SUPPLEMENTAL MATERIAL

SUPPLEMENTAL METHODS

STUDY DESIGN AND OVERSIGHT

Patients were enrolled by alternating assignment to receive oral ARRY-371797 (PF-07265803) at a dose of either 100 mg twice daily (bid) or 400 mg bid for 48 weeks. The first patient enrolled in the study received 100 mg bid, the second patient received 400 mg bid, and the dose assignment of subsequent patients continued to alternate, as determined by the study management team. Dose reductions to 200 mg bid for poor tolerability were allowed in the 400-mg bid group; further reduction was allowed to 100 mg bid for poor tolerability at 200 mg bid. Patients assigned to 100 mg bid could escalate to 400 mg bid at week 24 or later if the 6-minute walk test (6MWT) had not improved by ≥10% and there were no grade 3/4 adverse events (AEs). Patients had the option to roll over to a continuing treatment protocol after 48 weeks (ClinicalTrials.gov: NCT02351856).

PATIENTS

Adult patients diagnosed with primary DCM, stable New York Heart Association (NYHA) class II–IIIA HF with left ventricular ejection fraction (LVEF) ≤45% and a pathogenic mutation in the *LMNA* gene were eligible if they had received guidelines-based heart failure (HF) treatment with no dose reduction >50% or dose increase >100% in the prior 3 months. Patients were required to have a 6MWT performance indicating functional impairment.

Pathogenic mutations in the lamin A/C gene (*LMNA*) for inclusion of patients was determined by a Clinical Laboratory Improvement Amendments–certified clinical

laboratory before study enrollment. Patients were also required to have a left ventricular end-diastolic diameter >3.3 cm/m^2 (females) or 3.4 cm/m^2 (males) and/or a left ventricular ejection fraction ≤45%. An acceptable hematologic profile and adequate renal and hepatic function were also required. Patients were excluded if they had unstable cardiac symptoms requiring hospitalization, myocardial infarction, cardiac surgery, destabilizing cardiac arrhythmia, or serious systemic infection within 60 days of screening; New York Heart Association class IIIB or IV heart failure; prolonged corrected QT interval; clinically significant coronary artery disease; uncorrected primary valvular disease; or requirement for dialysis. Other exclusion criteria were initiation of cardiac resynchronization therapy within 180 days of screening; current receipt of, or likelihood of requiring, continuous intravenous inotrope infusion; presence of a ventricular assist device or near-term (within 6 months) need for device insertion; history of or near-term need for heart transplantation; near-term need for other cardiac surgery; or referral for hospice or end-of-life treatment.

STUDY ASSESSMENTS

The primary endpoint was change from baseline in 6MWT distance at 12 weeks. The 6MWT measures the distance that patients can quickly walk on a flat, hard surface of ≥30 m in 6 minutes as an estimate of functional capacity.[18,19] Three 6MWT assessments were performed (at screening, day –1, and day 1) to ensure proper training, to confirm patient eligibility, and to establish baseline values. Patients at screening were required to have a 6MWT distance of 100–350 m, or 100–450 m and a predicted distance value of ≤60%,[20] and stable NYHA class II–IIIA HF. At day –1 and day 1 (baseline), required values were a 6MWT distance of 100–400 m, or 100–475 m if the predicted distance value was ≤65%,[20] and stable NYHA class II–IIIA HF.

The key secondary endpoint, N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration, was measured at 4, 12, 24, 36, and 48 weeks, and, if applicable, 4 weeks after dose escalation. Other blood chemistry associated with improved cardiac function which was assessed included blood urea nitrogen, creatinine, also measured at 4, 12, 24, 36, and 48 weeks.

Additional secondary endpoints included change from baseline in 6MWT distance over time (4, 24, 36, and 48 weeks), 6MWT response (≥10% improvement in 6MWT distance by visit) and echocardiographic measures of left and right ventricular function, and change from baseline, determined by a central core laboratory (with the reader blinded to treatment assignment). Patient-reported outcomes of quality of life were also measured, using the Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary and Clinical Summary scores, with scores evaluated at 12, 24, 36, and 48 weeks. Missing item responses for quality of life measures were assumed to be the same

as the response to the scale's answered item(s). KCCQ scale scores were computed when ≥50% of the items were non-missing. If <50% of the items were non-missing, the scale score was set to missing. The KCCQ is a validated quality of life questionnaire developed to independently measure the participant's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life.[21] The Change the Management of Patients With Heart Failure (CHAMP-HF) registry in participants with heart failure with reduced ejection fraction indicated that an improvement of 5 or more points in KCCQ-OS was independently associated with decreased mortality and mortality or hospitalization for heart failure.[22]

Safety was evaluated by determining the incidence and severity of adverse events (AEs), clinical laboratory evaluations, physical examination, vital signs, and 12-lead electrocardiograms (ECGs) at 4, 12, 24, 36, and 48 weeks, and 4 weeks after dose escalation (if the patient had dose-escalated from ARRY-371797 (PF-07265803) 100 mg twice daily [bid] to 400 mg bid). The incidence of atrial and ventricular arrhythmias was evaluated using previously implanted intracardiac defibrillators, pacemakers, or 24-hour Holter monitoring at day 1, and at 12 and 24 weeks (and 36 and 48 weeks, if the patient had dose-escalated from 100 mg bid to 400 mg bid).

For laboratory, vital sign, ECG, echocardiograph, and arrhythmia assessments, a last observation on treatment value was defined as the last non-missing post baseline value on or before the last dosing date before the patient was withdrawn from study treatment. Medical history and AEs were coded using the Medical Dictionary for Regulatory Activities, version 16.1. AEs and laboratory data were graded for toxicity according to

the Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

STATISTICAL ANALYSIS

The sample size was determined empirically, based on typical sample sizes used for similar studies of safety and biomarkers. Expected enrollment was 12 patients (10% dropouts). Data shown are from the combined 100-mg bid and 400-mg bid dose cohorts, with the exception of dose–response analyses.

All enrolled patients who received ≥1 dose of ARRY-371797 (PF-07265803) were evaluated for safety. All patients who had ≥1 post baseline efficacy assessment were evaluated for efficacy. For the primary efficacy endpoint of 6MWT at week 12, analysis was based on all observed data. In an additional analysis, missing 6MWT data at week 12 (due to patient dropout) were imputed using the last post baseline assessment carried forward. Change and percentage change in 6MWT distance at week 12 and associated 80% confidence interval (CI) were calculated. In a post hoc analysis, a Student's paired t test was employed for analysis of absolute 6MWT distances at 12, 24, 36, and 48 weeks vs baseline; and NT-proBNP concentration at 12, 24, 36, and 48 weeks vs baseline. To examine dose–response relationship, due to limited numbers of samples across dose/time point, change from baseline was analyzed by plotting the mean by patient across treatment times (weeks 4–48) by starting dose. Data for other endpoints were summarized descriptively (mean, standard deviation [SD], median, minimum, maximum).

SUPPLEMENTAL TABLE

Table SI. Adverse Events (Reported in >1 Patient or Reported as Grade 3/4)

Adverse Events, n	All grades	Grade 3/4
Stomatitis	3	0
Rash	2	1
Acne	2	0
Upper respiratory tract infection	2	0
Liver function test abnormal	2	1
Accidental overdose*	2	0
Musculoskeletal pain	1	1
Neck pain	1	1
Pyrexia	2	1
Dry eye	2	0
Atrial fibrillation	2	1
Cardiac failure	1	1
Congestive cardiomyopathy	1	1
Ventricular tachycardia	1	1

*Two patients each took 2 additional capsules during the study, 1 patient at week 36 and 1 patient at week 48.

SUPPLEMENTAL FIGURES

Figure SI. Change from baseline over time in 6-minute walk test (6MWT) distance with ARRY-371797 (PF-07265803) treatment, completers analysis. SD indicates standard deviation.

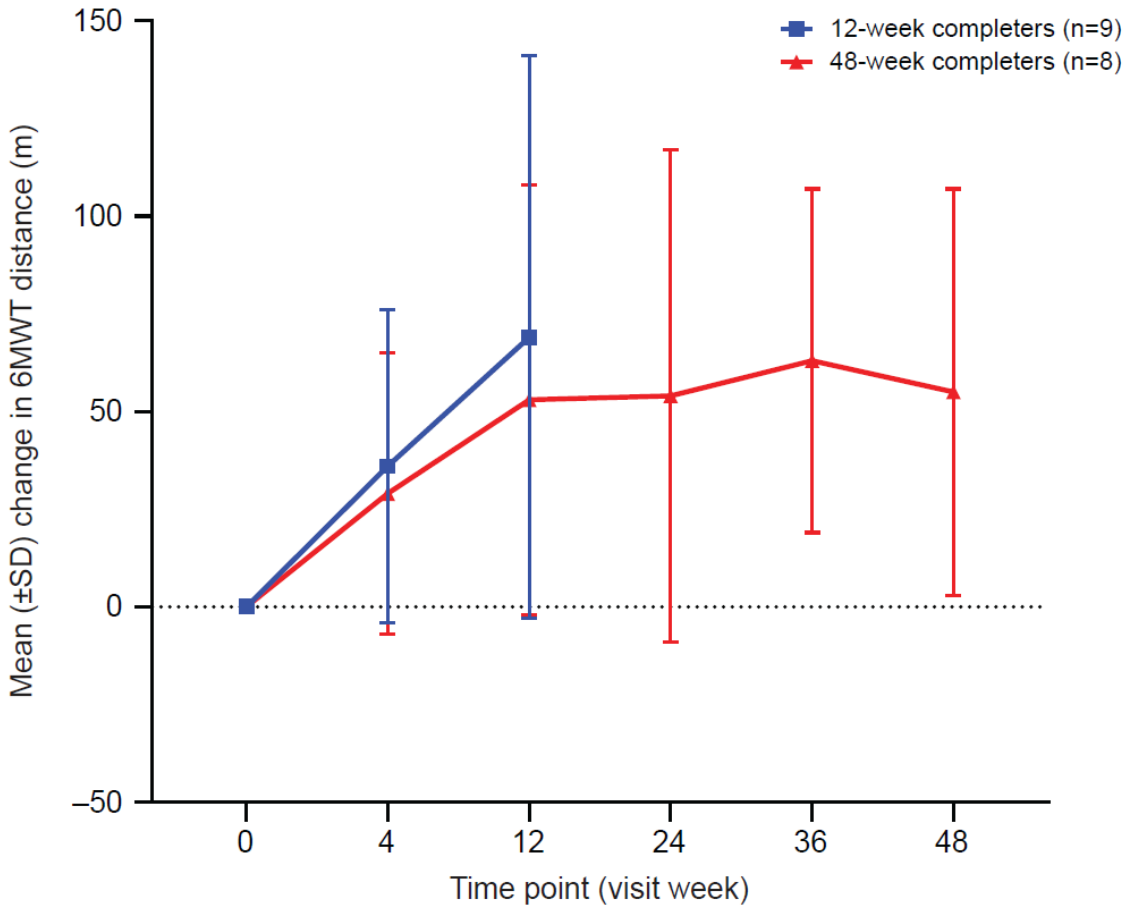

Figure SII. Mean percentage left ventricular ejection fraction (LVEF) and right ventricular fractional area (RVFA) over time with ARRY-371797 (PF-07265803) treatment. SD indicates standard deviation.

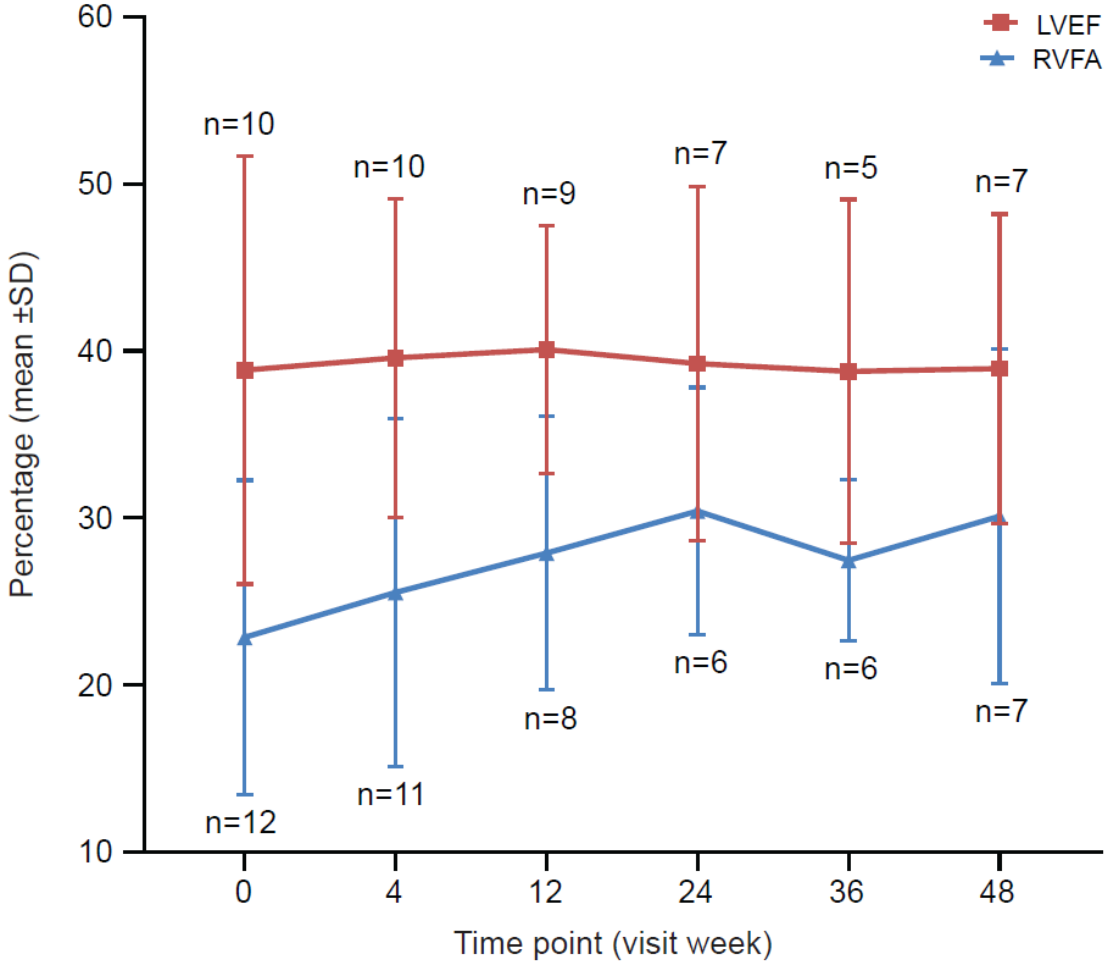

Figure SIII. Dose response for 6-minute walk test (6MWT) distance, N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration, and left ventricular ejection fraction (LVEF). For these analyses, the aggregated mean change from baseline for all time points for the efficacy endpoints (6MWT, NT-proBNP, and LVEF) by patient and dose was determined. Boxes show the interquartile range, and whiskers indicate the minimum and maximum values. bid indicates twice a day.