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SUPPLEMENTAL METHODS

Sample Size Estimation

Sample size estimation was initially determined based on a change from baseline in 6-minute walk test (6MWT) at week 12 from the completed phase 2 study (ClinicalTrials.gov identifier: NCT02057341). A sample size of 120 participants with New York Heart Association (NYHA) functional class II or III (60 patients per treatment arm) was calculated based on a 90% power to detect a mean difference of 35 m in change from baseline in 6MWT distance at week 12, assuming a standard deviation of 50 m, a 1.25% mortality rate up to week 12, and that 10% of patients would not have data recorded at week 12. In addition, it was planned that up to 40 NYHA class IV patients would be randomized for the evaluation of safety, including the composite outcome of worsening heart failure (WHF, defined as heart failure [HF]-related hospitalization or HF-related urgent care visit) or all-cause mortality.

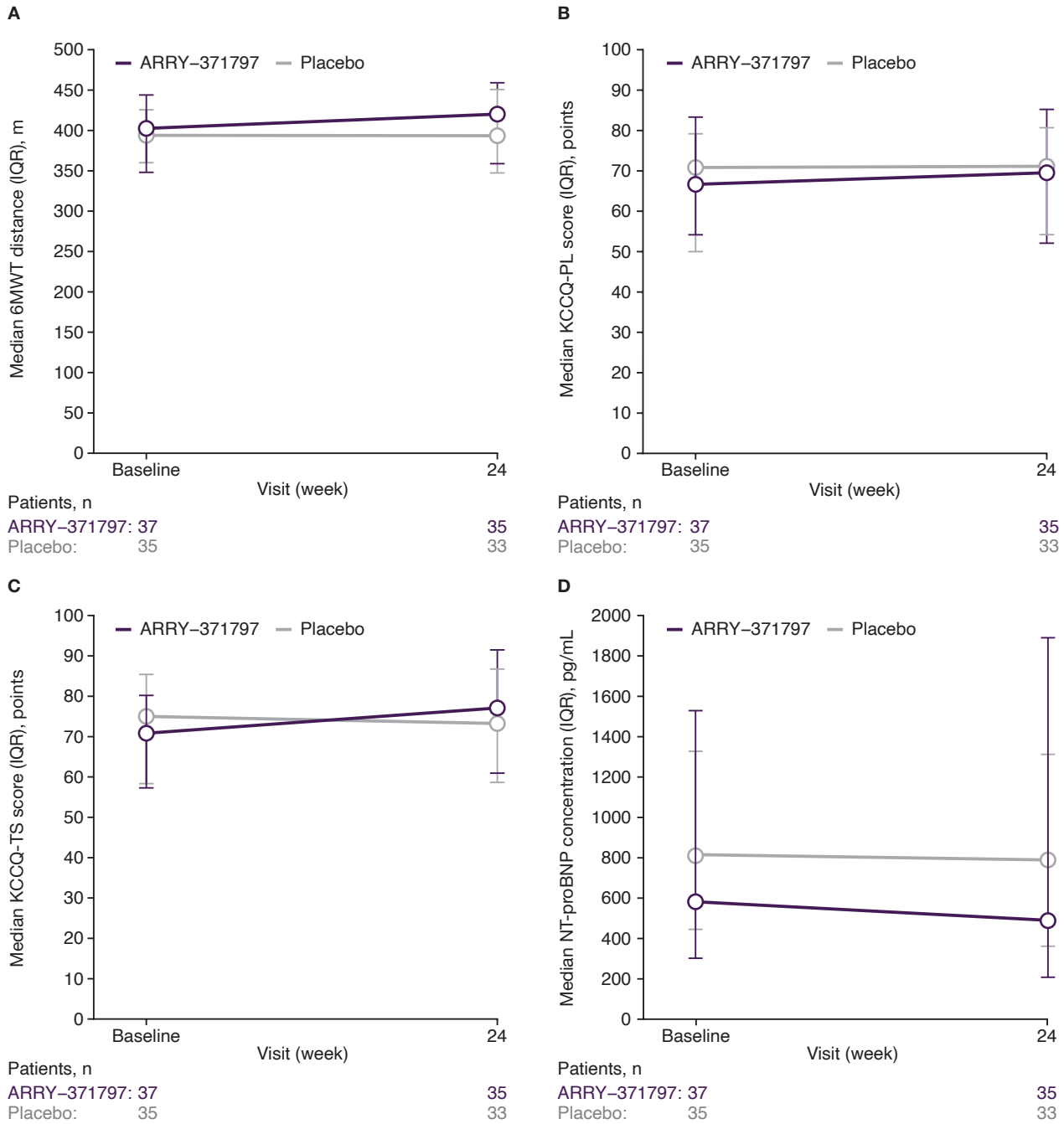
Interim analysis

As pre-specified in the protocol, an interim futility analysis of change from baseline in 6MWT at week 12 was performed after the first 60 randomized participants in NYHA functional class II or III had completed the week 12 assessment or discontinued from the study prior to week 12. At the time of the first interim futility analysis, the Data Monitoring Committee recommended continuing the study as designed. After the interim analysis described previously, a planned blinded sample size re-estimation for the primary outcome of change from baseline in 6MWT at week 24 was conducted by an internal review committee using blinded cumulative primary efficacy data from the interim data cohort. The sample size was increased to up to 200 eligible participants with symptomatic dilated cardiomyopathy due to an *LMNA* variant, including at

least 160 participants with NYHA functional class II or III (80 participants per treatment arm) and up to 40 participants with NYHA functional class IV.

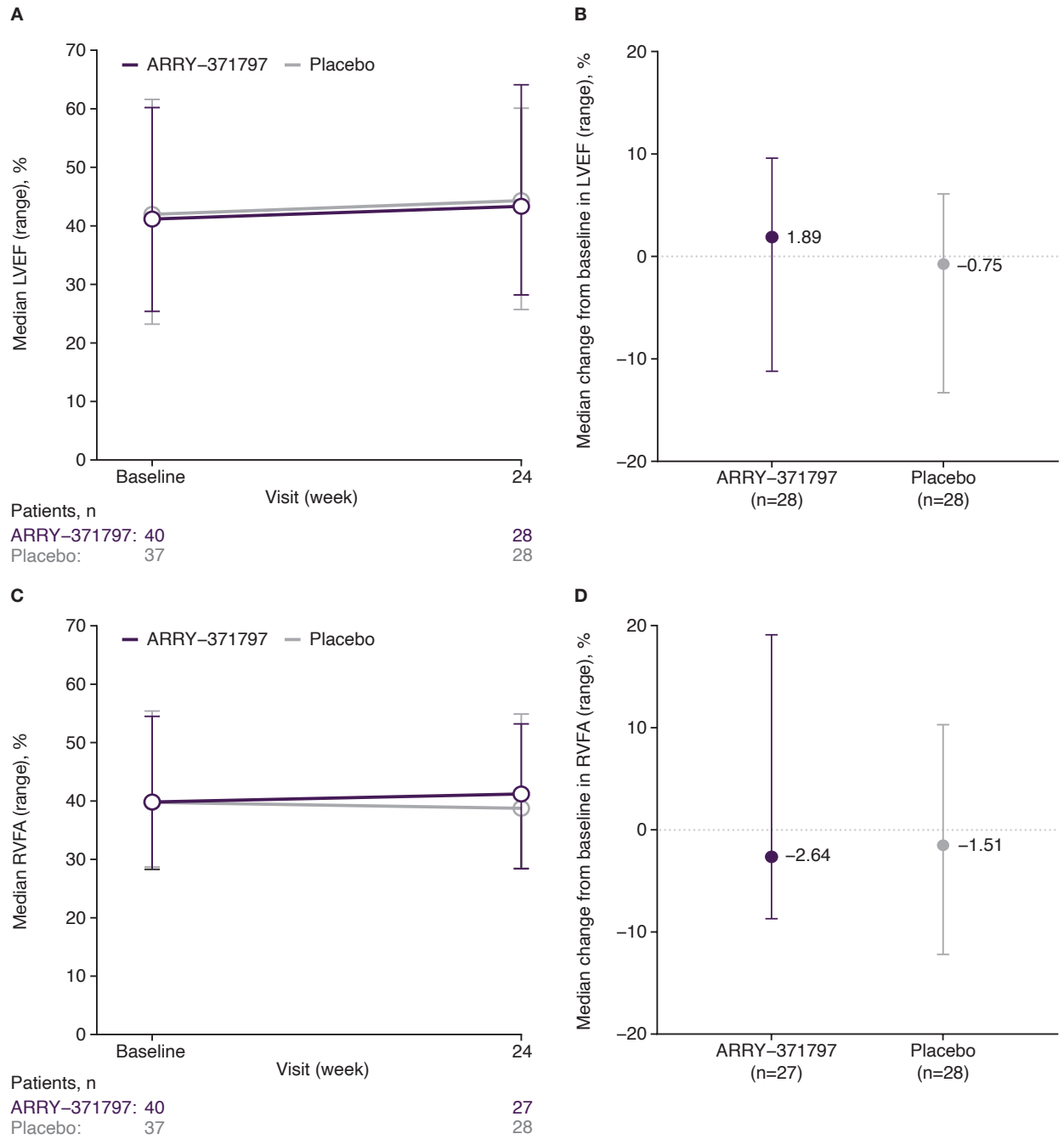
Given the change in timepoint of the primary outcome from 12 to 24 weeks and the longer-than-anticipated duration of the enrollment period, the sponsor conducted an additional interim futility analysis after the first 68 randomized participants in NYHA functional class II or III completed the week 24 assessment or discontinued before week 24. Futility was assessed based on change from baseline in 6MWT at week 24. Based on the results of the interim futility analysis, a decision was made by the sponsor to terminate the study due to the low conditional power for achieving the primary objective at the time of the final analysis (futility criteria were met).

Supplementary Figure S1. Median observed (A) 6MWT distance, (B) KCCQ-PL score, (C) KCCQ-TS score, and (D) NT-proBNP concentration from baseline to week 24.



Vertical bars indicate the IQR (25th and 75th percentile).
6MWT, 6-minute walk test; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PL, physical limitation; TS, total symptom.

Supplementary Figure S2. Observed median and median change from baseline in (A–B) LVEF and (C–D) RVFA at week 24 read by the central laboratory.



Vertical bars indicate the range (minimum and maximum value).
LVEF, left ventricular ejection fraction; RVFA, right ventricular fractional area.

Supplemental Tables

Supplementary Table S1. Concomitant Cardiovascular Medications by ATC Class and Preferred Term Taken at Any Time Alongside Study Treatment

	Concomitant	
	ARRY-371797	**Placebo**
n (%)	**(n=40)**	**(n=37)**
Any ATC class	**40 (100.0)**	**37 (100.0)**
Agents acting on the renin-angiotensin system	**36 (90.0)**	**34 (91.9)**
ARBs (other combinations)	24 (60.0)	20 (54.1)
ACE inhibitors	14 (35.0)	11 (29.7)
ARBs	4 (10.0)	11 (29.7)
ARBs and diuretics	0	1 (2.7)
Antihypertensive agents	**1 (2.5)**	**0**
Alpha-adrenoreceptor antagonists	1 (2.5)	0
Antithrombotic agents	**33 (82.5)**	**34 (91.9)**
Direct factor Xa inhibitors	22 (55.0)	22 (59.5)
Vitamin K antagonists	8 (20.0)	10 (27.0)
Platelet aggregation inhibitors, excluding heparin	6 (15.0)	9 (24.3)
Heparin group agents	4 (10.0)	6 (16.2)
Direct thrombin inhibitors	2 (5.0)	3 (8.1)
Enzyme*	1 (2.5)	0

Beta-blocking agents	**38 (95.0)**	**37 (100.0)**
Selective beta-blocking agents	27 (67.5)	27 (73.0)
Non-selective beta-blocking agents	10 (25.0)	5 (13.5)
Alpha- and beta-blocking agents	5 (12.5)	9 (24.3)
Calcium channel blockers	**3 (7.5)**	**1 (2.7)**
Dihydropyridine derivatives	3 (7.5)	0
Phenylalkylamine derivatives	0	1 (2.7)
Cardiac therapy	**20 (50.0)**	**14 (37.8)**
Antiarrhythmics		
Class IA	1 (2.5)	1 (2.7)
Class IB	4 (10.0)	5 (13.5)
Class III	15 (37.5)	13 (35.1)
Adrenergic and dopaminergic agents	2 (5.0)	4 (10.8)
Digitalis glycosides	2 (5.0)	1 (2.7)
Other cardiac preparations	2 (5.0)	0
Organic nitrates	0	1 (2.7)
Other cardiac stimulants	0	1 (2.7)
Other vasodilators used in cardiac disease	0	2 (5.4)
Phosphodiesterase inhibitors	0	1 (2.7)
Diuretics	**31 (77.5)**	**31 (83.8)**
Aldosterone antagonists	27 (67.5)	25 (67.6)
Loop diuretics (sulfonamides)	18 (45.0)	26 (70.3)

Thiazides	2 (5.0)	0
Lipid-modifying agents	**13 (32.5)**	**16 (43.2)**
HMG-CoA reductase inhibitors	12 (30.0)	16 (43.2)
Other lipid-modifying agents	4 (10.0)	1 (2.7)
Combinations of lipid-modifying agents	1 (2.5)	0
Fibrates	1 (2.5)	0

* The enzymes listed under the ATC code for (B01AD) included streptokinase, alteplase, anistreplase, urokinase, fibrinolysin, brinase, reteplase, saruplase, ancrod, drotrecogin alfa (activated), tenecteplase, and protein C.

Disease-relevant medications taken at any time alongside study treatment were classified by ATC classes (ATC Level 2) and preferred term (ATC Level 4). Patients can be counted once per ATC class but may have received medications under several preferred terms.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ATC, Anatomical Therapeutic Chemical.

Supplementary Table S2. Concomitant Procedures by Preferred Term During the Study

n (%)	ARRY-371797 (n=40)	Placebo (n=37)
Any concomitant procedure	16 (40.0)	17 (45.9)
Concomitant procedures in ≥5% of patients		
Investigations		
Colonoscopy	2 (5.0)	0
Cardiac catheterization	1 (2.5)	5 (13.5)
Echocardiogram*	0	2 (5.4)
Surgical and medical procedures		
Cardioversion	6 (15.0)	9 (24.3)
Implantable defibrillator replacement	5 (12.5)	2 (5.4)
Polypectomy	3 (7.5)	0
Cardiac ablation	1 (2.5)	3 (8.1)
Mitral valve repair	0	2 (5.4)
Other concomitant procedures of interest		
Cardiac device reprogramming	1 (2.5)	0
Cardiac resynchronization therapy	1 (2.5)	1 (2.7)
Atrial appendage closure	0	1 (2.7)
Heart transplant	0	1 (2.7)

* This refers to additional echocardiograms taken outside the study procedures for clinical care.

Serial transthoracic echocardiogram was protocoled.

Concomitant non-drug treatments or procedures were summarized as reported by the Principal Investigators in the clinical report forms.

Supplementary Table S3. PGI-S and PGI-C scores at week 24

n (%)	ARRY-371797 (n=40)	Placebo (n=37)
PGI-S	28 (70.0)	31 (83.8)
Over the past week, how would you describe the severity of your heart failure symptoms?		
None	4 (14.3)	6 (19.4)
Mild	11 (39.3)	10 (32.3)
Moderate	10 (35.7)	12 (38.7)
Severe	3 (10.7)	3 (9.7)
Very severe	0	0
Over the past week, how would you describe the severity of your physical activity limitations?		
None	6 (21.4)	6 (19.4)
Mild	5 (17.9)	7 (22.6)
Moderate	13 (46.4)	15 (48.4)
Severe	4 (14.3)	3 (9.7)
Very severe	0	0
PGI-C	28 (70.0)	29 (78.4)
Since you began taking medication on this clinical study, how would you describe the		

overall change (if any) in your heart failure symptoms?		
Very much better	1 (3.6)	1 (3.4)
Moderately better	3 (10.7)	2 (6.9)
A little better	7 (25.0)	6 (20.7)
No change	16 (57.1)	16 (55.2)
A little worse	0	2 (6.9)
Moderately worse	1 (3.6)	1 (3.4)
Very much worse	0	1 (3.4)
Since you began taking medication on this clinical study, how would you describe the overall change (if any) in your physical activity limitations?		
Very much better	1 (3.6)	1 (3.4)
Moderately better	3 (10.7)	0
A little better	3 (10.7)	4 (13.8)
No change	19 (67.9)	20 (69.0)
A little worse	1 (3.6)	3 (10.3)
Moderately worse	1 (3.6)	1 (3.4)
Very much worse	0	0

PGI-C, patient global impression of change; PGI-S, patient global impression of severity.

Supplementary Table S4. Serious TEAEs Reported in ≥1 Patient Regardless of Study Drug Relationship, by Primary System Organ Class and Preferred Term.

	All serious TEAEs		Serious and severe TEAEs*	
Patients, n (%)	**ARRY-371797 (n=40)**	**Placebo (n=37)**	**ARRY-371797 (n=40)**	**Placebo (n=37)**
Cardiac disorders				
Ventricular tachycardia	5 (12.5)	5 (13.5)	4 (10.0)	5 (13.5)
Ventricular fibrillation	2 (5.0)	3 (8.1)	2 (5.0)	2 (5.4)
Atrial fibrillation	1 (2.5)	2 (5.4)	1 (2.5)	1 (2.7)
Atrial flutter	1 (2.5)	1 (2.7)	1 (2.5)	1 (2.7)
Cardiac failure acute	1 (2.5)	2 (5.4)	1 (2.5)	2 (5.4)
Acute myocardial infarction	0	1 (2.7)	0	1 (2.7)
Cardiac failure	0	3 (8.1)	0	2 (5.4)
Cardiac failure congestive	0	1 (2.7)	0	1 (2.7)
Cardiogenic shock	0	1 (2.7)	0	1 (2.7)

Mitral valve incompetence	0	1 (2.7)	0	1 (2.7)
Ventricular arrhythmia	0	1 (2.7)	0	1 (2.7)
Gastrointestinal disorders				
Diarrhea	1 (2.5)†	0	1 (2.5)	0
Diarrhea hemorrhagic	1 (2.5)†	0	0	0
Gastrointestinal hemorrhage	1 (2.5)	0	1 (2.5)	0
Anal hemorrhage	0	1 (2.7)	0	1 (2.7)
Hepatobiliary disorders				
Biliary obstruction	1 (2.5)	0	1 (2.5)	0
Infections and infestations				
Gastroenteritis	1 (2.5)	0	1 (2.5)	0
Urinary tract infection	1 (2.5)	0	0	0
Urosepsis	1 (2.5)	0	1 (2.5)	0
Complicated appendicitis	0	1 (2.7)	0	1 (2.7)
Pneumonia bacterial	0	1 (2.7)	0	1 (2.7)

Injury, poisoning, and procedural complications				
Thoracic vertebral fracture	1 (2.5)	0	1 (2.5)	0
Investigations				
Ejection fraction decreased	1 (2.5)[†]	0	1 (2.5)	0
Musculoskeletal and connective tissue disorders				
Gouty arthritis	0	1 (2.7)	0	1 (2.7)
Neoplasms (benign, malignant, and unspecified)				
Papillary thyroid cancer	1 (2.5)	0	1 (2.5)	0
Prostate cancer	1 (2.5)	0	1 (2.5)	0
Nasal cavity cancer	0	1 (2.7)	0	0
Nervous system disorders				
Ischemic stroke	1 (2.5)	0	1 (2.5)	0

Cerebrovascular accident	0	1 (2.7)	0	1 (2.7)
Renal and urinary disorders				
Acute kidney injury	1 (2.5)	1 (2.7)	1 (2.5)	1 (2.7)
Reproductive system and breast disorders				
Prostatitis	0	1 (2.7)	0	1 (2.7)
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	0	1 (2.7)	0	1 (2.7)
Skin and subcutaneous tissue disorders				
Urticaria	1 (2.5)†	0	1 (2.5)	0

TEAEs were events that occurred on or after the first study drug dose and up to 30 days after the last dose.

* Serious TEAEs with grade ≥3. A patient is counted once within each preferred term and system organ class using the maximum grade observed (between grades 3, 4, or 5).

† Serious TEAEs (ARRY-371797 [n=4], placebo [n=0]) that were assessed as related to treatment.

TEAE, treatment-emergent adverse event.