

# Long-term data with idebenone on respiratory function outcomes in patients with Duchenne muscular dystrophy

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## Abstract

Decline in respiratory function in patients with DMD starts during early teenage years and leads to early morbidity and mortality. Published evidence of efficacy for idebenone on respiratory function outcomes is currently limited to 12 months of follow-up time. Here we report data collected as retrospective cohort study (SYROS) from 18 DMD patients not using glucocorticoids who were treated with idebenone (900 mg/day) under Expanded Access Programs (EAPs). The objective was to assess the long-term respiratory function evolution for periods On-Idebenone compared to periods Off-Idebenone in the same patients. The mean idebenone exposure in the EAPs was 4.2 (range 2.4–6.1) years. The primary endpoint was the annual change in forced vital capacity percent of predicted (FVC%p) compared between Off-Idebenone and On-Idebenone periods. The annual rate of decline in FVC%p was reduced by approximately 50% from  $-7.4\%$  (95% CI:  $-9.1$ ,  $-5.8$ ) for the Off-Idebenone periods to  $-3.8\%$  (95% CI:  $-4.8$ ,  $-2.8$ ) for the On-Idebenone periods ( $N=11$ ). Similarly, annual change in peak expiratory flow percent of predicted (PEF%p) was  $-5.9\%$  (95% CI:  $-8.0$ ,  $-3.9$ ) for the Off-Idebenone periods ( $N=9$ ) and reduced to  $-1.9\%$  (95% CI:  $-3.2$ ,  $-0.7$ ) for the On-Idebenone periods during the EAPs. The reduced rates of decline in FVC%p and PEF%p were maintained for several years with possible beneficial effects on the rate of bronchopulmonary adverse events, time to 10% decline in FVC%p and risk of hospitalization due to respiratory cause. These long-term data provide Class IV evidence to further support the disease modifying treatment effect of idebenone previously observed in randomized, controlled trials.

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## 1. Introduction

Duchenne muscular dystrophy (DMD) is characterized by relentlessly progressive muscle weakness leading to loss of motor function, cardiomyopathy, progressive spinal abnormality, respiratory function decline and death in early adulthood [1,2]. Respiratory function decline, a predominant cause of early mortality in DMD, results from the underlying weakness and degeneration of the respiratory muscle groups, notably the diaphragm, the intercostal and chest wall muscles, leading to impaired respiratory muscle strength. Respiratory function decline in DMD patients is currently irreversible and all patients will ultimately develop chronic respiratory insufficiency and require ventilator support [3,4]. There is currently no therapeutic intervention specifically approved for the treatment of respiratory dysfunction in patients with DMD.

In DMD respiratory function can be reliably measured as peak expiratory flow (PEF) or forced vital capacity (FVC), both expressed as percent of predicted (PEF%p, FVC%p) (reviewed in [4–6]). Abnormal respiratory function, defined as PEF%p or FVC%p falling below 80% of normal, typically occurs at around 10–14 years of age and coincides with the time of loss of ambulation. Thereafter, and over the course of about 10 years both PEF%p and FVC%p follow a co-linear decline [6–10] (reviewed in [4,11]).

Idebenone, a synthetic short-chain benzoquinone, improves mitochondrial function, restores ATP production and catalytically reduces reactive oxygen species, thereby addressing the muscle cell damaging consequences of dystrophin deficiency (as reviewed in [12]). Idebenone showed a cardio-protective effect and improved exercise performance in the dystrophin-deficient *mdx* mouse model of DMD [13].

A proof-of-concept, randomized, placebo-controlled phase 2 trial of 12 months duration in 21 DMD patients (DELPHI trial) provided initial evidence that idebenone has the potential to slow loss of respiratory function [14,15]. A confirmatory phase 3, randomized, placebo-controlled trial (DELOS trial) specifically investigated the efficacy of idebenone on respiratory function outcomes in 64 DMD patients (age 10–18 years, 92% non-ambulatory at baseline) who discontinued glucocorticoid (GC) use at least one year prior to study start [16,17]. Eligible patients had abnormal respiratory function, defined as PEF%p at baseline of less than 80%. Patients received idebenone ( $N=31$ ; 900 mg daily) or matching placebo ( $N=33$ ) for 12 months. The trial met its primary endpoint and demonstrated a statistically significant and clinically relevant reduction in the loss of PEF%p [16] at 12 months. The outcome of the primary endpoint was robust across pre-specified study populations and supported by consistent findings for changes in other respiratory function measures [16,18–20] and clinical outcomes [21].

At present, long-term data from the treatment of DMD patients with idebenone are still sparse, precluding the

interpretation whether the treatment effect of idebenone observed in randomized controlled trials of 12 months duration may persist over prolonged periods of time. Therefore, we collected data from patients receiving idebenone through Expanded Access Programs (EAPs) following their completion of the DELOS trial. Here we report the outcome of this retrospective cohort study (SYROS) with patients followed under routine clinical care, with the objective to assess the long-term respiratory function evolution during idebenone treatment compared to idebenone-free periods in patients with DMD.

## 2. Methods

### 2.1. Collection of data from expanded access programs

Requests by trial investigators were submitted to the sponsor of the DELOS trial (Santhera Pharmaceuticals, Pratteln, Switzerland), to provide idebenone for patients who had previously completed the trial. According to such requests, free of charge access to idebenone medication was subsequently governed by EAPs under applicable national rules and regulations (DELOS-Named Patient Program [DELOS-NPP] or DELOS Compassionate Use Program [DELOS-CUP]). Treatment of patients with idebenone ( $2 \times 150$  mg tablets 3 times daily with meals; total daily dose 6 tablets, 900 mg) according to the EAPs was under the sole discretion of the treating physician and data collection was performed according to standard of care clinical monitoring of the patients. Data collected from these patients, including data on respiratory function and disease progression/complications, were stored by the hospital responsible for the EAPs and are considered data obtained under routine clinical care.

The SYROS study protocol (describing the data collection procedure and analysis methods) and the Data Release Agreement form were approved by the independent ethics committees of all study sites involved before commencement of this retrospective cohort study. The study was conducted in compliance with the latest version of the Declaration of Helsinki, with the current requirements for Good Pharmacoeconomics Practices (GPP Guideline 2015), Good Pharmacovigilance Practices (GVP-Module VI) and with local laws and regulations. Available medical data collected under routine clinical care were recorded at the investigator sites. Data collected from the time the subject had completed the last visit (at month 12) of the DELOS trial until the most recent hospital visit available at the time of this data collection were retrieved from the patients' medical records and entered in the case record form by the site investigator. Only after patients had signed the Data Release Agreement, coded data using the former DELOS patient number as patient identifier for the present study were collected. The first patient's Data Release Agreement form was signed on 29 August 2017. The data collected covers a period from 30 August 2010 to 13 March 2018.

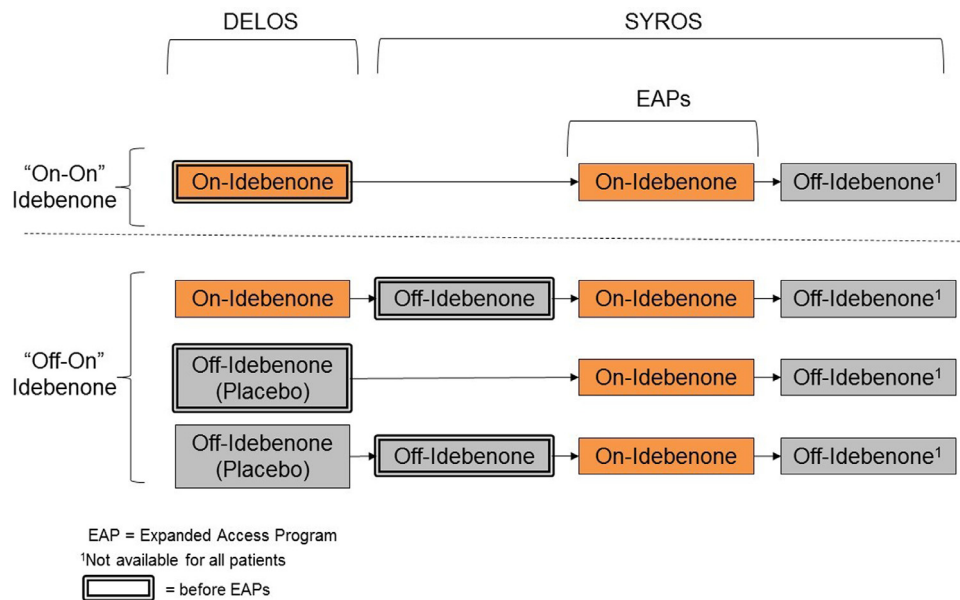


Fig. 1. Illustration of terminology used in this study

Schematic presentation; x-axis is not to scale for time. EAP: expanded access program. Double borders indicate periods preceding the initiation of treatment with idebenone under the EAPs.

## 2.2. Patient eligibility

Patients were included in the study if all of the following inclusion criteria were met: (i) patient had completed the DELOS trial (clinicaltrials.gov ID: NCT01027884; [16]) and was currently under the medical care of a study site with an ongoing EAP; (ii) patient had taken idebenone as part of the EAPs available in these countries, following his participation in the DELOS trial, and (iii) patient had provided a signed Data Release Agreement. There were no defined exclusion criteria. For this study long-term respiratory outcome data from 18 patients with DMD treated with idebenone between October 2011 and March 2018 were collected and analyzed.

## 2.3. Study objectives

The primary objective was to evaluate the long-term evolution of respiratory function during idebenone treatment (On-Idebenone), compared to the evolution during idebenone-free periods (Off-Idebenone) in patients with DMD. The secondary objective was to evaluate the effect of idebenone on clinically relevant disease milestones, medical events, treatment interventions and other relevant medications.

## 2.4. Data analysis and statistical methods

Data were transcribed from the case record form to an electronic database hosted by 4Pharma (Turku, Finland). The database was locked on 01 June 2018. Data from the intent-to-treat (ITT) data set are reported here. The ITT data analysis set included all patients who were included in the ITT population of the DELOS study and were enrolled to the present study under national EAPs.

The data analysis was conducted according to a Statistical Analysis Plan (SAP), which was finalized prior to data base lock. The SAP was written in a blinded manner without having any access to the SYROS study data. Data from both the DELOS trial and from the present study were used to evaluate the evolution of respiratory function under long-term idebenone treatment. The terminology used in this report is illustrated in Fig. 1. On-Idebenone treatment periods were defined as any periods of time when patients either received idebenone during the randomized DELOS trial (i.e., the idebenone treatment group of DELOS) or during the EAPs collected in the present SYROS study. Idebenone free periods, referred to as Off-Idebenone periods, were defined as any periods of time when patients did not receive idebenone, either during the randomized DELOS trial (i.e., the placebo group of DELOS) or after the completion of DELOS and collected in the present SYROS study.

Respiratory function outcomes, forced vital capacity (FVC) and peak expiratory flow (PEF), were normalized to percent of predicted (%p) as previously described [16].

To calculate the annual change in FVC%p and PEF%p, three data points from respiratory function assessments (baseline and at least two post-baseline assessments at least 6 months apart) were required for an analysis period to be deemed evaluable. A patient may have had temporary interruptions during the idebenone treatment while participating in the EAP program. Any interruption of idebenone treatment of less than 10% of the total duration of the On-Idebenone treatment periods were not considered as clinically relevant (see below). For the primary analysis of respiratory function change, the longest consecutive On-Idebenone period during the EAPs was compared to the preceding evaluable period, either to an On-Idebenone period

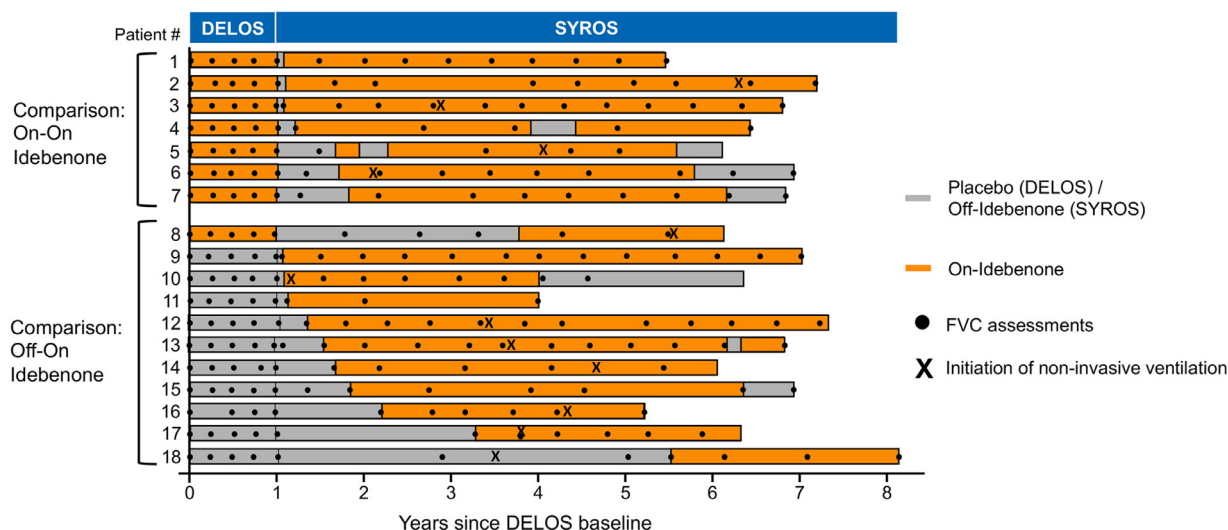


Fig. 2. By patient On-Idebenone and Off-Idebenone treatment periods and time points of respiratory function (FVC) assessments during DELOS and SYROS studies

By patient treatment assignment, On-Idebenone or Off-Idebenone, is color coded by orange and gray bars respectively. Patients are grouped into comparison “On-On” idebenone and “Off-On” idebenone according to the procedure described in methods. The time point when 12 of 18 patients started non-invasive ventilation (NIV) is indicated.

in the DELOS study (comparison “On-On” Idebenone) or an Off-Idebenone period before the EAPs (comparison “Off-On” Idebenone) (Fig. 1).

The annual change of respiratory function measures within each period (Off-Idebenone or On-Idebenone) was estimated using random coefficient regression models, applied separately for each analysis period. The random coefficient regression model included the respiratory function values analyzed (FVC%p, PEF%p) as response data, the baseline value as a covariate and the assessment time (years since the baseline) as a factor. The model included random slopes and intercepts. The annual changes in respiratory function outcomes (FVC%p, PEF%p) were estimated from the models along with standard error of the mean (SEM) and 95% confidence intervals (95% CI).

Time to event analyses were conducted using Kaplan–Meier methods and Cox models (for time to first event) and with mean cumulative function estimates based on proportional means models (for cumulative proportion of events by time, allowing multiple events), similarly as described in [21]. Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

## 2.5. Comparison to natural history data

To further aid interpretation of the long-term treatment effect of idebenone, annual change in FVC%p and PEF%p during the longest consecutive On-Idebenone periods from DELOS/SYROS were compared to data from patients followed by the Cooperative International Neuromuscular Research Group (CINRG) under the Duchenne natural history study protocol (CINRG-DNHS study; NCT00468832 [6,22]). For this comparison, the annual rate of change in FVC%p and

PEF%p were calculated in 2-year bins for the On-Idebenone periods of DELOS/SYROS. For comparison, matched data were extracted from the CINRG-DNHS. Specifically, a comparator dataset for each 2-year bin was generated with exactly the same baseline FVC%p or PEF%p data (see below). All values available during the 2-year period after crossing this baseline were used to calculate the annual rate of change in the external comparator dataset by random coefficient regression model as described above.

## 3. Results

### 3.1. Patient disposition

In total, 27 patients previously enrolled into the Phase 3 DELOS trial, received idebenone under EAP programs in 6 countries (Belgium, Germany, Netherlands, Spain, Sweden, Switzerland). Out of the 27 patients, two were excluded due to not signing the Data Release Agreement, one patient died during the EAP and 6 patients were excluded due to various other/administrative reasons (patient lost to follow-up ( $N=3$ ), treating physician not available for the data collection ( $N=2$ ) or the site was not included for administrative reasons ( $N=1$ )). The remaining 18 patients (from Belgium, Germany, Netherlands and Switzerland) were included in the SYROS ITT population. For details on patient disposition, see Supplement Fig. 1.

The Off-Idebenone and On-Idebenone periods from the DELOS randomized controlled study and the SYROS data collection for each patient are summarized in Fig. 2. Altogether 11 of the 18 patients were Off-Idebenone before idebenone treatment under the EAPs while the remaining 7 patients were On-Idebenone prior to starting the EAPs.



Table 1

Summary of demographics, disease status and respiratory function data for the DELOS and SYROS ITT populations.

	DELOS ITT population N=64	SYROS ITT population N=18
Age, years		
mean (SD)	14.3 (2.7)	13.3 (2.7)
median, (minimum-maximum)	14.0, (10.1, 19.0)	12.9, (10.1, 18.5)
Prior glucocorticoid use, n (%)		
Non-user	28 (43.8)	7 (38.9)
Previous user	36 (56.3)	11 (61.1)
Time since last glucocorticoid use, years		
n	36	11
mean (SD)	3.7 (2.1)	4.1 (1.9)
median, (minimum, maximum)	3.5, (0.9, 8.9)	4.2, (1.3, 6.9)
Ambulatory Status, n (%)		
Ambulatory	5 (7.8)	3 (16.7)
Non-ambulatory	59 (92.2)	15 (83.3)
Age at loss of ambulation, years		
n	59	15
mean (SD)	9.7 (1.5)	10.0 (1.7)
median, (minimum, maximum)	9.5, (7.2, 14.3)	9.8, (7.8, 12.8)
FVC%p		
mean (SD)	52.8 (18.1)	58.7 (17.6)
median, (minimum-maximum)	53.0, (22.6, 96.4)	61.5, (22.6, 96.4)
PEF%p		
mean (SD)	53.8 (11.8)	58.5 (10.2)
median, (minimum-maximum)	56.9, (29.1, 79.1)	59.1, (30.1, 77.7)

Data are as reported at baseline of DELOS (see Supplement Fig. 2A).

### 3.2. Duration of treatment and follow-up time

The mean exposure to idebenone in the EAPs was 4.2 years (range 2.4–6.1 years) in the 18 patients. Before the EAPs, the mean duration of follow-up for the 11 patients who were Off-Idebenone was 2.1 years (range 1.1–5.5 years), while mean exposure of idebenone was 1.0 years (range 1.0–1.0) in the 7 patients who were On-Idebenone prior to starting the EAP. In total, the exposure to idebenone treatment was 84.0 person years, consisting of 8.0 person years in the DELOS study and 76.0 person years in the EAPs. The total duration of Off-Idebenone periods was 32.3 person years, consisting of 10.0 person years during the placebo treatment in the DELOS study and 22.4 person years of follow-up as Off-Idebenone after DELOS. Details of the exposure and duration of follow-up for the ITT population of the SYROS study are summarized in Supplement Table 1.

### 3.3. Patient characterization

Table 1 summarizes patient demographics and respiratory function status for the SYROS ITT population and the DELOS ITT population at the time point of the DELOS baseline (see Supplement Fig. 2A). The mean age of the 18 patients enrolled into SYROS was 13.3 (range 10.1–18.5) years, while the mean age of the total DELOS ITT population was 14.3 (range 10.1–19.0) years. Whilst the protocol of the DELOS trial required that patients did not use glucocorticoids (GCs), no such restriction applied for the EAPs and there were two patients starting GC treatment during their participation in the EAPs. Twelve patients started

assisted ventilation (either nocturnal or daytime) during the EAPs. Generally, the SYROS ITT population was comparable to the DELOS ITT with regards to other demographic parameters and respiratory function status.

Similar comparative analysis of patient characteristics are shown in Supplement Table 2 for patients who were Off-Idebenone prior to the EAP ( $N=11$ ) and those who were On-Idebenone prior to the EAP ( $N=7$ ), constituting the “Off-On” idebenone comparison and the “On-On” idebenone comparison, as illustrated in Supplement Fig. 2B

### 3.4. Primary efficacy analysis: annual change in FVC%p and PEF%p while On-Idebenone in the EAPs, compared to period before the EAPs

Fig. 3 illustrates the On-Idebenone and Off-Idebenone treatment periods by patients for the primary analysis of annual change in FVC%p. In addition, the period while On-Idebenone in the EAPs and the last evaluable period preceding the EAPs are indicated by arrows.

When the annual change in FVC%p was compared for the “Off-On” idebenone group ( $N=11$ ) the rate was reduced by approximately 50% from  $-7.4\%$  (95% CI:  $-9.1, -5.8$ ) for the Off-Idebenone period prior to the EAPs to  $-3.8\%$  (95% CI:  $-4.8, -2.8$ ) for the On-Idebenone period during the EAP (Fig. 4A). As there were two patients starting GC use during participation in the EAPs, a sensitivity analysis was performed where the periods of GCs use were excluded from the analysis. The resulting annual rate of change for FVC%p was  $-7.4\%$  (95% CI:  $-9.1, -5.6$ ) for the Off-Idebenone period and  $-3.9\%$  (95% CI:  $-5.0, -2.9$ ) for the On-Idebenone period; these results were comparable to the analysis of the ITT population. In another sensitivity analysis all periods where patients ( $N=12$ ) used assisted ventilation (either nocturnal or daytime) were excluded from the analysis. The resulting annual rate of change for FVC%p was  $-6.8\%$  (95% CI:  $-11.7, -2.0$ ) for the Off-Idebenone period and  $-4.4\%$  (95% CI:  $-6.6, -2.2$ ) for the On-Idebenone period.

The annual change in PEF%p, a secondary endpoint, was  $-5.9\%$  (95% CI:  $-8.0, -3.9$ ) for the Off-Idebenone periods before to the EAPs ( $N=9$ ) and reduced to  $-1.9\%$  (95% CI:  $-3.2, -0.7$ ) for the On-Idebenone periods during the EAPs (Fig. 4B).

When carrying out similar comparisons for the “On-On” idebenone group, the annual rate of decline in FVC%p remained low both during the On-Idebenone periods before the EAPs and during the On-Idebenone period during the EAPs, with estimated rates of  $-0.7\%$  (95% CI:  $-3.7, 2.2$ ) and  $-3.9\%$  (95% CI:  $-5.4, -2.3$ ), respectively (Supplement Fig. 3A). Similar results were seen for the changes in PEF%p, with  $1.3\%$  (95% CI:  $-3.3, 5.8$ ) for the On-Idebenone periods before the EAP and  $-1.3\%$  (95% CI:  $-3.4, 0.8$ ) for the On-Idebenone periods during the EAPs (Supplement Fig. 3B).

By-patient data presentations with individual slope estimates from the random coefficient regression model for FVC%p for the Off-Idebenone periods are compared to slopes for the On-Idebenone periods as shown in Fig. 5A and B.

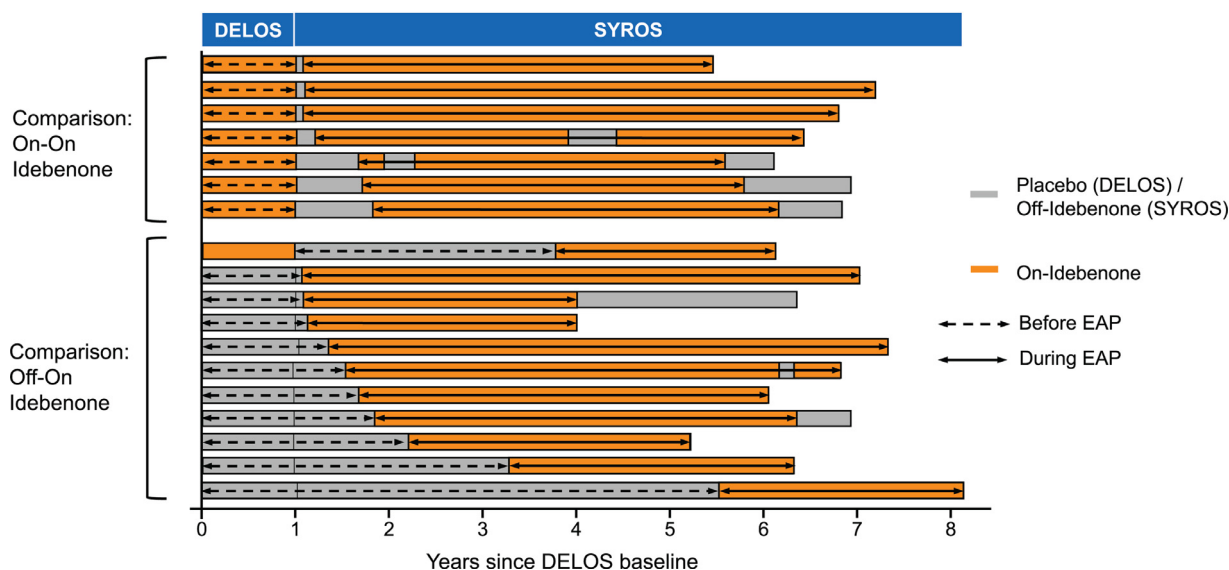


Fig. 3. Periods analyzed for annual change in FVC%p (primary efficacy outcome)

Primary analysis for annual change in FVC%p for the SYROS ITT population. Treatment periods On-Idebenone (orange) and Off-Idebenone (gray) over time (years since DELOS baseline). Top part: “On-On” idebenone treatment comparison. Bottom part: “Off-On” idebenone treatment comparison by patient. Dotted arrows: periods before idebenone treatment under EAPs; solid arrows: EAPs treatment periods.

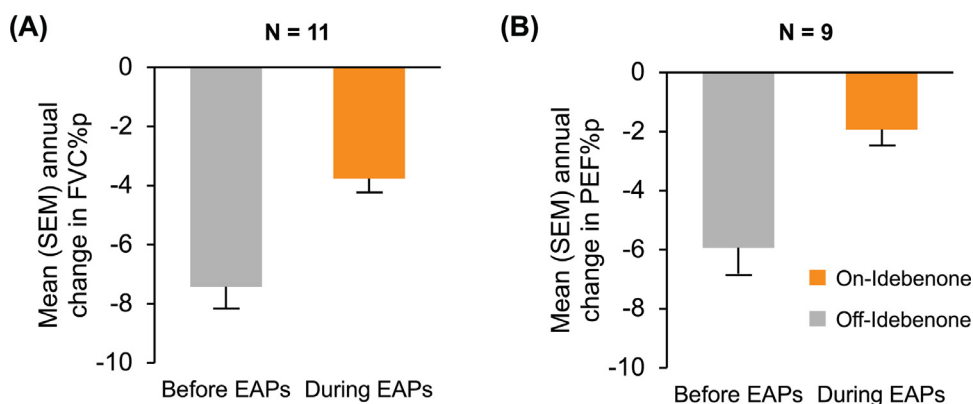


Fig. 4. Annual rate of change for FVC%p (A) and PEF%p (B) between Off-Idebenone and On-Idebenone treatment periods. Data are estimated mean (SEM) from the random coefficient regression model.

This representation illustrates the consistency of the result on a by-patient level. Similar results were seen for the slopes for PEF%p (Fig. 5C and D).

### 3.5. Long-term evolution in change of FVC%p and PEF%p under idebenone treatment

In a secondary analysis the annual changes in FVC%p and PEF%p were compared in 2-year bins to assess how the rate of change evolved with increasing treatment duration/follow-up time (Fig. 6). As shown, the annual decline in FVC%p remained stable for the entire follow-up time during each of the 2-year bins (Fig. 6A). A similar pattern was seen for changes over time in PEF%p (Fig. 6B).

To further interpret the annual change in FVC%p over the 6-year follow-up of DELOS/SYROS, we compared changes in subgroups of untreated patients from the CINRG-DNHS matched to the patients in the respective 2-year bins. As can be seen in Fig. 6, there is a consistently reduced annual rate

of decline in FVC%p and PEF%p for patients receiving long-term idebenone treatment compared to matched untreated patients from the natural history study. Furthermore, evaluable data were available during the Off-Idebenone periods in DELOS/SYROS for two years. As shown in Fig. 6 (gray bars), during this untreated period, the annual rate of decline in FVC%p and PEF%p was comparable to the untreated patients from the CINRG-DNHS and higher than in patients who were On-Idebenone.

One possible limitation of this analysis is the fact that the majority of patients in the SYROS study did not use GCs whilst patients in the CINRG-DNHS were both GC users and GC non-users.

### 3.6. Efficacy of long-term idebenone treatment on clinically relevant outcomes

Clinically relevant worsening in respiratory function is commonly defined as time to the first relative decline of 10%

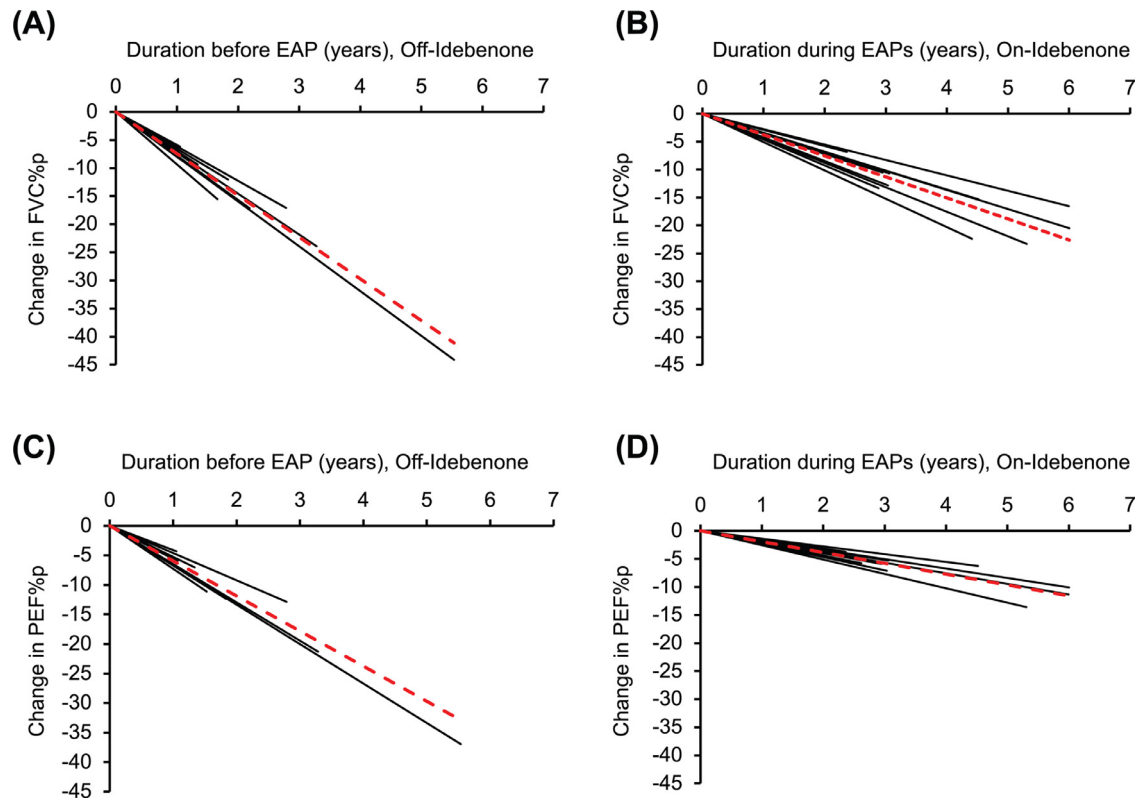


Fig. 5. Individual slopes over time by treatment period (Off-Idebenone, On-Idebenone).

By-patient random-effects estimates from the random coefficient regression model, representing the estimated deviation from the mean slope. The individual estimates (along with the mean slope) are shown for change in FVC%p (A, B) ( $N=11$ ) and PEF%p (C, D) ( $N=9$ ). Slopes for the Off-Idebenone periods are shown in (A) and (C) and for On-Idebenone treatments are shown in (B) and (D). X-axis: time of follow-up (years).

in FVC%p from baseline. This analysis was conducted by evaluating the time to event during the longest consecutive Off-Idebenone and On-Idebenone periods. Altogether 10 patients had a baseline value at the beginning of the longest consecutive Off-Idebenone period, while all 18 patients had a baseline value at the beginning of the longest consecutive On-Idebenone period, allowing for this analysis. The median time to the first 10% decline during the Off-Idebenone period was 0.63 years compared with 1.72 years during the On-Idebenone period (hazard ratio: 0.44), indicating that idebenone treatment prolonged the time to a 10% decline in FVC%p (Fig. 7).

We next investigated whether long-term treatment with idebenone could also influence the occurrence of bronchopulmonary adverse events (BAEs), which constitute clinically relevant complications in patients with DMD. As reported previously [21], BAEs were classified as adverse events that involve the larynx, trachea, bronchi, lower airways or lungs. During the Off-Idebenone periods, 5 patients (35.7%) reported 9 BAEs, i.e., 0.33 events per person-year of follow-up. During the On-Idebenone periods, 6 patients (33.3%) reported 8 BAEs, i.e., 0.10 events per person year of follow-up, representing a clear reduction in BAE events under idebenone treatment. The cumulative frequency of the BAEs as a function of time (Fig. 8) demonstrated clearly diverging trajectories for the cumulative occurrence of BAEs

between the On-Idebenone and Off-Idebenone treatment periods (hazard ratio: 0.32).

In line with a reduced frequency of BAEs, we also observed that patients during On-Idebenone periods required less systemic use of antibiotics. During the Off-Idebenone periods 3 patients (21.4%) reported 4 events of antibiotic use (i.e., 0.15 events per person year of follow-up) which was higher than systemic antibiotic use reported for On-Idebenone periods with 3 patients (16.7%) reporting 3 events (i.e., 0.04 events per person year of follow-up).

As previous data from the DELOS trial also showed that idebenone treatment reduced the rate of hospitalizations due to respiratory infections or other respiratory cause when compared to patients receiving placebo [21], it was of interest to assess the efficacy of idebenone on the risk of hospitalization due to respiratory cause also in the longer term. Table 2 provides a summary of events by category, the event rates per person year and number of patients during the Off-Idebenone and On-Idebenone periods.

The rates of hospitalizations due to respiratory infections or related disorders were smaller for the On-Idebenone periods (0.06 events per person year) compared with Off-Idebenone periods (0.15 events per person year), although interpretation is limited by the small number of events reported. Hospitalizations due to any reason were also lower in the On-Idebenone periods compared to the Off-

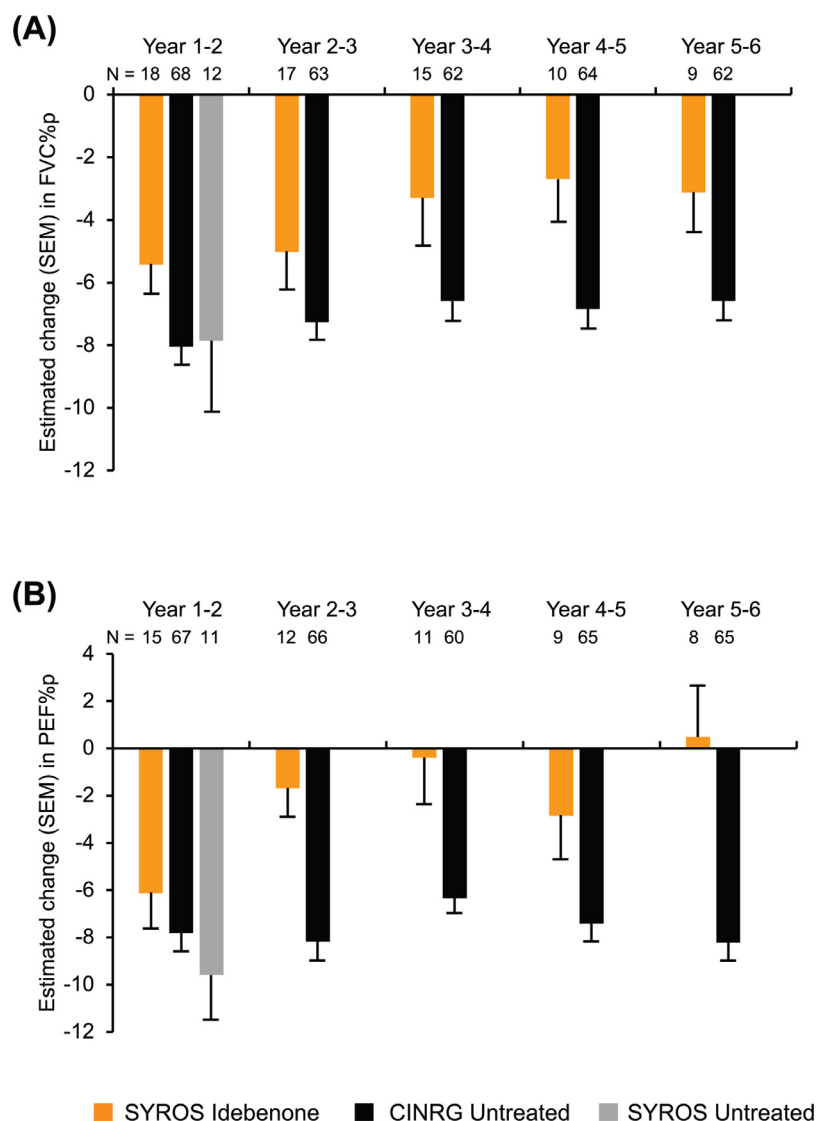


Fig. 6. Comparison in the evolution of annual rates of change in respiratory function outcomes for patients during On-Idebenone and Off-Idebenone periods and matched groups of untreated patients.

Annual rate of change in FVC%p (A) and PEF%p (B) are calculated from the longest consecutive On-Idebenone periods of the SYROS/DELOS studies (orange bars). Data from Off-Idebenone periods from SYROS/DELOS are shown for the first 2-year bins (gray bars), where such data were available. Data are estimated means (SEMs) from random coefficient regression models. Patients for the untreated natural history comparator groups were matched based on baseline FVC%p or PEF%p values respectively (black bars). Patient numbers/group are indicated and further details are provided in Supplement Table 3.

Table 2  
Reasons for and frequency of hospitalization.

Reason for hospitalization	Longest consecutive Off-Idebenone period N=14			Longest consecutive On-Idebenone period N=18		
	Number of events	Event rate (events/person year)	N (%)	Number of events	Event rate (events/person year)	N (%)
Respiratory infection or related disorder	4	0.15	2 (14.3)	5	0.06	5 (27.8)
All hospitalizations	13	0.48	5 (35.7)	24	0.29	12 (66.7)

Idebenone periods (0.29 versus 0.48 events per person year).

#### 4. Discussion

This study analyses the decline of respiratory function in patients with DMD not using GCs and treated with idebenone

under routine clinical care. Specifically, compared to untreated periods, idebenone-treated periods were associated with a reduced risk of declining by 10% in FVC%p and a reduced risk of experiencing patient-relevant outcomes, such as bronchopulmonary adverse events or hospitalizations due to respiratory cause. Overall, these findings add long-term data to the previously reported body of evidence



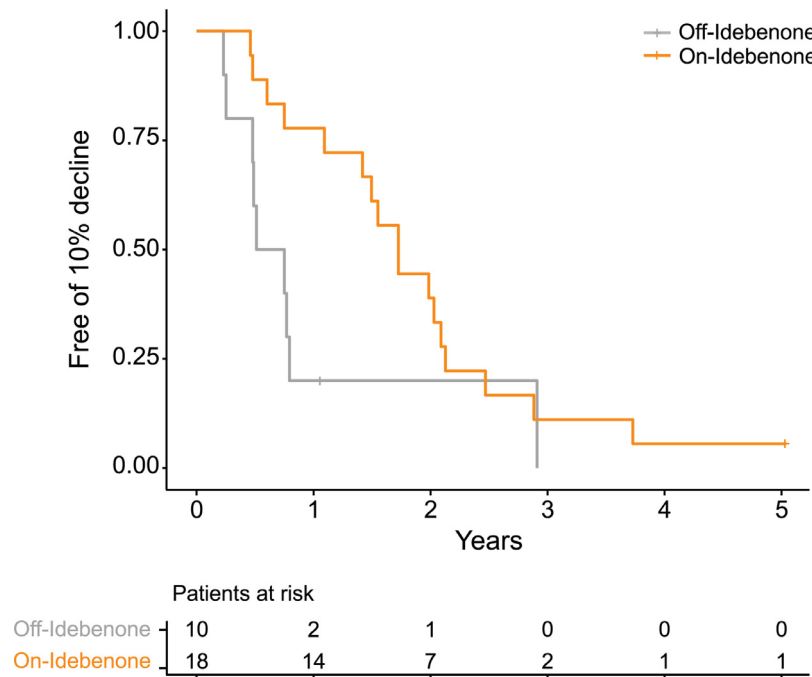


Fig. 7. Time to first decline of at least 10% (relative) in FVC%p by treatment.

Kaplan–Meier analysis (proportional means regression analysis) of time to first decline in FVC%p by treatment period.  $N=10$  patients for Off-Idebenone periods;  $N=18$  patients for On-Idebenone periods.

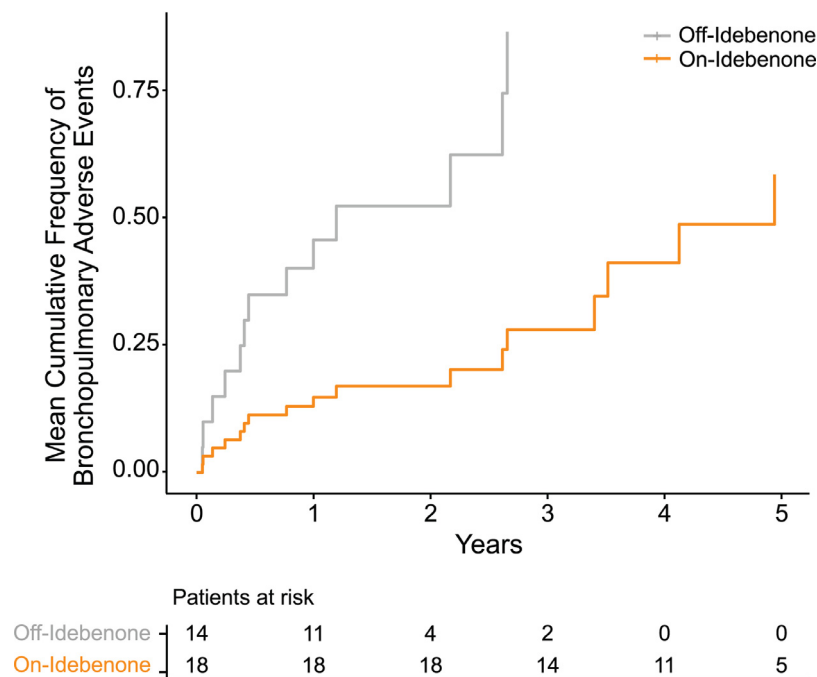


Fig. 8. Cumulative frequency plot for bronchopulmonary adverse events by treatment.

Kaplan–Meier analysis (proportional means regression model) for cumulative frequency of bronchopulmonary adverse events (BAEs) by treatment.  $N=14$  patients for Off-Idebenone periods;  $N=18$  patients for On-Idebenone periods.

[16,18–21], demonstrating that idebenone holds disease-modifying therapeutic potential to preserve respiratory function.

The present study is limited by the small sample size ( $N=18$ ), which represents 28% (18 of 64) of all patients randomized in the DELOS trial. The sample size was

governed only by the legal/regulatory framework and treating physicians' initiative to provide patients with unapproved medication under conditions of national Expanded Access Programs. The limited sample size is partially compensated by the extended follow-up time under which patients were monitored under routine clinical care, providing data from 76

person-years of idebenone treatment. To our knowledge, this is the longest period of exposure reported to an investigational drug in DMD outside that of GC use. Previously the longest follow-up time was 188 weeks (3.6 years) in drisapersen treated patients [23] and 180 weeks (3.5 years) in eteplirsen treated patients [24]; with 12 subjects followed-up in both studies.

Another limitation is that data were acquired during standard of care assessment in the real-world setting [25], and that no procedure insured the consistency of assessment methods across the sites or the systematic collection of all concomitant medication use, which could also have influenced the observed effects. It is however important to highlight that the frequency of FVC assessments was sufficiently regular to allow analysis and interpretation of the primary endpoint of the SYROS study, change in FVC%p.

The possible impact of patients' use of non-invasive ventilation ( $N=12$ ) or use of cough-assist devices cannot be excluded in this follow up study. Such possible impact was assessed in a sensitivity analysis excluding periods when patients reported NIV use. The annual rate of change in FVC%p for this sensitivity analysis was  $-6.8\%$  for Off-Idebenone periods compared to  $-4.4\%$  for On-Idebenone periods with overlapping confidence intervals.

To ensure data integrity, the collection of patient data and details of the analysis to be conducted was prospectively planned and described in a study protocol and Statistical Analysis Plan which was completed and signed off without data at hand.

In summary, these long-term data provide Class IV evidence [26] to further support the disease modifying treatment effect of idebenone previously observed in randomized, controlled trials.

Despite the limitations of this study, the difference observed in the annual rate of decline in respiratory function (FVC%p and PEF%p) between the Off-Idebenone and On-Idebenone periods appears clinically relevant for two reasons:

- (1) The reduced rate of decline in respiratory function and the smaller number of bronchopulmonary complications and hospitalization for respiratory events. Results from this non-controlled data collection appear to be in line with the results of the DELOS trial, that showed that fewer patients in the idebenone group compared to the placebo group experienced bronchopulmonary adverse events and serious adverse events leading to hospital admissions due to respiratory causes [21].
- (2) Long-term treatment with idebenone reduced the annual rate of decline in FVC%p by approximately 50% (from  $-7.4\%$  for Off-Idebenone periods to  $-3.8\%$  for On-Idebenone periods) for up to 6 years. A sustained reduction in the rate of decline of FVC%p indicates a potential therapeutic benefit as it could result in a delay in the need for assisted ventilation. Such a delay would be of unquestionable clinical benefit as demonstrated in patient and caregiver surveys [27,28], as it preserves the quality of life of patients and caregivers [29] and

reduces medical costs associated with non-invasive and invasive ventilation [30] and warrants further evaluation.

Several questions remain to be assessed to fully explore the therapeutic potential of idebenone in the treatment of DMD. A study in younger, predominantly ambulant patients would be useful to investigate the effect of idebenone on non-respiratory muscle, and more specifically on upper limb function which is the main function to preserve in patients with already established respiratory involvement [10]. The combined effect of idebenone and glucocorticoids on respiratory outcomes is currently under investigation in a large randomized, placebo-controlled study (SIDEROS, clinical trials.gov ID: NCT02814019).

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#### Supplementary materials

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