according to sponsor reporting standards.

In addition (except for the PK cohort), changes from baseline will be analyzed using an MMRM model, as described in Section 5.2.3. The MMRM model will be fitted to the change from baseline at all post-treatment timepoints up to Week 22 using the safety analysis set (as defined in Section 4). Additional terms for baseline LVEF, log GDF-15 concentrations from SV1 and baseline log NT-proBNP may be fitted in the model. The Main Cohort (Cohort A) and Cohort C will be reported combined, with data from the same treatment group combined across cohorts; Cohort D will be reported separately. Note that cohort will be included as a term in the statistical model when analysis includes data from more than one cohort.

Maximum increase/decrease from baseline for supine systolic and diastolic blood pressures and maximum increase/decrease from baseline for supine pulse rate will be summarized by treatment group (including ponsegromab combined) and overall, according to sponsor reporting standards.

Maximum absolute values and changes from baseline for supine vital signs will also be summarized descriptively by treatment group (including ponsegromab combined) and overall, using categories as defined in Appendix 5. Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post dose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

6.3. Other Endpoint(s)

Unless otherwise stated these analyses will be performed on the censored analysis sets, as defined in Section 4, using efficacy approaches 1, 3 and 4, as described in Section 5.2, unless otherwise stated.

6.3.1. Change from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22 (Cohorts A and D combined)

Analyses will use efficacy approach 4, as described in Section 5.2.

KCCQ-23 CSS, OSS, TSS and physical limitation will each be summarized and analyzed across all timepoints, in a similar manner to the main analysis of the primary endpoint, as outlined in Section 6.1.1.1. Note that cohort will be included as a term in the statistical model.

For KCCQ-23 CSS score, a supplementary analysis may also be performed. The summaries and analysis will mirror that described above, but will be restricted to participants with a KCCQ-23 CSS score at baseline < 75.

6.3.2. Response as defined by a ≥5-point increase from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22 (Cohorts A and D combined)

Analyses will use efficacy approach 4, as described in Section 5.2.

Responses as defined by a ≥5-point increase in KCCQ-23 CSS, OSS, TSS, and physical limitation score will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.2, with no imputation for missing data. Tables will include all post-baseline timepoints. Plots of the percentages over time will also be produced, with all treatments on the same plot for each score.

The percentage of responses (and 90% CIs) at Week 22 will also be reported by treatment after multiple imputation for missing values as per Section 5.3.4. These responses will also be analyzed separately using a logistic regression model with multiple imputation (as described in Section 5.2.4), where missing values will be imputed using multiple imputation as per Section 5.3.4. The logistic regression model will be fitted to the data at Week 22 only. Note that cohort will be included as a term in the statistical model.

For KCCQ-23 CSS score, a supplementary analysis may also be performed. The summaries and analysis will mirror that described above, but will be restricted to participants with a KCCQ-23 CSS score at baseline < 75.

6.3.3. Change from baseline in 6MWD at Week 22 (Cohorts A and D combined)

Analyses will use efficacy approach 4, as described in Section 5.2.

6MWD will be summarized and analyzed across all timepoints, in a similar manner to the main analysis of the primary endpoint, as outlined in Section 6.1.1.1. Note that cohort will be included as a term in the statistical model.

6.3.4. Change from baseline in PROMIS Fatigue 7a at Week 22 (Cohorts A and D combined)

Analyses will use efficacy approach 4, as described in Section 5.2.

PROMIS Fatigue 7a will be summarized and analyzed across all timepoints, in a similar manner to the main analysis of the primary endpoint, as outlined in Section 6.1.1.1. Note that cohort will be included as a term in the statistical model.

6.3.5. Response as defined by a ≥10-point and ≥15-point increase in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22 (Cohorts A, C and D)

Summaries and analyses will use efficacy approaches 1, 3 and 4 for all endpoints, as described in Section 5.2.

Responses as defined by a ≥10-point and ≥15-point increase in KCCQ-23 CSS, OSS, TSS, and physical limitation score will each be summarized, with no imputation for missing data, in a similar manner to the secondary endpoint, as outlined in 6.2.2. Note that for efficacy approaches 3 and 4, cohort will be included as a term in the statistical model.

For KCCQ-23 CSS score, a supplementary analysis may also be performed. Thes summaries will mirror that described above, but will be restricted to participants with a KCCQ-23 CSS score at baseline < 75.

6.3.6. Absolute and change from baseline in PGI-S at Week 22 and PGI-C at Week 22 (Cohorts A, C and D)

Summaries and analyses will use efficacy approaches 1, 3 and 4 for all endpoints, as described in Section 5.2.

Absolute values and change from baseline in PGI-S will be summarized descriptively by treatment group and timepoint as described in Section 5.2.2.

Absolute values in PGI-C will be summarized descriptively by treatment group and timepoint as described in Section 5.2.2.

6.3.7. Change from baseline in body weight at Week 22 (Cohorts A, C and D)

Summaries and analyses will use efficacy approaches 1, 3 and 4 for all endpoints, as described in Section 5.2.

Body weight will be summarized and analyzed across all timepoints, in a similar manner to the main analysis of the primary endpoint, as outlined in Section 6.1.1.1. Note that for efficacy approaches 3 and 4, cohort will be included as a term in the statistical model.

6.3.8. Change from baseline in daily activity measures based on accelerometry at Week 22 (Cohorts A, C and D)

Summaries and analyses will use efficacy approaches 1, 3 and 4 for all endpoints, as described in Section 5.2.

The priority daily activity endpoints will each be summarized, across all timepoints, in a similar manner to the main analysis of the primary endpoint, as outlined in Section 6.1.1.

Change from baseline in each of the endpoints will be analyzed using an ANCOVA model, as described in Section 5.2.5, using the Censored analysis sets (as defined in Section 4). Additional terms for cohort, baseline LVEF, log GDF-15 concentrations from SV1 and baseline log NT-proBNP will be fitted in the model, as appropriate. Note that for efficacy approaches 3 and 4, cohort will be included as a term in the statistical model.

The remaining additional daily activity endpoints will not be included in the CSR.

6.3.9. Serum unbound and total ponsegromab concentrations on Day 1 (predose) and Weeks 4, 8, 12, 16, 20, 22, 24, and 32 (Cohorts A, C and D)

PK analyses will be performed using the PK concentration analysis sets, as defined in Section 4. The Main Cohort (Cohort A) and Cohort C will be reported combined, with data from the same treatment group combined across cohorts; Cohort D will be reported separately.

Presentations for serum unbound and total concentrations of ponsegromab will include: -

- A listing of concentrations sorted by treatment group, participant and timepoint. The concentration listing will also include the actual times.
- A summary of concentrations by treatment group and timepoint, where the set of statistics will include n, arithmetic mean, SD, coefficient of variation (CV%), minimum, Q1, median, Q3, maximum, geometric mean, geometric CV%, and the number of concentrations above the LLQ
- Median concentration-time plot (on a semi-log scale, all treatments on the same plot), Q1 and Q3 may be included
- Mean (±SD) concentration-time plot (on a semi-log scale, all treatments on the same plot).
- Median trough concentration-time plot (on a linear scale, all treatments on the same plot), Q1 and Q3 may be included.
- Mean (±SD) trough concentration-time plot (on a linear scale, all treatments on the same plot).

6.3.10. Serum concentrations of GDF-15 on CCI [redacted] (Cohorts A, C and D)

PD analyses will be performed using the PD analysis sets, as defined in Section 4. The Main Cohort (Cohort A) and Cohort C will be reported combined, with data from the same treatment group combined across cohorts; Cohort D will be reported separately.

Presentations for CCI [redacted] GDF-15 serum concentration levels will include: -

- A listing of concentrations sorted by treatment group, participant and timepoint. The listing will also include the fold change from baseline and a column to indicate whether the absolute concentration value is below the healthy volunteer median level or not
- A summary of concentrations (absolute values and fold changes from baseline) by treatment group and timepoint, where the set of statistics will include (as data permit) n, arithmetic mean, SD, CV%, minimum, Q1, median, Q3, maximum, geometric mean, geometric CV% and the number of concentrations above the LLQ
- A summary of whether the absolute CCI [redacted] GDF-15 concentration value is below the healthy volunteer median level or not, by treatment group and timepoint, as described in Section 5.2.2
- Median concentration-time plots (for absolute values only) (on a linear scale, all treatments on the same plot), Q1 and Q3 may be included
- Mean (±SD, if appropriate) concentration-time plots (for absolute values only) (on a linear scale, all treatments on the same plot).

In all presentations, the fold changes will be presented as percent change from baseline ([fold change from baseline -1]*100).

6.3.11. Incidence of anti-ponsegromab antibodies (ADAs), and neutralizing antibodies (NAb) (Cohorts A, C and D)

Immunogenicity analyses will be performed on the immunogenicity analysis sets, as defined in Section 4. The Main Cohort (Cohort A) and Cohort C will be reported combined, with data from the same treatment group combined across cohorts; Cohort D will be reported separately.

Immunogenicity analyses will include:

- A listing of ADA and NAb results for all participants and, if appropriate, a listing of ADA and NAb data, including onset, duration, and titer for all ADA-positive participants
- A summary (both table and figure, if appropriate) of the overall incidence of ADA, incidence of NAb, as well as the percentage of participants who are ADA positive and NAb positive at each timepoint.

If appropriate (e.g. the number of ADA-positive participants is ≥3), the additional analyses below may be performed:

- A spaghetti plot of individual participant ADA and NAb titer over time
- A summary of ADA and NAb titer by time
- Analysis of unbound and total ponsegromab concentration by ADA and NAb status. This may include summary tables and box and/or spaghetti plots of concentration data by ADA and NAb status
- Analysis of unbound and/or total ponsegromab concentration by ADA and NAb titer tertile which may include summary tables and box plots of concentration data by titer tertile
- Analysis of CCI [redacted] GDF-15 concentration (as data permit) by ADA and NAb status which may include summary tables and box and/or spaghetti plots of concentration data by ADA and NAb status
- Analysis of CCI [redacted] GDF-15 concentration (as data permit) by ADA and NAb titer tertile which may include summary tables and a box plot of concentration data by titer tertile
- An individual plot of unbound and total ponsegromab concentration, CCI [redacted] GDF-15 concentration (as data permit), ADA and NAb titer in ADA-positive participants.

6.3.12. Fold change from baseline in NT-proBNP, hsCRP, albumin and pre-albumin at Week 22 (Cohorts A, C and D)

Summaries and analyses will use efficacy approaches 1, 3 and 4 for all endpoints, as described in Section 5.2.

For each analyte, the absolute values and fold changes from baseline will be summarized, across all timepoints, in a similar manner to the main analysis of the primary endpoint, as outlined in Section 6.1.1.

Fold change from baseline in NT-proBNP will be analyzed (on the $\log_e$ scale) across all timepoints, in a similar manner to the main analysis of the primary endpoint (with baseline on the $\log_e$ scale), as outined in Section 6.1.1. Note that for efficacy approaches 3 and 4, cohort will be included as a term in the statistical model.

Fold change from baseline in hsCRP, albumin and pre-albumin will be analyzed (on the $\log_e$ scale) using an ANCOVA model (with baseline on the $\log_e$ scale), as described in Section 5.2.5, using the Censored analysis sets (as defined in Section 4). Additional terms for cohort, baseline LVEF, log GDF-15 concentrations at SV1 and baseline log NT-proBNP will be fitted in the model, as appropriate. Note that for efficacy approaches 3 and 4, cohort will be included as a term in the statistical model.

All LS means and LS mean differences (including confidence intervals) will be back-transformed to give geometric LS means and ratios of geometric LS means.

6.3.13. Fold change from baseline in CCI (Cohorts A, C and D) and CCI (Cohorts C and D only) at Weeks 12 and 22

For CCI analyses will use efficacy approaches 1, 3 and 4, as described in Section 5.2. For CCI analysis will be performed separately for Cohort C and Cohort D.

For each endpoint, the absolute values and fold changes from baseline will be summarized, across all timepoints, in a similar manner to the main analysis of the primary endpoint, as outlined in Section 6.1.1.

Fold change from baseline will be analyzed (on the $\log_e$ scale) across all timepoints, in a similar manner to the main analysis of the primary endpoint (with baseline on the $\log_e$ scale), as outined in Section 6.1.1. All LS means and LS mean differences (including confidence intervals) will be back-transformed to give geometric LS means and ratios of geometric LS means. Note that for efficacy approaches 3 and 4, cohort will be included as a term in the statistical model.

Additionally, the % reduction in CCI will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.2, using the following categories:

- $\geq 20\%$
- $\geq 30\%$
- $\geq 40\%$

This categorical summary will be produced overall and also split by CCI GDF-15 (dichotomised using $<$ or $\geq$ overall study median level (based on the overall safety population) [or an alternative cut-point, if appropriate]) and separately by presence/absence of cachexia (based on inclusion 5a).

6.3.14. Clinical outcomes (Cohorts A, C and D)

The following sections are applied to adjudicated clinical outcome events. Summaries and analyses will use efficacy approaches 1, 3 and 4 for all endpoints, as described in Section 5.2.

6.3.14.1. Hierarchical composite endpoint of time to cardiovascular death, number of worsening HF events (hospitalization for HF, or urgent HF visit), time to first worsening HF event and change from baseline in KCCQ-23 CSS at Week 22

The hierarchical composite will be analyzed using the unmatched, win-ratio approach, as described in Section 5.2.9.

Additionally, the number of participants with the composite HF outcome (cardiovascular death, hospitalization for HF or urgent HF visits), and the number of participants with each individual component as their first event, will be summarized descriptively by treatment group, as described in Section 5.2.2. The presentation will also include the total number of combined cardiovascular deaths and worsening HF events (HF hospitalizations and urgent HF visits), including the total number of each component, summarized descriptively by treatment group, as described in Section 5.2.2.

The number of participants with the composite HF outcome (cardiovascular death, hospitalization for HF or urgent HF visits) over 22 weeks will also be analyzed using a logistic regression model (as described in Section 5.2.6), without any multiple imputation.

6.3.14.2. Time to first occurrence of the clinical composite of cardiovascular death, hospitalization for HF, or urgent HF visit

Time to first occurrence of the clinical composite (and the individual components: HF hospitalization, urgent HF visit, worsening HF event, cardiovascular death) will be summarized descriptively by treatment group, as described in Section 5.2.1.

A cumulative incidence plot, as described in Section 5.2.7, will be produced for the time to first occurrence of the clinical composite.

Time to first occurrence of the clinical composite (and the individual components: HF hospitalization, urgent HF visit, worsening HF event, cardiovascular death) will be analyzed using a Cox proportional hazards model, as described in Section 5.2.8. Note that for efficacy approaches 3 and 4, cohort will be included as a term in the statistical model.

6.3.14.3. Total number of days alive and out of the hospital over 22 weeks

The total number of days alive and out of the hospital over 22 weeks (DAOH), and the total number of days divided by the number of days of study participation (%DAOH), will be summarized descriptively by treatment group, as described in Section 5.2.1.

6.3.14.4. Total number of hospitalizations for HF and urgent HF visits over 22 weeks

The number of hospitalizations for HF and urgent HF visits over 22 weeks, as well as the combined total of these worsening HF events, and the total number of combined cardiovascular deaths and worsening HF events, and the total numbers divided by the

number of days of study participation, will be summarized descriptively by treatment group, as described in Section 5.2.1.

6.3.15. Serum unbound and total ponsegromab PK (Cohort B only) (Cohort B only)

PK analyses will be performed using the PK concentration and PK parameter analysis sets, as defined in Section 4, for the open-label, PK cohort (Cohort B) only.

Presentations for serum unbound and total concentations of ponsegromab will be produced as described in Section 6.3.9.

Additionally, the PK parameters listed in Section 3.3.15 for Day 1 after 1st dose and/or Day 85 after 4th dose, will be listed and summarized descriptively by dose group and timepoint in accordance with Pfizer data standards, as data permit, and will include the set of summary statistics as specified in the table below. Missing values will be handled as detailed in Section 5.3.

Table 3. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
AUC_{tau}, C_{max}, AUC_{tau} (dn), C_{max} (dn), C_{min}, C_{trough} CL/F, R_{ac}, $R_{ac,Cmax}$, PTR and Vz/F	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{1/2}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

To assess the relationship between the PK parameters and dose, dose normalized AUC_{tau}, and C_{max} will be plotted against dose (using a logarithmic scale), and will include individual participant values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. The values will be dose normalized (to a 1 mg dose) by dividing the individual values and raw geometric means by dose.

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

6.3.16. Serum concentrations of GDF-15 on CCI [redacted] (Cohort Bonly)

PD analyses will be performed using the PD analysis set, as defined in Section 4, for the open-label, PK cohort (Cohort B) only.

Presentations for CCI [redacted] GDF-15 serum concentration levels will be produced as described in Section 6.3.10.

6.3.17. Incidence of ADA, and NAb (Cohort B only)

Immunogenicity analyses will be performed, as described in Section 6.3.11, using the immunogenicity analysis set, as defined in Section 4, for the open-label, PK cohort (Cohort B) only. In addition, if appropriate, analysis of PK parameters (e.g AUC_{tau}) by ADA and NAb status or titer tertile will be performed.

6.3.18. Fold change from baseline in NT-proBNP at Weeks 12 and 16 (Open-label, PK Cohort [Cohort B] only)

This analysis will be performed on the censored analysis set, as defined in Section 4, for the open-label, PK cohort (Cohort B) only.

The absolute and fold changes from baseline for NT-proBNP will be summarized descriptively by treatment group and timepoint, as described in Section 5.2.1. Tables will include baseline and all post-baseline timepoints.

6.4. Subset Analyses

Additional analyses will be performed on KCCQ-23 CSS, 6MWD, NT-proBNP, eGFR and body weight (weight loss subgroup factor only), to assess the effect of the following subgroup factors, if appropriate:

- Screening CCI GDF-15: dichotomised using < or ≥ overall study median level (or an alternative cut-point, if appropriate).
- Screening CCI GDF-15: split by overall study quartile levels.
- 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 not

These analyses will be performed on the censored analysis sets, as defined in Section 4, using efficacy approaches 1, 3 and 4, as described in Section 5.2.

For each subgroup factor, absolute values and changes from baseline (or fold change from baseline, if appropriate) will be summarized descriptively by subgroup factor, treatment group and timepoint, as described in Section 5.2.1. Tables will include baseline and all post-baseline timepoints.

For each subgroup factor, change from baseline (or fold change from baseline, if appropriate) will be analyzed as described in Sections 6.1.1.1, 6.2.3, 6.3.12 and 6.3.13. Additional terms for the subgroup factor and its interaction with treatment group, time and the treatment-by-time interaction, will be included in the model. Other terms (eg, cohort, baseline LVEF, NYHA classification, GDF-15 concentration from SV1, baseline NT-proBNP) may be dropped from the model, as appropriate. Least squares means (and 90% CIs) and mean differences versus placebo (and 90% CIs) will be provided (and will be back-transformed to give geometric LS means and ratios of geometric LS means, if appropriate). No adjustments will be made for multiplicity. If the MMRM model cannot be fitted to the data, or the model is deemed inappropriate, the model may be simplified, or the analysis may not be performed.

Note that for efficacy approaches 3 and 4, cohort will be included as a term in the statistical model.

Additionally, screening CCI GDF-15 will be plotted vs Week 22 change from baseline (or fold change from baseline, as appropriate) for KCCQ-23 CSS, 6MWD, NT-proBNP and eGFR using a scatterplot. The plot will include all participants and may be colored/trellised by treatment group and other participant characteristics (e.g. cohort, NYHA, LVEF).

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Baseline summaries will be produced. The Main Cohort (Cohort A) and Cohort C will be reported combined, with data from the same treatment group combined across cohorts; the open-label, PK cohort (Cohort B) will be reported separately; Cohort D will be reported separately. Demographic data, prior and concomitant medications, GDF-15 concentrations (at screening, using the CCI assay), height (at screening), weight, BMI and mBMI (at baseline) and KCCQ-23 scores (at screening and baseline) will be summarized, as defined in Section 5.2.1 or 5.2.2 as appropriate. *In addition, a subset of medical history data will be reported; this may include* LVEF, etiology of HF, NYHA class, eGFR and whether the participant experienced a prior HF hospitalization*, 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.

6.5.2. Study Conduct and Participant Disposition (All Cohorts [A, B, C and D])

Participant evaluation groups will show participant disposition for each phase of the study (screening, double blind treatment and follow-up) and will additionally show which participants were analyzed for efficacy as well as for safety. Frequency counts and percentages will be supplied for participant discontinuation(s) (including reasons for discontinuation, e.g. lost to follow-up, withdrawal, death) by treatment group. The Main Cohort (Cohort A) and Cohort C will be reported combined, with data from the same treatment group combined across cohorts; the open-label, PK cohort (Cohort B) will be reported separately; Cohort D will be reported separately.

6.5.3. Retained Research Samples and other exploratory plasma biomarkers

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.

6.5.4. Population PK

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.

6.5.5. Concomitant Medications and Nondrug Treatments/Procedures (All Cohorts [A, B, C and D])

All prior and concomitant medication(s) as well as non-drug treatment(s)/procedure(s) will be reported according to current sponsor reporting standards. The Main Cohort (Cohort A) and Cohort C will be reported combined, with data from the same treatment group combined across cohorts; the open-label, PK cohort (Cohort B) will be reported separately; Cohort D will be reported separately. Similarly, the prior heart failure medications will be reported.

6.5.6. Treatment Compliance (All Cohorts [A, B, C and D])

A summary table of treatment compliance will be produced according to current sponsor reporting standards. The Main Cohort (Cohort A) and Cohort C will be reported combined, with data from the same treatment group combined across cohorts; the open-label, PK cohort (Cohort B) will be reported separately; Cohort D will be reported separately.

6.6. Safety Summaries and Analyses

6.6.1. Electrocardiograms (All Cohorts [A, B, C and D])

Analysis of ECGs will be performed using the corresponding safety analysis sets defined in Section 4. The *Main Cohort (Cohort A) and Cohort C will be reported combined*, with data from the same treatment group combined across cohorts*; the open-label, PK cohort (Cohort B) will be reported separately; Cohort D will be reported separately.*

Absolute values and changes from baseline in ECGs (heart rate, QT, QTcF, PR and QRS interval) will be summarized by treatment group (including ponsegromab combined) and overall, and timepoint, according to sponsor reporting standards. Tables will be paged by parameter.

Maximum increase from baseline for QTcF will be summarized by treatment group (including ponsegromab combined) and overall, according to sponsor reporting standards.

Maximum absolute values and changes from baseline for QTcF, PR and QRS will also be summarized descriptively by treatment group (including ponsegromab combined) and overall, using categories as defined in Appendix 5. Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned postdose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

Listings of participants with any single post dose value > 500 msec will also be produced for QTcF.

7. INTERIM ANALYSES

7.1. Introduction

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 the Protocol.

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 an additional interim analysis SAP or included in this main 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 of the Protocol *and will be further documented in an E-DMC charter.*

7.2. Interim Analyses and Summaries

Details of the ongoing unblinded safety reviews will be provided in the IRC/E-DMC charters.

7.2.1. Interim Analysis #1

An interim analysis is planned to be conducted after approximately 70% of randomized participants in the Main Cohort (Cohort A) reach the Week 22 visit or discontinue the study prior to that visit.

The participants to be included in the interim analysis are:

Interim Population	Description
Interim Safety Population	All Main Cohort (Cohort A) participants randomized prior to the date of data cutoff (08OCT2024).
Interim Efficacy Population	Main Cohort (Cohort A) participants who were randomized up to, and including, 07MAY2024, and complete the double-blind treatment phase

All interim analyses will be carried out using the relevant Analysis Set (as defined in Section 4) applied to the Interim Populations described above. Analyses will include data from the Main Cohort (Cohort A) only.

7.2.1.1. Efficacy Endpoints

A subset, or all, of the following efficacy analyses will be produced: -

For **KCCQ-23 CSS, 6MWD, NT-proBNP, hsCRP and eGFR**, the descriptive summaries and main statistical analyses, described in Sections 6.1.1.1, 6.2.3, 6.3.12 and 6.3.13, will be performed. The statistical analyses will only include the 300 mg dose group and placebo. Additionally, Bayesian predictive probabilities will be calculated for the 300 mg dose group versus placebo, for end of study success based on the MMRM/ANCOVA results at Week 22 (and additionally Week 12 for eGFR). The predictive probabilities will be calculated using the method described by Grieve (1991)[2], incorporating vague priors. Additionally, the categorical summaries will be produced for eGFR, as described in Section 6.3.13.

Additional subgroup analysis will be performed on KCCQ-23 CSS, 6MWD, NT-proBNP and eGFR, for screening CCI GDF-15 values (dichotomized using overall study median level) and cachexia presence/absence, as described in Section 6.4, excluding the descriptive summaries of absolute values. Summaries and analyses will only include the 300 mg dose group and placebo.

Note that eGFR summaries and analyses will be produced in separate outputs for the interim analysis.

For **total vector magnitude** and **non-sedentary physical activity**, the descriptive summaries described in Section 6.3.8, will be produced.

The number of participants with the **composite HF outcome** (cardiovascular death, hospitalization for HF or urgent HF visit) will be summarized and analyzed (using logistic regression), as described in Section 6.3.14.1. The statistical analyses will only include the 300 mg dose group and placebo. Additionally, Bayesian predictive probabilities will be calculated for the 300 mg dose group versus placebo, for end of study success based on the logistic regression results. The predictive probabilities will be calculated using the method described by Grieve (1991)[2], incorporating vague priors.

The time to the first occurrence of the clinical composite will be summarized and analyzed as described in Section 6.3.14.2. The plot and statistical analysis will only include the 300 mg dose group and placebo.

Note that the invetstigator-reported clinical outcome events will be used for this interim analysis.

7.2.1.2. Safety Endpoints

Adverse events, laboratory abnormalities and vitals will be summarized and analyzed as described in Section 6.2.5 and Section 6.6.1. A subset of these outputs, previously agreed with the C3651011 E-DMC, will be produced. Additional outputs for **lipid panel endpoints**, as described in Section 6.2.5.2 will also be produced.

7.2.1.3. Other Summaries

Baseline summaries will be produced, as described in Section 6.5.1, for both the interim Safety and Efficacy populations.

Treatment compliance will be produced, as described in Section 6.5.6.

7.2.2. Interim Analysis #2

An additional interim analysis may be performed after 100% of the planned participants in the ponsegromab 300 mg and placebo arms in the Main Cohort (Cohort A) complete their study participation through Week 22.

All interim analyses will be carried out using the relevant Analysis Set (as defined in Section 4) using data from the Main Cohort (Cohort A) only. The analyses will similar to the analyses detailed for interim analysis #1, but without predictive probabilities.

Additionally, for **body weight**, the descriptive summaries and statistical analysis, described in Section 6.3.7, will be performed. The statistical analysis will only include the 300 mg dose group and placebo. Additional subgroup analysis will be performed on body weight, for cachexia presence/absence, as described in Section 6.4, excluding the descriptive summaries of absolute values. This summary and analysis will only include the 300 mg dose group and placebo.

Additional outputs may also be produced, if required.

8. REFERENCES

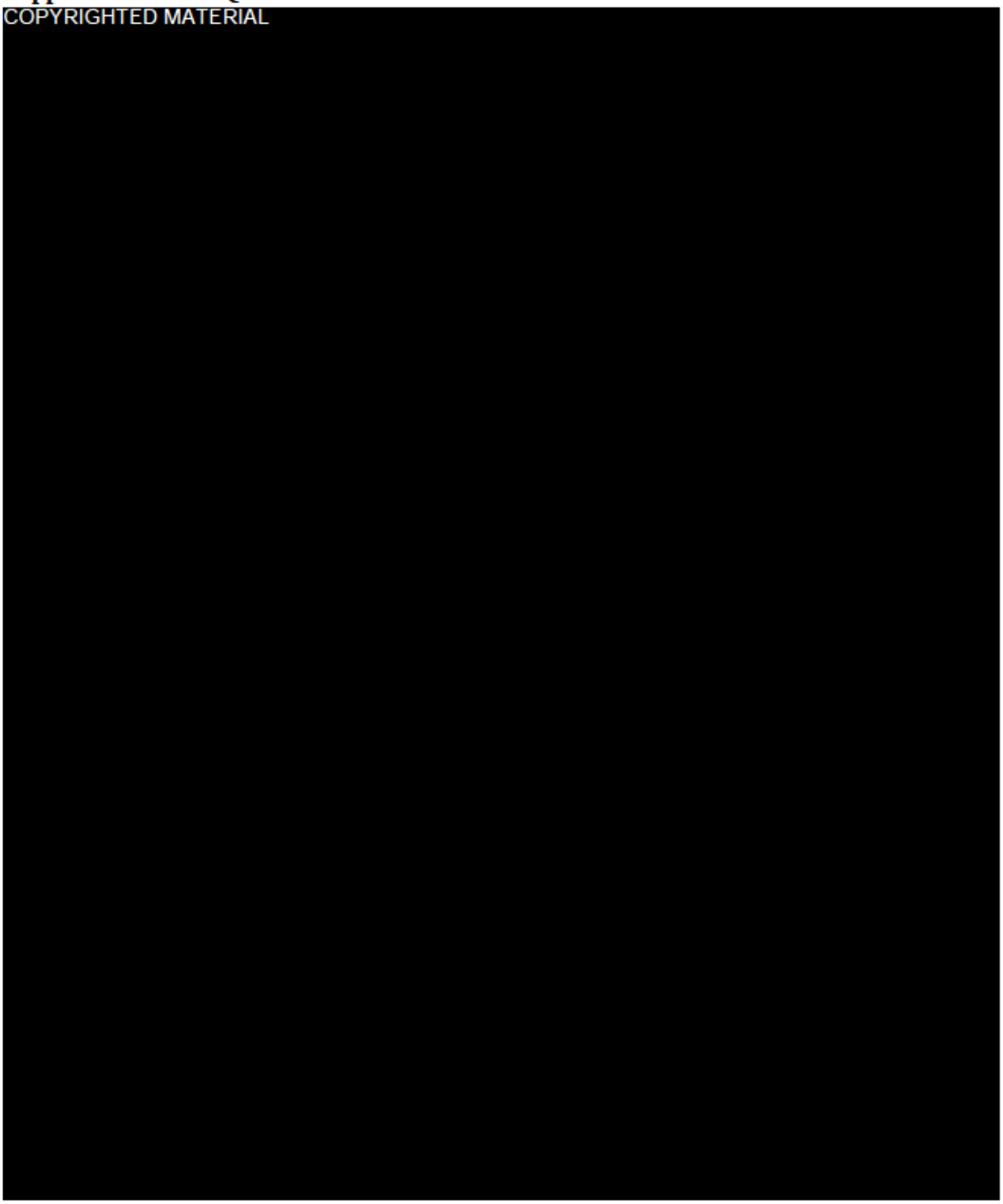
1. Rubin DB. Multiple Imputation for Nonresponse in Surveys. 1987; Wiley, New York.

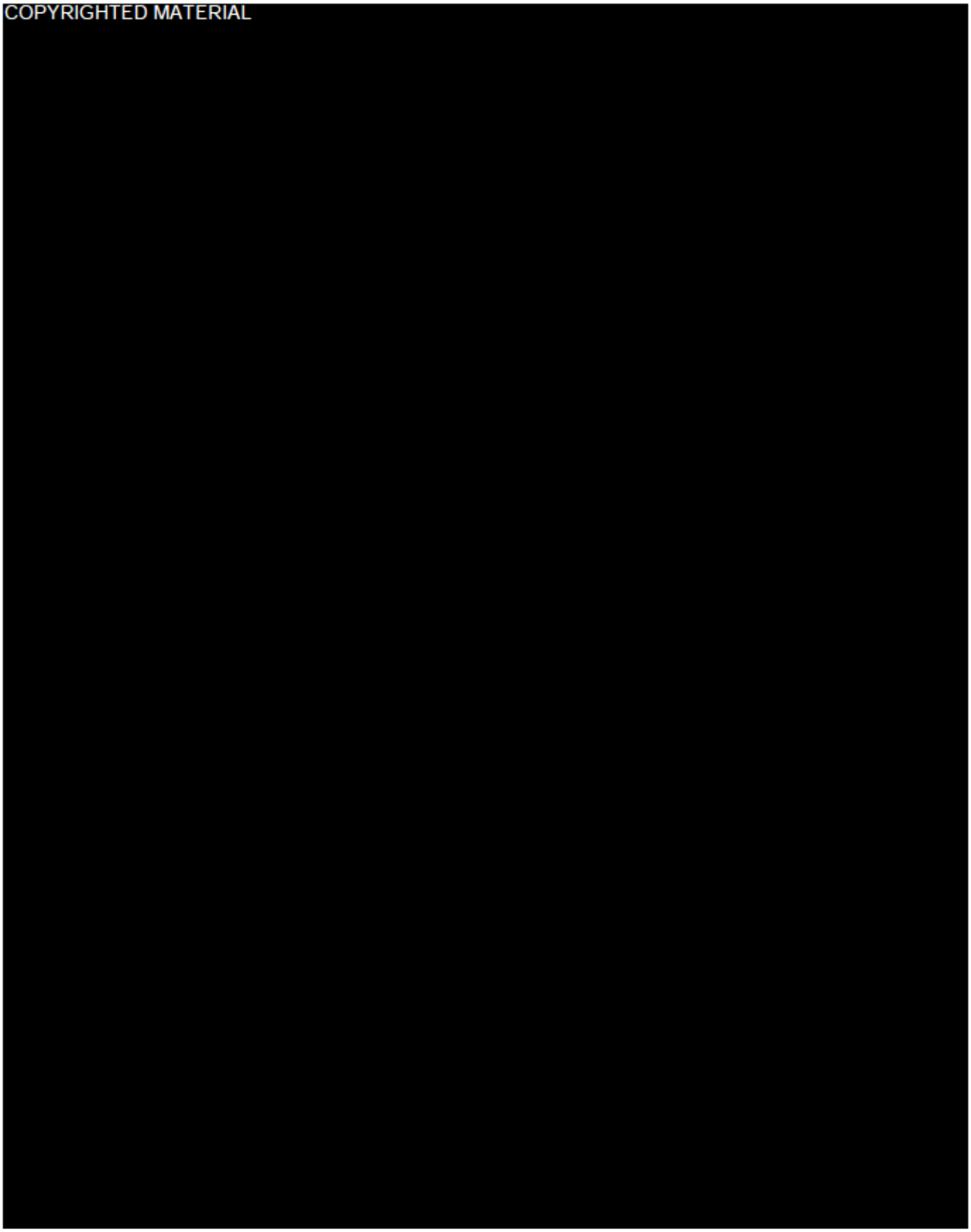
2. Grieve AP (1991) Predictive probability in clinical trials: Biometrics, 47(1) 323-9.

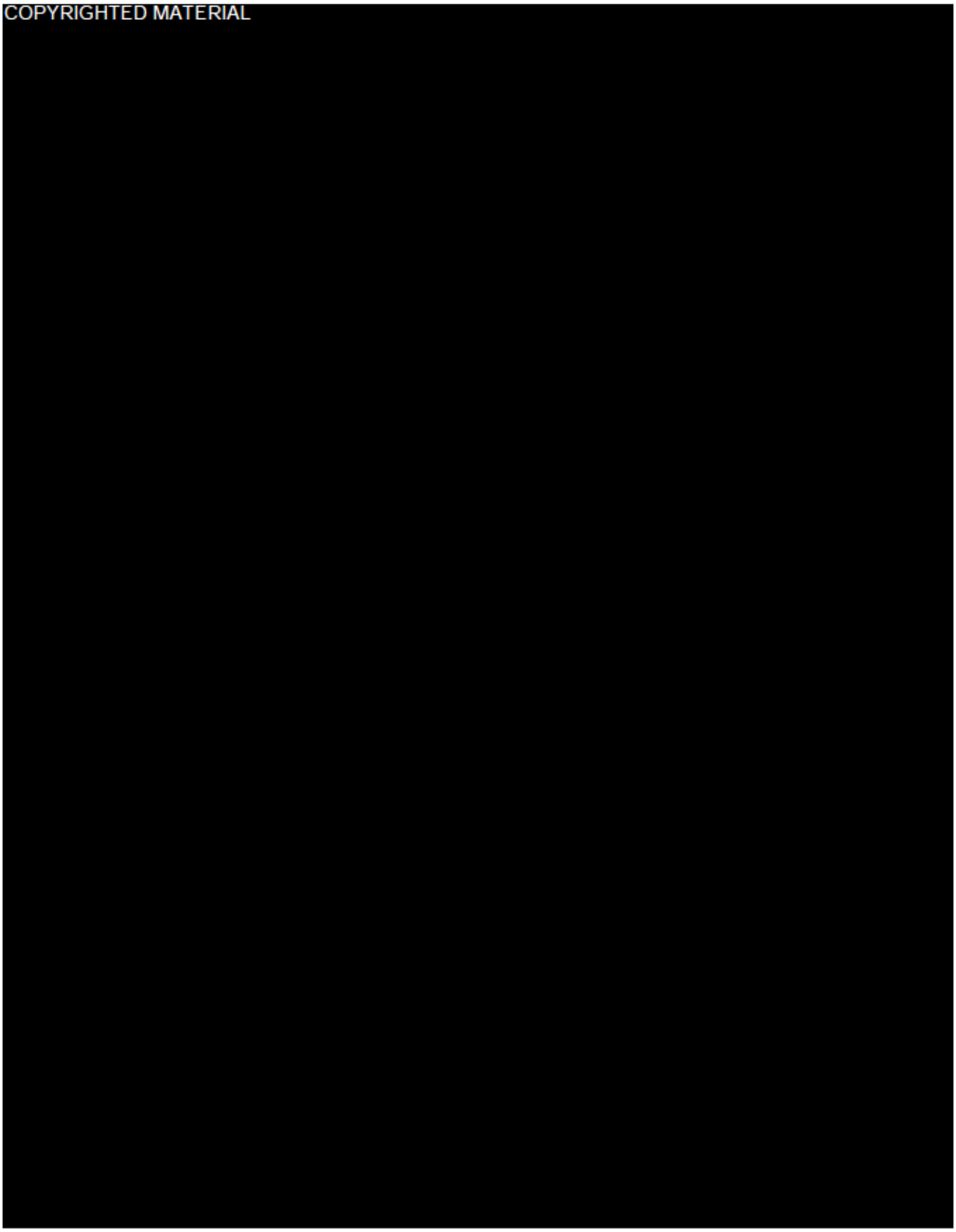
9. APPENDICES

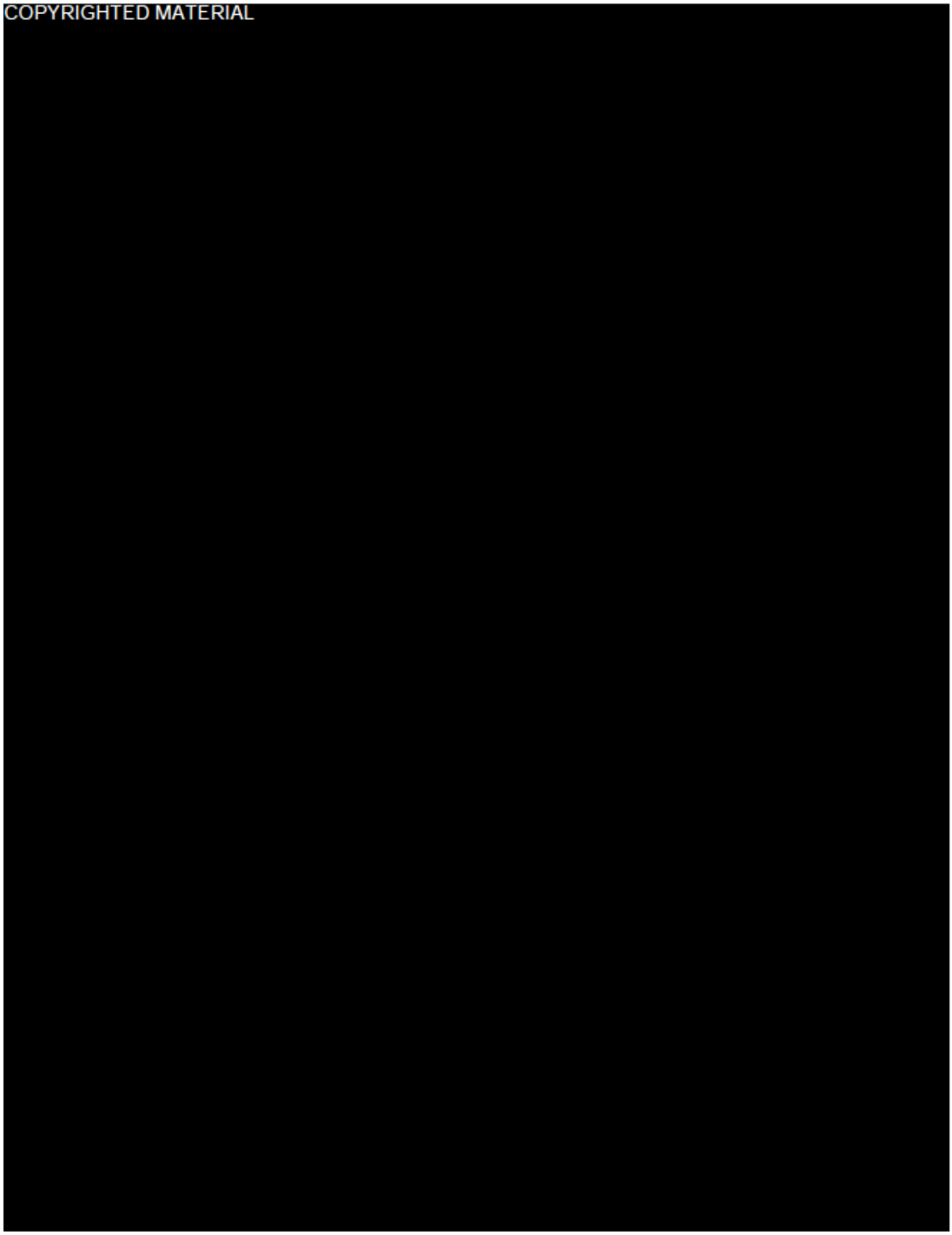
Appendix 1. KCCQ-23

Appendix 1.1. Full Questionnaire



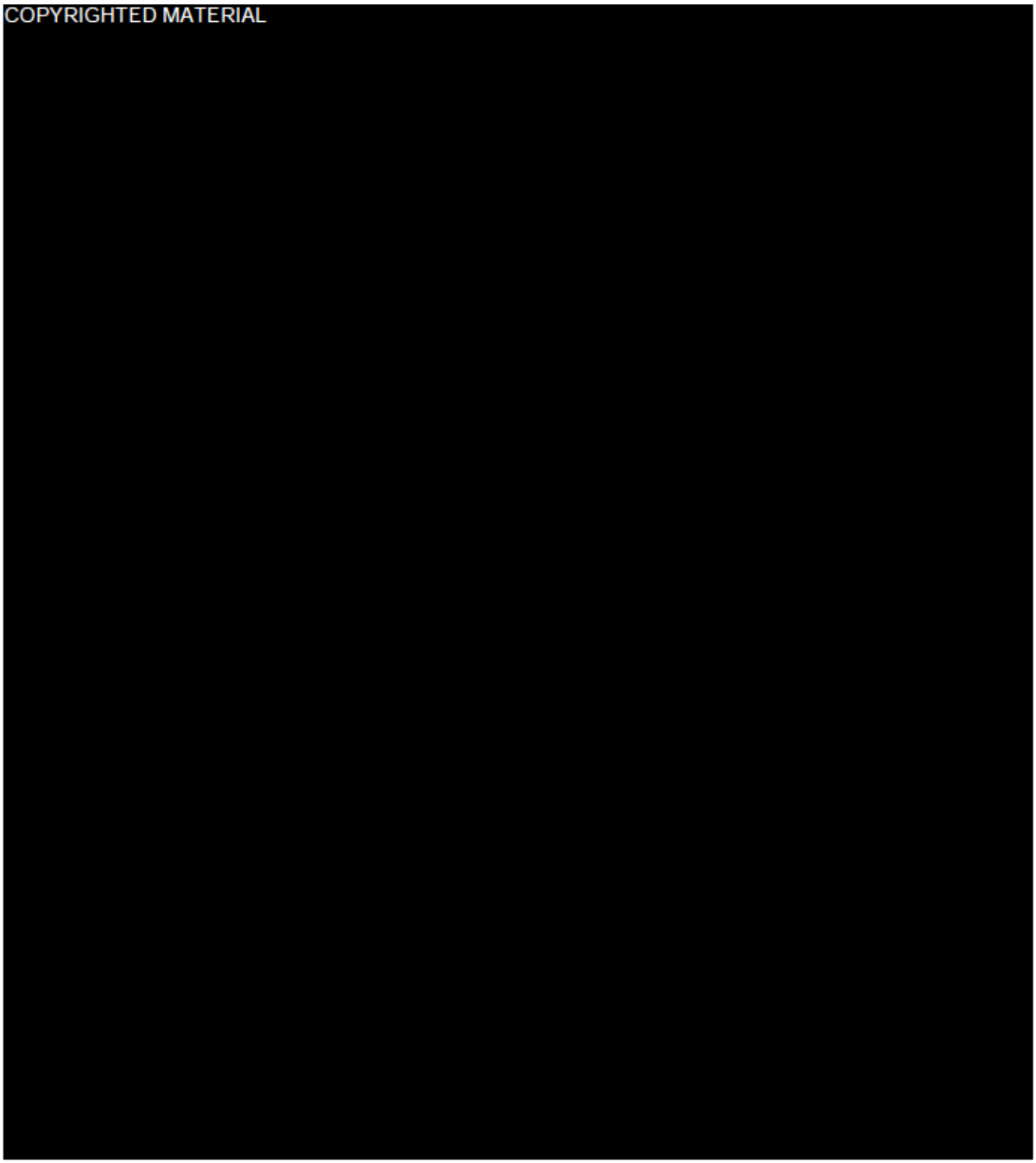


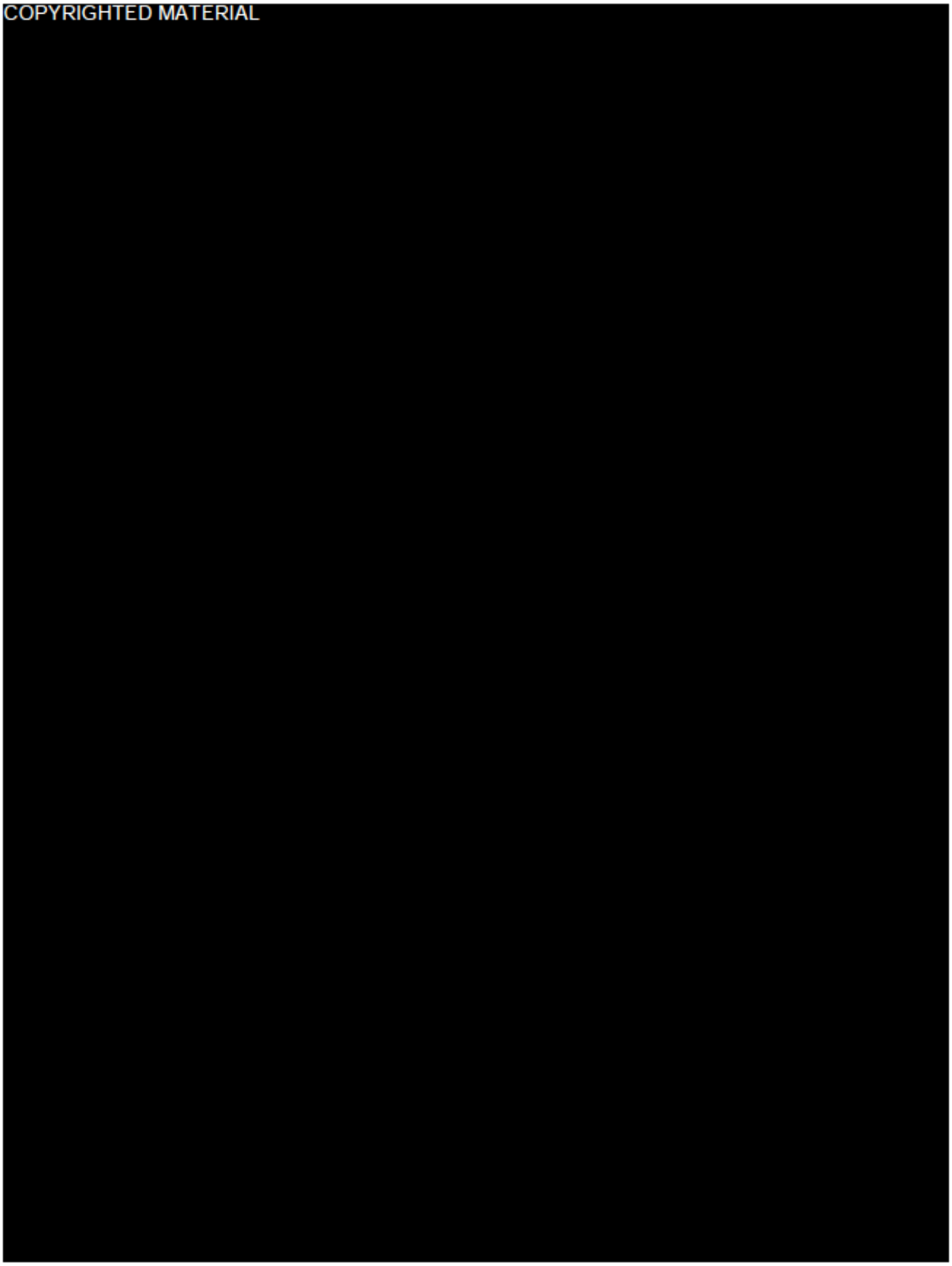


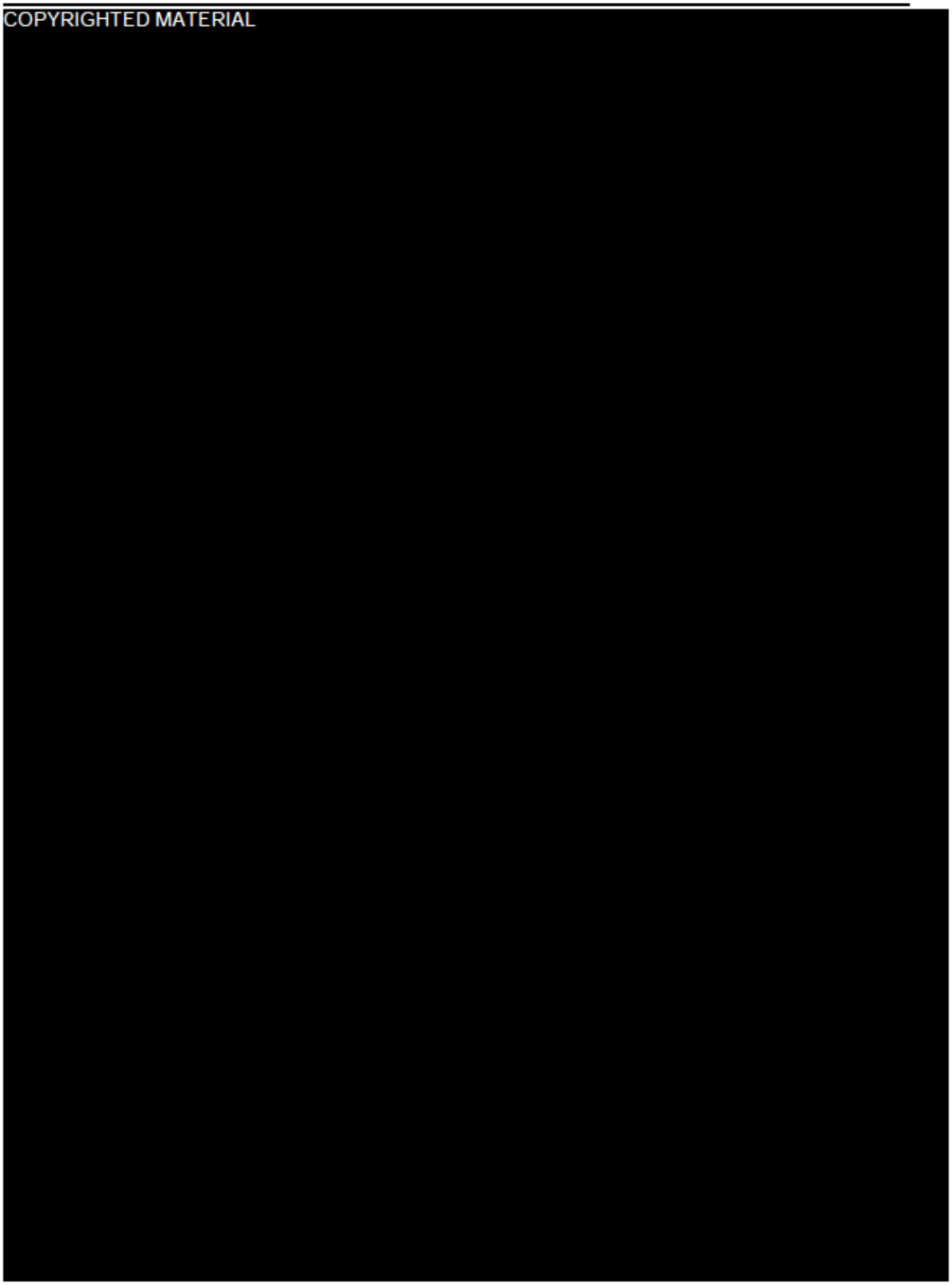


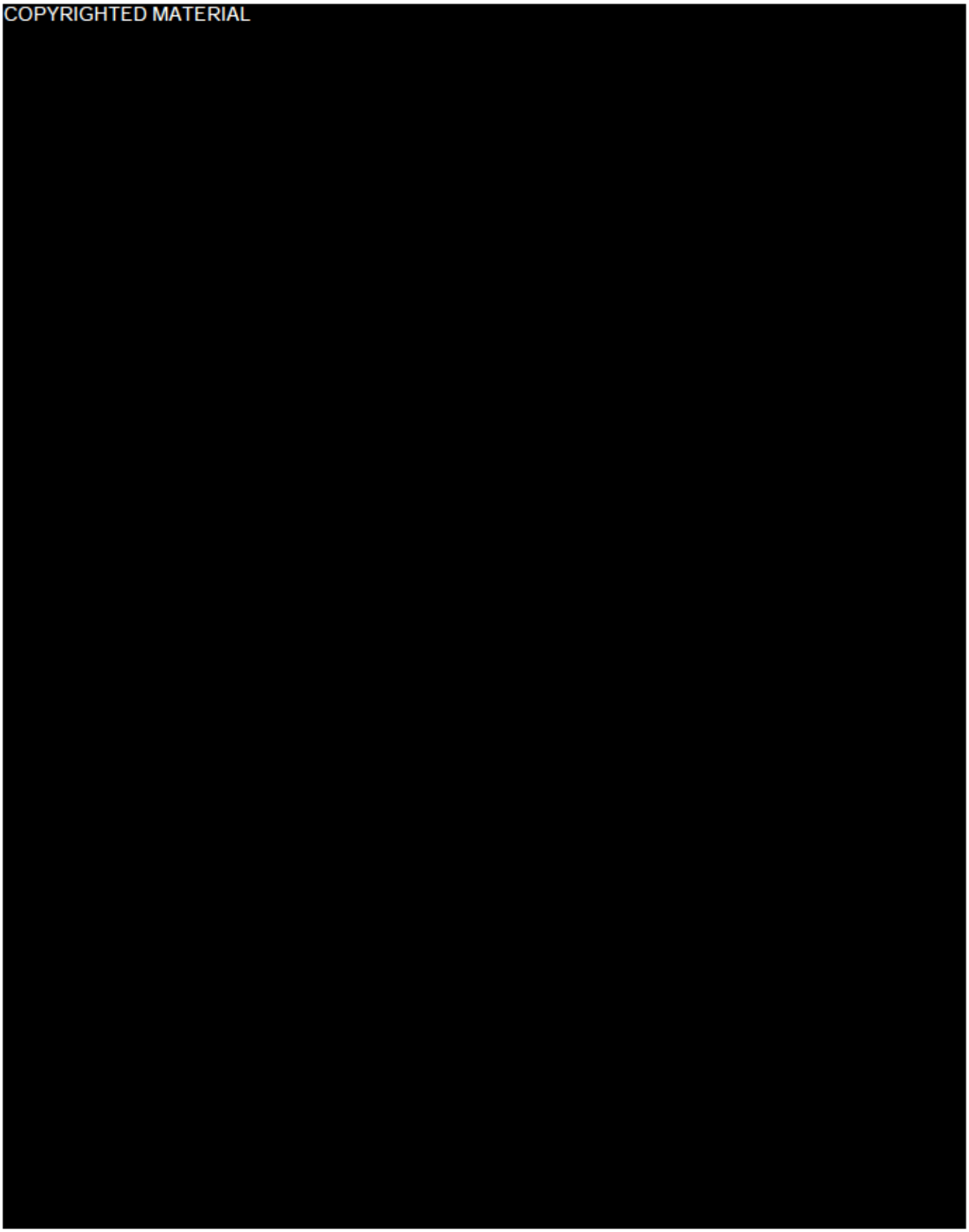
Appendix 1.2. Scoring Instructions

The Kansas City Cardiomyopathy Questionnaire
Scoring Instructions

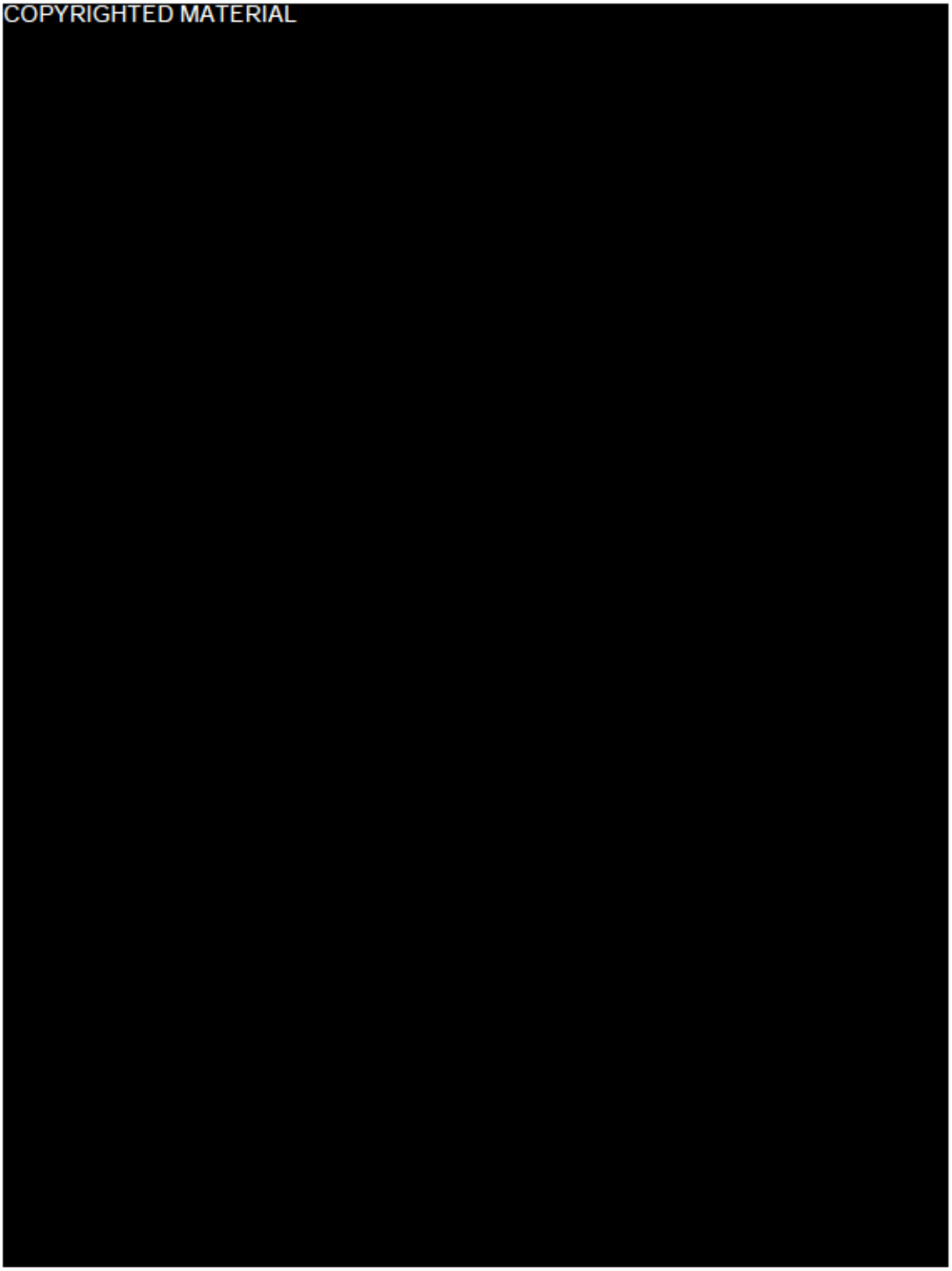








Appendix 2. PROMIS Score Conversion Tables



Appendix 3. Sampson Criteria

Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Programmatically Identifying Potential Cases of Anaphylaxis

A participant is said to have an episode fulfilling the Sampson Criteria if at least one of the following criteria is met:

Criterion 1: The participant experienced an onset of both Condition 1 and Condition 2 below, on the day of, or on the day after, study drug administration.

- Condition 1: a skin or mucosal membrane adverse event (AE) (using MedDRA PTs under Skin or Mucosal Membrane grouping),
- Condition 2: a respiratory compromise AE (using MedDRA PTs under the Respiratory grouping), or an end-organ dysfunction/reduced blood pressure AE (using MedDRA PTs under End-organ dysfunction or Reduced Blood Pressure grouping), or reduced systolic blood pressure (characterized by a PT of hypotension, blood pressure decreased or blood pressure systolic decreased).

Criterion 2: The participant experienced an onset of any 2 or more conditions below, on the day of, or on the day after, study drug administration.

- Condition 1: a skin or mucous membrane involvement AE (using MedDRA PTs under Skin or Mucosal Membrane grouping)
- Condition 2: a respiratory compromise AE (using MedDRA PTs under the Respiratory grouping);

- Condition 3: an end-organ dysfunction/reduced blood pressure AE (using MedDRA PTs under 'End-Organ Dysfunction or Reduced Blood Pressure grouping), or reduced systolic blood pressure (characterized by a PT of hypotension, blood pressure decreased or blood pressure systolic decreased);

- Condition 4: a gastrointestinal AE (using MedDRA PTs under the gastrointestinal grouping).

If the same specific AE belongs to more than one Condition/AE grouping above (i.e., 'Skin or Mucosal Membrane' grouping, 'Respiratory Compromise' grouping, 'End-Organ Dysfunction/ Reduced Blood Pressure' grouping, 'Gastrointestinal' grouping), the event should be assigned to not more than one of the above Conditions and in such a way as to maximize the number of Conditions fulfilled to support Criterion 2. For example, if the AE of Dyspnea (which belongs to the 'Respiratory Compromise' grouping) and the AE of Chest Pain (which may belong either to the 'Respiratory Compromise' grouping or to the 'End-Organ Dysfunction/ Reduced Blood Pressure' grouping) occurred, then the AE of Chest Pain will be assigned to the 'End-Organ Dysfunction/ Reduced Blood Pressure' grouping, so that Criterion 2 is fulfilled (if the AE of Chest Pain were assigned to the 'Respiratory Compromise' grouping, then Criterion 2 would not be fulfilled because the AE of Dyspnea also belongs to the 'Respiratory Compromise' grouping).

Criterion 3: The participant experienced reduced systolic blood pressure (characterized by a PT of hypotension, blood pressure decreased or blood pressure systolic decreased) on the day of, or on the day after, study drug administration, and at least 1 qualifying event. A qualifying event is defined as <u>any</u> of the following occurring during the current study or, if applicable, in the parent study from which the participant rolled over into the current study, after the first administration of the study drug (in the current or the parent study, as applicable) and before the administration of the same study drug associated with the current reduced systolic blood pressure event:

- An event meeting Criterion 1 or Criterion 2;

- An Injection Site reaction (ISR), as reported by the investigator;

- An AE under the Anaphylactic Reaction Standardised MedDRA Query (SMQ), or the Angioedema SMQ, or the Hypersensitivity SMQ, considered to be related to the study drug, as reported by the investigator.

For episodes with multiple AEs fulfilling more than one Sampson Criteria, the following hierarchy is used: Criterion 1, Criterion 2, Criterion 3. For example, when Criterion 1 is fulfilled, Criterion 2 and Criterion 3 are not evaluated.

Appendix 4. SAS Code

lgGDF = log[CCI] GDF-15 (at screening)
lgBNP = log NTproBNP (at baseline)

The following SAS code is to be used as a guide for implementation.

Example SAS code for MMRM Model:

NOTE: `cohort` will be included only when data from more than one cohort are included.

```
proc mixed data = dataset method=reml;
   class subjid treatment time;
   model cfb = treatment cohort LVEF lgGDF15 lgBNP base time base*time
               time*treatment / ddfm=kr residual outp=resid_out;
   repeated time /subject=subjid type = un;
   lsmeans treatment*time/diff cl alpha=0.1;
   ods output lsmeans=lsmeans_out;
   ods output diffs=diffs_out;
   ods output CovParms=CovParms_out;
run;
```

Example SAS code for Proportion of Responses (with multiple imputation):

Assume the SAS dataset is in a long format. The variable 'treatment' should be coded similar to 'Placebo', 'Ponsegromab 100 mg', 'Ponsegromab 200 mg', 'Ponsegromab 300 mg', so that 'Placebo' comes first.

NOTE: If a participant discontinues due to death, they should be included in the imputation, but once their value has been imputed then they should be classified as a non responder.

NOTE: `cohort` will be included only when data from more than one cohort are included.

```
proc sort data=analysis out=analysis_long;
   by subjid time treatment cohort LVEF GDF15 NTproBNP base;
run;

* Create wide dataset for multiple imputation;
proc transpose data= analysis_long out=analysis_wide prefix=wk;
   by subjid treatment cohort LVEF GDF15 NTproBNP base;
   id time;
   var cfb;
run;
```

```
* Perform multiple imputation;
proc mi data=analysis_wide seed=169 nimpute=20 out=analysis_mi;
   class treatment;
   fcs nbiter=10 reg(/details);
   var base treatment cohort LVEF lgGDF15 lgBNP wk4 wk8 wk12 wk16 wk20
       wk22;
run;

* Determine responders and non-responders at Week 22 for all imputed
  datasets;
data analysis_mi_22;
   set analysis_mi;
   if wk22 >= 5 and wk22 ne . then resp = 1;
   if wk22 < 5 and wk22 ne . then resp = 0;
run;

* Create datasets and combine proportions;
proc freq data=analysis_mi_22;
   tables _imputation_* treatment *resp / out=prop_mi outpct;
run;

data prop_mi_0;
   set prop_mi;
   if resp=0;
   keep _imputation_ treatment count;
   rename count=count_0;
run;
data prop_mi_1;
   set prop_mi;
   if resp=1;
   keep _imputation_ treatment count;
   rename count=count_1;
run;
data prop_mi_combined;
   merge prop_mi_0 prop_mi_1;
   by _imputation_ treatment;
   total = count_0 + count_1;
   p = count_1 / total;
   q = count_0 / total;
   se_p = sqrt((p*q)/total);
run;
proc sort data=prop_mi_combined;  by treatment _imputation_;  run;

proc mianalyze data=prop_mi_combined alpha=0.1;
   by treatment;
   modeleffects p;
   stderr se_p;
   ods output parameterestimates=prop_mi_out;
run;
```

Example SAS code for Logistic Regression Model (with multiple imputation):

The same imputed datasets as produced above for the 'Proportion of Responses' will be utilized. Note: the imputed dataset should be ordered with 'Resp'=1 first to ensure that the odds ratios are for a response = 1 and the reference group is Placebo.

NOTE: `cohort` will be included only when data from more than one cohort are included.

```
* Fit logistic regressions to each imputed dataset and combine results;
proc sort data=analysis_mi_22; by _imputation_ treatment descending resp;
run;

proc genmod data=analysis_mi_22 order=internal  descending;
   by _imputation_;
   class resp treatment;
   model resp = treatment cohort LVEF lgGDF15 lgBNP base
                / dist=bin link=logit alpha=0.1;
   lsmeans treatment / cl diff alpha=0.1 exp;
   ods output lsmeans=odds_mi diffs=oddsrat_mi;
run;

*Odds ratios;
data oddsrat_mi;
   set oddsrat_mi(where=(_TREATTXT="Placebo"));
   if TREATTXT = ' Ponsegromab 100 mg ' then treatment = 100;
   if TREATTXT = ' Ponsegromab 200 mg ' then treatment = 200;
   if TREATTXT = ' Ponsegromab 300 mg ' then treatment = 300;
   if treatment = . then delete;
   SE = StdErr;
run;
proc sort data=oddsrat_mi; by treatment _imputation_;  run;

proc mianalyze data=oddsrat_mi  alpha=0.1;
   by treatment;
   modeleffects estimate;
   stderr SE;
   ods output parameterestimates=OddsRatios_mi_out;
run;

data OddsRatios_mi_out;
   set OddsRatios_mi_out;
   oddsratio = exp(estimate);
   LCLoddsratio = exp(LCLMean);
   UCLoddsratio = exp(UCLMean);
run;
```

```
* Odds;
data odds_mi;
set odds_mi;
   if TREATTXT = 'Placebo' then treatment = 0;
   if TREATTXT = 'Ponsegromab 100 mg ' then treatment = 100;
   if TREATTXT = 'Ponsegromab 200 mg ' then treatment = 200;
   if TREATTXT = 'Ponsegromab 300 mg ' then treatment = 300;
   if treatment = . then delete;
   SE = StdErr;
run;
proc sort data=odds_mi; by treatment _imputation_;  run;

proc mianalyze data=odds_mi  alpha=0.1;
   by treatment;
   modeleffects estimate;
   stderr SE;
   ods output parameterestimates=Odds_mi_out;
run;

data Odds_mi_out;
   set Odds_mi_out;
   odds = exp(estimate);
   LCLodds = exp(LCLMean);
   UCLodds = exp(UCLMean);
run;
```

Example SAS code for ANCOVA:

NOTE: `cohort` will be included only when data from more than one cohort are included.

```
proc mixed data=dataset;
   class treatment;
   model cfb = treatment cohort LVEF lgGDF15 lgBNP base / residual
               outp=resid_out;
   lsmeans treatment / diff cl alpha=0.1;
   ods output lsmeans=lsmeans_out;
   ods output diffs=diffs_out;
run;
```

Example SAS code for Logistic Regression Model (without multiple imputation):

Note: the dataset should be ordered with 'Resp'=1 first to ensure that the odds ratios are for a response = 1 and the reference group is Placebo.

NOTE: `cohort` will be included only when data from more than one cohort are included.

```
* Fit logistic regression;
proc sort data=dataset; by treatment descending resp; run;

proc genmod data= dataset order=internal  descending;
   class resp treatment;
   model resp = treatment cohort LVEF lgGDF15 lgBNP
                / dist=bin link=logit alpha=0.1;
   lsmeans treatment / cl diff alpha=0.1 exp;
   ods output lsmeans=odds diffs=oddsrat;
run;

*Odds ratios;
data oddsrat;
   set oddsrat (where=(_TREATTXT="Placebo"));
   if TREATTXT = ' Ponsegromab 100 mg ' then treatment = 100;
   if TREATTXT = ' Ponsegromab 200 mg ' then treatment = 200;
   if TREATTXT = ' Ponsegromab 300 mg ' then treatment = 300;
   if treatment = . then delete;
   SE = StdErr;
run;
proc sort data=oddsrat; by treatment;  run;

data oddsrat;
   set oddsrat;
   oddsratio = exp(estimate);
   LCLoddsratio = exp(LCLMean);
   UCLoddsratio = exp(UCLMean);
run;

* Odds;
data odds;
set odds;
   if TREATTXT = 'Placebo' then treatment = 0;
   if TREATTXT = 'Ponsegromab 100 mg ' then treatment = 100;
   if TREATTXT = 'Ponsegromab 200 mg ' then treatment = 200;
   if TREATTXT = 'Ponsegromab 300 mg ' then treatment = 300;
   if treatment = . then delete;
   SE = StdErr;
run;
proc sort data=odds; by treatment;  run;

data odds;
   set odds;
   odds = exp(estimate);
   LCLodds = exp(LCLMean);
   UCLodds = exp(UCLMean);
run;
```

Example SAS code for Cumulative Incidence Plots:

```
proc lifetest data = dataset method=km plots=cif outcif=cifatrisk
intervals=0 to 20 by 4, 22;
   strata trt;
   time day*censor(1) / eventcode=0;
run;
```

NOTE: the censor variable has a value = 1 when the related time is censored and has a value = 0 when the event of interest occurs. There should be no other values available for this censored variable in this dataset (including missing values). If required, missing observations should be removed prior to analysis.

Example SAS code for Cox Proportional Hazards Model:

To obtain the hazard ratio and 90% CI use SAS proc phreg:

```
proc phreg data=dataset;
   class trt (ref='Placebo') / param=ref order=internal;
   model time*censor(1)= cohort LVEF lgGDF15 lgBNP KCCQ trt / ties=Breslow
         risklimits alpha=0.1;
   hazardratio 'Comparisons vs Placebo' trt / diff=ref alpha=0.1;
run;
```

NOTE: `cohort` will be included only when data from more than one cohort are included).

Example SAS code for Win-Ratio:

```
* alpha for 100*(1-alpha)% confidence interval;
%let alpha = 0.10;

* number of patients (sample size) in Treatment group;
%let n_trt = 10;

* number of patients (sample size) in Control group;
%let n_con = 10;


data trt;
   set HFdata;
   if treatment = "Ponsegromab";
   rename subject_ID = subid_trt cardio_death=death_trt t_death=t1_trt
                       HF_event=HF_trt t_HF=t2_trt CFB_KCCQ=KCCQ_trt;
run;
```

```
data ctrl;
   set HFdata;
   if treatment = "Placebo";
   rename subject_ID = subid_ctrl treatment=control
                       cardio_death=death_ctrl t_death=t1_ctrl
                       HF_event=HF_ctrl t_HF=t2_ctrl CFB_KCCQ=KCCQ_ctrl;
run;

**** Determine winner in each pair of treatment vs placebo patients ****;

proc sql;
   create table pwdata as
   select a.*, b.*
   from trt as a, ctrl as b
   order by subid_trt, subid_ctrl;
quit;


data compare;
   set pwdata;
   by subid_trt subid_ctrl;

   * win=0: winner not determined, win=1: winner determined or tie;
   win = 0;

   * wincat: winning category;
   * wincat='a','c','e','g' if Control patient won per Endpoint time to
     cardiovascular death, number of worsening HF events, time to 1st
     worsening HF event, CFB in KCCQ-23 at week 22, respectively;
   * wincat='b','d','f','h' if Treatment patient won per Endpoint time to
     cardiovascular death, number of worsening HF events, time to 1st
     worsening HF event, CFB in KCCQ-23 at week 22, respectively;
   * wincat='t' if a pair of patients are tied;
   wincat = ' ';

   if death_trt = 1 then do;
      if death_ctrl = 0 then wincat='a';
      * Control patient won per time to cardiovascular death;
      else if death_ctrl = 1 and t1_trt < t1_ctrl then wincat = 'a';
      * Control patient won per time to cardiovascular death;
      else if death_ctrl = 1 and t1_trt > t1_ctrl then wincat = 'b';
      * Treatment patient won per time to cardiovascular death;
      else if HF_trt > HF_ctrl then wincat = 'c';
      * Control patient won per number of worsening HF events;
      else if HF_trt < HF_ctrl then wincat = 'd';
      * Treatment patient won per number of worsening HF events;
      else if HF_trt > 0 and t2_trt <  t2_ctrl then wincat = 'e';
      * Control   patient won per time to first HF events;
      else if HF_trt > 0 and t2_trt >  t2_ctrl then wincat = 'f';
      * Treatment patient won per time to first HF events;
      else if KCCQ_trt ne '' and KCCQ_ctrl ne '' and KCCQ_trt < KCCQ_ctrl
            then wincat = 'g';
      * Control patient won per CFB in KCCQ;
      else if KCCQ_trt ne '' and KCCQ_ctrl ne '' and KCCQ_trt > KCCQ_ctrl
            then wincat = 'h';
```

```
      * Treatment patient won per CFB in KCCQ;
      if wincat ne ' ' then win = 1;
   end;

   if death_trt = 0 then do;
      if death_ctrl = 1 then wincat='b';
      * Treatment patient won per Endpoint time to cardiovascular death;
      else if death_ctrl = 0 and t1_trt < t1_ctrl then wincat = 'a';
      * Control  patient won, per time to cardiovascular death;
      else if death_ctrl = 0 and t1_trt > t1_ctrl then wincat = 'b';
      * Treatment patient won per time to cardiovascular death;
      else if HF_trt > HF_ctrl then wincat = 'c';
      * Control patient won per number of worsening HF events;
      else if HF_trt < HF_ctrl then wincat = 'd';
      * Treatment patient won, per number of worsening HF events;
      else if HF_trt > 0 and t2_trt <  t2_ctrl then wincat = 'e';
      * Control patient won per time to first HF events;
      else if HF_trt > 0 and t2_trt >  t2_ctrl then wincat = 'f';
      * Treatment patient won per time to first HF events;
      else if KCCQ_trt ne '' and KCCQ_ctrl ne '' and KCCQ_trt < KCCQ_ctrl
            then wincat = 'g';
      * Control patient won per CFB in KCCQ;
      else if KCCQ_trt ne '' and KCCQ_ctrl ne '' and KCCQ_trt > KCCQ_ctrl
            then wincat = 'h';
      * Treatment patient won per CFB in KCCQ;
      if wincat ne ' ' then win = 1;
   end;

   if wincat=' ' then wincat='t';  * the pair of patients are tied;
   if wincat ne ' ' then win = 1;
run;


******** Calculate win ratio and theta_K0 (theta_L0) ********;

options nocenter;
title 'Winning categories';
proc freq data=compare;
   tables wincat/missing out=win;
run;
```

```
data _win;
   wincat = 'a'; count = 0;
   output;
   wincat = 'b'; count = 0;
   output;
   wincat = 'c'; count = 0;
   output;
   wincat = 'd'; count = 0;
   output;
   wincat = 'e'; count = 0;
   output;
   wincat = 'f'; count = 0;
   output;
   wincat = 'g'; count = 0;
   output;
   wincat = 'h'; count = 0;
   output;
   wincat = 't'; count = 0;
   output;
run;

data win;
   merge _win win;
   by wincat;
run;

proc transpose data=win out=win2;
   var count;
   id wincat;
run;

data win2;
   set win2;
   win_trt = sum(b, d, f, h);
   win_con = sum(a, c, e, g);
   tie = t;

   total = sum(a, b, c, d, e, f, g, h, t);
   WinRatio = win_trt/win_con;
   theta_KL0 = (win_trt + win_con)/(2*total);

   label win_trt = 'number of winners in Treatment group'
         win_con = 'number of winners in Control group'
         tie = 'number of ties'
         total = 'total number of pairs'
         WinRatio = 'Win ratio'
         theta_KL0 = 'theta K0/L0';
run;

title 'Number of winners and win ratio';
proc print label;
   var theta_KL0 win_trt win_con WinRatio;
run;
```

```
proc sql noprint;
   select theta_KL0 into: theta_KL0
   from win2;
   select win_trt into: win_trt
   from win2;
   select win_con into: win_con
   from win2;
   select WinRatio into: WinRatio
   from win2;
run;
quit;

%put &theta_KL0 &win_trt &win_con &WinRatio;

******* Construct kernel functions *******;

* Kernel function K;
data K;
   set compare;
   by subid_trt subid_ctrl;
   if wincat in ('b', 'd', 'f', 'h') then k=1;  *** if Treatment won;
   else k=0;
run;

* Kernel function L;
data L;
   set compare;
   by subid_trt subid_ctrl;
   if wincat in ('a', 'c', 'e', 'g') then k=1;  *** if Control won;
   else k=0;
run;


******* Calculate variances *******;

%macro sig(dsin=, pid1=, pid2=, n1=, n2=, dsout=, varout=);
* dsin: input kernel function dataset (K/L);
* pid1: patient ID in the 1st group (pid_trt/pid_con);
* pid2: patient ID in the 2nd group (pid_trt/pid_con);
* n1: number of patients in the 1st group (&n_trt/&n_con);
* n2: number of patients in the 2nd group (&n_trt/&n_con);
* dsout: output dataset;
* varout: variable name of variance;

proc sort data=&dsin out=temp;
   by &pid1 &pid2;
run;

proc means data=temp noprint;
   by &pid1;
   var k;
   output out=temp2 sum=sum_1;
run;
```

```
proc sql;
   create table temp as
   select a.*, b.sum_1
   from temp as a left join temp2 as b
   on a.&pid1=b.&pid1
   order by &pid1, &pid2;
quit;

data temp;
   set temp;
   by &pid1 &pid2;
   sum_k = (k-&theta_KL0)*(sum_1 - k - (&n2-1) * &theta_KL0);
run;

proc means data=temp noprint;
   var sum_k;
   output out=&dsout sum=&varout;
run;

data &dsout;
   set &dsout;
   &varout = &varout * &n1 * &n2 / (&n2 - 1);
run;
%mend;

options mprint;
* Sigma square hat - t10;
%sig(dsin=K, pid1=subid_trt, pid2=subid_ctrl, n1=&n_trt, n2=&n_con,
dsout=sig2_trt1, varout=sig2_trt1);
* Sigma square hat - t20;
%sig(dsin=K, pid1=subid_ctrl, pid2=subid_trt, n1=&n_con, n2=&n_trt,
dsout=sig2_trt2, varout=sig2_trt2);

* Sigma square hat - c10;
%sig(dsin=L, pid1=subid_ctrl, pid2=subid_trt, n1=&n_con, n2=&n_trt,
dsout=sig2_con1, varout=sig2_con1);
* Sigma square hat - c20;
%sig(dsin=L, pid1=subid_trt, pid2=subid_ctrl, n1=&n_trt, n2=&n_con,
dsout=sig2_con2, varout=sig2_con2);

******* Calculate covariance *******;

%macro sig_cov(dsin1=, dsin2=, pid1=, pid2=, n1=, n2=, dsout=, varout=);
* dsin1: dataset of kernel function 1 (K/L);
* dsin2: dataset of kernel function 2 (K/L);
* pid1: patient ID in the 1st group (pid_trt/pid_con);
* pid2: patient ID in the 2nd group (pid_trt/pid_con);
* n1: number of patients in the 1st group (&n_trt/&n_con);
* n2: number of patients in the 2nd group (&n_trt/&n_con);
* dsout: output dataset;
* varout: variable name of variance;

proc sort data=&dsin1 out=temp1;
   by &pid1 &pid2;
run;
```

```
proc sort data=&dsin2 out=temp2;
   by &pid1 &pid2;
run;

proc means data=temp2 noprint;
   by &pid1;
   var k;
   output out=temp2_s sum=sum_1;
run;

proc sql;
   create table temp as
   select a.*, b.sum_1
   from temp1 as a left join temp2_s as b
   on a.&pid1=b.&pid1
   order by &pid1, &pid2;

   create table temp as
   select a.*, b.k as L
   from temp as a left join temp2 as b
   on a.&pid1=b.&pid1 and a.&pid2=b.&pid2
   order by &pid1, &pid2;
quit;

data temp;
   set temp;
   by &pid1 &pid2;
   sum_k = (k-&theta_KL0)*(sum_1 - L - (&n2-1) * &theta_KL0);
run;

proc means data=temp noprint;
   var sum_k;
   output out=&dsout sum=&varout;
run;

data &dsout;
   set &dsout;
   &varout = &varout * &n1 * &n2 / (&n2 - 1);
run;
%mend;

* Sigma hat - tc10;
%sig_cov(dsin1=K, dsin2=L, pid1=subid_trt, pid2=subid_ctrl, n1=&n_trt,
n2=&n_con, dsout=sig_trt_con1, varout=sig_trt_con1);
* Sigma hat - tc20;
%sig_cov(dsin1=K, dsin2=L, pid1=subid_ctrl, pid2=subid_trt, n1=&n_con,
n2=&n_trt, dsout=sig_trt_con2, varout=sig_trt_con2);
```

```
******* variance and covariance *******;

data sig;
   merge sig2_trt1 sig2_trt2 sig2_con1 sig2_con2 sig_trt_con1
sig_trt_con2;

   * Sigma square hat - t0;
   sig2_trt = sig2_trt1/&n_trt + sig2_trt2/&n_con;
   * Sigma square hat - c0;
   sig2_con = sig2_con1/&n_con + sig2_con2/&n_trt;
   * Sigma hat - tc0;
   sig_trt_con = sig_trt_con1/&n_trt + sig_trt_con2/&n_con;

   label sig2_trt = ' Sigma square hat - t0'
         sig2_con = ' Sigma square hat - c0'
         sig_trt_con = ' Sigma hat - tc0';

   Keep sig2_trt sig2_con sig_trt_con;
run;

title 'Variance and covariance';
   proc print data=sig label;
run;

data Winratio;
   set sig;
   * Sigma square hat of log(win ratio);
   sig2_log_wr = (sig2_trt + sig2_con - 2*sig_trt_con)/((&win_trt +
                 &win_con)*(&win_trt + &win_con)/4);

   * 100*(1-alpha)% CI of the win ratio;
   WR_L = exp(log(&WinRatio) - probit(1-&alpha/2)*sqrt(sig2_log_wr));
   WR_U = exp(log(&WinRatio) + probit(1-&alpha/2)*sqrt(sig2_log_wr));

   WinRatio = &WinRatio;
   alpha = &alpha;
   pval = (1-probnorm(abs(log(&WinRatio)/sqrt(sig2_log_wr))))*2;

   label sig2_log_wr = 'Sigma square hat of log(win ratio)'
         WR_L = "Lower limit of 100*(1-alpha)% CI of the Win ratio"
         WR_U = "Upper limit of 100*(1-alpha)% CI of the Win ratio"
         WinRatio = 'Win ratio'
         alpha = 'Alpha';
run;

title ' Win ratio and its 100*(1-alpha)% CI';
proc print data=Winratio label;
   var sig2_log_wr WinRatio WR_L WR_U alpha pval;
run;

data WR;
   merge Winratio win2;
   keep WinRatio sig2_log_wr WR_L WR_U alpha pval win_trt win_con tie
total;
run;
```

```
data WR;
   retain WinRatio sig2_log_wr WR_L WR_U alpha pval win_trt win_con tie
total;
   set WR;
run;
```

Appendix 5. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF

Absolute value of QTcF (msec)	>470 and ≤480	>480 and ≤500	>500
Increase from baseline in QTcF (msec)	>30 and ≤60	>60	

Categories for PR and QRS

PR (msec)	max. ≥300	
PR (msec) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (msec)	max. ≥140	
QRS (msec) increase from baseline	≥50% increase	

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120

Measurements that fulfill these criteria are to be listed.

Appendix 6. Immunogenicity Terms and Definitions

Term	Definition
Treatment-induced ADA	Baseline ADA titer is missing or negative and subject has ≥ 1 post-treatment positive ADA titer.
Treatment-boosted ADA	Baseline ADA titer is positive and subject has a ≥ 4-fold dilution increase (or other threshold value as defined in the SAP) in ADA titer from baseline in ≥ 1 post-treatment sample. If ADA titer is log10 transformed, a 4-fold dilution increase is equivalent to 0.602 unit increase in titer (log10) from baseline. If ADA titer is log2 transformed, a 4-fold dilution increase is equivalent to 2 unit increase in titer (log2) from baseline.
ADA-positive subject	A subject with ≥ 1 treatment-induced or treatment-boosted ADA response.
ADA-negative subject	An ADA evaluable subject without treatment-induced or treatment-boosted ADA response. Subject either has (1) all ADA-negative results throughout the study or (2) is ADA positive at baseline but did not become treatment-boosted post-dose.
ADA incidence	The percent of ADA-positive subjects in a treatment group/cohort or study.
Treatment-induced NAb	Baseline NAb titer is missing or negative or ADA-negative and subject has ≥ 1 post-treatment positive NAb titer.
Treatment-boosted NAb	Baseline NAb titer is positive and subject has a ≥ 4-fold dilution increase (or other threshold as defined in the SAP) in NAb titer from baseline in ≥ 1 post-treatment sample. If NAb titer is log10 transformed, a 4-fold dilution increase is equivalent to 0.602 unit increase in titer (log10) from baseline. If NAb titer is log2 transformed, a 4-fold dilution increase is equivalent to 2 unit increase in titer (log2) from baseline.
NAb-positive subject	An ADA-positive subject with ≥ 1 treatment-induced or treatment-boosted NAb response. For ADA-positive (treatment-boosted) subjects, subject is NAb positive only if the subject has ≥1 treatment-induced or treatment-boosted NAb response at the visit where the subject has a treatment-boosted ADA response. For visits where the subject did not show a boosted ADA response, the subject is classified as NAb-negative for the visit even if the subject has post-treatment positive NAb titer for that visit.
NAb-negative subject	NAb evaluable participant who is either (1) an ADA-negative subject or (2) an ADA-positive subject without treatment-induced or treatment-boosted NAb response (i.e. subject has all NAb-negative results throughout the study or subject is NAb positive at baseline but did not become treatment-boosted post-dose). Note: in the event a subject is ADA-positive at baseline but did not show a boosted response post-treatment, subject is classified as ADA-negative and NAb-negative at the subject level even if the subject has post-treatment positive NAb titer. As such all ADA-negative subjects are NAb-negative regardless of NAb titer data."
NAb incidence	The percent of NAb-positive subjects in a treatment group/cohort or study.
Duration of ADA and NAb response (subject-level definitions): recommended for studies with ≥ 16 weeks of ADA measurements	
Transient ADA	An ADA-positive subject with (1) a treatment-induced or treatment-boosted ADA sample detected only at 1 sampling time (excluding the last time point) post-treatment, or (2) treatment-induced or treatment-boosted ADA samples detected at ≥ 2 time points where the first and last positive samples (irrespective of any negative samples in between) are separated by < 16 weeks, and the subject's last sample is ADA negative.
Persistent ADA	An ADA-positive subject with first and last positive ADA samples (treatment-induced or treatment-boosted) detected over a period of ≥ 16 weeks post-treatment, irrespective of any negative samples in between.
Indeterminate ADA	An ADA-positive subject who is not persistent or transient.
Transient NAb	A NAb-positive subject with (1) a treatment-induced or treatment-boosted NAb sample detected only at 1 sampling time (excluding the last time point) post-treatment, or (2) treatment-induced or treatment-boosted NAb samples detected at ≥ 2 time points where the first and last positive samples (irrespective of any negative samples in between) are separated by < 16 weeks, and the subject's last sample is NAb negative or ADA negative.
Persistent NAb	A NAb-positive subject with first and last positive NAb samples (treatment-induced or treatment-boosted) detected over a period of ≥ 16 weeks post-treatment, irrespective of any negative samples in between.
Indeterminate NAb	A NAb-positive subject who is not persistent or transient.

Note: Duration of response (persistent, transient or indeterminate), on-treatment and off-treatment definitions are only applicable to ADA (or NAb)-positive subjects.

Appendix 7. List of Abbreviations

Abbreviation	Term
6MWD	6 Minute Walk Distance
6MWT	6 Minute Walk Task
ADA	anti-drug (ponsegromab) antibodies
AE	adverse event
ANCOVA	analysis of covariance
AUC_{tau}	area under the plasma concentration-time profile from time zero to time tau
BLQ	below the limit of quantitation
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CFB	change from baseline
%CFB	percent change from baseline
CI	confidence interval
CL/F	apparent clearance for oral dosing
C_{max}	maximum plasma concentration during the dosing interval
C_{min}	minimum plasma concentration during the dosing interval
CSR	clinical study report
CSS	clinical summary score
C_{trough}	trough concentration
CV	coefficient of variation
dn	dose normalized
DAOH	days alive and out of hospital
ECG	electrocardiogram or electrocardiography
E-DMC	external data monitoring committee
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
F/U	follow up
g	grams
GDF-15	growth differentiation factor 15
HDL	high-density lipoprotein
HF	heart failure
HRQL	health-related quality of life
hsCRP	high-sensitivity C-reactive protein
I-AE	Immunogenicity adverse event
ICD	informed consent document
IP	investigational product
IRC	independent review committee
ISR	injection site reaction
KCCQ-23	Kansas City Cardiomyopathy Questionnaire

Abbreviation	Term
kel	terminal phase elimination rate constant
kg	kilogram
L	liter
L5hr	average activity counts for the least active 5 hours of the day
lb	pound
LDL	low-density lipoprotein
LLQ	lower limit of quantification
LS	least-squares
LVEF	left ventricular ejection fraction
m	meters
M10hr	average activity counts for the most active 10 hours of the day
M15mins	maximum 15 mins of activity level
M6mins	maximum 6 mins of activity level
M60mins	maximum 60 mins of activity level
mBMI	modified BMI
MedDRA	medical dictionary for regulatory activities
mg	milligram
mins	minutes
mL	millilitre
mmHg	millimeters of mercury
MMRM	mixed-effects model with repeated measures
msec	millisecond
MVPA	moderate to vigorous physical activity
n	number
N/A	not applicable
NAb	neutralizing antibodies
NC	not calculated
ND	not done
NS	no sample
NT-proBNP	N-terminal pro-B type natriuretic peptide
NYHA	New York Heart Association
OSS	overall summary score
PCD	primary completion date
PD	pharmacodynamic(s)
PEF	preserved ejection fraction
pg	picogram
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	preferred term
PTR	peak-to-trough ratio

Abbreviation	Term
Q1	first quartile
Q3	third quartile
Q4W	every 4 weeks
QoL	quality of life
QQ	quantile-quantile
QTcF	corrected QT (Fridericia method)
R_{ac}	observed accumulation ratio
$R_{ac,}C_{max}$	observed accumulation ratio for Cmax
SAE	serious adverse event
SAP	statistical analysis plan
SC	sub-cutaneous
SD	standard deviation
SE	standard error
SMQ	standardized MedDRA query
SOP	standard operating procedure
SPSS	Statistical Package for the Social Sciences
SV1	screening visit 1
SV2	screening visit 2
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
T_{max}	time for C_{max}
TSS	total symptom score
CCI	[redacted]
Vz/F	apparent volume of distribution for oral dosing