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Efficacy of idebenone on respiratory function in patients with Duchenne muscular dystrophy not using glucocorticoids (DELOS): a double-blind randomised placebo-controlled phase 3 trial

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Summary

Background Cardiorespiratory failure is the leading cause of death in Duchenne muscular dystrophy. Based on preclinical and phase 2 evidence, we assessed the efficacy and safety of idebenone in young patients with Duchenne muscular dystrophy who were not taking concomitant glucocorticoids.

Methods In a multicentre phase 3 trial in Belgium, Germany, the Netherlands, Switzerland, France, Sweden, Austria, Italy, Spain, and the USA, patients (age 10–18 years old) with Duchenne muscular dystrophy were randomly assigned in a one-to-one ratio with a central interactive web response system with a permuted block design with four patients per block to receive idebenone (300 mg three times a day) or matching placebo orally for 52 weeks. Study personnel and patients were masked to treatment assignment. The primary endpoint was change in peak expiratory flow (PEF) as percentage predicted (PEF%p) from baseline to week 52, measured with spirometry. Analysis was by intention to treat (ITT) and a modified ITT (mITT), which was prospectively defined to exclude patients with at least 20% difference in the yearly change in PEF%p, measured with hospital-based and weekly home-based spirometry. This study is registered with ClinicalTrials.gov, number NCT01027884.

Findings 31 patients in the idebenone group and 33 in the placebo group comprised the ITT population, and 30 and 27 comprised the mITT population. Idebenone significantly attenuated the fall in PEF%p from baseline to week 52 in the mITT (–3·05%p [95% CI –7·08 to 0·97], p=0·134, *vs* placebo –9·01%p [–13·18 to –4·84], p=0·0001; difference 5·96%p [0·16 to 11·76], p=0·044) and ITT populations (–2·57%p [–6·68 to 1·54], p=0·215, *vs* –8·84%p [–12·73 to –4·95], p<0·0001; difference 6·27%p [0·61 to 11·93], p=0·031). Idebenone also had a significant effect on PEF (L/min), weekly home-based PEF, FVC, and FEV_1. The effect of idebenone on respiratory function outcomes was similar between patients with previous corticosteroid use and steroid-naive patients. Treatment with idebenone was safe and well tolerated with adverse event rates were similar in both groups. Nasopharyngitis and headache were the most common adverse events (idebenone, eight [25%] and six [19%] of 32 patients; placebo, nine [26%] and seven [21%] of 34 patients). Transient and mild diarrhoea was more common in the idebenone group than in the placebo group (eight [25%] *vs* four [12%] patients).

Interpretation Idebenone reduced the loss of respiratory function and represents a new treatment option for patients with Duchenne muscular dystrophy.

Funding Santhera Pharmaceuticals.

Introduction

Duchenne muscular dystrophy is the most common and devastating type of muscular dystrophy.[1] Progressive weakness of respiratory muscles leads to restrictive pulmonary disease that evolves into respiratory complications and early morbidity and mortality.[2–7] Glucocorticoids are the only medications that can slow the decline in muscle strength and function and delay the onset and progression of respiratory dysfunction.[8–10] However, not all patients with Duchenne muscular dystrophy respond to steroids to the same extent and the well known side-effects of steroids restrict their clinical use, particularly in non-ambulatory patients in the later stage of the disease. In a natural history study, 42% of patients with Duchenne muscular dystrophy aged 10 years and older had never used glucocorticoids or discontinued their use because of side-effects and tolerability limitations.[9] Consequently, for many patients with Duchenne muscular dystrophy there are no pharmacological treatment options at about the age when patients become non-ambulatory and the decline in their respiratory function becomes clinically relevant.

The short-chain benzoquinone idebenone is a potent antioxidant and inhibitor of lipid peroxidation that is capable of stimulating mitochondrial electron flux and cellular energy production.[11,12] The results of a placebo-controlled study in the *mdx* mouse showed

significant cardioprotective and voluntary exercise performance effects after idebenone treatment.[13] The findings from a phase 2 randomised placebo-controlled trial (DELPHI) showed beneficial effects of idebenone on early functional cardiac and respiratory markers.[14] An important finding from the DELPHI study was that patients treated with idebenone had stabilised peak expiratory flow as percentage predicted (PEF%p), a marker of expiratory muscle strength compared with a reduction in patients given placebo. Additional analyses indicated that the effect of idebenone on respiratory function outcomes was larger in patients not taking concomitant glucocorticoids.[15]

We investigated the efficacy, tolerability, and safety of idebenone in a confirmatory phase 3 trial in patients with Duchenne muscular dystrophy not taking concomitant glucocorticoids.

Methods

Study design and patients

Patients aged 10–18 years with a documented diagnosis of Duchenne muscular dystrophy were eligible for inclusion in this phase 3 trial. Recruiting centres were in Belgium, Germany, the Netherlands, Switzerland, France, Sweden, Austria, Italy, Spain, and the USA. A full list of inclusion, exclusion, and withdrawal criteria is provided in the appendix.

Patients were enrolled between July 27, 2009 (study start date), and Dec 14, 2012; the study end date (last patient completed the study[A: okay?]) was Jan 14, 2014.

Randomisation and masking

We used an interactive web response system to randomly allocate patients in a one-to-one ratio with a permuted block design with four patients per block to film-coated tablets of idebenone (150 mg per tablet, Raxone/Catena, Santhera Pharmaceuticals, Liestal, Switzerland; 300 mg three times a day, orally, during meals) or matching placebo for 52 weeks. Two siblings of patients who were already randomly allocated were assigned to the same group as their siblings to avoid mix up of study medication. Randomisation was balanced for PEF%p at baseline (two PEF%p strata: <40%p and 40–80%p). All study personnel and patients were masked to treatment group assignment. Compliance was monitored with entries in a patient's diary and pill counts. After enrolment, safety and efficacy were assessed during hospital visits at weeks 13, 26, 39, and 52. Additional safety assessments were undertaken 4 weeks after randomisation and at the follow-up visit 4 weeks after the week 52 visit or after early discontinuation of study medication. Patients were instructed and educated to assess their weekly respiratory function (peak expiratory flow [PEF] and forced expiratory volume in 1 s [FEV_1]) using the hand-held ASMA-1 device (usb model 4000, Vitalograph, Maids Moreton, UK) at home. The study had several protocol amendments, which are listed in the appendix.

The trial and any changes to the protocol were approved by relevant national authorities and the institutional review boards or independent ethics committees in the countries of the participating centres and done in accordance with good clinical practice and the principles of the Declaration of Helsinki. We obtained written informed consent from patients.

Outcomes

The primary objective was to assess the efficacy of idebenone, compared with placebo, in improving or reducing loss of respiratory function, measured by a qualified, trained, and certified evaluator at each centre in accordance with standardised procedures and international guidelines. Pulmonary function tests were done at each hospital visit with a Pneumotrac Spirometer 6800 (Vitalograph) and maximal static airway pressures were assessed with a MicroRPM instrument (Medical Supply Store, Chorley, UK). At each hospital visit, PEF and FEV_1 were also measured with the patient's portable ASMA-1

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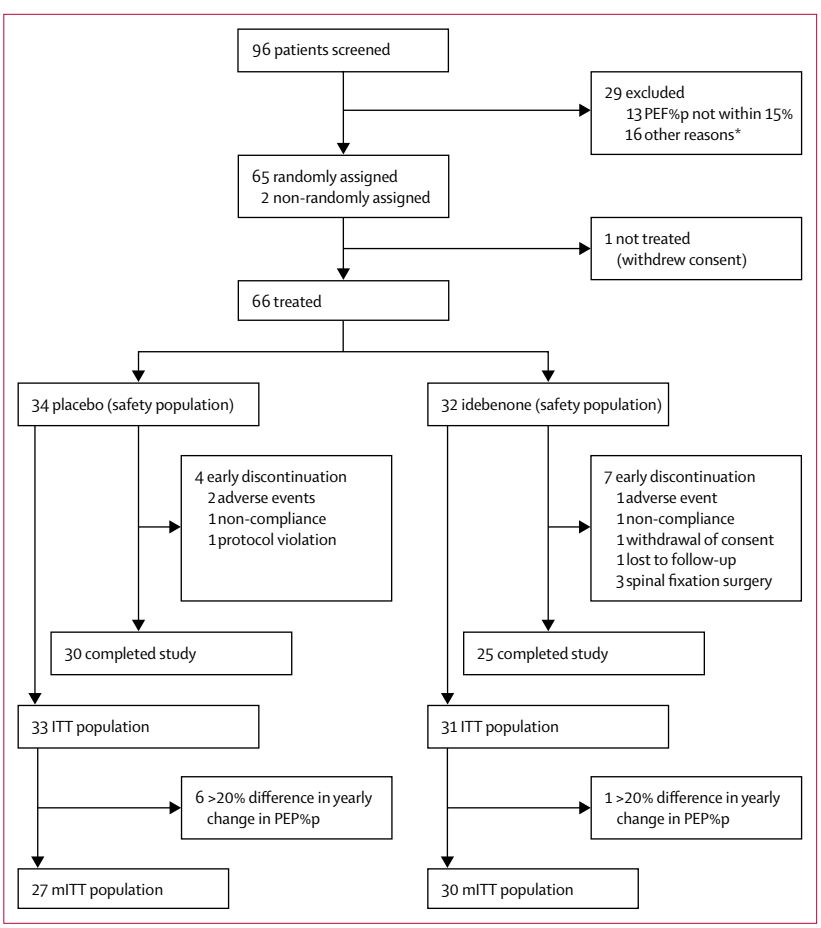

Figure 1: **Trial profile**
PEF%p=peak expiratory flow as percentage predicted. ITT=intention to treat. mITT=modified intention to treat. *Two patients were unable to form a mouth seal, two had PEF %p greater than 80% at baseline, two required assisted ventilation, one patient was using steroids, one required spinal fixation surgery, two patients were unable to comply with study procedures, one patient withdrew informed consent, one was a smoker, and four patients had one or more other reasons for exclusion.

device. The primary endpoint was the change in spirometer-measured PEF%p from baseline to week 52. Secondary respiratory efficacy endpoints were changes in PEF, forced vital capacity (FVC), FEV_1, maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), and peak cough flow—assessed during hospital visits at weeks 13, 26, 39, and 52. PEF and FEV_1 were also measured weekly at home with the portable ASMA-1 device. The highest value from a minimum of three and up to five consecutive manoeuvers was used for each assessment. Percentage predicted (%p) values were calculated with established equations (appendix).[16–21] Safety assessments were physical examination, vital signs, and blood or urine sampling. Cardiac function (transthoracic echocardiography and 12-lead electrocardiography [ECG]) was assessed for safety monitoring, but not as efficacy endpoints. Blood and urine analyses were done at BARC Europe NV (Gent, Belgium). Adverse events were graded for severity and relation to the study drug and coded with the MedDRA dictionary (version 14.0).

	Idebenone group (n=31)	Placebo group (n=33)
Age (years)	13·5 (2·7)	15·0 (2·5)
Weight (kg)	55·3 (18·3)	61·9 (18·0)
Height* (cm)	157·4 (11·3)	162·4 (12·4)
Body-mass index (kg/m²)	22·0 (5·9)	23·4 (5·6)
Ethnic origin		
White	29 (94%)	31 (94%)
Oriental	1 (3%)	0
Hispanic	0	1 (3%)
Other	1 (3%)	1 (3%)
Previous glucocorticoid use		
Yes	17 (55%)	19 (58%)
No	14 (45%)	14 (42%)
Time since last glucocorticoid use (years)	2·9 (1·8)	4·3 (2·2)
Patient in wheelchair	28 (90%)	31 (94%)
Baseline PEF%p		
<40%p	5 (16%)	7 (21%)
40–80%p	26 (84%)	26 (79%)
Baseline respiratory function test		
PEF%p	53·5 (10·3)	54·2 (13·2)
PEF (L/min)	217·7 (48·6)	233·8 (59·6)
FVC%p	55·3 (15·8)	50·4 (20·0)
FVC (L)	1·9 (0·5)	1·9 (0·5)
FEV_1%p	53·3 (15·1)	49·7 (18·3)
FEV_1 (L)	1·54 (0·33)	1·71 (0·57)
MIP%p	43·5 (22·2)	38·5 (16·9)
MIP (cm H_2O)	47·3 (24·4)	44·6 (16·9)
MEP%p	28·3 (12·2)	25·1 (12·2)
MEP (cm H_2O)	40·6 (15·6)	39·7 (16·6)
PCF (L/min)	243·0 (70·7)	256·4 (50·5)

Data are mean (SD) or number (%). ITT=intention-to-treat population. PEF%p=peak expiratory flow as percentage predicted. FVC%p=forced vital capacity as percentage predicted. FVC=forced vital capacity. FEV_1%p=forced expiratory volume in 1 s as percentage predicted. FEV_1=forced expiratory volume in 1 s. MIP%p=maximum inspiratory pressure as percentage predicted. MIP=maximum inspiratory pressure. MEP%p=maximum expiratory pressure as percentage predicted. MEP=maximum expiratory pressure. PCF=peak cough flow. *Derived from ulnar length.[20,21]

Table 1: **Demographic characteristics and baseline pulmonary function values in the ITT population**

Statistical analysis

A statistical analysis plan was prepared before the database was locked. The primary analysis of the primary endpoint (change in PEF%p from baseline to week 52) was to be made in a modified intention-to-treat population (mITT; appendix), which excluded patients with at least 20% difference in the yearly change in PEF%p measured with hospital-based spirometry and home-based ASMA-1 assessments. Like all the other endpoints, the primary endpoint was also calculated in the full ITT population. Continuous variables were analysed with a mixed model for repeated measurements with treatment group, visit, and interaction between treatment group and visit used as fixed factors in the model and baseline assessment used as a covariate. For responder analyses, responders were defined as patients who did not have deterioration in respiratory function tests. Responder rates were compared between treatment groups with the Cochran-Mantel-Haenszel test with missing data imputed with the last observation carried forward method. All hypotheses tested and 95% CIs presented were two-sided and p values of less than 5% were significant without adjustment for multiplicity and regarded as exploratory except for the primary endpoint. The sample size for the study provided 80% power to detect a difference of 10·3% in PEF%p. A planned futility analysis was done after all 64 patients had been randomly assigned and 37 had completed the trial. This analysis, done by the data and safety monitoring board, confirmed non-futility of the trial.

This study is registered with ClinicalTrials.gov, number NCT01027884.

Role of the funding source

The study funder was involved in the study design, and data gathering and analysis. The investigators and all authors had sole discretion in the data analysis and interpretation, writing of the report, and the decision to submit for publication.

Results

96 patients were screened and 29 were excluded from participation because they did not meet inclusion or exclusion criteria. 65 patients were randomly assigned and two patients were allocated to the same treatment as their randomly assigned siblings (figure 1). One patient never took study medication, resulting in 66 patients who were treated and included in the safety population (34 in the placebo group and 32 in the idebenone group). 55 patients completed the trial and 11 withdrew or

discontinued the drug during the study. The ITT population (33 patients in the placebo group and 31 in the idebenone group) excluded patients who were allocated to the same treatment as their siblings and the mITT population prospectively excluded seven patients (27 and 30 patients; appendix).

Patients' characteristics at baseline were balanced between the treatment groups (table 1), except for younger

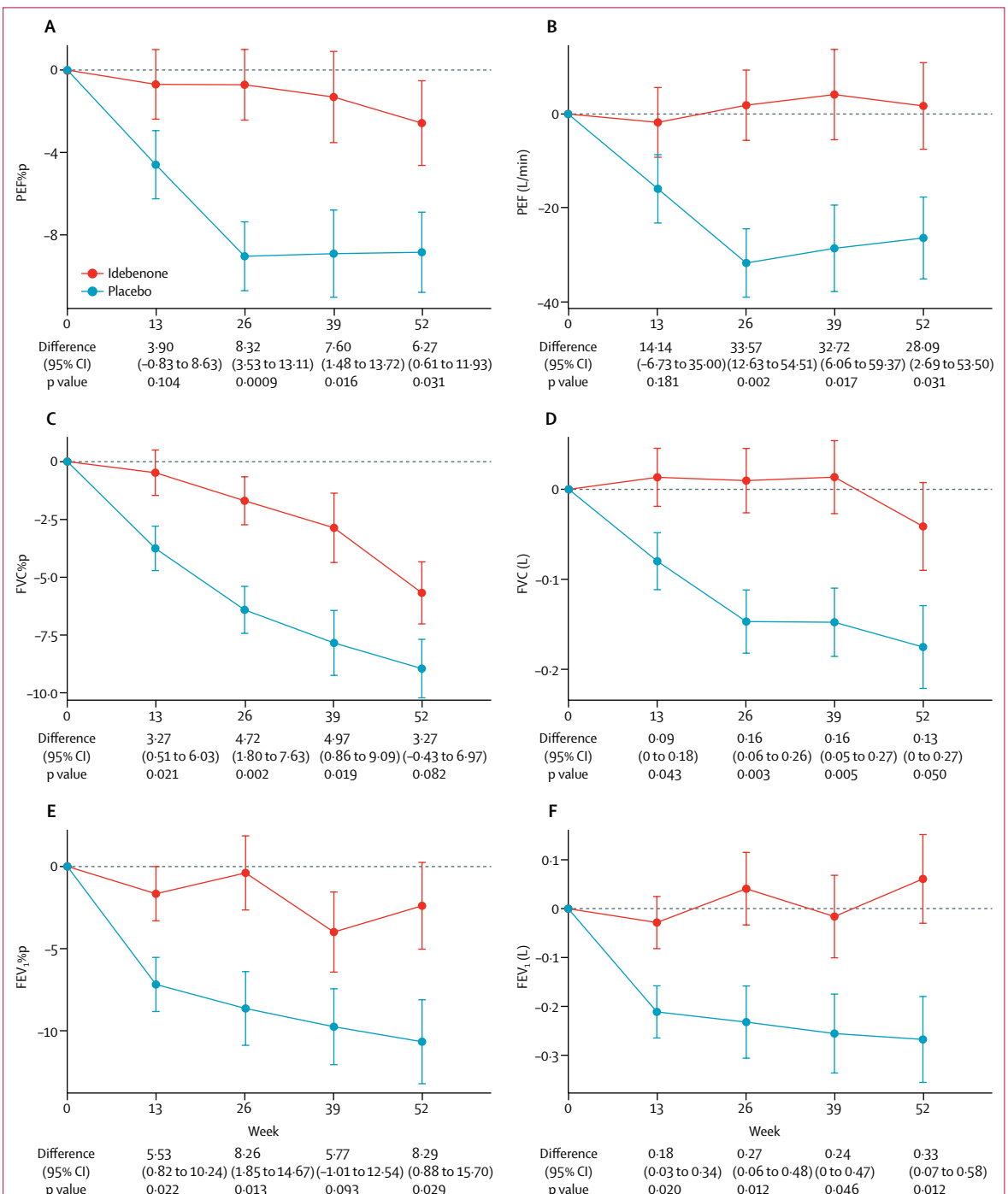

Figure 2: **Results of respiratory function test outcomes in the ITT population** [A: sorry for style reasons we can't replace "to" with a comma in 95% CIs]
(A) PEF%p. (B) PEF. (C) FVC%p. (D) FVC. (E) FEV_1%p. (F) FEV_1. Data are mean (SE), unless otherwise indicated; treatment differences and p values are shown for the between-group comparisons. ITT=intention-to-treat population. PEF%p=peak expiratory flow as percentage predicted. PEF=peak expiratory flow. FVC%p=forced vital capacity as percentage predicted. FVC=forced vital capacity. FEV_1%p=forced expiratory volume in 1 s as percentage predicted. FEV_1=forced expiratory volume in 1 s.

	Idebenone group (n=31)			Placebo group (n=33)			Group difference	
	Mean (SD)	Change (95% CI)	p value	Mean (SD)	Change (95% CI)	p value	Difference (95% CI)	p value
PEF%p								
Baseline	53·5 (10·3)			54·2 (13·2)				
Change from baseline (MMRM)								
Week 52		−2·57 (−6·68 to 1·54)	0·215		−8·84 (−12·73 to −4·95)	<0·0001	6·27 (0·61 to 11·93)	0·031
Weeks 13–52		−1·32 (−4·59 to 1·94)	0·421		−7·84 (−11·00 to −4·69)	<0·0001	6·52 (1·98 to 11·06)	0·006
PEF (L/min)								
Baseline mean (SD)	217·7 (48·6)			233·8 (59·6)				
Change from baseline (MMRM)								
Week 52		1·72 (−16·71 to 20·14)	0·853		−26·38 (−43·81 to −8·95)	0·004	28·09 (2·69 to 53·50)	0·031
Weeks 13–52		1·48 (−12·96 to 15·93)	0·838		−25·65 (−39·62 to −11·67)	0·001	27·13 (6·97 to 47·29)	0·009

ITT=intention to treat. MMRM=mixed model for repeated measurements. PEF=peak expiratory flow. PEF%p=peak expiratory flow as percentage predicted.

Table 2: **Change in PEF from baseline to week 52 and across all post-baseline assessment timepoints (weeks 13–52) in the ITT population**

age in the idebenone group. Time since last steroid use before enrolment in the trial was well above the required 12-month washout in both groups (table 1). At baseline more than 90% of patients were non-ambulatory and most patients presented with PEF%p of 40–80%p (table 1).

Compliance with study medication was good with similar exposures between treatment groups (mean 332·7 days [SD 71·9] in the idebenone group and 344·8 days [65·1] in the placebo group).

Patients were well balanced between treatment groups for baseline respiratory function variables (table 1). The primary efficacy variable (PEF%p), as measured with hospital-based spirometry or with the home-based ASMA-1 device, was similar between groups at baseline (appendix), confirming the reliability of the data obtained.

For the primary endpoint (mITT population), there was a significant fall in PEF%p by 9·01%p (95% CI −13·18 to −4·84; p=0·0001) from baseline to week 52 in the placebo group compared with a non-significant decline of 3·05%p (−7·08 to 0·97; p=0·134) in the idebenone group, resulting in a significant difference between treatment groups of 5·96%p (0·16 to 11·76; p=0·044) at week 52 and this represented a 66% reduction in loss of PEF%p. The effect of idebenone was significant at week 26 (p=0·007) and week 39 (p=0·034) and at all post-baseline assessment timepoints together (p=0·018). Baseline PEF%p values in the mITT population were well balanced (idebenone 53·1%p [SD 10·2] and placebo 54·3%p [13·5]). Similar results were obtained for the full ITT population with a significant decline in PEF%p from baseline to week 52 in the placebo group by 8·84%p (95% CI −12·73 to −4·95; p<0·0001) compared with a non-significant decline of 2·57%p (−6·68 to 1·54; p=0·215) in the idebenone group, resulting in significant differences between treatment groups at week 52 (6·27%p [0·61 to 11·93]; p=0·031) and at other study timepoints (figure 2A; table 2). Results for the primary endpoint, assessed with standard spirometry during hospital visits, were confirmed with the results for the secondary PEF endpoints, measured at home with the ASMA-1 device, through linear regression analysis for the yearly change (p=0·055) and mean of data obtained during 6 weeks around hospital visits (p=0·028; figure 3; appendix). Sensitivity analyses were done to assess the robustness of the results by applying different imputation methods for missing data in the ITT population, analysing a different population, and by excluding patients likely to affect the results (figure 3). The results show that the treatment effect was not altered by different assumptions about missing data or by the exclusion of data for patients defined as being in different populations.

Diverging trajectories between treatment groups were also noted in PEF with significant differences between treatment groups at week 52 (28·1 L/min [95% CI 2·69–53·50]; p=0·031) and at other visit timepoints (figure 2B; table 2; appendix). Other respiratory function endpoints such as FVC%p, FVC, FEV_1%p, and FEV_1 showed a consistent pattern with treatment differences, lending support to the efficacy of idebenone over placebo in the preservation of respiratory function (figure 2C–F; appendix). Change from baseline to week 52 was well correlated between PEF%p and FVC%p (r^2=0·333; p<0·0001; appendix). No significant differences were noted in the change from baseline to week 52 for MIP, MEP, and peak cough flow (data not shown). Also, no treatment effect was noted in upper limb strength (measured with hand-held myometry) and function (assessed with the Brooke's scale) and patient-reported outcomes assessed with Pediatric Quality of Life Inventory (data not shown).

Since the study population was a mix of patients who in the past had used glucocorticoids and patients who had never used steroids (table 1), it was of interest to assess whether previous steroid use affected the outcome of respiratory function tests. Post-hoc analysis showed that respiratory function test outcomes were similar between

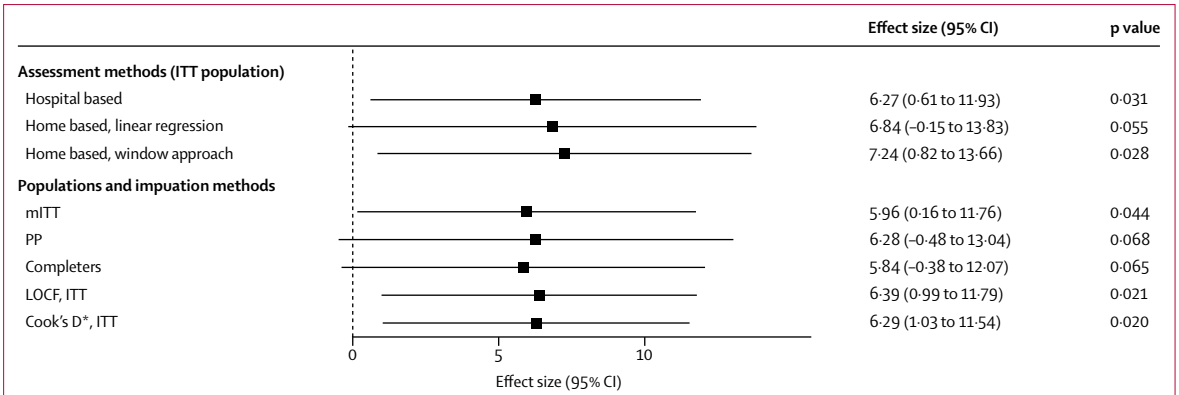

Figure 3: **Comparative effect sizes in favour of idebenone in PEF%p at week 52 with different assessment methods, populations, and methods of imputation for missing data**

PEF%p=peak expiratory flow as percentage predicted. mITT=modified intention to treat. PP=per protocol. LOCF=last observation carried forward. ITT=intention to treat. *Two patients (one in the placebo group and one in the idebenone group) were identified as affecting the result of the primary analysis; these patients were excluded in this post-hoc analysis.

	Idebenone group (n=31)	Placebo group (n=33)	p value*
Patients who did not deteriorate from baseline to week 52			
PEF%p	14 (45%)	8 (24%)	0·081
PEF	18 (58%)	9 (27%)	0·013
FVC%p	7 (23%)	3 (9%)	0·141
FVC	15 (48%)	6 (18%)	0·011
FEV_1%p	14 (45%)	4 (12%)	0·004
FEV_1	18 (58%)	11 (33%)	0·049
Patients who did not deteriorate by 10% or more from baseline to week 52			
PEF%p	22 (71%)	11 (33%)	0·003
PEF	26 (84%)	16 (48%)	0·003
FVC%p	13 (42%)	8 (24%)	0·135
FVC	24 (77%)	17 (52%)	0·032
FEV_1%p	18 (58%)	13 (39%)	0·138
FEV_1	22 (71%)	17 (52%)	0·114

Data are number (%), unless otherwise indicated. ITT=intention-to-treat population. PEF%p=peak expiratory flow as percentage predicted. FVC%p=forced vital capacity as percentage predicted. FVC=forced vital capacity. FEV_1%p=forced expiratory volume in 1 s as percentage predicted. FEV_1=forced expiratory volume in 1 s. *Cochran-Mantel-Haenszel test.

Table 3: **Responder rates in the ITT population for respiratory function test results**

patients with previous steroid use and steroid-naive patients (appendix). To investigate the effect of age, dichotomised age at baseline (≤14 years or >14 years) and the interaction between age and treatment group were included as fixed factors in the model in a post-hoc analysis. Both these factors were non-significant for PEF%p (p=0·384 and p=0·819) and FVC%p (p=0·141 and p=0·941), showing that age did not affect the outcome for PEF%p and FVC%p. Treatment effects were also assessed for the ITT patient subgroups separated by the median age (14 years). A positive treatment effect in favour of idebenone was evident from this post-hoc analysis for patients younger and older than 14 years of age (appendix).

Positive outcomes favouring idebenone over placebo were further supported by the results of prespecified responder analyses, which showed a higher proportion of idebenone-treated patients who did not deteriorate in respiratory function tests between baseline and week 52 (table 3).

Idebenone's effects were also supported with clinical findings. In a prespecified analysis, we counted the number of patients who at any time during the trial dropped below 160 L/min in peak cough flow, a clinically meaningful threshold below which cough is no longer effective enough to provide adequate mucociliary clearance and consensus care recommends mechanical cough assistance.[7,22,23] In the ITT population there were six (18%) of 33 patients in the placebo group but only one (4%) of 25 patients in the idebenone group above the threshold at baseline falling below the 160 L/min threshold. Moreover, the results of a post-hoc analysis showed that there were five (16%) of 32 patients in the placebo group but only one (3%) of 31 patients in the idebenone group who fell below 1 L in FVC, a clinically important threshold and predictor of early mortality.[24] Also, the number of patients reporting upper respiratory tract infection-related adverse events was lower in the idebenone group than in the placebo group (appendix). Similarly, there were more patients in the placebo group reporting lower respiratory tract infection-related adverse events (bronchitis and pneumonia) than in the idebenone group, although the difference was not significant (appendix).

Treatment with idebenone was safe and well tolerated. No deaths occurred during the study. Of the 66 patients included in the safety analyses, 62 (94%) had at least one adverse event: 30 (94%) in the idebenone group and 32 (94%) in the placebo group. Nasopharyngitis (26%) and headache (20%) were the most common adverse

Panel: **Research in context**

Systematic review

We searched PubMed and clinical trial registries for registrations and reports of randomised double-blind placebo-controlled trials of idebenone in the treatment of patients with Duchenne muscular dystrophy. We identified only one study (phase 2 DELPHI trial; ClinicalTrials.gov, number NCT00654784). The phase 3 DELOS trial of idebenone in patients with dystrophin-deficient muscular dystrophy was based on existing evidence: an observer-masked long-term placebo-controlled study in the *mdx* mouse model of Duchenne muscular dystrophy and the proof-of-concept phase 2 DELPHI trial in patients with Duchenne muscular dystrophy. The results of the animal model study showed phenotypic correction with substantial cardioprotection and voluntary exercise performance improvement. DELPHI's results showed a significant respiratory effect of idebenone on peak expiratory flow (primary endpoint in DELOS). The design of the DELOS trial was based on the DELPHI findings and scientific advice consultation with regulatory authorities. The DELPHI and DELOS trials had some differences in drug dosing and patients' characteristics. In DELPHI, idebenone was dosed at 450 mg daily (because of few safety data available at the time); in DELOS we used 900 mg daily. Patients in DELPHI were aged 8–16 years and were a mix of individuals not using concomitant glucocorticoids and those on steroids for Duchenne muscular dystrophy. The DELOS study population consisted of 10–18-year-old patients not taking concomitant glucocorticoids.

Interpretation

To the best of our knowledge, we report for the first time a phase 3 randomised controlled trial in patients with Duchenne muscular dystrophy with a positive outcome. Significant and clinically relevant results for primary and secondary endpoints showed that idebenone reduced the loss of respiratory function in 10–18-year-old patients with Duchenne muscular dystrophy who were not using concomitant glucocorticoids. Also, idebenone was safe and well tolerated. The relevance of modifying the natural course of respiratory disease in Duchenne muscular dystrophy is emphasised in clinical practice where respiratory failure leads to ventilator-dependency and continues to be the predominant cause of early death in patients with Duchenne muscular dystrophy.

events without differences in their incidence between the treatment groups (appendix). Transient and mild diarrhoea, a known side-effect of idebenone intake, was more common in idebenone-treated patients (25% *vs* 12%), whereas constipation was more common in the placebo group than in the idebenone group (18% *vs* 9%; appendix[A: okay?]). Most adverse events were of mild or moderate intensity. Serious adverse events were reported in 6% and severe adverse events in 3% of idebenone-treated patients and in 15% and 12% of placebo-treated patients, none of which were classified as related to intake of study medication (appendix). The adverse events that led to discontinuation of treatment were sleep apnoea syndrome (n=1) and diarrhoea (n=1) in the idebenone group and supraventricular arrhythmia and respiratory failure with pneumonia in the placebo group (all in same patient). None of the adverse events that led to premature discontinuation from the study were judged by the investigator to be related to study treatment. There was no evidence for a clinically relevant effect of idebenone on any haematological or clinical chemistry variable, vital signs, physical examinations, or results from ECG and echocardiography assessments.

Discussion

The DELOS trial met its primary objective and the results showed that idebenone significantly reduced the loss of respiratory function in patients with Duchenne muscular dystrophy.

Ventilatory support and the chronic use of glucocorticoids have contributed to increased longevity in patients with Duchenne muscular dystrophy. Nevertheless, respiratory complications continue to be a main cause of early morbidity and mortality in steroid-treated patients and a subset of patients with Duchenne muscular dystrophy do not respond to or do not tolerate steroid treatment. In an attempt to develop novel treatment options, and continuing from previous studies,[13,14] we have now investigated the efficacy and safety of idebenone in patients with Duchenne muscular dystrophy in the first ever successful phase 3 study of patients with this disease (panel).

Based on the results from a phase 2 study,[14] PEF was selected as the primary efficacy variable, which in the absence of bronchial obstruction is a measure of expiratory muscle strength. In patients with Duchenne muscular dystrophy, progressive weakness of chest wall muscles precedes weakness of the diaphragm (used mainly for inspiratory function) and leads to restrictive lung volume changes (ie, reduced FVC).[4,25–28] Compared with other respiratory variables, FVC is less sensitive to mild muscle weakness in the early stages of the disease.[9,29] Loss of lung volume initially results from the inability to pull up the respiratory system to total lung capacity and to push it down to residual volume. In the later stage of disease, additional restriction occurs as a result of progressive muscle fibrosis and changes in lung and chest wall recoil. Therefore, respiratory strength might be more sensitive to treatment intervention than is lung volume, because this is affected not only by respiratory muscle strength but also by thoracic wall compliance and deformities. Additionally, abnormal respiratory mechanics in Duchenne muscular dystrophy are not restricted to the lungs and chest wall and might also involve the upper airways.[30] Here, weakness of pharyngeal dilator muscles decreases upper airway calibre, causing an increase in upper airway resistance during inspiration, which imposes an increased mechanical load on the diaphragm and other inspiratory muscles.[31] Therefore, PEF is a measure not only of expiratory strength but also inspiratory effort and upper airway resistance.[32,33]

In the DELOS trial, there was a significant fall in PEF%p from baseline to week 52 in the placebo group compared with a non-significant decline in the idebenone group, resulting in a significant and clinically relevant idebenone treatment effect. No treatment effect was noted for MIP and MEP, which at baseline were more severely affected than were the expiratory flow and lung volume variables. These low baseline values are in line with previous data indicating that maximum static airway

pressures are regarded as early markers of respiratory dysfunction in Duchenne muscular dystrophy and their much reduced values at study start could have precluded the detection of any treatment effect.

Morbidity and mortality in patients with Duchenne muscular dystrophy are associated with progressive restrictive lung disease and irreversible loss of lung function, commonly measured as a reduction in FVC.[24] Therefore, reducing the decline in FVC, as shown in this trial, is of clinical relevance. In DELOS, the decrease in FVC in the placebo group is similar to recent natural history data in steroid-naive patients with Duchenne muscular dystrophy.[24,34] Furthermore, the idebenone effect size in DELOS is similar to outcomes reported for investigational treatments of idiopathic pulmonary fibrosis, another restrictive lung disease (appendix).[35,36]

Results from a phase 2 trial (DELPHI) showed a larger effect size of idebenone on respiratory function in patients not taking concomitant glucocorticoids than in patients who took steroids.[15] To account for this influence, only patients not using concomitant steroids were enrolled in DELOS. Subgroup analyses showed that the effect sizes in favour of idebenone for PEF, FVC, and FEV_1 were generally similar between patients who were steroid naive and those who had used steroids in the past for Duchenne muscular dystrophy. These results are in agreement with previous findings that lung volume measurements in past users of steroids are not different from steroid-naive patients,[9] indicating that the therapeutic effect of steroids on respiratory function is diminished after their discontinuation. Although data from the current trial were obtained in patients not using steroids, there is no reason a priori why idebenone could not also be exerting a treatment effect in patients using steroids concomitantly. However, it might be challenging to convincingly show this additive effect of idebenone on top of steroids.[15]

The results of DELOS showed a somewhat larger effect size for PEF%p and FVC%p in the subgroup of patients aged 14 years and younger than in the older patients (appendix), indicating that patients may derive a larger benefit from idebenone if treatment is initiated early.

Idebenone was safe and well tolerated with frequency and severity of adverse events that were similar between treatment groups, in line with previous reports.[14,37]

Limitations of this study are related to the sample size and treatment duration. The study had several protocol amendments (appendix), most notably an amendment that defined the final study population to the subgroup of patients not using glucocorticoids. No patients using concomitant glucocorticoids were enrolled in the study. The robustness of the outcome was assessed with sensitivity analyses by use of different imputation methods, by excluding patients whose inclusion might affect the outcome, and with different assessment methods and intervals. Overall, the data set is robust, thereby alleviating concerns that might result from the small sample size of the study. The duration of a placebo-controlled trial in children with Duchenne muscular dystrophy with advanced disease inevitably has to be limited by ethical reasons. Although a study of 12 months cannot provide data on hard outcome measures such as time to assisted ventilation or death, this limitation is mitigated by the consistency of the idebenone effects on respiratory function outcomes (PEF, FVC, and FEV_1) together with clinically relevant findings. Specifically, the proportion of patients with reductions in FVC or peak cough flow below crucial thresholds,[22–24,38] known to be predictive of imminent ventilatory failure, and the reduced number of upper airway tract infections in the idebenone group, are strongly supportive for the clinical meaningfulness of the idebenone effect. The overall number of lower airway tract infections reported during the 1-year follow-up was small and, therefore, no conclusion can be drawn. However, the numerical difference in favour of idebenone treatment is encouraging and merits further investigation during longer follow-up.

In the past, improved patient care with best-practice recommendations and the introduction of glucocorticoids has greatly increased the survival time of patients with Duchenne muscular dystrophy.[7,8,39,40] Nevertheless, loss of respiratory function continues to be a predominant cause of early morbidity and mortality in patients with Duchenne muscular dystrophy. Efficacy data from this trial show that idebenone significantly reduced the loss of respiratory function in patients with Duchenne muscular dystrophy who were not taking concomitant glucocorticoids. With its favourable safety and tolerability profiles, idebenone therefore is a suitable treatment option to ameliorate a life-threatening complication of Duchenne muscular dystrophy.

Contributors

GMB and TM contributed to the study concept, design, and conduct, analysis of data, and writing of the manuscript. TV, US, CSMS, MGD'A, GB, J-MC, NG, and CMM participated in the study conduct and reporting on behalf of the DELOS Study Group. RSF contributed to the study concept and design. CR coordinated the study analysis and prepared tables and figures. All authors participated in the preparation, review, and crucial revision of the report, which has been approved by each author.

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Declaration of interests

GMB was investigator for clinical trials in Duchenne muscular dystrophy sponsored by Santhera Pharmaceuticals, Prosensa Therapeutics, and GlaxoSmithKline. TV was an investigator for clinical trials of Duchenne muscular dystrophy sponsored by PTC Therapeutics, GlaxoSmithKline, Prosensa, and Santhera Pharmaceuticals; he serves as

a scientific advisory board member to Prosensa. US was an investigator for clinical trials sponsored by PTC Therapeutics, Lilly Pharma, Santhera Pharmaceuticals, Prosensa, and GlaxoSmithKline. CSMS has participated in trials sponsored by GlaxoSmithKline, Prosensa, and Santhera Pharmaceuticals. RSF has participated in studies of Duchenne muscular dystrophy sponsored by PTC Therapeutics, the US National Institutes of Health (UDP R01NS043264, Wellstone 5U54AR052646-03, Imaging DMD R01-AR056973, and FOR-DMD U01 NS061799-01A2), Lilly, Muscular Dystrophy Association, Sarepta, served as a member of the data and safety monitoring board for the Sarepta 201 study, and served as adviser to Catabasis. CMM has served as a consultant for trials unrelated to this scope of work for PTC Therapeutics, Prosensa, Sarepta, Eli Lilly, Pfizer, Halo Therapeutics, Cardero, and Mitokyne, and serves on external advisory boards related to Duchenne muscular dystrophy for PTC Therapeutics and Eli Lilly. TM is a regular employee of Santhera Pharmaceuticals. GMB and TM are co-inventors of relevant patent applications. The other authors declare no competing interests.

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Supplement Material

This appendix has been provided by the authors to give readers additional information about their work.

Supplement Table 1:

Inclusion Criteria:

1. Patients 10 - 18 years of age at Baseline.
2. Signed and dated informed consent.
3. Documented diagnosis of DMD or severe dystrophinopathy and clinical features consistent of typical DMD at diagnosis (i.e. documented delayed motor skills and muscle weakness by age 5 years). DMD should be confirmed by mutation analysis in the dystrophin gene or by substantially reduced levels of dystrophin protein (i.e. absent or <5% of normal) on Western blot or immunostain.
4. Ability to provide reliable and reproducible repeat PEF within 15% of the first assessment (i.e. Baseline vs. Screening).
5. Patients assessed by the investigator as willing and able to comply with the requirements of the study, possess the required cognitive abilities and are able to swallow study medication.

Exclusion Criteria:

1. Patients dependent on assisted ventilation at Screening and/or Baseline (defined as non-invasive nocturnal ventilation, daytime non-invasive ventilation or continuous invasive ventilation).
2. Patients with documented DMD-related hypoventilation for which assisted ventilation is needed according to current standard of care guidelines (e.g. FVC< 30%) or is required in the opinion of the Investigator.
3. Patients with a percent predicted PEF > 80% at Baseline.
4. Patients unable to form a mouth seal to allow precise respiratory flow measurements and mouth pressures.
5. Symptomatic heart failure (high probability of death within one year of Baseline) and/or symptomatic ventricular arrhythmias.
6. Participation in the previous Phase II or Phase II Extension study (SNT-II-001 or SNT-II-001-E) for idebenone.
7. Participation in any other therapeutic trial and/or intake of any investigational drug within 90 days prior to Baseline.
8. Use of carnitine, creatine, glutamine, oxatomide, or any herbal medicines within 30 days prior to Baseline.
9. Use of coenzyme Q10 or vitamin E (if taken at a dose of 5 times above the daily physiological requirement) within 30 days prior to Baseline.
10. Any previous use of idebenone.
11. Any concomitant medication with a depressive or stimulating effect on respiration or the respiratory tract.

12. Planned or expected spinal fixation surgery during the study period (as judged by the investigator).
13. Asthma, bronchitis/COPD, bronchiectasis, emphysema, pneumonia or the presence of any other non-DMD respiratory illness that affects PEF.
14. Chronic use of beta-2 agonists or any use of other bronchodilating medication (e.g. inhaled steroids, sympathomimetics, anticholinergics).
15. Moderate or severe hepatic impairment or severe renal impairment.
16. Prior or ongoing medical condition or laboratory abnormality that in the Investigator's opinion could adversely affect the safety of the subject.

    Please note: Patients who suffer from a severe, unstable condition including (but not limited to) cancer, auto-immune diseases, haematological diseases, metabolic disorders or immunodeficiencies, and who are at risk of an aggravation unrelated to the study condition, can only be included in the study if accepted in writing by the Sponsor's Medical Monitor.
17. Relevant history of or current drug or alcohol abuse or use of any tobacco/marijuana products/smoking
18. Known individual hypersensitivity to idebenone or to any of the ingredients/excipients of the study medication
19. Systemic glucocorticoid therapy
    a. Chronic use of systemic glucocorticoid therapy for DMD related conditions within 12 months of Baseline (the "12 month non-use period")
    b. More than 2 rounds of acute systemic glucocorticoid burst therapy (of ≤2 week duration) for non-DMD related conditions within the 12 month non-use period
    c. Use of any round of systemic glucocorticoid burst therapy of longer than 2 weeks duration within the 12 month non-use period
    d. Use of systemic glucocorticoid burst therapy less than 8 weeks prior to baseline

Withdrawal Criteria (patients were not replaced):

1. Spinal fixation surgery
2. Initiation of assisted ventilation
3. Acute hospitalization for treatment of complications associated with DMD disease progression
4. Intake of prohibited medication
5. Non-compliance to study procedures
6. Intake of any other investigational drug
7. Any intercurrent medical condition affecting patient’s safety or compliance with trial procedures
8. Any violation of the steroid non-user rule defined above

Supplement Table 2: History of DELOS Study and Protocol Amendments

Important Study Events and Protocol Amendments		**Rationale/Comment**
July 2009: First patient enrolled		
(1) Sep 2009	Introduction of Group Sequential Design (of already pre-specified subgroups; cohort 1: glucocorticoid non-users; cohort 2: glucocorticoid users	To allow a pre-specified futility analysis and re-assessment of the planned sample size prior to expanding enrolment to glucocorticoid using patients.
	Introduction of definitions for "Glucocorticoid non-users"	To allow unambiguous enrolment criteria for glucocorticoid non-users
	Introduction of regular (weekly) assessment of PEF by the patient at home (in addition to assessment s during study site visits)	Introduction of ASMA-1 device
	Discontinuation of handgrip strength assessment (handheld myometry upper limb unchanged)	Commercially available equipment was found not sensitive enough to reliably to record impaired grip strength in patients with advanced disease
	Removal of cough frequency assessment as study endpoint	No fully validated ambulatory cough monitoring device was commercially available
	Introduction of muscle strength and motor function testing at the Screening Visit	To familiarize patients and with the test procedures prior to Baseline visit
(2) Feb 2010	Allow enrolment of siblings of randomized patients	Siblings were allocated to the same treatment to avoid mix-up of study medication
(3) Aug 2010	Introduction of second PEF assessment at every study visit	To minimize the effect of fatigue, and to avoid unnecessary exclusions of patients and reduce data variability
(4) July 2011	Increase sample size of glucocorticoid non users	To ensure sufficiently large data base with patients post Amendment 3
(5) Dec 2012	Amendment of sample size required for pre-specified futility analysis	Determined that pre-specified futility analysis was to be conducted with 60 patients randomized
April 2013: Futility analysis (all 65 glucocorticoid non user patients enrolled at this time). Study not futile		
(6) June 2013	Amendment of time point for starting recruitment of glucocorticoid using patients	Decision to recruit or not to recruit glucocorticoid users (cohort 2) will be made following final analysis of the glucocorticoid non-user subgroup (cohort 1)
Dec 2013: Statistical analysis plan (including proposal to limit the study to glucocorticoid non-users) submitted to FDA for review and comment.		
(7) April 2014	Termination of the study following planned analysis of glucocorticoid non-user subgroup	Based on all recruited patients (glucocorticoid non-users only).
	Amendment of Type I error rate	No correction required as multiple testing for efficacy removed (only one study population)
	Introduction of secondary endpoint: annual rate of change in PEF measured by ASMA-1 device	To allow use of all available ASMA-1 data to determine change in PEF during study period
May 2014: Data base lock and data unblinding		

Note: not reflected are changes to the Study Administrative Structure (such as changes in study personnel, contact details etc), precision of protocol language, and minor text changes.

Supplement Table 3:

Formulas used to calculate percentage predicted values of respiratory function parameters

Percent predicted variable (Reference)	**Formula**
PEF%p (Godfrey et al., 1970; Quanjer et al., 1989)	PEF*100 / (- 422·8 + 5·288 x height)
FVC%p (Hankinson et al., 1999)	FVC*100 / ((-0·2584 - (0·20415 * age)) + (0·010133 * (age^2)) + ((0·00018642 * (height^2))*1))
MEP%p (Domenech-Clar et al., 2003)	MEP*100 / (7·619 + (7·806 * age) + (0·004 * height * weight))
MIP%p (Domenech-Clar et al., 2003)	-MIP*100 / (–27·020 – (4·132 * age) – (0·003 * height * weight))
FEV1%p (Hankinson et al., 1999)	FEV1*100 / ((-0·7453 - (0·04106 * age)) + (0·004477 * (age^2)) + ((0·00014098 * (height^2))*1))

Normalized pulmonary function values were calculated using weight and height (derived from ulna length) obtained at clinic visits.

Supplement Table 4:

Available data sets for respiratory function endpoints

Population	Endpoint/Analysis	Idebenone N	Placebo N	Total N	Comment
Safety	all safety analyses	32	34	66	1
mITT	PEF (MMRM)	30	27	57	2
ITT	PEF (MMRM)	31	33	64	3
	FVC (MMRM)	31	33	64	3
	PEF (linear regression analysis)	30	30	60	4
	FEV1 (MMRM)	26	27	53	5
PP	Sensitivity analysis for PEF (MMRM)	21	27	48	6
All Completers	Sensitivity analysis for PEF (MMRM)	24	29	53	7

1: All subjects who received at least one dose of study medication (includes 2 siblings allocated to treatment)

2: Prospectively excluded 7 patients from the ITT population with a difference of $\geq 20\%$ in PEF measured by hospital-based spirometry and home-based ASMA-1 assessments

3: Includes all randomized subjects who have received at least one dose of study medication

4: Includes all patients from the ITT population who provided at least six months of data collected by ASMA-1 device

5: Includes all patients in the ITT population with available data

6: Includes all patients in the ITT population who completed the study per protocol

7: Includes all patients in the ITT population who completed the study

MMRM: mixed model for repeated measurements

Supplement Table 5:

Comparison of PEF percent predicted measurements

	Idebenone[1]	**Placebo**[1]	**Treatment difference**[2]
Spirometry at hospital visits with Pneumotrac Spirometer	53·5 (10·3); -2·57 (-6·68, 1·54); p=0·22	54·2 (13·2); -8·84 (-12·73, -4·95); p<0·001	6·27 (0·61, 11·93); p=0·031
Home-based ASMA-1 device: Rate of yearly change by linear regression method[3]	53·9 (10·6); -2·48 (-7·39, 2·44); p=0·32	50·1 (14·8); -9·32 (-14·2, -4·40); p<0·001	6·84 (-0·15, 13·83); p=0·055
Home-based ASMA-1 device: Mean change from baseline to Week 52 (average for period 3 weeks prior to 3 weeks after hospital visits)	53·1 (12·3); -1·77 (-6·38, 2·84); p=0·45	51·8 (14·8); -9·01 (-13·48, -4·55); p<0·001	7·24 (0·82, 13·66); p=0·028

Baseline data: descriptive statistics; Change from baseline to week 52 as mean (95% CI) from mixed model for repeated measurements (ITT population).

[1] Baseline: mean (SD); Change from baseline to week 52: mean (95% CI); p-value

[2] at week 52 from mixed model of repeated measures: Mean (95% CI); p-value

[3] for patients who provided at least 6 months of data (idebenone: N=30, placebo N=30)

Supplement Table 6:

Change in FVC from baseline to week 52 and across all post-baseline assessment timepoints (week 13-52).

FVC%p	**Idebenone (N=31)**		**Placebo (N=33)**		**Group Difference**	
Baseline mean (SD)	55·3 (15·8)		50·4 (20·0)			
Change from Baseline (MMRM)	Estimated Change (95% CI)	p-value	Estimated Change (95% CI)	p-value	Estimated Difference (95% CI)	p-value
Week 52	-5·67 (-8·36, -2·99)	0·001	-8·95 (-11·47, -6·42)	<0·001	3·27 (-0·43, 6·97)	0·082
Week 13-52	-2·68 (4·68, -0·68)	0·009	-6·74 (-8·65, -4·82)	<0·001	4·06 (1·28, 6·84)	0·005

FVC [L]	**Idebenone (N=31)**		**Placebo (N=33)**		**Group Difference**	
Baseline mean (SD)	1·9 (0·5)		1·9 (0·5)			
Change from Baseline (MMRM)	Estimated Change (95% CI)	p-value	Estimated Change (95% CI)	p-value	Estimated Difference (95% CI)	p-value
Week 52	-0·04 (-0·14, 0·06)	0·402	-0·18 (-0·27, -0·08)	<0·001	0·13 (-0·00, 0·27)	0·050
Week 13-52	-0·00 (-0·06, 0·06)	0·972	-0·14 (-0·19, -0·08)	<0·001	0·14 (0·05, 0·22)	0·003

Supplement Table 7:

Change in FEV1 from baseline to week 52 and across all post-baseline assessment timepoints (week 13-52).

FEV1%p	**Idebenone (N=26)**		**Placebo (N=27)**		**Group Difference**	
Baseline mean (SD)	53·3 (15·1)		49·7 (18·3)			
Change from Baseline (MMRM)	Estimated Change (95% CI)	p-value	Estimated Change (95% CI)	p-value	Estimated Difference (95% CI)	p-value
Week 52	-2·40 (-7·71, 2·92)	0·369	-10·68 (-15·82, -5·55)	<0·001	8·29 (0·88, 15·70)	0·029
Week 13-52	-2·11 (-5·85, 1·63)	0·262	-9·08 (-12·73, -5·42)	<0·001	6·96 (1·71, 12·21)	0·010

FEV1 [L]	**Idebenone (N=26)**		**Placebo (N=27)**		**Group Difference**	
Baseline mean (SD)	1·54 (0·33)		1·71 (0·57)			
Change from Baseline (MMRM)	Estimated Change (95% CI)	p-value	Estimated Change (95% CI)	p-value	Estimated Difference (95% CI)	p-value
Week 52	0·06 (-0·12, 0·24)	0·506	-0·27 (-0·44, -0·09)	0·004	0·33 (0·07, 0·58)	0·012
Week 13-52	0·01 (-0·12, 0·14)	0·828	-0·24 (-0·37, -0·11)	<0·001	0·26 (0·07, 0·44)	0·007

Supplement Table 8:

Baseline values, change to week 52 and effect sizes for respiratory function tests in the subgroups of steroid naïve patients and previous steroid users (ITT population; post-hoc analysis).

Assessment	Subgroup	Treatment	Baseline mean (SD)	Change Week 52 mean (95%CI)	Effect Size mean (95%CI)
PEF%p	Steroid Naive	Idebenone (N=14)	54·9 (9·2)	-3·75 (-10·58, 3·08)	6·19 (-3·39, 15·77)
		Placebo (N=14)	55·5 (12·7)	-9·95 (-16·66, -3·23)	
	Previous Steroid Users	Idebenone (N=17)	52·3 (11·2)	-1·22 (-6·66, 4·22)	6·73 (-0·66, 14·13)
		Placebo (N=19)	53·2 (13·8)	-7·95 (-12·96, -2·95)	
FVC%p	Steroid Naive	Idebenone (N=14)	55·7 (18·7)	-5·75 (-10·57, -0·93)	3·34 (-3·48, 10·17)
		Placebo (N=14)	47·3 (19·2)	-9·09 (-13·87, -4·31)	
	Previous Steroid Users	Idebenone (N=17)	55·0 (13·5)	-5·50 (-8·66, -2·34)	3·22 (-1·05, 7·49)
		Placebo (N=19)	52·7 (20·7)	-8·72 (-11·58, -5·86)	
FEV1%p	Steroid Naive	Idebenone (N=11)	58·9 (17·6)	-4·44 (-12·09, 3·20)	7·92 (-2·71, 18·56)
		Placebo (N=12)	44·5 (15.0)	-12·37 (-19·59, -5·15)	
	Previous Steroid Users	Idebenone (N=15)	49·2 (11.9)	-0·10 (-8·13, 7·94)	10·07 (-1·15, 21·30)
		Placebo (N=15)	53·9 (20·0)	-10·17 (-18·00, -2·34)	

Supplement Table 9:

Baseline values, change to week 52 and group differences for respiratory function tests in the subgroups of patients below/above median age (14 years) (ITT population; post-hoc analysis).

Assessment	Age Group	Treatment	Baseline mean (SD)	Change Week 52 mean (95%CI)	Group Difference mean (95%CI)
PEF%p	≤ 14 y	Idebenone (N=19)	54·7 (9·7)	-1·71 (-7·48, 4·06)	7·29 (-1·77, 16·35)
		Placebo (N=13)	59·1 (12·3)	-9·00 (-15·94, -2·06)	
	> 14 y	Idebenone (N=12)	51·5 (11·3)	-4·42 (-10·90, 2.05)	4·20 (-3·86, 12·27)
		Placebo (N=20)	51·0 (13·0)	-8·63 (-13·43, -3.83)	
FVC%p	≤ 14 y	Idebenone (N=19)	62·7 (12·7)	-6·10 (-10·79, -1·41)	3·83 (-3·44, 11·10)
		Placebo (N=13)	67·1 (18·0)	-9·94 (-15·48, -4·40)	
	> 14 y	Idebenone (N=12)	43·6 (13·2)	-6·08 (-8·40, -3·77)	1·76 (-1·13, 4·66)
		Placebo (N=20)	39·6 (12·4)	-7·85 (-9·56, -6·13)	
FEV1%p	≤ 14 y	Idebenone (N=16)	59·8 (13·7)	-0·83 (-9·56, 7·90)	8·02 (-6·47, 22·51)
		Placebo (N=9)	64·4 (12·3)	-8·85 (-20·40, 2·70)	
	> 14 y	Idebenone (N=10)	42·9 (11·0)	-3·50 (-9·98, 2·98)	8·87 (0·85, 16·89)
		Placebo (N=18)	42·3 (16·3)	-12·37 (-17·09, -7·65)	

Supplement Table 10: Analysis of respiratory tract infection-related adverse events (ITT population)

	Idebenone (N=31)	**Placebo (N=33)**	**p-value[1]**
Respiratory Tract Infection -related AEs	20 (14)	44 (23)	0·076
Upper Respiratory Tract	15 (11)	34 (20)	0·051
Nasopharyngitis	12 (8)	11 (9)	
Upper Respiratory Tract Infection	2 (2)	10 (6)	
Rhinitis	1	8 (6)	
Pharyngitis	0	2 (2)	
Viral Infection	0	2 (2)	
Laryngitis	0	1	
Lower Respiratory Tract	5 (4)	10 (7)	0·512
Bronchitis	5 (4)	7 (6)	
Pneumonia	0	3 (2)	

Data are number of adverse events reported and (number of patients reporting adverse events)

[1]Fisher's Exact Test for the number of patients reporting adverse events

Supplement Table 11:

Adverse Events occurring in more than 2 patients by preferred term (Safety Population)

	Idebenone (N=32)			Placebo (N=34)			Total (N=66)		
	Events	Patients		Events	Patients		Events	Patients	
	n	n	%	n	n	%	n	n	%
Nasopharyngitis	12	8	25·0	11	9	26·5	23	17	25·8
Headache	13	6	18·8	15	7	20·6	28	13	19·7
Diarrhoea	10	8	25·0	6	4	11·8	16	12	18·2
Bronchitis	5	4	12·5	7	6	17·6	12	10	15·2
Constipation	4	3	9·4	6	6	17·6	10	9	13·6
Pyrexia	6	5	15·6	4	3	8·8	10	8	12·1
Upper respiratory tract infection	2	2	6·3	10	6	17·6	12	8	12·1
Gastroenteritis	7	6	18·8	1	1	2·9	8	7	10·6
Rhinitis	1	1	3·1	8	6	17·6	9	7	10·6
Abdominal pain	4	3	9·4	5	3	8·8	9	6	9·1
Back pain	2	2	6·3	6	4	11·8	8	6	9·1
Rhinorrhoea	3	3	9·4	2	2	5·9	5	5	7·6
Left ventricular failure	3	3	9·4	1	1	2·9	4	4	6·1
Blood phosphorus increased	1	1	3·1	4	3	8·8	5	4	6·1
Nausea	2	1	3·1	2	2	5·9	4	3	4·5
Vomiting	1	1	3·1	3	2	5·9	4	3	4·5
Influenza like illness	2	2	6·3	2	1	2·9	4	3	4·5
Otitis media	3	3	9·4	0	0	0	3	3	4·5
Electrocardiogram abnormal	3	2	6·3	1	1	2·9	4	3	4·5
Scoliosis	2	2	6·3	1	1	2·9	3	3	4·5
Chromaturia	3	3	9·4	0	0	0	3	3	4·5
Nasal congestion	2	2	6·3	1	1	2·9	3	3	4·5
Oropharyngeal pain	2	2	6·3	1	1	2·9	3	3	4·5
Seborrhoeic dermatitis	1	1	3·1	2	2	5·9	3	3	4·5

Supplement Table 12:

Serious Adverse Events by Preferred Term (Safety Population)

	Idebenone (N=32)			Placebo (N=34)			Total (N=66)		
	Events	Patients		Events	Patients		Events	Patients	
	n	n	%	n	n	%	n	n	%
At least 1 Serious AE	2	2	6·3	13	5	14·7	15	7	10·6
Pneumonia	0	0	0	3	2	5·9	3	2	3·0
Acute respiratory failure	0	0	0	1	1	2·9	1	1	1·5
Dehydration	0	0	0	1	1	2·9	1	1	1·5
Femur fracture	0	0	0	1	1	2·9	1	1	1·5
Nasopharyngitis	0	0	0	1	1	2·9	1	1	1·5
Pulmonary microemboli	0	0	0	1	1	2·9	1	1	1·5
Pyrexia	0	0	0	1	1	2·9	1	1	1·5
Respiratory failure	0	0	0	1	1	2·9	1	1	1·5
Vomiting	0	0	0	1	1	2·9	1	1	1·5
Tendinous contracture	0	0	0	2	1	2·9	2	1	1·5
Sleep apnoea syndrome	1	1	3·1	0	0	0	1	1	1·5
Urticaria	1	1	3·1	0	0	0	1	1	1·5

Supplement Table 13:

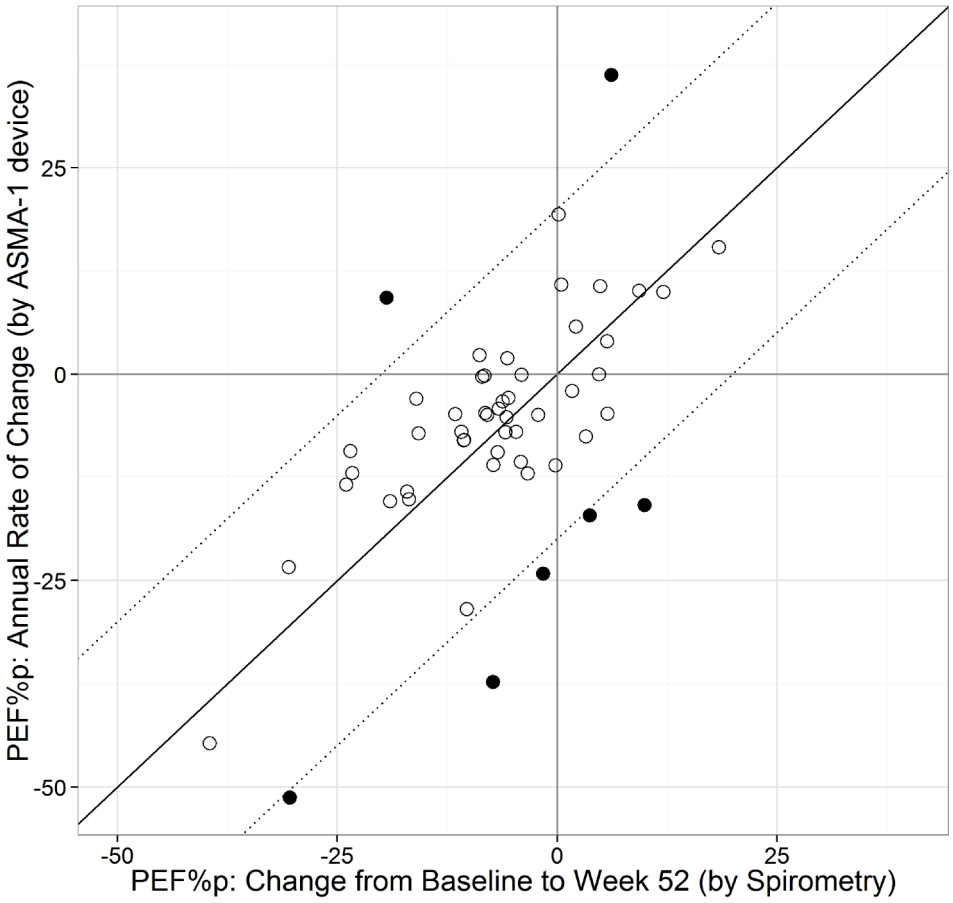
Severe Adverse Events by Preferred Term (Safety Population)

	Idebenone, N=32			Placebo, N=34			Total, N=66		
	Events	Patients		Events	Patients		Events	Patients	
	n	n	%	n	n	%	n	n	%
At least 1 Severe AE	**1**	**1**	**3·1**	**7**	**4**	**11·8**	**8**	**5**	**7·6**
Pneumonia	0	0	0	2	2	5·9	2	2	3·0
Femur fracture	0	0	0	1	1	2·9	1	1	1·5
Osteoporosis	0	0	0	1	1	2·9	1	1	1·5
Post-traumatic pain	0	0	0	1	1	2·9	1	1	1·5
Respiratory failure	0	0	0	1	1	2·9	1	1	1·5
Scoliosis	0	0	0	1	1	2·9	1	1	1·5
Sleep apnea syndrome	1	1	3·1	0	0	0	1	1	1·5

Supplement Figure 1:

Scatter plot comparing the changes in PEF%p values from Baseline to Week 52 obtained by spirometry (abscissa) and the annual rate of change in PEF%p measured by the ASMA-1 device (ordinate).

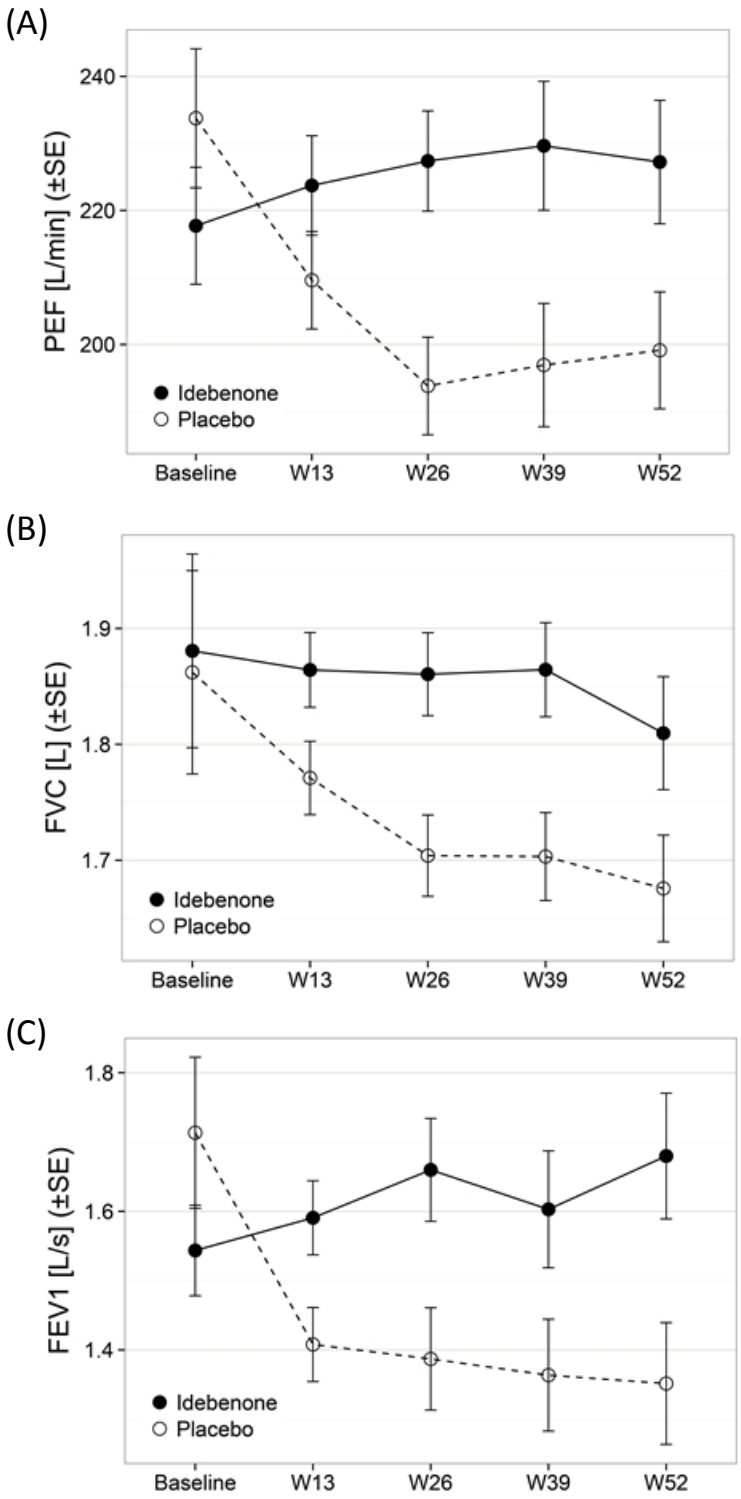
The mITT population excluded patients with a difference of ≥ 20% between both methods (indicated in black).



Dotted lines indicate the 20% boundaries.

Supplement Figure 2:

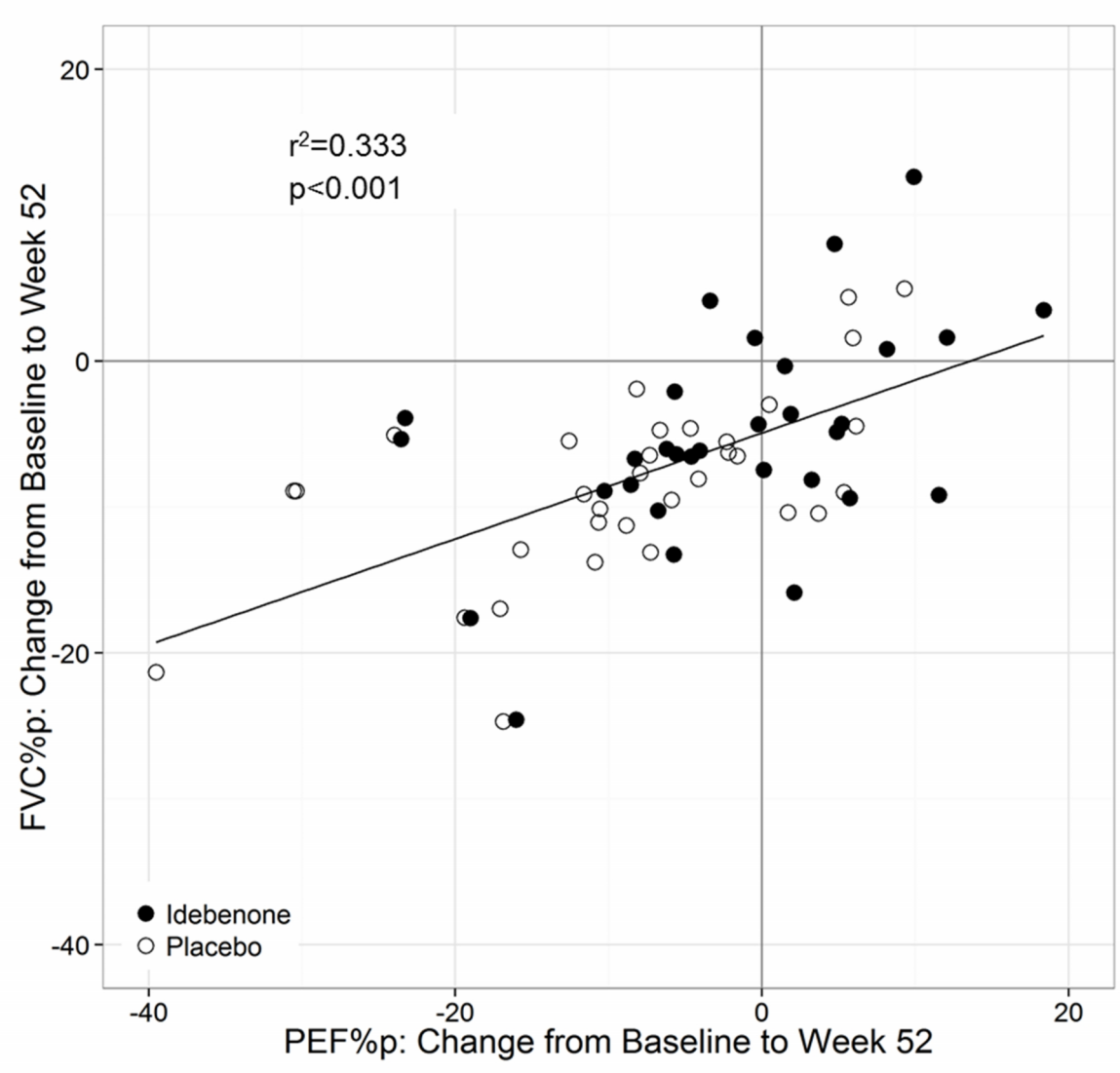
Trajectories of change from baseline for PEF (**A**), FVC (**B**) and FEV1 (**C**)



Data are estimated mean (± SEM) from mixed model for repeated measurements from the ITT population (PEF: N=31 for idebenone; N=33 for placebo; FVC: N=31for idebenone; N=33 for placebo; FEV1: N=26 for idebenone; N=27 for placebo).

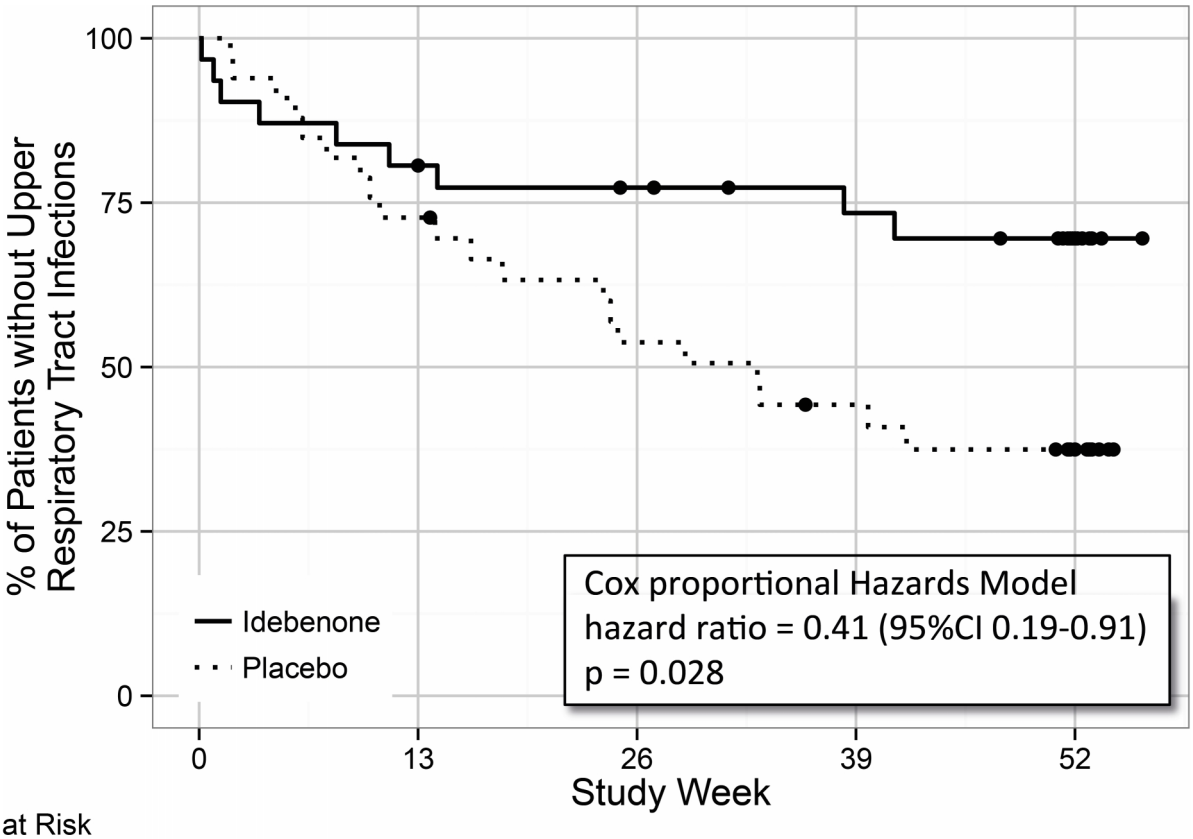
Supplement Figure 3:

Correlation of individual changes in PEF%p and FVC%p at Week 52 (post-hoc analysis).



Supplement Figure 4:

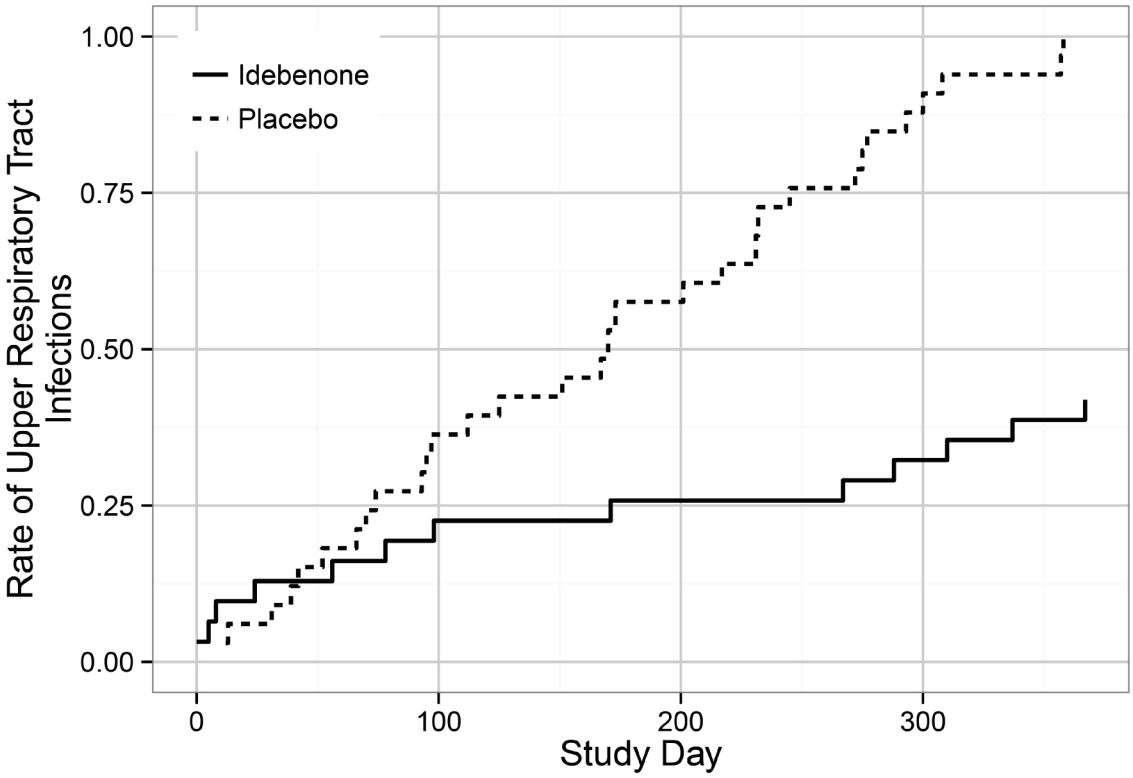
Kaplan Meier Plot for the Time to Upper Respiratory Tract Infection and patients at risk (post-hoc analysis).



at Risk					
Idebenone	31	24	22	19	8
Placebo	33	24	17	13	6

Supplement Figure 5:

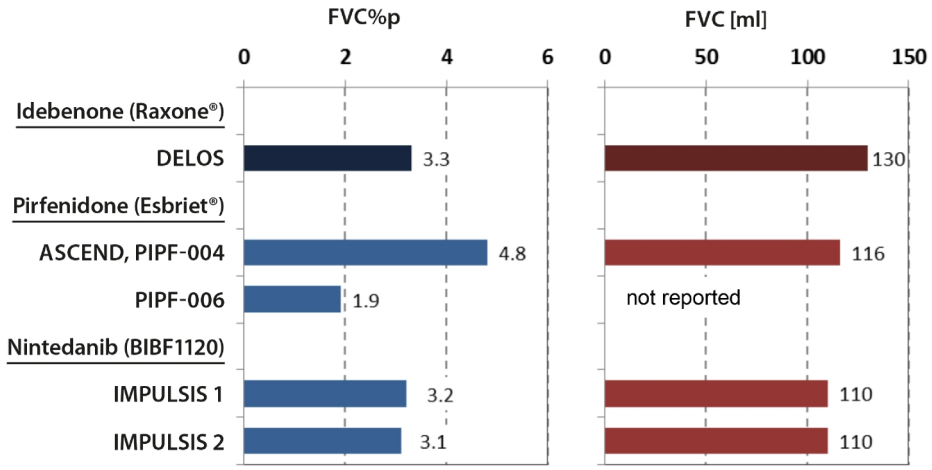
Rate of Upper Respiratory Tract Infections (post-hoc analysis)



Cumulative Response Plot for reported AEs associated with upper respiratory tract infections during the on-treatment period of the study.

Supplement Figure 6:

Comparative effect sizes for FVC reported for DMD (with idebenone) and idiopathic pulmonary fibrosis (with pirfenidone and nintedanib) following 1 year of treatment



Data sources:

PIPF-004 and PIPF-006: Noble et al. (2011) Lancet 377:1760; data at week 48 (Fig. 2); data at week 52 (linear slope analysis): Fig S2

PIPF-004 and PIPF-006: Europ. Public Assessment Report EPAR: Tables 7 and 12

IMPULSIS 1and IMPULSIS 2: Richeldi et al. (2014) NEJM 370: 2071; data at week 52 (Table 2)