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)

Study Intervention Number:	ARRY-371797 (PF-07265803)
Study Intervention Name:	p38 MAP Kinase Inhibitor
US IND Number:	CCI
EudraCT Number:	2017-004310-25
Protocol Number:	C4411002 (Array-797-301)
Phase:	3

Protocol Amendment Summary of Changes Table

Document History		
Document/Version	**Version Date**	**Summary and Rationale for Changes**
Amendment 8	09Feb2022	Modified protocol sections to include a change in the number of participants randomized into the study and updated the Section 9.2 Sample Size Determination. Rationale: Following a planned interim futility analysis, a blinded sample size re-estimation was performed for the primary efficacy endpoint of change from baseline in 6MWT at Week 24 to maintain sufficient study power to detect a clinically meaningful treatment effect for the primary efficacy endpoint. Updated Section 9, Statistical Considerations, to include the following changes: 1) Section 9.3, Analysis Sets, modified the definition of Efficacy Analysis Dataset and NYHA Class IV Analysis dataset by removing the inclusion criterion "with a LMNA gene mutation that is pathogenic, likely pathogenic or VUS". Rationale: A correction was made to clarify that all randomized participants will be included in the respective analyses. 2) Section 9.2, Sample Size Determination, added results of the blinded sample size re-estimation. Rationale: A planned sample size re-estimation was completed following the interim futility analysis. 3) Section 9.4.5.1, Hierarchical Testing, updated the hierarchical testing procedure to move NT-proBNP after the composite endpoint of time of all-cause mortality or worsening heart failure. Rationale: Updates were made based on regulatory feedback. 4) deleted the text specifying that fifty-two (52) events are required to assess the composite endpoint of time to first occurrence of all-cause mortality or worsening of heart failure. Rationale: The event rate will be continually monitored throughout the course of the study and further details will be included in the SAP on the assessment of the composite endpoint. 5) Removed duplicate sentences in the

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		primary efficacy analysis section. Rationale: To align with the Statistical Analysis Plan. Modified Section 6.1, Study Intervention(s) Administered, to include direct-to-participant shipment of study intervention if permitted by local regulations. Rationale: To allow the option of study intervention to be shipped to the participant's home between study visits that are every 24 weeks. Modified Section 6.6.1, Dose Interruptions, Reductions, and Discontinuations 1) to specify that if an AE occurs and it's not considered related to study intervention, dosing does not have to be reduced or modified, if in the investigator's opinion the AE is due to the underlying disease. Rationale: To allow the investigator to use clinical judgment not to reduce dose if an AE is caused by the participants underlying disease. 2) to specify that dose reduction should be considered as an option before permanently discontinuing study intervention. Rationale: Dose reductions are allowed per protocol and this sentence was added to provide additional clarification. Updated Section 4.3 Justification for Dose to state the 400 mg BID dose of ARRY-371797 (PF-07265803) appeared to be associated with larger favorable changes in NT-proBNP levels than the 100 mg BID dose in an analysis of aggregated mean change from baseline at all time points. Rationale: To align text with the Phase 2 (Array-797-001 [C4411001] final CSR and IB. Updated Section 10, Appendix 8: Cautionary Concomitant Medications. Rationale: The list of medications with known TdP risks was accessed and updated on 07Jan2022. Updated Section 2.1 Study Rationale and

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		Section 2.2 Background. Rationale: To include data from the completed Phase 2, long-term rollover extension study ARRAY-797-001 (C4411001). Modified Section 6.1.3, Administration. Rationale: To clarify that participants should abstain from all food 2 hours prior and 2 hours after dosing. Updated Section 6.4, Study Intervention Compliance. Rationale: To clarify study intervention dosing compliance must be reviewed by the site personnel at each visit using the participant diary and discussed with the participant at each visit. Modified Section 9.4.3.7.1, Population Pharmacokinetic/Pharmacodynamic Analyses, to indicate that early unblinding is planned when ≥90% of participants have reached 24 weeks post-randomization (or discontinued prior to the Week 24 visit). The unblinding will be limited to the PK data (ie, no efficacy data). Rationale: For PK modeling purposes. Modified Section 1.3 and Section 4.1.2 to specify that following the Week 60 visit, all subsequent on-site clinic visits will be every 24 weeks. Added the footnote "aa" to specify that starting at Week 72, a phone contact visit must be performed every 24 weeks to assess pregnancy (at-home urine pregnancy test), SAE/AEs, HF-related hospitalizations, HF-related urgent care visits, assess any changes to concomitant medications and assess status of study intervention and ensure the participant dosing diary is completed. Rationale: A site visit every 12 weeks is no longer required in efforts to reduce the burden on participants remaining on study intervention after approximately 1 year after randomization.

Document History		
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		Modified the open-label SoA to reflect: 1) for participants randomized to ARRY-371797 (PF-07265803) in the double-blind period visits will be every 24 weeks; 2) for participants randomized to placebo during the double-blind period clinic visits will be every 24 weeks following the week 24 visit. Rationale: To reduce the burden on participants. Removed CRT from Section 7.1, Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal. Rationale for Change: CRT may be part of standard of care for some participants with dilated cardiomyopathy. CRT initiation and adjustment is now permitted for enrolled participants. Updated Section 1.1, Synopsis and Section 4.1.1, Prescreening and Screening for Randomized Double-blind Treatment Period to clarify that participants who have multiple *LMNA* variants identified by an accredited local laboratory will be enrolled on the variant with the highest classification tier. Rationale: There is a potential for a participant to have multiple *LMNA* variants. Updated the Pfizer protocol number in the document header and title page; updated footnote "a" and "m" in Section 1.3 SoA; and Section 5.1.1.1, Prescreening for Participants, with Pre-Identified (P/LP)/VUS *LMNA* mutation. Rationale: Implemented changes documented in the PACL dated 14Apr21. Section 2.2.3.2, Nonclinical Drug Metabolism, was updated to include results from nonclinical studies completed. Rationale: Nonclinical drug metabolism was finalized and additional data were generated to inform potential DDI.

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		Section 2.2.3.3 Nonclinical Toxicity and Safety, was updated to include phototoxicity results and text was updated to align with IB. Rationale: provide most current nonclinical data results. Section 2.2.4.3 Clinical Efficacy and 2.2.4.4 Clinical Safety sections were updated to include final study results from the Phase 2 rollover extension study (Array-797-001). Rationale: The Clinical Study Report for study Array-797-001 was finalized on 29-Jun-2021. Updated Section 8.4 Adverse Events and Serious Adverse Events and Section 10.3. Appendix 3: Adverse Events Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting. Rationale: To align with Pfizer's required protocol template language. Updated Section 1.1 Synopsis and Section 3 Objectives, estimands and Endpoints. Rationale: Simplified by removing each specified timepoint given that the measurement will be assessed throughout the double-blind period. Updated Section 1.3, SoA, adding footnote "y" and added Appendix 10.10.1 country specific requirements in Japan. Rationale: Implemented changes documented in the PACL dated 31-May-2021. Updated bilirubin criterion in Section 5.1.2, 5.1.3, and 5.1.4. Rationale: To align with Pfizer's required protocol template language. Added the study name (REALM-DCM) to the title page. Rationale: Study name and branding were implemented after protocol version 7 approval.

Document History		
Document/Version	**Version Date**	**Summary and Rationale for Changes**
		Typos and inconsistencies were corrected, minor clarifications were added, sections were harmonized, language that is not applicable has been removed throughout the protocol. Rationale: Editorial updates.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale

In the completed Phase 2 study ARRAY-797-231, treatment with ARRY-371797 (PF-07265803) resulted in rapid (<4 weeks), sustained increases in functional capacity in participants with lamin A/C gene mutation (*LMNA*)-related DCM. Improvements on the 6MWT compared to baseline, the primary endpoint, were mirrored by favorable changes in NT-proBNP levels, LVEF and RV fractional area. ARRY-371797 (PF-07265803) was generally well tolerated. The AEs for most participants were mild to moderate, and only 1 participant discontinued the study because of a treatment-related AE. In the completed long-term rollover extension study ARRAY-797-001 (C4411001), ARRY-371797 (PF-07265803) was generally well tolerated, with evidence suggesting preserved exercise capacity over an extended period of follow-up. Preserved exercise capacity was mirrored by favorable trends in NT-proBNP levels.

Based on these clinical data, inhibition of p38 MAPK with the selective p38α inhibitor ARRY-371797 (PF-07265803) may provide a novel therapeutic approach and has the potential to fill an unmet medical need for the treatment of symptomatic *LMNA*-related DCM and merits further clinical investigation.

Objectives, Estimands, and Endpoints

The primary objective of the study is to evaluate the effect of ARRY-371797 (PF-07265803) on functional capacity as measured by the 6-minute walk test (6MWT) compared to placebo in patients with symptomatic DCM due to a *LMNA* gene mutation. The table below describes the study objectives including secondary and CCI objectives and corresponding endpoints.

Participants who discontinue study treatment 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.

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 Class (NYHA) 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.

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

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

Overall 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 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 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.

Prescreening and Screening:

All participants with DCM who meet the prescreening eligibility criteria for the study will be assessed for the presence of eligible *LMNA* mutation(s) using an assay performed by an accredited clinical laboratory.

The central accredited clinical laboratory will be used to assess *LMNA* mutation status if the *LMNA* mutation status is unknown at time of prescreening or if the genetic test was not performed by an accredited clinical laboratory. The *LMNA* mutation test results from the central accredited clinical laboratory must be available and confirmed prior to entering the screening period.

Participants with an identified pathogenic (P), likely pathogenic (LP) or variant of uncertain significance (VUS) *LMNA* mutation status documented by results from an accredited clinical laboratory can enter the screening period. Participants who have multiple *LMNA* variants identified will be enrolled on the variant with the highest classification tier and the variant with the highest classification will be reported in the eCRF.

Randomized Double-Blind Treatment Period:

All eligible participants will return to the clinic for assessment at the baseline visit (Day 1) prior to randomization. Randomization will be initially stratified based on NYHA class: Class II/III or Class IV. Randomization for the 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 mutation type (pathogenic, likely pathogenic or VUS). On Day 1, eligible participants will be randomized (1:1) to 400 mg BID ARRY-371797 (PF-07265803) or placebo.

Participants will continue on study intervention (eg, study treatment) as long as the participant has not met predefined criteria for treatment discontinuation. All participants should have a treatment discontinuation visit as soon as possible after the final dose of study treatment. A safety follow-up visit will occur approximately 30 days after the last dose of study intervention. Participants who discontinue study treatment 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. All participants will subsequently be followed for HF-related hospitalization, HF-related urgent care visits and OS until death or initiation of the open-label treatment period, whichever occurs first (see Section 8.2.6). Every effort should be made to obtain these data.

ARRY-371797 (PF-07265803) Open-Label Treatment Period:

After the primary analysis has been performed (all participants have had the opportunity to be followed for at least 24 weeks in the randomized double-blind treatment period) and an evaluation of the composite endpoint consisting of all-cause mortality or worsening heart failure (HF-related hospitalization or HF-related urgent care visits) has been completed (see Section 8.2.6), eligible participants may receive open-label treatment with ARRY-371797 (PF-07265803). The criteria for dose interruptions, reductions, and discontinuations of ARRY-371797 (PF-07265803) in the open-label treatment period will be identical to those used during the randomized period.

Open-Label Period for Participants Randomized to ARRY-371797 (PF-07265803):

After treatment unblinding, participants randomized to ARRY-371797 (PF-07265803) will receive the same dose in the open-label period of the study that they received at the end of the double-blinded period (ie, 400 mg BID, 200 mg BID, or 100 mg BID).

Open-Label Period for Participants Randomized to Placebo:

After treatment unblinding, participants randomized to placebo will undergo eligibility assessment concurrent with the open-label baseline visit and, if eligible, will receive ARRY-371797 (PF-07265803) at a starting dose of 400 mg BID in the open-label period of the study.

Number of Participants

Following a planned blinded sample size re-estimation, up to 200 eligible participants with symptomatic cardiomyopathy due to *LMNA* mutations 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 , at approximately 60 to 90 investigational centers, globally. The sample size determination is detailed in Section 9.2.

Intervention Groups and Duration

The study consists of a maximum of a 35-day screening phase, followed by a randomized, double-blind treatment period and then an open-label ARRY-371797 (PF-07265803) treatment period and survival follow-up.

Participants may continue to receive study intervention as long as no treatment discontinuation criteria are met.

Participants will be randomized (1:1) to the following groups:

- ARRY-371797 (PF-07265803): 400 mg BID (4×100 mg tablets, BID)

  (800 mg total daily dose)

- Matching placebo: 4 tablets BID (8 tablets daily)

Placebo and active intervention tablets will be identical in appearance during the double-blind treatment period to maintain the study blind.

If a participant has safety or tolerability issues at 4 tablets BID (ARRY-371797 (PF-07265803) [400 mg BID] or placebo), study intervention may be reduced to 2 tablets BID (ARRY-371797 (PF-07265803) [200 mg BID] or placebo) as described in this protocol. If a participant has tolerability issues at 2 tablets BID (ARRY-371797 (PF-07265803) [200 mg BID] or placebo), study intervention may be further reduced to 1 tablet BID (ARRY-371797 (PF-07265803) [100 mg BID] or placebo) as described in Section 6.6 of this protocol.

If study intervention is not well tolerated at any dose level, treatment will be permanently discontinued for that participant. See Section 7.1 Discontinuation of Study Intervention for details.

Data Monitoring Committee or Other Independent Oversight Committee

Data Monitoring Committee:

The DMC will be responsible for reviewing safety and PK data at regular intervals during the randomized portion of the study. Additionally, the DMC will review efficacy data at a formal interim futility analysis planned after the first 60 Class II/III randomized participants have completed the Week 12 assessment or have discontinued from the study prior to Week 12. A separate DMC Charter will be established that outlines DMC membership and specifies what data will be reviewed, instructions for unblinding of data, along with the timing and frequency of the reviews. DMC recommendations will be provided to the sponsor in compliance with the DMC Charter.

Steering Committee:

The SC will be appointed by the sponsor prior to the initiation of the study. The SC will include selected principal investigators from the study, leading experts in HF cardiomyopathy, and sponsor representatives. The SC will be involved in the oversight of the study and will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. Details on the role of the SC and working procedures will be defined in the SC Charter.

Clinical Events Committee:

The CEC will be appointed by the sponsor, or its representative, prior to the initiation of the study. The CEC will be responsible for reviewing safety data to aid in adjudicating cause for hospitalizations for the composite endpoint of all-cause mortality or worsening heart failure (HF-related hospitalizations or HF-related urgent care visits) only. Details on the role of the CEC and working procedures will be defined in the CEC Charter.

Statistical Methods

Hierarchical Testing:

The testing strategy controls Type I error across primary and selected secondary endpoints. If the van Elteren test of the primary endpoint is found to be statistically significant at 0.05 (2-sided) alpha, then a sequential testing plan will be implemented for testing the secondary endpoints.

Secondary endpoints will be analyzed in hierarchical order as follows:

- Week 24 change from baseline in KCCQ domains of PL and TSS
- Composite endpoint consisting of all-cause mortality or worsening heart failure (HF-related hospitalization or HF-related urgent care visit)
- Week 24 change from baseline in NT-proBNP

Efficacy Analyses:

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) is performed.

Primary Analysis of Change from Baseline in 6MWT at 24 Weeks:

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 a rank-based non-parametrical approach. Specifically, the test of superiority will be based on the van Elteren test, a stratified extension of the Wilcoxon rank sum test, with deaths

assigned the worst rank ordered from shortest to longest survival time and discontinuations from study the next lowest rank ordered based on their time to discontinuation, followed by changes in 6MWT for all other participants. Participants will be stratified into 4 groups according to baseline 6MWT quartile. Missed assessment while a participant remains in the trial at or beyond Week 24 will be modelled using the method of MCMC 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 Week 24 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 discontinue due to post randomization events (eg, AEs or perceived lack of efficacy). ARRY-371797 (PF-07265803) will be declared superior to placebo if the null hypothesis of no difference between ARRY-371797 (PF-07265803) and placebo is rejected at the significance level of 0.05 (2-sided). The p-value will be supplemented with a stratified win ratio statistic (and 95% CI) based on the same ranking rules.

Two additional summaries will be provided to interpret the van Elteren test as follows:

- In analyzing the contribution of death and discontinuation components to the primary efficacy analysis, the summaries on number of deaths and discontinuations from study prior to Week 24, and the reasons for withdrawals from study will be provided. It is expected that the death rates will not be negatively affected by the active treatment.

- A stratified Hodges-Lehmann (HL) estimator of the treatment difference (with 95% CI) will be used to describe the treatment effect on the change from baseline in 6MWT at Week 24. Missing data at Week 24 due to issues outside of the study (eg, COVID-19) will be imputed based on a MAR assumption. Missing data at Week 24 for discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy) will be imputed using control-based multiple imputation. Imputations following death will not be utilized as imputed values for participants who died prior to the assessment timepoint would not be interpretable.

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. An empirical cumulative distribution function (eCDF) plot of change from baseline in 6MWT at Week 24 will also be generated for those participants with observed 6MWT at Week 24.

Interim Analysis:

An interim futility analysis was performed after the first 60 randomized participants in NYHA Class II/III had completed the Week 12 assessment or discontinued from the study prior to Week 12. At this analysis, the DMC utilized the futility boundary to consider

whether the study should continue to completion or stop early for futility. At the time of the planned interim futility analysis, the DMC recommended to continue the study as designed.

Blinded Sample Size Re-estimation:

Following the interim analysis for futility, a planned blinded sample size re-estimation for the primary endpoint of change from baseline at Week 24 was conducted using blinded cumulative primary efficacy data from the interim data cut . Specifically, a blinded, pooled analysis of both treatment groups for estimating variability of change from baseline in 6MWT at Week 24 and current overall event rates for deaths and study discontinuations prior to Week 24 was performed and compared to the assumption used in planning the study. Following a 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.

In addition to the sample size re-estimation for the primary endpoint, the sponsor will continually 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.. The statistical analysis plan will provide an assessment of the expected number of events needed to rule out an upper bound of 1.8 or 2 under various scenarios for given hazard ratios.

Safety Analyses:

All AEs will be coded using MedDRA. Incidence tables of participants with AEs will be presented for all AEs by maximum severity, SAEs, AEs assessed as related to study intervention, and AEs resulting in discontinuation of study intervention. Changes in ECG and laboratory measurements will be summarized using descriptive statistics by arm over time. The nature and frequency of arrhythmias will be tabulated for analysis by arm over time.

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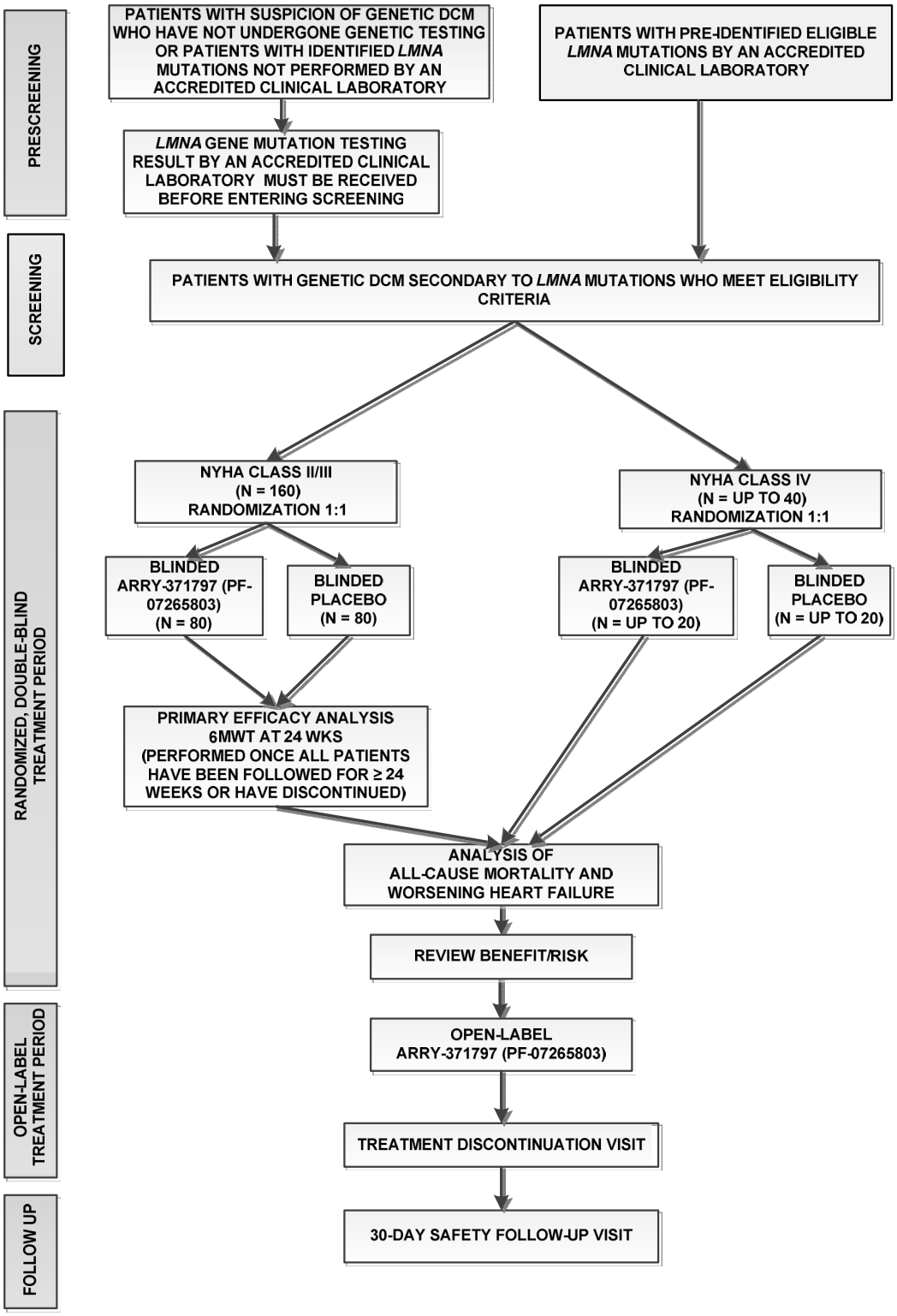
[redacted]

1.2. Schema


PRESCREENING
SCREENING
RANDOMIZED, DOUBLE-BLIND TREATMENT PERIOD
OPEN-LABEL TREATMENT PERIOD
FOLLOW UP
PATIENTS WITH SUSPICION OF GENETIC DCM WHO HAVE NOT UNDERGONE GENETIC TESTING OR PATIENTS WITH IDENTIFIED LMNA MUTATIONS NOT PERFORMED BY AN ACCREDITED CLINICAL LABORATORY
PATIENTS WITH PRE-IDENTIFIED ELIGIBLE LMNA MUTATIONS BY AN ACCREDITED CLINICAL LABORATORY
LMNA GENE MUTATION TESTING RESULT BY AN ACCREDITED CLINICAL LABORATORY MUST BE RECEIVED BEFORE ENTERING SCREENING
PATIENTS WITH GENETIC DCM SECONDARY TO LMNA MUTATIONS WHO MEET ELIGIBILITY CRITERIA
NYHA CLASS II/III (N = 160) RANDOMIZATION 1:1
NYHA CLASS IV (N = UP TO 40) RANDOMIZATION 1:1
BLINDED ARRY-371797 (PF-07265803) (N = 80)
BLINDED PLACEBO (N = 80)
BLINDED ARRY-371797 (PF-07265803) (N = UP TO 20)
BLINDED PLACEBO (N = UP TO 20)
PRIMARY EFFICACY ANALYSIS 6MWT AT 24 WKS (PERFORMED ONCE ALL PATIENTS HAVE BEEN FOLLOWED FOR ≥ 24 WEEKS OR HAVE DISCONTINUED)
ANALYSIS OF ALL-CAUSE MORTALITY AND WORSENING HEART FAILURE
REVIEW BENEFIT/RISK
OPEN-LABEL ARRY-371797 (PF-07265803)
TREATMENT DISCONTINUATION VISIT
30-DAY SAFETY FOLLOW-UP VISIT

1.3. Schedule of Activities

The SoA tables provide an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

In response to the ongoing global pandemic COVID-19, and the increasing restrictions and concerns on public health, Pfizer has provided alternative solutions to accommodate study procedures during this time. Operational alternatives for some tests, procedures, and assessments are presented in Appendix 7: Alternative Measures During Public Emergencies.

Schedule of Activities for All Participants in the Randomized Double-Blind Period

Procedure or Assessment Abbreviations used in this table may be found in Appendix 10.	**Pre-screening**	**Screening Period**		**Baseline Visit[a] (Day 1)**	**Randomized Double-Blind Period**						**Follow-up Period**		
		Screening Visit (Day -35 to Day -7)	**Day -1 Visit (Day -1)**		**Week 4[i] Day 29 (±3 days)**	**Week 8[i] Day 57 (±7 days)**	**Week 12[i] Day 85 (±7 days)**	**Week 24[i] Day 169 (±7 days)**	**Week 36, 48, 60 and every subsequent 24 weeks [z] (±7 days)**	**Phone Contact Visit every 24 weeks starting at Week 72[aa] (±7 days)**	**Treatment Discon-tinuation Visit**	**Safety Follow-up Visit (30 days after last dose ±5 days)**	**Survival Follow-up**
Prescreen Informed Consent	X												
Prescreening IRT registration	X												
LMNA Genetic Analysis for Eligibility[b]	X												
Main Informed Consent		X											
Confirm Eligibility Criteria/Medical History		X[c]		X									
Demography		X											

Schedule of Activities for All Participants in the Randomized Double-Blind Period

Procedure or Assessment Abbreviations used in this table may be found in Appendix 10.	**Pre-screening**	**Screening Period**		**Baseline Visit[a] (Day 1)**	**Randomized Double-Blind Period**						**Follow-up Period**		
		Screening Visit (Day -35 to Day -7)	**Day -1 Visit (Day -1)**		**Week 4[i] Day 29 (±3 days)**	**Week 8[i] Day 57 (±7 days)**	**Week 12[i] Day 85 (±7 days)**	**Week 24[i] Day 169 (±7 days)**	**Week 36, 48, 60 and every subsequent 24 weeks [z] (±7 days)**	**Phone Contact Visit every 24 weeks starting at Week 72[aa] (±7 days)**	**Treatment Discon-tinuation Visit**	**Safety Follow-up Visit (30 days after last dose ±5 days)**	**Survival Follow-up**
Prior/Concomitant Medications[d]		X	X	X	X	X	X	X	X	X	X	X	
HIV, TSH, Hepatitis B/C		X											
Serum Pregnancy Test[e,f]		X											
Serum FSH Test[g]		X											
Complete Physical Exam[h]		X											
Brief Physical Exam				X	X	X	X	X	X		X	X	
PRO (KCCQ, PGI-S, PGI-C, EQ-5D-5L)[k]				X[l]			X	X	X		X		
6MWT/Borg[j,w]		X[m]	X	X[n]	X		X	X	X		X		
Activity Monitoring		X	→								X		
Vital Sign Measurement		X		X	X	X	X	X	X		X	X	
Hematology/Chemistry Blood Samples[f]		X[o]		X[o]	X[o]	X[o]	X[o]	X[o]	X[o]		X	X	
Urinalysis		X[o]		X[o]	X[o]	X[o]	X[o]	X[o]	Every 24 weeks [o]		X	X	
Randomize Participant via IRT System				X									

Schedule of Activities for All Participants in the Randomized Double-Blind Period

Procedure or Assessment Abbreviations used in this table may be found in Appendix 10.	**Pre-screening**	**Screening Period**		**Baseline Visit[a] (Day 1)**	**Randomized Double-Blind Period**						**Follow-up Period**		
		Screening Visit (Day -35 to Day -7)	**Day -1 Visit (Day -1)**		**Week 4[i] Day 29 (±3 days)**	**Week 8[i] Day 57 (±7 days)**	**Week 12[i] Day 85 (±7 days)**	**Week 24[i] Day 169 (±7 days)**	**Week 36, 48, 60 and every subsequent 24 weeks [z] (±7 days)**	**Phone Contact Visit every 24 weeks starting at Week 72[aa] (±7 days)**	**Treatment Discon-tinuation Visit**	**Safety Follow-up Visit (30 days after last dose ±5 days)**	**Survival Follow-up**
Urine Pregnancy Test[e]				X			X	X	X	X	X	X	
12-Lead ECGs[j]				X[p]	X[p]		X[p]				X		
Echocardiogram[j]		X		X	X		X	X	Every 24 weeks		X		
Arrhythmia Assessment[j,q]			X				X	X	X		X	X	
PK Blood Sample[f]				X[r]	X[r]	X[r]	X[r]	X[r]			X[s]		
PD Blood Sample[f]				X[t]	X[t]	X[t]	X[t]	X[t]					
Blood Sample for *LMNA in vitro* diagnostic development[x]				X									
Dispense Study Intervention				X	X	X	X	X	X				
Review Dosing Diary					X	X	X	X	X	X	X		
Assess AEs[y]		X[u]	X[u]	X[u]	X	X	X	X	X	X	X	X	
Assess Hospitalization/ER/Urgent Care Visits		X	X	X	X	X	X	X	X	X	X	X	X[v]
Survival Follow-up[v]													X

Schedule of Activities for All Participants in the Randomized Double-Blind Period

Procedure or Assessment Abbreviations used in this table may be found in Appendix 10.	Pre-screening	Screening Period		Baseline Visit[a] (Day 1)	Randomized Double-Blind Period						Follow-up Period		
		Screening Visit (Day -35 to Day -7)	Day -1 Visit (Day -1)		Week 4[i] Day 29 (±3 days)	Week 8[i] Day 57 (±7 days)	Week 12[i] Day 85 (±7 days)	Week 24[i] Day 169 (±7 days)	Week 36, 48, 60 and every subsequent 24 weeks [z] (±7 days)	Phone Contact Visit every 24 weeks starting at Week 72[aa] (±7 days)	Treatment Discon-tinuation Visit	Safety Follow-up Visit (30 days after last dose ±5 days)	Survival Follow-up

a. The baseline visit should occur within 3 days of the Day -1 visit. Note: The maximum screening period from the Screening Visit to Day 1 cannot exceed 35 days.
b. The central accredited clinical laboratory will be used to assess *LMNA* mutation status if the *LMNA* mutation status is unknown at time of prescreening or if the genetic test was not performed by an accredited clinical laboratory. The *LMNA* mutation test results from the central accredited clinical laboratory must be available and confirmed prior to entering the screening period. Participants with identified pathogenic, likely pathogenic or VUS *LMNA* mutation status documented by results from an accredited clinical laboratory can enter in the screening period.
c. Includes history of use of tobacco, alcohol, and drugs of abuse.
d. Includes all prescription and nonprescription drugs, vitamins, and dietary or herbal supplements administered within 35 days prior to Day 1.
e. Required for WOCBP only. Must be completed prior to dosing. Urine pregnancy tests are required every 12 weeks during the randomized double-blind period. Pregnancy tests will also be done whenever 1 menstrual cycle is missed (or when potential pregnancy is otherwise suspected).
f. Blood collection to be performed in accordance with the methods described in the Laboratory Manual.
g. Required for postmenopausal females <60 years of age.
h. Includes height (at screening) and weight.
i. Participants who discontinue study treatment prior to Week 24 should continue to have all assessments performed as scheduled through the Week 24 Visit.
j. Screening echocardiogram will be done locally and will be used to determine eligibility. These assessments for Class IV participants are optional; however, if any of these procedures are completed during the course of the trial, the results should be captured. Following the week 24 visit, an echocardiogram will be done every 24 weeks thereafter.
k. Perform KCCQ first, followed by PGI-S and PGI-C before other visit assessments. Participants should complete the EQ-5D-5L after the PGI questionnaires.
l. KCCQ and PGI-S collected at baseline, PGI-C not collected at baseline.
m. Screening visit 6MWT must be completed at least 27 days prior to the baseline 6MWT on Day -1.
n. Complete 6MWT before completing other baseline activities in order to confirm participant eligibility.
o. Collection of hematology/chemistry blood sample and urinalysis sample prior to dosing. Following the week 24 visit, urinalysis will be collected every 24 weeks thereafter.
p. ECGs will be performed predose and 2 hours (± 30 min) postdose through Week 12. Must be performed prior to blood collection or vital sign measurement, where applicable.
q. Detected by ICD/CRT-D applicable device interrogation.
r. Collection of PK blood sample: Baseline: predose, Week 4: predose, Week 8 predose and 2 samples at approximately 1.5 hours (± 1 hour postdose, at least 15 minutes apart) and after vital signs measurements, Week 12: predose and 5 hours (± 1 hour), Week 24: predose and 5 hours (± 1 hour), Treatment Discontinuation: Any time during clinic visit.
s. Only collected if participant discontinues treatment prior to the Week 24 Visit.
t. Collection of PD blood sample: predose at all visits and additionally at 1.5 hour (± 1 hour) postdose at Week 8.
u. Any AE that occurs from the signing of the informed consent until first dose of study intervention (or placebo) is to be recorded on the AE eCRF.
v. Participants will be followed for overall survival and HF-related hospitalizations or HF-related urgent care visits approximately every 3 months per phone call until death, lost to follow-up, withdrawal of consent or initiation of the open-label treatment period, whichever occurs first.

Schedule of Activities for All Participants in the Randomized Double-Blind Period

Procedure or Assessment Abbreviations used in this table may be found in Appendix 10.	Pre-screening	Screening Period		Baseline Visit[a] (Day 1)	Randomized Double-Blind Period						Follow-up Period		
		Screening Visit (Day -35 to Day -7)	Day -1 Visit (Day -1)		Week 4[i] Day 29 (±3 days)	Week 8[i] Day 57 (±7 days)	Week 12[i] Day 85 (±7 days)	Week 24[i] Day 169 (±7 days)	Week 36, 48, 60 and every subsequent 24 weeks [z] (±7 days)	Phone Contact Visit every 24 weeks starting at Week 72[aa] (±7 days)	Treatment Discon-tinuation Visit	Safety Follow-up Visit (30 days after last dose ±5 days)	Survival Follow-up

w. 6MWT will include the Borg fatigue assessment both before and after the walk assessment. The 6MWT should be done predose on clinic visit days.
x. A 2 mL blood sample will be collected and sent to the central laboratory for participants who did not use central laboratory to confirm eligibility.
y. Only in Japan, adverse events will be assessed by telephone contact at Week 2 [Day 15 (± 3 days)]. Participants will be instructed to visit site if requested by the investigator.
z. Following the Week 60 visit, all subsequent on-site clinic visits will be conducted every 24 weeks while the participant remains on study intervention.
aa. Starting at Week 72, a phone contact visit must be performed and every subsequent 24 weeks to assess pregnancy (at-home urine pregnancy test for WOCBP), SAE/AEs, HF-related hospitalizations, HF-related urgent care visits, assess any changes to concomitant medications and assess status of study intervention and ensure the participant dosing diary is completed.

Schedule of Activities for Open-Label Period

Procedure or Assessment Abbreviations used in this table may be found in Appendix 10.	**Baseline Visit (Day 1)**	**Open-Label Period**					**Follow-up Period**	
		Week 4 (±3 days)	**Week 8 (±7 days)**	**Week 12 (±7 days)**	**Week 24 (±7 days)**	**Every subsequent 24 weeks (±7 days)**	**Treatment Discontinuation Visit**	**Safety Follow-up Visit (30 days after last dose ±5 days)**
Clinic Visits for Participants Randomized to ARRY-371797 (PF-07265803)						X	X	X
Clinic Visits for Participants Randomized to Placebo[a]	X	X	X	X	X	X	X	X
Confirm Eligibility Criteria[a]	X							
PRO (KCCQ, PGI-S, PGI-C, EQ-5D-5L)[c]	X			X	X	X	X	
Concomitant Medications[d]	X	X	X	X	X	X	X	X
Brief Physical Exam[e]	X	X	X	X	X	X	X	X
6MWT/Borg[b,f,g]	X	X		X	X	X	X	
Vital Sign Measurement	X	X	X	X	X	X	X	X
Hematology/Chemistry Blood Samples[h]	X	X[i]	X[i]	X[i]	X[i]	X[i]	X	X
Urinalysis	X	X[i]	X[i]	X[i]	X[i]	Every 24 weeks[i]	X	X
Urine Pregnancy Test[j]	X			X	X	X	X	X
12-Lead ECGs[f,k]	X[k]	X[k]		X[k]			X	
Echocardiogram[f]	X	X	X	X	X	Every 24 weeks	X	
Arrhythmia Assessment[f,l]				X	X	X	X	X

Schedule of Activities for Open-Label Period

Procedure or Assessment Abbreviations used in this table may be found in Appendix 10.	**Baseline Visit (Day 1)**	**Open-Label Period**					**Follow-up Period**	
		Week 4 (±3 days)	**Week 8 (±7 days)**	**Week 12 (±7 days)**	**Week 24 (±7 days)**	**Every subsequent 24 weeks (±7 days)**	**Treatment Discontinuation Visit**	**Safety Follow-up Visit (30 days after last dose ±5 days)**
Dispense Study Interventional[m]	X	X	X	X	X	X		
Review Dosing Diary		X	X	X	X	X	X	
Assess AEs	X	X	X	X	X	X	X	X

a. Participants who cross over from placebo to ARRY-371797 (PF-07265803) intervention must meet all inclusion criteria, and none of the exclusion criteria as listed in Section 5.1.4, and Section 5.2.3, respectively.
b. 6MWT will include the Borg fatigue assessment both before and after the walk assessment. The 6MWT should be done predose on clinic visit days.
c. Perform KCCQ first, followed by PGI-S,PGI-C, and EQ-5D-5L before all other visit assessments. PGI-C is not collected at baseline.
d. Includes all prescription and nonprescription drugs, vitamins, and dietary or herbal supplements.
e. Includes weight.
f. These assessments for Class IV participants are optional. If any of these procedures are completed during the course of the trial, the results should be captured. Following the Week 24 visit, an echocardiogram will be performed every 24 weeks thereafter.
g. Complete 6MWT after KCCQ and PGI-S but before completing other baseline activities in order to confirm participant eligibility.
h. Blood collection to be performed in accordance with the methods described in the Laboratory Manual.
i. Collection of hematology/chemistry blood sample and urinalysis sample prior to dosing. Following the Week 24 visit, urinalysis will be collected every 24 weeks thereafter.
j. Required for WOCBP only. Must be completed prior to dosing. Urine pregnancy tests are required every 12 weeks during the open-label period. Pregnancy test will also be done whenever a menstrual cycle is missed or when potential pregnancy is otherwise suspected.
k. ECGs will be performed predose and 2 hours (± 30 min) postdose through Week 12. Must be performed prior to blood collection or vital sign measurement, where applicable.
l. Detected by ICD/CRT-D applicable device interrogation.
m. Participants who received PF-07265803 in the double-blind period will continue to have study intervention dispensed every 24 weeks.

2. INTRODUCTION

ARRY-371797 (PF-07265803) is a potent and selective, oral small molecule inhibitor of the α isoform of p38 MAPK. Mutations in the *LMNA* gene encoding nuclear lamina components cause nuclear envelope dysfunction leading to altered nuclear activity, impaired structural dynamics and aberrant cell signaling including activation of p38α MAPK signaling pathways. Structural alterations in the nuclear envelope and connected cytoskeleton resulting from *LMNA* make cardiomyocytes highly susceptible to damage even by physiological mechanical stress, leading to a disease specific maladaptive activation of the p38α MAPK. Activation of p38 MAPK has been observed in the hearts of animal models and adult patients with *LMNA*-related DCM compared to wild-type/healthy individuals. Inhibition of p38 MAPK in this disease setting may halt aberrant apoptosis and cardiac remodeling resulting in improved cardiac function.

2.1. Study Rationale

In the completed Phase 2 study ARRAY-797-231, treatment with ARRY-371797 (PF-07265803) resulted in rapid (<4 weeks), sustained increases in functional capacity in participants with *LMNA*-related DCM (described in Section 2.2.4.3). Improvements on the 6MWT compared to baseline, the primary endpoint, were mirrored by favorable changes in NT-proBNP levels, LVEF, and RV fractional area. ARRY-371797 (PF-07265803) was generally well tolerated. The AEs for most participants were mild to moderate, and only 1 participant discontinued the study because of a treatment-related AE. In the completed long-term rollover extension study ARRAY-797-001 (C4411001), ARRY-371797 (PF-07265803) was generally well tolerated, with evidence suggesting preserved exercise capacity over an extended period of follow-up. Preserved exercise capacity was mirrored by favorable trends in NT-proBNP levels.

Based on these clinical data, inhibition of p38 MAPK with the selective p38 inhibitor ARRY-371797 (PF-07265803) may provide a novel therapeutic approach and has the potential to fill an unmet medical need for the treatment of symptomatic *LMNA*-related DCM and merits further clinical investigation.

2.1.1. Rationale for Selection of the Primary Efficacy Endpoint

The 6MWT is a measure of participant exercise tolerance as an estimate of functional capacity. Improvement in 6MWT is a direct measure of a favorable therapeutic intervention and is associated with reduced morbidity and mortality in heart failure patients.[1,2,3,4,5] Change in 6MWT distance has been the most commonly utilized primary endpoint in clinical studies conducted for regulatory approval of therapies in participants with PAH. In studies of ambrisentan, bosentan, and riociguat, improvements versus placebo in mean 6MWT distance in PAH participants were 32 m (range of 6% to 13% increase), 54 m (range of 8% to 19% increase), and 36 m (range of 8% to 11% increase), respectively, across a number of clinical studies.[6,7,8] In heart failure with reduced ejection fraction, a 30-to-50m increase in 6MWT distance was associated with significant improvement in NYHA functional class and health-related Qol, and was utilized as an endpoint for *de novo* medical devices approval intended for unmet medical need for life threatening and irreversibly debilitating diseases and conditions.[9]

2.1.2. Rationale for Selection of the Secondary Endpoint - Composite Endpoint of All-Cause Mortality or Worsening Heart Failure (HF-related hospitalization or HF-related urgent care visits)

An important evaluation in determining the safety of PF-07265803 treatment will include an estimate of the effect on overall survival. *LMNA*-related DCM is a rare condition limiting clinical trial sample size, and the mortality rate expected during this study (approximately 10%) further precludes a statistically rigorous evaluation of the treatment effect on overall survival. Thus, an assessment of worsening heart failure (WHF) including HF-related hospitalizations or HF-related urgent care visits will be analyzed as part of a composite endpoint (see Section 9.4.3.4).

Heart failure is a progressive condition and the need for treatment to manage worsening HF signs and symptoms in the outpatient, emergency department, or hospitalization setting, is associated with worse prognosis.[10] The use of worsening heart failure as part of a composite endpoint is supported by large prospective and retrospective studies indicating that worsening of heart failure, directly correlate with an increase in mortality risk.[11] Overall, patients admitted for HF have a high event rate (>50%), with a mortality rate between 10% and 15% and a re-hospitalization rate within 6 months after discharge of 30% to 40%.[12,13,14,15,16] In the real-world setting, worsening of heart failure is associated with a 2-year mortality rate of 22.5% with more than 50% of patients being rehospitalized within 30 days of the worsening event.[14]

Taken together, these data from multiple large clinical studies indicate that WHF correlate strongly with mortality, supporting the use of a composite endpoint that considers both WHF and all-cause mortality to assess the potential for increased mortality risk from ARRY-371797 (PF-07265803) treatment. To standardize data collection, HF-related hospitalizations and HF-related urgent care visits will be adjudicated by an independent Clinical Events Committee (see Section 9.4.3.4).

2.2. Background

2.2.1. *LMNA*-Related Dilated Cardiomyopathy

Lamins are critical protein components of the nuclear lamina, which lie between the inner nuclear membrane and the chromatin. They provide structural support for the cell nucleus, and participate in many different nuclear processes, including chromatin organization, connecting the nucleus to the cytoplasm, gene transcription, and mitosis. Mutations in the *LMNA* gene encoding nuclear lamina components cause nuclear envelope dysfunction leading to altered nuclear activity, impaired structural dynamics and aberrant cell signaling including activation of p38α MAPK signaling pathways. Structural alterations in the nuclear envelope and connected cytoskeleton resulting from *LMNA* mutations make cardiomyocytes highly susceptible to damage even by physiological mechanical stress, leading to a disease specific maladaptive activation of the p38α MAPK.

Mutations in *LMNA* cause a variety of human diseases, known collectively as laminopathies. DCM, which is also referred to as non-ischemic HFrEF, is one of the more common phenotypes associated with *LMNA* mutations. Mutations in the *LMNA* gene are the second

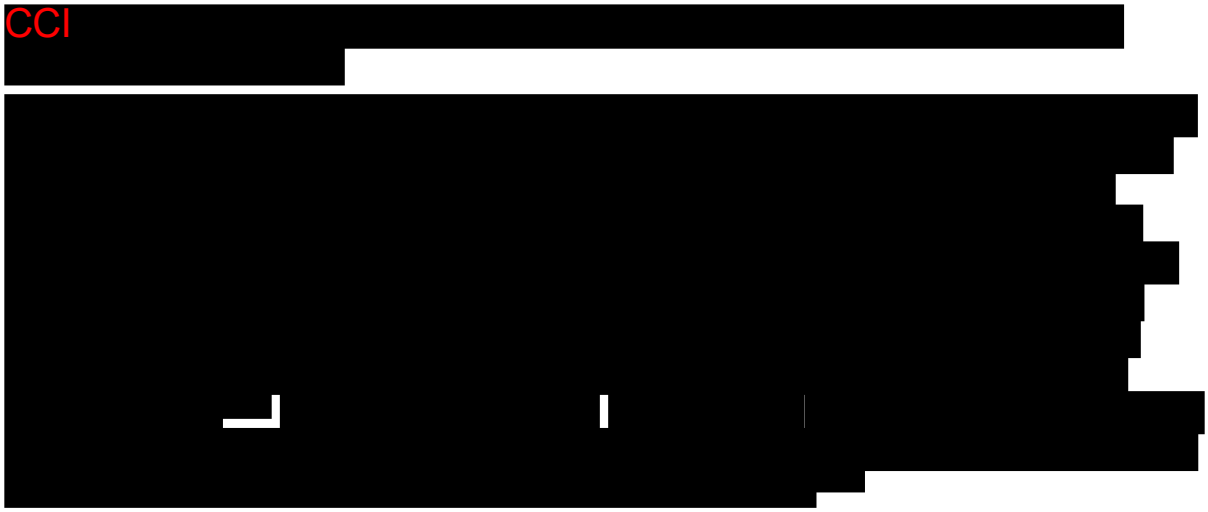
most common cause of idiopathic DCM after those in TTN[17] and account for around 6% of all cases. *LMNA*-related DCM can present as a *de novo* mutation or more frequently as an autosomal dominant inheritance, and is usually accompanied by CCD. *LMNA*-related DCM is a rare disease affecting less than 5 persons per 10,000 both in EU[18] and in the US[19].

Patients with *LMNA*-related DCM frequently suffer from atrioventricular conduction defects and have a significantly increased risk of sudden death due to ventricular arrhythmias.[17] The majority of patients with *LMNA*-related DCM follow a clinical course starting with CCD 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 HF.

Although the age of presentation in *LMNA*-related DCM varies, the age of onset typically appears to be in the third and fourth decades.[17,19,20,21] Furthermore, *LMNA*-related DCM patients have a more malignant clinical course than other DCM types, due to high rates of progressive HF and sudden cardiac death from ventricular tachyarrhythmia, despite conventional HF therapies, unless prevented by an ICD.[22,23,24] Spontaneous improvement is not seen in *LMNA*-related DCM, and while the response to conventional HF therapies has not been fully characterized in this specific form of DCM, the relentless progression of disease despite conventional medical therapies suggests that it is poor.

Currently, there is no effective, disease-specific treatment available for *LMNA*-related DCM. To date, treatment is limited to conventional therapies for heart failure with reduced ejection fraction(angiotensin-converting-enzyme inhibitors , angiotensin 2 receptor blockers or angiotensin receptor-neprilysin inhibitor, beta blockers, sodium-glucose cotransporter-2 inhibitors, aldosterone antagonists, and diuretics) which do not address the etiology of the disease . Progressive deterioration in LV function and refractory HF symptoms are often treated with resynchronization therapy (bi-ventricular pacing). Risk of SCD is managed with ICD or CRT-D. In patients whose disease continues to progress in spite of aggressive cardiovascular management, left ventricular assist device (LVAD) and cardiac transplantation may be considered.

CCI



2.2.3. Nonclinical Studies with ARRY-371797 (PF-07265803)

Detailed information regarding nonclinical studies of ARRY-371797 (PF-07265803) is presented in the IB.

2.2.3.1. Nonclinical Pharmacology

Numerous in vitro and in vivo studies were performed to evaluate and confirm the ability of ARRY-371797 (PF-07265803) to interact with its intended target, p38 MAPK. In enzyme studies, ARRY-371797 (PF-07265803) inhibits p38α with a half maximal inhibitory concentration (IC_{50}) of 8.2 nM. In cellular studies, ARRY-371797 (PF-07265803) is a potent inhibitor of p38-mediated downstream phosphorylation of HSP27 in HeLa cells with an IC_{50} of 17 nM. This compound has demonstrated little to no activity against over 210 enzymes, receptors, channels, and transporters.

Two in vivo murine models of *LMNA*-related DCM have allowed exploration of pathophysiologic mechanisms of disease progression and novel therapies for these conditions. In vivo studies have demonstrated that p38 MAPK is activated in murine models of *LMNA*-related DCM and that this activation of p38 MAPK precedes the development of cardiac dysfunction. ARRY-371797 (PF-07265803) has been tested in the homozygous *LMNA* H222P model of EDMD with cardiomyopathy (EDMD2, MIM:181350) and in the homozygous *LMNA* N195K model of *LMNA*-related DCM, one of the original *LMNA* mutations linked to familial DCM with conduction defects (CMD1A, OMIM:150330.0006).[29,30] These 2 nonclinical models bracket the spectrum of phenotypes (EDMD2: cardiac and skeletal muscle disease and DCM: cardiac disease only). Results from these studies confirm that treatment with ARRY-371797 (PF-07265803) improves cardiac

structure and function and reduces myocardial apoptosis. In these mouse studies, the LV functional measures of LVEDD/body weight and LVESD/body weight are indices that correlate with the human clinical study endpoints of LVEDVI and LVESVI, respectively. The measure of LVEF is common to both mouse and human echocardiography. In addition, ARRY-371797 (PF-07265803) improves survival in the murine *LMNA*-related DCM model (LMNA N195K).

2.2.3.2. Nonclinical Drug Metabolism

In vitro experiments indicated that ARRY-371797 (PF-07265803) has moderate membrane permeability and may be a substrate for active P-gp efflux. ARRY-371797 (PF-07265803) was moderately, but reversibly, bound to plasma proteins in vitro across mouse, monkey, and human plasma, as was AR00420643, the principal acid metabolite in vivo. AR00420643(PF-07327859), is formed in in vitro incubations with liver microsomes, hepatocytes, plasma, or blood. Other, less abundant, metabolites that are found in vitro or in vivo are a result of oxidative metabolism. No glucuronide conjugates were detected in hepatocyte incubations. No human specific metabolites were detected in liver microsomes or hepatocytes.

Multiple Phase 1 enzymes (CYPs, FMOs, amidases, and esterases) are involved in the metabolism of ARRY-371797 (PF-07265803). In vitro CYP-mediated metabolism was primarily by CYP3A4 and CYP2D6; however, these enzymes do not generate the principal acid metabolite in vivo. Other Phase 1 enzymes (FMOs, amidases, and esterases) convert ARRY-371797 (PF-07265803) to the acid metabolite AR00420643 (PF-07327859) in vitro.

ARRY-371797 (PF-07265803) and its metabolites were weak inhibitors of the major CYP isoforms in vitro (CYPs 1A2, 2B6, 2C8, CYP2C19, CYP2D6, CYP3A). The principal acid metabolite (AR00420643, PF-07327859) and the N-desmethyl acid metabolite (AR00486705) are weak inhibitors of CYP2C9. Based on circulating concentrations at the clinical dose of 400 mg BID, ARRY-371797 (PF-07265803) and metabolites have a low potential to elicit a DDI due to competitive inhibition of CYP enzymes.

ARRY-371797 (PF-07265803) is a time-dependent inhibitor of CYP2D6 and the lactam metabolite (AR00428028) is a time-dependent inhibitor of CYP3A4. In in vitro studies in human hepatocytes, ARRY-371797 (PF-07265803) and its metabolites are inducers of CYP3A mRNA, while only metabolites AR00420643 and AR00428028 induce CYP2B6 mRNA and enzyme activity. Based on potential for mixed induction/inhibition of CYP3A4, the net effect of ARRY-371797 (PF-07265803) interaction with drugs that are identified as CYP3A4 substrates cannot be predicted. Based on in vitro results, following coadministration of ARRY-371797 (PF-07265803) there is a potential for induction of CYP2B6 and potential for time-dependent inhibition of CYP2D6.

ARRY-371797 (PF-07265803) has a low potential to elicit clinically relevant DDIs involving UGT enzymes or interactions with transporters BCRP, OAT1/3, OATP1B1/3, or OCT1/2, or MATE1/2K . ARRY-371797 (PF-07265803) is a weak inhibitor of MDR1 (P-gp), a DDI with substrates of MDR1 cannot be ruled out.

2.2.3.3. Nonclinical Toxicity and Safety

Nonclinical toxicity studies have indicated that ARRY-371797 (PF-07265803) was tolerated at repeat oral doses of up to 30 mg/kg BID in rats and monkeys with GI side effects and minimal clinical pathology changes. Microscopic changes of skeletal muscle myofiber degeneration were reversible in monkeys administered doses of up to 100 mg/kg BID for 28 days. Microscopic findings of skeletal muscle myofiber degeneration in rats administered ARRY-371797 (PF-07265803) for 28 days were partially reversible with respect to severity and incidence at 100 mg/kg BID (200 mg/kg/day). In the chronic dosing studies for up to 26 weeks in rats and 9 months in monkeys at doses up to 30 mg/kg BID, there were no adverse microscopic findings. In general, administration of ARRY-371797 (PF-07265803) at doses of up to 30 mg/kg BID was tolerated in-life in rats and monkeys in the chronic toxicity studies. Administration of ARRY-371797 (PF-07265803) to monkeys for up to 3 months was associated with microscopic findings of skeletal muscle fiber changes, with no associated clinical chemistry changes. These skeletal muscle changes were reversible after the 1-month recovery phase and not observed following 9 months of total dosing or following the 3-month, dose-free recovery phase. Evidence of gastric irritation and increased gastric fluid secretion was observed in safety pharmacology GI studies in rats after a single oral dose of 100 mg/kg of ARRY-371797 (PF-07265803). After repeat administration of ARRY-371797 (PF-07265803) increased incidence of watery stools/feces were observed during the dosing phase in monkeys and generally resolved after dosing cessation during the recovery phases.

ARRY-371797 (PF-07265803) had no significant effects on ophthalmologic examinations, coagulation parameters, troponins (evaluated only in monkeys), or urinalysis parameters after administration of doses of up to 100 mg/kg BID in rats and monkeys for 28 consecutive days and up to 30 mg/kg BID in the chronic dosing studies in rats and monkeys. Increases in liver enzymes (ALT and AST), total bilirubin, BUN, glucose levels, and decreases in potassium levels were observed in rats after administration of ARRY-371797 (PF-07265803) at doses of up to 100 mg/kg BID in the 28 day study only. Mild to moderate increases in liver enzymes (ALT and/or AST) were observed in monkeys. Reversible increases in lymphocytes were observed in rats. These clinical pathology changes did not appear to have any functional or pathological consequences. No ECG, heart rate, and blood pressure abnormalities related to ARRY-371797 (PF-07265803) administration were observed in monkeys.

There was no evidence of genotoxicity in the 2 in vitro assays (bacterial reverse mutation or mouse lymphoma) and the in vivo assay (mouse micronucleus). The genotoxicity tests were conducted at concentrations of the standard limits for these test systems. There is little to no risk of phototoxicity with the administration of ARRY-371797(PF-07265803). The embryo-fetal developmental toxicity studies support the exclusion of pregnant women from clinical studies of ARRY-371797 (PF-07265803) and the continued requirement that WOCBP use appropriate contraception.

2.2.4. Clinical Experience with ARRY-371797 (PF-07265803)

ARRY-371797 (PF-07265803) has been investigated in 10 completed placebo-controlled clinical studies involving 485 participants treated for up to 12 weeks, including 5 Phase 1 studies in healthy participants and 5 studies (1 Phase 1b and 4 Phase 2) in participants with painful inflammatory conditions (RA, AS, OA, and postsurgical pain).

ARRY-371797 (PF-07265803) has also been evaluated in a completed Phase 2 study in 12 participants treated up to 48 weeks (Study ARRAY 797-231) with ARRY-371797 (PF-07265803) in participants with *LMNA*-related DCM, and in a completed open-label long-term rollover extension study (ARRAY-797-001) from ARRAY-797-231 in 8 participants assessed at Weeks 48, 72, 96, 120, and 144 from Phase 2 study baseline.

Detailed information regarding clinical studies of ARRY-371797 (PF-07265803) is presented in the IB.

2.2.4.1. Clinical Pharmacokinetics

The clinical PK of ARRY-371797 (PF-07265803) and AR00420643 have been evaluated in healthy participants following single- and repeat-dose administration. Following single doses of ARRY-371797 (PF-07265803), exposure of ARRY-371797 (PF-07265803) increased in a dose-proportional manner up to the highest dose evaluated (2000 mg total daily dose). After repeat-dose administration, exposure increased in a nearly dose-proportional manner. The maximal plasma concentrations (C_{max}) were generally observed approximately 1 to 2 hours following dose administration with consistent plasma concentration-time profile shapes at all doses evaluated. The terminal half-life ($t_{½}$) was approximately 1.5 to 5 hours and was dose-dependent, with longer $t_{½}$ at higher doses. Less than 2-fold accumulation was observed (1.3 to 1.8). In general, low-to-moderate inter-subject variability was observed for exposure-related PK parameters. CCI [redacted]

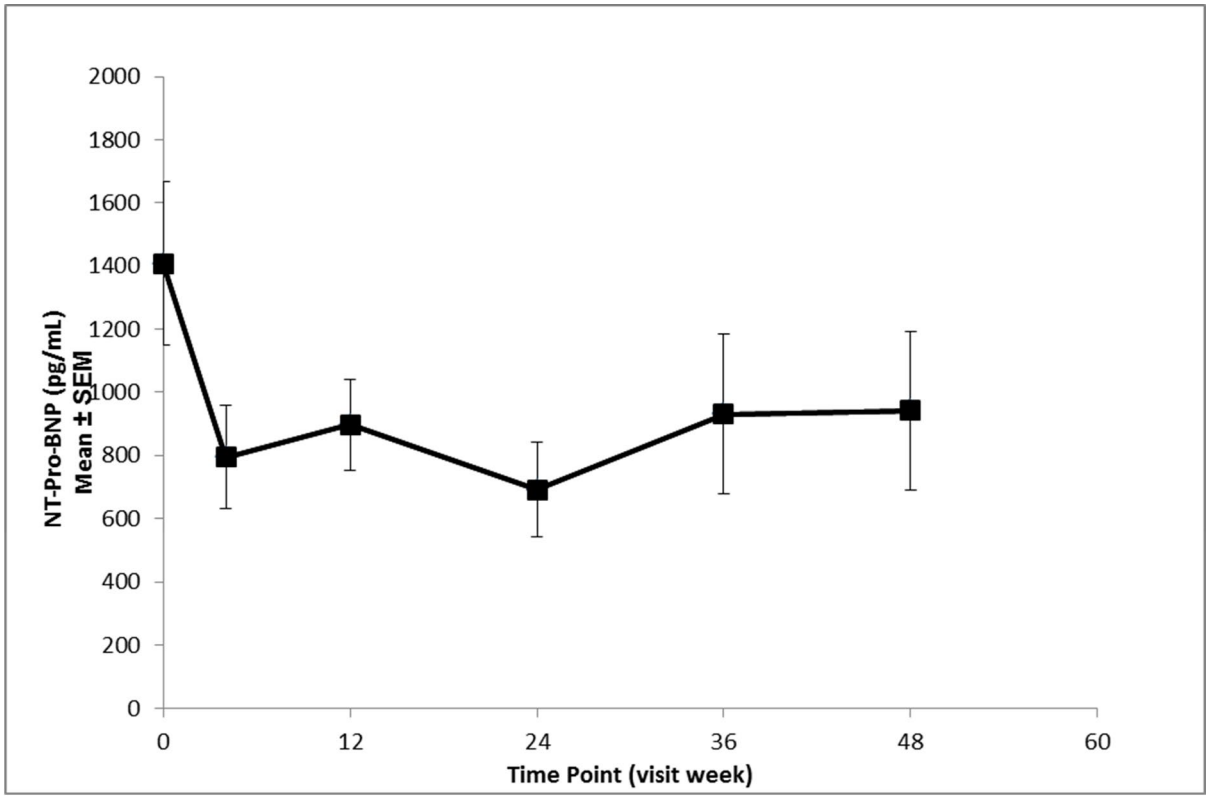
The metabolite (AR00420643)-to-parent ratio ranged from approximately 9 to 22, with higher exposures to the metabolite, AR00420643, observed relative to the parent, ARRY-371797 (PF-07265803). Additional circulating metabolites were analyzed in Study ARRAY-797-231, including a lactam (AR00428028) and N-desmethyl product of the acid metabolite (AR00486705). Geometric mean metabolite-to-parent ratio at Week 4 was 13.5 predose (n = 10) and 0.766 at 1 to 2 hours postdose (n = 12) for AR00428028 and 2.65 predose (n = 10) and 0.327 1-2 hours postdose (n = 12) for AR00486705.

Exposure was also assessed with sparse sampling in the RA, AS, OA, and postsurgical pain participant populations. Although formal PK analyses were not performed, evaluation of plasma concentration data indicated that exposure to ARRY-371797 (PF-07265803) was comparable to that in healthy participants.

2.2.4.2. Clinical Pharmacodynamics

Treatment-related changes in BNP and NT-proBNP have been documented as predictors of patient-centered outcomes in chronic heart failure, including improvements in symptoms, quality of life and exercise capacity.[31] In Clinical Study ARRAY-797-231, decreases from baseline in NT-proBNP by original assigned dose ranged from 5.3 to 508.8 pmol/L for the 100 mg BID group and from 192.0 to 610.6 pmol/L for the 400 mg BID group. The overall (dose groups combined) mean decrease in NT-proBNP at Weeks 4, 12, 24, 36, and 48 were 559.7, 444.9, 340.6, 296.5, and 284.0 pmol/L, respectively. The mean change in NT-proBNP for the dose groups combined is shown in Figure 1.

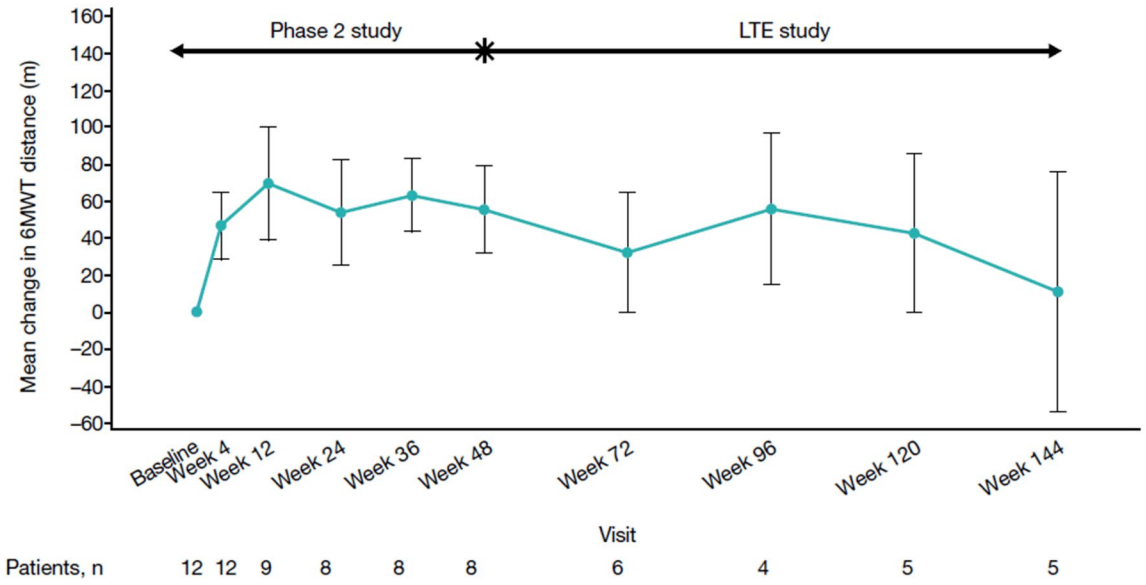
Figure 1. Mean NT-proBNP Over Time from Study ARRAY-797-231



2.2.4.3. Clinical Efficacy

In Study ARRAY-797-231, the efficacy of 48 weeks of treatment with ARRY-371797 (PF-07265803) at 2 dose levels (100 mg BID [N = 6] or 400 mg BID [N = 6]) was investigated in 12 stable participants with symptomatic *LMNA*-related DCM. The primary efficacy endpoint was the change from baseline in 6MWT at Week 12. Both dose groups showed improvements in distance at this time point. Participants in this study were allowed to continue to receive ARRY-371797 (PF-07265803) on a rollover protocol. Eight participants were enrolled and the mean 6MWT improved by >30 m (>10% mean increase) from Phase 2 study baseline up to Week 120. The change in 6MWT data through Week 144 with both dose groups combined is shown in Figure 2.

Figure 2. Mean Change in 6MWT Over Time From Studies ARRAY-797-231 and ARRAY-797-001 – Combined Dose Groups



80% CI of the mean 6MWT distance is included for each time point.
6MWT, 6-minute walk test; LTE, long-term extension.

A total of 4 participants in the 100 mg BID group and 1 participant in the 400 mg BID group showed at least 10% improvement in 6MWT at Week 12. The overall mean change at Week 12 in 6MWT for the dose groups combined was 69.4 m (22.5% increase from baseline). An approximate 10% improvement in 6MWT is considered to be clinically meaningful based on discussions with clinical experts and on FDA approvals for PAH drugs where 6MWT improvements ranged from 6% to 19%.[6,7,8,32]

The secondary efficacy endpoint for the 6MWT was the change from baseline at Weeks 4, 24, 36, and 48, and 4 weeks after dose escalation. These results were supportive of the primary endpoint. Improvements in 6MWT distance ranged from approximately 39.3 to 86.6 m (12.5% to 28.6% increase) for the 100 mg BID group and 23.7 to 69.3 m (8.0% to 20.8% increase) for the 400 mg BID group. At Week 28 (or 4 weeks after dose escalation), participants who were dose escalated to 400 mg BID showed an improvement in 6MWT of 77.7 m (24.3% increase from baseline). The overall (dose groups combined) mean changes in 6MWT at Weeks 4, 24, 36, and 48 were 46.7, 53.8, 63.0, and 55.3 m, respectively.

Echocardiographic parameters tended to be variable between visits. In general, measurements of LVEF and RV fractional area suggested overall stability of, or a trend for improvements in, left or RV function with ARRY-371797 (PF-07265803) treatment.

2.2.4.4. Clinical Safety

In 5 completed Phase 1 studies of ARRY-371797 (PF-07265803) in healthy participants, ARRY-371797 (PF-07265803) demonstrated an acceptable safety profile when administered at single doses up to 900 mg QD, up to 400 mg/day for 14 days and up to 2000 mg/day for 7 days. The most commonly reported AEs in participants receiving ARRY-371797 (PF-07265803) were dizziness, headache, diarrhea, nausea, and acne; the incidence of these AEs was not clearly related to the ARRY-371797 (PF-07265803) dose, nor to the duration of exposure.

No clinically meaningful association has been observed between treatment with ARRY-371797 (PF-07265803) and abnormalities in hematology or urinalysis parameters. In participants with knee pain due to OA (Study ARRAY-797-223), mild elevations in CK and AST, and mild reductions in mean arterial pressure were observed in participants receiving ARRY-371797 (PF-07265803). No other association between treatment with ARRY-371797 (PF-07265803) and changes in vital signs in any of the clinical studies has been observed.

While there is no nonclinical evidence of QT prolongation, in a pooled analysis across clinical studies, there is some evidence for dose-related prolongation of QTcF compared with placebo in participants receiving ARRY-371797 (PF-07265803). The magnitude of mean placebo-adjusted QTcF prolongation at T_{max} for the dose of 400 mg BID is approximately 8 msec.

2.2.4.4.1. Clinical Safety in Participants with *LMNA*-related Dilated Cardiomyopathy

In Study ARRAY-797-231, the safety of 48 weeks of treatment with ARRY-371797 (PF-07265803) at 2 dose levels (100 mg BID [N = 6] or 400 mg BID [N = 6]) was investigated in 12 stable participants with symptomatic *LMNA*-related DCM. All 12 participants were evaluated for safety. Table 1 summarizes AEs reported in >1 participant or reported as Grade 3/4 severity in Study ARRAY-797-231.

Table 1. Summary of Adverse Events, Regardless of Causality, Reported in >1 Participant or Reported as Grade 3/4 (Study ARRAY-797-231)

Preferred Term	ARRY-371797 N = 12	
	All Grades n (%)	Grade 3/4 n (%)
Stomatitis	3 (25.0)	0
Accidental overdose[a]	2 (16.7)	0
Acne	2 (16.7)	0
Atrial fibrillation	2 (16.7)	1 (8.3)
Dry eye	2 (16.7)	0
Liver function test abnormal	2 (16.7)	1 (8.3)
Pyrexia	2 (16.7)	1 (8.3)
Rash	2 (16.7)	1 (8.3)
Upper respiratory tract infection	2 (16.7)	0
Cardiac failure	1 (8.3)	1 (8.3)
Congestive cardiomyopathy	1 (8.3)	1 (8.3)
Musculoskeletal pain	1 (8.3)	1 (8.3)
Neck pain	1 (8.3)	1 (8.3)
Ventricular tachycardia	1 (8.3)	1 (8.3)

a. Two participants each took 2 additional capsules during the study, one participant at Week 36 and 1 participant at Week 48.
Preferred terms are sorted by descending order of frequency in the ARRY-371797 all-grades column.
AEs were coded using MedDRA v16.1.

There were no deaths during the study. SAEs were reported in 3 participants (25%). In the 400 mg BID group, 1 participant experienced SAEs of Grade 3 atrial fibrillation and Grade 4 cardiac failure and abnormal liver function tests; the latter was assessed as related to concomitant amiodarone treatment. In the 100 mg BID group, 1 participant experienced SAEs of ventricular tachycardia and congestive cardiomyopathy and another participant experienced SAEs of pyrexia, musculoskeletal pain, neck pain, and subcorneal pustular dermatosis (all Grade 3). All SAEs resolved and were assessed by the investigator as not related to study intervention. No nonserious Grade 3/4 AEs were reported.

Events resulting in treatment discontinuation were reported in 3 participants (25%). In the 400 mg BID group, 1 participant experienced Grade 4 cardiac failure assessed as not related to study intervention and another participant experienced Grade 2 stomatitis assessed as treatment related. In the 100 mg BID group, 1 participant experienced Grade 3 congestive cardiomyopathy assessed as not related to study intervention.

In the long-term rollover extension study to the Phase 2 study in patients with *LMNA*-related DCM (Study ARRAY-797-001; N = 8), treatment with ARRY-371797 (PF-07265803) was well tolerated. Six participants (75.0%) experienced SAEs, none of which were considered related to study intervention. The most frequently reported TEAEs were ventricular tachycardia in 5 participants (62.5%) and accidental overdose in 4 participants (50.0%; no associated AEs were reported) and cardiac failure congestive, diarrhea, dyspnea, and orthostatic hypotension in 2 participants (25.0%) each. Two participants (25.0%) were

discontinued from study intervention due to TEAEs of heart transplant and cardiac failure congestive, respectively; neither were considered related to study intervention. There were no deaths during the study. Additional information regarding the safety of ARRY-371797 (PF-07265803) is presented in the IB.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of ARRY-371797 (PF-07265803) may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention ARRY-371797 (PF-07265803)		
An identified risk associated with this study intervention is stomatitis. It is a common (≥1/100 to <1/10) event in the protocol population.	The potential risks are based on adverse events reported in early studies of ARRY-371797.	AEs will be monitored on an ongoing basis. Instructions for managing potential cases of stomatitis are provided (see Section 6.6).

2.3.2. Benefit Assessment

The clinical safety and efficacy profile of ARRY-371797 (PF-07265803) as observed in the Phase 2 study (Clinical Study ARRAY-797-231) of participants with *LMNA*-related DCM indicated that ARRY-371797 (PF-07265803) is overall well tolerated and demonstrated some trends towards improvement in exercise capacity (6MWT distance) and other measures of HF severity.

In this study, the efficacy of 48 weeks of treatment with ARRY-371797 (PF-07265803) at 2 dose levels (100 mg BID [N = 6] or 400 mg BID [N = 6]) was investigated in 12 stable participants with symptomatic *LMNA*-related DCM. The primary efficacy endpoint was the change from Baseline in 6MWT at Week 12 and both dose groups showed improvements in distance at this time point.

In the long-term rollover extension study to the Phase 2 study in participants with *LMNA*-related DCM (ARRAY-797-001 [C4411001]; N=8). The clinical safety and efficacy were assessed up to at least 96 weeks. The mean duration of exposure from the start of the rollover study was 113.1 weeks. ARRY-371797 (PF-07265803) was generally well tolerated, with evidence suggesting preserved exercise capacity over an extended period of follow-up. Preserved exercise capacity was mirrored by favorable trends in NT-proBNP levels.

2.3.3. Overall Benefit/Risk Conclusion

The benefit/risk assessment remains favorable for continuing the development of ARRY-371797 (PF-07265803) in participants with *LMNA*-related DCM.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Study objectives and corresponding endpoints are provided in the Table 3 below.

Per protocol, participants who discontinue study treatment 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.

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 Class (NYHA) 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 participants 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 only: Change from baseline in N-terminal pro-brain natriuretic peptide (NT-proBNP) at Weeks 4, 12, and 24.
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.
CCI [redacted]	[redacted]

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

This protocol will use an independent endpoint adjudication Clinical Events Committee (CEC) to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

4. STUDY DESIGN

4.1. Overall 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 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. A schematic of the study design is presented in Section 1.2. The sample size was increased following 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 9.2.

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 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.

The study will have an independent DMC to review safety and PK data at regular intervals and efficacy data at a formal interim futility analysis (Section 9.6.1). A study SC will be involved in oversight of the study and will ensure transparent management of the study according to the protocol (Section 9.6.2). A CEC will be utilized to adjudicate causes for HF-related hospitalizations and HF-related urgent care visits (Section 9.6.3).

A central laboratory will be used for analyses of ECGs, ECHO, NT-proBNP, and safety laboratory assessments; local laboratories will be used for analyses of ECHO at screening only to determine eligibility.

Pre-defined in the protocol, a formal interim futility analysis was performed on the 6MWT data at Week 12 after the first 60 randomized NYHA Class II/III participants had completed the Week 12 assessment or otherwise discontinued from the study prior to Week 12.

4.1.1. Prescreening and Screening for Randomized Double-Blind Treatment Period

All participants with DCM who meet the prescreening eligibility criteria for the study will be assessed for the presence of eligible *LMNA* mutation(s) using an assay performed by an accredited clinical laboratory.

The central accredited clinical laboratory will be used to assess *LMNA* mutation status if the *LMNA* mutation status is unknown at time of prescreening or if the genetic test was not performed by an accredited clinical laboratory. The *LMNA* mutation test results from the central accredited clinical laboratory must be available and confirmed prior to entering the screening period.

Participants with an identified pathogenic (P), likely pathogenic (LP) or VUS *LMNA* mutation status documented by results from an accredited clinical laboratory can enter the screening period. Participants who have multiple *LMNA* variants identified will be enrolled on the variant with the highest classification tier and the variant with the highest classification will be reported in the eCRF.

All participants will qualify for the study based on cardiac function, symptoms, and other eligibility factors during screening. The NYHA Class II/III participants will also qualify for the study based on their functional capacity (6MWT). All eligible participants (NYHA Class II/III and IV [if feasible]) will return to the clinic for assessment at the Day -1 visit. There must be at least 27 days between the 6MWT performed during screening and the 6MWT performed at the Day -1 visit.

4.1.2. Randomized Double-Blind Treatment Period

All eligible participants will return to the clinic for assessment at the baseline visit (Day 1) prior to randomization. Randomization will be initially stratified based on NYHA class: Class II/III or Class IV. Randomization for 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) results, and mutation type (pathogenic/likely pathogenic or VUS). On Day 1, eligible participants will be randomized (1:1) to 400 mg BID ARRY-371797 (PF-07265803) or placebo.

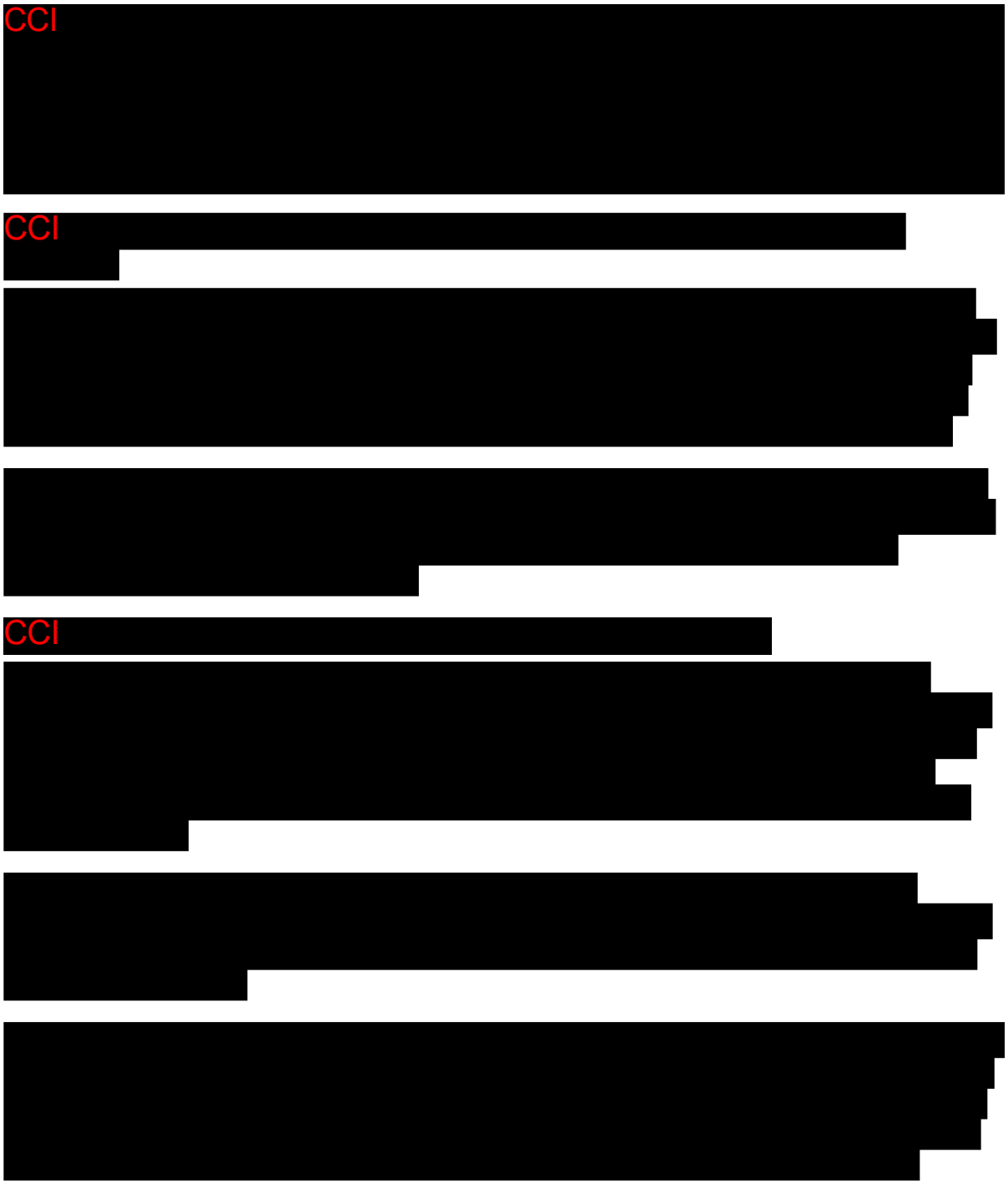
During the randomized, double-blind period, Class II/III participants will attend clinic visits at Weeks 4, 8, 12, 24, 36, 48, 60 and every 24 weeks thereafter during which efficacy and/or safety assessments will be performed. Starting at Week 72, a phone contact visit must be conducted every subsequent 24 weeks to assess at home urine pregnancy testing (WOCBP only), assess SAE/AEs and HF-related hospitalizations/HF-related urgent care visits. In addition, assessment of any changes to concomitant medications and assess status of study intervention and ensure the participant dosing diary is completed. Class IV participants should be encouraged to attend visits in the clinic at Weeks 4, 8, 12, 24, 36, 48, 60 and every 24 weeks thereafter whenever feasible, based on the participant's overall condition and mobility. If the Class IV participant cannot attend clinic visits, remote assessments after the baseline visit (Day 1) may be performed.

Safety assessments include the monitoring of AEs/SAEs, clinical laboratory tests (hematology, clinical chemistry, urinalysis, and pregnancy tests), physical examinations, vital signs, ECGs, and arrhythmia assessments according to the SoA. All concomitant medications and/or therapies will be recorded. Efficacy assessments include the 6MWT, ECHOs, and PRO assessments per the SoA. In addition, participants will have pre and postdose blood samples collected per the SoA to characterize the plasma PK of ARRY-371797 (PF-07265803) and its metabolites in this participant population. Participants will also have blood samples collected per the SoA in order to characterize PD markers. For the Class IV participants, some assessments are considered optional based on whether the participant is ambulatory or not. The following assessments are considered optional for the Class IV participants: 6MWT, ECGs, ECHO, arrhythmia assessment, PK assessment, and PD assessment. If a Class IV participant enters the study unable to complete any of these assessments, but later during the course of the study is able to complete them, these assessments should then be completed.

Participants will continue on study treatment as long as the participant has not met predefined criteria for treatment discontinuation. All participants should have a treatment discontinuation visit as soon as possible after the final dose of study intervention. A safety follow-up visit will occur approximately 30 days after the last dose of study intervention. Participants who discontinue study treatment 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. All participants will subsequently be followed for HF-related hospitalization or HF-related urgent care visit (see Section 8.2.6) and OS until death or initiation of the open-label treatment period, whichever occurs first (see Section 8.12). Every effort should be made to obtain these data.

CCI [redacted]

[redacted]



4.2. Scientific Rationale for Study Design

Refer to Section 2.1 for the Study Rationale.

4.3. Justification for Dose

In more than 100 healthy participants and relatively healthy participants, 400 mg BID ARRY-371797 (PF-07265803) has proven to be a well-tolerated dose. In Study

ARRAY-797-223, 41 participants with OA of the knee received 400 mg BID for 28 days, and this dosing regimen was well tolerated. In PD studies using clinical samples, 400 mg QD doses of ARRY-371797 (PF-07265803) provided inhibition of PD markers p38 pathway inhibition (cytokines, CRP) of greater than 80% (Study ARRAY-797-101). In a clinical study of pain relief (Study ARRAY 797-221), 400 mg QD of ARRY-371797 (PF-07265803) provided maximal effect (associated with p38 MAPK inhibition), with 200 mg ARRY-371797 (PF-07265803) providing significantly less benefit.

Doses utilized in the nonclinical studies of *LMNA*-related DCM, where positive effects on cardiovascular function and survival were demonstrated, provided exposure consistent with clinical exposure observed with 200 to 400 mg BID of ARRY-371797 (PF-07265803).

Study ARRAY-797-231 was a Phase 2, two-arm study designed to investigate the efficacy and safety of 48 weeks of treatment with ARRY-371797 (PF-07265803) in 12 stable participants with *LMNA*-related DCM. In this study, participants were alternately assigned to receive ARRY-371797 (PF-07265803) at 100 mg BID or 400 mg BID resulting in n = 6 per dose group. Participants in the 100 mg BID dose group were allowed to dose escalate to 400 mg BID after 24 weeks of treatment. Three participants dose escalated to 400 mg BID after their Week 24 visits and all 3 remained at the 400 mg BID dose through Week 48. In this study ARRY-371797 (PF-07265803) was generally well tolerated; most AEs were mild and only 1 participant discontinued due to a study intervention-related AE. The 400 mg BID dose of ARRY-371797 (PF-07265803) appeared to be associated with larger favorable changes in NT-proBNP levels than the 100 mg BID dose in an analysis of aggregated mean change from baseline at all time points. The safety and efficacy data from these clinical studies provide justification for the 400 mg BID dose regimen proposed in this study.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study. End of the study will occur 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.

See Section 6.7 for information regarding intervention after the end of the study. The sponsor will notify all applicable regulatory agencies in accordance with local requirements when the study has ended.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

Participants must fulfill all of the following inclusion criteria and none of the exclusion criteria to be eligible for randomization into the study.

In order to maintain diversity in the genetic pool enrolled in the study, no more than 10% of participants with the same mutation will be enrolled in the study.

Questions regarding participant eligibility should be addressed to the sponsor or delegate prior to enrollment.

5.1. Inclusion Criteria

5.1.1. Prescreening Eligibility Criteria for *LMNA* Mutation Testing

The following criteria define eligibility for prescreening:

5.1.1.1. Prescreening for Participants with Pre-Identified P/LP/VUS *LMNA* Mutation by an Accredited Clinical Laboratory

1. Provide a signed and dated informed consent document prior to initiation of any study-related procedures. Participants under guardianship or partial guardianship will be eligible unless prohibited by local laws or by local/central ethic committees.

2. Age ≥18 years at time of informed consent.

3. NYHA functional Class II, III, or IV.

4. Participant will have an ICD (implanted at least 4 weeks prior to initiation of study intervention) or CRT-D (CRT initiated at least 6 months prior to initiation of study intervention, and defibrillation function activated at least 4 weeks prior to initiation of study intervention). Devices must include pacing capabilities or a separate pacemaker must be present.

5. Participant will have symptomatic DCM with pre-identified P/LP/VUS *LMNA* mutation. The test result must be obtained from an accredited clinical laboratory.

6. Participant will have a history of reduced EF and at least one of the following:

    a. Cardiac conduction disease, including sinus node arrest with junctional rhythms or atrioventricular conduction block of at least first degree, ie, PR interval ≥220 msec during sinus rhythm.

    b. Family history of early onset HF/arrhythmia consistent with a diagnosis of idiopathic DCM.

    c. History of paroxysmal or sustained supraventricular arrhythmias, including atrial fibrillation, atrial flutter, supraventricular tachycardia, or sick sinus syndrome.

    d. History of paroxysmal or sustained ventricular arrhythmias including ventricular tachycardia, and ventricular fibrillation.

7. No documented history of a clinical illness or condition other than *LMNA* mutations that is associated with HF or, in the judgment of the investigator, would make the participant inappropriate for study participation.

5.1.1.2. Prescreening for Participants with Unknown *LMNA* Mutation Status or with an Identified *LMNA* Mutation Result not Performed by an Accredited Clinical Laboratory

1. Provide a signed and dated prescreening informed consent document prior to initiation of any study-related procedures. Participants under guardianship or partial guardianship will be eligible unless prohibited by local laws or by local/central ethic committees.

2. Age ≥18 years at time of informed consent.

3. NYHA functional Class II, III, or IV.

4. Participant will have an ICD (implanted at least 4 weeks prior to initiation of study intervention) or CRT-D (CRT initiated at least 6 months prior to initiation of study intervention), and defibrillation function activated at least 4 weeks prior to initiation of study intervention. Devices must include pacing capabilities or a separate pacemaker must be present.

5. Participant will have a history of reduced EF and at least one of the following:

    a. Cardiac conduction disease, including sinus node arrest with junctional rhythms or atrioventricular conduction block of at least first degree, ie, PR interval ≥220 msec during sinus rhythm.

    b. Family history of early onset HF/arrhythmia consistent with a diagnosis of idiopathic DCM.

    c. History of paroxysmal or sustained supraventricular arrhythmias, including atrial fibrillation, atrial flutter, supraventricular tachycardia, or sick sinus syndrome.

    d. History of paroxysmal or sustained ventricular arrhythmias including ventricular tachycardia, and ventricular fibrillation.

6. No documented history of a clinical illness or condition that, in the judgment of the investigator, would make the participant inappropriate for study participation.

5.1.2. Inclusion Criteria for NYHA Functional Class II and III Participants

Participants of NYHA functional Class II or III must meet all of the following criteria at screening to be eligible for randomization into the study:

1. Provide a signed and dated informed consent document prior to initiation of any study-related procedures. Participants under guardianship or partial guardianship will be eligible unless prohibited by local laws or by local/central ethic committees.

2. Age ≥18 years at time of informed consent.

3. Participants with symptomatic *LMNA*-related DCM defined as all of the following:

    a. Gene positive for a pathogenic, likely pathogenic or VUS mutation in the *LMNA* gene as determined by an accredited clinical laboratory;

    b. NYHA functional Class II or III that has been stable for at least 3 months;

    c. Evidence of cardiac impairment as determined by LVEF ≤50%.

4. Participant will have an ICD (implanted at least 4 weeks prior to initiation of study intervention) or CRT-D (CRT initiated at least 6 months prior to initiation of study intervention and defibrillation function activated at least 4 weeks prior to initiation of study intervention). Devices must have activated pacing capabilities or a separate pacemaker must be present.

5. Objective functional impairment evidenced by a reduction in 6MWT; participants must meet all of the following 6MWT criteria:

    a. Screening: 6MWT distance >100 m but ≤450 m, AND

    b. Day -1 visit: 6MWT distance >100 m but ≤485 m, AND

    c. Baseline visit (Day 1): 6MWT distance >100 m but ≤485.

6. In the judgment of the investigator, the participant has impaired function due to symptomatic DCM rather than any noncardiac comorbidity that can significantly impair function.

7. Stable medical and/or device therapy consistent with regional (eg, AHA/ACC or ESC) guidelines at the investigator discretion, without change in HF drug(s) dose in the past 1 month.

8. Acceptable hematology laboratory values within 35 days prior to Day 1:

    a. Hemoglobin >9.5 g/dL;

    b. WBC count >2500/µL;

    c. Platelet count >100,000/µL.

9. Acceptable hepatic and renal function laboratory values within 35 days prior to Day 1:

    a. AST and/or ALT ≤4.0×ULN;

    b. Total bilirubin <2×ULN (except for Gilbert's syndrome);

    c. eGFR >30 mL/min/1.73 m^2 (using the sMDRD formula). In the event sMDRD cannot be determined due to the lack of collection of appropriate data (eg, race), CrCL >30 mL/min (using the Cockroft-Gault formula).

10. If participant is female and of childbearing potential, she must not be pregnant or breastfeeding or plan to become pregnant during the duration of the trial. She must have a negative serum β-HCG test within 7 to 35 days prior to Day 1 and consent to ongoing urine pregnancy testing during the course of the study.

11. Male participants and female participants of childbearing potential must agree to use a highly effective method of contraception as defined in the study protocol (Section 5.3.1).

12. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

5.1.3. Inclusion Criteria for NYHA Functional Class IV Participants

Participants of NYHA functional Class IV must meet all of the following criteria at screening to be eligible for randomization into the study:

1. Provide a signed and dated informed consent document prior to initiation of any study-related procedures. Participants under guardianship or partial guardianship will be eligible unless prohibited by local laws or by local/central ethic committees.

2. Age ≥18 years at time of informed consent.

3. Participants with symptomatic *LMNA*-related DCM defined as all of the following:

    a. Gene positive for a pathogenic, likely pathogenic or VUS mutation in the *LMNA* gene as determined by an accredited clinical laboratory;

    b. NYHA functional Class IV that has been stable for at least 1 month

    c. Evidence of cardiac impairment as determined by EF ≤50%.

4. Participant will have an ICD (implanted at least 4 weeks prior to initiation of study intervention) or CRT-D (CRT initiated at least 6 months prior to initiation of study intervention and defibrillation function activated at least 4 weeks prior to initiation of study intervention). Devices must have activated pacing capabilities or a separate pacemaker must be present.

5. Stable medical and/or device therapy consistent with regional (eg, AHA/ACC or ESC) guidelines at the investigator discretion, without change in HF drug(s) dose in the past 1 month.

6. Acceptable hematology laboratory values within 35 days prior to Day 1:

   a. Hemoglobin >9.0 g/dL;

   b. WBC count >2,500/μL;

   c. Platelet count >100,000/μL.

7. Acceptable hepatic and renal function laboratory values within 35 days prior to Day 1:

   a. AST and/or ALT ≤4.0×ULN;

   b. Total bilirubin <2×ULN (except for Gilbert's syndrome);

   c. eGFR >30 mL/min/1.73 m^2 (using the sMDRD formula). In the event sMDRD cannot be determined due to the lack of collection of appropriate data (ie, race), CrCL >30 mL/min (using the Cockroft-Gault formula).

8. If participant is female and of childbearing potential, she must not be pregnant or breastfeeding or plan to become pregnant during the duration of the trial. She must have a negative serum β-HCG test within 7 to 35 days prior to Day 1 and consent to ongoing urine pregnancy testing during the course of the study.

9. Male participants and female participants of childbearing potential must agree to use a highly effective method of contraception as defined in the study protocol (Section 5.3.1).

10. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

5.1.4. Inclusion Criteria for Participants Who Cross Over From Placebo to ARRY-371797 (PF-07265803) Treatment in the Open-Label Period

Participants of NYHA functional Class II, III, or IV must meet all of the following criteria at the open-label baseline visit to be eligible for initiating treatment in the open-label period of the study:

1. Must be currently on this study (on treatment, defined as no longer than 21 days of treatment interruption unless approved by medical monitor [Section 6.6.1]).

2. Acceptable hematology laboratory values:

   a. Hemoglobin > 9.0 g/dL;

   b. WBC count > 2,500/µL;

   c. Platelet count > 100,000/µL.

3. Acceptable hepatic and renal function laboratory values:

   a. AST and/or ALT ≤4.0×ULN;

   b. Total bilirubin <2.0×ULN (except for Gilbert's syndrome);

   c. eGFR >30 mL/min/1.73 m2 (using the sMDRD formula). In the event sMDRD cannot be determined due to the lack of collection of appropriate data (ie, race), CrCL >30 mL/min (using the Cockroft-Gault formula).

4. If participant is female and of childbearing potential, she must not be pregnant or breastfeeding or plan to become pregnant during the duration of the trial. She must have a negative urine pregnancy test at the open-label baseline visit and consent to ongoing urine pregnancy testing during the study.

5. Male participants and female participants of childbearing potential must agree to use a highly effective method of contraception as defined in the study protocol (Section 5.3.1).

6. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

5.2. Exclusion Criteria

5.2.1. Exclusion Criteria for NYHA Functional Class II and III Participants

Participants of NYHA functional Class II or III meeting any of the following criteria at screening are ineligible for randomization into the study:

1. Presence of other form(s) of cardiomyopathy contributing to HF (eg, inflammatory or infiltrative cardiomyopathy), clinically significant cardiac anatomic abnormality (eg,LV aneurysm), clinically significant coronary artery disease (eg, coronary revascularization, exercise -induced angina) or uncorrected, hemodynamically significant (ie, moderate-severe) primary structural valvular disease not due to HF, per investigator judgment.

2. Currently receiving intermittent or continuous IV inotrope infusion, or presence of a ventricular assist device, or history of prior heart transplantation. Participants listed for cardiac transplantation may be enrolled provided transplantation is not likely to occur in the next 6 months.

3. Any of the following within 3 months prior to screening: myocardial infarction, cardiac surgical procedures (other than for pacemaker/ICD/CRT-D implantation or replacement), acute coronary syndrome, serious systemic infection with evidence of septicemia, or any major surgical procedure requiring general anesthesia.

4. Currently receiving or deemed at high risk of requiring chronic renal replacement therapy (eg, hemodialysis or peritoneal dialysis) within 6 months.

5. Initiation of CRT within 6 months prior to screening.

6. Likelihood, in the investigator's opinion, of undergoing cardiac transplantation, LVAD or other device implantation, or other invasive therapeutic cardiac procedure within the next 6 months; or of requiring continuous IV inotropic treatment, or referral for hospice or end-of-life treatment.

7. Treatment with any investigational agent(s) for HF within 35 days prior to Day 1.

8. Malignancy that is active or has been diagnosed within 3 years prior to screening, except surgically curatively resected in situ malignancies or surgically cured early breast cancer, prostate cancer, skin cancer (basal cell carcinoma, squamous cell carcinoma), thyroid cancer, or cervical cancer, or, with prior review by the medical monitor, other early stage surgically curatively resected malignancies with less than a 20% expected 2-year recurrence rate.

9. Noncardiac condition that limits lifespan to <1 year.

10. Serum positive for hepatitis B surface antigen, viremic hepatitis C, or HIV at screening.

11. Medical, psychiatric, cognitive, or other conditions that compromise the participant's ability to understand the participant information, comply with the study protocol, or complete the study.

12. Any severe concurrent disease or condition (eg, active systemic infection) that, in the judgment of the investigator, would make the participant inappropriate for study participation.

13. Prior exposure to ARRY-371797 (PF-07265803).

14. Prior randomization into this clinical study.

15. Participants with an underlying condition that may impact the ability of the 6MWT to reflect changes in cardiovascular function such as: an orthopedic condition that limits walking abilities (eg, severe arthritis), significant musculoskeletal pathology, significant COPD that limits exercise tolerance, or any other condition that, according to the investigator's assessment, significantly limits a participant's performance on the 6MWT independently from the participant's cardiomyopathy.

16. Documented hypersensitivity/allergy or clinically significant intolerance to any component of drug product.

5.2.2. Exclusion Criteria for NYHA Functional Class IV Participants

Participants of NYHA functional Class IV meeting any of the following criteria at screening are ineligible for randomization into the study:

1. Presence of other form(s) of cardiomyopathy contributing to HF (eg, inflammatory or infiltrative cardiomyopathy), clinically significant cardiac anatomic abnormality (eg, LV aneurysm), clinically significant coronary artery disease (eg, coronary revascularization, exercise-induced angina) or uncorrected, hemodynamically significant (ie, moderate-severe) primary structural valvular disease not due to HF per investigator judgment.

2. Presence of a ventricular assist device, or history of prior heart transplantation. Participants listed for cardiac transplantation may be enrolled.

3. Treatment with any investigational agent(s) for HF within 35 days prior to Day 1.

4. Malignancy that is active or has been diagnosed within 3 years prior to screening, except surgically curatively resected in situ malignancies or surgically cured early breast cancer, prostate cancer, skin cancer (basal cell carcinoma, squamous cell carcinoma), thyroid cancer, or cervical cancer, or, other early stage surgically curatively resected malignancies with less than a 20% expected 2-year recurrence rate.

5. Non-cardiac condition that limits lifespan to <1 year.

6. Serum positive for hepatitis B surface antigen, viremic hepatitis C, or HIV at screening.

7. Medical, psychiatric, cognitive, or other conditions that compromise the participant's ability to understand the participant information, comply with the study protocol, or complete the study.

8. Any severe concurrent disease or condition (eg, active systemic infection) that, in the judgment of the investigator, would make the participant inappropriate for study participation.

9. Prior exposure to ARRY-371797 (PF-07265803).

10. Prior randomization into this clinical study.

11. Documented hypersensitivity/allergy or clinically significant intolerance to any component of drug product.

5.2.3. Exclusion Criteria for Participants Who Cross Over From Placebo to ARRY-371797 (PF-07265803) Treatment in the Open-Label Period

Participants of NYHA functional Class II, III, or IV meeting any of the following criteria at the open-label baseline visit are ineligible for initiating treatment in the open-label period of the study.

1. Presence of other form(s) of cardiomyopathy contributing to HF (eg, inflammatory or infiltrative cardiomyopathy) or clinically significant cardiac anatomic abnormality (eg, LV aneurysm), clinically significant coronary artery disease (eg, coronary revascularization, exercise-induced angina) per investigator judgment or uncorrected, hemodynamically significant (ie, moderate-severe) primary structural valvular disease not due to HF

2. Presence of a ventricular assist device or history of prior heart transplantation. Participants listed for cardiac transplantation may be enrolled.

3. Currently receiving or deemed at high risk of requiring chronic renal replacement therapy (eg, hemodialysis or peritoneal dialysis) within 6 months.

4. Treatment with any investigational agent(s) for HF at the open-label baseline visit.

5. Malignancy that is active or has been diagnosed within 3 years prior to screening, except surgically curatively resected in situ malignancies or surgically cured early breast cancer, prostate cancer, skin cancer (basal cell carcinoma, squamous cell carcinoma) thyroid cancer, or cervical cancer or, other early stage surgically curatively resected malignancies with less than a 20% expected 2-year recurrence rate.

6. Non-cardiac condition that limits lifespan to <1 year.

7. Medical, psychiatric, cognitive, or other conditions that compromise the participant's ability to understand the participant information, comply with the study protocol, or complete the study.

8. Any severe concurrent disease or condition (eg, active systemic infection) that, in the judgment of the investigator, would make the participant inappropriate for study participation.

9. Documented hypersensitivity/allergy or clinically significant intolerance to any component of drug product.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its

consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

Consumption of food will be restricted from 2 hours prior to and 2 hours after study intervention administration. Other dietary restrictions should be generally consistent with accepted treatment guidelines for participants with HF.

5.3.3. Restrictions on Physical Activity

Participants should abstain from strenuous exercise (eg, heavy lifting, weight training, and aerobic activity) for 48 hours prior to each clinic visit.

5.4. Screen Failures

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

Participants who fail to qualify for study eligibility upon initial screening may be rescreened a maximum of 4 additional times.

Prescreening and screening procedures for the randomized double-blind treatment period are summarized in Section 4.1.1.

6. STUDY INTERVENTION

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

For the purposes of this protocol, study intervention refers to ARRY-371797 (PF-07265803) or placebo.

6.1. Study Intervention(s) Administered

Participants will be randomized (1:1) to receive 4 x 100 mg tablets BID of study intervention (either ARRY-371797 (PF-07265803) or placebo) during the double-blind period of the study. Both active treatment (ARRY-371797 (PF-07265803)) and placebo will be supplied

by the sponsor as brown capsule-shaped film coated tablets in 100 mg dose strength (or placebo) for oral administration.

Table 2. Dose Levels of Study Intervention

	ARRY-371797 (PF-07265803)	Matching Placebo
Dose Level 1	400 mg BID (4×100 mg tablets BID)	4 tablets BID
Dose Level -1	200 mg BID (2×100 mg tablets BID)	2 tablets BID
Dose Level -2	100 mg BID (1×100 mg tablet BID)	1 tablet BID

Study intervention may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for ARRY-371797 (PF-07265803). Pfizer does not permit the shipment of study intervention by mail. The tracking record of shipments, including temperature monitoring data, and the chain of custody of ARRY-371797 (PF-07265803) must be kept in the participant's source documents/medical records.

6.1.1. Manufacturing and Formulation

ARRY-371797 (PF-07265803) is supplied by the sponsor as brown capsule-shaped film-coated tablets in 100 mg dose strength for oral administration. The ARRY-371797 (PF-07265803) film-coated tablets consist of ARRY-371797 (PF-07265803) drug substance, microcrystalline cellulose, lactose monohydrate, hydroxypropylcellulose, croscarmellose sodium, colloidal silicon dioxide, glyceryl dibehenate, talc, magnesium stearate, sodium hydrogen carbonate, and a commercial film coating (Opadry® 200, Colorcon).

Placebo, identical in appearance to the study intervention, is supplied by the sponsor as brown capsule-shaped film-coated tablets for oral administration. The placebo tablets consist of lactose monohydrate, microcrystalline cellulose, magnesium stearate, and a commercial film coating (Opadry® 200, Colorcon).

6.1.2. Packaging and Labeling

ARRY-371797 (PF-07265803) 100 mg tablets and placebo tablets will be packaged in HDPE bottles with an induction seal and child-resistant closure. Bottles will contain a precounted number of tablets required for the appropriate dosage and treatment duration between visits. Bottles for the ARRY-371797 (PF-07265803) 100 mg tablets and placebo tablets will be labeled, at a minimum, with a unique identifier (medication number), the lot number, contents (number of tablets), dosage strength, storage conditions, and the name and address of the sponsor. Labels will be in the local language and comply with the legal requirements for each country.

6.1.3. Administration

All participants will take their first dose of study intervention in the clinic on the morning of the baseline visit (Day 1). Dosing should occur at roughly the same time each day and subsequent doses should be taken by the participant approximately every 12 hours.

The dose administered on PK sampling days at the baseline visit and Weeks 4, 8, 12, and 24 will be administered in the clinic under the supervision of site personnel or under the supervision of a physician or home health care nurse (or similarly qualified person) for home-based visits to NYHA Class IV participants, if applicable. Study intervention should be given after all questionnaires have been completed and predose blood samples for clinical laboratory assessments and PK have been collected. The date and exact time of administration should be noted by site personnel or a physician or home health care nurse (or similarly qualified person) and recorded in the eCRF.

Study intervention is to be taken orally without food. Participants should abstain from all food 2 hours prior to and 2 hours after dosing. Participants will swallow the study intervention whole with approximately 240 mL (~8 oz) of water and will not chew the tablet(s) prior to swallowing.

Participants should not take extra doses of study intervention to compensate for doses missed for AEs or any other reason. If a participant vomits at any time after dosing, the dose of study intervention should not be readministered.

Participants will receive a diary dispensed at each visit to document self-administered BID dosing of study intervention to include the dose taken (number of tablets), the date and time of dosing, and if any doses were missed and the reason for the missed dose. Participants will be instructed to return any unused study intervention and the participant dosing diary to the site at each visit. Corresponding study intervention administration information will be reported in the eCRF.

The pharmacist or appropriately trained and designated study personnel or study nurse, or a physician or home health care nurse for home visits, will ensure that the appropriate dose is dispensed and will provide the participant with at least the appropriate number of tablets for the number of doses to be taken prior to the next scheduled visit. The study site personnel will train the participant and/or the participant's caregiver on dosing procedures for the study intervention.

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage

conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

- Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the Pharmacy Manual/IP Manual.

- Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

- Study interventions should be stored in their original containers.

- Site staff will instruct participants on the proper storage requirements for take-home study intervention.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All study intervention that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. Returned study intervention must not be redispensed to the participants.

- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual/IP Manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the Pharmacy Manual/IP Manual.

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the study intervention using the IRT system. A second staff member will verify the dispensing. The participant should be instructed to

maintain the product in the bottles provided throughout the course of dosing and return the bottles to the site at the next study visit.

The site pharmacist will allocate the appropriate bottle(s) of study intervention (ARRY-371797 (PF-07265803) or placebo) to each randomized participant, as per the IRT system. Site personnel are required to maintain accurate inventory records.

Complete dispensing instructions, dosing instructions, including the timing of study intervention administration and instructions for missed doses will be provided in the Pharmacy Manual/IP Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization, double-blinding of study intervention and use of multiple study sites are elements of the study design that are employed to minimize bias during the study.

To minimize the potential for bias, study participants, all investigational site personnel, and all sponsor personnel directly involved with the conduct of the study (ie, with the exception of personnel involved in drug supply and safety reporting for fulfillment of regulatory requirements) will remain blinded to treatment assignment and aggregate data summaries until the primary analysis has been performed and an evaluation of the composite endpoint comprised of all-cause mortality and HF-related hospitalization or HF-related urgent care visit has been completed. Further exceptions will be made if the blind is broken according to the methods described in Section 6.3.2. The outsourced bioanalytical laboratory will be permitted to analyze PK samples in an ongoing basis, as sample stability is projected to be shorter than the study duration. The sponsor-designated bioanalytical laboratory will analyze all samples, both those on the active and control arm, thereby unblinding treatment assignment. No randomization data will be shared with the bioanalytical vendor in an ad hoc manner. The bioanalytical laboratory is permitted to transfer bioanalytical data to an unblinded CRO for generation of tables and figures for the DMC meeting and for the purposes of re-assay of PK samples as needed. The sponsor is permitted to review bioanalytical data where participant identifiers are omitted or replaced with dummy identifiers as part of the open review of the DMC meeting. The randomization schedule will be generated and managed by a statistician not assigned to support the study.

6.3.1. Early unblinding of PK data may be exercised to facilitate completion of these analyses for regulatory submissions in a timely fashion. See Section 9.4.3.7.1 for details.Allocation to Study Intervention

Blinded treatments will be assigned according to a computerized central randomization list using IRT system. The IRT system will assign blinded study intervention to each participant.

For participants entering either the randomized double-blind treatment period or the ARRY-371797 (PF-07265803) open-label treatment period, responsible site personnel will identify the study intervention bottle(s) to dispense to the participant by using the IRT system which will provide the medication number(s) at each dispensing visit. Site personnel will add the participant number to the label.

6.3.2. Breaking the Blind

Prior to the initiation of the study, each site will be instructed on the method for breaking the blind as described in the Safety Reference Manual. The blind should be broken only in the event of a safety emergency for which, in the opinion of the treating physician and/or sponsor medical monitor, knowledge of the treatment assignment will influence the appropriate medical response. If an emergency occurs that requires unblinding of an individual participant, the medical monitor should be contacted prior to unblinding the participant, if possible. If not possible, the sponsor medical monitor should be contacted as soon as possible after unblinding has occurred.

If the blind is broken for any participant, the site will be required to provide additional information, including actions taken, on the eCRF. Complete training regarding the designation of persons authorized to request emergency unblinding and the process for unblinding a participant will be provided to investigational sites at or before the study initiation visit and will be described in the Safety Reference Manual.

6.4. Study Intervention Compliance

Throughout the study, participants are required to record the time and date of each dose of study intervention, if any doses were missed, and the reason for the missed dose in the participant dosing diary. Dosing compliance will be reviewed by the site personnel at each visit using the participant diary and discussed with the participant at each visit. Any clarifications provided by the participant should be recorded in the participant source documents. Corresponding study intervention administration information will be reported in the eCRF.

6.5. Concomitant Therapy

Unless specifically prohibited, concomitant medications can be administered at the investigator's discretion to conform to standard practice during the treatment period. Ancillary treatments will be administered according to labeled instructions as medically indicated for participants. As with any novel therapeutic for which limited clinical experience exists, investigators should exercise caution when prescribing concomitant medications with ARRY-371797 (PF-07265803). Investigators should contact the sponsor when they are unsure whether a drug should be prescribed to a participant in this study.

All concomitant medications are to be recorded on the eCRF using generic drug names when possible.

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

6.5.1. Prohibited Therapies/Treatment

The following therapies are prohibited for the NYHA Class II/III participants after signing informed consent and will lead to early withdrawal:

- Continuous or intermittent IV inotrope infusion

- Chronic renal replacement therapy (eg, hemodialysis or peritoneal dialysis)
- Cardiac transplantation, LVAD or other device implantation, other cardiac surgery, or any invasive therapeutic cardiovascular-related procedure after initiation of study intervention.
- Use of other investigational drugs for HF
- Use of investigational devices

- For the NYHA Class IV participants, the use of other investigational drugs for HF and the use of devices are prohibited after signing informed consent and will lead to early withdrawal.

6.5.2. Cautionary Use of Concomitant Medications while on Study Intervention

Particular caution should be exercised when:

- Considering treatment with a drug known to prolong QT interval and have a known risk of causing torsades de pointes (see Appendix 8). While there is no nonclinical evidence of QT prolongation, in a pooled analysis across clinical studies, there is some evidence for dose-related prolongation of the QT interval corrected for heart rate using Fridericia's formula (QTcF), compared with placebo in patients receiving PF-07265803 (PF-07265803). The magnitude of mean placebo-adjusted QTcF prolongation at the time to reach peak plasma exposure (Tmax) for the dose of 400 mg BID is approximately 8 msec. The investigator will make a benefit-risk judgement prior to initiating therapy by considering the participant's prognosis.
- Considering treatment with drugs that are identified as sensitive clinical substrates of CYP3A4, CYP2B6, CYP2D6, or MDR1 (reference: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#inhibitors, Table 3-1 and 5-1). The net effect of ARRY-371797 (PF-07265803) interaction with these drugs is not known. The investigator should make a benefit-risk judgement prior to initiating therapy by considering the participant's prognosis and interpretation of ECG findings.

6.6. Dose Modification

6.6.1. Dose Interruptions, Reductions, and Discontinuations

Throughout the study, doses of study intervention (ARRY-371797 (PF-07265803) or placebo) may be interrupted, reduced, or stopped as necessary for AEs.

Guidelines for dose modifications due to the common AEs reported in prior ARRY-371797 (PF-07265803) clinical trials and other AEs considered related to study intervention are provided in Table 3. These modifications apply to both the double-blind and open-label periods of the study.

If an individual participant has safety or tolerability issues at 4 x100 mg tablets BID (ARRY-371797 (PF-07265803) or placebo), blinded study intervention may be reduced to 2 x100 mg tablets BID (ARRY-371797 (PF-07265803) or placebo). In addition, a second dose reduction from 2 x 100 mg tablets BID (ARRY-371797 (PF-07265803) or placebo) to 1 x 100 mg tablet BID (ARRY-371797 (PF-07265803) or placebo), is allowed due to safety or tolerability issues. Dose reduction should always be considered as an option before permanently discontinuing study intervention.

Once a dose has been reduced, all subsequent doses should remain at that dose level unless further reduction, interruption, or discontinuation of study intervention is warranted.

If an AE occurs that is not considered related to study intervention, dosing does not have to be reduced or modified, if in the investigator's opinion the AE is due to the underlying disease. Decisions regarding dose interruptions or modifications will be based on the investigator's clinical judgement.

If study intervention is not well tolerated at any dose level by an individual participant despite dose reduction, treatment will be permanently discontinued for that participant.

If study intervention has been interrupted for more than 21 days, it cannot be restarted in the randomized, double-blind period unless approved by the medical monitor.

Table 3. Guidelines for ARRY-371797 (PF-07265803) Dose Modifications for Adverse Events

Worst Observed Toxicity Grade (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials) (unless noted otherwise)	Dose Modifications for Study Treatment (Dose reduction should always be considered as an option before permanently discontinuing study intervention).
Anemia	
Grade 3 Hemoglobin 8.0-9.4* g/dL (* For Class IV/Open-label participants who enroll with hemoglobin between 9 and 9.4, interruption should occur if hemoglobin <9.0)	Interrupt study intervention until resolved to hemoglobin ≥9.5 g/dL (*or returns to >9.0), then If resolved in <21 days, resume study treatment at current dose level or consider resume at next lower dose level If not resolved in <21 days, resume study treatment at next lower dose level
Grade 4 Hemoglobin <8.0 g/dL, transfusion indicated Potentially life-threatening	Permanently discontinue study treatment
Stomatitis	Inflammation of the mouth and lips, characterized by circumscribed, inflammatory and necrotic erosive lesions
Grade 1 Combined area of ulcers <1 cm, nonblanchable erythema of intact skin with associated warmth or edema	Consider topical therapy, eg, OTC medications or acyclovir and reassess within ≤7 days Maintain dose level of study treatment and reassess within ≤7 days

Table 3. Guidelines for ARRY-371797 (PF-07265803) Dose Modifications for Adverse Events

Worst Observed Toxicity Grade (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials) (unless noted otherwise)	Dose Modifications for Study Treatment (Dose reduction should always be considered as an option before permanently discontinuing study intervention).
Grade 2 Combined area of ulcers 1-2 cm, partial thickness skin or mucosal loss	**First occurrence:** Consider topical therapy, eg, OTC medications or acyclovir, and reassess within ≤7 days If condition resolves ≤7 days, maintain study treatment at current dose level If condition worsens or does not improve with topical therapy, reduce study treatment to next lower dose level and reassess within ≤7 days If condition resolves, resume study treatment at reduced dose level If condition worsens or does not improve, interrupt study treatment until resolved to Grade ≤1 **Second Occurrence:** Consider topical therapy, eg, OTC medications or acyclovir, and reassess within ≤7 days If condition worsens or does not improve with topical therapy, interrupt study treatment until resolved to Grade ≤1 If condition resolves, resume study treatment at next lower dose level
Grade 3 Combined area of ulcers >2 cm, full thickness skin or mucosal loss involving damage to or necrosis of subcutaneous tissue	**First occurrence:** Interrupt study intervention, consider systemic therapy, eg, valacyclovir and reassess within ≤7 days and then weekly If condition resolves in ≤21 days, resume study treatment at next lower dose level If condition worsens or does not improve, permanently discontinue study treatment **Second occurrence:** Permanently discontinue study treatment
Grade 4 Any size ulcer with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures	Permanently discontinue study treatment
Skin Rash	Including acne, dermatitis, erythema, rash, maculo-papular rash, seborrheic dermatitis

Table 3. Guidelines for ARRY-371797 (PF-07265803) Dose Modifications for Adverse Events

Worst Observed Toxicity Grade (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials) (unless noted otherwise)	Dose Modifications for Study Treatment (Dose reduction should always be considered as an option before permanently discontinuing study intervention).
Grade 2 Rash covering 10% to 30% BSA with or without symptoms (eg, pruritus, burning, tightness), limiting instrumental ADL	**First Occurrence:** Maintain dose level of study treatment and rash should be closely monitored Initiate specific therapy for rash Reassess within ≤14 days If rash resolves, continue study treatment at current dose level If rash worsens or does not improve, interrupt study intervention until resolved to Grade ≤1 **Second Occurrence:** Interrupt study treatment, reassess within ≤14 days If rash resolves, resume study treatment at next lower dose level If rash worsens or does not improve, interrupt study intervention until resolved to Grade ≤1. If rash resolves, resume study intervention at next lower dose level
Grade 3 Rash covering >30% BSA with or without symptoms (eg, pruritus, burning, tightness), limiting instrumental ADL	**First Occurrence:** Interrupt study intervention until resolved to Grade ≤1. Reassess weekly Once resolved to Grade ≤1, resume study treatment at current dose level or at next lower dose level Consider referral to dermatologist and manage per recommendation **Second Occurrence:** Interrupt study treatment until resolved to Grade ≤1. Reassess weekly Resume study treatment at next lower dose level Consider referral to dermatologist and manage per recommendation
Grade 4 Life-threatening consequences, urgent intervention indicated	Permanently discontinue study treatment

Table 3. Guidelines for ARRY-371797 (PF-07265803) Dose Modifications for Adverse Events

Worst Observed Toxicity Grade (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials) (unless noted otherwise)	Dose Modifications for Study Treatment (Dose reduction should always be considered as an option before permanently discontinuing study intervention).
CK Elevations	If AE is not considered related to study intervention, dosing does not have to be reduced or modified, if in the investigator's opinion the AE is due to the underlying disease.
Grade 2 CK >1.6-3.0×ULN	**If asymptomatic:** Maintain dose level of study intervention and reassess CK in 7-21 days If not resolved in <21 days, reduce study intervention to next lower dose level **If symptomatic (muscle pains, spasms):** Reduce study intervention to next lower dose until resolved to Grade ≤1, then If resolved in <21 days, resume dose level If not resolved in <21 days, continue study intervention at lower dose level
Grade 3 CK 3.1-10.0×ULN	**If asymptomatic:** Maintain dose level of study intervention and monitor closely; measure CK weekly for 3 weeks If not resolved in <21 days, reduce study treatment to next lower dose level **If symptomatic (muscle pain, spasms):** Interrupt study intervention until resolved to Grade ≤1 and monitor closely, then If resolved in <21 days, reduce study treatment to next lower dose level If not resolved in <21 days, permanently discontinue study treatment
Grade 4 CK >10.0×ULN	**If asymptomatic:** Interrupt study intervention until resolved to Grade ≤1 and monitor closely, then If resolved in <21 days, reduce study treatment to next lower dose level If not resolved in <21 days, permanently discontinue study treatment **If symptomatic (muscle pain, spasms, weakness):** Permanently discontinue study intervention

Table 3. Guidelines for ARRY-371797 (PF-07265803) Dose Modifications for Adverse Events

Worst Observed Toxicity Grade (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials) (unless noted otherwise)	Dose Modifications for Study Treatment (Dose reduction should always be considered as an option before permanently discontinuing study intervention).
Liver Function-Related Adverse Events	Stop study treatment and contact the Medical Monitor if a participant meets potential DILI / Hy's law criteria. Refer to Appendix 5 (Liver safety: suggested actions and follow up assessments) for further details.
Diarrhea	
Grade 2 4-5 stools or 400-800 g/24 hours	If the event is non-persistent Grade 2, maintain dose level of study intervention and monitor until stabilization or resolution **First occurrence:** If the event is a persistent or intolerable Grade 2 AE not responsive to a specific therapy, interrupt study treatment for ≤21 days until resolved to Grade ≤1 then resume study treatment at current dose or at the next lower dose level. If resolution within 21 days is not reached, please contact the Medical Monitor **Second occurrence:** If the event is a persistent or intolerable Grade 2 AE not responsive to a specific therapy, interrupt study treatment for ≤21 days until resolved to Grade ≤1 then resume study treatment at the next lower dose level If resolution within 21 days is not reached, please contact the Medical Monitor
Grade 2 See above but complicated by requirement for outpatient IV hydration OR **Grade 3** 6 or more watery stools or >800 g/24 hours or requires outpatient IV hydration	Interrupt study intervention until resolved to Grade ≤1 If the event resolves ≤21 days, then study treatment may be resumed at next lower dose level If resolution within 21 days is not reached, please contact the Medical Monitor
Grade 4 Life-threatening consequences, urgent intervention indicated, eg, ER visit or hospitalization	Permanently discontinue study treatment

Table 3. Guidelines for ARRY-371797 (PF-07265803) Dose Modifications for Adverse Events

Worst Observed Toxicity Grade (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials) (unless noted otherwise)	Dose Modifications for Study Treatment (Dose reduction should always be considered as an option before permanently discontinuing study intervention).
Nausea, vomiting	
Grade 2 >2 episodes (separated by 5 minutes) in 24 hours or some interference with activity	If the event is non-persistent Grade 2, maintain dose level of study treatment and monitor until stabilization or resolution **First occurrence:** If the event is a persistent or intolerable Grade 2 AE not responsive to a specific therapy, interrupt study treatment for ≤21 days until resolved to Grade ≤1 then resume study intervention at current dose or at the next dose level. If resolution within 21 days is not reached, please contact the Medical Monitor **Second occurrence:** If the event is a persistent or intolerable Grade 2 AE not responsive to a specific therapy, interrupt study treatment for ≤21 days until resolved to Grade ≤1 then resume study intervention at the next lower dose level If resolution within 21 days is not reached, please contact the Medical Monitor
Grade 3 Prevents daily activity, requires outpatient IV hydration	Interrupt study intervention until resolved to Grade ≤1. If the event resolves ≤21 days, then study treatment may be resumed at next lower dose level
Grade 4 Life-threatening consequences, urgent intervention indicated, eg, ER visit or hospitalization for hypotensive shock	Permanently discontinue study treatment
Headache	
Grade 2 Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	If the event is non-persistent Grade 2, maintain dose level of study intervention and monitor until stabilization or resolution If the event is a persistent or intolerable Grade 2 AE not responsive to a specific therapy, interrupt study treatment for ≤21 days until resolved to Grade ≤1, then study treatment may be resumed at the current dose or at the next dose level. If resolution within 21 days is not reached, please contact the Medical Monitor

Table 3. Guidelines for ARRY-371797 (PF-07265803) Dose Modifications for Adverse Events

Worst Observed Toxicity Grade (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials) (unless noted otherwise)	Dose Modifications for Study Treatment (Dose reduction should always be considered as an option before permanently discontinuing study intervention).
Headache (cont.)	
Grade 3 Significant; Any use of narcotic pain reliever or prevents daily activity	Interrupt study intervention until resolved to Grade ≤1. **First occurrence:** If the event resolves ≤21 days, then study treatment may be resumed at the current dose level or at the next lower dose level If resolution within 21 days is not reached, please contact the Medical Monitor **Second occurrence:** If the event resolves ≤21 days, then study treatment may be resumed at next lower dose level If resolution within 21 days is not reached, please contact the Medical Monitor
Grade 4 ER visit or hospitalization	Permanently discontinue study treatment
Study intervention treatment-related adverse events	
Grade 2 Moderate severity: Some interference with activity not requiring medical intervention	If the event is non-persistent Grade 2, maintain dose level of study treatment and monitor until stabilization or resolution If the event is a persistent or intolerable Grade 2 AE not responsive to a specific therapy, interrupt study treatment for ≤21 days until resolved to Grade ≤1, then study treatment maybe resumed at the current dose or at the next lower dose level If resolution within 21 days is not reached, please contact the Medical Monitor
Grade 3 Severe severity: Prevents daily activity; requires outpatient medical intervention	Interrupt study treatment until resolved to Grade ≤1 **First occurrence:** If the event resolves ≤21 days, then study intervention may be resumed at the current dose level or at the next lower dose level If resolution within 21 days is not reached, please contact the Medical Monitor **Second occurrence:** If the event resolves ≤21 days, then study treatment may be resumed at next lower dose level If resolution within 21 days is not reached, please contact the Medical Monitor

Table 3. Guidelines for ARRY-371797 (PF-07265803) Dose Modifications for Adverse Events

Worst Observed Toxicity Grade (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials) (unless noted otherwise)	Dose Modifications for Study Treatment (Dose reduction should always be considered as an option before permanently discontinuing study intervention).
Grade 4 Potentially Life-threatening: Life-threatening consequences; urgent intervention indicated, eg, ER visit or hospitalization	Permanently discontinue study treatment

6.7. Intervention After the End of the Study

Availability of ARRY-371797 (PF-07265803) following the study's closure through either a separate rollover extension protocol or expanded access/compassionate use, if the investigator and participant desire to continue treatment, would be at the discretion of the sponsor and subject to local conditions and regulations.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study treatment . Reasons for permanent discontinuation of study treatment include the following:

- Withdrawal of consent to treatment;
- LVAD placement, cardiac transplant;
- Unacceptable AE(s) or failure to tolerate study intervention;
- Pregnancy or initiation of breastfeeding;
- Protocol violation that, in the opinion of the investigator and/or sponsor, renders the participant unsuitable for further study intervention;
- Study treatment interruption longer than 21 days, unless approved by medical monitor;
- Discretion of investigator.

Note that discontinuation of study treatment does not represent withdrawal from the study. If study treatment is permanently discontinued prior to the Week 24 visit, the participant will remain in the study to continue to have all assessments performed as scheduled through the Week 24 visit. Every effort should be made to obtain these data. All participants will subsequently be followed for OS, HF-related hospitalization and HF-related urgent care visits

approximately every 3 months via phone call until death, lost to follow-up, withdrawal of consent or initiation of the open-label treatment period, whichever occurs first (see Section 8.12). See the SoA for data to be collected at the time of discontinuation of study treatment and follow-up for any further evaluations that need to be completed. Every effort should be made to obtain these data.

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

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

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

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

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only

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

7.2.2. Replacement of Participants

Participants who discontinue prior to study completion will not be replaced.

7.3. Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

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

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

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

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

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

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these deviations from protocol-required tests and procedures in a timely manner.

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

8.1. Screening Assessments

All participants must have confirmation of the presence of an eligible *LMNA* mutation by documentation from an accredited clinical laboratory before proceeding to screening.

8.1.1. Participant Demographics and Other Baseline Characteristics

Demographics, prior medications/therapies/procedures (including all prescription and nonprescription drugs, vitamins, and dietary or herbal supplements) that were administered/conducted within 35 days prior to Day 1, and current medications will be recorded. Past and present medical history considered by the investigator to be significant will also be recorded.

8.1.2. Follicle-Stimulating Hormone

Postmenopausal females under 60 years of age will be required to have a serum FSH measurement at the screening visit to assess childbearing potential. If the participant is postmenopausal and has high FSH level in the postmenopausal range at the screening visit, they are considered nonchildbearing and pregnancy tests will not be required during the study.

8.1.3. Human Immunodeficiency Virus, Hepatitis B, and Hepatitis C Serology

All participants are required to have negative screening serology tests per central laboratory for HIV, hepatitis B surface antigen, and hepatitis C antibody to participate in the study. Participants with a screening serology positive for hepatitis C antibody must have a negative nucleic acid test to participate in the study.

8.2. Efficacy Assessments

For Class II and III participants, the 6MWT should be performed at approximately the same time of day at each study visit after the baseline visit and ideally, one of the first assessments to be performed. The PRO assessments should be performed before the 6MWT has been completed, starting with KCCQ, followed by the PGI assessments and ending with the EQ-5D-5L. The ECHO assessment should be performed after the 6MWT has been completed. For Class IV participants, the 6MWT is optional based on whether the participant is ambulatory or not and should only be completed if the investigator feels that the participant can complete the test without undue harm.

Participants who discontinue study treatment prior to Week 24 should continue to have all efficacy assessments (PRO, 6MWT, ECHO) performed as scheduled through the Week 24 visit.

8.2.1. 6-Minute Walk Test

The 6MWT will be performed at the time points specified in the SoA, including at screening, at the Day -1 visit and at the baseline visit (Day 1), using the methods described in the 6MWT Study Manual based on the ATS Statement: Guidelines for the Six-Minute Walk Test.[33] If the test is deemed unusable by the CPC Core Laboratory, the 6MWT will need to be repeated. The 6MWT is to be performed by all Class II and III participants, and as feasible for Class IV participants. The Borg fatigue scale will be administered before and after the walk distance assessment as part of the 6MWT.

Sites will designate specific site staff to perform the 6MWT. Designated staff performing the 6MWT will be required to complete initial 6MWT training prior to conducting any 6MWT for the trial. Refresher 6MWT training will be provided as needed.

The 6MWT will be performed 3 times (screening, Day -1, and baseline) to confirm participant eligibility and establish the baseline value for the primary endpoint. The screening visit 6MWT must be performed at least 27 days prior to the Day -1 visit. The screening visit 6MWT will ensure proper participant familiarization has occurred prior to the baseline assessment. The screening visit 6MWT must have a distance of >100 m but ≤450 m and the participant must be symptomatic for DCM per investigator judgment in order to remain eligible. The Day -1 and baseline visit (Day 1) 6MWTs must have distances of >100 m but ≤485 m and the participant must be symptomatic for DCM per investigator judgment in order to remain eligible. The tests should be performed 1 day apart when possible and no more than 3 days apart. Calculation of change from baseline will be based on the average of the Day -1 and baseline visit (Day 1) 6MWT results.

8.2.2. Activity Monitoring

An activity monitor will be placed on the participant's wrist during the screening period and then worn continuously for the duration of the randomized study period in free-living conditions only if the participant agrees to wear the device. Wrist monitors are expected to be used only on ambulatory participants.

Activity monitoring data will be collected continuously during the randomized study period capturing real-life activities and movement patterns. Participants who discontinue study treatment prior to Week 24 will continue to wear the activity monitor and will have all assessments performed as specified in the SoA through the Week 24 Visit.

8.2.3. N-Terminal Pro-Brain Natriuretic Peptide

Blood samples for analysis of NT-proBNP will be performed as part of the clinical chemistry sample collections at the time points specified in the SoA and will be measured by a central laboratory at screening and all subsequent time points.

8.2.4. Echocardiogram

The 2D ECHO complete with contrast, if available, will be performed by trained personnel at the time points specified in the SoA, including during screening.

The screening ECHO will be performed at the local laboratory to determine eligibility and will only include assessment of LV: systolic and diastolic function; size, mass, and geometry. The results from the local laboratory will be used during screening to determine eligibility for the study (these are not submitted to the central laboratory).

All the other assessments will be standard transthoracic 2D ECHOs (with contrast, if available, to optimize accuracy and precision of intracardiac measurements) and will include:

- LV: systolic and diastolic function; size, mass, and geometry
- RV size and function; pulmonary artery size
- Left atrial dimensions, volumes, and pressures
- Valvular (aortic, mitral, tricuspid, and pulmonary) stenosis and regurgitation (severity); TAPSE
- PASP, IVC caliber

8.2.5. Patient-Reported Outcomes

8.2.5.1. Kansas City Cardiomyopathy Questionnaire (KCCQ)

Participants will complete the KCCQ at the time points specified in the SoA. At each visit, the KCCQ should be completed prior to the other visit assessments.

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. Response options vary by question. Domain scores are transformed to a 0 to 100 range; higher scores indicate better health status.

8.2.5.2. Patient Global Impression

Participants will rate the severity of their heart failure symptoms and physical activity limitations during the past week on the 2 Patient Global Impression-Severity (PGI-S) questions. 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 Patient Global Impression-Change (PGI-C) questions. The PGI-S will be completed first followed by the PGI-C after completing the KCCQ. Participants will complete the PGI-S and the PGI-C at the time points specified in the SoA. These data will be used to provide an anchor to define thresholds for improvements in KCCQ.

8.2.5.3. EuroQoL EQ-5D-5L

The EQ-5D-5L (5 levels version) is a brief, self-administered generic health status instrument that takes approximately 5 minutes to complete.[34] The instrument consists of two parts. In the first part, respondents are asked to rate their current health state on 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with each dimension having five levels of function ranging from "No problem" to "Extreme problems." The scores from the five dimensions may be used to calculate a single index value, also known as a utility score. On the second part respondents rate their current health state on a Visual Analog Scale (EQ-5D VAS) with endpoints labeled "best imaginable health state" (score of 100) and "worst imaginable health state" (score of 0).

Participants will complete the EQ-5D-5L as specified in the SoA. Participants should complete the EQ-5D-5L after the Patient Global Assessment questionnaires.

8.2.6. Assessment of Composite Endpoint of All-Cause Mortality or Worsening Heart Failure (HF-Related Hospitalization or HF-Related Urgent Care Visits)

All HF-related hospitalization and urgent outpatient visits will be collected during the study. Inpatient hospitalizations are to be reported as SAEs per Appendix 3 and Section 8.4.1 and all outpatient urgent care, and ER visits less than 24 hours must be recorded on the urgent outpatient/ER visit eCRF form.

All necessary documentation must be submitted for adjudication (see Section 9.6). Supportive documentation requested for adjudication may include the following: hospital discharge summary, chest X-ray report, prescription sheets/medication administration records, ECHO report, relevant laboratory reports (eg, for peak BNP/NT-proBNP), and reports for other investigations undertaken (eg, cardiac MRI, radionuclide ventriculogram scan, pulmonary artery catheterization).

If study treatment is discontinued prior to the Week 24 visit, the participant will remain in the study to continue to have all assessments performed as scheduled through the Week 24 visit. Every effort should be made to obtain these data. All participants will subsequently be followed for survival status, HF-related hospitalization and HF-related urgent care visits (see Section 8.12) approximately every 3 months via phone call until death, lost to follow-up, withdrawal of consent, or initiation of the open-label treatment period. Every effort should be made to obtain these data.

8.3. Safety Assessments

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

8.3.1. Medical History

Significant (at the investigator's discretion) past and present medical history will be recorded at the screening and baseline visits only. Any history of use of tobacco, alcohol, and drugs of abuse will be recorded at the screening visit. Any history of muscular dystrophy including Limb-girdle MD type 1B (LGMD1B), autosomal dominant Emery-Dreifuss MD/EDMD2, congenital muscular dystrophy should be recorded. Any ongoing condition observed prior to the initiation of study intervention will be recorded as medical history. Any new condition or worsening of a pre-existing condition during study conduct after the start of study intervention or at any time after consent, if thought to be related to a study procedure, will be recorded as an AE.

8.3.2. Physical Examinations

Physical examinations (either a complete or brief physical examination) will be performed by trained medical personnel at the time points specified in the SoA.

Both the complete and brief physical examinations should carefully evaluate the cardiovascular and pulmonary system, including but not limited to peripheral pulses, edema, breathing, jugular venous distension, and/or other signs of worsening HF. A complete physical examination, including height and body weight measurements, will be performed at the screening visit.

- Complete physical examination: General physical well-being will be assessed by evaluation of HEENT, neck, back (including renal assessment), cardiovascular (including peripheral pulses, edema, breathing, jugular venous distension, and/or other signs of worsening HF), lungs, abdomen (including liver, spleen, bowel sounds), lymph nodes, musculoskeletal system (including spine, joints, muscles, bursae), neurological system (including cranial nerves, reflexes, sensation, strength), skin (including nails and hair), and other conditions of note. Signs or symptoms of muscular dystrophy should be specifically noted.

A brief physical examination, including body weight measurement, will be performed at all other visits, but may include further evaluation if any areas of concerns are identified.

- Brief physical examination: General physical well-being will be assessed by brief evaluation of the skin, HEENT, cardiovascular (including peripheral pulses, edema, breathing, jugular venous distension, and/or other signs of worsening HF), lungs, abdomen, extremities, new-onset or worsening of muscular dystrophy and other conditions of note.

All physical examinations occurring on dosing days must be performed prior to study intervention administration. Any treatment-emergent abnormal findings will be recorded as AEs.

8.3.3. Vital Signs

Vital signs (BP, PR, respiratory rate, and temperature) will be measured by trained medical personnel at the time points specified in the SoAs, including the screening visit and the baseline visit (Day 1).

Sitting BP will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg after 5 minutes of rest. The participant's back should be supported and feet on the floor. The same arm (preferably the dominant arm) will be used throughout the study. The same size BP cuff and method (automated or manual), which has been properly sized and calibrated, will be used to measure BP throughout the study. The use of automated devices for measuring BP and PR is preferred; when done manually, PR will be measured in the brachial or radial artery for at least 30 seconds.

8.3.4. Arrhythmia Assessment

An arrhythmia assessment will be performed at the time points specified in the SoA.

Incidence of new discharge, conduction system disease, supraventricular or ventricular arrhythmias will be assessed by an ICD/CRT-D applicable device interrogations. ECG values of potential clinical concern are listed in Appendix 6. The assessment of the results will be completed by the PI or delegate and the assessment will include any interrogations performed in between study visits. In the scenario where patient's device was interrogated between visits, results of the reading should be recorded for the period. Results will be analyzed and recorded.

8.3.5. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTcF intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) will not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

ECG data will be submitted to a central laboratory for measurement. The final ECG report from the central laboratory should be maintained in the participant's source documentation and be the final interpretation of the ECG recording. Any clinically significant changes from the baseline/Day 1 ECG may potentially be AEs (Appendix 6) and should be evaluated further, as clinically warranted.

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

When ECGs are to be performed at the same visits as study intervention administration, blood collection and/or vital sign measurements, ECGs should be performed first. Abnormal ECGs may be repeated at the investigator's discretion. Details regarding ECG procedures and transmittals will be provided in an ECG Manual.

ECG values of potential clinical concern are listed in Appendix 6.

8.3.6. Clinical Safety Laboratory Assessments

A central laboratory will be used to analyze all blood and urine samples collected at screening and throughout the study for hematology, clinical chemistry, and urinalysis laboratory tests. Information on the collection of blood and urine samples and their shipment to the central laboratory will be outlined in the Laboratory Manual.

Local site laboratories may be utilized, in addition to the central laboratory, if more rapid results are required for treatment decisions or participant safety. If a local site laboratory sample is taken, then part of the blood sample obtained for local site laboratory assessment should also be sent to the central laboratory for analysis. Local site laboratory results obtained during the study will only be captured in the eCRF if the investigator determines they are needed to clarify why a treatment decision was made or an AE was recorded.

All blood and urine laboratory test collections must be performed prior to study intervention dosing.

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues. Results should be recorded on the Unscheduled Lab eCRF.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with

the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.3.7. Pregnancy Testing

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

All WOCBP are required to undergo a serum pregnancy assessment at screening and urine pregnancy assessments during the study at the time points specified in the SoA. Any positive test will result in immediate cessation of study intervention administration.

All urine collections for pregnancy tests must be performed and assessed prior to study intervention dosing. A negative result should be confirmed and documented in source documents and in EDC.

During the double-blind period, an at-home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL will be used by all WOCBP to perform a urine pregnancy test starting at Week 72 and then every subsequent 24 weeks. The pregnancy test outcome is documented in the participant's source documents/medical records. If the pregnancy test is positive, the EDP should be reported (Section 8.4.5). Confirm that the participant is adhering to the contraception method(s) required in the protocol.

8.4. Adverse Events and Serious Adverse Events

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

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

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

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 30 calendar days, after the last administration of the study intervention.

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

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

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

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

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

All participants will be followed for survival follow-up after a participant discontinues study intervention. During the survival follow-up period, survival status, and HF-related hospitalizations and HF-related urgent care visits will be assessed approximately every 3 months via phone call until death, lost to follow-up, or withdrawal of consent. HF-related hospitalizations and HF-related urgent care visits reported during the survival follow-up period are to be recorded on the HF-related hospitalization CRF. SAEs occurring after the active reporting period has ended should be reported to the sponsor promptly if the

investigator considers the event to be reasonably related to the study intervention. See Section 8.12 for event follow-up during the survival follow-up period.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-up of AEs and SAEs

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

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

Further information on follow-up procedures is given in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion.

- A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then exposes his female partner prior to or around the time of conception.

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 30 days after the last dose of study intervention for female participants and until 30 days after last dose of study intervention for male participants.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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

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

- Spontaneous abortion including miscarriage and missed abortion;

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

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

8.4.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

See sections 8.2.6 and 8.3.4.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

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

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

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

Medication errors include:

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

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

If applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

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

8.5. Treatment of Overdose

For this study, any dose of ARRY-371797 (PF-07265803) greater than 800 mg within a 24-hour time period will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of ARRY-371797 (PF-07265803) (whichever is longer).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**

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

8.6. Pharmacokinetics

Venous blood samples for measurement of plasma concentrations of ARRY-371797 (PF-07265803) and metabolites will be drawn at the following times/visits as specified in the SoA.

- Baseline: predose
- Week 4: predose
- Week 8: predose and 2 samples, approximately 1.5 hours (± 1 hours) postdose and at least 15 minutes apart
- Week 12: predose and 5 hours (± 1 hour) postdose
- Week 24: predose and 5 hours (± 1 hour) postdose
- Treatment Discontinuation Visit: Any time during clinic visit

All Class II/III participants will have PK blood samples collected during the randomized, double-blind period. Class IV participants will have PK blood samples drawn during the baseline and Weeks 4, 8, 12, and 24 visits if the participant is ambulatory and has clinic visits on the specified nominal week visits. A PK blood sample will be drawn at any time during clinic visit, but after vital sign measurement during the treatment discontinuation visit if discontinuation occurs prior to the randomized, double-blind period Week 24 visit (as

feasible for Class IV participants). No PK blood samples will be collected during the ARRY-371797 (PF-07265803) open -label treatment period or after Week 24 of the randomized, double-blind period.

The date and actual time of each PK blood sample, both prior to and after dose, should be recorded. In addition to analyses of ARRY-371797 (PF-07265803), AR00420643, AR00428028, and AR00486705, CCI [redacted] Results and analytical methodologies from this analysis will be described in a separate standalone report, if deemed appropriate.

Study visits for PK sampling should be scheduled in the morning so that a proper predose PK blood sample can be collected. On these visit days, the morning dose of study intervention should be taken at the study site, only after collecting the predose PK sample. Predose sampling information should include the date and actual time of the previous evening dose (except Day 1), including the dose amount taken. Postdose sampling information should include the date and actual time of the morning dose, including the dose amount taken.

For days when PK blood samples are to be drawn, the predose sample (except Day 1) should not be collected if the participant has missed 3 or more consecutive doses of ARRY-371797 (PF-07265803) prior to sample collection and the postdose sample should only be collected if the participant takes the intended morning dose on the day of PK sampling. Deviations related to this should be recorded in the eCRF.

Complete instructions for sample processing, handling and shipment will be provided in the Laboratory Manual.

CCI [redacted]

8.8. Genetics

8.8.1. Lamin A/C Genetic Testing

Participants will be eligible for the study based on results from an accredited clinical laboratory findings of a pathogenic, likely pathogenic, or VUS *LMNA* gene mutation following applicable regional genetic variant interpretation guidelines. The sponsor offers the option of using a central clinical laboratory to perform the sample analysis to verify eligibility.

At Day 1, a 2 mL blood sample for potential *LMNA in vitro* diagnostic development will be collected for participants who did not use the central laboratory to verify eligibility.

Complete instructions for sample collection, handling, and shipment will be provided in the Laboratory Manual.

8.9. Biomarkers

Biomarkers other than those listed in Sections 8.2.3 and 8.7 are not evaluated in this study.

8.10. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.11. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.12. Survival Follow-up

If study treatment is discontinued prior to the Week 24 visit, the participant will remain in the study to continue to have all assessments performed as scheduled through the Week 24 visit. Every effort should be made to obtain these data. All participants will subsequently be followed for survival status, HF-related hospitalizations and HF-related urgent care visits approximately every 3 months via phone call until death, lost to follow-up, or withdrawal of consent, or initiation of the open-label treatment period.

HF-related hospitalizations and HF-related urgent care visits reported during the survival follow-up period are to be recorded on the HF-related hospitalization CRF. SAEs occurring after the active reporting period has ended should be reported to the sponsor promptly if the investigator considers the event to be reasonably related to the study intervention (see Section 8.4.1).

Phone calls are acceptable when clinic visits are not already performed. Vital status may be ascertained from family, caregivers, or public records, where appropriate. All CV therapies and interventional treatments started during the survival follow-up period must be recorded on the post double-blind CV treatment and CV surgical and medical procedure eCRF.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

For the primary endpoint, the null hypothesis is that the treatment groups for ARRY-371797 (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 ARRY-371797 (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. ARRY-371797 (PF-07265803) will be declared superior to placebo if the null hypothesis of no difference between ARRY-371797 (PF-07265803) and placebo is rejected at the significance level of 0.05 (2-sided).

The testing strategy controls Type I error across primary and selected secondary endpoints. If the van Elteren test of the primary endpoint, is found to be statistically significant at 0.05 (2sided) alpha, then a pre-specified hierarchical order for testing the secondary endpoints of Week 24 changes from baseline in the KCCQ domains of PL score and TSS, the composite endpoint consisting of all-cause mortality or worsening heart failure (HF-related hospitalization or HF-related urgent care visit), and the Week 24 change from baseline in NT-proBNP, each at the 0.05 level, will be used to maintain the overall alpha at 0.05.

9.1.1. Estimands

The primary objective of the study is to evaluate the effect of ARRY-371797 (PF-07265803) on functional capacity as measured by the 6MWT compared to placebo in patients with symptomatic LMNA-related DCM. Per protocol, participants who discontinue study treatment 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.

9.2. Sample Size Determination

Following a pre-specified blinded sample size re-estimation, at least 160 Class II and III participants will be included in the efficacy analysis set (EAS). In addition, up to 40 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 for the primary evaluation of efficacy 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 α=0.05 if the true treatment effect is 35 m, there is a SD of 50 m 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 a previous study.
- 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 one standard deviation (SD) above the mean compared to participants one 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 9.5, blinded data at the time of the interim 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 a 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.

9.3. Analysis Sets

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]
Safety Analysis Set (SAS)	The SAS will include all participants who received at least one dose of study intervention regardless of NYHA functional class. Participants will be analyzed according to the initial treatment and dose received. This analysis set will be used for the WHF, all-cause mortality, and safety endpoints.
Pharmacokinetic Analysis Set	The PK set will consist of all participants who receive at least one dose of PF-07265803 and have at least one quantifiable postdose PK blood collection with associated valid bioanalytical results.

9.4. Statistical Analyses

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

9.4.1. General Considerations

Endpoints will be summarized by ARRY-371797 (PF-07265803) and placebo groups. Unless otherwise stated, the primary presentation of efficacy analyses will be based on the EAS. The primary analysis will be performed when all randomized participants in the efficacy population have had the opportunity to be followed for at least 24 weeks and an evaluation of the composite endpoint comprised of all-cause mortality and worsening heart failure (HF-related hospitalization or HF-related urgent care visit) is performed.

9.4.2. Primary Endpoint(s)

9.4.2.1. Primary Efficacy Analysis of Change From Baseline in 6MWT at Week 24

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-parametric approach. ARRY-371797 (PF-07265803) will be declared superior to placebo if the null hypothesis of no difference between ARRY-371797 (PF-07265803) and placebo is rejected at the significance level of 0.05 (2-sided). The p-value will be supplemented with a stratified win ratio statistic (and 95% CI) based on the same ranking rules.

Two additional summaries will be provided to interpret the van Elteren test.

- In analyzing the contribution of death and discontinuation components to the primary efficacy analysis, the summaries on number of deaths and discontinuations from study prior to Week 24, and the reasons for withdrawals from study will be provided. It is expected that the death rates will not be negatively affected by the active treatment.

- A stratified Hodges-Lehmann (HL) estimator of the treatment difference (with 95% CI) will be used to describe the treatment effect on the change from baseline in 6MWT at Week 24. Missing data at Week 24 due to issues outside of the study (eg, COVID-19) will be imputed based on a MAR assumption. Missing data at Week 24 for discontinuation due to post randomization events (eg, AEs or perceived lack of efficacy) will be imputed using control-based multiple imputation. Imputations following death will not be utilized as imputed values for participants who died prior to the assessment timepoint would not be interpretable.

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. An empirical cumulative distribution function (eCDF) plot of change from baseline in 6MWT at Week 24 will also be generated for those participants with observed 6MWT at Week 24.

For purposes of determining the p-value from the van Elteren test as well as an estimate of the win-ratio and corresponding confidence interval, data will be ranked as follows ordered from lowest (worst) to highest rank.

- Participants who die before Week 24 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 Week 24 are ranked based on survival time, instead of time to study discontinuation.

- Participants who are alive at last contact but discontinued the study prior to Week 24, and do not have a Week 24 6MWT completed, will be ranked next, ordered based on

their time to discontinuation. These participants are defined as 'dropouts' for the purpose of describing the analyses.

- Participants who remain in the trial at or beyond Week 24 but who have a missing Week 24 6MWT (eg, due to COVID-19) will have missing values imputed for the endpoint using the method of MCMC 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 Week 24 but have monotone missing data 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, 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) in Week 24 6MWT to greatest increase.

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).

The van Elteren test, which is a stratified extension of the Wilcoxon Rank Sum Test and the stratified win ratio will be calculated on each imputed dataset. The results from these multiple datasets will be pooled for overall inference in a way that account for the variability between imputations based on Rubin's rule. 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. The statistical significance of Week 24 6MWT will be based on the asymptotic, continuity corrected p-value.

Participants will be placed into one of 4 strata according to the quartiles of baseline 6MWT as follows:

Participants will be included in stratum one if their overall rank is $\leq 0.25*n$. Participants will be included in stratum two if their overall rank is $\leq 0.5*n$ and $>0.25*n$

Participants will be included in stratum three if their overall rank is $\leq 0.75*n$ and $>0.5*n$

Participants will be included in stratum four if their overall rank is $>0.75*n$

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

The change from baseline in 6MWT at Week 4 and Week 12 will be analyzed descriptively using the same methods and ranking algorithm replacing Week 24 with the corresponding time point.

9.4.2.2. Sensitivity Analyses

For the primary endpoint, sensitivity analyses will be performed to assess the robustness of the primary analysis result under different assumptions. . Full details will be provided in the SAP.

9.4.3. Secondary Endpoint(s)

9.4.3.1. Kansas City Cardiomyopathy Questionnaire Domains of TSS and PL

The TSS, CSS, PL Score, and OSS of the KCCQ will be summarized at both Weeks 12 and 24 using the same method as described for the primary endpoint analysis. The HL estimates and associated 95% CIs will be presented and constructed in the same way as used for 6MWT. However, only TSS and the PL score will be included in the formal testing hierarchy.

Additionally, participants will be defined as having improved for PL and TSS at Week 24 if their score improves (increases) by a predefined threshold versus baseline at Week 24. In this analysis, missing data due to death or discontinuation from study will be considered a nonresponse by setting the endpoint to nonresponsive. The proportion of participants with an improvement will be analyzed using the Cochran-Mantel-Haenzel chisquare test with the stratification factors used at randomization. The stratification factor for P/LP or VUS may be removed if there is insufficient number of events in the stratum. Percentage of participants responding in each arm will be summarized using exact binomial 95% CIs.[35] The predefined threshold will be defined in the SAP prior to unblinding of the database.

Descriptive statistics of the KCCQ domains over time will also be provided.

The eCDF plots of change from baseline in PL and TSS at Week 24 will be provided for participants who completed the KCCQ at Week 24.

9.4.3.2. Patient Global Impression Scores

After completion of the KCCQ, participants will be asked about their PGI-S and their PGI-C. For PGI-S, at each visit the proportion of participants with at least a one category and at least a 2 category improvement will be summarized at each visit by treatment arm. For PGI-C, at each visit the proportion of participants who describe their change in overall status as moderately or very much better and very much better will be summarized by treatment arm.

PGI-S and PGI-C data will also be used to interpret improvement thresholds for TSS and PL based on a blinded assessment, performed prior to unblinding of data within this study. The thresholds will be defined by correlating changes in TSS and PL with changes in PGI-S and PGI-C.

9.4.3.3. Change From Baseline in N-terminal Pro-Brain Natriuretic Peptide at Weeks 4, 12, and 24

As part of the hierarchical testing strategy, the change from baseline of Week 4, 12, and 24 NT-proBNP will be analyzed separately using the same method as described for the analysis

of 6MWT handling deaths and dropouts in the same way. Likewise, HL estimates and associated 95% CIs will be presented and constructed in the same way as used for 6MWT. Only the 24-week endpoint will be alpha controlled.

9.4.3.4. The Composite Endpoint of Time to First Occurrence of All-Cause Mortality or Worsening Heart Failure (HF-related hospitalization or HF-related urgent care visit)

An episode of worsening heart failure is either a hospitalization or an urgent visit for heart failure confirmed by the CEC as per the criteria in Appendix 9.

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 been treated for a confirmed worsening heart failure adjudicated event. 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 and treatment arm as the covariate. The stratification factor for P/LP or VUS may be removed if there is insufficient number of events in the stratum. 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.

Additionally, analyses of hospitalization for HF and urgent HF visit will be performed to examine the contribution of each component of the composite endpoint.

9.4.3.5. Overall Survival

Overall survival is defined as time from randomization until death due to any cause. Participants who do not have a death date by the data cut-off date will be censored for OS at their last contact date. Overall survival 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 based on the strata as assigned at randomization and treatment arm as the covariate.

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

9.4.3.6. Safety Analysis

All participants who receive at least one dose of study intervention will be included in the safety analyses.

9.4.3.6.1. Adverse Events

AEs will be coded using MedDRA. Incidence tables of participants with AEs will be presented for all AEs by maximum severity, serious AEs, AEs assessed as related to study intervention, and AEs resulting in discontinuation of study intervention.

9.4.3.6.2. Other Secondary Safety Endpoints

The nature and frequency of arrhythmias will be tabulated for analysis. Changes in ECG and laboratory measurements will be summarized using descriptive statistics by arm over time.

9.4.3.7. Pharmacokinetic Analysis

Plasma concentrations of ARRY-371797 (PF-07265803) and its metabolites (AR00420643, AR00428028, and AR00486705) will be summarized using descriptive statistics by nominal time and visit. Results from the analysis of samples from participants randomized to the placebo arm will be used only to qualitatively assess consistency of results with respect to the randomization.

9.4.3.7.1. Population Pharmacokinetic/Pharmacodynamic Analyses

PK parameters for participants in the PK Set may be determined for ARRY-371797 (PF-07265803) and metabolites (AR00420643, AR00428028, and AR00486705) using a model-based approach to estimate PK parameters (eg, C_{max} and AUC) and their respective variability. PK data may be pooled with prior data from other studies with intensive sampling to estimate population parameters and derive Empirical Bayes Estimates of PK parameters for participants in this study.

Details of these analyses will be provided in a specific standalone modeling plan and results will be reported separately.

Pharmacokinetic/Pharmacodynamic (PK/PD) modeling of ARRY-371797 (PF-07265803) treatment group may be done using efficacy and/or safety endpoints compared to the corresponding endpoints in the placebo arm. The basic PK/PD model will consist of structural variables for treatment arm and the time points out to 24 months. Additional important covariates (such as demographics) may be added to the PK/PD model during the model building process. Details of any PK/PD analyses will be provided in a pre-defined analysis plan and will be reportedly separately.

Early unblinding for PK modeling purposes is planned when ≥ 90% of participants have reached 24 weeks post-randomization (or discontinued prior to the Week 24 visit). Unblinding will be limited to the PK data (ie, no efficacy data will be provided to the analysts/programmers). PK analysts and programmers will be listed on the early unblinding for PK/PD form in accordance with applicable Pfizer standard operating procedures for releasing randomization codes, early unblinding and breaking the study blind. These data programmers and analysts will not serve on this C4411002 study team after the PK early unblinding.

These data analysts and programmers will be unblinded early to build the PK and models for study readout. Information, such as drug concentration, that may unblind the study will not be reported to investigator sites or other Pfizer personnel, who will all remain blinded. There will be no impact on the study conduct, analysis, or reporting based on the early unblinding of the PK data. The results of these analyses will be reported in a separate pharmacometrics analysis report.

CCI [redacted]

CCI [redacted]

CCI [redacted]

9.4.5. Other Analyse(s)

9.4.5.1. Hierarchical Testing

The testing strategy controls Type I error across primary and selected secondary endpoints. If the van Elteren test of the primary endpoint is found to be statistically significant at 0.05 (2-sided) alpha, then a sequential testing plan will be implemented for testing the secondary endpoints.

Secondary endpoints will be analyzed in hierarchical order as follows:

- Week 24 change from baseline in KCCQ domains of PL and TSS
- Composite endpoint consisting of all-cause mortality or worsening heart failure (HF-related hospitalization or HF-related urgent care visit)
- Week 24 change from baseline in NT-proBNP

9.5. Interim Analyses

An interim futility analysis was performed after the first 60 randomized participants in NYHA Class II/III had completed the Week 12 assessment or discontinued prior to Week 12. Change from baseline in the 6MWT at Week 12 was evaluated for this purpose in these analyses. The DMC utilized the futility boundary to consider whether the study should continue to completion or stop early for futility. The objective of this interim futility analysis was not to terminate the study early for the benefit of efficacy, therefore, there was no adjustment of alpha for the review. The details on the interim futility stopping boundary for the 6MWT at Week 12 is described in the SAP.

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

Blinded Sample Size Re-estimation

Following the interim analysis for futility, a planned blinded sample size re-estimation for the primary endpoint of change from baseline at Week 24 was conducted using blinded cumulative primary efficacy data from the interim data cut. Specifically, a blinded, pooled analysis of both treatment groups for estimating variability of change from baseline in 6MWT at Week 24 and current overall event rates for deaths and study discontinuations prior to Week 24 was performed and compared to the assumption used in planning the study.

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 . The statistical analysis plan will provide an assessment of the expected number of events needed to rule out an upper bound of 1.8 or 2 under various scenarios for given hazard ratios.

The blinded sample size re-estimation was performed by a reporting statistician who is not a member of the study team and who will maintain independence from the study team for the duration of the trial. A detailed description of interim futility analysis and blinded sample size re-estimation is documented in the SAP.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use a DMC. The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail.

The DMC will be responsible for ongoing monitoring of the efficacy and safety of participants in the study according to the charter. The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

9.6.1. Data Monitoring Committee

The DMC will be responsible for reviewing safety and PK data at regular intervals during the randomized portion of the study. Additionally, the DMC will review efficacy data at a formal interim futility analysis planned after the first 60 Class II/III randomized participants have completed the Week 12 assessment or have discontinued from the study prior to Week 12. A separate DMC charter will be established that outlines DMC membership and specifies what data will be reviewed, instructions for unblinding of data, along with the timing and frequency of the reviews. DMC recommendations will be provided to the sponsor in compliance with the DMC charter.

9.6.2. Steering Committee

The SC will be appointed by the sponsor prior to the initiation of the study. The SC will include selected principal investigators from the study, leading experts in HF cardiomyopathy, and sponsor representatives. The SC will be involved in the oversight of the study and will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. Details on the role of the SC and working procedures will be defined in the SC charter.

9.6.3. Clinical Events Committee

The CEC will be appointed by the sponsor, or by it's representative, prior to the initiation of the study. The CEC will be responsible for reviewing safety data to aid in adjudicating cause for hospitalizations for the composite endpoint of all-cause mortality or worsening heart failure (HF-related hospitalizations or HF-related urgent are visits) only. Details on the role of the CEC and working procedures will be defined in the CEC charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

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

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

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

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

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

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

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

A copy of the informed consent document(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new informed consent document.

Unless prohibited by local requirements or IRB/EC decision, the informed consent document will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data Sharing

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

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

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is

responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic form and are password protected to prevent access by unauthorized third parties.

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

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

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

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

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

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

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant’s medical records. The investigator will promptly

provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

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

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

Definition of what constitutes source data can be found in the monitoring plan.

Description of the use of computerized system is documented in the Data Validation Manual.

10.1.8. Study and Site Start and Closure

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

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

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

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory

requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The conditions regulating dissemination of the information derived from this study are described in the Clinical Trial Agreement.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the inspection readiness electronic system.

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an Emergency Contact Card (ECC) at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 4. Protocol -Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC Platelets WBC Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Albumin Alkaline phosphatase AST GGT ALT Bicarbonate (CO_2) Total bilirubin BUN Calcium Chloride 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 pH Protein	At screening only: • HIV, Hepatitis B and C • TSH • eGFR calculation • LMNA mutation If applicable: • Serum pregnancy test • Urine pregnancy test • FSH

Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

AE Definition

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  - Is associated with accompanying symptoms.
  - Requires additional diagnostic testing or medical/surgical intervention.
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

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

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

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

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

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

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

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

Assessment of Intensity

The severity rating of an AE refers to its intensity. The severity of each AE will be determined by the Investigator using the Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (US Department of Health and Human Services 2007), or modified grading parameter as specified in the dose modification table. For events that are not addressed by these guidelines, severity will be categorized according to the following criteria:

Grade 1	MILD; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	MODERATE; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Grade 3	SEVERE; severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

Grade 4	LIFE-THREATENING; life-threatening consequences; urgent intervention indicated
Grade 5	FATAL

Assessment of Causality

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

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

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

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 30 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

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

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4.

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below during the intervention period and for at least 30 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with high user dependency, as described below during the intervention period and for at least 30 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition, a second effective method of contraception, as described below, must be

used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

- female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

Highly Effective Methods That Have Low User Dependency

5. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
6. Intrauterine device.
7. Intrauterine hormone-releasing system.
8. Bilateral tubal occlusion.
9. Vasectomized partner.

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

Highly Effective Methods That Are User Dependent

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

- Oral (it is recommended that participants experiencing vomiting or diarrhea should be counseled to use non-oral methods of contraception);
- Intravaginal;
- Transdermal;
- Injectable.

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

- Oral (it is recommended that participants experiencing vomiting or diarrhea should be counseled to use non-oral methods of contraception);
- Injectable.

12. Sexual abstinence:

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

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3×ULN AND a TBili value >2×ULN with no evidence of hemolysis and an alkaline phosphatase value <2×ULN or not available.

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

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

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

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

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

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

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

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

10.6. Appendix 6: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AEs

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

ECG Findings That May Qualify as SAEs

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

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

ECG Findings That Qualify as SAEs

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

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

10.7. Appendix 7: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures is expected to cease upon the return of business as usual (including the lifting of any quarantines and travel bans/advisories).

Alternative Facilities for Safety Assessments

In the event that a participant is unable to attend onsite visits, every effort will be made to follow up with the participant by phone contact at the time of scheduled visit per the SoA. Video contact can be used if permitted by local regulations. The study participants must be reminded to promptly communicate to the investigative site staff any change in their health status. During the phone (or video) contact, at a minimum, the following information must be collected and reviewed:

AE(s) including SAE(s) and concomitant medication(s) since last contact. AEs/SAEs reporting process must be followed per Section 8.4.

If at any time, in the investigator's judgment, the safety of a study participant is at risk due to an inability to adequately conduct required safety evaluations, strong consideration should be given to discontinuing the study participant from study intervention. Such a determination should be made in consultation with the sponsor's medical monitor.

Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- Hematology, Blood Chemistry and Pregnancy testing

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

The investigative site staff must ensure to collect the local laboratory reference ranges and certifications/accreditations for filing at the investigational site. In addition, the local laboratory will be recorded on the Form 1572.

Study Intervention:

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

Assessment of the study participant's overall condition and laboratory test results prior to the administration of study intervention remains the responsibility of the investigator or medically qualified staff and should be performed in accordance with the protocol, irrespective of whether additional study intervention supply is dispensed or shipped.

- Participants should be reminded that dosing diaries must be maintained per protocol and reminded to return unused study intervention and completed dosing diaries, as required by protocol, when possible.

- Dispensation of extra drug supply to the study participant at a clinic visit (preferred option) or direct shipment via courier to a study participant's home (as allowed by local applicable laws and regulations) is permitted provided the investigator site staff assesses and determines that it is appropriate to do so, and the study participant verbally consents to this. The study participant's consent should be well documented in the medical record.

- If extra dispensation or direct shipment of study intervention to a study participant is necessary, please contact the sponsor in advance so that guidance/instructions can be provided, and study intervention supply can be tracked as the global COVID-19 pandemic situation continues to evolve.

10.8. Appendix 8 Cautionary Concomitant Medications while on Study Intervention

Drugs with known TdP risks. Downloaded from https://crediblemeds.org/new-drug-list/, filtered to include only "Known Risk of TdP" drugs. Accessed 07 Jan 2022.

Generic Name	Brand Names (Partial List)	Drug Class
Aclarubicin *(Only on Non US Market)*	Aclacin, Aclacinomycine, Aclacinon, Aclaplastin, Jaclacin	Anti-cancer
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor
Arsenic trioxide	Trisenox	Anti-cancer
Astemizole *(Removed from US Market)*	Hismanal	Antihistamine
Azithromycin	Zithromax, Zmax	Antibiotic
Bepridil	Vascor	Antianginal
Cesium Chloride	Energy Catalyst	Toxin
Chloroquine	Aralen	Antimalarial
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic
Chlorprothixene *(Only on Non US Market)*	Truxal	Antipsychotic
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic
Cisapride *(Removed from US Market)*	Propulsid	GI stimulant
Citalopram	Celexa, Cipramil	Antidepressant, SSRI
Clarithromycin	Biaxin, Prevpac	Antibiotic
Cocaine	Cocaine	Local anesthetic
Disopyramide	Norpace	Antiarrhythmic
Dofetilide	Tikosyn	Antiarrhythmic
Domperidone *(Only on Non US Market)*	Motilium, Motillium, Motinorm Costi, Nomit	Antiemetic

Generic Name	Brand Names (Partial List)	Drug Class
Donepezil	Aricept	Cholinesterase inhibitor
Dronedarone	Multaq	Antiarrhythmic
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic / Antiemetic
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery- Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Antibiotic
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E, Exodus, Esto, Seroplex, Elicea, Lexamil, Lexam, Entact, Losita, Reposil, Animaxen, Esitalo, Lexamil	Antidepressant, SSRI
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic
Fluconazole	Diflucan, Trican	Antifungal
Gatifloxacin *(Removed from US Market)*	Tequin	Antibiotic
Grepfloxacin *(Removed from US Market)*	Raxar	Antibiotic
Halofantrine *(Only on Non US Market)*	Halfan	Antimalarial
Haloperidol	Haldol, Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol, Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic
Hydroquinidine (Dihydroquinidine) *(Only on Non US Market)*	Serecor	Antiarrhythmic
Hydroxychloroquine	Plaquenil, Quineprox	Antimalarial, Anti-inflammatory
Ibogaine *(Only on Non US Market)*		Psychedelic
Ibutilide	Corvert	Antiarrhythmic

Generic Name	Brand Names (Partial List)	Drug Class
Levofloxacin	Levaquin, Tavanic	Antibiotic
Levomepromazine (Methotrimeprazine) *(Only on Non US Market)*	Nosinan, Nozinan, Levoprome	Antipsychotic
Levomethadyl acetate *(Removed from US Market)*	Orlaam	Opioid agonist
Levosulpiride *(Only on Non US Market)*	Lesuride, Levazeo, Enliva	Antipsychotic
Meglumine antimoniate *(Only on Non US Market)*	Glucantime	Antiparasitic
Mesoridazine *(Removed from US Market)*	Serentil	Antipsychotic
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opioid agonist
Mobocertinib	Exkivity	Tyrosine kinase inhibitor
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic
Nifekalant *(Only on Non US Market)*	Shinbit	Antiarrhythmic
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic
Oxaliplatin	Eloxatin	Anti-cancer
Papaverine HCl (Intra- coronary)		Vasodilator, Coronary
Pentamidine	Pentam	Antifungal
Pimozide	Orap	Antipsychotic
Probucol *(Removed from US Market)*	Lorelco	Antilipemic
Procainamide	Pronestyl, Procan	Antiarrhythmic

Generic Name	Brand Names (Partial List)	Drug Class
Propofol	Diprivan, Propoven	Anesthetic, general
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic
Roxithromycin *(Only on Non US Market)*	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin	Antibiotic
Sertindole *(Only on Non US Market)*	Serdolect, Serlect	Antipsychotic, atypical
Sevoflurane	Ultane, Sojourn	Anesthetic, general
Sotalol	Betapace, Sotalex, Sotacor	Antiarrhythmic
Sparfloxacin *(Removed from US Market)*	Zagam	Antibiotic
Sulpiride *(Only on Non US Market)*	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Antipsychotic, atypical
Sultopride *(Only on Non US Market)*	Barnetil, Barnotil, Topral	Antipsychotic, atypical
Terfenedine *(Removed from US Market)*	Seldane	Antihistamine
Terlipressin *(Only on Non US Market)*	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss	Vasoconstrictor
Terodiline *(Only on Non US Market)*	Micturin, Mictrol	Muscle relaxant
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic
Vandetanib	Caprelsa	Anti-cancer

10.9. Appendix 9: Definitions of Heart Failure Events

Hospitalization for Heart Failure: Must meet ALL of the following criteria

The participant is admitted to the hospital with a primary diagnosis of HF.

1. The participant's length-of-stay extends for at least 24 hours (or a change in calendar day if the admission and discharge times are unavailable).

2. The participant exhibits documented new or worsening symptoms due to HF on presentation including **at least ONE** of the following:

a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)

b. Decreased exercise tolerance

c. Fatigue

3. The participant has objective evidence of new or worsening HF, consisting of **at least TWO** physical exam findings **OR** one physical exam finding and at least ONE laboratory criterion, including:

   a. Physician examination findings considered to be due to heart failure, including new or worsened:

      i. Peripheral edema

      ii. Increasing abdominal distension or ascites (in the absence of primary hepatic disease)

      iii. Pulmonary rales/crackles/crepitations

      iv. Increased jugular venous pressure and/or hepatojugular reflux

      v. S_3 gallop

      vi. Clinically significant or rapid weight gain thought to be related to fluid retention

   b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presenting, including:

      i. Increased BNP/NT-proBNP concentrates consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 p/mL). In participants with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.

      ii. Radiological evidence of pulmonary congestion

iii. Non-invasive diagnostic evidence of clinically significant elevated left-or right--sided ventricular filling pressure or low cardiac output.

OR

iv. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥18 mmHg, central venous pressure ≥12 mm/Hg, or a cardiac index <2.2 L/min/m^2

4. The participant receives initiation or intensification of treatment specifically for HF, including **at least ONE** of the following:

   a. Augmentation in oral diuretic therapy

   b. Intravenous diuretic or vasoactive agent (eg, inotrope, vasopressor, or vasodilator)

   a. Mechanical or surgical intervention, including:

      i. Mechanical circulatory support (eg, intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)

      ii. Mechanical fluid removal (eg, ultrafiltration, hemofiltration, dialysis)

An Urgent Heart Failure Visit: Is an event that meets all of the following:

1. The participant has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for HF hospitalization.

2. All signs and symptoms for HF hospitalization (ie, symptoms, physical examination findings/laboratory evidence of new or worsening HF, as indicated above) must be met.

3. The participant receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient.

Source: Hicks K, Hung H, Mahaffey K, et al. Standardized definitions for cardiovascular and stroke endpoint events in clinical trials. Clinical Data Interchange Standards Consortium (Standardized Data Collection for Cardiovascular Trials Initiative); August 20, 2014. 2017.

10.10. Appendix 10: Country Specific Requirements

10.10.1. Japan

Electrocardiograms

NOTE: The cardiologist confirms ECG data immediately after measuring ECG, and if ECG data meets ECG values of "ECG Findings of Potential Clinical Concern" listed in Appendix 6, the investigator's clinical judgment and the background regarding whether dose interruptions, reductions, and discontinuations of study intervention are needed must be documented.

Contraception Methods

In accordance with Japanese regulations regarding the use of contraceptive methods, the following contraceptive methods should be used in Japan.

Highly Effective Methods That Have Low User Dependency

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

Highly Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral (it is recommended that participants experiencing vomiting or diarrhea should be counseled to use non-oral methods of contraception)
- Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence

needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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

- Male or female condom with or without spermicide;
- Diaphragm;
- A combination of male condom with diaphragm (double-barrier methods).

10.10.2. France

Contrat Unique

1. GCP Training

   Before enrolling any participants, the investigator and any subinvestigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will do the same before performing study-related duties. For studies of applicable duration, the investigator and subinvestigators will complete Pfizer GCP Training or equivalent every 3 years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Study Intervention

   No participants or third-party payers will be charged for study intervention.

3. Urgent Safety Measures

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

4. Termination Rights

   Pfizer retains the right to discontinue development of ARRY-371797 (PF-07265803) at any time.

10.11. Appendix 11: Abbreviations

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

Abbreviation	Term
2D	2-dimensional
6MWT	6-minute walk test
ACC	American College of Cardiology
ACMG	American College of Medical Genetics and Genomics
ADL	activities of daily living
AE	adverse event
AHA	American Heart Association
ALT	alanine aminotransferase
AS	ankylosing spondylitis
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the plasma concentration-time curve
β-HCG	beta-human chorionic gonadotropin
BID	twice daily
BNP	brain natriuretic peptide
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
C	Celsius
CCD	Cardiac conduction disease
CDISC	Clinical Data Interchange Standards Consortium
CEC	clinical events committee
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
C_{max}	maximal plasma concentration
CO_2	carbon dioxide (bicarbonate)
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CrCL	creatinine clearance
CRO	contract research organization
CRP	C-reactive protein
CRT	cardiac resynchronization therapy
CRT-D	cardiac resynchronization therapy defibrillator
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
CRT	cardiac resynchronization therapy
CSS	Clinical Summary Score
CT	Clinical Trial

Abbreviation	Term
CV	cardiovascular
CYP	cytochrome P450
DCM	dilated cardiomyopathy
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
EAS	efficacy analysis set
EC	ethics committee
ECC	Emergency Contact Card
eCDF	empirical cumulative distribution function
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDMD	Emery-Dreifuss muscular dystrophy
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EF	ejection fraction
EMA	European Medicines Agency
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
ER	emergency room
ERK	extracellular signal-regulated kinase
ESC	European Society of Cardiology
EU	European Union
EudraCT	European Clinical Trials Database
FAS	full analysis set
FDA	Food and Drug Administration
FMO	flavin-containing monooxygenase
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HDPE	high-density polyethylene
HEENT	head, eyes, ears, nose, throat
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HFS	hospitalization-free survival
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HL	Hodges-Lehmann
HR	hazard ratio
HSP27	heat shock protein 27
HRT	hormone replacement therapy

Abbreviation	Term
HRU	healthcare resource utilization
IA	Interim Analysis
IB	investigator's brochure
IC_{50}	half-maximal inhibitory concentration
ICD	implantable cardioverter defibrillator
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IL	interleukin
IP	Investigational Product
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRT	interactive response technology system
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVC	inferior vena cava
JNK	c-Jun N-terminal kinase
KCCQ	Kansas City Cardiomyopathy Questionnaire
LMNA	gene encoding the lamin A/C protein
LOCF	last observation carried forward
LP	likely pathogenic
LTE	long-term extension
LV	left ventricle, left ventricular
LVAD	left ventricular assist device
LVEDD	left ventricular end diastolic diameter
LVEDVI	left ventricular end diastolic volume index
LVEF	left ventricular ejection fraction
LVESD	left ventricular end systolic diameter
LVESVI	left ventricular end systolic volume index
MAO	monoamine oxidase
MAP3K	mitogen-activated protein kinase kinase kinase
MAPK	mitogen-activated protein kinase
MAPKK	mitogen-activated protein kinase kinase
MAR	missing at random
MD	muscular dystrophy
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov chain Monte Carlo
MI	multiple imputation
MMRM	mixed models for repeated measurements
mRNA	messenger ribonucleic acid
MRI	magnetic resonance imaging
msec	millisecond
N	number of participants

Abbreviation	Term
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OA	osteoarthritis
OTC	over-the-counter
OS	overall survival
OSS	Overall Summary Score
P	pathogenic
p-p38	phospho-p38
PACL	Protocol Administrative Change Letter
PAH	pulmonary arterial hypertension
PASP	pulmonary artery systolic pressure
PD	pharmacodynamics(s)
PGI	Patient Global Impression
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
P-gp	permeability glycoprotein
PK	pharmacokinetic(s)
PL	Physical Limitation
PPS	per-protocol set
PR	ECG interval from the onset of P wave to the onset of the QRS complex
PRO	patient-reported outcomes
QA	quality assurance
QD	once daily
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
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RA	rheumatoid arthritis
RBC	red blood cell
RV	right ventricular
RVEDD	right ventricular end-diastolic diameter
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SAS	safety analysis set
SC	steering committee
SCD	sudden cardiac death
SD	standard deviation
SEM	standard error of the mean
sMDRD	Simplified Modification of Diet in Renal Disease
SoA	schedule of activities

Abbreviation	Term
SOP	standard operating procedure
SRSD	single reference safety document
SS	safety set
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal half-life
TAPSE	tricuspid annular plane systolic excursion
TEAE	treatment-emergent adverse event
TdP	torsades de pointes
T_{max}	time to maximum plasma exposure
TNFα	tumor necrosis factor-alpha
TOC	Table of Contents
TSH	thyroid-stimulating hormone
TSS	Total Symptom Score
TTN	titin
ULN	upper limit of normal
UGT	uridine 5'-diphospho Glucuronosyltransferase
US	United States
VAS	Visual Analog Scale
VUS	variant of uncertain significance
WBC	white blood cell
WHF	worsening heart failure
WOCBP	woman/women of childbearing potential

10.12. Appendix 12: Protocol Amendment History

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

Protocol Amendment Summary of Changes Table

Document History		
Document/Version	**Version Date**	**Summary and Rationale for Changes**
Protocol Version 7	17Feb2021	Changed primary endpoint change from baseline in 6MWT at 12 weeks to 24 weeks. Rationale: Clinical relevance of durability of response up to 24 weeks as per regulatory feedback. Update previous safety hospitalization free survival composite endpoint by adding heart failure related urgent care visits as a part of worsening heart failure. Rationale: clinical relevance of including in the statistical analysis events already being collected and adjudicated. Statistical changes included: 1) clarifications on the sample size assumptions and a blinded sample size re-estimation after IA futility for the primary endpoint, 2) implementation of the blinded monitoring of cumulative event counts for the composite endpoint of all-cause mortality and worsening heart failure throughout the study to assess impact on the sample size, 3) additional details on the primary analysis and imputation method, and 4) updates on the analysis method on the composite endpoint for all-cause mortality and worsening heart failure, and the hierarchical testing. Rationale: To align with the changes in the primary endpoint and the composite endpoint to assess all-cause mortality and worsening heart failure. Added cautionary use of CYP3A4 inhibitors and inducers. Rationale: Based on emerging data suggesting potential for mixed induction/inhibition of CYP3A4, the effect of

Document History		
Document/Version	**Version Date**	**Summary and Rationale for Changes**
		PF-07265803 (ARRY-371797) interaction with drugs that are identified as being metabolized by CYP3A4 is not known. Updated minimum Frequency of Pregnancy Testing to every 12 weeks rather than monthly. Rationale: Sponsor's reproductive safety guidelines no longer requires every 4 weeks. CCI  In Class II/III participants, added measures of efficacy on change from baseline in Borg fatigue scale of 6MWT at Weeks 4, 12 and 24, and every 12 weeks after. Rationale: To obtain a more complete understanding of the change from baseline in the Borg fatigue scale of 6MWT. CCI 

Document History		
Document/Version	**Version Date**	**Summary and Rationale for Changes**
		[redacted] Rationale: To obtain a more complete understanding of recurrent HF-related hospitalizations, change in daily activity measures, and change in health status and physical activity. Allow the use of an accredited clinical laboratory rather than limiting genetic testing to a central laboratory for determination of LMNA variants and to allow participants with LMNA variant of uncertain significance (VUS) to be enrolled. Rationale: To align with the genetic testing requirements in the completed Phase 2 trial, which did not utilize a single central laboratory. Genetic testing has become more routine and is now commonly performed in many clinical laboratories. LMNA-DCM is a diagnosis of exclusion. Genetic test results of VUS may change to LP/P as more clinical cases are confirmed. Modified the introduction and background section. Rationale: Updated to provide clarification and further information based on review of the literature. Updated kinship language to allow for no more than 10% of participants enrolled with the same mutation rather than 4 individuals from a single family. Rationale: Modified to have a holistic view of entire population and mutations, and

Document History		
Document/Version	**Version Date**	**Summary and Rationale for Changes**
		considering family members can have different mutations. Modified inclusion criteria language to clarify if a participant has a CRT-D, defibrillation must be activated at least 4 weeks prior to initiation of study intervention. Rationale: To ensure proper functionality of the defibrillator function prior to study intervention. Modified inclusion criteria to expand the cardiovascular conditions required at prescreening. Rationale: To ensure the appropriate participants are being prescreened. Remove 6MWT % predicted distance (Troosters et al 1999) from 6MWT inclusion criteria. Rationale: Eligibility to be based on absolute distance walked vs % predicted as the perceived prognostic value of the % predicted is not superior to the absolute distance observed via the 6MWT The screening ECHO can be done locally and is not required to be sent to central laboratory. Rationale: Streamline the screening process and requirements. Removed 24-hour Holter monitoring language and clarify arrythmia assessment requirements. Rationale: All participants are required to have an ICD/CRT device at study entry and can be monitored continuously. Reduced the number of ECGs and no longer require triplicate ECG. Rationale: Unnecessary burden of ECGs given that participants have an ICD/CRT device in place. Modified the survival follow-up section to include HF-related hospitalizations and HF-

Document History		
Document/Version	**Version Date**	**Summary and Rationale for Changes**
		related urgent care visits being collected as part of the analysis. Added an Alternative Measures during Public Emergences appendix. Rationale: A COVID-19 contingency plan was issued in a PACL dated 20May2020 and the language was updated to align with Pfizer's required protocol template language. Protocol v6 dated 09Mar2020 was moved into the Sponsor's protocol template. Rationale: To align with Pfizer's standard template language.

Protocol Version 6	09 March 2020	At the time of this protocol amendment, the study had been initiated at 66 study centers and 28 participants had been randomized. Protocol version 6 was generated to include the following key changes:
		• Update to Exclusion #10 for Class II/III and duplicate Exclusion #7 for Class IV based on an administrative letter submitted 09 Apr 2019.
		  • Rationale: To modify the list of slow growing or curatively resected malignancies to allow participants to be enrolled.
		• Updated inclusion criteria language to ensure that ICD/CRT-D devices also include pacing capabilities.
		  • Rationale: To be certain that all devices have pacing capabilities.
		• Regarding the number of participants required at the interim analysis and the futility boundary for early stopping.
		  • Rationale: To reduce the error rate of making an incorrect decision of early stopping for futility at the interim analysis.
		• To update the power of the primary analysis from 80% to approximately 90% for the

Document History		
Document/Version	**Version Date**	**Summary and Rationale for Changes**
		primary endpoint of change from baseline in the 6MWT at Week 12. • Rationale: Power increase from 80% to approximately 90% is as a result of the change in the timing of the interim analysis as well as a change in the method for determining the futility boundary. • To update language relating to the sensitivity analysis for the primary endpoint. • Rationale: To remove detailed descriptions of sensitivity analysis and provide them in the SAP. • Update language around abnormal labs as AEs. • Rationale: To comply with the requested wording from a Health Authority and to align with the Global protocol template. • Add risk/benefit section (the changes are in alignment with the IB). • Rationale: To comply with the requested wording from a Health Authority and to align with the Global protocol template. • Updated language around the responsibilities of the DMC. • Rationale: To clarify that the DMC is reviewing safety and PK throughout the study but only efficacy data at prespecified timepoints. • To add the compound designation "PF-07265803" to ARRY-371797. • Rationale: To reflect a new compound designation and align with the IB. • Corrected Table 6, Schedule of Events for Open-Label Period • Rationale: Corrected the footnote in the schedule of arrythmia assessments to align assessments with Section 8.5.1.2.9.
Protocol Version 5	17 January 2019	At the time of this protocol amendment, the study had been initiated at 46 study centers and 7 participants had been randomized. Protocol

Document History		
Document/Version	**Version Date**	**Summary and Rationale for Changes**

		version 5 was generated to include the following key changes:
		[redacted]
		• To clarify that participants will have the opportunity to be followed for at least 24 weeks prior to the primary analysis being performed.
		  • Rationale: The Week 24 assessment is not required for this analysis.
		• To reduce the number of participants needed at the interim analysis, to occur after
		  • NYHA Class II/III participants have completed the Week 12 assessment or have discontinued before Week 12, rather than after 60 participants have met the same criteria.
		  • Rationale: To obtain a more rapid evaluation of potential efficacy.
		• To update the power of the primary analysis from 90% to 80% for the primary endpoint of change from baseline in the 6MWT at Week 12.
		  • Rationale: By including the interim analysis with a futility boundary of 17 meters, the overall study power is 80%. At the interim analysis, the predictive power will be ≥40% to continue the study.
		• For the interim analysis, descriptions of analysis of the pooled standard deviation of change from baseline 6MWT data and the blinded assessment of powering assumptions at the interim analysis were deleted. Text now specifies that the change from baseline in 6MWT at Week 12 will be analyzed

Document History		
Document/Version	**Version Date**	**Summary and Rationale for Changes**
		nonparametrically, as in the primary analysis. The futility boundary is updated to be based on predictive power. • Rationale: To remove detailed descriptions of the pooled analysis of standard deviation of change from baseline 6MWT data, descriptions of the blinded assessment of powering assumptions and futility boundaries from the protocol and provide them only in the SAP. • To change inclusion criteria that describe the timing of testing for acceptable hematology, hepatic and renal function, lengthening the period for obtaining acceptable values from within 3 weeks to within 35 days prior to Day 1. • Rationale: To align collection of these laboratory data with the duration of the screening period. • To clarify that blood collection for central analysis of the LMNA gene mutation for participants with known LMNA mutation per local lab may be performed during screening. • Rationale: To provide a better sequence of assessments at sites. • To increase the number of times that participants can be rescreened. • Rationale: To provide more opportunities for participants to meet study entry criteria.
Protocol Version 4	27 August 2018	At the time of this protocol amendment, the study had been initiated at 13 study centers and 4 participants had been randomized. Protocol version 4 was generated to include the following key changes: • To classify HFS and OS as efficacy endpoints rather than safety endpoints, therefore adding a new secondary objective. • Rationale: To clarify which endpoints are safety related.

Document History		
Document/Version	**Version Date**	**Summary and Rationale for Changes**

		• To clarify that the open-label phase of the study will begin seamlessly after the primary analysis is completed.
		  • Rationale: To clarify the transition between the randomized and open-label phases of the study.
		• To clarify the description of the end of study and update the conditions necessary to continue treatment after the end of study in a protocol amendment or separate rollover protocol, as permitted by local regulations and only after Health Authority and EC approval.
		  • Rationale: To clarify when the study will end and under what circumstances participants can continue to receive study intervention.
		• To allow the use of ECHOs obtained from local laboratories in complying with screening requirements.
		  • Rationale: Locally performed reads of ECHOs can document an EF ≤50% during screening. The central result is no longer needed to assess eligibility.
		• To change the timing of when LMNA mutation status must be confirmed by the central laboratory. Deleterious LMNA mutation status must be confirmed prior to randomization. Participants may satisfy screening criteria with either local or central LMNA results.
		  • Rationale: To ensure that all participants who receive study intervention have the LMNA mutation.
		• To standardize wording describing which assessments will be conducted when feasible for NYHA Class IV participants and to allow flexibility in determining which assessments must be conducted in clinic.

Document History		
Document/Version	**Version Date**	**Summary and Rationale for Changes**
		• Rationale: To provide consistency and flexibility for participants who are not ambulatory. • To increase the duration of the screening period from 28 to 35 days prior to Day 1 and update the timing of all assessments during the screening period throughout the protocol. • Rationale: To extend the screening window for flexibility of scheduling participants around weekends and holidays. • To permit unblinded bioanalytical data to be transferred to an unblinded CRO for reassay of PK samples. • Rationale: To allow for reanalysis of discrepant bioanalytical results from PK samples as the study duration is projected to be longer than the stability of the measured analytes. • To modify the inclusion criteria related to signing informed consent to add that participants under guardianship or partial guardianship will be eligible unless prohibited by local laws by ECs. • Rationale: To clarify that there may be differences in the ability of these participants to participate in the study, depending on the site's location. • To add inclusion criteria to require affiliation to a social security system or beneficiary status, if applicable. • Rationale: To include standard language for all possible applicable country regulations. • To delete the inclusion criteria that required that participants have serum NT-proBNP >400 pg/mL. • Rationale: To allow enrollment of participants based on LMNA mutation status and clinical criteria.

Document History		
Document/Version	**Version Date**	**Summary and Rationale for Changes**

		• To modify the exclusion criteria for all participants pertaining to pregnancy or breastfeeding to also exclude participants who plan to become pregnant during the duration of the trial.
		  • Rationale: Any participant planning to become pregnant should be excluded from the trial.
		• To add an exclusion criterion for the NYHA functional Class II and III participants in order to exclude participants with an underlying condition that may impact the ability of the 6MWT to reflect changes in cardiovascular function.
		  • Rationale: To ensure that the 6MWT reflects changes in cardiovascular function.
		• To add exclusion criteria for participants who have hypersensitivity or intolerance to the drug product and to add information on the commercial film coating used in manufacturing.
		  • Rationale: To reduce the potential risk to participants who receive treatment.
		• To prohibit donation of sperm or ova during treatment and for 90 days after the last dose for sperm and 30 days after the last dose for ova. Also, to clarify the description of when contraceptives are required.
		  • Rationale: To prevent potential damage to sperm and ova that are donated or that might result in a pregnancy.
		• To clarify and make the timing of laboratory tests (ie, PK tests, PD tests, and assessment of renal function status) and collection of vital signs and ECGs consistent throughout the protocol.
		  • Rationale: To reduce the potential for site error.
		• To require IXRS contact during the screening visit.

Document History		
Document/Version	**Version Date**	**Summary and Rationale for Changes**
		• Rationale: To track participants who are in prescreening versus screening. • To specify that the EAS will include participants with a confirmed LMNA deleterious mutation and to remove the requirement that there is a maximum of 5 participants in the EAS who do not have a centrally confirmed LMNA mutation. • Rationale: This amendment requires that all participants who are randomized into the study possess a centrally confirmed LMNA mutation. • To correct a typographic error in the description of the statistical analysis of the KCCQ domains of TSS and PL. • Rationale: To provide clarity regarding the planned analysis. • To specify that the log of the ratio of Week 4, 12, and 24 NT-proBNP values will be analyzed. • Rationale: To provide clarity that the log ratio will be analyzed.
Protocol Version 3	26 March 2018	At the time of this protocol amendment, the study had not been initiated at any study centers and no participants had been treated. Protocol version 3 was generated to include the following key changes: • To require central laboratory evaluations at screening instead of local laboratory evaluations. • Rationale: To maintain consistent collection of data throughout the study. • To add that the DMC will review PK data. • Rationale: To clarify that the DMC will review all pertinent data. • To add Borg fatigue assessments as part of the 6MWT. • Rationale: To align with all aspects of the 6MWT per the ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS

Document History		
Document/Version	**Version Date**	**Summary and Rationale for Changes**

		statement: Guidelines for the Six-minute Walk Test.
		• To modify the inclusion criteria pertaining to the ICD/CRT-D in order to clarify a time frame in which the ICD/CRT-D could be implanted/initiated.
		  • Rationale: To provide a window of time to have these devices implanted/initiated to provide flexibility to the participants.
		• To modify Appendix 3 in order to change the definition of HF-related hospitalization and to provide a definition for HF-related urgent visits.
		  • Rationale: To align with CDISC Guidance "Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials".
		• To clarify that survival follow-up will only be collected during the randomized period and not the open-label period.
		  • Rationale: To clarify that data will not be collected after the endpoint has been reached in the randomized period.
		• To add a rationale for the secondary safety endpoint pertaining to HFS.
		  • Rationale: To provide justification for this secondary endpoint.
		• To modify the statistical methodology used for estimation and testing of treatment effects.
		  • Rationale: To align the use of stratification in the estimation approach of the primary endpoint with the testing approach; to clarify the hierarchical testing procedure to align with intended labeling claims; to add and remove sensitivity analyses to more appropriately characterize and assess robustness of the treatment effect estimates; and, to update the approach to analysis of PROs.

Document History		
Document/Version	**Version Date**	**Summary and Rationale for Changes**
Protocol Version 2	23 October 2017	Generated to include US regulatory guidance and also included clarifications and corrections.
Protocol Version 1	10 March 2017	Developed to support discussions with the US regulatory authorities but was not submitted to investigational sites, IRBs/ECs, or regulatory authorities outside the US.

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