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ORIGINAL ARTICLE

Characterization and natural history of patients with *LMNA*-related dilated cardiomyopathy in the phase 3 REALM-DCM trial

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Abstract

Aims *LMNA*-related dilated cardiomyopathy (DCM) is a rare disease with an incompletely defined phenotype. The phase 3 REALM-DCM trial evaluated a potential disease-modifying therapy for *LMNA*-related DCM but was terminated due to futility without safety concern. This study utilized pooled data from REALM-DCM to descriptively characterize the phenotype and progression of *LMNA*-related DCM in a contemporary cohort of patients using common heart failure (HF) measures.

Methods REALM-DCM enrolled patients with stable *LMNA*-related DCM, an implanted cardioverter defibrillator or cardiac resynchronization therapy defibrillator, and New York Heart Association (NYHA) Class II/III HF symptoms.

Results Between 2018 and 2022, 77 patients took part in REALM-DCM. The median patient age was 53 years (range: 23–72), and 57% were male. Overall, 88% of patients had a pathogenic or likely pathogenic *LMNA* variant, and 12% had a variant of uncertain significance with a concordant phenotype. Among patients with confirmed sequencing, 55% had a missense variant. Atrial fibrillation was present in 60% of patients; 79% of all patients had NYHA Class II and 21% had NYHA Class III HF symptoms at baseline. Median (range) left ventricular ejection fraction (LVEF), 6 min walk test (6MWT) distance, Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration at baseline were 42% (23–62), 403 m (173–481), 67 (18–97) and 866 pg/mL (57–5248), respectively. LVEF, 6MWT distance and KCCQ-OS score were numerically lower in patients who had NYHA Class III versus II symptoms at baseline (LVEF: 38% vs. 43%; 6MWT distance: 326 vs. 413 m; and KCCQ-OS score: 43 vs. 70), whereas NT-proBNP concentration was higher (1216 vs. 799 pg/mL). Median follow-up was 73 weeks (range: 0.4–218; 73 in NYHA Class II and 75 in NYHA Class III). Patients displayed variable change from baseline in 6MWT, KCCQ-OS and NT-proBNP values during follow-up. Overall, 25% of patients experienced ventricular tachycardia, and 8% had ventricular fibrillation. Ten (13%) patients met the composite endpoint of worsening HF (adjudicated HF-related hospitalization or urgent care visit) or all-cause death; six had NYHA Class II and four had NYHA Class III at baseline. All-cause mortality occurred in 6 (8%) patients; three had NYHA Class II and three had NYHA Class III symptoms at baseline.

Conclusions Findings confirm the significant morbidity and mortality associated with *LMNA*-related DCM despite the standard of care management. Typical measures of HF, including 6MWT distance, KCCQ-OS score and NT-proBNP concentration, were variable but correlated with NYHA class. An unmet treatment need remains among patients with *LMNA*-related DCM. NCT03439514.

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Keywords dilated cardiomyopathy; genetic diseases; heart failure; laminopathies; phase 3 clinical trial

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Introduction

Variants in the *LMNA* gene, which encodes the lamin A and C proteins, are the cause of several clinical syndromes including dilated cardiomyopathy (DCM).[1] The pathogenesis of *LMNA*-related DCM is unclear, but preclinical studies have suggested that several processes are altered in cardiomyocytes, including activation of pro-inflammatory, apoptotic, fibrotic and mitogen-activated protein kinase pathways.[2–4]

LMNA-related DCM is a progressive and malignant disease characterized by left ventricular systolic dysfunction, conduction disorders and arrhythmias that can be life-threatening.[5–8] It is inherited as an autosomal dominant trait with typical symptom onset around 30–50 years of age and high penetrance (albeit with variable expressivity) by age 60 years in family studies.[5,9,10] Thrombo-embolic events and sudden death are more common among patients with *LMNA*-related DCM than in patients with other forms of DCM.[11–14]

Guideline-directed medical therapy for heart failure (HF) is commonly adopted for patients with *LMNA*-related DCM, but there are no data showing it to be disease-modifying.[15,16] Implanted cardioverter defibrillators (ICDs) and cardiac resynchronization therapy defibrillators (CRT-Ds) are standard of care, and heart transplantation may be necessary in patients with progressive deterioration in cardiac function or refractory arrhythmias.[6,17]

The phenotype of patients with *LMNA*-related DCM is not well characterized. The recently terminated phase 3 REALM-DCM trial (NCT03439514) was the largest prospective clinical study in patients with *LMNA*-related DCM conducted to date.[18] This study pooled data from REALM-DCM treatment arms to provide detailed characterization of phenotype and progression in a contemporary cohort of patients with *LMNA*-related DCM and contributes new data on commonly used measures of HF progression including the 6 min walk test (6MWT), the Kansas City Cardiomyopathy Questionnaire (KCCQ) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration in this population.[19]

Methods

The detailed methods for this analysis are described in the supporting information. A full report of the REALM-DCM multinational, randomized, double-blind, placebo-controlled phase 3 trial has been published (NCT03439514).[18] The trial assessed the efficacy and safety of ARRY-371797 (PF-07265803) in patients with *LMNA*-related DCM and New York Heart Association (NYHA) Class II/III HF symptoms. The trial was terminated early after a futility analysis revealed that it was unlikely to meet the primary endpoint.[19]

REALM-DCM was conducted in accordance with the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines, and regional laws and regulations, including privacy laws. The protocol was reviewed by the institutional review board or ethics committee at each site, and all patients provided written informed consent.

Results

Patients

From April 2018 to October 2022, 77 patients took part in REALM-DCM (Figure 1). Of these, 61 had NYHA Class II and 16 had NYHA Class III HF symptoms at baseline. The trial was terminated early by the sponsor in late 2022. Prior to that, 9 of 61 (15%) patients who had NYHA Class II symptoms and 7 of 16 (44%) who had NYHA Class III symptoms discontinued due to withdrawal of consent, death, loss to follow-up or other reasons.

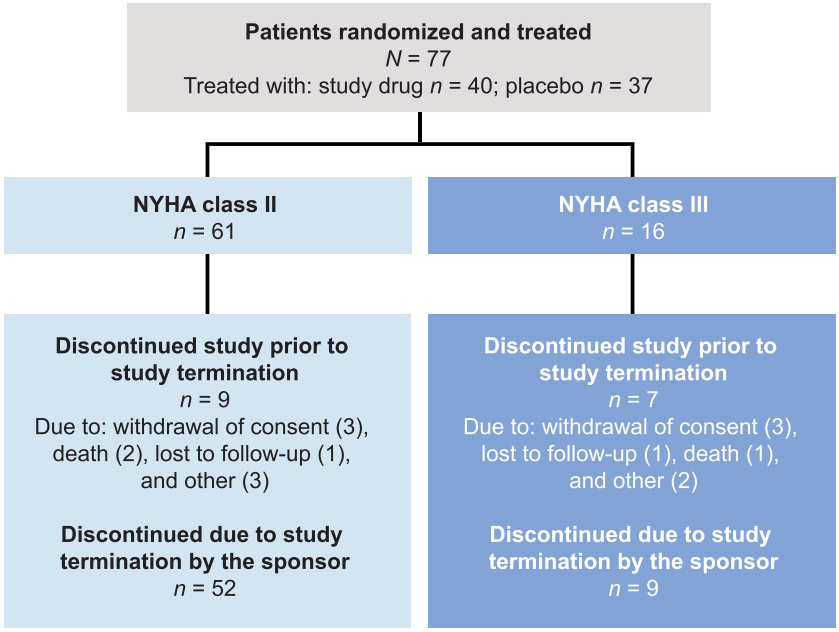
The median follow-up duration among all patients was 73 weeks [inter-quartile range (IQR) 93; min 0.4, max 218]. Median follow-up was 73 weeks (IQR 58; min 0.4, max 218) in patients who had NYHA Class II symptoms and 75 weeks (IQR 137; min 4, max 213) in patients who had NYHA Class III symptoms.

Baseline demographics and clinical characteristics

Baseline demographics and clinical characteristics of patients in REALM-DCM are presented in Table 1. The median age of patients was 53 years, 57% were male, 96% were indicated by the investigator to be White and 64% lived in Europe. The median 6MWT distance was 403 m, the median left ventricular ejection fraction (LVEF) was 42%, the median NT-proBNP concentration was 866 pg/mL, and the median KCCQ Overall Summary (OS), Physical Limitation (PL), Clinical Summary (CS) and Total Symptom (TS) scores indicated fair to

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Figure 1 Patient disposition. NYHA, New York Heart Association.



good health status (range: 67–73). Among all patients, the median right ventricular fractional area was 40% (range: 28%−55%), and the median (range) troponin I, troponin T, creatine kinase and sodium plasma concentrations were 0.3 μg/L (0.3−1.2; *n* = 73), 23 ng/L (12.0−90.0; *n* = 73), 90 U/L (26.0−689.0) and 140 mmol/L (133.0−144.0), respectively. Patients who had NYHA Class III symptoms were slightly older and more likely to be female, to live in North America and to have more abnormal clinical characteristics (numerically lower median 6MWT distance, LVEF and KCCQ subscale scores, alongside a higher median NT-proBNP concentration) at baseline than those who had NYHA Class II symptoms.

REALM-DCM enrolled patients with a confirmed *LMNA* variant [according to the American College of Medical Genetics and Genomics (ACMG) criteria] using local laboratory results; 88% of patients had a pathogenic or likely pathogenic (P/LP) variant, and 12% had a variant of uncertain significance (VUS) with symptoms and clinical findings highly suggestive of *LMNA*-related DCM. There was a similar proportion of patients with P/LP variants among those who had NYHA Class III versus II (94% vs. 87%) symptoms at baseline. Patient samples underwent secondary analysis by a central laboratory to confirm this classification and obtain the variant sequence. Among all patients with confirmed variant sequences, 55% had a missense *LMNA* variant and 45% had a non-missense variant (variants listed in Table S1). The variant was not determined prior to trial termination for one patient, and another was found not to have a relevant variant and was discontinued from the trial. Around half of patients in each NYHA group had a missense variant (56% of those in Class II and 50% of those in Class III with confirmed variant sequences).

Medical history and comorbidities reported as MedDRA preferred terms by the investigators are presented in Table S2. The most common baseline comorbidities were atrial fibrillation (60%) and hypertension (33%). Ventricular tachycardia was a comorbidity in 18%, atrial flutter in 9%, complete atrioventricular block in 6%, muscular dystrophy in 6% and ventricular fibrillation in 3%. Patients with conditions that impact 6MWT performance were excluded, and no objective clinical phenotyping of skeletal muscle function was conducted.

Standard of care medications taken by patients before and during REALM-DCM are presented in Table S3. Per the inclusion criteria, all patients had an ICD or CRT-D and were stable on their current treatment regimen. Beta-blockers, medications acting on the renin-angiotensin system, antithrombotic medications and diuretics were the most common medication types taken during the trial (97%, 91%, 87% and 81%, respectively). One third of patients (34%) took concomitant sodium–glucose co-transporter-2 inhibitors.

Change in typical measures of HF during follow-up

The range of achieved 6MWT distances was wide at all time points and in all groups. Numerically lower median distances were observed through the majority of follow-up in patients who had NYHA Class III versus II symptoms at baseline

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Table 1 Baseline demographics and clinical characteristics.

	NYHA Class II $n = 61$	NYHA Class III $n = 16$	Overall population $N = 77$
Age at screening (years)			
Mean (SD)	51 (11.4)	55 (9.7)	52 (11.1)
Median (range)	52 (23–72)	54 (39–68)	53 (23–72)
Sex, *n* (%)			
Male	36 (59.0)	8 (50.0)	44 (57.1)
Female	25 (41.0)	8 (50.0)	33 (42.9)
Race, *n* (%)			
White	59 (96.7)	15 (93.8)	74 (96.1)
Asian	1 (1.6)	1 (6.3)	2 (2.6)
Black or African American	1 (1.6)	0	1 (1.3)
Region where residing, *n* (%)			
North America	15 (24.6)	13 (81.3)	28 (36.4)
Europe	46 (75.4)	3 (18.8)	49 (63.6)
BMI[a] (kg/m^2), median (range)	26 (17.5–44.1)	29 (16.4–44.2)	26 (16.4–44.2)
LMNA variant classification[b], *n* (%)			
P/LP	53 (86.9)	15 (93.8)	68 (88.3)
VUS	8 (13.1)	1 (6.3)	9 (11.7)
LMNA variant type, *n* (%)			
Missense	33 (54.1)	8 (50.0)	41 (53.2)
Non-missense	26 (42.6)	8 (50.0)	34 (44.2)
Other[c]	2 (3.3)	0	2 (2.6)
6MWT distance (m), median (range)	413 (238.5–480.5)	326 (173.0–441.1)	403 (173.0–480.5)
LVEF[d] (%), median (range)	43 (23.4–61.6)	38 (23.2–60.2)	42 (23.2–61.6)
NT-proBNP (pg/mL), median (range)	799 (56.8–5248.3)	1216 (142.4–5000.0)	866 (56.8–5248.3)
KCCQ score, median (range)			
OS	70 (28.1–97.4)	43 (18.2–71.1)	67 (18.2–97.4)
PL	75 (25.0–100.0)	39 (12.5–66.7)	67 (12.5–100.0)
CS	75 (30.2–100.0)	44 (20.8–70.8)	68 (20.8–100.0)
TS	75 (35.4–100.0)	56 (19.8–80.2)	73 (19.8–100.0)

Abbreviations: 6MWT, 6 min walk test; ACMG, American College of Medical Genetics and Genomics; BMI, body mass index; CS, Clinical Summary; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OS, Overall Summary; P/LP, pathogenic or likely pathogenic; PL, Physical Limitation; SD, standard deviation; TS, Total Symptom; VUS, variant of uncertain significance.
[a]BMI missing for one patient who had NYHA Class II symptoms at baseline.
[b]Defined by the ACMG framework.
[c]One patient was enrolled based on findings from the local laboratory, and the variant sequence was not collected by the central laboratory before trial termination. One patient was found not to have a relevant variant and was discontinued from the trial.
[d]Enrolment was determined using local measures. The presented values are baseline readings taken at the central facility, and due to variability, some are >50%.

(295–383 vs. 337–429 m at all assessments). Gradual declines in 6MWT distance were observed after ~100 weeks of follow-up in all groups (Figure S1). As trends for reduction occurred when the number of patients per group was low (13 or fewer in each group) and results are biased by patient dropout, longitudinal changes should be interpreted with caution.

Median KCCQ subscale scores among patients who had NYHA Class II symptoms at baseline were nearly always ≥75 (Figure S2). Patients who had NYHA Class III symptoms at baseline consistently reported numerically lower median KCCQ subscale scores (often between 25 and 49) than those who had NYHA Class II symptoms. All four KCCQ subscales (OS, PL, CS and TS) showed very wide variability, and there was significant patient dropout over time (Figure S3).

In patients who had NYHA Class II symptoms at baseline, the median NT-proBNP concentration was generally between 400 and 600 pg/mL and remained stable throughout follow-up (Figure S4). At most time points, NT-proBNP concentration was numerically higher in patients who had NYHA Class III compared with Class II symptoms at baseline, and was nearly always >900 pg/mL. The change from baseline was variable in all groups but did not indicate any clinically significant change over the first ~100 weeks of follow-up.

There were no clinically significant changes in troponin I, troponin T or creatine kinase plasma concentrations over follow-up (Figure S5).

Overall safety

Detailed safety data by treatment group are presented in the primary publication of the trial.[18] As in the previous phase 2 studies, the clinical profile of ARRY-371797 was found to be similar to placebo.[20–23]

Of the 77 treated patients, 36 had ICD discharge and anti-tachycardia pacing data reported from the Week 12 visit, and 29 patients had ICD discharge and pacing data from the Week 24 visit. Of these, 3 (8%) patients had at least one ap-

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propriate discharge at Week 12 and 2 (7%) patients at Week 24. Two (6%) patients had ventricular tachycardia episodes that were treated with pacing at Week 12 and 1 (3%) patient at Week 24. The duration of each recording was not retained.

Adverse events were reported independently of the adjudicated worsening HF (WHF) findings. Among all patients, 69 (90%) reported a total of 584 treatment-emergent adverse events (TEAEs). The most commonly reported TEAEs in any MedDRA system organ class are shown in Table S4; ventricular tachycardia (25%), a positive SARS-CoV-2 test (23%) and diarrhoea (21%) were the three most prevalent TEAEs. Serious and severe (grade ≥3) TEAEs were reported by 40% (n = 31) and 47% (n = 36) of all patients, respectively. Treatment was discontinued due to a TEAE in 20% (n = 15) of patients.

Twenty (26%) patients reported a serious cardiac disorder TEAE during the trial; of these, 12 had NYHA Class II (20% of all who had NYHA Class II) and 8 had NYHA Class III (50% of Class III) symptoms at baseline. These TEAEs were related to HF (preferred terms of acute cardiac failure, cardiac failure or congestive HF) in 7 patients and ventricular tachyarrhythmia in 13 patients (preferred terms of ventricular tachycardia, ventricular fibrillation and ventricular arrhythmia). Other serious cardiac disorder TEAEs included atrial fibrillation (n = 3 patients); atrial flutter (n = 2); and acute myocardial infarction, cardiogenic shock and mitral valve incompetence (n = 1 each).

Among the 41 patients with a confirmed missense *LMNA* variant, 17 (41%) had a severe TEAE or non-severe TEAE that led to trial discontinuation. This included potentially disease-related TEAEs in 10 (25%) patients (6 in NYHA Class II and 4 in NYHA Class III). Among the 34 patients with a confirmed non-missense *LMNA* variant, 17 (50%) had a severe TEAE or non-severe TEAE that led to trial discontinuation, including potentially disease-related TEAEs in 13 (38%) patients (10 in NYHA Class II and 3 in NYHA Class III). In the overall population, potentially disease-related severe TEAEs or non-severe TEAEs that led to trial discontinuation were numerically more common in patients who had NYHA Class III versus II [44% (n = 7/16) vs. 26% (n = 16/61)] symptoms at baseline.

WHF and mortality

Among the 77 treated patients, 10 (13%) met the composite endpoint of WHF (defined as any HF-related hospitalization or HF-related urgent care visit, as adjudicated by a committee) or all-cause death during the trial (Table 2). Of these, six had NYHA Class II (10% of all NYHA Class II) and four had NYHA Class III (25% of Class III) symptoms at baseline. The first event was an HF-related hospitalization in six patients and an all-cause death in four patients. The time to the first event was 2, 14, 39, 156, 239 and 407 days in the six patients who had NYHA Class II symptoms at baseline. Events at Days 2, 14 and 239 were all-cause deaths, while events at Days 39, 156 and 407 were WHF. The two deaths that occurred early in the study were due to ventricular tachycardia after 2 days of randomized treatment, and bacterial pneumonia after 14 days of randomized treatment, respectively. The time to the first event was 28, 119, 276 and 547 days in the four patients who had NYHA Class III symptoms at baseline. The event at Day 119 was death due to anoxic brain injury occurring 57 days after randomized treatment discontinuation (as described below), while events at Days 28, 276 and 547 were WHF. Findings by NYHA class should be interpreted with caution due to low numbers of patients meeting the composite endpoint in each subgroup.

Including both first and subsequent events, six deaths occurred during the trial; two occurred while taking randomized trial treatment (as described above), and four were recorded in patients who had discontinued randomized treatment (one due to respiratory failure 121 days after completing 28 days of treatment, one due to pancreatic neoplasia 176 days after completing 63 days of treatment, one due to disease progression 255 days after completing 537 days of treatment and one due to anoxic brain injury following post-heart transplant primary graft dysfunction 57 days after completing 62 days of

Table 2 Composite endpoint of adjudicated WHF or all-cause mortality.

	NYHA Class II n = 61	NYHA Class III n = 16	Overall population N = 77
Patients who met composite endpoint of WHF or all-cause death, n (%)	6 (9.8)	4 (25.0)	10 (13.0)
First event, n (%)			
HF-related hospitalization	3 (4.9)	3 (18.8)	6 (7.8)
Death	3 (4.9)	1 (6.3)	4 (5.2)
Urgent HF hospital visit	0	0	0
Any occurrence (first and recurrent), n (%)			
HF-related hospitalization	5 (8.2)	4 (25.0)	9 (11.7)
Death	3 (4.9)	3 (18.8)	6 (7.8)
Urgent HF hospital visit	0	1 (6.3)	1 (1.3)

Abbreviations: HF, heart failure; NYHA, New York Heart Association; WHF, worsening HF (includes committee-adjudicated events of HF-related hospitalization and urgent HF-related hospital visits).

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treatment). Three of the deceased patients had NYHA Class II symptoms at baseline, and three had NYHA Class III symptoms at baseline.

Discussion

LMNA-related DCM is a rare and progressive condition associated with significant cardiac symptoms.[6] Studies have previously reported a heterogeneous clinical phenotype for patients with *LMNA*-related DCM, with varying degrees of structural heart disease and arrhythmic activity.[1,6,9,10,24–28] Analysis of data collected during the REALM-DCM trial has allowed unique characterization of symptomatic patients with *LMNA*-related DCM over a median of ~1.4 years and a maximum of ~4 years of follow-up. Findings confirm the significant morbidity and mortality of *LMNA*-related DCM despite management with standard of care therapy. They also provide valuable new insights into the applicability of typical measures of HF, such as 6MWT distance, KCCQ score and NT-proBNP concentration, in the monitoring of patients with *LMNA*-related DCM.

REALM-DCM enrolled patients who were stable on standard of care therapy, had an ICD or CRT-D, and NYHA Class II or III HF symptoms at baseline. Patients receiving standard of care are an important subpopulation, representing many patients with *LMNA*-related DCM. Despite stability, disease-related conduction disorders and arrhythmia comorbidities were commonly reported. This demonstrates the ongoing burden for patients and confirms that life-threatening arrhythmias may be the predominant clinical presentation prior to advanced HF (i.e., NYHA Class IV).[6] Consistent with the literature, a slightly higher proportion of patients with a non-missense *LMNA* variant had a severe and potentially disease-related TEAE, or a non-severe and potentially disease-related TEAE that resulted in trial discontinuation, as compared with patients with a missense *LMNA* variant.[24,29–31] Baseline differences in 6MWT distance, KCCQ score and NT-proBNP concentration were evident between patients who had NYHA Class II compared with Class III symptoms at baseline, which is consistent with their common use as proxy measures of HF; however, these measures showed minimal progression and a high degree of variability throughout the REALM-DCM trial. Moreover, the burden of recurrent arrhythmias (which were common in this study) may not be well captured in the KCCQ, presenting a potential limitation of this instrument in the characterization of patients with *LMNA*-related DCM. During a median follow-up duration of ~1.4 years, several measures demonstrated clinical progression and mortality among patients in REALM-DCM, including a 12% rate of adjudicated HF-related hospitalization and a mortality rate of 8%, where three of six deaths were due to disease-related or potentially disease-related conditions. Along with evidence of ongoing comorbidities and disease-related TEAEs, this suggests that the typical HF measures used as key measures in REALM-DCM poorly captured the disease burden and progression in this trial. The small sample size and the short median duration of the trial may be responsible for such findings. Further characterization of the clinical profile and progression patterns in patients with *LMNA*-related DCM will be valuable in identifying suitable disease progression outcomes in this patient population.

Limitations

There were several notable limitations to this analysis. Firstly, treatment and placebo groups were combined for this analysis. Though the trial ended due to futility, there may be some small treatment effects that influence the apparent natural history. Secondly, the enrolment criteria for REALM-DCM were designed to select a subpopulation of patients with *LMNA*-related DCM, leading to selection bias and a cohort that may not reflect the wider patient population who are at different stages of their disease journey. Additionally, patients with conditions that might impact 6MWT were excluded, which prevented patients with a muscular impairment phenotype from joining. Thirdly, as the trial methodology focused on the primary and secondary efficacy endpoints, there are limited data available describing arrhythmia burden and myocardial remodelling. Lastly, because REALM-DCM was terminated early, the trial comprised fewer patients than planned and some data were missing. Relatively few patients (n = 16) had NYHA Class III symptoms at baseline, and so our findings by NYHA class should be interpreted with caution. Differences in follow-up duration also make the interpretation of longitudinal measures challenging.

Conclusions

Patients with *LMNA*-related DCM and NYHA Class II or III HF who were stable on standard of care therapy showed evidence of notable symptom burden and disease progression over a median follow-up of ~1.4 years in REALM-DCM. Typical measures of HF progression, including the 6MWT, KCCQ subscale scores and NT-proBNP concentration, correlated with NYHA class at baseline. Findings confirm the significant morbidity and mortality of *LMNA*-related DCM and highlight the ongoing need for a better understanding of disease phenotypes and underlying mechanisms.

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Conflict of interest statement

PG-P has served as a speaker in scientific meetings for Alexion, Alnylam, BridgeBio, Ionis/AstraZeneca, BMS, Novo Nordisk and Pfizer; has received funding from Alnylam and Pfizer for scientific meeting expenses; and has received consultancy fees from Alnylam, Attralus, BridgeBio, Neuroimmune, AstraZeneca, Novo Nordisk, Alexion, Intellia, LEXEO, BMS, Cytokinetics, Rocket and Pfizer. His institution has received research grants/educational support from Alnylam, AstraZeneca, BridgeBio, Intellia, Novo Nordisk and Pfizer. NKL has received consultancy fees from MyoKardia, Bristol Myers Squibb, Tenaya, Array BioPharma and Pfizer. GS reports consulting fees from Novartis, Impulse Dynamics, Novo Nordisk and Biotronik and speaker and honoraria from Novartis, Bayer, AstraZeneca, Boston Scientific, Vifor Pharma, Menarini and Akcea. TR-V has been a speaker in scientific meetings for Alnylam, Pfizer, Amicus and Takeda; has received funding from Alnylam, Pfizer, Bayer and Chiesi for scientific meeting expenses; and has received consultancy fees from Alnylam, AstraZeneca, BMS, Amicus, Sanofi and Pfizer. His institution has received research grants/educational support from Pfizer, Boston and Abbott. SGP has received consultancy fees from Cardurion and Boston Scientific and research grant support from Solid Biosciences and Cardurion. JSW has received consultancy fees from MyoKardia, Foresite Labs, Pfizer and HealthLumen, and his institution has received research support from Bristol Myers Squibb and Pfizer. AO has received consulting or advisory board fees from Bristol Myers Squibb, Cytokinetics, Pfizer, BioMarin, Tenaya, Lexicon, Stealth and Renovacor and grant support from Bristol Myers Squibb. PE has received consultancy fees from Pfizer, BioMarin, Sarepta, Novo Nordisk and BMS. CAM has received consultancy fees from Affinia, Array BioPharma, AstraZeneca, Bayer, Bristol Myers Squibb, Design Therapeutics, Dewpoint, DiNAQOR, Merck, MyoKardia, Novartis and Pfizer and grant support from Bayer, Merck, Novartis and Sanofi. DPJ has received consultancy fees from ADRx, Alexion, Cytokinetics, LEXEO, Novo Nordisk, Pfizer and Tenaya Therapeutics. HL and FSA are employees of Pfizer and hold stock and/or stock options. KA has no relevant disclosures.

Data availability statement

Upon request and subject to review, the trial sponsor, 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. All authors had full access to all the study data. FSA and HL take responsibility for its integrity and the data analysis.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. (A) Observed and (B) change from baseline in 6MWT distance.
Figures S2. Observed (A) KCCQ-OS, (B) -PL, (C) -CS, and (D) -TS scores.
Figure S3. Change from baseline in (A) KCCQ-OS, (B) -PL, (C) -CS, and (D) -TS scores.
Figure S4. (A) Observed and (B) change from baseline in NT-proBNP concentration.
Figure S5. Observed plasma concentrations of (A) troponin I, (B) troponin T and (C) creatine kinase.
Table S1. *LMNA* variants.
Table S2. Medical history and comorbidities by frequency.
Table S3. Prior and concomitant standard of care medications.
Table S4. Treatment-emergent adverse events in >5% of patients by frequency.

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