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Idebenone as a novel, therapeutic approach for Duchenne muscular dystrophy: Results from a 12 month, double-blind, randomized placebo-controlled trial

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Abstract

Early mortality in Duchenne muscular dystrophy (DMD) is related to cardiac and respiratory complications. A phase IIa double-blind randomized placebo-controlled clinical trial was conducted to investigate the tolerability and efficacy of idebenone therapy in children with DMD. Twenty-one DMD patients (aged 8–16 years) were randomly assigned to daily treatment with 450 mg idebenone (Catena®) ($n = 13$) or placebo ($n = 8$) for 12 months. All subjects completed the study and idebenone was safe and well tolerated. Idebenone treatment resulted in a trend ($p = 0.067$) to increase peak systolic radial strain in the left ventricular inferolateral wall, the region of the heart that is earliest and most severely affected in DMD. A significant respiratory treatment effect on peak expiratory flow was observed ($p = 0.039$ for PEF and $p = 0.042$ for PEF percent predicted). Limitations of this study were the small sample size, and a skewed age distribution between treatment groups. Data from this study provided the basis for the planning of a confirmatory study.

Keywords: Duchenne; Muscular dystrophy; Treatment; Idebenone; Cardiac; Cardiomyopathy; Respiratory function

1. Introduction

Duchenne muscular dystrophy (DMD) is the most common and devastating type of muscular dystrophy worldwide [1]. Besides progressive weakness of the skeletal muscles leading to loss of ambulation by age 10–12 years, DMD patients develop cardiac and respiratory complications that lead to early morbidity and mortality. Progressive weakness of respiratory muscles leads to reduced cough and airway clearance, and later to a restrictive pulmonary syndrome that evolves into respiratory insufficiency during the late second or third decade [2–4]. The large majority of DMD patients also develop progressive dilated cardiomyopathy typically during adolescence or as young adults. Due to the limited ambulatory status of the patients, the cardiac dysfunction may remain asymptomatic for a relatively long period but ultimately it can result in clinical heart failure, arrhythmia and sudden death. Following improvements in respiratory care including ventilatory assistance, cardiac disease has become a leading cause of death in DMD [5–7]. The cardiac involvement in DMD is progressive but, compared to skeletal muscle involvement, evolves later in life. However,

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subclinical regional myocardial damage in particular cardiac segments is already detectable early in the course of DMD, at a stage when global ventricular function as assessed by conventional echocardiographic parameters is still normal. Especially reduced systolic myocardial deformation (strain, strain rate) in the left ventricle (LV) inferolateral wall is an early marker of the disease, being associated with regional fibrotic histological changes, preceding more generalized myocardial dysfunction and being predictive of later adverse cardiac outcome [8–11].

Causative gene identification and pathophysiologic insights have fuelled increasing experimental therapeutic research efforts for DMD. Nevertheless, currently no curative treatment exists, and whilst corticosteroids have proven to slow down disease progression, their long-term use is hampered by significant adverse effects [12]. Idebenone (2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone) is a short-chain benzoquinone with strong anti-oxidant activities, which in addition improves mitochondrial respiratory chain function and cellular energy production [13,14]. A recent preclinical study reported the first evidence of a potential therapeutic role for idebenone in dystrophin-deficient muscular dystrophy [15]. In this observer-blinded placebo-controlled *in vivo* study, early-initiated and prolonged idebenone treatment was significantly cardioprotective and improved voluntary exercise performance in the homologous *mdx* mouse model of DMD. Based on the preclinical evidence, the current phase IIa randomized controlled clinical trial aimed to investigate the efficacy and tolerability of idebenone in children with DMD, focusing on cardiac and respiratory endpoints.

2. Methods

2.1. Patients

Participants were 8–16 year old males with confirmed DMD and subclinical myocardial dysfunction (reduced systolic strain of <50% in LV inferolateral wall) at screening. Other inclusion criteria were: if on chronic steroids (prednisone, deflazacort) and/or cardiac medications (β-blocker, diuretics) stable dosage ⩾6 and ⩾3 months, respectively, prior to inclusion (with further stable dosage during the trial); and ability to provide reproducible upper limb quantitative muscle testing. Exclusion criteria included use of angiotensin converting enzyme inhibitors (ACEi); use of coenzyme Q10, idebenone, creatine, glutamine, oxatomide, or any herbal medicines within the last 6 months; symptomatic cardiomyopathy or heart failure, LV fractional shortening (M-mode) <20% and/or ejection fraction <40%; previous history or presence of ventricular arrhythmias and significant concomitant illness. Patients on ACEi were excluded to avoid a confounding effect of the ACEi treatment on the cardiac measurements. The study complies with the Declaration of Helsinki and the protocol was approved by the UZ Leuven Institutional Review Board, and written informed consent and assent was obtained.

2.2. Study conduct, study drug and dosing

This study was registered (NCT00654784) and conducted at UZ Leuven under GCP conditions. Patients were enrolled between October 2005 and July 2006, with follow-up occurring until August 2007. Before study initiation, a list of block randomization numbers and corresponding treatment numbers was computer generated by a third party (Averion International, Switzerland). Treatment assignments were maintained by the third party and only made available after the trial was complete and the database locked. Within 2 weeks of randomization, patients attended a screening visit including informed consent/assent, inclusion/exclusion criteria, physical exam including vital signs, cardiac, respiratory and muscle strength assessments, electrocardiography (ECG), cardiac biomarkers, and safety blood/urine samples. Eligible patients were randomized in a double-blind fashion and allocated without further stratification in a 2:1 ratio (randomized block design with permuted blocks of size six) to receive oral idebenone (CATENA®, 150 mg film coated tablets from Santhera Pharmaceuticals, Switzerland) or matching placebo, three times daily (during meals) for 52 weeks. Study medication was provided as pre-packaged kits marked with the appropriate treatment number. Compliance was monitored by entries in a patient diary, by pill count, and by assessment of idebenone serum levels. Efficacy assessments were performed at screening (baseline values) and at weeks 26, 52 (end of therapy) and 56 (follow-up visit). Safety assessments were at weeks 4, 13, 26, 52 and 56, and patients were contacted by telephone at week 39. Blood samples for idebenone pharmacokinetics were taken at screening and weeks 26 and 52.

2.3. Objectives and endpoints

The primary efficacy endpoint was defined as the difference between idebenone treatment and placebo for the change from baseline to week 52 in peak systolic radial strain in the LV inferolateral wall. Secondary efficacy endpoints included global cardiac and other regional myocardial function properties, respiratory function, quantitative muscle strength, cardiac biomarkers, and clinical global impression of change. Secondary safety endpoints included the number, type and severity of adverse events, safety blood and urine sampling, ECG and clinical global assessment of tolerability.

2.4. Efficacy and safety assessments and pharmacokinetics

2.4.1. Echocardiographic measurements

2D echocardiograms were performed using a Vivid7 ultrasound scanner (GE Ultrasound, Horten, Norway) using a 3.5 MHz transducer as described [9,16]. Briefly,

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standard parasternal and apical views were obtained. M-mode images from a short axis view at papillary muscle level were used to measure LV end-diastolic and end-systolic dimensions, septal and inferolateral wall thickness and LV fractional shortening (FS). Left atrial dimensions were measured from a parasternal long-axis M-mode. All dimensions were corrected for body surface area (BSA). If image quality allowed, a modified Simpson's method was used to calculate LV ejection fraction (EF). Diastolic LV function was assessed using blood pool Doppler measurements of mitral and pulmonary venous flow and tissue Doppler measurements at the mitral lateral and septal annulus. Isovolumetric relaxation time was obtained from a Doppler recording between LV inflow and outflow.

2D color tissue Doppler imaging (TDI) data were acquired from the apical 4-chamber view using narrow sector views for each individual wall (interventricular septum (IVS), LV lateral wall and right ventricular (RV) free wall). The parasternal short axis view at the papillary muscle was used to acquire radial TDI data in the LV inferolateral wall. Each individual wall was aligned with the direction of the echobeam (angle <15°). Color Doppler velocities were recorded at a frame rate >150 frames/s and three cardiac cycles were recorded for each acquisition. Data were stored in raw data format on the hospital server (Heartlab, Agfa, Belgium) and data were uploaded in the EchoPac workstation (GE Ultrasound, Horten, Norway) for off-line analysis. TDI datasets were analyzed using the Speqle 4© research software (University of Leuven, Leuven, Belgium). From the color Doppler datasets regional myocardial velocities and natural strain rate (SR) and strain (ε) were derived. Longitudinal peak systolic, early and late diastolic myocardial velocities, peak systolic SR and end-systolic ε were estimated in the basal, mid, and apical segments of the IVS, LV anterolateral and RV free wall using a sample area of 10 mm. Radial tissue Doppler velocities and peak systolic strain rate and strain were measured from the short-axis color TDI datasets using a 5 mm sample area in the axial direction and 10 mm in the lateral direction. All data were acquired by one experienced sonographer specially trained for this project. All investigators were blinded to the patient treatment until the completion of data acquisition and analysis. The off-line echocardiographic analysis was performed after each efficacy analysis. Thus the observer was not blinded to the data time points. The intraobserver variability of the regional deformation data (radial ε and SR measurements in the LV inferolateral wall) was assessed by one reader analyzing 10 randomly chosen data sets twice, the inter-observer variability was determined by two readers analyzing these same 10 data sets as described in more detail elsewhere [17].

2.4.2. Cardiac biomarkers

Blood samples for brain natriuretic peptide (pro-BNP) and cardiac troponin-I (cTnI) were taken prior to muscle strength assessment for each visit [18,19].

2.4.3. Respiratory function assessments

Testing was performed by one evaluator with longstanding expertise. Testing was performed with the patient sitting, following a standardized order. Lung volumes (forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1)) were measured using a handheld Koko spirometer (PDS Instrumentation, Louisville, USA). Maximum inspiratory pressures (MIP; in cm H_2O and % predicted [20]) were measured using a Magnehelic® manometer (Dwyer Instrument, Michigan City Ind, USA) connected to a mouthpiece. Peak expiratory flow (PEF; in L/min and % predicted [21]) was measured using a portable peak flow meter (Mini–Wright, Clement Clarke International). For all parameters the highest values from three consecutive recordings were used [22].

2.4.4. Muscle strength and clinical global assessments

Skeletal muscle strength was assessed by one experienced evaluator using a pediatric-focused quantitative muscle testing (QMT) system (CQMS: CINRG Quantitative Measurement System) based upon maximal voluntary isometric contraction [23]. Muscle groups tested included bilateral hand grip, elbow flexors and extensors. A composite upper limb score (QMT arms: sum of bilateral elbow flexors and extensors) was also calculated. The ambulatory status of patients was recorded. Clinical global impression of change (compared to baseline) and of tolerability was rated by the investigator on a 7- and 5-point scale, respectively, based on interviews with patient and parents/caregiver [24].

2.4.5. Safety assessments and idebenone pharmacokinetics

These included physical exam, vital signs, blood/urine sampling, and 12-lead ECG. Blood and urine analyses were performed at BARC Europe NV (Gent, Belgium). Adverse events (AEs) were graded for severity (mild, moderate or severe) and relationship to study drug (probable, possible, unlikely or unrelated) and coded using the MedDRA dictionary Version 8.1. Plasma concentrations of idebenone and metabolites were determined as described [25].

2.5. Data collection and statistical analysis

With a total sample size of 21 patients allocated in a 2:1 ratio to idebenone and placebo, a 15% difference between the two groups for the primary endpoint could be detected with 80% power and a one-sided significance level of 5%. A standard deviation of 12% was assumed for both treatment groups. The statistical and analytical plans were prepared prior to database lock. All efficacy analyses were performed with the intent to treat population on the observed cases data set. No interim analyses were planned or performed. The comparison between the two treatment groups was conducted using the *t*-test. The underlying normal distribution assumption was assessed using the Shapiro–Wilk test. If the assumption was violated, the Wilcoxon rank sum test (exact test) for two sample data was used.

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A one-sided significance level of 5% was used to test for superiority of idebenone *versus* placebo. No adjustments for multiple comparisons or baseline characteristics were performed. Intra- and inter-observer variability of cardiac TDI measurements was assessed using Bland–Altman statistics including the calculation of the mean bias (average difference between measurements) and statistical significance of the mean bias in paired *t*-test (null hypothesis is bias equals zero). Also the coefficient of variation (COV) was calculated (SD of difference divided by the average of the paired samples).

3. Results

Twenty-one participants were included and randomly assigned in a 2:1 ratio to receive idebenone ($N = 13$) or placebo ($N = 8$) (Fig. 1). Except for patient age, demographics at baseline were not different between both groups (Table 1). At inclusion, the idebenone treatment group was significantly older than the placebo control group (13.4 ± 2.1 years *versus* 10.8 ± 1.9 years; $p = 0.01$). This difference had an impact on the disease stage and severity at baseline. More patients in the idebenone treatment group were wheelchair-bound (54% in the idebenone group *versus* 25% in the placebo group). In both groups the same proportion of patients received concomitant glucocorticoid treatment. None of the included patients were on any cardiac medication (ACE inhibitor, β-blocker, diuretics, any other).

3.1. Treatment compliance, safety and tolerability, pharmacokinetics

Based on the patient diary entries and tablet counts, patient treatment compliance was excellent for all patients. There were no drug discontinuations or patient drop-outs.

Table 1
Baseline characteristics and demographics of study groups.

	Placebo	Idebenone	
	8 Subjects	13 Subjects	*p*-Value
Age [years]	10.8 ± 1.9	13.4 ± 2.1	0.01[a]
Race			
Caucasian/white	7	13	nd
Black	1	0	
Height [cm]	144.6 ± 11.9	150.8 ± 20.8	0.466[a]
Weight [kg]	40.5 ± 7.0	45.1 ± 18.3	0.507[a]
BMI [kg/m^2]	19.6 ± 3.9	19.3 ± 4.3	0.898[a]
Ambulatory patients [*N*] (%)	6 (75.0%)	6 (46.2%)	0.367[b]
Glucocorticoid users [*N*] (%)	5 (62.5%)	8 (61.5%)	0.999[b]

Data expressed as mean ± standard deviation or number of subjects (% of group).
nd, not determined.
[a] Two tailed *t*-test.
[b] Two-tailed Fisher's exact test.

In total 92 adverse events (all mild or moderate) were reported, equally distributed between both treatment groups (Table 2). Gastro-intestinal complaints, infections and headache were the most frequently reported AEs. Two moderate serious AEs occurred (traumatic fractures, one in each treatment group), neither was judged to be related to study medication. A total of 9 patients (42.9%) had clinical AEs that were assessed by the investigator as possibly or probably related to study treatment. There was no significant difference between the treatment groups in the clinical global impression of tolerability (data not shown).

Pharmacokinetic data indicated that the drug was quickly absorbed and reached maximum concentrations around 2 h post ingestion (data not shown). Idebenone plasma concentrations were relatively low, while plasma levels of the QS10 metabolite were more than 10 times

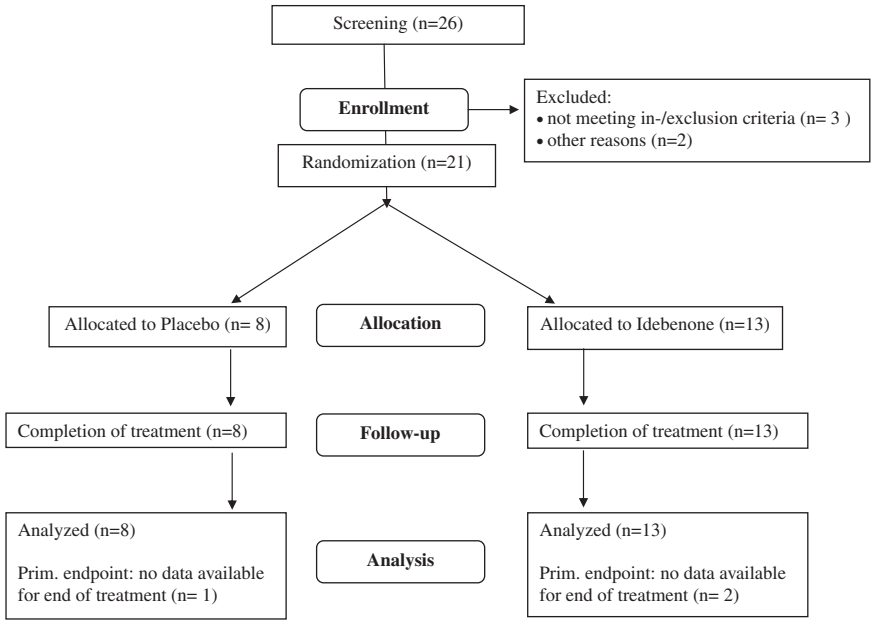

Fig. 1. Study flow chart and patient allocation.

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Table 2
Most common[a] adverse events.

MedDRA preferred term	Idebenone N = [13]		Placebo N = [8]	
	n	%	n	%
Upper respiratory tract infection	4	30.8	2	25.0
Blood cholesterol increased	1	7.7	2	25.0
Diarrhoea	1	7.7	2	25.0
Gastrointestinal infection	2	15.4	1	12.5
Migraine	1	7.7	2	25.0
Rhinitis	2	15.4	1	12.5
Viral infection	2	15.4	1	12.5
Abdominal pain	2	15.4	0	0.0
Abdominal pain upper	0	0.0	2	25.0
Breath sounds abnormal	1	7.7	1	12.5
Bronchitis	1	7.7	1	12.5
Chest pain	1	7.7	1	12.5
Femur fracture	1	7.7	1	12.5
Fungal skin infection	1	7.7	1	12.5
Headache	2	15.4	0	0.0
Pharyngitis	1	7.7	1	12.5
Respiratory tract infection	2	15.4	0	0.0
Vomiting	1	7.7	1	12.5

[a] $\geqslant 10\%$ for any treatment group.

higher than those of idebenone, which is comparable to observations in healthy controls (data not shown) [25].

3.2. Echocardiographic results

3.2.1. Intra- and inter-observer variability of radial deformation parameters assessed by tissue Doppler imaging (TDI)

Intra- and inter-observer variability of tissue Doppler strain measurements has been reported in normal pediatric controls and in pediatric patients with anthracycline toxicity [16,26]. As DMD patients have more difficult echocardiographic windows we assessed the intra- and inter-observer variability for strain and strain rate measurements in the current study population. Results for the primary efficacy variable, peak systolic radial strain in the LV inferolateral wall, are summarized in Table 3. Good reproducibility was obtained for the peak systolic radial strain measurements with higher variability for the strain rate measurements. Similar results were obtained for the longitudinal strain and strain rate measurements although the variability in these measurements was higher (data not shown), possibly related to difficulties in obtaining optimal alignment in the apical views.

3.2.2. Echocardiographic measurements

Echocardiographic cardiac dimensions and global functional systolic and diastolic parameters were not different between both treatment groups at baseline and after 52 weeks of treatment (Table 4). Baseline peak systolic radial strain values in the LV inferolateral wall (primary efficacy variable) were significantly lower in the idebenone group compared to the placebo group (Table 5), probably related to the older age of the idebenone group. After 52 weeks idebenone evoked a mean increase (improvement) from baseline in peak systolic radial strain values of 17.3%, compared to a mean increase from baseline of 7.5% in the placebo group ($p = 0.067$) (Fig. 2A and Table 5).

To account for the significant baseline difference in this parameter caused by the age imbalance, data were analysed also as percentage change from baseline. In this pre-specified but secondary analysis, idebenone led to a 75.5% higher-than-placebo change ($p = 0.030$) from baseline (104.4% *versus* 28.9%). Based on individual response analysis a more pronounced idebenone effect could be noted in patients with the lowest radial strain values at baseline (data not shown). No significant changes in peak systolic radial strain rate values were observed although there was a trend for improvement. For the longitudinal strain measurements a treatment effect could only be observed in the LV mid-lateral segment (improvement in idebenone group *versus* slight deterioration in placebo group (Fig. 2B); $p = 0.063$ for difference in absolute change (Table 5); $p = 0.039$ for difference in percentage change). The changes in peak systolic longitudinal strain and strain rates in the other segments (LV lateral, IVS and RV free wall) were not different between the idebenone and placebo groups. Similarly, calculating a global longitudinal strain value for the LV and IVS regions combined (i.e. average of the data for the LV lateral mid, LV lateral apex, LV lateral basal, IVS mid, IVS apex and IVS basal segments) for the baseline and week 52 time-points did not show a difference between idebenone and placebo groups (global longitudinal strain at baseline: $-19.73 \pm 7.7\%$ (mean $\pm$ SD) for placebo, $-19.25 \pm 8.3\%$ for idebenone; global longitudinal strain at week 52: $-20.06 \pm 7.0\%$ for placebo, $-19.58 \pm 5.0\%$ for idebenone). Global systolic function (FS and

Table 3
Intra-and inter-observer variability assessed by Bland–Altman statistics for peak systolic radial strain and strain rate measurements in the LV inferolateral wall.

	Average[a]	Bias[a]	COV	% Difference	p-Value
Intra observer variability-peak systolic radial strain	30 ± 6	1.6 ± 3.1 (−4.4; 7.6)	10.1	8.5	0.13
Intra observer variability-peak systolic radial strain rate	2.21 ± 0.7	0.1 ± 0.2 (−0.22; 0.42)	7.4	7.3	0.08
Inter-observer variability-peak systolic radial strain	31 ± 7	-2.8 ± 4.7 (−12.1; 6.5)	15.4	10.8	0.55
Inter-observer variability- peak systolic radial strain rate	2.2 ± 0.5	-0.08 ± 0.5 (−1.15; 1.0)	25.0	14.6	0.89

[a] Data is mean $\pm$ standard deviation (and 95% confidence intervals for bias); COV: coefficient of variation. All *p*-values for the intra- and inter-observer variability (bias) were not significant, indicating acceptable reliability.

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Table 4
General and geometric cardiac parameters.

	Baseline (BL)		Week 52	
	Placebo ($n = 8$)	Idebenone ($n = 13$)	Placebo ($n = 8$)	Idebenone ($n = 13$)
Cardiac general				
Heart rate [bpm]	91.49 ± 17.79	90.82 ± 12.21	87.88 ± 17.37	92.00 ± 12.80
Systolic blood pressure [mmHg]	110.0 ± 9.01	106.5 ± 6.81	110.1 ± 10.8	111.2 ± 8.1
Diastolic blood pressure [mmHg]	65.96 ± 8.94	66.54 ± 7.21	69.00 ± 9.49	67.15 ± 9.70
Cardiac geometry				
Inferolateral wall thickness [mm]	6.18 ± 0.47	6.17 ± 1.24	6.05 ± 0.95	6.08 ± 1.12
Inferolateral wall thickness/BSA [mm/m^2]	4.91 ± 0.61	4.67 ± 0.99	4.50 ± 1.01	4.46 ± 0.89
Septal thickness [mm]	7.12 ± 1.05	7.26 ± 1.18	7.55 ± 0.99	6.84 ± 1.35
Septal thickness/BSA [mm/m^2]	5.63 ± 0.77	5.51 ± 1.03	5.56 ± 0.87	4.99 ± 1.01
LV end diastolic diameter [cm]	4.48 ± 0.60	4.54 ± 0.38	4.52 ± 0.76	4.67 ± 0.48
LV end diastolic diameter/BSA [cm/m^2]	3.57 ± 0.67	3.47 ± 0.62	3.36 ± 0.79	3.42 ± 0.51
LV end systolic diameter [cm]	3.06 ± 0.52	3.28 ± 0.39	3.16 ± 0.55	3.33 ± 0.45
LV end systolic diameter/BSA [cm/m^2]	2.45 ± 0.55	2.50 ± 0.48	2.34 ± 0.55	2.44 ± 0.37

BSA, body surface area; data expressed as mean ± standard deviation.

EF) was normal at baseline in both treatment groups, and did not significantly change during the study (Table 5). The same applies to cardiac diastolic function parameters with no obvious abnormalities at baseline and no significant changes during the course of the study (data not shown).

3.3. Effect on cardiac biomarkers

Pro-BNP levels were higher at baseline in the idebenone group and decreased during treatment although the change was not statistically significant (Table 5). In the placebo group pro-BNP levels tended to increase during the study period but the change was not significant. Cardiac troponin I (cTnI) levels were normal at baseline and remained within normal ranges in both groups (Table 5).

3.4. Respiratory function testing and skeletal muscle strength

Respiratory strength measures (peak expiratory flow and static mouth pressures) were assessed as markers for early respiratory involvement, while spirometry measures (FVC, FEV1) monitored restrictive pulmonary changes; all measures were pre-specified secondary study endpoints. There was a significant treatment effect favoring idebenone on peak expiratory flow (L/min and % predicted). Despite their older age, the idebenone cohort increased in PEF and PEF % predicted, whilst this parameter deteriorated in the placebo cohort (Table 6 and Fig. 2C). A similar but non-significant trend was observed for the maximum inspiratory pressure (MIP and MIP % predicted; Table 6 and Fig. 2D). FVC and FEV1 were borderline abnormal at baseline and no between-group differences were observed for the changes during the course of the study (Table 6).

There were no significant between-group differences in upper limb muscle strength (Table 6). During the course of the study 2 patients in the placebo cohort and 1 patient in the idebenone cohort became non-ambulatory (Table 6).

4. Discussion

This trial investigated the efficacy, safety and tolerability of one-year idebenone treatment on cardiac, respiratory and skeletal muscle function in 8–16 year old DMD patients. The primary outcome parameter was the effect on radial myocardial deformation (peak systolic radial strain) in the LV inferolateral wall segment in patients with overall preserved global systolic function. Secondary efficacy endpoints were changes in other cardiac functional parameters, respiratory function and skeletal muscle strength. Idebenone was safe and well tolerated and treatment compliance was excellent. Compared to patients on placebo, patients receiving idebenone showed a trend for improvement of peak systolic radial strain in the LV inferolateral wall. Respiratory assessments showed that patients on idebenone significantly improved in respiratory strength (PEF) whilst patients on placebo deteriorated; no differences between treatment groups were observed for measures of restrictive pulmonary disease (FVC and FEV1). An important limitation of the current study was the relative small number of patients, which in combination with the fixed dose of idebenone given to a wide range of patient ages and body weights prevented us from correlating the observed effects with drug exposure. In interpreting the data from this study it should also be considered that no correction for multiple testing was applied. In addition, the unfortunate age difference between the treatment and placebo groups complicated the interpretation of the study results. Larger randomized controlled studies are required to further investigate the potential therapeutic role of idebenone in DMD.

In view of the limited duration and other limitations of human clinical trials, especially for a slowly progressive and complex childhood orphan disease such as DMD, sensitive and reliable early diagnostic disease markers are required to allow efficacy assessments of protective therapeutic interventions. Selecting a less sensitive parameter

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Table 5
Systolic cardiac function and cardiac biomarkers.

	Baseline (BL)		Week 52		Change (Week 52 – BL)		p-Value[a]
	Placebo	Idebenone	Placebo	Idebenone	Placebo	Idebenone	
Regional myocardial function							
Peak systolic radial strain LV inferolateral wall [%]	33.71 ± 9.75 ($n = 8$)	22.88 ± 9.10 ($n = 13$)	42.80 ± 10.98 ($n = 7$)	39.74 ± 9.31 ($n = 11$)	7.5 ± 12.0 ($n = 7$)	17.3 ± 13.1 ($n = 11$)	0.067
Peak systolic radial strain rate LV inferolateral wall [s^{-1}]	3.25 ± 0.93 ($n = 8$)	2.27 ± 0.65 ($n = 13$)	3.28 ± 0.58 ($n = 7$)	2.72 ± 0.67 ($n = 11$)	0.0 ± 0.9 ($n = 7$)	0.5 ± 0.6 ($n = 11$)	0.100
Peak systolic longitudinal strain [%]							
LV lateral mid	−18.96 ± 5.08 ($n = 8$)	−14.67 ± 6.39 ($n = 12$)	−18.77 ± 5.89 ($n = 7$)	−19.27 ± 5.60 ($n = 10$)	0.9 ± 4.7 ($n = 7$)	−4.1 ± 7.1 $n = 10$)	0.063
LV lateral apex	−17.92 ± 1.94 ($n = 6$)	−21.14 ± 7.71 ($n = 12$)	−17.75 ± 5.28 ($n = 7$)	−19.43 ± 4.58 ($n = 9$)	0.1 ± 4.2 ($n = 5$)	1.4 ± 6.8 ($n = 9$)	0.360
LV lateral basal	−13.21 ± 5.13 ($n = 8$)	−15.01 ± 9.95 ($n = 12$)	−17.74 ± 5.35 ($n = 7$)	−15.15 ± 4.20 ($n = 10$)	−3.4 ± 3.7 ($n = 7$)	1.1 ± 8.7 ($n = 9$)	0.117
Peak systolic longitudinal strain [%]							
IVS mid	−29.54 ± 6.30 ($n = 8$)	−25.50 ± 6.57 ($n = 13$)	−27.75 ± 7.02 ($n = 7$)	−22.37 ± 5.12 ($n = 12$)	1.9 ± 7.5 ($n = 7$)	2.7 ± 8.3 ($n = 12$)	0.581
IVS apex	−16.22 ± 9.54 ($n = 8$)	−19.11 ± 7.60 ($n = 13$)	−15.08 ± 5.85 ($n = 7$)	−19.16 ± 5.80 ($n = 12$)	1.9 ± 12.0 ($n = 7$)	−1.2 ± 7.8 ($n = 12$)	0.251
IVS basal	−22.10 ± 3.54 ($n = 8$)	−19.52 ± 7.47 ($n = 13$)	−23.27 ± 5.66 ($n = 7$)	−21.41 ± 3.56 ($n = 11$)	−0.6 ± 4.8 ($n = 7$)	−2.3 ± 6.5 ($n = 11$)	0.281
Peak systolic longitudinal strain [%]							
RV apex	−32.72 ± 10.04 ($n = 7$)	−29.51 ± 10.94 ($n = 13$)	−33.50 ± 8.93 ($n = 6$)	−31.46 ± 8.73 ($n = 10$)	0.1 ± 8.3 ($n = 6$)	−3.7 ± 14.0 ($n = 10$)	0.277
RV basal	−39.32 ± 13.60 ($n = 7$)	−35.64 ± 7.19 ($n = 13$)	−41.94 ± 16.26 ($n = 7$)	−42.63 ± 10.00 ($n = 10$)	−2.6 ± 15.8 ($n = 7$)	−7.6 ± 9.8 ($n = 10$)	0.217
Global LV function							
Fractional shortening [%]	29.32 ± 2.76 ($n = 8$)	28.00 ± 4.29 ($n = 13$)	30.92 ± 3.45 ($n = 8$)	29.42 ± 5.44 ($n = 13$)	1.6 ± 2.6 ($n = 8$)	1.4 ± 4.1 ($n = 13$)	0.375
Ejection fraction modified Simpson's [%]	49.96 ± 2.18 ($n = 7$)	50.25 ± 5.22 ($n = 13$)	50.41 ± 5.47 ($n = 7$)	47.47 ± 8.35 ($n = 12$)	0.4 ± 5.5 ($n = 7$)	−1.9 ± 9.8 ($n = 12$)	0.717
Cardiac index [L/min/m^2]	2.99 ± 1.06 ($n = 7$)	3.21 ± 0.79 ($n = 11$)	2.66 ± 0.63 ($n = 8$)	3.03 ± 1.05 ($n = 13$)	−0.2 ± 0.9 ($n = 7$)	−0.1 ± 0.9 ($n = 11$)	0.415
Cardiac output [L/min]	4.32 ± 0.84 ($n = 7$)	3.90 ± 0.57 ($n = 11$)	3.63 ± 0.92 ($n = 8$)	4.13 ± 1.32 ($n = 13$)	−0.5 ± 0.7 ($n = 7$)	0.1 ± 1.3 ($n = 11$)	0.112
Cardiac biomarkers							
Brain natriuretic peptide, pro-BNP [ng/L]	52.6 ± 35.20 ($n = 8$)	138.1 ± 262.7 ($n = 13$)	64.3 ± 55.28 ($n = 8$)	101.9 ± 128.26 ($n = 13$)	11.6 ± 51.4 ($n = 8$)	−36.2 ± 141.7 ($n = 13$)	0.163
Cardiac troponin I, cTnI [μg/L]	0.10 ± 0.18 ($n = 8$)	0.07 ± 0.07 ($n = 13$)	0.05 ± 0.06 ($n = 8$)	0.08 ± 0.10 ($n = 13$)	−0.1 ± 0.1 ($n = 8$)	0.0 ± 0.1 ($n = 13$)	0.977

LV, left ventricle; IVS, interventricular septum; RV, right ventricle. Data expressed as mean ± standard deviation.
[a] One-sided p-values.

reflecting advanced disease would either require to study older patient populations, which would be in contrast with the concept of a protective disease-modifying approach, or would require to perform very long-term follow-up trials which in practice are extremely difficult.

Therefore, as its primary cardiac outcome measure this study has used peak systolic radial strain in the LV inferolateral wall, an early marker of systolic dysfunction in DMD. Tissue Doppler-derived myocardial deformation indices provide a quantitative method to evaluate regional LV contractility and dysfunction [27]. In a dog model for DMD early reduction in regional peak myocardial gradients was associated with fibrotic changes [11]. In young DMD patients without overt echocardiographic changes, regional myocardial dysfunction, especially in the LV inferolateral segments, precedes overt and global systolic cardiac dysfunction, and the early changes were shown to be predictive of later cardiac outcome [8–10]. Although there is no direct evidence that reduced strain/strain rate is predictive of long-term heart failure and death, there is increasing evidence suggesting that deterioration of strain is progressive and can be associated with regional myocardial fibrosis. Specifically, by MRI tagging in DMD patients reduction in circumferential strain was observed during serial follow-up prior to changes in ejection fraction [28,29]. In addition, there is evidence that regional tissue/fibrotic changes can be present in Duchenne muscular dystrophy and that regional myocardial fibrosis is associated with reduced myocardial strain [30,31]. Results from the current study are in agreement with this emerging picture,

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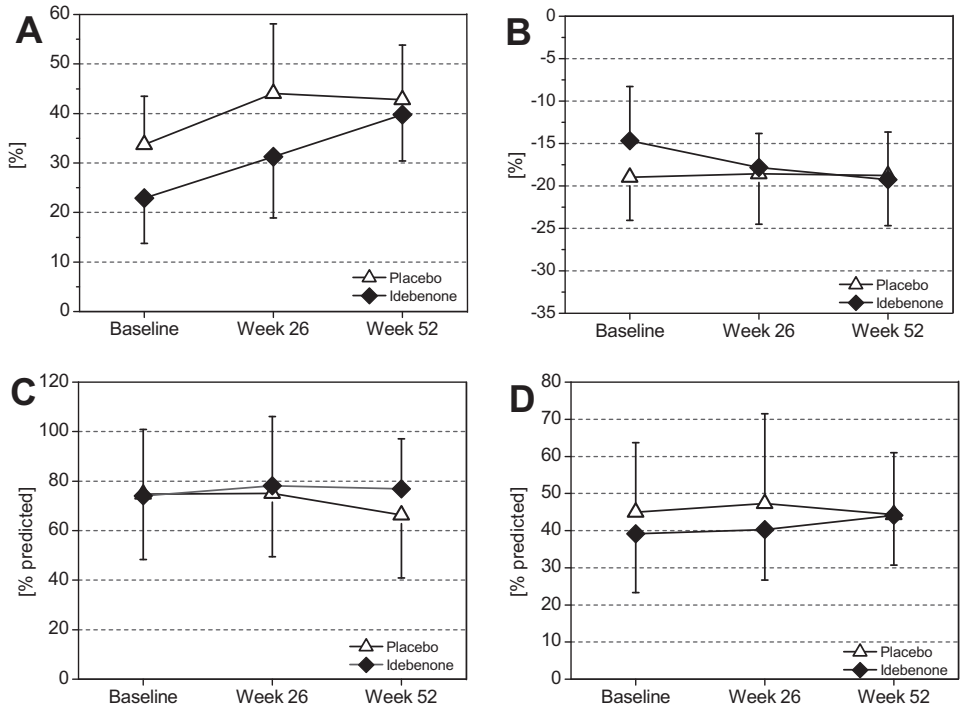

Fig. 2. Effects of idebenone *versus* placebo on cardiac and respiratory functional parameters. Change from baseline to Week 26 and Week 52 for peak systolic radial strain LV inferolateral wall (primary endpoint) (A), peak systolic longitudinal strain LV lateral mid (B), peak expiratory flow (PEF) % predicted (C), and maximum inspiratory pressure (MIP) % predicted (D). Data is mean ± SD.

Table 6
Respiratory function and skeletal muscle strength/ambulation.

	Baseline (BL)		Week 52		Change Week 52–BL		*p*-Value[b]
	Placebo	Idebenone	Placebo	Idebenone	Placebo	Idebenone	
Respiratory function							
FVC [L]	1.93 ± 0.38 ($n = 8$)	2.19 ± 0.58 ($n = 13$)	2.08 ± 0.59 ($n = 8$)	2.33 ± 0.67 ($n = 13$)	0.15 ± 0.29 ($n = 8$)	0.14 ± 0.31 ($n = 13$)	0.529
FVC [% predicted]	80.6 ± 28.87 ($n = 8$)	76.5 ± 25.58 ($n = 13$)	82.6 ± 37.11 ($n = 8$)	75.3 ± 24.79 ($n = 13$)	2.0 ± 11.0 ($n = 8$)	−1.2 ± 6.4 ($n = 13$)	0.793
FEV1 [L]	1.70 ± 0.39 ($n = 8$)	1.97 ± 0.59 ($n = 13$)	1.81 ± 0.52 ($n = 8$)	2.08 ± 0.71 ($n = 13$)	0.10 ± 0.27 ($n = 8$)	0.11 ± 0.37 ($n = 13$)	0.484
FEV1 [% predicted]	81.9 ± 29.68 ($n = 8$)	76.5 ± 23.94 ($n = 13$)	81.5 ± 35.80 ($n = 8$)	74.5 ± 23.88 ($n = 13$)	−0.4 ± 9.2 ($n = 8$)	−2.0 ± 9.2 ($n = 13$)	0.651
PEF [L/min]	243.8 ± 73.7 ($n = 8$)	261.5 ± 93.9 ($n = 13$)	230.0 ± 67.8 ($n = 8$)	292.3 ± 90.6 ($n = 13$)	−13.8 ± 51.0 ($n = 8$)	30.8 ± 54.4 ($n = 13$)	0.039
PEF [% predicted]	74.8 ± 26.49 ($n = 8$)	74.1 ± 26.75 ($n = 13$)	66.3 ± 25.38 ($n = 8$)	76.9 ± 20.13 ($n = 13$)	−8.5 ± 13.8 ($n = 8$)	2.8 ± 13.8 ($n = 13$)	0.042
MIP [cm H_2O]	−39.4 ± 16.57 ($n = 8$)	−40.0 ± 16.58 ($n = 13$)	−41.9 ± 15.34 ($n = 8$)	−47.3 ± 14.09 ($n = 13$)	−2.5 ± 6.6 ($n = 8$)	−7.3 ± 13.0 ($n = 13$)	0.173
MIP [% predicted]	45.0 ± 18.69 ($n = 8$)	39.2 ± 15.89 ($n = 13$)	44.3 ± 16.66 ($n = 8$)	44.1 ± 13.38 ($n = 13$)	−0.8 ± 7.3 ($n = 8$)	4.8 ± 13.0 ($n = 13$)	0.142
Upper limb muscle strength/ambulation							
QMT grip [lbs]	40.31 ± 27.44 ($n = 8$)	33.48 ± 16.43 ($n = 13$)	43.94 ± 32.91 ($n = 8$)	34.07 ± 17.28 ($n = 13$)	3.6 ± 7.4 ($n = 8$)	0.6 ± 7.2 ($n = 13$)	0.820
QMT arms [lbs]	30.21 ± 25.04 ($n = 7$)	20.81 ± 8.77 ($n = 12$)	30.21 ± 28.54 ($n = 7$)	18.95 ± 8.74 ($n = 12$)	0.0 ± 4.6 ($n = 7$)	−1.9 ± 3.2 ($n = 12$)	0.843
Ambulatory/group size[a] (%)	6/8 (100)	6/13 (100)	4/8 (66.6)	5/13 (83.3)	−2 (−33.4)	−1 (−16.7)	0.409[c]

FVC (forced vital capacity); FEV1 (forced expiratory volume 1 s); PEF (peak expiratory flow); MIP (maximal inspiratory pressure); QMT grip (sum of right and left grip strength); QMT arms (sum of right and left elbow flexors and elbow extensors).

[a] Number of subjects ambulatory at baseline set to 100%.

[b] One-sided *p*-values.

[c] Fisher's exact test, one-sided *p*-value. Data expressed as mean ± standard deviation.

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as at baseline both treatment groups had normal global systolic and diastolic function but already decreased myocardial deformation especially in the LV inferolateral segments. The reliability of segmental myocardial velocity and deformation imaging with Tissue Doppler echocardiography has been reported previously in normal and diseased pediatric patient populations. Also in the current study population we found that the intra- and inter-observer variability was acceptable and within the range of most echocardiographic measurements [17].

The interpretation of the current study results is complicated by the unfortunate age difference between the idebenone and placebo groups. This resulted in a significant difference in peak systolic radial strain at baseline between both treatment groups, which is in line with previous reports showing progressive abnormalities in this parameter with increasing age of DMD patients [9]. This age-related baseline difference influenced the direct comparison of the absolute changes from baseline between the two treatment groups, and therefore the data were also analyzed additionally as percentage change from baseline. Compared to patients on placebo, patients receiving idebenone showed a significantly higher percentage change from baseline in peak systolic radial strain measurements in the LV inferolateral segment. It is not fully understood why the placebo group showed a small improvement rather than a decline in this parameter, particularly in the first 6 months of the study. The observed change was non-significant and within the reported 8–10% measurement variability range and a possible influence of other factors, such as concomitant steroid treatment, cannot be excluded.

Although showing a trend in the same direction, no significant difference between the treatment groups was obtained for the peak systolic radial strain rate measurements in the same cardiac segment. This could potentially be explained by the higher variability in the strain rate measurements. Peak systolic longitudinal strain in the mid segment of the LV lateral wall also showed a trend for improvement in the idebenone treatment group compared to the placebo group. Obviously, data from a larger confirmatory study with adequate stratification are needed to better understand the impact of concomitant (steroid) treatment on functional cardiac parameters, to distinguish a true treatment effect from the natural course of change and to correlate observed changes with an improved overall global cardiac outcome.

The current study also investigated potential effects of 12 months idebenone treatment on respiratory function and skeletal muscle strength. Because the respiratory involvement is progressive and in general relatively mild in the age range studied in this trial, parameters of both early (PEF and MIP) and late (FVC) respiratory involvement were included. In DMD progressive respiratory muscle weakness is the major factor in the development of restrictive pulmonary disease and respiratory insufficiency [2–4]. FVC has been shown to be predictive of survival, but this parameter usually does not decline until patients become wheelchair bound and the onset of this decline is further delayed by the use of glucocorticoids [32]. In the absence of bronchial obstruction, PEF and MIP are considered early measures of expiratory muscle force [33]. Likewise, reduced maximal airway pressures have been shown to be amongst the first sign of respiratory dysfunction in DMD, preceding the restrictive lung volume changes that result from muscle fibrosis [34,35]. In the current study population (majority of patients being ambulatory and on glucocorticoids), FVC was only mildly decreased at baseline and was not influenced by idebenone treatment. In contrast parameters for respiratory muscle weakness (PEF, MIP) deteriorated in the placebo group but improved in the idebenone group, with a statistically significant treatment effect of idebenone on PEF.

The observed effects of idebenone can be explained by its ability to facilitate electron flux along the mitochondrial respiratory chain and to reduce oxidative stress [14,36,37], pathways that have been implicated in the pathophysiology of dystrophin-deficient muscular dystrophy [38–40]. The current study was based on this scientific rationale and followed previous long-term controlled clinical preclinical findings in the homologous *mdx* mouse, which provided the first evidence for a potential therapeutic role of idebenone in dystrophin-deficient muscular dystrophy [15].

In conclusion, the current Phase IIa study explored the potential disease-modifying effect of idebenone on the progression of early functional cardiac and respiratory parameters in DMD, a disease where the associated cardiomyopathy and respiratory failure are responsible for early death of patients. A larger, randomized controlled study is currently ongoing to further investigate the potential therapeutic role of idebenone in DMD.

Conflict of interest

The investigators had sole discretion over study design, collection, analysis, and interpretation of data, writing of the report, and decision to submit it for publication. TM is a regular employee and stock and option holder of Santhera Pharmaceuticals and GMB and TM are co-inventors of relevant patent applications. All other authors have no conflicts of interest.

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