ORIGINAL ARTICLE

REALM-DCM: A Phase 3, Multinational, Randomized, Placebo-Controlled Trial of ARRY-371797 in Patients With Symptomatic *LMNA*-Related Dilated Cardiomyopathy

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BACKGROUND: *LMNA* (*lamin A/C*)-related dilated cardiomyopathy is a rare genetic cause of heart failure. In a phase 2 trial and long-term extension, the selective p38α MAPK (mitogen-activated protein kinase) inhibitor, ARRY-371797 (PF-07265803), was associated with an improved 6-minute walk test at 12 weeks, which was preserved over 144 weeks.

METHODS: REALM-DCM (NCT03439514) was a phase 3, randomized, double-blind, placebo-controlled trial in patients with symptomatic *LMNA*-related dilated cardiomyopathy. Patients with confirmed *LMNA* variants, New York Heart Association class II/III symptoms, left ventricular ejection fraction ≤50%, implanted cardioverter-defibrillator, and reduced 6-minute walk test distance were randomized to ARRY-371797 400 mg twice daily or placebo. The primary outcome was a change from baseline at week 24 in the 6-minute walk test distance using stratified Hodges-Lehmann estimation and the van Elteren test. Secondary outcomes using similar methodology included change from baseline at week 24 in the Kansas City Cardiomyopathy Questionnaire-physical limitation and total symptom scores, and NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentration. Time to a composite outcome of worsening heart failure or all-cause mortality and overall survival were evaluated using Kaplan-Meier and Cox proportional hazards analyses.

RESULTS: REALM-DCM was terminated after a planned interim analysis suggested futility. Between April 2018 and October 2022, 77 patients (aged 23–72 years) received ARRY-371797 (n=40) or placebo (n=37). No significant differences (*P*>0.05) between groups were observed in the change from baseline at week 24 for all outcomes: 6-minute walk test distance (median difference, 4.9 m [95% CI, −24.2 to 34.1]; *P*=0.82); Kansas City Cardiomyopathy Questionnaire-physical limitation score (2.4 [95% CI, −6.4 to 11.2]; *P*=0.54); Kansas City Cardiomyopathy Questionnaire-total symptom score (5.3 [95% CI, −4.3 to 14.9]; *P*=0.48); and NT-proBNP concentration (−339.4 pg/mL [95% CI, −1131.6 to 452.7]; *P*=0.17). The composite outcome of worsening heart failure or all-cause mortality (hazard ratio, 0.43 [95% CI, 0.11–1.74]; *P*=0.23) and overall survival (hazard ratio, 1.19 [95% CI, 0.23–6.02]; *P*=0.84) were similar between groups. No new safety findings were observed.

CONCLUSIONS: Findings from REALM-DCM demonstrated futility without safety concerns. An unmet treatment need remains among patients with *LMNA*-related dilated cardiomyopathy.

REGISTRATION: URL: https://classic.clinicaltrials.gov; Unique Identifiers: NCT03439514, NCT02057341, and NCT02351856.

Key Words: ARRY-371797 ■ cardiomyopathy, dilated ■ heart failure ■ lamin type A ■ walk test

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WHAT IS NEW?

- REALM-DCM was the first phase 3, randomized, controlled, interventional trial of a disease-modifying therapy in patients with *LMNA* (*lamin A/C*)-related dilated cardiomyopathy.
- The trial was terminated early after a planned interim analysis suggested futility.

WHAT ARE THE CLINICAL IMPLICATIONS?

- An unmet treatment need remains among patients with *LMNA*-related dilated cardiomyopathy. Despite the early termination, the data gathered from REALM-DCM are valuable by forming the largest prospective data set to characterize *LMNA*-related dilated cardiomyopathy to date.
- Findings from this study can potentially contribute to the development and design of future genetically informed clinical trials for *LMNA*-related cardiomyopathy and other rare cardiovascular diseases.

Nonstandard Abbreviations and Acronyms

6MWT	6-minute walk test
AE	adverse event
BID	twice daily
DCM	dilated cardiomyopathy
HF	heart failure
HR	hazard ratio
IQR	interquartile range
KCCQ	Kansas City Cardiomyopathy Questionnaire
***LMNA*-DCM**	*lamin A/C*-related dilated cardiomyopathy
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PL	physical limitation
TEAE	treatment-emergent adverse event
TS	total symptom

*L*MNA (*lamin A/C*)-related dilated cardiomyopathy (DCM) is a life-threatening condition arising from penetrant *LMNA* gene variants that are inherited in an autosomal dominant pattern.[1] The estimated prevalence of DCM is 1:250 to 1:2500, with ≈35% of cases being familial.[2,3] Among adult-onset DCM cases, *LMNA* variants have been identified in ≈0.5% to 5% of patients and are associated with a high risk of arrhythmias and progression to heart failure (HF).[2,4,5] The typical onset of *LMNA*-related DCM is around 30 to 40 years, commonly presenting with atrioventricular conduction disease and atrial arrhythmias that later progress to DCM, ventricular arrhythmias that are poorly correlated with left ventricular ejection fraction (LVEF), and refractory HF. Sudden cardiac death may be the presenting symptom in some patients.[6–8] One study showed that, by the age of 45 years, 69% of patients with symptomatic *LMNA*-related DCM had experienced a major cardiac event, received a heart transplant, or died.[9]

The exact pathophysiologic mechanisms of *LMNA*-related DCM are unclear, but cellular stress and hyperactivation of the p38 MAPK (mitogen-activated protein kinase) pathway have been observed in animal models and in biopsies from the hearts of patients with *LMNA*-related DCM.[10,11] There are currently no disease-specific therapies for these patients.[12] Current treatment recommendations rely on symptomatic management with guideline-directed medical therapy and disease-specific primary prevention of sudden cardiac death. However, in limited studies, the efficacy of even maximal guideline-directed medical therapy has been suboptimal in *LMNA*-related DCM, revealing an unmet clinical need.[13,14]

ARRY-371797 (also known as PF-07265803) is a potent and selective oral p38α MAPK inhibitor previously hypothesized as a potential treatment for *LMNA*-related DCM. In a completed 48-week, open-label, nonrandomized, phase 2 trial (NCT02057341) of 12 patients with New York Heart Association (NYHA) class II/III symptomatic *LMNA*-related DCM, treatment with ARRY-371797 (400 or 100 mg twice daily [BID]; pooled) was associated with significant improvement in functional capacity (assessed in the 6-minute walk test [6MWT]), reduction in NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentration, and stable LVEF at 12 weeks.[12,15] The improvements in 6MWT distance and reductions in NT-proBNP concentration were maintained in 8 patients who were treated continuously for up to 144 weeks in a long-term extension study (NCT02351856).[16,17] Furthermore, no major side effects were associated with ARRY-371797 treatment.[12,15–17]

This article reports the findings of a subsequent multicenter, randomized, double-blind, placebo-controlled, phase 3 study (REALM-DCM [NCT03439514]) investigating the efficacy and safety of ARRY-371797 in patients with symptomatic *LMNA*-related DCM.

METHODS

The REALM-DCM study protocol was approved by the independent review board or ethics committee at each participating site and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization–Good Clinical Practice guidelines. All patients provided written, informed consent. An independent end point adjudication committee, whose members were unaware of the trial group assignments, determined whether investigator-reported events met the definition of HF-related hospitalizations or urgent care visits.

Patients

Adult patients (≥18 years of age) were eligible to participate in REALM-DCM if they had symptomatic *LMNA*-related DCM with decreased LVEF ≤50% by echocardiography (adjudicated centrally, with or without LV dilatation); carried a confirmed *LMNA* variant categorized as pathogenic, likely pathogenic, or of uncertain significance but with a phenotype highly suggestive of *LMNA*-related DCM as assessed by the Investigator; NYHA functional class II/III HF symptoms that were stable for ≥3 months; reduced 6MWT distance (>100 to ≤450 m at screening and >100 to ≤485 m at day −1 and baseline); stable medical and device therapy consistent with regional guidelines[18,19]; and an implantable cardioverter-defibrillator implanted ≥4 weeks before initiation of study intervention. Upon protocol amendment, implantable cardioverter-defibrillator devices were required to have pacing capabilities, or a pacing-capable co-implant must have been present. The phenotypes of patients carrying *LMNA* variant of uncertain significance were assessed, and eligibility was confirmed by the investigators. Although patients with NYHA functional class IV HF symptoms were eligible to participate in this study, none were enrolled.

Patients were excluded if they met any of the following criteria: other forms of cardiomyopathy contributing to HF; clinically significant coronary artery disease; non-HF−related primary structural valvular disease; receiving intravenous inotrope therapy; initiation of cardiac resynchronization therapy in the prior 6 months before the initiation of study intervention; a history of heart transplantation or anticipated heart transplantation in the next 6 months; implantation of a ventricular assist device; myocardial infarction or cardiac surgical procedures in the 3 months before screening; anticipated to require renal replacement therapy within 6 months; or a life span−limiting (<1 year) noncardiac condition; an underlying condition that may impact the ability of the 6MWT to reflect changes in cardiovascular function (eg, orthopedic conditions that limit a patient's walking abilities, significant musculoskeletal pathology, or any other condition that limits a patient's performance on the 6MWT independently from their cardiomyopathy as assessed by the Investigator).

Treatment

Enrolled patients were randomized (1:1) to ARRY-371797 400-mg oral tablets BID or matching placebo, stratified by baseline 6MWT distance (average of day −1 and baseline: <320 or ≥320 m) and *LMNA* variant type (phenotype/likely pathogenic or, after protocol amendment, variant of uncertain significance). Throughout the study, dose reductions to 200 mg BID, or further to 100 mg BID, were allowed if the patient had safety or tolerability issues. The patient received all subsequent treatment at the reduced dose unless interruption or discontinuation of the study drug was warranted.

Outcomes and Statistical Analysis

Based on the findings from a planned interim futility analysis conducted on data from the first 68 randomized patients who completed week 24 or discontinued before week 24, the sponsor decided to terminate the study in August 2022 due to low conditional power to achieve the primary objective at the time of the final analysis.[20] All ongoing patients discontinued treatment, attended a discontinuation visit, and underwent a subsequent safety follow-up visit 30 days later. The initial primary efficacy outcome was a change from baseline in 6MWT distance at week 12. The calculation of the initial sample size and expected effect size is described in the Supplemental Methods. Based on regulatory feedback, this was amended to week 24 in a blinded manner without alpha spending. The van Elteren test was used to assess the difference between ARRY-371797 and placebo groups stratified by baseline 6MWT quartiles. Patients who died before week 24 were given the lowest rank (from shortest to longest survival), followed by patients who discontinued from the study for any reason before week 24 (ordered based on their time to study discontinuation). For patients who remained in the trial at or beyond week 24 and had a missing assessment, missing values were imputed using the Markov chain Monte Carlo multiple imputation method. Treatment effect was estimated using the stratified Hodges-Lehmann method by baseline 6MWT quartiles based on patients who survived to week 24. For patients who discontinued before week 24 due to postrandomization events (eg, adverse events), missing values were imputed using copy-reference multiple imputation, assuming similarity between treatment groups.

Secondary efficacy outcomes included change from baseline at week 24 in the Kansas City Cardiomyopathy Questionnaire (KCCQ)-physical limitation (PL) and total symptom (TS) scores and NT-proBNP concentration, all analyzed with the same methodology as the primary outcome but with the van Elteren test stratified by baseline KCCQ-PL or TS scores or NT-proBNP concentration, respectively. Patient global impression of severity and change were summarized descriptively. Exploratory efficacy outcomes included the observed change from baseline in LVEF and right ventricular fractional area at week 24 assessed by echocardiography and read by a central laboratory.

Cardiovascular safety was assessed using a composite outcome of time-to-first event of adjudicated worsening heart failure (WHF), defined as HF-related hospitalization or urgent care visit, or all-cause mortality. Overall survival was also assessed. The composite outcome and overall survival were summarized using the Kaplan-Meier method. Hazard ratio (HR) was estimated using the Cox proportional hazards model stratified by baseline NYHA functional class (II or III) and 6MWT distance (<320 or ≥320 m) and included treatment arm as a covariate. Safety outcomes also included the incidence and severity of treatment-emergent adverse events (TEAEs).

Materials and Data Availability

Upon reasonable request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

RESULTS

Patients

In REALM-DCM, 485 patients suspected of having *LMNA*-related DCM were prospectively consented

to and prescreened. The main reasons for prescreen and screen failures were the absence of an eligible *LMNA* variant (n=283, 58%) and asymptomatic status (defined as NYHA functional class I [n=125; 26%]). Between April 2018 and October 2022, 77 patients (ARRY-371797 [n=40], placebo [n=37]) aged 23 to 72 years with NYHA functional class II/III HF symptoms were enrolled at 31 sites in 6 countries (Figure 1; Table 1). Overall, baseline characteristics and demographics between the 2 treatment groups were broadly similar. Most of the enrolled patients were male (57%), White (96%), and carried a known phenotype or likely pathogenic *LMNA* variant (88%) or a variant of uncertain significance (12%). Of the 77 enrolled patients, 75 had *LMNA* variants with DNA sequence data determined by the central laboratory (ARRY-371797 [n=39], placebo [n=36]). In the ARRY-371797-treated group, 56% of patients (n=22/39) had a missense *LMNA* variant, and 44% (n=17/39) had a nonmissense variant. Respective proportions in the placebo group were 53% (n=19/36) and 47% (n=17/36; Table 2). Nonmissense variants included nonsense (ARRY-371797 [23%, n=9] versus placebo [17%, n=6]), frameshift (15% [n=6] versus 14% [n=5]), splice acceptor (3% [n=1] versus 14% [n=5]), and silent (3% [n=1] in each group) changes (Table 2). Baseline comorbidities included atrial fibrillation (ARRY-371797 58% [n=23] versus placebo 62% [n=23]), atrial flutter (10% [n=4] versus 8% [n=3]), and complete atrioventricular block (10% [n=4] versus 3% [n=1]).

The medications relevant to the management of *LMNA*-related DCM taken by patients at any time alongside study treatment (concomitant) are presented in Table S1. Most notably, nearly all patients were concomitantly receiving a beta-blocker (ARRY-371797 [95%] versus placebo [100%]), a renin-angiotensin system-acting agent (90% versus 92%), or an antithrombotic agent (either an antiplatelet agent or anticoagulant: 83% versus 92%). During the study, 40% of patients in the ARRY-371797 group and 46% in the placebo group were reported to have received a concomitant procedure (Table S2), including cardioversion (ARRY-371797 [15%] versus placebo [24%]), implantable defibrillator replacement (13% versus 5%), or cardiac ablation (3% versus 8%).

Primary Efficacy Outcome: Change From Baseline in 6MWT Distance at Week 24

Five participants (ARRY-371797 [n=3], placebo [n=2]) discontinued the study before week 24 due to the sponsor's decision to terminate the study for futility and were excluded from the primary analysis. Of the 72 patients included in the primary analysis, 4 died (2 in each treatment group). Four discontinued from the study (ARRY-371797 [n=3], placebo [n=1]) for reasons other than death before week 24, and the values for these patients were imputed.

The median observed 6MWT distance at baseline and week 24 is plotted in Figure S1. The median change from baseline in 6MWT distance at week 24 was 21 m (95% CI, −22.8 to 51.5) in the ARRY-371797 group and 3 m (95% CI, −11.5 to 33.7) in the placebo group (Figure 2A). No significant difference between groups was found in the van Elteren rank-sum test (2-sided *P*=0.82). The treatment difference, as calculated using the Hodges-Lehmann estimation, was 4.9 m (95% CI, −24.2 to 34.1).

Secondary Efficacy Outcomes

The median observed KCCQ-PL score, KCCQ-TS score, and NT-proBNP concentration at baseline and week 24 are plotted in Figure S1. The median change from baseline at week 24 in the ARRY-371797 and placebo groups is plotted in Figure 2B through 2D. For all 3 outcomes, no significant differences between treatment groups were found in the van Elteren rank-sum test (2-sided *P* values: KCCQ-PL 0.54; KCCQ-TS 0.48; NT-proBNP 0.17). Treatment differences, as calculated using the Hodges-Lehmann estimation of treatment effect, were 2.4 points (95% CI, −6.4 to 11.2), 5.3 points (95% CI, −4.3 to 14.9), and −339.4 pg/mL (95% CI, −1131.6 to 452.7), respectively (Figure 2B through 2D).

In the patient global impression survey at week 24, 75% of patients in the ARRY-371797 group and 71% in the placebo group reported mild to moderate HF symptom severity (Table S3), whereas 11% and 10%, respectively, reported severe symptoms. When considering change since the start of the study, 39% of ARRY-371797-treated and 31% of placebo-treated patients reported overall improvement in their HF symptoms ("a little better" to "very much better"), whereas 4% versus 7% reported worsening ("moderately" to "very much" worse) at week 24.

Exploratory Efficacy Outcomes: Change From Baseline in LVEF and Right Ventricular Fractional Area at Week 24

The observed median changes from baseline (range) in LVEF at week 24 were 1.9% (−11.2% to 9.6%) in the ARRY-371797 group and −0.8% (−13.3% to 6.1%) in the placebo group. The respective observed median (range) changes from baseline in the right ventricular fractional area were −2.6% (−8.7% to 19.1%) and −1.5% (−12.2% to 10.3%; Figure S2).

Safety Outcomes

Patients were treated with ARRY-371797 for a median (range) of 37.6 (0.1−182.1) weeks or placebo for 50.1
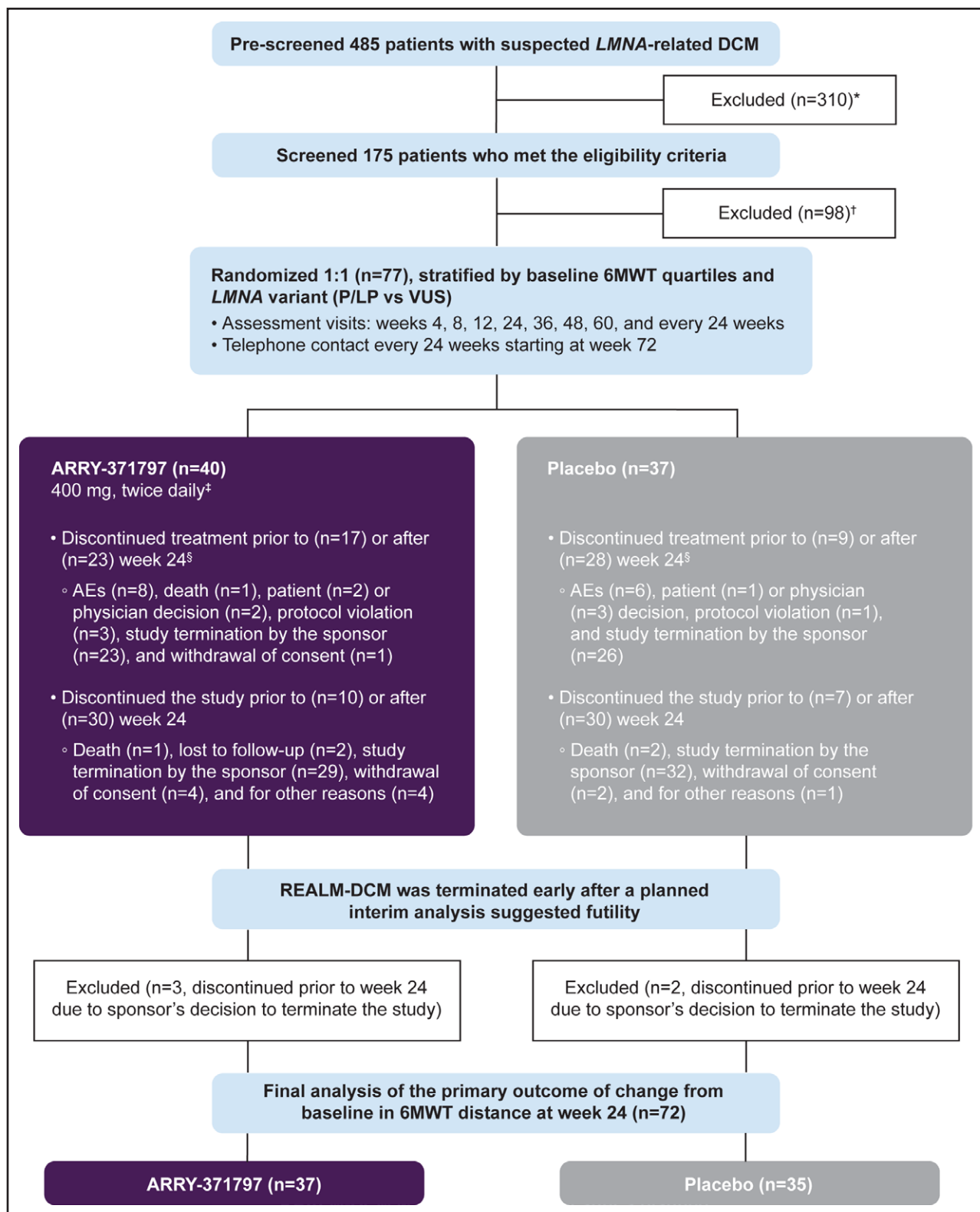
Figure 1. Study design and patient disposition.

6MWT indicates 6-minute walk test; AE, adverse event; BID, twice daily; DCM, dilated cardiomyopathy; KCCQ, Kansas City Cardiomyopathy Questionnaire; *LMNA*, lamin A/C; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PL, physical limitation; and TS, total symptom. *Prescreen failure included patients who signed the prescreening informed consent but did not sign the main study informed consent. †Screen failure included patients who signed the prescreening and main study informed consent but were not subsequently randomized. ‡Dose reduction for safety or tolerability were allowed throughout this study. The ARRY-371797 400 mg BID dose could be reduced to 200 mg BID and subsequently to 100 mg BID if necessary. §Patients who discontinued treatment can stay in the study for additional follow-up.

Table 1. Baseline Demographics and Clinical Characteristics

	ARRY-371797, n=40	Placebo, n=37
Age, y		
Mean (SD)	49.6 (12.0)	54.8 (9.5)
Median (range)	51.0 (23.0–72.0)	54 (24.0–69.0)
Sex, n (%)		
Female	18 (45.0)	15 (40.5)
Male	22 (55.0)	22 (59.5)
Race, n (%)		
White	38 (95.0)	36 (97.3)
Asian	2 (5.0)	0
Black or African American	0	1 (2.7)
Region, n (%)*		
North America	16 (40.0)	12 (32.4)
Europe	24 (60.0)	25 (67.6)
BMI, kg/m²		
Mean (SD)	26.7 (6.5)†	28.2 (6.5)‡
Median (range)	26.1 (16.4–44.1)†	26.4 (19.1–44.2)‡
6MWT distance		
Mean (SD), m	388.1 (66.3)	378.5 (66.3)
Median (range), m	407.1 (237.9–480.5)	393.9 (173.0–464.9)
<320 m, n (%)	8 (20.0)	5 (13.5)
NYHA class, n (%)		
II	33 (82.5)	28 (75.7)
III	7 (17.5)	9 (24.3)
LMNA variant pathogenicity, n (%)		
P/LP	35 (87.5)	33 (89.2)
VUS	5 (12.5)	4 (10.8)
LVEF§		
Mean (SD), %	41.8 (9.9)	41.3 (10.1)
Median (range), %	41.2 (25.4–60.2)	42.0 (23.2–61.6)
<35%, n (%)	11 (27.5)	11 (29.7)
RVFA, %		
Mean (SD)	40.1 (6.8)	39.9 (6.0)
Median (range)	39.8 (28.3–54.5)	39.8 (28.7–55.4)
NT-proBNP, pg/mL		
Mean (SD)	1120.3 (1042.8)	1385.4 (1297.5)
Median (range)	723.6 (56.8–4533.9)	883.0 (142.4–5248.3)
Creatinine clearance, mL/min		
Mean (SD)	122.1 (51.4)	119.7 (54.5)‖
Median (range)	108.5 (61.0–276.0)	105.5(38.0–250.0)‖
Troponin I, µg/L		
Mean (SD)	0.3 (0.1)¶	0.3 (0.1)#
Median (range)	0.3 (0.3–1.2)¶	0.3 (0.3–0.8)#
KCCQ score, points		
Mean (SD)		
PL	65.1 (21.0)	64.4 (23.3)
TS	70.0 (18.5)	71.3 (18.7)
Median (range)		
PL	66.7 (12.5–95.0)	70.8 (12.5–100.0)
TS	72.4 (19.8–100.0)	75.0 (29.2–100.0)

(Continued)

Table 1. Continued

	ARRY-371797, n=40	Placebo, n=37
Treatment duration, weeks		
Mean (SD)	54.7 (53.7)	68.2 (53.9)
Median (range)	37.6 (0.1–182.1)	50.1 (2.0–208.0)

6MWT indicates 6-minute walk test; BMI, body mass index; KCCQ, Kansas City Cardiomyopathy Questionnaire; LP, likely pathogenic; NT-proBNP, N-terminal pro-B-type natriuretic peptide; P, pathogenic; PL, physical limitation; RVFA, right ventricular fractional area; TS, total symptom; and VUS, variant of uncertain significance.

*Patients were from 6 different countries: Belgium, Canada, Italy, Spain, United Kingdom, and United States.

†ARRY-371797, n=39.

‡Placebo, n=37.

§Patients were enrolled with local laboratory readings, which may not always match with the central laboratory reading summarized here.

‖Placebo, n=36.

¶ARRY-371797, n=38.

#Placebo, n=35.

(2.0–208.0) weeks (Table 1). Kaplan-Meier and Cox proportional hazard analyses showed no significant difference in the composite outcome of first WHF or all-cause mortality in the ARRY-371797 (no WHF, 3 deaths) and placebo (6 WHF, 1 death) groups. The composite HR (ARRY-371797 versus placebo) was 0.43 ([95% CI, 0.11–1.74]; P=0.23; Figure 3A). Throughout the study, 3 deaths were reported in each group, with an HR for all-cause mortality of 1.19 ([95% CI, 0.23–6.02]; P=0.84; Figure 3B). No deaths were considered by the investigator to be related to the study drug. The reported causes of death in the ARRY-371797 group were pancreatic neoplasia, ventricular tachycardia, and anoxic brain injury from sequelae of primary graft dysfunction after heart transplantation due to refractory ventricular arrythmias, and in the placebo group, bacterial pneumonia, respiratory failure, and disease progression.

The overall safety profile of ARRY-371797 was similar to that observed in previous studies of the drug.[12,16] Dose reductions for any reason (28% versus 8%) and due to TEAEs (13% versus 3%) were more common in patients treated with ARRY-371797 versus placebo. Excluding patients who discontinued due to termination of the study by the sponsor, a higher proportion of patients treated with ARRY-371797 versus placebo discontinued from the study (28% versus 14%) and from the study drug (43% versus 30%; Table 3). Sixty-nine patients reported TEAEs, including 88% (35/40) in the ARRY-371797 group and 92% (34/37) in the placebo group (Table 3). The most commonly reported TEAEs in the placebo versus ARRY-371797 group were ventricular tachycardia (30% versus 20%), SARS-CoV-2 test positive (19% versus 28%), and dyspnea (19% versus 3%). The most commonly reported TEAEs in the ARRY-371797 versus placebo group were diarrhea (30% versus 11%), SARS-CoV-2 test positive, and dizziness (23% versus 11%). Patients treated with ARRY-371797 reported fewer serious (25% versus 57%) or severe (≥grade 3: 40%

Table 2. *LMNA* Variants as Determined by the Central Laboratory

LMNA variant type	CDS change	Protein change	Pathogenicity	ARRY-371797, n=39*	Placebo, n=36†
Missense				22 (56.4)	19 (52.8)
	c.1A>T	p.Met1Ile	P	1 (2.6)	1 (2.8)
	c.3G>C	p.Met1Ile	P	0	1 (2.8)
	c.481G>A	p.Glu161Lys	P	1 (2.6)	1 (2.8)
	c.568C>T	p.Arg190Trp	P	1 (2.6)	0
	c.1072G>A	p.Glu358Lys	P	0	1 (2.8)
	c.1621C>T	p.Arg541Cys	P	1 (2.6)	0
	c.82C>T	p.Arg28Trp	LP	1 (2.6)	1 (2.8)
	c.253C>G	p.Leu85Val	LP	1 (2.6)	1 (2.8)
	c.274C>T	p.Leu92Phe	LP	1 (2.6)	0
	c.418_438dup	p.Leu140_Ala146dup	LP	2 (5.1)	0
	c.497G>C	p.Arg166Pro	LP	1 (2.6)	0
	c.569G>A	p.Arg190Gln	LP	3 (7.7)	1 (2.8)
	c.618C>G	p.Phe206Leu	LP	1 (2.6)	0
	c.646C>T	p.Arg216Cys	LP	0	2 (5.6)
	c.710T>C	p.Phe237Ser	LP	0	1 (2.8)
	c.949G>A	p.Glu317Lys	LP	1 (2.6)	1 (2.8)
	c.992G>A	p.Arg331Gln	LP	0	2 (5.6)
	c.1129C>T	p.Arg377Cys	LP	1 (2.6)	1 (2.8)
	c.1130G>A	p.Arg377His	LP	0	2 (5.6)‡
	c.1318G>A	p.Val440Met	LP	0	1 (2.8)
	c.1412G>A	p.Arg471His	LP	1 (2.6)	0
	c.99G>T	p.Glu33Asp	VUS	0	1 (2.8)
	c.238G>T	p.Ala80Ser	VUS	0	1 (2.8)
	c.250G>A	p.Glu84Lys	VUS	1 (2.6)	0
	c.356G>C	p.Arg119Pro	VUS	1 (2.6)	0
	c.1567G>A	p.Gly523Arg	VUS	1 (2.6)	0
	c.1634G>A	p.Arg545His	VUS	2 (5.1)	0
Nonmissense				17 (43.6)	17 (47.2)
Nonsense				9 (23.1)	6 (16.7)
	c.673C>T	p.Arg225Ter	P	2 (5.1)	0
	c.961C>T	p.Arg321Ter	P	2 (5.1)	3 (8.3)
	c.1541G>A	p.Trp514Ter	P	1 (2.6)	0
	c.65C>A	p.Ser22Ter	LP	1 (2.6)	1 (2.8)
	c.243C>G	p.Tyr81Ter	LP	1 (2.6)	0
	c.339dupT	p.Lys114Ter	LP	1 (2.6)	0
	c.619C>T	p.Gln207Ter	LP	0	1 (2.8)
	c.1294C>T	p.Gln432Ter	LP	1 (2.6)	0
	c.1330G>T	p.Glu444Ter	LP	0	1 (2.8)
Frameshift				6 (15.4)	5 (13.9)
	c.958delC	p.Leu320fs	P	1 (2.6)	0
	c.1397delA	p.Asn466IlefsTer14	P	1 (2.6)	0
	c.240delC	p.Tyr81fs	LP	0	2 (5.6)
	c.571del	p.Val191fs	LP	1 (2.6)	1 (2.8)
	c.814_815delGA	p.Asp272fs	LP	0	1 (2.8)
	c.1248delC	p.Lys418SerfsTer62	LP	1 (2.6)	0
	c.1276_1277delAG	p.Ser426ProfsTer11	LP	1 (2.6)	0
	c.1304_1307dupGCAC	p.Ser437fs	LP	1 (2.6)	0

(*Continued*)

Table 2. **Continued**

LMNA variant type	CDS change	Protein change	Pathogenicity	ARRY-371797, n=39*	Placebo, n=36†
	c.1489_1506delinsG	p.Ile497GlyfsTer49	LP	0	1 (2.8)
Splice acceptor				1 (2.6)	5 (13.9)
	c.357-2A>G		P	0	2 (5.6)
	c.1609-1G>A		P	1 (2.6)	0
	c.1158-1G>A		LP	0	1 (2.8)
	c.1489-1G>C		LP	0	1 (2.8)
	c.1969-1G>T		VUS	0	1 (2.8)
Silent				1 (2.6)	1 (2.8)
	c.1146C>T	p.Gly382Gly	LP	1 (2.6)	1 (2.8)

Values are n (%). Variants were identified by Sanger sequencing conducted at the central laboratory. CDS indicates coding sequence; LP, likely pathogenic; P, pathogenic; and VUS, variant of uncertain significance.

*Of the 40 patients randomized to ARRY-371797, 1 patient was enrolled based on data from the local laboratory and had missing variant data from the central laboratory. This patient carried a P/LP *LMNA* variant.

†Of the 37 patients randomized to placebo, 1 was enrolled based on initial central laboratory results indicating the patient was carrying a VUS. However, subsequent testing found no eligible *LMNA* variant. This patient was discontinued from the study.

‡One patient in the placebo group carrying the c.1130G>A LP variant also had 2 VUS (missense, c.1489-16C>G; missense, c.1566C>T [p.Cys522Cys]).

versus 54%) TEAEs compared with those treated with placebo (Table 3; Table S4).

DISCUSSION

The phase 3 REALM-DCM study evaluated the efficacy and safety of ARRY-371797 in patients with symptomatic *LMNA*-related DCM carrying *LMNA* variants that are either phenotype/likely pathogenic (88%, n=68) or of uncertain significance (12%, n=9). Based on the findings of a planned interim analysis, this study was terminated early due to futility.

REALM-DCM enrolled 77 patients aged 23 to 72 years from Europe (64%) or North America (36%) with NYHA functional class II (79%) or III (21%) HF symptoms. Of the 75 patients with a central laboratory-determined *LMNA* variant, 55% had a missense change and 45% a nonmissense change.

There was no significant difference between the ARRY-371797 and placebo groups in the primary efficacy outcome of median change from baseline in 6MWT distance after 24 weeks of treatment (2-sided P=0.82; Hodges-Lehmann median difference: 4.9 m). Similarly, there were no significant differences between treatment groups in the median change from baseline at week 24 in KCCQ-PL score, KCCQ-TS score, NT-proBNP concentration, LVEF, and right ventricular fractional area, or between groups in the patient global impression survey at week 24. The composite end point of first WHF or all-cause mortality had a nonsignificant HR of 0.43 ([95% CI, 0.11−1.74]; P=0.23), and overall survival was similar between groups (HR, 1.19 [95% CI, 0.23−6.02]; P=0.84). Overall findings from the REALM-DCM trial demonstrated similar efficacy with ARRY-371797 and placebo. The safety findings for ARRY-371797 were consistent with previous studies.[12,16]

The limited data on *LMNA* genotype-phenotype associations and the natural history of *LMNA*-related DCM impede the diagnosis of patients and limit their effective treatment.[21–24] Some previous studies have suggested that nonmissense *LMNA* variants may be associated with a worse prognosis than missense variants, but such studies are readily confounded in rare familial conditions.[23,25–27] A mechanistic understanding of *LMNA*-related DCM will be necessary to understand any variant-specific effects on the natural history and prognosis of the disease.

REALM-DCM was the first phase 3, randomized, controlled interventional trial of a disease-modifying treatment in patients with *LMNA*-related DCM, and despite the early termination, the data gathered are valuable in the characterization of this disease and, pivotally, will provide benefit to study patients and their families.

For studies on rare diseases such as *LMNA*-related DCM, identifying eligible participants and determining clinically relevant outcome measures are challenging.[28] It is inevitable that sample sizes will be relatively modest and potentially constrain adequate statistical powering, particularly in patient populations with variable phenotypes and no quantitative mechanistic end points. Genetic evaluation of patients with nonischemic DCM is recommended for cascade screening but is not widely used outside of tertiary medical centers. There are many pathological *LMNA* variants, and an understanding of detailed genotype-phenotype associations is still emerging, which contributes to the heterogeneity of patient study populations. In this study, the observed median change from baseline in 6MWT distance, KCCQ-PL and -TS scores, and NT-proBNP concentration were highly variable, possibly due to this heterogeneity and the small sample size. Moreover, the
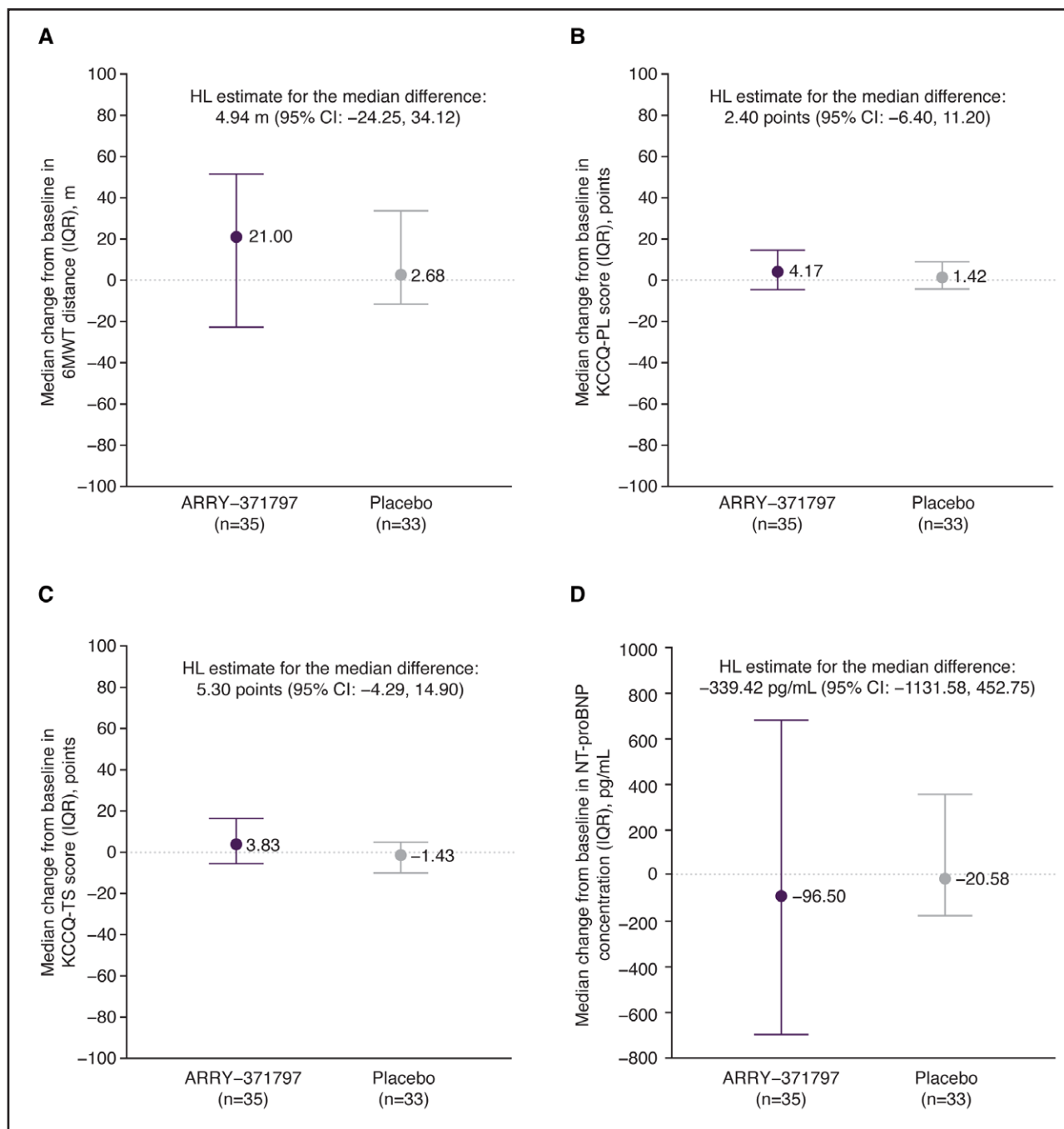
**Figure 2. Primary and secondary efficacy outcomes.**
Change from baseline in median 6MWT distance (**A**), KCCQ-PL score (**B**), KCCQ-TS score (**C**), and NT-proBNP concentration (**D**) at week 24. Vertical bars indicate the IQR (25th and 75th percentile). 6MWT indicates 6-minute walk test; HL, Hodges-Lehmann; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PL, physical limitation; and TS, total symptom.

most appropriate primary efficacy outcome measures for this population have not been established. Although this trial was focused on outcomes commonly used in trials of patients with HF, patients with *LMNA*-related DCM are also at high risk of clinically significant arrythmias, and arrythmia burden may be a key efficacy outcome for consideration in future trials.[5,8,29] In addition, extracardiac manifestations of *LMNA*-related disease

may be useful adjunct end points in future studies of *LMNA*-related DCM.

Limitations

The limitations of this study, as detailed above, include the early termination, modest enrollment, and the heterogeneous nature of the patient population, which
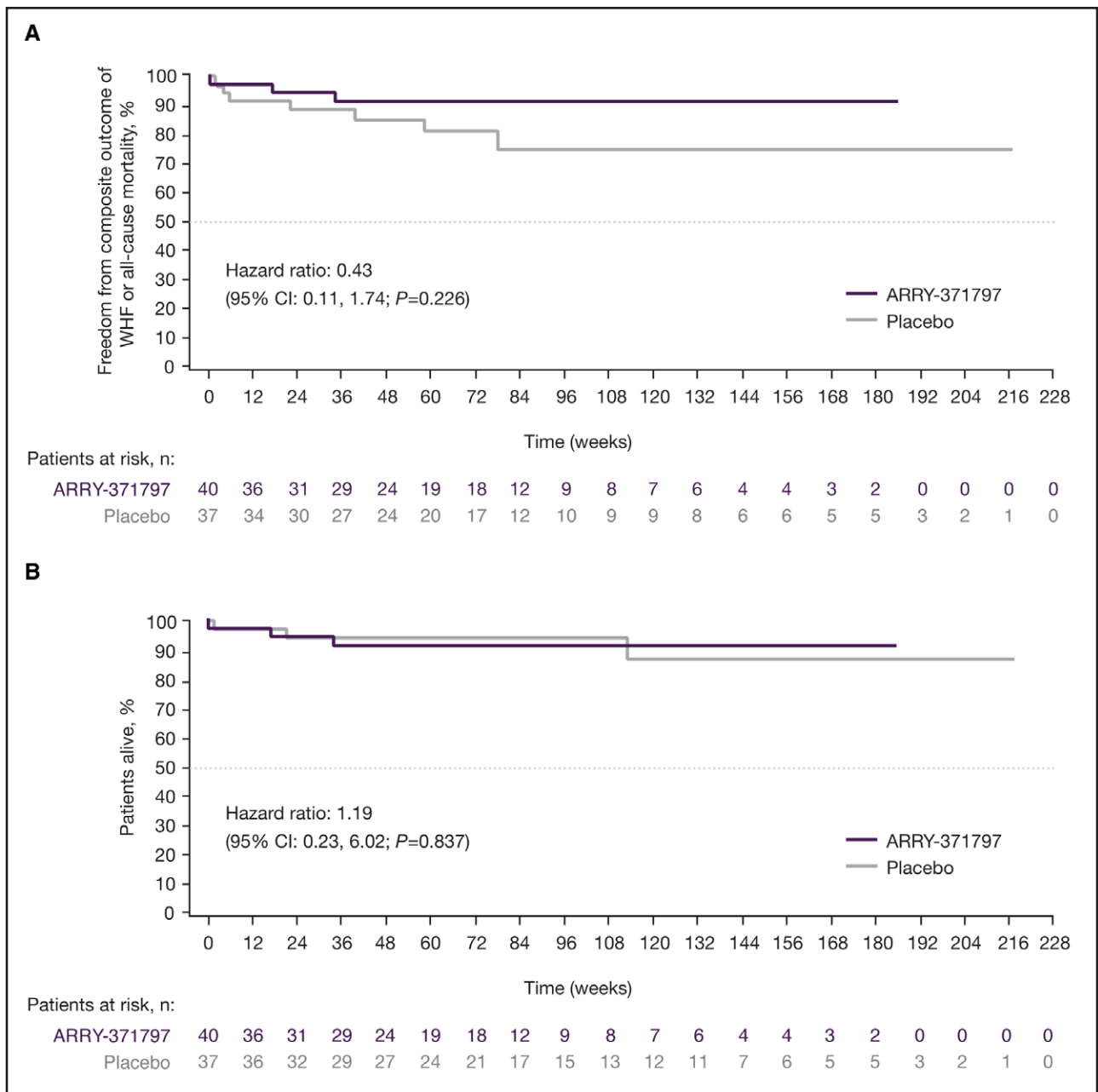
Figure 3. Composite outcome and survival analyses.
Kaplan-Meier plots of the composite outcome of all-cause mortality or WHF (**A**) and overall survival (**B**). Cox proportional hazard analysis was stratified by New York Heart Association functional class (II vs III) and baseline 6-minute walk test (6MWT) distance (<320 m vs ≥320 m). WHF indicates worsening heart failure.

further constrained the ability to detect treatment-related changes. The COVID-19 pandemic posed additional challenges to patient enrollment and follow-up. REALM-DCM enrolled a subset of patients with symptomatic, stable *LMNA*-related DCM who were receiving standard-of-care therapy. As cardiac impairment in enrolled patients was determined using LVEF ≤50% (with or without LV dilatation), some patients might have hypokinetic nondilated cardiomyopathy (HNDCM), defined as LV or biventricular global systolic dysfunction without dilatation (LVEF <45%), that is not explained by abnormal loading conditions or coronary artery disease.[30] However, HNDCM was not a widely used term during study inception.[31] Also, the study cohort included patients with *LMNA* variants of uncertain significance and excluded patients with *LMNA*-related muscular dystrophy that limited their ability to perform the 6MWT. Overlap of the *LMNA* cardiac phenotype with coexisting limb-girdle muscular dystrophy type 1B symptoms may still have confounded exercise capacity and stamina. For these reasons, the study cohort may not be reflective of the broader patient population with *LMNA*-related DCM.

Table 3.　Study Discontinuations and TEAEs, Including All Causalities, by System Organ Class and Preferred Term

	ARRY-371797, n=40	Placebo, n=37
No. of TEAEs*	320	264
Participants discontinued from study†	11 (27.5)	5 (13.5)
Patients discontinued from study drug†,‡	17 (42.5)	11 (29.7)
Patients with TEAEs†	35 (87.5)	34 (91.9)
Leading to dose reduction or interruption	16 (40.0)	5 (13.5)
Leading to study drug discontinuation	9 (22.5)	6 (16.2)
Patients with serious TEAEs	10 (25)	21 (56.8)
Patients with severe TEAEs (≥grade 3)	16 (40.0)	20 (54.1)
TEAEs in ≥10% of patients in either group		
Cardiac disorders		
Ventricular tachycardia	8 (20.0)	11 (29.7)
Atrial fibrillation	7 (17.5)	6 (16.2)
Atrial flutter	4 (10.0)	2 (5.4)
Ventricular fibrillation	2 (5.0)	4 (10.8)
Cardiac failure acute	2 (5.0)	4 (10.8)
Cardiac failure	0	5 (13.5)
Gastrointestinal disorders		
Diarrhea	12 (30.0)	4 (10.8)
Nausea	7 (17.5)	5 (13.5)
Stomatitis	5 (12.5)	0
Upper abdominal pain	3 (7.5)	4 (10.8)
General disorders and administration site conditions		
Fatigue	4 (10.0)	3 (8.1)
Investigations		
SARS-CoV-2 test positive	11 (27.5)	7 (18.9)
Nervous system disorders		
Dizziness	9 (22.5)	4 (10.8)
Headache	4 (10.0)	6 (16.2)
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	1 (2.5)	7 (18.9)
Skin and subcutaneous tissue disorders		
Dermatitis	5 (12.5)	1 (2.7)
Vascular disorders		
Hypotension	4 (10.0)	4 (10.0)

Values are n (%) unless indicated otherwise. TEAE indicates treatment-emergent adverse event.

*TEAEs were events that occurred on or after the first study drug dose and up to 30 days after the last dose. Adverse events were reported using Medical Dictionary for Regulatory Activities version 25.0.

†Participants who discontinued due to termination by the sponsor were excluded.

‡Participants who discontinued from study were also included in those who discontinued from the study drug.

Furthermore, the measures or biomarkers used in this study to determine efficacy have not been validated in patients with *LMNA*-related DCM and may be suboptimal.[32–35] In some studies of disease-modifying therapies in patients with HF with reduced ejection fraction, no significant improvements in 6MWT distance or KCCQ scores were observed, despite reductions in morbidity or mortality.[36,37] Although no significant differences between the ARRY-371797 and placebo groups were observed in all outcomes in this study, future trials may further investigate the effects of p38α MAPK inhibition in patients with *LMNA*-related DCM.

Conclusions

The phase 3 REALM-DCM study of ARRY-371797, a p38α MAPK inhibitor, was terminated early due to futility for the primary efficacy outcome. An unmet need for genetically informed treatment persists for patients with *LMNA*-related DCM. Despite the lack of treatment differences identified, findings from REALM-DCM represent the largest and most robust prospectively gathered clinical data set for genotype-phenotype correlations and natural history evaluations of *LMNA*-related DCM captured to date. These will contribute toward a better disease understanding and optimized design for future trials.

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Supplemental Material

Supplemental Methods
Tables S1–S4
Figures S1 and S2

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