Protocol C4411002

A PHASE 3, MULTINATIONAL, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ARRY-371797 (PF-07265803) IN PATIENTS WITH SYMPTOMATIC DILATED CARDIOMYOPATHY DUE TO A LAMIN A/C GENE MUTATION

(REALM-DCM)

Statistical Analysis Plan
(SAP)

Version: **4.0**

Date: **20Jun2022**

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APPENDICES

1. VERSION HISTORY

This statistical analysis plan (SAP) for Study C4411002 (previously ARRAY-797-301) is based on Protocol Amendment 8 dated 09Feb2022.

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
03Mar2021	Amendment 7 17Feb2021	Not applicable (N/A)	N/A
Amendment 1 03June2021 Version 2.0	Amendment 7 17Feb2021	1.Updated the testing orders of NT-proBNP and KCCQ PL and TSS domains in the hierarchical testing procedure in Section 5.1 as requested by FDA.	1. Clarified that the KCCQ PL domain score is tested prior to the TSS in the endpoint hierarchy; Moved NT-proBNP in the hierarchical testing procedure after the composite endpoint of time to first worsening heart failure or all-cause mortality.
		2. Provided additional details on blinded sample size re-estimation in Section 7.1 Interim Analysis.	2. Added the detailed specifications on re-estimating study sample size based on the interim blinded data.
		3. Added clarification regarding primary method to describe the treatment effect and additional missing data summary in Section 6.1.1.	3. Clarified that the primary method to describe the treatment effect for the primary efficacy endpoint will be a stratified HL median difference in the change of 6MWT from baseline at Week 24, and that the win ratio will be used as a supportive analysis; added additional descriptive summary on missing data reason and imputation type.
		4. Editorial changes in Section 5.2.1.	4. Moved the description of stratified win-ratio method as a supportive analysis after the stratified HL method.
		5. Clarified the testing order on the KCCQ PL prior to the KCCQ TSS in Section 6.2.2 to be consistent with Section 5.1.	5. Added a sentence that the KCCQ PL will be tested first followed by the KCCQ TSS.
		6. Updated Appendix 2 to align Programming Specifications with imputation algorithm in Section 5.3.1.	6. Inserted the SAS statements on imputing monotone missing values under MAR; Added the number of days on treatment as a covariate in the imputation model for intermittent and monotone missing data.

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
		7. Updated Appendix 3 to extend analysis visit window to account for the potential impact of COVID-19 pandemic on follow-ups.	7. Extended analysis visit window to ± 3 weeks from ± 2 weeks for efficacy variables collected at the Week 12 visit or after in the randomized period.
Amendment 2 22Mar2022 Version 3.0	Amendment 8 09Feb2022	1.Updated the title page to include study name and branding implemented after protocol version 7 approval. 2.Updated Sections 2.1, 3.2, and 3.3, 6.3 to remove specified timepoints to be consistent with protocol amendment. 3.Updated Section 2.2 to reflect the new study sample size based on the blinded sample size re-estimation (BSSR) for the primary endpoint and added clarification on survival follow-up. 4.Modified the definition of the Efficacy Analysis Dataset and NYHA Class IV Analysis dataset to include all randomized participants in the respective analyses in Section 4. 5.Updated Sections 5.1 and 7.1 to reflect the new study sample size based on the completed BSSR for the primary endpoint following the interim futility analysis. The sentences referencing 52 events required to assess the composite all-cause mortality or worsening heart failure (WHF) was removed after adding more text to Section 7.1 clarifying the number of events on all-cause mortality or WHF needed under various scenarios. 6.Updated Section 6.1.1 to add a responder analysis and cumulative distribution plot to characterize the treatment effect on the primary endpoint.	1.Added the study name (REALM-DCM) to the title page. 2.Removed specified timepoint in secondary and CCI endpoints given measurements are assessed throughout the double-blind period. 3.Included a change in the number of participants randomized into the study and added the text regarding survival follow-up. 4.Removed the inclusion criterion "with a LMNA gene mutation that is pathogenic, likely pathogenic or VUS" in the definition of Efficacy Analysis Dataset and NYHA Class IV Analysis dataset. 5.Added the text regarding the DMC recommendation to continue the study as designed based on futility analysis and a change in the number of participants randomized into the study based on the BSSR. Additional sample size calculation was added to assess the number of events needed under various scenarios for blinded monitoring of the composite endpoint of time to first occurrence of all-cause mortality or WHF. The text specifying 52 events are required to assess the composite endpoint was removed. 6.Added the details on the definition of the responder analysis and the cumulative distribution plot of responses by change from baseline in 6MWT to Week 24.

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
		7.Updated Section 6.1.2 to add a new sensitivity analysis to the primary endpoint using a mixed-effect model for repeated measure (MMRM).	7.Included a detailed description of the MMRM specification.
Amendment 3 20Jun2022 Version 4.0		1. Updated Section 4 to add an interim analysis set used for interim futility assessment on change from baseline in 6MWT at Week 24. 2. Updated Sections 5 and 7 to add an additional interim analysis to assess futility based on change from baseline in 6MWT at Week 24 given the change in timepoint of the primary endpoint from 12 to 24 weeks and the longer than anticipated duration of the enrollment period.	1. Provide the definition of interim analysis set corresponding to the interim futility analysis on change from baseline in 6MWT at Week 24. 2. Included detailed specifications on the interim futility analysis of change from baseline in 6MWT at Week 24.

2. INTRODUCTION

Dilated cardiomyopathy due to lamin A/C gene mutations (*LMNA*-related DCM) can present as a *de novo* mutation or more frequently as an autosomal dominant inheritance, and is usually accompanied by supraventricular and ventricular arrhythmias and/or conduction system disease (CSD). The majority of patients with *LMNA*-related DCM follow a clinical course starting with CSD and/or arrhythmias in early to mid-adulthood, with some early mortality due to sudden cardiac arrest from a fatal arrhythmia or embolus. Over time, most patients progress to DCM, which can lead to rapidly progressive heart failure (HF). Currently, there is no effective, disease-specific treatment available for *LMNA*-related DCM. To date, treatment is limited to conventional therapies for HF with reduced ejection fraction (angiotensin-converting-enzyme inhibitors, angiotensin 2 receptor blockers or angiotensin receptor-neprilysin inhibitor, beta blockers, aldosterone receptor antagonists, inhibitors of sodium-glucose cotransporter 2 and diuretics) which are largely symptomatic and supportive. Progressive deterioration in left ventricular (LV) function and refractory HF symptoms are often treated with resynchronization therapy (bi-ventricular pacing [CRT]). Risk of sudden cardiac death (SCD) is managed with placement of an implantable cardioverter defibrillator (ICD) or CRT defibrillator (CRT-D). In patients whose disease continues to progress in spite of aggressive cardiovascular management, left ventricle assist device and cardiac transplantation may be considered.

The C4411002 pivotal Phase 3 study will evaluate the clinical efficacy and safety of PF-07265803 in participants with symptomatic *LMNA*-related DCM who meet study eligibility criteria.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4411002. 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. Any deviations from this analysis plan will be described in the clinical study report (CSR).

2.1. Study Objectives, Endpoints, and Estimands

Study objectives and corresponding endpoints are provided in Table 2 below. Participants who discontinue study treatment or have study drug interruption prior to Week 24 will continue to have all assessments performed as scheduled through the Week 24 Visit. All data collected during the study will be included for the analyses of efficacy regardless of discontinuation of study treatment or study drug interruption.

The estimand for the primary and secondary endpoints will employ a combination of a treatment policy strategy and a composite strategy. For the intercurrent event of death (due to any cause) and study discontinuation prior to the analysis time point, a composite strategy will be used, where death and study discontinuation will be considered unfavorable and represented by lowest (worst) set of ranks of a combined outcome variable as described in Section 5.2.1. For premature discontinuation of randomized treatment, a treatment policy strategy will be used.

Table 2. Study Objective and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
Evaluate the effect of ARRY-371797 (PF-07265803) on functional capacity (as measured by the 6 Minute Walk Test [6MWT]) compared to placebo.	New York Heart Association (NYHA) Class II/III participants only: Change from baseline in 6MWT at Week 24.
Secondary:	**Secondary:**
Evaluate additional measures of efficacy of ARRY-371797 (PF-07265803) compared to placebo in the randomized period.	NYHA Class II/III patients only: Change from baseline in 6MWT at Weeks 4 and 12. NYHA Class II/III participants only: Change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ) Physical Limitation (PL) and Total Symptom Score (TSS) domains at Weeks 12 and 24. NYHA Class II/III participants only: Change from baseline in Patient Global Impression (PGI) scores at Weeks 12 and 24: • Patient Global Impression of Severity (PGI-S); • Patient Global Impression of Change (PGI-C). NYHA Class II/III participants: Change from baseline in N-terminal pro-brain natriuretic peptide (NT-proBNP) at Weeks 4, 12, and 24.

Table 2. Study Objective and Endpoints

Objectives	Endpoints
Evaluate the impact of ARRY-371797 (PF-07265803) on composite endpoint of all-cause mortality, or worsening heart failure (WHF).	Defined as the time from randomization to the first occurrence of any event of death due to any cause, or worsening heart failure (HF-related hospitalization or HF-related urgent care visit).
Evaluate the impact of ARRY-371797 (PF-07265803) on overall survival (OS).	OS
Evaluate the safety of ARRY-371797 (PF-07265803) compared to placebo.	Safety as determined by: • Incidence and severity of Adverse Events (AEs); • Changes in clinical safety laboratory tests, vital signs, and 12 lead electrocardiography (ECGs); • Incidence and severity of ventricular or atrial arrhythmias detected using existing ICD/cardiac resynchronization therapy defibrillator (CRT-D) or other applicable device interrogations.
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Table 2. Study Objective and Endpoints

Objectives	Endpoints
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

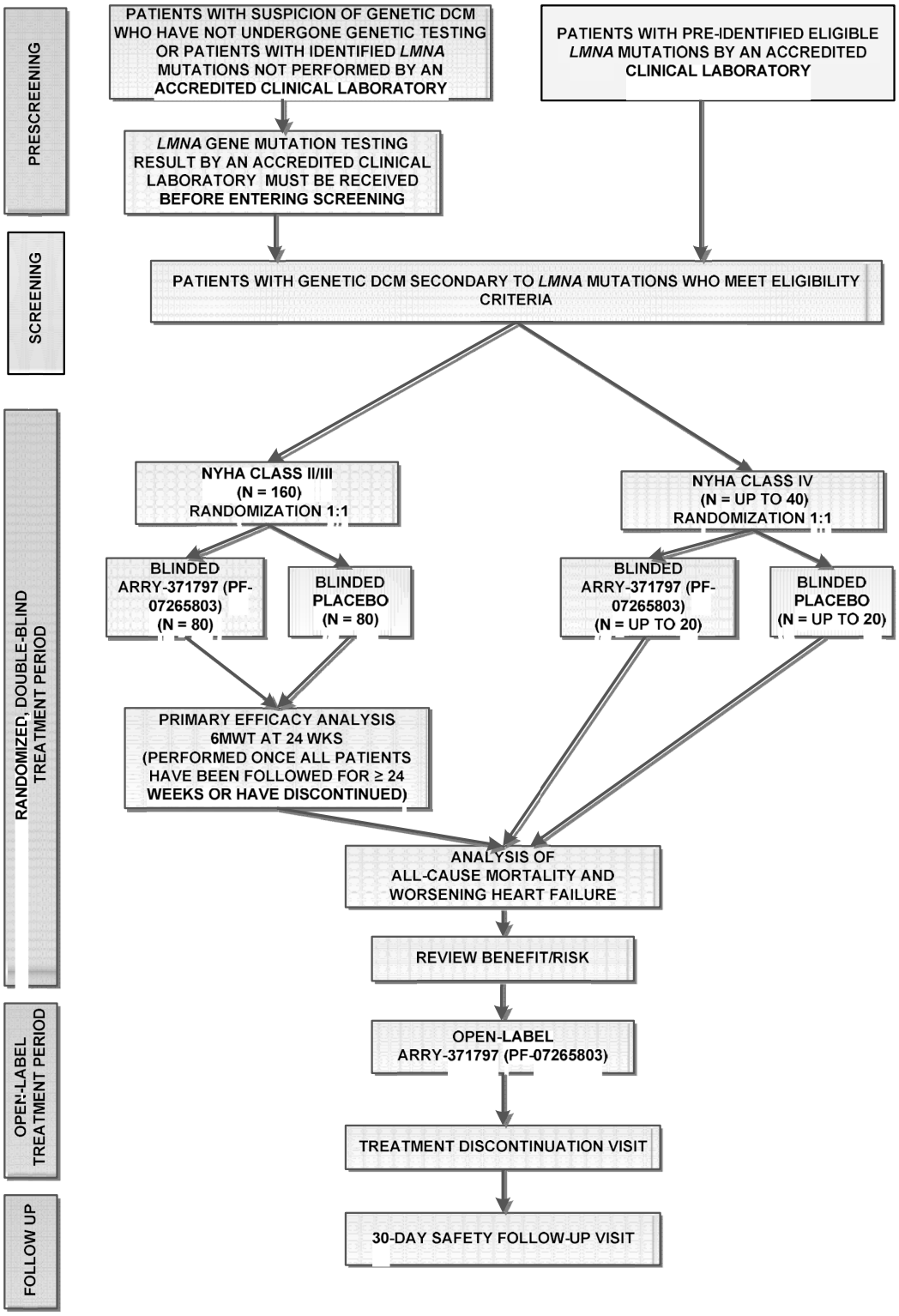
2.2. Study Design

This multinational Phase 3 study will evaluate the efficacy, safety, and PK following treatment with ARRY-371797 (PF-07265803) compared with placebo (1:1 randomization) in at least 160 participants with *LMNA*- related DCM in NYHA functional Class II and III. Additional *LMNA*-related DCM in NYHA functional Class IV participants (up to 40) may be randomized (1:1) and will be assessed for overall safety and time from randomization to HF-related hospitalization, HF-related urgent care visits or death due to any cause, in addition to PK and efficacy, if feasible. The sample size was increased following completion of a planned blinded sample size re-estimation. Up to 200 eligible participants with symptomatic cardiomyopathy due to *LMNA* mutations will be randomized, at approximately 60 to 90 investigational centers, globally. The sample size determination is detailed in Section 5.1.

The study will be conducted in 2 parts: a randomized, double-blind treatment period, followed by an ARRY-371797 (PF-07265803) open-label treatment period. During the randomized, double-blind period, participants, investigators, site personnel, and the sponsor personnel directly involved with the conduct of the study will remain blinded to assigned treatment. The double-blind period will continue until the primary analysis which includes an assessment of the primary efficacy endpoint and completion of an evaluation of a composite endpoint consisting of all-cause mortality or worsening heart failure (HF-related hospitalization or HF-related urgent care visits). Following the primary analysis, a seamless transition to the open-label phase may begin and ongoing treatments will be unblinded and participants receiving placebo may initiate treatment with ARRY-371797 (PF-07265803) provided eligibility criteria are met. The end of the study is reached once the last participant has had the opportunity to be followed for at least 24 weeks in the open-label period of the study or has discontinued from the study.

Participants who discontinue study drug prior to Week 24 should continue to have all assessments performed as scheduled through the Week 24 Visit. Every effort should be made to obtain these data. During the randomized period of the study, all patients enrolled in the study will be followed for survival approximately every 3 months until death, lost to follow-up, or withdrawal of consent, or initiation of the open-label treatment period, whichever occurs first. Phone calls are acceptable when clinic visits are not already performed. Vital status may be ascertained from family, caregivers, or public records, where appropriate.

Figure 1. Study Schema



DCM=dilated cardiomyopathy; LMNA=gene encoding the lamin A/C protein; NYHA=New York Heart Association; 6MWT=6 Minute Walk Test.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

- NYHA Class II/III participants: Change from baseline in 6MWT at Week 24.

3.2. Secondary Endpoint(s)

- NYHA Class II/III participants: Change from baseline in 6MWT at Weeks 4 and 12.
- NYHA Class II/III participants: Change from baseline in KCCQ PL and TSS domains at Weeks 12 and 24.

The KCCQ measures the effects of symptoms, functional limitations, and psychological distress on an individual's health-related quality of life. The KCCQ has 23 items which assess the ability to perform activities of daily living, frequency and severity of symptoms, the impact of these symptoms, and health-related quality of life (QoL). Response options vary by question. Summaries on distinct domains derived from the individual questions in the KCCQ are provided in Appendix 4.1. Domain scores are transformed to a 0 to 100 range; higher scores indicate better health status.

- NYHA Class II/III participants: Change from baseline in PGI scores at Weeks 12 and 24:
  - PGI-S;
  - PGI-C.

Participants will rate the severity of their heart failure symptoms and physical activity limitations during the past week on the 2 PGI-S questions (see Appendix 4.2). Participants will rate the overall change (if any) in their heart failure symptoms and physical activity limitations since they began taking the study medication on the 2 PGI-C questions (see Appendix 4.2). The PGI-S will be completed first followed by the PGI-C after completing the KCCQ. These data will be used to provide an anchor to define thresholds for improvements in KCCQ.

- NYHA Class II/III participants: Change from baseline in NT-proBNP at Weeks 4, 12, and 24
- The composite endpoint of all-cause mortality, or WHF: Defined as the time from randomization to the first occurrence of any event of death due to any cause, or worsening heart failure (HF-related hospitalization or HF-related urgent care visit).
- OS
- Safety as determined by:
  - Incidence and severity of AEs;

- Changes in clinical safety laboratory tests, vital signs and 12-lead ECGs;
- Incidence and severity of ventricular or atrial arrhythmias detected using existing ICD/CRT-D or other applicable device interrogations.

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3.4. Baseline Variables

Randomization is initially stratified based on NYHA class: Class II/III or Class IV. NYHA Class II/III participants will be further stratified by the average of the Day -1 and Baseline Visit (Day 1) 6MWT (<320 m or ≥320 m), and *LMNA* mutation type (pathogenic/likely pathogenic [P/LP] or variants of unknown significance [VUS]).

In all 6MWT analyses, baseline will be calculated as the average of the non-missing 6MWT assessments recorded at assessment Day -1 and baseline (prior to randomization). Calculated baseline values for the 6MWT will be labeled as "Baseline (Calculated)" in the outputs to distinguish them from the Baseline visit values collected on the electronic case report form (eCRF). Baseline (Calculated) 6MWT values will be used in stratified efficacy analyses where analyses will be stratified by quartiles of baseline 6MWT.

Baseline for secondary and CCI endpoints is defined as the last observation up to and including Baseline Visit (Day 1).

3.5. Safety Endpoints

Safety will be assessed by medical history, physical examinations, vital signs, ECG including ICD/CRT-D interrogations, clinical laboratory tests, and the spontaneous reporting of AEs, in all participants who received at least 1 dose of study intervention. Unscheduled safety assessments may be performed at any time during the study to assess any perceived safety concerns.

3.5.1. Adverse Events

Medical Dictionary for Regulatory Activities (MedDRA) will be used to classify all AEs with respect to system organ class (SOC) and preferred term (PT).

The treatment emergent safety reporting period is defined as the period from the date of the first dose up to 30 days after the last dose of the study drug. An AE is considered a treatment-emergent adverse event (TEAE) if the event started during that reporting period.

Safety endpoints will be assessed by:

- Incidence of TEAEs.
- Incidence of Serious Adverse Events (SAEs).

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit red blood cells (RBC) Platelets white blood cells (WBC) Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Albumin Alkaline phosphatase aspartate aminotransferase (AST) Gamma-glutamyltransferase (GGT) alanine aminotransferase (ALT) Bicarbonate (CO_2) Total bilirubin blood urea nitrogen (BUN) Calcium Chloride creatine kinase (CK) Creatinine Glucose Magnesium Inorganic Phosphate Potassium Total protein Sodium Uric acid Direct bilirubin (if total bilirubin values are abnormal) NT-proBNP Troponins C-reactive protein	Blood Glucose Ketones Leukocytes hydrogen ion concentration (pH) Protein	<u>At screening only:</u> • Human immunodeficiency virus (HIV), Hepatitis B and C • thyroid-stimulating hormone (TSH) • estimated glomerular filtration ratio (eGFR) calculation • LMNA mutation If applicable: • Serum pregnancy test • Urine pregnancy test • follicle-simulating hormone (FSH)

- Incidence of AEs leading to discontinuation.

3.5.2. Laboratory Data

Laboratory testing will be performed at screening and throughout the study. The tests detailed in the table below will be performed by the central laboratory.

3.5.3. Other Safety Assessments

- Complete physical examination and brief physical examination.
- Vital Signs: parameters include blood pressure (systolic and diastolic), pulse rate, respiratory rate, and temperature.
- Arrhythmia assessment: incidence of new and clinically significant ventricular or atrial arrhythmias will be assessed by an ICD/CRT-D applicable device interrogations.
- ECG: A single 12-Lead ECG produces the following parameters: heart rate, PR, QT, corrected QT intervals (ie,correcting QT Fridericia method [QTcF]), and QRS complex. The ECG will also be interpreted for clinically significant findings.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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

Participant Analysis Set	Description
Full Analysis Set (FAS)	The FAS will consist of all randomized participants. Participants in the FAS will be analyzed according to the treatment to which they were randomized.
Efficacy Analysis Set (EAS)	The EAS will include all NYHA functional Class II or III randomized participants. Participants will be analyzed according to the treatment to which they were randomized.
CCI [redacted]	[redacted]
Interim Analysis Set 1 (IAS1)	A subset of the EAS which includes the first 60 randomized NYHA Class II or III participants with a *LMNA* gene mutation that is pathogenic, likely pathogenic or VUS. This analysis set will be used for interim futility assessment on change from baseline in 6MWT at Week 12 .
Interim Analysis Set 2 (IAS2)	A subset of the EAS which includes the first 68 randomized NYHA Class II or III participants with a *LMNA* gene mutation that is pathogenic, likely pathogenic or VUS. This analysis set will be used for interim futility assessment on change from baseline in 6MWT at Week 24.
Safety Analysis Set (SAS)	The SAS will include all participants who received at least 1 dose of study intervention regardless of NYHA functional class. Participants will be analyzed according to the initial treatment received. This analysis set will be used for the WHF, all-cause mortality, and safety endpoints.

Participant Analysis Set	Description
Pharmacokinetic Set (PK)	The PK set will consist of all participants who receive at least 1 dose of PF-07265803 and have at least 1 quantifiable postdose PK blood collection with associated valid bioanalytical results.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

Sample Size Determination

Following a pre-specified blinded sample size re-estimation, at least 160 NYHA Class II and III participants will be included in the EAS. In addition, up to 40 NYHA Class IV participants may be enrolled (randomized 1:1 to PF-07265803 and placebo) CCI [redacted]

Sample size estimation was initially determined based on a change from baseline in 6MWT at Week 12. Following a protocol amendment to update the primary endpoint to change from baseline in 6MWT at Week 24, the same assumptions were applied given the protocol requirement for participants who discontinue study treatment to continue with follow-up through at least Week 24 and the anticipated low mortality rate within the study population. Sample size and assumptions prior to the pre-specified blinded sample size re-estimation are outlined below. The blinded sample size re-estimation was performed by an internal team who are not directly involved with the day-to-day activities of the study. To ensure the integrity of the trial the specific assumptions resulting in the increase in sample size will not be disclosed until the time of primary reporting.

With 60 participants per treatment arm the study will have approximately 90% power to demonstrate a statistically significant effect for the primary endpoint of Week 24 6MWT change from baseline, at a 2-sided a=0.05 if the true treatment effect is 35 meters, there is a standard deviation (SD) of 50 meters for the change from baseline and 10% of participants do not have data recorded at Week 24. This assessment was made by simulation and further assuming that:

- The correlation between the baseline and Week 24 values for the 6MWT is 0.44 as observed in the completed Phase 2 study ARRAY-797-231.
- Data are analyzed using a stratified Wilcoxon Rank-sum test with participants stratified into 4 groups according to baseline quartile of 6MWT.
- 1.25% of participants die before Week 24 and are given the worst set of ranks ordered according to their survival time.

- The participants who are alive and who do not have data recorded at Week 24 are given a tied ranking worse than any participant with data recorded and better than any participant who died before Week 24.

- The probability of dropout is related to outcome so that dropout is half as likely for participants with Week 24 6MWT values more than 1 standard deviation (SD) above the mean compared to participants 1 SD below the mean.

- An interim futility analysis will be performed after the first 60 randomized NYHA Class II/III participants from the EAS population have completed the Week 12 assessment or have discontinued prior to Week 12.

As noted in Section 7.1, blinded data at the time of the interim futility analysis were utilized to evaluate the rates of deaths and study discontinuation prior to Week 24, and the standard deviation for the change from baseline in 6MWT at Week 24 to allow for a reassessment of the sample size. Following completion of the planned blinded sample size re-estimation, up to 200 eligible participants with symptomatic cardiomyopathy due to *LMNA* will be randomized, including at least 160 participants with NYHA functional Class II or III and up to 40 participants with NYHA functional Class IV.

Primary Efficacy Analysis

For the primary endpoint, the null hypothesis is that the treatment groups for PF-07265803 and placebo do not differ with respect to functional capacity. The alternative hypothesis of interest is that there is a difference in functional capacity in favor of PF-07265803. Functional capacity will be measured by change from baseline in 6MWT at Week 24 with a rank-based test to account for deaths or withdrawals prior to Week 24 (see Section 6.1). PF-07265803 will be declared superior to placebo if the null hypothesis of no difference between PF-07265803 and placebo is rejected at the significance level of 0.05 (2-sided).

If the primary endpoint of change from baseline in 6MWT at Week 24 is statistically significant, inferential testing on secondary endpoints will be performed in the following hierarchical order: Week 24 change from baseline in the KCCQ PL score, Week 24 change from baseline in the KCCQ TSS, the composite endpoint comprised of all-cause mortality or worsening heart failure (HF-related hospitalization or HF-related urgent care visit), and NT-proBNP. To maintain the overall alpha at 0.05, each hypothesis will be tested at the 0.05 level if the endpoint earlier in the hierarchy is deemed statistically significant. CCI [redacted]

Interim Futility Analysis for Change from Baseline in 6MWT at Week 12

An interim futility analysis of change from baseline in 6MWT at Week 12 was performed after the first 60 randomized NYHA Class II/III participants had completed the Week 12 assessment or discontinued from the study prior to Week 12. The non-binding futility boundary was calculated as function of information using Hwang-Shih-DeCani spending function with gamma = -1.54. The one-sided p-value boundary for information fraction equal to 0.5 was 0.315 at the interim look. As the objective of this interim futility analysis

was not to terminate the study early for the benefit of efficacy, no adjustment of alpha is needed as a result of the interim analysis. At the time of the planned interim futility analysis, the DMC recommended to continue the study as designed.

Blinded Sample Size Re-Estimation and All-Cause Mortality or WHF Event Monitoring

Following the interim analysis for futility described above, a blinded sample size re-estimation for the primary endpoint of change from baseline in 6MWT at Week 24 was conducted by an internal BSSR review committee using blinded cumulative primary efficacy data from the interim data cut. Specifically, a blinded, pooled analysis across treatment groups was used to estimate variability of change from baseline in 6MWT assessments at Week 24 and the overall event rates for deaths and discontinuations prior to Week 24. Further details on blinded sample size re-estimation are described in Section 7.1 Interim Analysis.

In addition to the sample size re-estimation for the primary endpoint, the sponsor will monitor the pooled (blinded) cumulative event counts for the composite safety endpoint comprising of all-cause mortality or worsening of heart failure throughout the study. Further details on the blinded assessment of the composite endpoint are provided in Section 7.1.

Interim Futility Analysis for Change from Baseline in 6MWT at Week 24

Given the change in timepoint of the primary endpoint from 12 to 24 weeks and the longer than anticipated duration of the enrollment period, an additional interim futility analysis based on the primary endpoint of change from baseline in 6MWT at Week 24 will be conducted after the first 68 randomized NYHA Class II/III participants have completed the Week 24 assessment or discontinued from the study prior to Week 24 (see Section 7).

5.2. General Methods

Analysis results will be presented using descriptive statistics. For continuous variables, the number of participants (n), mean, SD or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented. For binary and categorical variables, the number and percentage of subjects in each category will be presented.

All statistical tests will be 2-sided and performed at the 5% significance level unless otherwise specified.

5.2.1. Analyses for Continuous Endpoints

For the analyses of the primary and secondary endpoints (ie, 6MWT, KCCQ, and NT-proBNP), a rank-based non-parametric approach will be used that accounts for deaths or discontinuations from study prior to the analysis time point. Participants who died will be ranked below those who discontinued from study, and those participants, in turn, will be ranked below all those who completed the study. The relative ranks will be determined by survival time among those participants who died and by length of time in the study among those who discontinued from study. The p-value from the van Elteren test will be provided

to assess the statistical significance of the treatment difference between PF-07265803 and placebo.

The following summaries will be provided to describe the treatment effect:

- A summary of the stratified Hodges-Lehmann (HL) median difference between treatment groups in the change from baseline to the analysis time point and corresponding 95% CI (primary description of the treatment effect).
- A stratified win-ratio and corresponding 95% confidence interval (CI).
- A summary of the number of deaths and discontinuations prior to the analysis time point on each treatment arm.

The Van Elteren Test and Algorithm for Ranking

The van Elteren test is an extension of the stratified Wilcoxon Rank-sum test. In the van Elteren test, each stratum is weighted by $1/(n_k + 1)$, where n_k denotes the total number of participants in stratum k. Participants will be placed into 1 of 4 strata according to the quartiles of baseline value of the 6MWT endpoint as follows:

- Participants will be included in stratum 1 if their overall rank is $\leq 0.25*n$.
- Participants will be included in stratum 2 if their overall rank is and $>0.25*n$ and $\leq 0.5*n$.
- Participants will be included in stratum 3 if their overall rank is $>0.5*n$ and $\leq 0.75*n$.
- Participants will be included in stratum 4 if their overall rank is $>0.75*n$.

  where n is the total number of participants in the EAS.

After multiple imputation (see Section 5.3.1) and prior to analysis, the continuous primary and secondary endpoints (ie, 6MWT, KCCQ, and NT-proBNP) at each time point of interest will be ranked as follows ordered from lowest (worst) to highest rank on each imputed dataset.

- Participants who die prior to the analysis time point will be given the lowest set of ranks ordered from shortest to longest survival time. Note that participants who have discontinued from study and then died prior to the analysis timepoint are ranked based on survival time, instead of time to study discontinuation.
- Participants who discontinue from study prior to the analysis time point for any reason will be ranked next lowest ordered based on their time to discontinuation.
- Participants who remain in the trial at or beyond the analysis time point but who have a missing assessment in the endpoint (eg, due to COVID-19) will have missing values imputed for the endpoint using the method of Markov chain Monte Carlo (MCMC) multiple imputation (MI) assuming a multivariate normal distribution over all variables

included in the imputation model. This imputation will be done by treatment group with number of days on treatment, baseline values, and values observed at Weeks 4, 12, 24, and 36 included in the imputation. For participants who do not die or discontinue the study prior to the analysis time point but have monotone missing data and subsequently discontinue the study at a later timepoint, missing data will be imputed under missing at random (MAR) for those who discontinue due to issues outside of the study (eg, due to COVID-19) and imputed using control-based MI for those who discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy).

- The imputed values from those with the missing assessment will be used along with the observed values from all other participants to rank the remaining participants from greatest reduction (change less than 0) to greatest increase for the endpoint at the analysis time point.

The van Elteren test will be performed on each imputed dataset. The statistical significance of the analysis will be based on the asymptotic, continuity corrected p-value. The results from these multiple datasets will be pooled using the Rubin's rule (see Section 5.3.1).

Stratified Hodges-Lehmann (HL) Estimator

A stratified HL estimate will be used to describe the treatment effect (magnitude of change) for the endpoint at the analysis time point. Participants will be stratified by baseline 6MWT quartiles. Missing data due to issues outside of the study (eg, due to COVID-19 pandemic) will be imputed based on a missing at random (MAR) assumption. Missing data for discontinuation due to post randomization events (eg, AE or perceived lack of efficacy) will be imputed using control-based MI (see Section 5.3.1). Imputations following death will not be utilized as imputed values for participants who died prior to the assessment timepoint would not be interpretable.

In each multiply imputed dataset, the within stratum HL estimate will be calculated as the median of the n_{1k}*n_{2k} pairwise differences between n_{1k} and n_{2k} participants in the 2 treatment arms. The overall stratified HL estimate is then calculated in each multiply imputed dataset as a weighted average of the within stratum HL estimates by weighting each stratum HL estimate by $w_k = (n_k + 1)/\Sigma(n_k + 1)$. That is $\hat{\Delta}_{HL} = \sum_{k=1}^{S} w_k \hat{\Delta}_k$, where $\hat{\Delta}_k$ is the HL estimator in the k^{th} stratum and $\sum_{k=1}^{S} w_k = 1, w_k > 0$. This linear combination $\hat{\Delta}$ HL is asymptotically median unbiased and normally distributed with standard error given by $SE = \sqrt{\sum_{k=1}^{S} (W_k SE_j)^2}$. Thus, as with van Elteren and win ratio, the overall stratified HL estimates calculated for each imputation can then be pooled using the Rubin's rule (see Section 5.3.1).

The Win Ratio and Algorithm for Defining Winners/Losers/Ties

A stratified win ratio will be used to aid in the interpretation of the van Elteren test. It is essentially the ratio of the win proportion for the active treatment to the win proportion for the control group. The win ratio is connected to the Mann-Whitney U test under the

framework of prioritized pairwise comparisons (Dong, 2020).[1] The treatment is beneficial compared to the control if the win ratio is greater than 1.

The stratified win ratio is based on the principle that each participant in the PF-07265803 group is compared with every participant in the placebo group within each stratum (ie, baseline 6MWT quartile) in a pair-wise manner. Applying the same ranking algorithm used in the van Elteren test, the pair-wise comparison proceeds in hierarchical fashion using time to death for those who died prior to the analysis time point first, followed by time to discontinuation from study for those who discontinued prior to the analysis time point, and then changes from baseline in the endpoint at the time point.

The detailed algorithm defining for 'Win', 'Loss' and 'Tie' is provided in Table 3 below. For each pair, the active treatment participant (PF-07265803) is labelled as a 'winner' or a 'loser' based on status at or prior to the analysis time point (eg, Week 24 for the primary analysis). The win ratio is the total number of winners divided by the total numbers of losers.

Table 3. Algorithm Defining for Win/Loss/Tie at a Given Time Point

		Placebo		
		Died time X_P	**Alive/discontinued from study time Y_P**	**Alive/ change from baseline Z_P**
Active treatment (PF-07265803)	**Died time X_A**	If $X_A < X_P$, then Category = 'Loss' for active treatment If $X_A > X_P$, then Category = 'Win' for active treatment Else category = 'Tie'	Category = 'Loss' for active treatment	Category = 'Loss' for active treatment
	Alive/discontinued from study time Y_A	Category = 'Win' for active treatment	If $Y_A < Y_P$, then Category = 'Loss' for active treatment If $Y_A > Y_P$, then Category = 'Win' for active treatment Else category = 'Tie'	Category = 'Loss' for active treatment
	Alive/change from baseline Z_A	Category = 'Win' for active treatment	Category = 'Win' for active treatment	If $Z_A < Z_P$, then Category = 'Loss' for active treatment If $Z_A > Z_P$, then Category = 'Win' for active treatment Else Category = 'Tie'

Footnote: if a participant withdrew and then died prior to the analysis timepoint, the participant will be counted as death.

The stratified win ratio is achieved by counting the wins separately within each stratum (ie, stratum-specific wins) and then combining the stratum-specific wins to estimate the stratified win ratio. A weighting, defined as the reciprocal of the stratum size, is used in this calculation. The variance estimate of the stratified win ratio will be calculated based on Equation (8) of Dong, et al (2018).[2]

This process produces a stratified win ratio for each imputed dataset. As with the van Elteren test, the results from these multiple datasets will be pooled using the Rubin's rule (see Section 5.1).

5.2.2. Analyses for Binary Endpoints

For analysis of the binary endpoints, observations after death or discontinuation from study, or missing values for any reasons will be handled by setting the endpoint to nonresponsive. This method of handling missing response is known as missing response as non-response (MR-NR). A Cochran-Mantel-Haenszel (CMH) test stratified by stratification factors at randomization (see Section 3.4) will be used as a test for proportions of participants (see Section 6.2.2). The stratification factor for P/LP vs VUS will be removed if the number of events in the stratum by either treatment group is less than 2. P-value from the CMH test, the estimate of proportion, difference in proportion and the corresponding 95% CI of participants with response at each visit between PF-07265803 versus placebo will be presented.

5.2.3. Analyses for Categorical Endpoints

The frequency and percentage for each category will be presented for categorical endpoints.

5.2.4. Analyses for Time-to-Event Endpoints

Time-to-event endpoints including the composite endpoint of all-cause mortality and worsening heart failure and OS will be summarized using the Kaplan-Meier method and estimated survival curves will be displayed graphically when appropriate. Graphs will describe the number of participants at risk over time. The median, quartiles, and probabilities of an event at points in time will be estimated by the Kaplan-Meier method. The number of subjects at risk, number of events and number of censored observations will be summarized.

Time-to-event endpoints will also be analyzed using the Cox proportional hazards model with treatment and the strata as assigned at randomization (see Section 3.4) as the covariates. The stratification factor for P/LP vs VUS will be removed if the number of events in the stratum by either treatment group is less than 2. The hazard ratio, its 90% and 95% 2-sided CIs will be calculated.

5.3. Methods to Manage Missing Data

5.3.1. Continuous Endpoints

MI approach will be used to handle missing data in the analyses of primary and secondary endpoints (ie, 6MWT, KCCQ, and NT-proBNP) through the Week 24 visit. The extent and pattern of missing data for the primary and secondary endpoints will be summarized separately by treatment group.

There are 2 sources that contribute to missing data for the efficacy measures which will be handled using MI:

1) Premature discontinuation from study.

2) Missed assessments while the participants remain in the trial (eg, due to COVID-19 pandemic).

Note that the protocol specifies that participants who discontinued study treatment prior to Week 24 should continue to have all assessments performed as scheduled through the Week 24 Visit. Therefore, such participants are not considered as a source of missing data.

Missing data due to issues outside of the study (eg, due to COVID-19 pandemic) will be imputed based on a MAR assumption. In the van Elteren test, premature discontinuation from study are incorporated in the endpoint definition through the ranking rules (see Section 5.2.1). Missing data for discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy) will be imputed using a control-based MI (see Section 5.3.1) in the stratified HL estimation of treatment effect for the primary and secondary endpoints (see Section 6.1.1 and Section 6.2). Additional sensitivity analysis using a control-based MI for discontinuations from study due to heart failure prior to analysis time point in the PF-07265803 will be performed (see Section 5.3.1 and Section 6.1.2.3).

The MI procedure replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute. This is a 4-step process.

Step 1 (imputing intermittent missing data): The dataset will be converted into monotone missing pattern by imputing intermittent missing data as the first step. Intermittent missing values will be imputed using the MCMC method assuming a multivariate normal distribution over all variables included in the imputation model. This imputation will be done by treatment group with number of days on treatment, baseline 6MWT, and values observed at Weeks 4, 12, 24 and 36 included in the imputation. This procedure will generate 100 multiply imputed datasets. The monotone data will then be imputed with monotone regression method.

Step 2 (imputing monotone missing data): Monotone missing data due to study withdrawal related to COVID-19 pandemic or monotone missing data while participants ongoing at the data cutoff will be imputed under MAR. Imputation will be undertaken within each treatment arm with number of days on treatment, mutation type (VUS vs P/LP), baseline and previous values as covariates. Monotone missing values for participants with study withdrawal for other reasons by the data cutoff date will be imputed using the imputation model built from the placebo group, ie, assuming the missing data in the treatment group will have a profile that equals the profile of the placebo group (ie, a copy-reference imputation). Number of days on treatment, mutation type (VUS vs P/LP), baseline 6MWT, and all prior assessments will be included as covariates in the monotone imputation model. The sample SAS statement can be found in Appendix 2.

Step 3 (performing analysis using each imputed dataset): These multiple imputed datasets will be analyzed using data methods specified in Section 5.2.1. The van Elteren test, the

stratified win ratio, and the stratified HL estimates will be calculated on each of the 100 imputed datasets.

Step 4 (combine results): Resulting treatment effect parameter estimators and standard errors from each of 100 multiple imputed datasets from Step 3 will be combined to obtain the pooled treatment effect and variance parameter estimators according to Rubin's rules. Note that Rubin's rules for combining multiply imputed estimates are based on asymptotic theory.

For pooling results from the van Elteren tests on the imputed datasets, additional steps outlined below need to be undertaken in using the Rubin's rule.

- Let $S_{MI} = \frac{1}{M}\sum_{k=1}^{M} S_k$ represent the mean van Elteren statistics across M imputations, where S_k denotes the van Elteren statistic for each imputation.
- Let $\bar{W} = \frac{1}{M}\sum_{k=1}^{M} W_k$ represent the average within-imputation variance, where W_k denotes the variance estimate of the van Elteren statistics within each imputation.
- Let $B = \frac{1}{M-1}\sum_{k=1}^{M} (S_k - S_{MI})^2$ be the between-imputation variance of the van Elteren statistics.
- Let $T_{MI} = \bar{W} + (1 + \frac{1}{M})B$ be the total variance across imputations.
- Let $v = (M-1)\left[1 + \frac{\bar{W}}{(1+\frac{1}{M})B}\right]^2$ be the degrees of freedom for the t-distribution.

The test statistic is $T = \frac{S_{MI} - E_0(S)}{\sqrt{T_{MI}}}$, where $E_0(S)$ is expected value of S under the null hypothesis of no treatment effect. The $E_0(S)$ is subtracted from each S_{MI} input so the procedure's reported null test comparing S_{MI} to 0 yields the appropriate null test without any additional computation.

With regard to pooling results from the win ratio tests on the imputed datasets, since the distribution of the log (win ratio) is better approximated by a normal distribution for finite n (Dong et al, 2016),[3] the logarithm of the stratified win ratios will be applied prior to the Rubin's rules. The combined estimate of the stratified win ratio and CI on logarithmic scale can then be back transformed to get the overall pooled estimate for the stratified win ratio and its 95% CI.

With regard to pooling HL estimates from the imputed data sets, since the linear combinations Δ_{HL} are asymptotically median unbiased and normally distributed with standard error given by $SE = \sum_{k=1}^{S} (W_k SE_{jk})^2$, these estimates are used to produce the final Hodges-Lehmann estimator.

5.3.2. Binary Endpoints

For binary endpoints analyzed at each scheduled visit separately (see Section 6.2.2 and Section 6.2.3), participants with missing data at a time point for any reason will be defined as MR-NR at that time point.

6. ANALYSES AND SUMMARIES

The primary analysis will be performed when all randomized participants in NYHA Class II/III have had the opportunity to be followed for at least 24 weeks (or otherwise withdrawn) and an evaluation of the composite endpoint consisting of all-cause mortality and worsening heart failure (HF-related hospitalization or HF-related urgent care visit) can be performed. For analysis purposes, all dated assessments for efficacy will be categorized into analysis windows. Analysis windows for primary, secondary, and CCI endpoints are provided in Appendix 3.

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6.1. Primary Endpoint(s)

6.1.1. Primary Analysis

The change from baseline (based on the average of the Day-1 and baseline visit 6MWT results) in 6MWT at Week 24 will be analyzed in the NYHA Class II/III participants using the van Elteren test, a rank-based non-parametrical approach (see Section 5.2.1). PF-07265803 will be declared superior to placebo if the null hypothesis of no difference between PF-07265803 and placebo is rejected at the significance level of 0.05 (2-sided).

The primary method to describe the treatment effect for change from baseline in 6MWT at Week 24 will be a stratified HL median difference (with 95% CI) (see Section 5.2.1). The stratified HL median difference of Week 24 change from baseline in 6MWT between PF-07265803 and placebo will be estimated for participants surviving 24 weeks. Imputations for missing data are described in Section 5.2.1. Number of missing measurements at Week 24, reasons for missingness, and the type of imputation used (MAR, copy-reference, etc.) will be summarized.

As supportive analysis, a stratified win ratio statistic (and 95% CI) as described in Section 5.2.1 will be reported using the same ranking used in the hypothesis testing to aid in the interpretation of the van Elteren test.

In analyzing the contribution of death and discontinuation components to the primary efficacy analysis, descriptive summaries on number of deaths and discontinuations from study prior to Week 24, and the reasons for withdrawals from study will be provided.

For participants with observed 6MWT at Week 24, actual values and change from baseline at Week 24 will be summarized using descriptive statistics (N, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment.

Improvement in 6MWT will be categorized into the following: ≥15m, ≥30m, ≥45m, ≥60m, ≥75m. Percent of participants in each category of 6MWT based on observed change from baseline to Week 24 will be tabulated by treatment arm. A cumulative distribution of responses for PF-07265803 vs Placebo will also be generated, with observed change from baseline to Week 24 on the X-axis and the percentage of participants experiencing a change value of X points or above on the Y axis.

6.1.2. Sensitivity Analyses

6.1.2.1. Sensitivity Analysis Using a Mixed-Effect Model for Repeated Measures (MMRM)

A MMRM model will be used for treatment comparison of change from baseline for participants who survive to Week 24. The MMRM will include treatment arm, visit, interaction of treatment arm and visit as fixed effects and baseline 6MWT as a covariate and all data up to Week 24. The unstructured covariance matrix will be used to model the within-subject variance-covariance errors. If the algorithm does not converge, the Toeplitz, first-order autoregressive or compound symmetric covariance structure will be considered in the order listed until convergence is obtained. The MMRM analysis assumes MAR without explicitly imputing missing data. Rubin's method will be used to pool the MMRM estimates, standard errors and 95% confidence interval across the 100 multiply imputed datasets. Least square mean difference, its 95% CI and p-value will be tabulated for treatment comparison.

6.1.2.2. Sensitivity Analysis Using Trimmed Mean in Combination With MI

To assess the sensitivity to the missing rates due to death and study discontinuation, a trimmed means analysis combining with multiple imputation will be performed on the EAS by treating death and study discontinuation prior to Week 24 as worst outcomes and trimming an equal fraction of these unfavorable outcomes from each treatment group to examine the robustness of primary efficacy results. Missing data at Week 24 due to issues out of study (eg, due to COVID-19 pandemic) will be imputed under MAR using MI. The combination of MI and the trimmed means approach can improve estimates when the assumptions of each hold (Ocampo, et al 2019).[5]

The trimmed mean method assumes that all subjects meeting trimming criteria (ie, death and study discontinuations) have equally bad non-numerical outcomes and will be ranked the worst. In the trimmed mean approach combining with MI, the missing data from participants who missed the 6MWT assessment while remaining in the study during the assessment window, will be imputed based on the distribution of the observed outcomes from participants who completed the week 24 visit given the MAR assumption. Imputation will be undertaken within treatment group with number of days on treatment, baseline and previous values as covariates. The imputed values from those with the missing assessment and the observed values from those who completed the assessment will be used to rank the remaining participants from greatest reduction (change less than 0) to greatest increase. An equal fraction of the worst outcomes will then be trimmed from each treatment group based on the ranked data. The fraction trimmed is pre-specified at a fixed percentage (ie, 30%) to ensure all patients who have died or discontinued from study prior to Week 24 are trimmed.

MI relies on the asymptotically normal distribution which applies to the trimmed mean. The trimmed mean analysis estimates the difference between the means of the included upper proportion of the outcome distribution for each treatment arm. Imputed data are utilized to calculate trimmed means estimates on each imputed dataset. The least squares mean difference in change from baseline to Week 24 for PF-07265803 minus Placebo and its standard error will be calculated using an analysis of covariance (ANCOVA) with treatment and baseline as covariates. Rubin's rules will be used to summarize the results of the trimmed means applied to each partially imputed dataset.

The 95% CI of the difference in trimmed means for treatment groups and p-value for testing the null hypothesis of no difference in the trimmed means will be calculated by 1,000 permutation tests using random shuffling the treatment assignments within the datasets.

6.1.2.3. Sensitivity Analysis to Assess the Impact of Heart Failure Determined Withdrawal

In this sensitivity analysis, missing value for participants with study withdrawal related to adjudication-confirmed HF-related events in the PF-07265803 arm will be imputed based on the distribution of the values in the placebo arm, while the missing data for any other reasons will be imputed under MAR (see Section 5.3.1). Note that imputations for participants who have died prior to Week 24 are not performed.

The imputed data sets can be used for the van Elteren test, stratified win ratio, and for the stratified HL estimation, with deaths excluded from the HL estimation. Rubin's rule will be applied to pool multiply imputed estimates for overall inference (see Section 5.2.1 and Section 5.3.1). The ranking for the van Elteren test is as follows:

- Participants who die before Week 24 will be given the lowest set of ranks according to their survival time (as in the primary analysis). Note if a patient withdrew and then died prior to the analysis timepoint, the patient will be counted as death.

- Participants who discontinue from study prior to Week 24 due to heart failure will have Week 24 values imputed based on the distribution of the Week 24 values in the placebo arm (see Section 5.3.1).

- Participants who discontinued prior to Week 24 for reason other than heart failure will have 6MWT values imputed under MAR using MI (see Section 5.3.1).

- Participants who remain in the trial at or beyond Week 24 but who have a missing Week 24 6MWT assessment (eg, due to COVID-19) will have 6MWT values imputed under MAR using MI (as in the primary analysis).

- The imputed values will be used along with the observed values from all other participants to rank the remaining participants from greatest reduction (change less than 0) in Week 24 6MWT to greatest increase (as in the primary analysis).

6.1.2.4. Sensitivity Analysis to Assess the Impact of the COVID-19 Pandemic

The COVID-19 pandemic has impacted study conduct leading to participants missing visits and for some participants the 6MWT course changed after the baseline visit due to COVID-19 restrictions having impacted the original course. Additional sensitivity analyses may be performed to address the potential impact of COVID-19-related changes to study conduct on the primary efficacy analysis:

- Exclude data from participants who had a change in the 6MWT course after baseline visit.

- Exclude data from participants at a given site who would have had endpoint assessment during disruptions period, regardless of post-randomization outcomes (see FDA, 2020 guidance).[4] In this approach, all potentially impacted participants will be identified through the site location and randomization dates that are associated with endpoint ascertainment. The impacted period for each region and/or site will be defined prior to unblinding.

For the sensitivity analyses related to the impact of COVID-19 as described above, data will be ranked and analyzed in the same way as described for the primary efficacy analysis (see Section 6.1.1). P-value from the van Elteren test, stratified win ratio and HL estimate of treatment difference in 6MWT will be provided along with summaries on deaths and withdrawals by treatment group (see Section 5.2.1).

6.2. Secondary Endpoint(s)

6.2.1. Change From Baseline in 6MWT at Weeks 4 and 12 in NYHA Class II/III Participants

The change from baseline in 6MWT at Weeks 4 and 12 will be summarized using the same method as described for the primary endpoint analysis (see Section 5.2.1 and Section 6.1.1). However, the nominal p-value produced based on van Elteren test will be for exploratory purpose only.

In addition, a plot for the mean observed change from baseline (SE) of 6MWT at each timepoint (ie, Weeks 4, 12, and 24, and every 12 weeks) will be provided by treatment to support the durability of efficacy on 6MWT.

6.2.2. Change From Baseline in KCCQ Domains at Weeks 12 and 24 in NYHA Class II/III Participants

The TSS, Clinical Summary Score (CSS), PL score and Overall Summary Score (OSS) of the KCCQ will be analyzed at both Weeks 12 and 24 using the same method as described for the primary endpoint analysis (see Section 5.2.1 and Section 6.1.1). Missing data will be handled in the same fashion as the analysis of 6MWT at Week 24 (see Section 5.3.1). Likewise, the HL estimates and associated 95% CIs will be presented and constructed in the same way as used for 6MWT (see Section 5.2.1). Only PL and TSS will be included in the formal testing hierarchy comparing the difference between treatment arms (PL will be tested first followed by TSS).

Additionally, participants will be defined as having improved for PL and TSS at Week 24 if their score improves (increases) by a pre-defined threshold vs baseline at Week 24. In this analysis, participants with missing data at a time point for any reason will be defined as MR-NR at that time point (see Section 5.2.2). The proportion of participants with an improvement will be analyzed using the CMH test as described in Section 5.2.2. The pre-defined threshold will be defined prior to unblinding of the database. The analyses to establish the pre-defined threshold will be described in a supplemental analysis plan. The threshold analysis results will be reported separately from the CSR.

Descriptive statistics of the KCCQ domains at each visit will also be provided.

6.2.3. Change From Baseline in PGI Scores at Weeks 12 and 24 in NYHA Class II/III Participants

For each question on the PGI-S, the number and proportion of participants with at least a 1-category and at least a 2-category improvement from baseline will be summarized at each visit by treatment arm. Participants with missing data at a time point for any reason will be defined as MR-NR at that time point. Any participant who has a baseline assessment of none or mild will be excluded from the denominator in calculating the proportion.

For each question on the PGI-C, the number and proportion of participants who describe their change in overall status as "Moderately better" or "Very much better" will be summarized at each visit by treatment arm. Participants with missing data at a time point for any reason will be defined as MR-NR at that time point.

PGI-S and PGI-C data will also be used to interpret improvement thresholds for the PL and TSS based on a blinded assessment, which will be performed prior to unblinding of the data. The thresholds will be defined by evaluating the relationship between changes on the PL and TSS and changes in the corresponding PGI-S and PGI-C questions. The details about the analyses to establish the pre-defined threshold will be described in a supplemental PRO SAP.

6.2.4. Change From Baseline in NT-proBNP at Weeks 4, 12, and 24 in NYHA Class II/III Participants

As part of the hierarchical testing strategy described in Section 6.2, the change of Week 24 NT-proBNP from baseline will be analyzed using the same method as described for the primary analysis (see Section 5.2.1 and Section 6.1.1). Missing data will be handled in the same fashion as the analysis of 6MWT at Week 12 (see Section 5.3.1). Likewise, the HL estimates and associated 95% CIs will be presented and constructed in the same way as used for 6MWT (see Section 5.2.1).

The change of Week 4 and Week 12 NT-proBNP from baseline will also be analyzed. Only the 24-week endpoint will be alpha controlled for the hierarchical testing. The p-value from the van Elteren test on Week 4 and Week 12 NT-proBNP will be for exploratory purpose only.

6.2.5. The Composite Time to First Occurrence of All-Cause Mortality or Worsening Heart Failure

An episode of worsening heart failure is either a hospitalization or an urgent visit for heart failure confirmed by the clinical event committee (CEC) as per the criteria in Protocol Appendix 9. Only adjudicated and confirmed events will be included in the analyses.

The composite endpoint measures the time from randomization to the first occurrence of death from any cause, or worsening heart failure defined as HF-related hospitalization or a HF-related urgent care visit and will include all data recorded while the participant is on study, including while in follow-up. Participants will be censored at the latest time they are known to be alive and have not experienced any HF-related hospitalization or a HF-related urgent care visits.

The composite endpoint will be summarized using the Kaplan-Meier method and compared between treatment groups using a stratified Cox model using the strata as assigned at randomization (see Section 3.4) and treatment arm as a fixed effect. The stratification factor for P/LP vs VUS will be removed if the number of events in the stratum by either treatment group is less than 2. The upper confidence limit of a 2-sided 90% CI for the HR will be compared, using the SAS, to a value of 2 to rule out an excess risk. A 95% CI will also be presented. As a supportive analysis, the composite endpoint will be analyzed using the EAS.

Additionally, analyses of time to HF-related hospitalization and time to urgent care visit will be performed to examine the contribution of each component of the composite endpoint, with date of death from any cause as an additional point of censoring.

6.2.6. Overall Survival

Overall Survival (OS) is defined as time from randomization until death due to any cause and will include all data recorded while the participant is on study, including while in follow-up. For a participant who did not complete the study, ie, who was lost to follow-up or withdrew consent, if the vital status for the participant can be retrieved from public information, the vital status (dead or alive) at the end of the study collected from public sources will be included in the analysis of death from any cause. Participants who do not have a death date will be censored for OS at their last contact date. OS will be calculated for all participants and summarized by treatment arm using the Kaplan-Meier method and compared between treatment arms using a stratified Cox model as described in Section 5.2.4.

The primary analysis of OS will be based on the SAS and supportive analyses will be performed using the EAS.

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6.4. Subset Analyses

Subgroup analyses for the primary endpoint and for alpha-controlled secondary endpoints will be performed if the sample size is sufficient within each individual subgroup.CCI The objective of the subgroup analyses is to investigate the consistency of treatment effect across subgroups of clinical importance. The study is not powered for statistical significance within the subgroups. The subgroups of interest include:

- Mutation type (P/LP vs VUS);
- NYHA Class (II vs III);
- Baseline 6MWT stratum (<320 meters vs ≥320 meters);

- Race (Caucasian vs non-Caucasian);
- Region (North America vs Rest of the World);
- Age (≥18 to <35 years; ≥35 to <50 years; ≥50 to 65 years; and ≥65 years);
- Gender (male vs female).

Key safety analyses will be provided by demographic subgroup (age, gender, race). These analyses include AEs by PT (related and all-cause); SAEs by PT (related and all-cause); AEs leading to study drug discontinuation and deaths.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographics and baseline characteristics listed in Section 3.4 will be summarized.

6.5.2. Study Conduct and Participant Disposition

The below participant populations/sets will be summarized for PF-07265803 and placebo:

- Enrolled;
- Randomly assigned to investigational product;
- Treated;
- Each analysis dataset (FAS, EAS, NYHA Class IV, SAS, PK).

Participant disposition (eg, discontinuation from treatment, discontinuation from study, reason for discontinuation, completed study, and ongoing) will be summarized for PF-07265803 and placebo.

Medication errors will be listed.

6.5.3. Study Treatment Exposure and Compliance

Duration of exposure to study drug, and average daily dose will be summarized by treatment arm.

- Duration of exposure (weeks) = (last dose date – first dose date + 1)/7;
- Average daily dose (mg/day) = cumulative dose (mg) / number of actual dosing days.

  where cumulative dose (mg) is calculated as total dose given during the study treatment exposure, and number of actual dosing days is calculated as [duration of exposure (days) – number of days of interruption].

Duration of exposure will also be categorized by time intervals (ie, <4 weeks, ≥4 – <8 weeks, ≥8 – <12 weeks, ≥12 – <24 weeks, ≥24 – <52 weeks, ≥52 – <104 weeks, ≥104 – <156 weeks, ≥156 weeks) for which frequency counts and percentages of participants will be provided. Frequency counts and percentages of participants who have dose reductions or interruptions, and the corresponding reasons, will be summarized.

The percentage of study drug compliance for the overall treatment period will be derived for each participant as the number of actual dosing days (excluding days of interruption) relative to the duration of exposure (day). A participant will be considered compliant with the dosing regimen if he or she receives 80% to 120% of the expected number of doses, in accordance with the protocol. The number and percentage of participants who are compliant with the dosing regimen will be summarized.

6.5.4. Concomitant Medications and Nondrug Treatments

The World Health Organization (WHO)-Drug coding dictionary will be used to classify concomitant medications.

The number and percent of participants who took each concomitant medication will be provided for PF-07265803 and placebo.

6.6. Safety Summaries and Analyses

Safety data will be summarized descriptively, where appropriate. Categorical outcomes (eg, AEs) will be summarized by participant counts and percentage. Continuous outcome (eg, pulse rate, etc) will be summarized using n, mean, median, standard deviation. Change from baseline in vital signs will also be summarized. Participant listings will be produced for these safety endpoints accordingly.

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 AE or a group of AEs. 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 descriptive analyses.

6.6.1. Adverse Events

AEs for participants who discontinue from the study due to AEs will be listed and summarized by SOC and PT for PF-07265803 and placebo.

Incidence of TEAEs (all causalities and treatment-related) will be summarized by SOC and incidence and severity of TEAEs (all causalities and treatment related) will be summarized by SOC and PT for PF-07265803 and placebo.

Deaths and SAEs will be listed and incidence of SAEs (all causalities) will be summarized by SOC and PT for PF-07265803 and placebo.

6.6.2. Laboratory Data

Incidence of laboratory test abnormalities will be summarized for PF-07265803 and placebo without regard to baseline abnormality, for normal baseline, and for abnormal baseline. Additionally, changes from baseline to last observation in laboratory test parameters will be summarized descriptively for PF-07265803 and placebo.

6.6.3. Vital Signs

Observed values and changes from baseline in vital sign parameters will be summarized descriptively for PF-07265803 and placebo by visit.

6.6.4. Electrocardiograms and Arrhythmia Assessment

Changes from baseline in ECG parameters will be summarized descriptively for PF-07265803 and placebo by visit. The nature and frequency of arrhythmias will be tabulated by PF-07265803 and placebo.

6.6.5. Physical Examination

Physical examination data will be listed.

7. INTERIM ANALYSES

7.1. Introduction

Interim Futility Analysis for Change from Baseline in 6MWT at Week 12

A formal, non-binding, interim futility analysis of change from baseline in 6MWT at Week 12 was performed after the first 60 randomized participants in the EAS had the opportunity to be assessed at the Week 12 visit (ie, participants who completed the Week 12 visit, or discontinued the study prior to Week 12). As the objective of this interim futility analysis was not to terminate the study early for the benefit of efficacy, no adjustment of alpha is needed as a result of this interim analysis.

The data cut-off date for the interim futility analysis was made when the 60th randomized participants with NYHA Class II/III reached 12 weeks, or discontinued the study prior to Week 12. The interim futility analysis at Week 12 was comprised of all those 60 participants. The interim analysis of change of 6MWT from baseline to Week 12 was summarized using the same methodology as described for the primary analysis in Section 5.2.1 and Section 6.1.1. The p-value from the van Elteren test was reported, and the stratified HL estimate on treatment effect was included.

The non-binding futility boundary was calculated as function of information using Hwang-Shih-DeCani spending function with gamma = -1.54. With 50% information at the interim analysis (ie, 60 out of 120 randomized participants in the EAS who had the opportunity to complete the Week 12 assessment, including those who discontinued prior to Week 12), the futility boundary would be crossed if the one-sided p-value from the primary analysis of change from baseline in 6MWT at Week 12 is ≥0.315. The exact futility boundary was to be updated based on the actual number of participants and information fraction included at the

interim; however no changes were required as the 50% fraction was achieved at the time of the interim analysis.

The analysis of changes from baseline in 6MWT at 24 weeks was performed at the interim based on a subset of the 60 randomized participants who completed a Week 24 visit, and all participants with a time difference of at least 24 weeks between the date of randomization and the targeted clinical cut-off. Note deaths or study discontinuations among participants who were randomized 24 or more weeks prior to the targeted clinical cut-off date were included.

Week 4 6MWT change from baseline was summarized descriptively. The number and percentage of deaths and discontinuations prior to Weeks 4, 12, and 24, and the reasons for discontinuations were provided.

The interim futility analysis was performed by an independent team of statistician(s) and programmer(s) and the results were unblinded only to the external data monitoring committee (DMC). The DMC evaluated the primary endpoint of the study and utilized the futility boundary to consider whether the study should continue to completion or stop early for futility. The futility boundary was a guideline for the DMC and was not a binding rule; interpretation of the efficacy data relative to the boundary was made by the DMC in the context of the entire study results, and recommendations made to the Sponsor accordingly.

At the time of the first planned interim futility analysis, the DMC recommended to continue the study as designed.

Blinded Sample Size Re-Estimation and All-Cause Mortality or WHF Event Monitoring

Following the interim analysis for futility, a planned blinded sample size re-estimation for the primary endpoint of change from baseline in 6MWT at Week 24 was conducted by an internal BSSR review committee using blinded cumulative primary efficacy data from the interim data cut. The BSSR committee did not have access to the unblinded data.

A similar simulation model utilized to determine the initial sample size (see Section 5.1) was utilized for sample size re-estimation using the pooled estimate for the baseline 6MWT assessment, the variance for the change from baseline in 6MWT at Week 24, the pooled event rates for death and the pooled event rates for study discontinuation (excluding deaths) prior to Week 24 estimated from the interim analysis data cut. Modifications to the simulation utilized at the time of the initial sample size calculation are detailed in a separate document and were mainly a result of pooled estimates at the time of sample size re-estimation where the initial sample size considered estimated values on the placebo arm.

This blinded sample size re-estimation procedure was conducted by an independent blinded statistician who was not a member of the DMC or the study team. The final decision on sample size and power for this study was determined by the internal BSSR committee, independent of the study team. Following completion of the planned blinded sample size re-estimation, up to 200 eligible participants with symptomatic cardiomyopathy due to LMNA will be randomized, including at least 160 participants with NYHA functional Class II or III

and up to 40 participants with NYHA functional Class IV. The rationale for the increase in sample size have been documented but will not be disclosed until the time of primary reporting.

Blinded sample size reassessment based on updating a nuisance parameter such as pooled common variance or event rate does not inflate the type I error. Therefore, there will be no adjustment to alpha due to this blinded sample size re-estimation procedure.

Details on the role of the internal BSSR committee and working procedures are defined in a separate BSSR Charter.

In addition to the sample size re-estimation for the primary endpoint, the study team will monitor the pooled (blinded) cumulative event counts for the composite safety endpoint of all-cause mortality or WHF throughout the study. The expected number of events on death or WHF needed to rule out an upper bound of 2-sided CI for a non-inferiority margin of 1.8 or 2 with time to the first composite event analysis under various scenarios for given HR is provided in Table 4.

Table 4. Expected Number of Events on Death or WHF to Rule Out a Non-inferiority HR Margin of 1.8 or 2 with Time to the First Composite Event Analysis

Statistical Power	Expected Effect size (HR)	Non-inferiority Margin=2		Non-inferiority Margin=1.8	
		90% CI	95% CI	90% CI	95% CI
80%	0.9	39	50	52	66
	0.95	45	57	61	77
	1	52	66	72	91
90%	0.9	54	66	72	88
	0.95	62	76	84	103
	1	72	88	100	122

Interim Futility Analysis for Change from Baseline in 6MWT at Week 24

Given the change in timepoint of the primary endpoint from 12 to 24 weeks following protocol amendment #7 and the longer than anticipated duration of the enrollment period, an additional interim futility analysis of change from baseline in 6MWT at Week 24 will be conducted after the first 68 randomized NYHA Class II/III participants having completed the Week 24 assessment or discontinued from the study prior to Week 24 (ie, 42.5% information following the sample size re-estimation). The assessment of futility will be based on change from baseline in 6MWT at Week 24 using a Hwang-Shih-DeCani spending function with gamma =6.7. With 42.5% information at the interim analysis (ie, 68 out of 160 randomized participants completed the Week 24 visit or otherwise having died or withdrawn from the study prior to Week 24), the futility boundary will be crossed if the one-sided p-value based on the van Elteren test is > 0.05.

The interim futility analysis of change of 6MWT from baseline to Week 24 will be summarized using the same methodology as described for the primary analysis in Section 5.2.1 and Section 6.1.1. The p-value from the van Elteren test will be reported, and the stratified HL estimate on treatment effect will be included. An independent team of statistician(s) and programmer(s) will be responsible for performing the interim analyses for the DMC. Detailed implementation of the interim analysis is described in the DMC Charter (separate documentation).

7.2. Interim Analyses and Summaries

7.2.1. Interim Futility Analysis

The following summaries were provided for the interim futility analysis on change from baseline in 6MWT at Week 12:

- Summary of Deaths and Discontinuations Prior to the Analysis Timepoint (Weeks 4, 12, and 24)
- Summary of Observed Values of 6MWT and Change from Baseline at Week 4, 12, and 24
- Van Elteren Test Results and Stratified Hodges-Lehmann Estimator of 6MWT Change from Baseline at Week 12
- Van Elteren Test Results and Stratified Hodges-Lehmann Estimator of 6MWT Change from Baseline at Week 24
- Line Graph of Mean Observed Change from Baseline in 6MWT at Weeks 4, 12, and 24 for PF-07265803 and placebo
- Van Elteren Test Results and Stratified Hodges-Lehmann Estimator of 6MWT Change from Baseline at Week 12: Sensitivity Analysis to Assess the Impact of Heart Failure Determined Withdrawal at Week 12
- Van Elteren Test Results and Stratified Hodges-Lehmann Estimator of 6MWT Change from Baseline at Week 24: Sensitivity Analysis to Assess the Impact of Heart Failure Determined Withdrawal at Week 24

The following summaries are planned for the interim futility analysis on change from baseline in 6MWT at Week 24:

- Summary of Deaths and Discontinuations Prior to Week 24
- Summary of Observed Values of 6MWT and Change from Baseline at Week 24
- Van Elteren Test Results and Stratified Hodges-Lehmann Estimator of 6MWT Change from Baseline at Week 24

8. REFERENCES

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9. APPENDICES

Appendix 1. Summary of Primary and Secondary Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Change from Baseline in 6MWT at Weeks 4, 12, and 24				
Change from baseline in 6MWT at Week 24	Primary analysis	EAS	**Hypothesis testing:** Deaths prior to week 24 will be assigned the worst rank and discontinuations from study prior to week 24 the next lowest rank, followed by changes in 6MWT for all other participants. All data collected regardless of discontinuation of randomized treatment will be included. Intermittent missing data will be imputed with MCMC. For participants who do not die or discontinue the study prior to Week 24 but have monotone missing Week 24 and subsequently discontinue the study at a later timepoint, missing data will be imputed under MAR for those who discontinue due to issues outside of the study (eg, COVID-19) and imputed using control-based MI for those who discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy). **Estimation of treatment effect (magnitude of change in 6MWT):** Missing data due to issues outside of the study (eg, COVID-19) will be imputed under MAR. Missing data for discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy) will be imputed using control-based MI. Imputations following death will not be utilized as imputed values for participants who died prior to the assessment timepoint would not be interpretable. Intermittent missing data will be imputed with MCMC.	van Elteren and win ratio stratified by baseline 6MWT quartile Stratified Hodges-Lehmann estimator by baseline 6MWT quartile
Change from baseline in 6MWT at Week 24	Summary	EAS	Observed 6MWT and change from baseline Number of deaths and discontinuations prior to the analysis time point	N/A

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Change from baseline in 6MWT at Week 24	Sensitivity	EAS	Death and study discontinuation prior to analysis time point will be treated as worst outcomes with an equal fraction trimmed from each treatment group. Missing data due to issues out of study (eg, due to COVID-19 pandemic) will be imputed under MAR using MI.	Trimmed Mean in combination with MI
Change from baseline in 6MWT at Week 24	Sensitivity	EAS	Missing value for participants with study withdrawal related to adjudication-confirmed HF-related events in the PF-07265803 arm will be imputed based on the distribution of the values in the placebo arm. Intermittent missing data will be imputed with MCMC and all other monotone missing data will be imputed under MAR. All else the same as the primary analysis.	van Elteren and win ratio stratified by baseline 6MWT quartile Stratified Hodges-Lehmann estimator by baseline 6MWT quartile
Change from baseline in 6MWT at Week 24	Sensitivity	EAS	Data from participants with a change in the 6MWT course from baseline visit will be excluded. All else the same as the primary analysis.	van Elteren and win ratio (95% CI) stratified by baseline 6MWT quartile Stratified Hodges-Lehmann estimator by baseline 6MWT quartile
Change from baseline in 6MWT at Week 24	Sensitivity	EAS	Data from participants at a given site impacted by COVID-19 disruptions period regardless of post-randomization outcomes will be excluded. All else the same as the primary analysis.	van Elteren and win ratio stratified by baseline 6MWT quartile Stratified Hodges-Lehmann estimator by baseline 6MWT quartile

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Change from baseline in 6MWT at Week 12	Main analysis	EAS	**Hypothesis testing:** Deaths prior to week 12 will be assigned the worst rank and discontinuations from study prior to week 12 the next lowest rank, followed by changes in 6MWT for all other participants. All data collected regardless of discontinuation of randomized treatment will be included. Intermittent missing data will be imputed with MCMC. For participants who do not die or discontinue the study prior to Week 12 but have monotone missing Week 12 and subsequently discontinue the study at a later timepoint, missing data will be imputed under MAR for those who discontinue due to issues outside of the study (eg, COVID-19) and imputed using control-based MI for those who discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy). **Estimation of treatment effect (magnitude of change in 6MWT):** Missing data due to issues outside of the study (eg, COVID-19) will be imputed under MAR. Missing data for discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy) will be imputed using control-based MI. Imputations following death will not be utilized as imputed values for participants who died prior to the assessment timepoint would not be interpretable. Intermittent missing data will be imputed with MCMC.	van Elteren and win ratio stratified by baseline 6MWT quartile Stratified Hodges-Lehmann estimator by baseline 6MWT quartile
Change from baseline in 6MWT at Week 12	Summary	EAS	Observed 6MWT and change from baseline Number of deaths and discontinuations prior to the analysis time point	N/A
Change from baseline in 6MWT at Week 12	Sensitivity	EAS	Missing value due to discontinuation from study due to heart failure in the PF-07265803 arm will be imputed based on the distribution of the values in the placebo arm. Intermittent missing data will be imputed with MCMC and all other monotone missing data will be imputed under MAR.	van Elteren and win ratio stratified by baseline 6MWT quartile Stratified Hodges-Lehmann estimator by

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
			All else the same as the primary analysis.	baseline 6MWT quartile
Change from baseline in 6MWT at Week 4	Main analysis	EAS	**Hypothesis testing:** Deaths prior to Week 4 will be assigned the worst rank and discontinuations from study prior to Week 4 the next lowest rank, followed by changes in 6MWT for all other participants. All data collected regardless of discontinuation of randomized treatment will be included. Intermittent missing data will be imputed with MCMC. For participants who do not die or discontinue the study prior to Week 4 but have monotone missing Week 4 and subsequently discontinue the study at a later timepoint, missing data will be imputed under MAR for those who discontinue due to issues outside of the study (eg, COVID-19) and imputed using control-based MI for those who discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy). **Estimation of treatment effect (magnitude of change in 6MWT):** Missing data due to issues outside of the study (eg, COVID-19) will be imputed under MAR. Missing data for discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy) will be imputed using control-based MI. Imputations following death will not be utilized as imputed values for participants who died prior to the assessment timepoint would not be interpretable. Intermittent missing data will be imputed with MCMC.	van Elteren and win ratio stratified by baseline 6MWT quartile Stratified Hodges-Lehmann estimator by baseline 6MWT quartile
Change from baseline in 6MWT at Week 4	Summary	EAS	Observed 6MWT and change from baseline Number of deaths and discontinuations prior to the analysis time point	N/A

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Change from Baseline in KCCQ PL and TSS at Weeks 12 and 24				
Change from baseline in KCCQ PL at Week 12	Main analysis	EAS	**Hypothesis testing:** Deaths prior to Week 12 will be assigned the worst rank and discontinuations from study prior to Week 12 the next lowest rank, followed by changes in KCCQ PL for all other participants. All data collected regardless of discontinuation of randomized treatment will be included. Intermittent missing data will be imputed with MCMC. For participants who do not die or discontinue the study prior to Week 12 but have monotone missing Week 12 and subsequently discontinue the study at a later timepoint, missing data will be imputed under MAR for those who discontinue due to issues outside of the study (eg, COVID-19) and imputed using control-based MI for those who discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy). **Estimation of treatment effect (magnitude of change in KCCQ PL):** Missing data due to issues outside of the study (eg, COVID-19) will be imputed under MAR. Missing data for discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy) will be imputed using control-based MI. Imputations following death will not be utilized as imputed values for participants who died prior to the assessment timepoint would not be interpretable. Intermittent missing data will be imputed with MCMC.	van Elteren and win ratio stratified by baseline 6MWT quartile Stratified Hodges-Lehmann estimator by baseline 6MWT quartile
Change from baseline in KCCQ PL at Week 12	Summary	EAS	Observed KCCQ PL and change from baseline	N/A
Change from baseline in KCCQ PL at Week 24	Main analysis	EAS	**Hypothesis testing:** Deaths prior to Week 24 will be assigned the worst rank and discontinuations from study prior to Week 24 the next lowest rank, followed by changes in KCCQ PL for all other participants. All data collected regardless of discontinuation of randomized treatment will be included. Intermittent missing data will be imputed with MCMC. For participants who do not die or discontinue the study prior to	van Elteren and win ratio stratified by baseline 6MWT quartile

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
			Week 24 but have monotone missing Week 24 and subsequently discontinue the study at a later timepoint, missing data will be imputed under MAR for those who discontinue due to issues outside of the study (eg, COVID) and imputed using control-based MI for those who discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy). **Estimation of treatment effect (magnitude of change in KCCQ PL):** Missing data due to issues outside of the study (eg, COVID-19) will be imputed under MAR. Missing data for discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy) will be imputed using control-based MI. Imputations following death will not be utilized as imputed values for participants who died prior to the assessment timepoint would not be interpretable. Intermittent missing data will be imputed with MCMC.	Stratified Hodges-Lehmann estimator by baseline 6MWT quartile
Change from baseline in KCCQ PL at Week 24	Summary	EAS	Observed KCCQ PL and change from baseline	N/A
Responder analysis of change from baseline in KCCQ PL at Week 24	Summary	EAS	All data collected will be included regardless of intercurrent events. A participant with a missing data for any reason will be considered a non-responder for the visit of interest.	Cochran-Mantel-Haenszel test stratified by stratification factors at randomization
Change from baseline in KCCQ TSS at Week 12	Main analysis	EAS	**Hypothesis testing:** Deaths prior to Week 12 will be assigned the worst rank and discontinuations from study prior to Week 12 the next lowest rank, followed by changes in KCCQ TSS for all other participants. All data collected regardless of discontinuation of randomized treatment will be included. Intermittent missing data will be imputed with MCMC. For participants who do not die or discontinue the study prior to Week 12 but have monotone missing Week 12 and subsequently discontinue the study at a later timepoint, missing data will be imputed under MAR for those who discontinue due to issues	van Elteren and win ratio stratified by baseline 6MWT quartile

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
			outside of the study (eg, COVID) and imputed using control-based MI for those who discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy). **Estimation of treatment effect (magnitude of change in KCCQ TSS):** Missing data due to issues outside of the study (eg, COVID-19) will be imputed under MAR. Missing data for discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy) will be imputed using control-based MI. Imputations following death will not be utilized as imputed values for participants who died prior to the assessment timepoint would not be interpretable. Intermittent missing data will be imputed with MCMC.	Stratified Hodges-Lehmann estimator by baseline 6MWT quartile
Change from baseline in KCCQ TSS at Week 12	Summary	EAS	Observed KCCQ TSS and change from baseline	N/A
Change from baseline in KCCQ TSS at Week 24	Main analysis	EAS	**Hypothesis testing:** Deaths prior to Week 24 will be assigned the worst rank and discontinuations from study prior to Week 24 the next lowest rank, followed by changes in KCCQ TSS for all other participants. All data collected regardless of discontinuation of randomized treatment will be included. Intermittent missing data will be imputed with MCMC. For participants who do not die or discontinue the study prior to Week 24 but have monotone missing Week 24 and subsequently discontinue the study at a later timepoint, missing data will be imputed under MAR for those who discontinue due to issues outside of the study (eg, COVID) and imputed using control-based MI for those who discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy). **Estimation of treatment effect (magnitude of change in KCCQ TSS):** Missing data due to issues outside of the study (eg, COVID-19) will be imputed under MAR. Missing data for discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy) will be imputed using control-based	van Elteren and win ratio stratified by baseline 6MWT quartile Stratified Hodges-Lehmann estimator by

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
			MI. Imputations following death will not be utilized as imputed values for participants who died prior to the assessment timepoint would not be interpretable. Intermittent missing data will be imputed with MCMC.	baseline 6MWT quartile
Change from baseline in KCCQ TSS at Week 24	Summary	EAS	Observed KCCQ TSS and change from baseline	N/A
Responder analysis of change from baseline in KCCQ TSS at Week 24	Summary	EAS	All data collected will be included regardless of intercurrent events. A participant with a missing data for any reason will be considered a non-responder for the visit of interest.	Cochran-Mantel-Haenszel test stratified by stratification factors at randomization
Change from Baseline in PGI Scores at Weeks 12 and 24				
Change from Baseline in PGI Scores at Weeks 12	Summary	EAS	All data collected will be included regardless of intercurrent events. A participant with a missing data for any reason will be considered a non-responder for the visit of interest.	NA
Change from Baseline in PGI Scores at Weeks 24	Summary	EAS	All data collected will be included regardless of intercurrent events. A participant with a missing data for any reason will be considered a non-responder for the visit of interest.	NA
Change from Baseline in NT-proBNP at Weeks 4, 12, and 24				
Change from baseline in NT-proBNP at Week 4	Main analysis	EAS	**Hypothesis testing:** Deaths prior to Week 4 will be assigned the worst rank and discontinuations from study prior to Week 24 the next lowest rank, followed by changes in NT-proBNP for all other participants. All data collected regardless of discontinuation of randomized treatment will be included. Intermittent missing data will be imputed with MCMC. For	van Elteren and win ratio stratified by baseline 6MWT quartile

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
			participants who do not die or discontinue the study prior to Week 4 but have monotone missing Week 4 and subsequently discontinue the study at a later timepoint, missing data will be imputed under MAR for those who discontinue due to issues outside of the study (eg, COVID) and imputed using control-based MI for those who discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy). **Estimation of treatment effect (magnitude of change in NT-proBNP):** Missing data due to issues outside of the study (eg, COVID-19) will be imputed under MAR. Missing data for discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy) will be imputed using control-based MI. Imputations following death will not be utilized as imputed values for participants who died prior to the assessment timepoint would not be interpretable. Intermittent missing data will be imputed with MCMC.	Stratified Hodges-Lehmann estimator by baseline 6MWT quartile
Change from baseline in NT-proBNP at Week 4	Summary	EAS	Observed NT-proBNP and change from baseline	N/A
Change from baseline in NT-proBNP at Week 12	Main analysis	EAS	**Hypothesis testing:** Deaths prior to Week 12 will be assigned the worst rank and discontinuations from study prior to Week 12 the next lowest rank, followed by changes in NT-proBNP for all other participants. All data collected regardless of discontinuation of randomized treatment will be included. Intermittent missing data will be imputed with MCMC. For participants who do not die or discontinue the study prior to Week 12 but have monotone missing Week 12 and subsequently discontinue the study at a later timepoint, missing data will be imputed under MAR for those who discontinue due to issues outside of the study (eg, COVID) and imputed using control-based MI for those who discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy).	van Elteren and win ratio stratified by baseline 6MWT quartile

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
			Estimation of treatment effect (magnitude of change in NT-proBNP): Missing data due to issues outside of the study (eg, COVID-19) will be imputed under MAR. Missing data for discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy) will be imputed using control-based MI. Imputations following death will not be utilized as imputed values for participants who died prior to the assessment timepoint would not be interpretable. Intermittent missing data will be imputed with MCMC.	Stratified Hodges-Lehmann estimator by baseline 6MWT quartile
Change from baseline in NT-proBNP at Week 12	Summary	EAS	Observed NT-proBNP and change from baseline	N/A
Change from baseline in NT-proBNP at Week 24	Main analysis	EAS	**Hypothesis testing:** Deaths prior to Week 24 will be assigned the worst rank and discontinuations from study prior to Week 24 the next lowest rank, followed by changes in NT-proBNP for all other participants. All data collected regardless of discontinuation of randomized treatment will be included. Intermittent missing data will be imputed with MCMC. For participants who do not die or discontinue the study prior to Week 24 but have monotone missing Week 24 and subsequently discontinue the study at a later timepoint, missing data will be imputed under MAR for those who discontinue due to issues outside of the study (eg, COVID) and imputed using control-based MI for those who discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy). **Estimation of treatment effect (magnitude of change in NT-proBNP):** Missing data due to issues outside of the study (eg, COVID-19) will be imputed under MAR. Missing data for discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy) will be imputed using control-based MI. Imputations following death will not be utilized as imputed values for participants who died prior to the assessment	van Elteren and win ratio stratified by baseline 6MWT quartile Stratified Hodges-Lehmann estimator by baseline 6MWT quartile

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
			timepoint would not be interpretable. Intermittent missing data will be imputed with MCMC.	
Change from baseline in NT-proBNP at Week 24	Summary	EAS	Observed NT-proBNP and change from baseline.	N/A
The Composite Endpoint of All-Cause Mortality or Worsening Heart Failure				
Time to first occurrence of all-cause mortality or worsening heart failure	Main analysis	SAS/EAS	All available data will be included. Missing data will not be imputed.	Kaplan-Meier method and stratified Cox regression by strata at randomization, where appropriate
Component analysis of time to HF-related hospitalization and time to urgent care visit	Supportive analysis	SAS	All available data will be included. Missing data will not be imputed.	Kaplan-Meier method and stratified Cox regression by strata at randomization, where appropriate
Overall Survival				
Time to All-Cause Mortality	Main analysis	SAS/EAS	All available data will be included. Missing data will not be imputed	Kaplan-Meier method and stratified Cox regression by strata at randomization, where appropriate

Appendix 2. Programming Specifications

The following sample SAS statement provides the framework for the MI method specified in Section 5.3.1.

```
/* Convert dataset into monotone missing data pattern (impute intermittent missing data) */

PROC MI data=<dataset> nimpute=1000 seed=349782 out=<dataset1>;
EM MAXITER = 1000 ;
VAR tmtrt baseline week4-week36;
MCMC chain=multiple nbiter=500 niter=500 impute=monotone initial=em
(maxiter=1000);
BY treatment;
RUN;

/* Impute monotone missing value under MAR*/

PROC MI data=<dataset1>  seed=229856 nimpute=1 out=<dataset2>;
CLASS mutation;
MONOTONE reg(/details);
VAR mutation tmtrt baseline week4 week12 week24;
BY _imputation_ treatment _;
RUN;

/* Impute monotone missing value under MNAR*/

PROC MI data=<dataset1>  seed=287561 nimpute=1 out=<dataset2>;
CLASS treatment mutation;
MONOTONE reg(/details);
MNAR model(week4-week12/ modelobs=(trt='0'));  /* trt='0' represents placebo */
VAR mutation tmtrt baseline week4 week12 week24;
BY _imputation_;
RUN;

/* Combine results*/

PROC MIANALYZE data=<dataset3>;
MODELEFFECTS estimate;
STDERR;
RUN;
```

Sample SAS code for the van Elteren analysis specified in Section 5.2.1 is given below.

```
PROC NPAR1WAY data=<dataset4> (refclass= '0');
CLASS treatment;
VAR value;
STRATA bstrata/ranks=stratum weights=stratum Wilcoxon ;
ODS output WilcoxonStrataTest=<dataset3>;
RUN;
```

Sample SAS code for the stratified HL analysis specified in Section 5.2.1 is given below.

/* Step 1: output the within-stratum HL estimate, and the standard error of the HL estimate with the HL option in SAS PROC NPAR1WAY */

PROC NPAR1WAY data=<dataset5> HL (refclass=**'0'**); /*refclass='0' represents placebo*/
CLASS treatment;
VAR value;
OUTPUT out=HLdata;
BY bstrata;
RUN;

/* Step 2: calculate stratified HL estimate as weighted averages of the within-stratum HL estimates where the weights are proportional to the strata sizes $w_k = (n_k + 1)/\sum(n_k + 1)$ */

PROC DATA= HLdata;
wj=(nstrata+1)/wtot;
asy_HL=_HL_*wj;
asy_var=(E_HL*wj)*(E_HL*wj);
RUN;

Appendix 3. Definition and Use of Visit Windows in Reporting

The below analysis windows will be used for the efficacy variables in the randomized period. If two or more visits fall into the same window, keep the one closest to the Target Day. If two visits are equaled distant from the Target Day in absolute value, the later visit should be used.

An analysis visit window ± 3 weeks will be applied for efficacy variables collected at the protocol-defined visits (ie, the Week 12 visit or after) with the exception of the Week 4 visit. For the Week 4 visit, an analysis visit window ± 2 weeks will be used.

Visit Label	Target Day	Definition [Day window]
Screening		Days -35 to -1
Baseline	Day 1, Baseline	Day 1
Week 4	29	Days 15 to 43
Week 12	85	Days 64 to 106
Week 24	169	Days 148 to 190
Similarly for every subsequent 12 weeks*		

*An analysis visit window ± 3 weeks will be applied

If a participant dies within a visit window but has a 6MWT assessment within the window the 6MWT value will be used, even if the death date is closer to the intended visit study day than the 6MWT date. For example, if a participant has a 6MWT on study day 80, but dies on study Day 84, the 6MWT from study Day 80 will be used.

Safety endpoints (eg, vital signs) will be summarized by study visits if required.

Appendix 4. Endpoint Derivations

Appendix 4.1. Kansas City Cardiomyopathy Questionnaire (KCCQ)

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item self-administered questionnaire developed to independently measure the participant's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life (QOL) within a 2-week recall period. Summaries on distinct domains that are derived from the individual questions in the KCCQ are provided below. The column "Evaluable Criteria" indicates that the domain score will not be evaluable unless the required number of questions have been completed.

Domain	Questionnaire Number	Evaluable Criteria
Physical Limitation	1	At least 3 items from the 6-part question completed
Symptom		
Symptom Frequency	3, 5, 7, 9	At least 2 questions completed
Symptom Burden	4, 6, 8	At least 1 question completed
Self-efficacy	11, 12	Not analyzed
Quality of Life	12, 13, 14	At least 1 question completed
Social Limitation	15	At least 2 items from the 4-part question completed

In addition, the following summary scores are derived based on individual domain scores:

- **Total Symptom Score** (TSS) includes symptom frequency scores and symptom burden scores.
- **Clinical Summary Score** (CSS) includes total symptom and physical limitation scores to correspond with NYHA Classification.
- **Overall Summary Score** (OSS) includes the total symptom, physical limitation, social limitations and quality of life scores.

For each domain score, the response to each question is converted to a percentage between 0 and 100 by subtracting one from the individual score and dividing by the number of possible responses minus one with the worst outcome assigned a value of 1 and the best outcome a value corresponding to the number of possible responses. Therefore, a higher score reflects better health status. For example, for questions 5 and 7, where there are 7 possible responses, if a participant completed 'several times a day' their percentage score would be 100*(2-1)/6 = 17%. For questions 1 and 15, the responses of 'Limited for other reasons or did not do' and 'Does not apply or did not do for other reasons' are not scored and treated as missing.

Appendix 4.2. Patient Global Impression Scales

PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S) SCALE

Question 1:

Over the past week, how would you describe the severity of your heart failure symptoms (eg, fatigue, edema, palpitations, etc)?

Choose ONE.

_None

_Mild

_Moderate

_Severe

_Very severe

Question 2:

Over the past week, how would you describe the severity of your physical activity limitations (eg, dressing, walking, climbing stairs, etc)?

Choose ONE.

_None

_Mild

_Moderate

_Severe

_Very severe

Patient's Signature: _____

PATIENT GLOBAL IMPRESSION OF CHANGE (PGI-C) SCALE

Question 1:

Since you began taking medication on this clinical study, how would you describe the overall change (if any) in your heart failure symptoms (eg, fatigue, edema, palpitations, etc)?

Choose ONE.

_Very much Better

_Moderately Better

_A little Better

_No Change

_A little Worse

_Moderately Worse

_Very much Worse

Question 2:

Since you began taking medication on this clinical study, how would you describe the overall change (if any) in your physical activity limitations (eg, dressing, walking, climbing stairs, etc)?

Choose ONE.

_Very much Better

_Moderately Better

_A little Better

_No Change

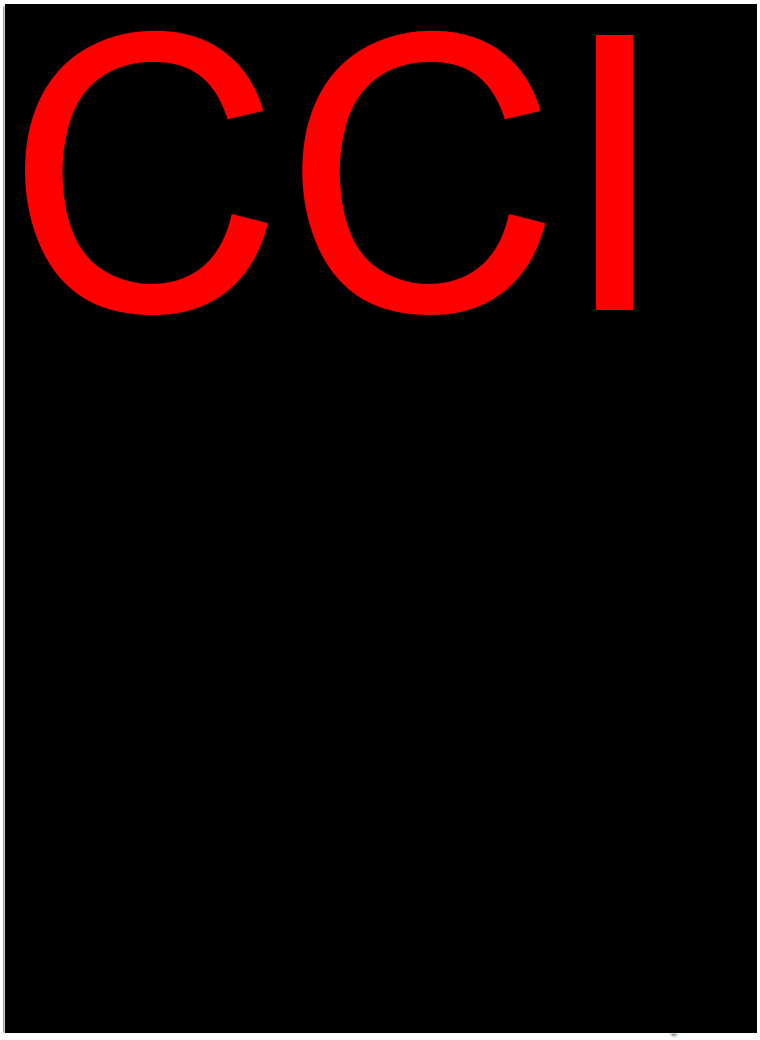
_A little Worse

_Moderately Worse

_Very much Worse

Patient's Signature: _____

CCI



Appendix 5. List of Abbreviations

Abbreviation	Term
6MWT	6 Minute Walk Test
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BSSR	blinded sample size re-estimation
BUN	blood urea nitrogen
CEC	clinical event committee
CK	creatine kinase
CI	confidence interval
CO_2	carbon dioxide (bicarbonate)
C_{max}	maximum observed concentration
CMH	Cochran-Mantel-Haenszel
CRT	cardiac resynchronization therapy
CRT-D	cardiac resynchronization therapy defibrillator
CSD	conduction system disease
CSR	clinical study report
CSS	clinical summary score
DCM	dilated cardiomyopathy
DMC	data monitoring committee
EAS	efficacy analysis set
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ECG	electrocardiogram
eGFR	estimated glomerular filtration ratio
EQ-5D-5L	EuroQol 5 Dimension 5 Level
FAS	full analysis set
FSH	follicle-simulating hormone
GGT	Gamma-glutamyltransferase
HF	heart failure
HIV	human immunodeficiency virus
HL	Hodges-Lehmann
HR	hazard ratio
IAS	interim analysis set
ICD	implantable cardioverter defibrillator
IVC	inferior vena cava
KCCQ	Kansas City Cardiomyopathy Questionnaire
LMNA	gene encoding the lamin A/C protein
LV	left ventricular
LVEF	left ventricular ejection fraction
LVEDVI	left ventricular end diastolic volume indices

Abbreviation	Term
LVESVI	left ventricular end systolic volume indices
MAPK	mitogen-activated protein kinase
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov chain Monte Carlo
MI	multiple imputation
MR-NR	missing response as non-response
MVPA	moderate to vigorous physical activity
N/A	not applicable
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OS	overall survival
OSS	overall summary score
P/LP	pathogenic/likely pathogenic
PA	physical activity
PASP	pulmonary artery systolic pressure
PD	pharmacodynamic(s)
PGI	Patient Global Impression
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
pH	hydrogen ion concentration
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic
PL	physical limitation
PR	ECG interval from the onset of P wave to the onset of the QRS complex
PRO	patient-reported outcome
PT	preferred term
Q1	first quartile
Q3	third quartile
QOL	quality of life
QT	QT interval: a measurement of the time between the start of the Q wave and the end of the T wave in an ECG
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cells
RV	right ventricular
RVEDD	right ventricular end-diastolic diameter
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SCD	sudden cardiac death
SD	standard deviation
SE	standard error
SOC	system organ class

Abbreviation	Term
TAPSE	tricuspid annular plane systolic excursion
TEAE	treatment emergent adverse events
TSH	thyroid-stimulating hormone
TSS	total symptom score
VAS	visual analog scale
VUS	variant of unknown significance
WBC	white blood cells
WHF	worsening heart failure
WHO	World Health Organization