30 April 2020
EMA/CHMP/629264/2020
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment Report

Puldysa

International non-proprietary name: idebenone

Procedure No. EMEA/H/C/005123/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACE	Angiotensin converting enzyme
ADRs	Adverse drug reactions
AEs	Adverse Events
ASMF	Active Substance Master File = Drug Master File
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AR(1)	Autoregressive Covariance Structure
AST	Aspartate Aminotransferase
ATP	(1) Adenosine Triphosphate (2) According to Protocol
AUC	Area Under the time versus Concentration curve
BAEs	Bronchopulmonary Adverse Events
BMI	Body Mass Index
B/R	Benefit / Risk
C_{max}	Maximum Concentration in human plasma
CDMI	Colour Doppler Myocardial Imaging
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CINRG-DNHS	Cooperative International Neuromuscular Research Group-Duchenne Natural History Study
CMA	Conditional marketing authorisation
CMHT	Cochran-Mantel-Haenszel Test
CPHM	Cox Proportional Hazard Model
CoQ10	Coenzyme Q10, CoQ10
CRF	Case Report Form
CS	Compound Symmetry Covariance Structure
CV-2619, SNT-MC-17, IDE, I	Idebenone
CYP	Cytochrome P450
DDI	Drug-Drug Interaction
DELOS-NPP	DELOS Named Patient Programs
DELOS-CUP	DELOS Compassionate Use Programs
DMD	Duchenne Muscular Dystrophy
DMSO	Dimethyl sulfoxide
DSC	Differential Scanning Calorimetry
DSMB	Data and Safety Monitoring Board
EAP	Expanded Access Program
EC	European Commission
ECG	Electrocardiogram
EF	Ejection Fraction
EMA	European Medicines Agency
ERA	Environmental Risk Assessment

ETC	Electron Transport Chain
FEV_1	Forced Expiratory Volume in one second
FEV_1p%	Forced Expiratory Volume in one second percentage predicted
FRDA	Friedreich's Ataxia
FS	Fractional Shortening
FVC	Forced Vital Capacity
FVC%p	Forced Vital Capacity percentage predicted
GCs	Glucocorticoids
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GGT	Gamma-Glutamyl Transpeptidase
GMP	Good Manufacturing Practice
GPP	Good Pharmacoepidemiology Practice
HDPE	High Density Polyethylene
hERG	human ether-a-go-go related gene
HHM	Hand-Held Myometry
HPLC	High Performance Liquid Chromatography
HR	Hazard Ratio
IC_{50}	Inhibitory Concentration 50
IC_{20}	Inhibitory Concentration 20
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Report
IFR	Inspiratory Flow Reserve
ITT	Intent-to-Treat
IU	International Units
IWRS	Interactive Web Response System
LD_{50}	Lethal Doses 50
LHON	Leber's Hereditary Optic Neuropathy
LOCF	Last Observation Carried Forward
LV	Left ventricular
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MEP	Maximum Expiratory Pressure
MEP%p	Maximum Expiratory Pressure percentage predicted
MFM	Motor Function Measure
MicroRPM	Micro Respiratory Pressure Meter
MIP	Maximum Inspiratory Pressure
MIP%p	Maximum Inspiratory Pressure percentage predicted
MMRM	Mixed Model Repeated Measures
MS	Mass Spectrometry
MRD	Maximum Repeatable Dose
N, n	Number of observations

NA	Not applicable
NOAEL	No-Observed-Adverse-Effect Level
OC	Observed Cases
OLE	Open-Label Extension
PASS	Post-authorisation safety study
PCF	Peak Cough Flow
PD	Pharmacodynamics
PedsQL™	Pediatric Quality of Life Inventory TM
PEF	Peak Expiratory Flow
PEF%p	Peak Expiratory Flow percentage predicted
PK	Pharmacokinetic(s)
PMRM	Proportional Means Regression Models
popPK	Population Pharmacokinetic(s)
PP	Per-Protocol
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Terms
PUL	Performance of the Upper Limb
QMT	Quantitative Muscle Testing
QS10	6-(9-carboxynonyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone
QS10-C	Conjugates of QS10
QS4	6-(3-carboxypropyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone
QS6	6-(5-carboxypentyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone
QS8	6-(7-carboxyheptyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone
QTc	Interval measured from the beginning of the QRS to the end of the T wave, corrected for heart rate
RGC	Retinal Ganglion Cell
RMP	Risk Management Plan
ROS	Reactive Oxygen Species
SAE	Serious Adverse Event
SAG	Scientific Advisory Group
SAP	Statistical Analysis Plan
SD	Standard Deviation
SEM	Standard Error of the Mean
SmPC	Summary of Product Characteristics
$T_{1/2}$	Terminal half-live
t.i.d.	Three times daily
TEAEs	Treatment Emergent Adverse Events
ULN	Upper Limit of Normal
UN	Unstructured Covariance Structure
V'I,max(FVC)	Inspiratory flow during maximum effort maneuverer
V'I,max(t)	Inspiratory flow during tidal breathing

1. CHMP Recommendation

Based on the review of the data and the applicant's response to the CHMP LoQ on quality, safety, efficacy, the application for Puldysa, in the treatment of

"Puldysa is indicated for the treatment of respiratory dysfunction in patients with Duchenne muscular dystrophy not using glucocorticoids"

is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

Questions to be posed to additional experts

N/A

Inspection issues

GMP inspection

N/A

GCP inspection

N/A

New active substance status

N/A

Additional data exclusivity /Marketing protection

N/A

Similarity with authorised orphan medicinal products

It is considered that Puldysa is not similar to ataluren within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Derogation from market exclusivity

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication for Puldysa in the conditional MA is as follows:

'Puldysa® is indicated for the treatment of respiratory dysfunction in patients with Duchenne muscular dystrophy not using glucocorticoids'.

2.1.2. Epidemiology and risk factors

Duchenne muscular dystrophy (DMD) is a rare X-linked genetic disease that primarily affects males (incidence of up to 1 in 3,500 live male births worldwide). It is disabling, and ultimately fatal.

2.1.3. Aetiology and pathogenesis

DMD is caused by mutations in the gene for dystrophin, a protein expressed in skeletal, respiratory, and cardiac muscle as well as the central nervous system (Bushby et al., 2010a). Dystrophin is a subsarcolemmal protein that acts as structural link between the muscle cell membrane, muscle cytoskeleton, and extracellular matrix where it acts as a shock absorber to resist the mechanical stresses that occur during cycles of muscle contraction and relaxation, stabilising muscle cell membranes and preventing contraction-induced cell membrane damage (Vila et al., 2017). In the absence of dystrophin, the shear stress placed on cell membranes during contraction causes membrane damage and subsequently degeneration of muscle fibers.

The muscle membrane injury caused by the dystrophin deficiency leads to increased intracellular calcium (Ca2+) accumulation (Dunn et al., 1991, Culligan et al., 2002). The excessive Ca2+ load within mitochondria leads to mitochondrial dysfunction, a reduction in resting adenosine triphosphate (ATP) levels, increased production of cell-damaging reactive oxygen species (ROS) and elevated levels of oxidative stress, and a depletion of mitochondria over time (Pauly et al., 2017, Cole et al., 2002, Rybalka et al., 2014, Timpani et al., 2015). The mitochondrial dysfunction further decreases the ability of repair functions of the muscle, decreases the ability of the muscle to function properly and accelerates the induction of muscle death. Once functional muscle tissue has been lost and replaced by fat and fibrotic tissue, the muscle damage is irreversible (Kinali et al., 2011).

2.1.4. Clinical presentation and diagnosis

DMD is typically diagnosed at age 3-5 years when children start to show signs of physical disability including difficulty in walking. Patients experience progressive muscle weakness and become non-ambulant in early teenage years (Bushby 2010a).

Respiratory function decline (Gayraud et al., 2010; Henricson et al., 2013; Mayer et al., 2015) and cardio-pulmonary complications which starts from the age of 10-12 years, are the major cause of morbidity and early mortality in DMD (Bushby et al., 2010b). Progressive respiratory insufficiency requires the use of non-invasive and, in some circumstances, invasive ventilation which, following the loss of ambulation, is the second irreversible disease milestone in DMD greatly impacting the patients' quality of life.

Respiratory function is routinely monitored in patients with DMD as change in forced vital capacity (FVC) or peak expiratory flow (PEF); both expressed as percent of predicted (FVC%p, PEF%p) to account for maturational changes over time.

2.1.5. Management

Currently, there are no medications that can cure or reverse the pathology of DMD. The primary goal of current interventions is to slow or stabilise disease progression, prolong patients' ability to manage the activities of daily living, delay time to clinically relevant milestones such as loss of ambulation and the need for assisted ventilation, and manage the complications of DMD according to the latest standard of care guidelines (Birnkrant et al., 2018a, 2018b, 2018c).

Glucocorticoids (GCs) are not approved for the treatment of DMD in the EU but are part of the current standard of care for the treatment of DMD (Matthews et al., 2016, Henricson et al., 2013; McDonald et

al., 2018b; Birnkrant et al., 2018a; 2018b). Early and continued use of GCs treatment has been shown to prolong the time to loss of ambulation and delays the onset of respiratory function decline (e.g. McDonald et al., 2018b). However, once respiratory function starts to decline GCs use does not alter the rate of decline. Chronic administration of GCs is associated with well described poorly tolerated side effects (Bushby et al., 2010a; Ricotti et al., 2012). These side effects are often the reason given why a significant proportion of patients eventually stop GCs therapy. At any time, approximately 40% of patients with DMD have either never used GCs or have discontinued GCs treatment (Henricson et al., 2013), with the highest proportion in the post ambulatory phase of DMD.

At present, there is one product approved for DMD in the EU: Translarna™ (ataluren), an oxadiazole for dystrophin restoration therapy. Ataluren is indicated for the treatment of DMD resulting from a nonsense mutation in the dystrophin gene in ambulatory patients aged 2 years and older. Only 10 – 15% of DMD patients have a confirmed nonsense mutation (Dent et al., 2005) and are thus eligible for treatment with ataluren, thereby limiting the potential benefit of this agent to a relatively small group of individuals. It primarily focuses on restoring dystrophin levels in early childhood with the aim to prevent or delay the loss of ambulation and preserve upper and lower limb function.

2.2. About the product

The therapeutic activity of idebenone is based on its ability to protect mitochondrial function. This is due to its catalytic antioxidant properties, combined with its ability to restore ATP production. The quinone ring of idebenone, in its reduced form, is a powerful antioxidant that reduces oxidative stress within the myocyte, which protects the mtDNA and components of the mitochondrial Electron Transport Chain (ETC). Idebenone efficiently eliminates ROS such as superoxide radicals and is recycled by mitochondrial and cytosolic reductases (Haefeli et al. 2011; Ravasz, 2018), which makes idebenone a catalytic antioxidant. This antioxidative function enables idebenone to prevent ROS-induced damage that impairs mitochondrial integrity. Furthermore, idebenone is able to shuttle between the cytoplasm and mitochondrial matrix and circumvent the mitochondrial complex I dysfunction reported in DMD by transferring electrons from cytoplasmic and mitochondrial NAD(P)H directly to complex III of the ETC (Haefeli et al. 2011, Ravasz, 2018). Both mechanisms reinitiate the flow of electrons through the ETC, reactivating the proton pumping activity of complexes III and IV and the subsequent generation of ATP (Haefeli et al. 2011). The combined actions of idebenone may delay or prevent the initiation of mitochondrial-driven muscle cell death (Buyse et al., 2015b). Idebenone's mechanism of action is targeting mitochondrial processes and is independent of the mutational status of the patient. Idebenone therefore, provides benefits across a wider range of patients including those at an advanced stage of the disease.

The claimed indication is: 'Puldysa® is indicated for the treatment of respiratory dysfunction in patients with Duchenne muscular dystrophy not using glucocorticoids. The recommended dose is 900 mg/day idebenone (300 mg, 3 times a day, with food).

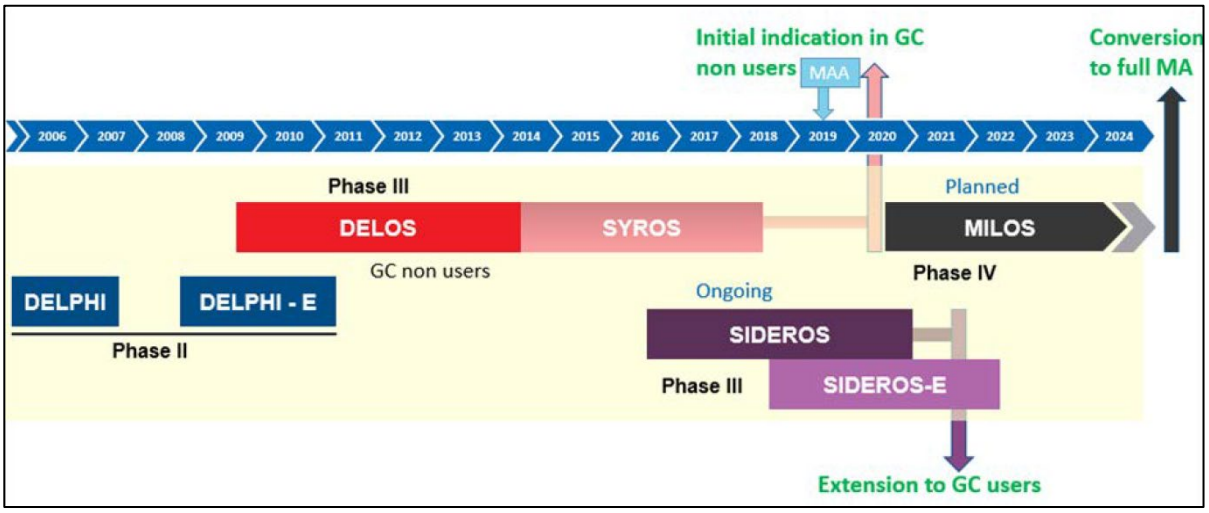
2.3. The development programme/compliance with CHMP guidance/scientific advice

An overview of the clinical development programme for Puldysa in DMD is provided in the table below.

The Clinical development programme of Puldysa includes main and supportive clinical studies with several ancillary reports containing additional (*post hoc*) analyses. The main clinical studies comprise the DELPHI study (with the ancillary analysis report SNT-IR-011), the DELOS study (with the ancillary analyses reports SNT-IR-009, SNT-IR-010, SNT-IR-015 and SNT-IR-017) and the SYROS study. The supportive studies include the DELPHI-extension study and the report SNT-IR-016. In addition, the phase III study SIDEROS (SNT-III-012) is currently ongoing with its extension SIDEROS-E (SNT-III-012-E).

Furthermore, the company is planning the post-authorization confirmatory study MILOS (SNT-IV-009). In addition, safety data are also derived from one study in patients with Leber's hereditary optic neuropathy (LHON) (RHODOS), five studies in patients with Friedreich's Ataxia (FRDA) (NICOSIA, MICONOS, MICONOS-E, IONIA, IONIA-E) and six phase I studies in healthy volunteers (Figure 1).

Figure 1: Overview of the idebenone Clinical development programme in DMD



DELPHI, DELPHI-E, DELOS and SYROS (new data) were the completed studies included in this MAA. DELPHI (Phase II) and DELOS (Phase III pivotal study for the CMA in GC non-users) were placebo-controlled studies, and DELPHI-E and SYROS were their respective OLE studies. The placebo-controlled Phase III SIDEROS study and its OLE SIDEROS-E study were ongoing at the time of the submission of this MAA and may be used later to extend the indication to GC users. MILOS is the planned Phase IV post-authorisation confirmatory outcome study.
GCs = glucocorticoids; MAA = Marketing Authorisation Application; OLE = Open-Label Extension

The applicant received scientific advice from the EMA in 2008 and 2019.

- ***Protocol assistance idebenone (SNT-MC17):*** *EMA/CHMP/629264/2020 (Procedure No.: EMEA/H/SA/561/2/2008/PA/SME/II*
- ***Protocol assistance idebenone (Puldysa):*** *EMA/CHMP/SAWP/182538/2019 (Procedure No.: EMEA/H/SA/561/5/2019/PA/SME/II)*

EMA interactions led to discussions on:

- Design aspects of the DELOS study, including recommendations on the clinical endpoints and definition of the patient population based on the level of lung function. In 2008, the choice of PEF%p as the primary endpoint was considered to be potentially problematic. The applicant was advised that *"in principle, the lung function parameter which is a) best validated and b) most sensitive to change should be the primary variable".* Furthermore, it was advised that "*if PEF% predicted is chosen as the primary efficacy variable, every effort should be taken to collect all material related to the validation of the chosen endpoint".* These points will be further elaborated in the discussion about the choice of PEF%p as the primary endpoint in the DELOS study.
- Design aspects regarding primary endpoint, secondary endpoints, study population, external comparator group, matching plan and schedule of efficacy assessment of the confirmatory phase IV MILOS study. These points will be further discussed in light of the assessment of the acceptability of MILOS as the confirmatory study in this CMA procedure.

There is a specific CHMP guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy (EMA/CHMP/236981/2011) that was partly followed by the applicant.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

Active substance:

A declaration of the Qualified Person of the applicant Santhera Pharmaceuticals (Deutschland) GmbH, Germany regarding Good Manufacturing Practice (GMP) compliance of the active substance is available for the involved manufacturers.

Letter of Access: Letter of Access has been provided.

Finished product:

Manufacturing sites including development sites, testing sites, packaging sites, batch release and importation sites were clearly stated and the appropriate GMP documentations was provided for most of them.

GLP

All pivotal studies performed with Puldysa were conducted in accordance with the Good Laboratory Practice (GLP) Standards and Regulations for Nonclinical Laboratory Studies, as adopted and published by the Organisation for Economic Cooperation and Development.

GCP

According to the applicant, all applicant-sponsored clinical studies were conducted according to Good Clinical Practice (GCP), the Declaration of Helsinki, Directive 2001/20/EC, Guideline for GCP ICH (International Conference on Harmonization) E6.

However, one issue regarding a GCP aspect came up during the assessment of the SYROS study. In this study, the primary endpoint in the protocol was defined to be PEF%p. However, with the preparation of the Statistical Analysis Plan (SAP) the choice of the primary outcome variable was made dependent on actual data availability of respiratory function read-outs, leading to a set of rather different analysis scenarios to eventually address the general study objective. From a formal GCP perspective, changing the primary endpoint of a study would principally require a substantial amendment. Such an amendment was not prepared and hence was not part of the submitted dossier. However, as a maintenance of the effect could not be shown anyway and the applicant will not be able to change the GCP compliance issue retrospectively, there will be not further questions posed regarding GCP compliance at this stage.

2.5. Type of application and other comments on the submitted dossier

Legal basis

The applicant Santhera Pharmaceuticals (Deutschland) GmbH, hereafter referred to as Santhera, is requesting consideration of a Conditional Marketing Authorisation (CMA) for Puldysa® film-coated tablets containing 150 mg idebenone for the treatment of respiratory dysfunction in patients with DMD not using GCs. Idebenone is a short-chain benzoquinone and is already approved under the tradename of Raxone® in the orphan indication of LHON in the European Union (EU/1/15/1020/001) since 8 September 2015. Raxone is a hybrid medicinal product, as defined in Article 10(3) of Directive 2001/83/EC. The reference medicinal product is Mnesis 45 mg tablets (authorised in Italy since 1993) which contains the same active substance. Mnesis is authorised for the treatment of cognitive and behavioural deficits due to cerebral pathologies of vascular or degenerative origin.

In June 2016, the applicant submitted a Type II variation for extension of the indication for idebenone for the treatment of patients with DMD. Based on the data available at the time of the review, a negative opinion by the Committee for Medicinal Products for Human Use (CHMP) was adopted.

The dossier for Puldysa is submitted as a separate Marketing Authorisation Application (MAA), with a new name and a new indication; however, the dose and formulation are the same as for LHON (900 mg/day (300 mg; 3 x daily)). An authorisation to submit a duplicate MAA under Article 82(1) of Regulation 726/2004 was obtained from the European Commission (EC).

The data package submitted in this application support the following proposed indication:

'Puldysa is indicated for the treatment of respiratory dysfunction in patients with Duchenne muscular dystrophy not using glucocorticoids.

Idebenone was initially developed by Takeda Pharmaceuticals Co Ltd as 45 mg tablets. It was authorised in 1993 in Italy (Mnesis®, MA number A.I.C N 027586015) and then in Portugal (Idecortex®, Cerestabon®), as well as some non-EU countries for the treatment of cognitive and behavioural deficits due to cerebral pathologies of vascular or degenerative origin. In France, Mnesis had also received nominative temporary authorisations for the treatment of various mitochondrial diseases, including FRDA and LHON.

The regulatory data protection for Mnesis has expired.

Raxone was approved as a hybrid medicinal product, using Mnesis as the reference product. As for Raxone, the application for a Marketing authorisation (MA) for Puldysa is based on a hybrid application under Article 10(3) of Directive 2001/83/EC using Mnesis 45 mg idebenone tablets as the reference medicinal product.

Puldysa tablets differ from Mnesis tablets on the strength (150 mg vs. 45 mg). The recommended daily dose of Puldysa is 900 mg vs. 90 mg of Mnesis, both administered orally. Therefore, bioequivalence between these products will not be shown. Additionally, Puldysa will be used in a different indication than is currently approved for Mnesis.

Conditional marketing authorisation

The applicant requested a CMA for Puldysa. The MAA for Puldysa is eligible for consideration for a CMA on two separate grounds within the scope of Article 2 of Commission Regulation (EC) No 507/2006:

1) It is intended to treat a "seriously debilitating disease or life-threatening disease"; and

2) It is a medicinal product designated as an orphan medicinal product in accordance with Article 3 of Regulation (EC) No 141/2000

Furthermore, for a CMA the following four requirements have to be fulfilled: a positive benefit-risk balance, the applicant is likely to provide comprehensive data, unmet medical need and the benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Positive benefit/risk balance:

The applicant argues that the data collected in the clinical development program and published natural history studies is robust and demonstrates clinically meaningful long-term effects for patients in delaying reduction in respiratory function. Furthermore, it is stated that Puldysa demonstrates good tolerability and a benign safety profile and there is no evidence of any safety issue.

It is likely that the applicant will be able to provide comprehensive data:

In order to further characterise the benefit-risk profile of Puldysa film-coated tablets and to facilitate the annual re-assessment of the product, the applicant commits to provide data from the SIDEROS/SIDEROS-E study, as well as data from a new proposed confirmatory clinical trial (MILOS), in a timely manner.

MILOS (planned) will be a Phase IV confirmatory, 2-part, randomised, placebo and externally controlled multicentre study:

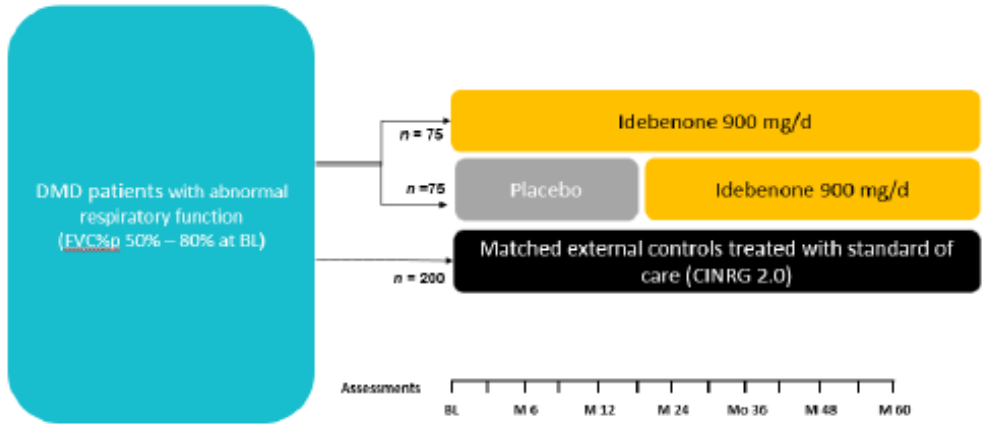
• Part 1 (Randomised, placebo-controlled): Patients randomised (1:1) to idebenone, or placebo in addition to standard of care.

• Part 2 (Externally-controlled): All patients treated with idebenone in addition to standard of care.

Data will be matched and compared with external controls from Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG-DNHS) 2.0 study. The goal is to enrol a minimum of 200 DMD patients. Efficacy assessments will include time to reaching the criteria for initiation of assisted ventilation in patients who are not acutely unwell and >15 days after medical therapy for an acute respiratory illness. Annual rate of decline in the total score of the Performance of the Upper Limb (PUL) module will also be measured as a secondary endpoint.

As the MILOS study is evaluating the time to reaching clinically relevant outcomes, including the initiation of assisted ventilation as a primary endpoint, it is anticipated to be a long study (i.e., up to 5 years) and therefore, the results will only be available post-approval. The design of the MILOS study is shown in Figure 2.

Figure 2: Design of the MILOS study



DMD: Duchenne Muscular Dystrophy; FVC%p: Forced Vital Capacity percentage predicted; BL: Baseline; CINRG: Cooperative International Neuromuscular Research Group

The design of the MILOS study has undergone protocol assistance to ensure that it meets the requirements for the confirmatory trial. The applicant is planning to start the MILOS study upon agreement on the final protocol from CHMP. The applicant acknowledges that the proposed MILOS study will be long (about 5 years); as suggested by the EMA Guideline on Clinical Investigation of Medicinal Products for the Treatment of Duchenne and Becker Muscular Dystrophy. However, it is important to note that while the MILOS study is ongoing, data from the SIDEROS study are expected to be available in 2022 and will be submitted to extend the indication of idebenone to all DMD patients irrespective of GC use.

Unmet medical needs will be addressed:

Currently, there are no medications that cure or reverse the pathology of DMD. The goal of current interventions is to help slow or stabilise disease progression, prolong patients' ability to manage the activities of daily living, delay the onset of subsequent muscle deterioration, and manage the complications of DMD according to the latest standard of care guidelines (Birnkrant et al., 2018a; Birnkrant 2018b).

At present, there is one product approved for DMD in the EU: Translarna™ (ataluren), an oxadiazole for dystrophin restoration therapy. Ataluren is indicated for the treatment of DMD resulting from a nonsense mutation in the dystrophin gene in ambulatory patients aged 2 years and older. Only 10 – 15% of DMD patients have a confirmed nonsense mutation (Dent et al., 2005) and are thus eligible for treatment with ataluren, thereby limiting the potential benefit of this agent to a relatively small group of individuals.

GCs to modulate inflammation are the current standard of care for the treatment of DMD (Matthews et al., 2016; Bushby et al., 2010a, Henricson et al., 2013; McDonald et al., 2018b; Birnkrant et al., 2018a; Birnkrant et al., 2018b), but have not been approved for this use in the EU. Continuous GCs treatment from age 5 years onwards has been shown to delay the time to loss of ambulation by 2-3 years and to reduce the subsequent risk of progressive scoliosis while also delaying the loss of upper limb function after the patient becomes non-ambulant. Additionally, GCs treatment delays the onset of respiratory function decline by approximately 2-3 years, but once respiratory function declines below the lower limit of normal (below 80% of predicted), GCs use does not alter the rate of decline of respiratory function. From that point, respiratory function continues to decline linearly and unabated from the age of approximately 10-12 years through the early 20s (Henricson et al., 2013; Mayer et al., 2015; Mayer et al., 2017; McDonald et al., 2018a; McDonald et al., 2018b) at a rate similar to GC non-users. Chronic administration of GCs is associated with known side effects (Bushby 2010a; Ricotti 2012). These side effects can negatively affect the benefit-risk balance of GCs use and are often the reason cited why patients eventually stop GCs therapy. At any time, approximately 40% of DMD patients have either never used GCs or have already discontinued GCs treatment (Henricson et al., 2013), with the highest proportion in the post-ambulatory phase of DMD.

There are no approved treatments for treatment of respiratory dysfunction in DMD patients. Current treatment strategies, with the exception of idebenone, are primarily focused on restoring dystrophin in early childhood with the aim to prevent or delay the loss of ambulation thereby preserving lower and upper limb strength and motor function. These treatments are restricted to certain mutation types and therefore, will only benefit a minority of DMD patients. Idebenone represents a unique therapeutic modality as it is not restricted by mutational status due to its mechanism of action on mitochondrial processes and therefore, has the benefit of providing additional efficacy across a wider range of patient groups at a stage of disease that is a major contributor to significant morbidity and mortality.

<u>The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required:</u>

DMD is a life-threatening disease with limited treatment options. The weakness in respiratory muscle strength characteristic of DMD (following loss of ambulation) steadily worsens leading to respiratory insufficiency and the need for assisted ventilation, followed by eventual respiratory failure and death. Although GCs use can delay the onset of respiratory function decline in DMD patients, once decline is established, the rate of functional loss is not affected by GCs use and some patients cannot tolerate or maintain GCs treatment. Thus, there is an urgent unmet medical need for alternative treatment options for the management of respiratory function decline, particularly in patients not taking GCs.

The active ingredient of Puldysa, idebenone, is already approved for treatment of LHON. Hence the safety profile of the product is well established. The use of the product will be closely monitored through product information and routine pharmacovigilance, such as periodical review every 6 months of cumulative data.

The ongoing clinical program, as well as the proposed confirmatory study, aim to confirm the results from the DELOS study and thereby further enhance the benefit-risk profile of Puldysa to ensure safe and effective use of the product for treatment of respiratory dysfunction in patients with DMD.

Based on the above information, the applicant considers that Puldysa film-coated tablets meet the requirements of the conditional authorisation Regulation as described in Article 4(1)(d) of Commission Regulation (EC) 507/2006. Therefore, in the absence of unacceptable risk to the patients from treatment with Puldysa film-coated tablets, the benefits, which will be replicated as per the proposal provided in this document, outweigh the risk and merit immediate availability of the product.

Orphan designation

An EU Orphan Drug Designation was granted for idebenone in DMD on 20 March 2007 (EU/3/07/437).

Similarity with orphan medicinal products

The MAA contained a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products. Assessment of these claims is appended. Based on this assessment report, Idebenone is not similar to Ataluren regarding therapeutic indication, mechanism of action and principal molecular structure.

PRIME

Not applicable.

Accelerated assessment

Not applicable.

Marketing authorisation under exceptional circumstances

Not applicable.

Biosimilarity

Not applicable.

Additional data exclusivity/ marketing protection

Not applicable.

Information on paediatric requirements

Not applicable

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as film-coated tablet containing 150 mg of idebenone as active substance.

Other ingredients in the tablet core and in the film-coating were stated.

The product is available in white high-density polyethylene bottles with white polypropylene child-resistant tamper-evident twist-off caps containing 180 film-coated tablets.

3.1.2. Active Substance

There is no need for additional documents to improve the documentation of the quality of the active substance.

Idebenone is an active substance that is not subject of an official compendium.

An ASMF in CTD-format has been provided by ASMF holder.

General Information

Adequate information is given on physical form, melting point, specific optical rotation, partition coefficient, solubility, potential isomerism, dissociation constant, hygroscopicity, polymorphism.

The active substance exhibits no stereogenic centres.

Manufacture, process controls and characterisation

Manufacture

Idebenone active substance is manufactured by three manufacturing sites.

Characterisation

Elucidation of structure and other characteristics

The investigations described in this section (elemental analysis, IR, ^{13}C-NMR, ^{1}H-NMR, MS, UV, XRDP, DSC) establish that the structure of idebenone active substance is in accordance with the proposed structure and is adequate. Representative chromatograms/spectra were given.

The molecule has no asymmetric atom.

Impurities

Potential impurities, residual solvents, elemental impurities arising from the route of synthesis were adequately discussed. An adequate safety risk assessment following ICH M7 is missing.

Please note that Active Substance Master File (ASMF) has been already assessed during an approved centralised procedure using the same ASMF. Therefore, this is acceptable. Nevertheless, please note there is one comment in the restricted part.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specification

Idebenone is an active substance that is not subject of an official compendium.

Maximum daily intake: 900 mg (e.g. Martindale current edition).
The specification covers

Appearance, colour, identity by IR, melting point, water, sulphated ash, heavy metals, residual catalysts by ICP-AES, residual solvents by GC, related substances by High Performance Liquid Chromatography (HPLC), assay by HPLC, particle size by laser diffraction and microbial purity.

Analytical procedures

Methods have been described sufficiently. Where applicable Ph. Eur. monograph tests have been used.

Methods have been adequate validated. Validation reports have been provided for assay, particle size, related substances, residual catalysts and residual solvents.

Stress tests have been performed (heat, light, Ph, oxidising agents). For further information please refer to section stability.

Batch analyses

Results from three recent production-scale batches manufactured and analysed were given. Information on batch number, manufacturing date, manufacturing site, batch size, tested parameters, acceptance criteria and test results was given. The batch data comply with the proposed specification. Consistency and uniformity of the active substance are demonstrated.

Justification of specification

Idebenone is tested according to the corresponding guidelines and in-house/ Ph. Eur. monographs specification limits. For comment on ICH Q3D compliance please refer to the respective section in the finished product. Mode of preparation, purification, and analytical results are given for all used standards. Structure of all impurity standards have been confirmed with adequate methods (1H-NMR, MS) for all used standards.

Container closure

The active substance idebenone packaging material was described.

It is stated that the plastic bags may have an impregnation with an antistatic agent and may be dyed Antistatic BD Transparent comply with the current Regulations for food contact. The polymers used as raw material comply with EU regulation 10/2011 according to the applicant.

The primary packaging complies with 21 CFR 177.1520 (olefin polymers) and with EU regulation 10/2011 including amendments (declaration of conformity has been given). IR- spectra has been provided. Specification and CoA of the primary packaging material are provided.

Stability

The information given in the section post-approval stability protocol and stability commitments is sufficient.

Conclusion on Stability data

The analytical procedures are the same as the ones used for routine control (refer to section 3.2.S.4).

Container closure is the same as described in S.6. Batches from one manufacturing site were packed in bags placed in cardboard drums and batches from another site in bags placed in polyethylene drums.

Stability data under long term (25°C) and accelerated (40°C) conditions have been provided according to the corresponding guideline.

No changes in any of the test results (stability indicating parameters: appearance, colour, water, assay related substances) were observed in the long-term testing and accelerated testing. There is no difference between stability data for Idebenone manufactured. The manufacture and testing of Idebenone active substance is the same at both sites.

A re-test period of 60 months is justified. No special storage conditions are required.

Polymorphic stability has been confirmed by data.

Photo-stability testing was done according to ICH Q1B.

According to the given data, it can be concluded that the used method for related substances is stability indicating.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

P.1 Description and Composition of the Finished product

Description and composition of the finished product was given including the function of the excipients and the related quality standards.

The use of colorant sunset yellow in the formulation is properly justified in section P.2.

P.2 Pharmaceutical Development

Adequate discussion on physicochemical properties of the active substance is provided.

The compatibility of the active substance with excipients is confirmed by the provided stability data. The excipients chosen has been adequately discussed.

Polymorphic stability data which confirm that idebenone film-coated tablets 150 mg are stable during long-term storage up to 5 years plus storage under accelerated conditions for 4 months have been provided. Test for polymorphic form is not included in finished product specifications, which is justified.

Development of the dissolution method is described in section P.5.3.

Influence of the compression force on dissolution rate is marginal within a range of 60 to 100 N core hardness.

Commonly used high density polyethylene (HDPE) bottles with a polypropylene twist-off cap with a nominal content of 50 ml and 100 ml were selected as container closure system, which is comprehensible because daily dose of idebenone is 900 mg, i.e. 6 tablets.

Reduced microbiological testing has been justified.

Elemental impurities risk assessment for Idebenone 150 mg film coated tablets according to ICH Q3D is given. Data show that the total amount of each elemental impurity in the maximum daily dose of the finished product is below its corresponding 30% PDE control threshold. Additional controls are not required.

There is further discussion awaited concerning administration through feeding tubes and suitability/acceptability.

Manufacture of the product and process controls

The names and addresses and responsibilities of all manufacturers involved in manufacture, packaging and testing are given. Manufacturer and primary packaging site are identical.

Range of batch size is given production batch size was given. Given information on sub-batches is acceptable. More information about bulk packaging/stability is awaited.

A flow chart of the successive steps, indicating the components used for each step including any in-process controls and a brief narrative description (preparation of granules (mixing, granulation, drying), compression mixture (screening, blending), compression, preparation of film-coating suspension, coating, packaging) was given. Leak test is performed as IPC during finished product packaging step.

The manufacturing process is a standard process. No intermediates are isolated during the manufacturing process. Critical steps have been outlined and are controlled during the manufacturing process with justified limits.

Process validation was performed within the proposed batch size range and analytical results are given. The process parameters for the preparation of the granules (mixing time, kneading time, drying temperature and residue on drying), for the compression mixture (blending and uniformity), for the compression (weight and hardness), for the tablet core (content of active substance), for the preparation of film-coating suspension (homogenous suspension), for the coating (average weight) were given. The provided process validation data are acceptable.

Adequate compliance statement in line with the Note for Guidance on start of shelf-life of the finished dosage form is provided.

Control of Excipients

Information given is acceptable.

Product specification, analytical procedures, batch analysis

Specification

Specification data was outlined.

Dimensions of the film-coated tablet is outlined. Identity is measured with adequate methods (HPLC and UV). Not testing of polymorphic form has been justified by data. For further information please refer to section P.2. The content limits of idebenone are in compliance with the corresponding directive and guideline.

The recommended dose is 900 mg/day idebenone. Set limit for each unspecified impurity is justified. Limit for total impurities is acceptable. Dissolution limit is acceptable. Uniformity of dosage units by mass/weight variation is performed according to the harmonized method of Ph. Eur. The AV-value is stated. Microbial limit tests are performed according to Ph. Eur. and adequate limits are set. It is considered acceptable not to routinely test for microbiological purity.

Used methods are mentioned in the finished product specification. For all analytical procedures reference to paragraph number in section P.5.2 is made, which is acceptable for the Rapporteur.

The quality relevant parameter hardness was not included in the finished product specification. Hardness is performed as in-process control. Provided stability data justify not including a test for hardness in the finished product specification.

It is stated that test for water content is not required because idebenone is not hygroscopic. The dosage form is a film-coated tablet and residue on drying is tested as in-process control. Taking this into concern not including a test for water in the finished product specification is justified.

Analytical Procedures

Non-pharmacopoeial methods have been described sufficiently. Where applicable Ph. Eur. monograph tests have been used.

Validation of Analytical Procedures: Method for assay, identity and related substances has been shown to be stability indicating and the method is confirmed to be suitable for its intended use. Respective chromatograms have been provided.

Method for dissolution has been shown to be discriminatory and the method is confirmed to be suitable for its intended use. Respective dissolution profiles/spectra have been provided.

For microbial purity it was demonstrated that under the test conditions used the total viable aerobic count, including yeasts and moulds, and the test for E.coli can be performed without interference of Idebenone on the growth of microorganisms.

Batch Analyses

Information on batch number, manufacturing date, manufacturing site, batch size, tested parameters, use of batches, acceptance criteria and test results was given. The batch data comply with the proposed specification. Consistency and uniformity of the finished product are demonstrated.

Stability of the product

A brief summary for the stability data was given (Batch number, date of manufacture, batch scale, storage conditions, and study duration available data). The stability batches were manufactured using the commercial process and scale; results for six batches were presented.

Studies were carried out in accordance with current ICH/CPMP guidelines (long term, intermediate, accelerated). Stability protocol was given, and the parameters tested in the studies are justified. The methods used are the same as those described in P.5. They are well validated and have been shown to be stability indicating.

The containers used in the stability studies are the same as those proposed for routine storage. Three batches are packed in 75 mL HDPE bottle with a PP CR tamper evident cap (packaging used in clinical trial) and another three batches are packed in 100 mL HDPE bottle with a PP CR tamper evident cap (commercial packaging).

There were no trends during the tested period. Stability data comply with the proposed specification.

The proposed shelf life and storage conditions are adequate (stability data up to 60 months under long term conditions): shelf-life of 5 years in HDPE bottles without storage remark.

Stability data after opening were given. One of the batches was chosen towards the end of its shelf life. The analytical methods used for in-use stability testing were the same as those used for release testing (see section 3.2.P.5.2). The specifications given in section 3.2.P.5.1 were applied. For the validation of the analytical procedures see sections 3.2.P.5.3. The produced idebenone film-coated tablets 150 mg are of consistent quality during the tested period after first opening. Declaration of an in-use shelf life and additional storage conditions are not necessary.

Photo stability testing of idebenone film-coated tablets 150 mg was performed according to the ICH guideline Q1B. Idebenone film-coated tablets 150 mg are not light sensitive.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Active Substance

Idebenone is an active substance that is not subject of an official compendium. An ASMF in CTD-format has been provided by ASMF holder for the active substance idebenone. There are no open issues concerning the ASMF open part and the ASMF restricted part.

Finished Product

Puldysa film-coated tablets 150 mg is proposed as finished product. Manufacturing of finished product, chemical/physical QC testing of finished product and primary and secondary packaging sites were stated. Batch Certification and market release site was also stated. Assessment of the information on the finished product can be found in the Quality AR. In view of recent discussions on potential presence of nitrosamine impurities a major objection is raised. Furthermore, the other concern concerning site of physical importation of the product has been upgraded to major objection because this question was not answered satisfactorily.

3.2. Non-clinical aspects

3.2.1. Introduction

The MAA for Puldysa® (idebenone) is a duplicate of Raxone MA. Additionally, the application follows a hybrid route and therefore relies on some registered information for the reference medicinal product Mnesis®, approved in Italy.

This submission is a hybrid application according to Article 10(3) of Directive 2001/83/EC as amended and Mnesis® 45 mg tablets (active substance: idebenone, MA number A.I.C N 027586015) is the reference medicinal product which was authorised in Italy in 1993 based on a full stand-alone application (MA holder: Takeda Pharmaceuticals Co Ltd).

Based on the hybrid route of the application, the EU nonclinical dossier partially cross-refers to the Mnesis data, generated by the originator company Takeda Pharmaceutical Company Limited (Takeda) that originally developed idebenone for treatment of cognitive impairment. Santhera Pharmaceuticals has full access to these data, and some are provided in the current marketing application. The pivotal Takeda safety studies were conducted in compliance with GLP and many of these Takeda studies have also been described in the published literature. Adequate numbers of animals have been used in these studies, and the extent of observations and investigations performed within the studies conforms to applicable standards.

3.2.2. Pharmacology

Primary pharmacodynamics studies

Idebenone is a synthetic analogue of ubiquinone (coenzyme Q10). Puldysa acts as an electron carrier in the mitochondrial ETC, inhibits lipid peroxidation and protects cell membranes and mitochondria from oxidative damage.

Idebenone has been reported to utilise and activate Complex I-independent metabolic pathways (Rauchova et al., 2006; Haefeli et al., 2011; Giorgio et al., 2012; Erb et al., 2012) and an idebenone-dependent metabolic pathway that transfers energy equivalents from the cytosol directly into the mitochondrial ETC has been reported by Haefeli et al., (2011). Reduced idebenone has furthermore been

reported to demonstrate a high degree of inhibition of ROS formation, as well as to protect both mitochondrial Complex II and Complex III from oxidative damage due to elevated levels of ROS. ROS is also thought to trigger the permeability transition pore and cytochrome C release from mitochondria, leading to cellular apoptosis and degeneration of skeletal muscle in DMD.

The MAA is based on primary pharmacodynamics (PD) studies conducted in support of the indication of LHON. These studies included data from *in vitro* isolated mitochondria from different tissues suggests that idebenone activity effects on cellular electron transfer can help restoring mitochondrial respiration. The submitted *in vitro* study (SNT-P-005) shows that idebenone increases the Retinal ganglion cell (RGC) viability after a rotenone treatment at doses tested. Significant protection by idebenone was seen at concentrations ≥10nM. However, the protective effect was dependent on the duration of idebenone pre-incubation and only one parameter was studied which is why the clinical relevance of this study is limited. It is well-known that the loss of vision in LHON patients is due to the apoptotic cell death of the RGCs. The prevention of retinal neurotoxicity and the recovery of vision loss have been studied *in vivo* in several LHON models (SNT-P-001, SNT-P-002, and SNT-P-008). To simulate the situation of a mutated mitochondrial complex I, rotenone (a potent mitochondrial complex I inhibitor) was used in these studies. A slight protection of the retinal tissue studied was observed in addition to an increase on the markers of retinal diseases and cellular stress; glutamine synthetase and Müller cell gliosis.

In relation with the intended indication, the applicant has carried out a series of additional *in vitro* and *in vivo* primary PD studies.

Puldysa was tested by the applicant in a blinded and placebo-controlled study in the homologous dystrophin-deficient mdx mouse (SNT-MC-17), a well-established and relevant animal model for DMD, to evaluate its ability to reduce the disease state after both short-term (10 weeks) and long-term (9 months) treatment. The main finding of this indication-specific nonclinical pharmacology study was that pre-symptom-initiated and long-term idebenone treatment significantly prevented cardiac diastolic dysfunction, preserved cardiac systolic contractile reserve and thus blocked the development of lethal acute heart failure during a dobutamine-mediated stress protocol. Furthermore, idebenone reduced cardiac inflammation and fibrosis, and improved voluntary running performance in the mdx mouse.

The PD effect for the proposed DMD indication was further supported by an *in vitro* study in excised perfused rat hearts (C-14-499) and an *in vivo* study on ischaemic cardiac muscles of anesthetized dogs with coronary stenosis (C-14-498) at clinically relevant concentrations and dosages.

Secondary pharmacodynamics studies

In regard of the secondary PD no studies were submitted, and the applicant refers to the approved information of the reference product Mnesis. As the present MAA is a hybrid application, aspects already evaluated for the reference product were not re-discussed. No further secondary PD data was provided.

Safety pharmacology programme

For the safety pharmacology the applicant referred to the approved product Mnesis. However, the provided Safety Pharmacology studies demonstrate that Idebenone was without effect on either the central nervous system or somatic nervous systems, although a slight decrease in body temperature of rats was observed at 300 mg/kg, orally. Furthermore, Idebenone was without effect on intestinal transport in mice and on gastric secretion in rats.

In the *in vitro* human ether-a-go-go related gene (hERG) assay (RCC A07143), idebenone significantly inhibited the tail currents of the hERG channel with an IC_{50} (concentration of a drug that is required for 50% inhibition *in vitro*) of approximately 10 µM (nominal) (5.54 µM (actual)). The IC_{50} and IC_{20} (concentration of a drug that is required for 20% inhibition *in vitro*) concentrations were approximately 95- and 9-fold greater, respectively, than the mean maximum idebenone concentration in human plasma

(C_{max}) following repeat dosing of 750 mg t.i.d. (C_{max} = 19.2ng/mL), a dose which is above the current intended clinical DMD dose of 300 mg t.i.d. (900 mg/day). No findings on QTc (corrected QT) were evident *in vivo* as measured in conscious, telemetered dogs as a part of a 39-week toxicology study in dogs (RCC 859414). In this study, no effects on QT interval or other electrocardiogram (ECG) parameters, respiratory rate, or tidal and minute volume were observed at doses up to 500 mg/kg. Idebenone demonstrated no effects on the QTc interval experienced in the 39-week GLP toxicology study in Beagle dogs at oral doses up to 1000 mg/kg/day, where animals showed significantly greater systemic exposures. In this study part, the animals were dosed after feeding to increase absorption of idebenone (mean C_{max} values at Week 39 were 959 and 1090 ng/mL in males and females, respectively). Taken together the *in vitro* and *in vivo* safety data in animals demonstrated no overt cardiovascular safety concerns with respect to the clinical use of Idebenone.

In addition to the Safety Pharmacology core battery, (hERG assay, cardiovascular system in telemetered dogs and respiratory parameter measures), the applicant provided a modified Irwin screen, performed in male Wistar rats (6/group) (RCC 859415) to evaluate possible pharmacological effects of Idebenone on the general behaviour of the rat.

The totality of provided safety pharmacology data in animals demonstrate no evident safety concerns with respect to the clinical use of idebenone for the treatment of DMD.

3.2.3. Pharmacokinetics

The pharmacokinetic (PK) of Puldysa has been evaluated in different species: in mice, rats, dogs, and humans.

A single dose study in rats involving doses of 30, 300, 500 and 1000 mg/kg idebenone revealed rapid absorption. However, high inter-individual variability was observed. C_{max} was already reached after 0.25 h and idebenone was no longer detectable in plasma samples after 4 h. Plasma concentrations increased in a dose-dependent manner up to the dose of 500 mg/kg whereas no further increase in plasma levels was detected at the 1000 mg/kg dose.

Moreover, a PK study was performed in dogs to comparatively evaluate the PK profile of 5 different formulations for oral and oromucosal treatment.

After oral administration of 14C-labelled idebenone in rats and dogs, idebenone was rapidly absorbed and 14C reached a peak at 15 minutes in both species. Overall, the data indicate that idebenone has a pharmacokinetic profile which is consistent with its lipophilic physicochemical characteristics as absorption is enhanced by food. The terminal half-live ($T_{1/2}$) of total radioactivity in plasma of rats and dogs after oral administration of 14C-idebenone was 4.5 and 15.4 h, respectively. A plateau in absorption was observable in both species. Although the plateau was massively different in the two animal species (2500 mg/kg in the rat / 100-500 mg/kg in the dog), this effect is known for a lipophilic compound with limited solubility in an aqueous environment. However, the detected differences in bile concentrations of the gastrointestinal tracts of rats versus dogs may be an explanation for the differences in the observed plateaus in absorption.

Following repeated oral dosing over a 21-day period, mean levels of idebenone in vitreous humour or aqueous humour were approximately 6% or 28-48% of the plasma concentrations, respectively. No accumulation of idebenone or its metabolites was found in the plasma or in the eye of exposed animals.

After oral or intravenous dosing 14C-idebenone was found in relatively high concentrations within 15 minutes in the liver and kidneys and later in the intestine and other highly perfused organs of the rat. No accumulation was seen in any tissue studied after repeated dosing.

Furthermore, various published reports have been summarised. Idebenone was found in relatively high concentrations within minutes after dosing in the liver and kidneys, plasma and later in the intestine and highly perfused organs. Data showed that a considerable amount of unchanged idebenone was distributed in the mitochondrial fraction (34.4%) in the brain.

Studies performed in pregnant rats showed idebenone in both foetal plasma and tissues from pregnant rats, suggesting that the compound crossed the placenta. The levels of radioactivity in foetal plasma and tissues at 2 and 6 h after administration were about 20% of the levels in maternal plasma. Idebenone and/or its metabolites were also excreted into rat milk in moderate amounts. No accumulation was reported after repeated dosing in rats.

Although Idebenone is well absorbed, it undergoes extensive pre-systemic metabolism. The compound is highly protein bound /plasma protein binding was >99.9%, 98.0%, and 98.5% for idebenone and 99.9%, 99.5%, and 98.8% for QS10 in rat, dog, and human plasma, respectively), and it penetrates the brain. In accordance with its mechanism of action, Idebenone is rapidly metabolised and drug-derived material is excreted into urine and bile. The metabolism of idebenone by reduction to idebenone hydroquinone and oxidative side chain reduction and subsequent/prior conjugation is fast and extensive.

The main metabolites are conjugates of QS10, QS6, and QS4 in rats, and conjugates of idebenone hydroquinone and QS4 in dogs.

Idebenone is extensively metabolised in mice and all of the metabolites measured in plasma were present at higher levels than idebenone (i.e., QS4>QS6>QS10>idebenone).

The metabolic profile of idebenone was qualitatively similar in rats and dogs compared with humans.

During the procedure, the applicant provided results from and *in vitro* study investigating the potential of the main human plasma metabolite, dihydro idebenone 1(4)-Osulfate D-glucuronide (IDEB-HQ-O-Sulf/D-Gluc) to inhibit Cytochrome P450 Isoenzymes. It was agreed that this metabolite is not inhibitor of the cytochrome P450 isoforms CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and *CYP3A4 in vitro* at concentrations up to 25 µM.

3.2.4. Toxicology

As the application for Puldysa® (idebenone) is a duplicate of Raxone® MA, and the application follows a hybrid route, this MAA relies on some registered information of the reference medicinal product Mnesis®, approved in Italy.

A systematic package of toxicology studies has been completed with idebenone to support a marketing application for the treatment of Duchenne Muscular Dystrophy DMD. The nonclinical program relies significantly on nonclinical data generated by Takeda. However, additional toxicology studies were performed by Santhera to address gaps in the nonclinical toxicology data.

Due to the change of both the manufacturer and the manufacturing process, Santhera performed a series of studies with the aim of demonstrating toxicological equivalence between the two preparations of idebenone, in order to enable the use of the already existing data generated by Takeda, supporting the current submission. In these studies, which were described by the applicant as "bridging studies", no direct comparison of the two products (pre- and post-manufacturing change) was shown. However, since Puldysa is a synthetic analogue of coenzyme Q10 and in compliance with 3R regulations, it is acceptable not to compare the two products concurrently within the same studies. The provided toxicity studies were conducted in full compliance with GLP and ICH guidelines.

As no human specific metabolite has been identified, mice, rats and dogs were considered to be the relevant animal models for the toxicity assessment. The main findings in the animal toxicity studies with

idebenone can be summarised as follows: Idebenone was absorbed rapidly after repeated oral administration, with no evidence of accumulation of idebenone or its metabolites. Biotransformation was rapid and extensive and most of the circulating idebenone-derived material was present as metabolites.

Single dose toxicity

In single dose toxicity studies, idebenone was of low acute toxicity, presenting a lethal dose 50% (LD_{50}) value of more than >10 000 mg/kg following p.o. and s.c. administration and 700-800 mg/kg (i.p.) in mice and rats respectively.

Repeat dose toxicity

Idebenone was tested in oral repeat-dose toxicity studies in rats (up to 26 weeks) and Beagle dogs (up to 39 weeks). In studies ≥ 5 weeks rats and dogs were exposed to idebenone oral doses up to 500 mg/kg/day. In another short animal study, rats were dosed up to 2500 mg/kg/day for 2 weeks.

In rodents (mice and rats), the target organ was the forestomach. The no-observed-adverse-effect level (NOAEL) was considered to be 500 mg/kg/day. Although local changes to the forestomach were only seen in the middle and high dose animals, the applicant was requested to discuss the relevance of these findings in the forestomach and a potential clinical impact thereof. During the procedure, the applicant clarified that there is no anatomical correlate of the rat forestomach in humans and the concentrative function of the rodent organ is the likely explanation as to why the idebenone-related effects were seen in the rat. The applicant also provided clinical and historical data to support that although the target organ in the rat was the forestomach, the lesions observed in the forestomach of this species are considered to be of little relevance to human safety. In dogs, at doses up to 500 mg/kg/day, no systemic toxicity and no target organ toxicity was identified. The only effects in this species were clinical signs, including gastrointestinal disturbances such as loose feces, diarrhoea, and emesis which, in early studies, were considered to limit the maximum repeatable dose (MRD). The NOAEL was established at 500 mg/kg/day in this species. By feeding animals before dosing and providing additional supportive care (i.e., extended feeding period and tinned meat), higher doses were tolerated in the dog and in a 39-week chronic toxicity study in dogs the NOAEL was increased to 750 mg/kg/day. In the dog study, clinical signs of GI disturbances and emesis were the only signs of toxicity induced.

Collected data from the Santhera repeat-dose toxicity studies supported the findings obtained in the Takeda studies, with no significant differences noted, verifying the outcome of the Takeda nonclinical safety program.

Genotoxicity

Based on the hybrid nature of this application, the applicant referred to the reference product Mnesis. In addition to the original studies conducted by Takeda, the applicant conducted additional genotoxicity studies. Idebenone was not genotoxic in the *in vitro* bacterial mutagenicity assays and chromosome aberration assays in addition to *in vivo* micronucleus tests. However, idebenone demonstrated a clastogenic potential *in vitro*, which was possibly attributable to its redox properties.

Carcinogenicity

No carcinogenicity studies were performed by the applicant. The applicant referred to the reference medical product Mnesis. The SmPC of the reference product states that no carcinogenicity concerns are expected from the administration of idebenone, as there was no evidence to suggest that idebenone is a carcinogen based on the results of dietary carcinogenicity studies conducted in mice and rats at doses up to 2000 and 1000 mg/kg/day, respectively. The applicant's approach is considered acceptable.

Reproduction toxicity

Idebenone had no effects on fertility and general reproductive performance and there was no evidence of embryotoxic or teratogenic effects. The calculated exposure margins for 500 mg/kg (parent idebenone) in rats were 16-23 (AUC_{ss}) times the average exposure for the highest recommended dose in human.

Toxicokinetic data

Toxicokinetic data generated from the juvenile animal toxicity study in which rats were treated daily for four weeks at doses up to 1000 mg/kg/day (the NOAEL was considered to be 200 mg/kg/day) indicate suitable safety margins. This was verified following administration of idebenone to humans and exposures in dogs (based on AUC comparison at the NOAEL of 750 mg/kg/day in dogs, multiples of 19.79 to 21.80). The dosing regimen for the proposed treatment of DMD is 2 film-coated tablets, 3 times a day (t.i.d.), resulting in a daily, chronic dose of 900 mg (corresponding to 15mg/kg/dy) per patient. Concentrations of idebenone in dog plasma were 25 – 28 times higher at C_{max}, when compared with the C_{max} observed in man, receiving 2250 mg Raxone, which corresponds to a dose 2.5 times higher than the intended treatment dose for DMD patients. Toxicokinetic data indicate that sufficient safety margins exist following administration of idebenone to humans and exposures in animals, based on AUC comparison.

Other toxicity studies

Studies in Juvenile Animals

In the juvenile toxicity study, bone densitometry investigations revealed some differences in the bone content of the femur and lumbar vertebrae between the treated and control rats at the end of the treatment period. However, the main differences concerned the high dose females. The differences in the males and lower dose-treated groups of females, some of which attained statistical significance, were generally due to the influence of one or two isolated animals and did not show a dose-relationship. The content and density of the trabecular and cortical bone tissue tended to be lower in the high dose females than in the controls, and the effects were more evident in the lumbar vertebrae than in the femur. In all groups, the heavier rats tended to have a greater bone content, suggesting an association with the lower body weights in the high dose group. This tendency was no longer evident in animals examined after attaining sexual maturity. Some intergroup differences were again visible at this time, in correlation with differences in body weight, but the distribution of the individual data did not suggest any persistent effects of treatment. It was therefore concluded that post-weaning exposure of the female rat to Puldysa at the high dose level of 1000 mg/kg/day induced transient changes in bone density that were consistent with the observed treatment-related growth retardation.

The transient differences in bone density consistent with the lower body weights of the high dose females may have been a reflection of immaturity associated with the observed treatment-related growth retardation. This difference was no longer evident after when animals attained sexual maturity. The differences in bone density may have been a reflection of immaturity associated with the lower body weights of the high dose females.

During the procedure, the applicant was requested to discuss the possible etiology for the bone densitometry findings observed in high dose females in this study and potential implications of this non-clinical finding for human use. The reason for the apparent sensitivity of female juvenile rats compared to males with respect to the bone densitometry findings could not be elucidated with the available data. Nonetheless, the elaborated response provides adequate considerations supporting the conclusion that safety concerns in paediatric patients are considered limited from non-clinical perspective. The lower bone content (femur and lumbar vertebrae) was not related to systemic exposure of idebenone as these were same in both sexes while bone effect was observed in female high dose only. Moreover, dose 200

mg/kg/d where no adverse effect was observed represents 8.49x and 9.92x multiples of the human exposure for males and females, respectively (AUC_{0-24h} at Week 4). At 1,000 mg/kg/day (where the bone densitometry findings were observed) the average idebenone AUC_{0-24h} values represent multiples of the human exposure of 53.66x and 64.92x in males and females, respectively. Finally, bone changes were reversible and the difference to vehicle-treated group was no longer evident after when animals attained sexual maturity. In addition to the nonclinical data discussed above, the applicant conducted an evaluation of the available clinical information in order to assess the potential safety concerns in paediatric patients. Taken into account the well-recognized pathophysiological and iatrogenic (e.g. long-term use of GCs) factors contributing to the deterioration of bone health in DMD patients, the available safety data did not indicate a substantial impairing effect of idebenone on the bone metabolism and density in DMD patients.

Impurities

Furthermore, impurity A is considered qualified, as increasing the levels of this major impurity to 0.68% showed no additional toxicity when comparing data of this spiked repeated dose toxicity study generated in rats with earlier reported data.

Photosafety

Idebenone does not absorb light within the range of natural sunlight at the wavelength of 290-700nm. According to the ICH guideline S10 on "Photosafety Evaluation of Pharmaceuticals" (*EMA/CHMP/ICH/752211/2012*) there is no need for further photosafety testing with idebenone.

3.2.5. Ecotoxicity/environmental risk assessment

The environmental risk assessment (ERA) was prepared according to Directive 2001/83/EC and the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use (EMEA 2006) considering the Questions and Answers document on this guideline (EMA 2016). The presented report evaluated the potential risks to the environment from the use of idebenone, for the treatment of LHON and DMD. The environmental data previously submitted in the original dossier of the same applicant served as a basis for the revised ERA for this application.

Santhera Pharmaceuticals holds an EU MA of the active pharmaceutical ingredient idebenone for the treatment of LHON (Raxone®) taking place at the onset of visual disturbance. This ERA supports the MAA for idebenone (Puldysa®) in DMD, which is also an orphan disease (ORPHA Number 98896, Orphanet 2019).

According to the pertinent European Q&A document (EMA/CHMP/SWP/44609/2010), an Fpen-refinement is only acceptable, if it is based on published prevalence data and/or treatment regime. Therefore, the prevalence for the proposed indication from the Orphanet-Report and from the orphan documents are acceptable.

During the procedure, the applicant was asked to update the $PEC_{surfacewater}$ calculation in phase I with prevalence data only for the current indication and considering 100 % market share. An update $PEC_{surfacewater}$ calculation in phase I was provided as requested. As the newly calculated $PEC_{surfacewater}$ is not above the limit of 0.01 µg/L, no complete phase II assessment will be required.

3.2.6. Discussion on non-clinical aspects

The application for Puldysa® (idebenone) is a duplicate of Raxone MA. Additionally, the application follows a hybrid route and therefore relies on some registered information for the reference medicinal product Mnesis®, approved in Italy.

Idebenone is a synthetic analogue of ubiquinone (coenzyme Q10). Puldysa acts as an electron carrier in the mitochondrial ETC, inhibits lipid peroxidation and protects cell membranes and mitochondria from oxidative damage which is thought to lead to cellular apoptosis and degeneration of skeletal muscle in DMD. This MAA was based on primary PD studies conducted in support of the indication of LHON. In relation with the intended indication, the applicant carried out a series of additional *in vitro* and *in vivo* primary PD studies supporting a favourable effect of idebenone on cardiac muscle in mice, rats and dogs. In regard of the secondary PD no studies were submitted, and the applicant referred to the approved information of the reference product Mnesis®. The totality of provided safety pharmacology data in animals demonstrated no evident safety concerns with respect to the clinical use of idebenone for the treatment of DMD.

The PK of Puldysa was evaluated in different species: in mice, rats, dogs, and humans. Overall the PK properties of Puldysa were characterized by a rapid absorption enhanced by food, a rapid and broad distribution particularly to highly perfused organs including the brain with no evidence of accumulation of idebenone or its metabolites. Biotransformation was rapid and most of the circulating idebenone-derived material was present as metabolites. Following extensive metabolism, Puldysa is eliminated by subsequent biliary/fecal excretion. Plasma protein binding was very high for idebenone and QS10 in all species. The metabolic profile of idebenone was qualitatively similar in rats and dogs compared with humans. During the procedure, the applicant provided results from and *in vitro* study investigating the potential of the metabolite IDEB-HQ-O-Sulf/D-Gluc (main human plasma metabolite), to inhibit Cytochrome P450 Isoenzymes. It was agreed that this metabolite is not inhibitor of the cytochrome P450 isoforms CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 *in vitro* at concentrations up to 25 µM. Studies performed in rats suggested that the compound crossed the placenta and that idebenone and/or its metabolites were also excreted into rat milk in moderate amounts.

Due to the change of both the manufacturer and the manufacturing process, bridging studies were performed by the applicant with the aim of demonstrating toxicological equivalence between the two preparations of idebenone in order to enable the use of the existing data generated by Takeda to support the current submission. During the procedure, the applicant was requested to provide further clarification about the local changes to the forestomach seen in in the middle and high dose animals and the bone densitometry findings in female juvenile rats compared to males. Regarding the first finding, the applicant´s position that local changes to the forestomach were considered to be of little relevance to human safety was agreed by CHMP as these local changes could be explained by the concentrative function of the rodent organ. Regarding the second finding, even though the rationale behind this finding could not be elucidated by the applicant, it was agreed that available non-clinical and clinical safety data did not indicate a substantial impairing effect of idebenone on the bone metabolism and density in DMD patients.

Summarising, a complete nonclinical safety program was conducted for idebenone, comprising single and repeated dose toxicology, genotoxicity, carcinogenicity, developmental and reproductive toxicology, and special toxicology studies. Puldysa did not show any major or serious adverse toxicological effects in animals. A sufficient safety margin exists between exposure in humans following administration of 2250 mg idebenone/day, and as such also at the lower clinical dose envisaged to be used in DMD patients of 300 mg t.i.d. (900 mg/day, corresponding to 15mg/kg/day), and the exposures in rats and dogs.

In regard of the Environmental Risk Assessment, the $PEC_{surfacewater}$ calculation in the ERA phase I were appropriately updated with prevalence data only for the current indication and considering 100 % market share.

3.2.7. Conclusion on non-clinical aspects

The review of non-clinical data available for Puldysa indicates no preclinical major issue for concern. All non-clinical other concerns raised in the dy80 AR were solved satisfactorily.

3.3. Clinical aspects

3.3.1. Introduction

Puldysa was characterised in a clinical pharmacology program including 4 studies in healthy subjects.

The Clinical development programme of Puldysa included main and supportive clinical studies with several ancillary reports containing additional (*post hoc*) analyses. The main clinical studies comprised the DELPHI study (with the ancillary analysis report SNT-IR-011), the DELOS study (with the ancillary analyses reports SNT-IR-009, SNT-IR-010, SNT-IR-015 and SNT-IR-017) and the SYROS study. The supportive studies included the DELPHI-E open label extension (OLE) study and the report SNT-IR-016. In addition, the phase III study SIDEROS (SNT-III-012) was ongoing with its OLE SIDEROS-E study (SNT-III-012-E) and the applicant provided the protocols for these studies in this MAA. Furthermore, the applicant provided the protocol for the post-authorization confirmatory study MILOS (SNT-IV-009). In addition, safety data were also derived from one study in patients with LHON (RHODOS), five studies in patients with FRDA (NICOSIA, MICONOS, MICONOS-E, IONIA, IONIA-E) and six phase I studies in healthy volunteers.

- ***Tabular overview of clinical studies***

- **Table 1: Overview of studies**

Type of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product, Dosage regimen, Route of Administration	Number of subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study status, Type of report
Phase I Bioavailability	SNT-I-001	Module 5.3.1.1.	Food effect on the PK of idebenone and its metabolites at two dose strengths	Open, parallel group, randomised, cross-over, single dose	idebenone Group A: 150 mg Group B: 5 x 150 mg Oral administration	28	Healthy subjects	Single dose	Completed Full
Phase I Bioavailability	SNT-I-002	Module 5.3.1.1.	PK of idebenone and its metabolites after a single oral dose of 150 mg idebenone	Open, single 150 mg dose	idebenone 150 mg Oral administration	8	Healthy subjects	Single dose	Completed Full
Phase I Bioavailability	SNT-I-003	Module 5.3.1.1.	PK of idebenone and its metabolites after multiple dosing at two dose strengths	Open, parallel group, randomised, single and repeated t.i.d dose	idebenone Group A: 1x150 mg t.i.d., Group B: 5 x 150 mg t.i.d. Oral administration	25	Healthy subjects	2 weeks	Completed Full
Phase I Bioavailability	SNT-I-004	Module 5.3.1.1.	PK of idebenone and its metabolites after a single oral dose of 7 x 150 mg idebenone	Open, single 7 x 150 mg dose	idebenone Single dose 7 x 150 mg Oral administration	8	Healthy subjects	Single dose	Completed Full
Phase II Clinical Efficacy and Safety	DELPHI SNT-II-001	Module 5.3.5.1	To determine whether treatment with idebenone improves or delays the decline in cardiac function in patients with cardiac dysfunction associated with DMD	Double blind, randomised, placebo controlled, single centre	idebenone 1 x 150 mg t.i.d. Oral administration	21	Patients with Duchenne Muscular Dystrophy	12 months	Completed Full
Phase II Clinical Efficacy and Safety (Long term)	DELPHI-E SNT-II-001-E	Module 5.3.5.2	To gather long-term data on the safety and tolerability of idebenone in DMD patients	Open-label uncontrolled study	Idebenone Patients weight ≤45 kg: 1 x 150 mg t.i.d Patients weight >45 kg: 2 x 150 mg t.i.d Oral administration	19	Patients with Duchenne Muscular Dystrophy	24 months	Completed Full

Type of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product, Dosage regimen, Route of Administration	Number of subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study status, Type of report
Phase III Clinical Efficacy and Safety	DELOS SNT-III-003	Module 5.3.5.1	To assess the efficacy of idebenone, compared to placebo, in improving respiratory function or delaying the loss of respiratory function in patients with Duchenne Muscular Dystrophy	Randomised, double-blind, placebo-controlled parallel group	idebenone 2 x 150 mg t.i.d. Oral administration	65	Patients with Duchenne Muscular Dystrophy	12 months	Completed Full
Retrospective data collection (Long term)	SYROS SNT-CRS-003	Module 5.3.5.2	To evaluate the long-term evolution of respiratory function during idebenone treatment compared to the evolution during idebenone-free periods in patients with DMD who after completing the DELOS trial received idebenone treatment as part of EAPs, the DELOS NPP, and/or DELOS CUP	Retrospective data collection from patients with DMD who received idebenone under EAPs after completion of DELOS	idebenone 2 x 150 mg t.i.d. Oral administration	18	Patients with Duchenne Muscular Dystrophy	Mean (min-max) exposure to idebenone in the EAPs: 4.2 years (2.4 – 6.1	Completed Full

Furthermore, the applicant provided the protocols of the currently ongoing phase III study SIDEROS (and its extension SIDEROS-E) and the planned phase IV confirmatory study MILOS:

SNT-III-012 (SIDEROS) Ongoing	60 United States, Austria, Belgium, France, Germany, Israel, Italy, the Netherlands, Spain, Sweden, Switzerland, and United Kingdom	September 2016 Estimated completion date: H1 2021 Current: 202 (as of 1 Mar 2019) Enrolment goal: 266	Randomised, double-blind, placebo-controlled, parallel-group	Idebenone, oral administration with meals 300 mg t.i.d. (900 mg/day) or placebo 18 months (78 weeks)	To assess the efficacy of idebenone compared to placebo, in delaying the loss of respiratory function in patients with DMD receiving glucocorticoid steroids as measured by changes in FVC%p using hospital-based spirometry	Not yet available Planned 266 Idebenone: 133 Placebo: 133	Not yet available	Documented diagnosis of DMD (severe dystrophino-pathy) and clinical features consistent with a typical DMD diagnosis Patients using GCs	Primary: Change from baseline to Week 78 in FVC%p assessed by hospital-based spirometry Secondary: Change from baseline in PEF%p and FEV1%p; rate of BAEs, time to clinically relevant worsening (first 10% relative decline in FVC%p) during the treatment period; hospitalisations due to respiratory causes, change from baseline in IFR
SNT-III-012-E (SIDEROS-E) Ongoing	Same as SIDEROS	July 2018 Estimated completion date: 2023 Current: 24 (as of 1 Mar 2019) Enrolment goal: 200	Open-label, uncontrolled study for patients who completed SIDEROS	Idebenone, oral administration with meals 300 mg t.i.d. (900 mg/day) 18 months	Long-term safety and evolution of respiratory function during the 18 months after SIDEROS study completion.	Not yet available	Not yet available	Completion of SIDEROS study	Primary endpoints were safety parameters Secondary endpoints: FVC%p, PEF%p, FEV1%p

Study ID **Status**	**Number of Study Centres Location(s)**	**Study Start Enrolment Status, Date Total Enrolment/ Enrolment Goal**	**Design Control Type**	**Study & Control Drugs Dose, Route & Regimen** **Duration**	**Study Objective**	**No. of Patients by Arm Treated/ Completed Study Drug Dosing**	**Gender M/F Median Age (Range)**	**Diagnosis Inclusion Criteria**	**Primary Endpoint(s)** **Main Secondary Endpoint(s)**
Planned Phase IV Study									
SNT-IV-009 MILOS[c] EMA Scientific Advice received on protocol Planned	Multicentre Number of centres and location to be determined	Post authorisation Enrolment goal: 156 (External control group from contemporaneous prospectively planned natural history study, CINRG 2.0 study: 200)	2-part, randomised, placebo and externally controlled multicentre study	Part 1: idebenone, oral adm. with meals, 300 mg t.i.d. (900 mg/d) or placebo in addition to standard of care for 1 year. Part 2: Idebenone oral adm. with meals, 300 mg t.i.d. (900 mg/d) in addition to standard of care for 1 to 4 years.	To assess the effect of idebenone, in comparison to standard of care, in extending the time to reaching the criteria for initiation of assisted ventilation in patients with DMD who have abnormal respiratory function.	Not available yet	Not available yet	Patients aged at least 10 years with documented diagnosis of DMD or severe dystro-phinopathy and clinical features consistent of typical DMD. FVC%p ≤80% and >50% at baseline. GC users and GC non-users	Primary: Time to reaching the criteria for initiation of assisted ventilation Secondary: Annual rate of decline of : PUL module, FVC%p PEF%p, total score of Egen K, and PROM score. Time to events Full list in Protocol synopsis

3.3.2. Pharmacokinetics

Introduction

The PK of idebenone have been previously characterized and reviewed in the MA dossier for Raxone® in the LHON indication (EMEA/H/C/003834). The MAA for Puldysa® (idebenone) is a duplicate of Raxone® MA and further follows a hybrid route and therefore relying on some registered information for the reference medicinal product Mnesis®, approved in Italy.

Compared to the Raxone® MAA dossier, some updates were provided including several clinical pharmacology studies conducted earlier by Takeda (holder of the reference medicinal product Mnesis). These provide information on the PK of idebenone, the *in vivo* drug-drug interaction (DDI) potential and

the PK in special populations. In addition, further studies using human biomaterial were conducted to complete the understanding of idebenone's metabolism and *in vitro* drug-drug interaction potential and the population PK models were extended to include the data from DMD patients.

PK data on idebenone were available from 4 Phase I clinical trials in healthy volunteers; studies SNT-I-001, SNT-I-002, SNT-I-003 and SNT-I-004. Two studies (SNT-I-002, SNT-I-004) were single-dose studies performed to characterise the PK of idebenone over a seven-fold dose range (150 mg to 1050 mg idebenone). A third study (SNT-I-003) investigated the PK profile following a single oral dose and after repeated three times daily (t.i.d.) oral dosing for 2 weeks. In SNT-I-003, the urinary excretion of idebenone as well as the plasma PK and its metabolites were assessed. This study was performed at two different dose levels (150 mg t.i.d. and 750 mg t.i.d.). In the fourth study (SNT-I-001), the effect of a high-fat meal on the PK of idebenone given as a single tablet of 150 mg and as five tablets of 150 mg was investigated. In the DMD development plan drug concentrations of idebenone and its metabolites idebenone-C, QS10, QS10-C, QS6, QS6-C, QS4 and QS4-C were only determined in the phase II DELPHI study.

Analytical methods

Analytical methods have been previously assessed. Three new studies have been submitted, SBQ-16085 for method validation for the quantitative determination of total Idebenone+Idebenone-C, QS4+QS4-C, QS6+QS6-C and QS10+QS10-C in human plasma by LC-MS/MS, SBQ-16028 and SBQ-17013 for method validation for the quantitative determination of Idebenone, QS10, QS6 and QS4 in human plasma by LC-MS/MS. During the procedure, the applicant was requested to provide additional long-term stability derived from study SBQ-16085 as well as the missing report for SBQ-17013. For studies SBQ-17013 and SBQ-16085 the missing amendments were provided with sufficient data on long term stability of idebenone, QS4, QS6 and QS10.

Absorption

Idebenone was shown to be rapidly absorbed when taken orally and the maximum plasma levels were observed about 1 hours after administration (with a median range between 0.67 (0.33 -2.00) and 1.33 (0.67 – 2.67) hours after single and repeated administration).

Bioavailability after oral administration of idebenone shows considerable variability after single or repeated doses. Absolute bioavailability of idebenone has not been studied as no IV administration has been investigated.

Concomitant food intake increases the exposure of idebenone. On average, at 750 mg, C_{max} and AUC_{0-t} values under fed condition were 4.5 and 6.7-fold greater, respectively, than those under fasted condition.

Distribution

In vitro studies using human biomaterial showed that idebenone is highly protein bound in human plasma. The value obtained in the most recent study using equilibrium dialysis is 98.5%, which is in line with the binding of 93.0-99.7% observed in an older study using ultrafiltration. Protein binding is also high for metabolites QS10 (98.8%) and QS6 (92.3%) in human plasma, but lower for QS4 (75.2%).

Experimental data showed that idebenone passes the blood-brain barrier and is distributed at significant concentrations in cerebral tissue.

Metabolism and Elimination

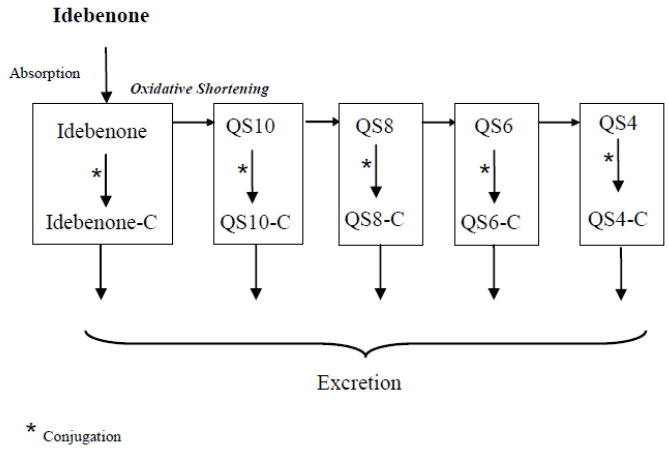
Idebenone undergoes extensive first-pass metabolism after oral dosing. The two major metabolic pathways of idebenone are quinone reduction of idebenone to form the hydroquinone (IDEB-HQ) and subsequent conjugation and the oxidation to form QS10 and further side-chain shortening by β-oxidation

to form QS8, QS6, and QS4. Additionally, the direct conjugation of the terminal alcohol to form Idebenone-D-glucuronide (IDEB-D-Gluc) was also observed.

Following oral administration IDE is rapidly metabolised via oxidative shortening of the side chain to yield QS10, QS6, QS8 and QS4. IDE 1 and these metabolites concomitantly undergo conjugation via glucuronidation and sulphatation to yield conjugated moieties (Figure 3). None of these metabolites are active.

The metabolites of IDE are conjugated and excreted, predominantly by the kidney. QS4+QS4-C were the most prominent drug-derived material in urine, representing, on average, 49.3 to 68.3 % of the total amount of drug administered. QS6+QS6-C represented 6.45 to 9.76 %, whereas the amount of QS10+QS10-C and IDE+IDE-C was close to 1% or below.

Figure 3: Idebenone metabolic pathway



Dose proportionality and time dependency

Systemic exposure to idebenone (C_{max} and AUC) increased approximately dose proportionally (or close to dose proportionality); for a doubling in dose, AUC for IDE was predicted to increase 1.78 to 2.52-fold.

Systemic exposure to idebenone metabolites IDE+IDE-C, QS10+QS10-C, QS6+QS6-C, and QS4+QS4-C (C_{max} and AUC) increased approximately dose proportionally; for a doubling in dose, AUC for IDE+IDE-C, QS10+QS10-C, QS6+QS6-C, and QS4+QS4-C was predicted to increase 1.65 to 2.43-fold.

Pharmacokinetics in target population

Limited PK information is available in the target population. In the DMD development plan drug concentrations were not systematically measured. For DMD, plasma concentrations of idebenone and its metabolites idebenone-C, QS10, QS10-C, QS6, QS6-C, QS4 and QS4-C were only determined in the DELPHI study. The data were evaluated using the existing population pharmacokinetics (popPK) model and the analysis showed that overall exposure of idebenone and idebenone-C were similar at measured timepoints (week 26 and week 52) in the DMD patients in this study and were comparable to the exposure after a two-week treatment in healthy male subjects.

Special populations

Puldysa has not been studied in elderly nor in children under 10.

According to the pooled popPK analysis a considerable effect according to body weight is not expected in clinical practice regarding the targeted patient population. The other covariates tested (age, gender, race, dose, health status (healthy subjects, LHON patients and FRDA patients), body mass index (BMI),

creatinine clearance, Aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin and disease status) were not found to significantly affect PK parameters, no specific recommendations are made.

New data on PK of idebenone in subjects with renal/ or hepatic impairment were provided by two studies conducted in the 1990ies by Takeda. In these studies, a different tablet formulation, as compared to the film-coated to be marketed formulation has been used.

Effects of renal impairment on the PK have been investigate in study CV-2619/EC070. Single dose PK were determined following administration of a 120 mg idebenone dose in 12 male subjects with mild to moderate renal impairment (creatinine clearance <40ml/min/1.73m2), 2 male subjects on haemodialysis during an interdialytic interval and 41 healthy subjects at comparable age to the patients. Although idebenone is not excreted unchanged, renal excretion is the main elimination route of idebenone metabolites. Exposure of idebenone and idebenone metabolites were increased with AUC-∞ values about 50% higher in renally impaired subjects compared to subjects with normal renal function.

Effects of hepatic impairment on the PK have been investigate in study CV-2619/EC071. Single dose pharmacokinetics were determined following administration of a 120 mg idebenone dose in 12 male subjects with mild to moderate hepatic impairment (n=5 Child-Pugh Score A, n=7 Child-Pugh Score B) and 31 healthy subjects at comparable age. 2.3-fold higher values for AUC0-∞ for IDEB+IDEB-C and 2.6-fold higher values for QS10+QS10-C were detected in hepatically impaired subjects compared with age-matched healthy subjects. No dose adjustment is recommended.

Interactions

The applicant has previously performed in-vitro investigations to characterise idebenone's interactive potential. According to the results of these investigations (induction and inhibition studies) this potential appears to be low. Two additional in-vitro studies have been conducted in human liver microsomes (CYP0104_R82 and CYP0104_R85) indicating that idebenone is not a time-dependent inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4 and that there was no inhibition of CYP enzymes with the main idebenone metabolite. The risk for DDI involving P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2 is therefore considered low.

In study SNT-I-017 the effect of concomitant midazolam intake was investigated. Following oral administration of 300 mg idebenone t.i.d., midazolam metabolism was not considerably modified. After repeated administration C_{max} and AUC of midazolam were increased by 28% and 34%, respectively, when midazolam was administered in combination with 300 mg idebenone t.i.d., indicating that idebenone is a weak CYP3A4 inhibitor.

Data from four DDI studies investigating the effect of idebenone on the PK of amitriptyline, fluvoxamine, lithium and donepezil have been presented by the applicant (CV-2619/EC075, CV-2619/EC076, CV-2619/EC074, CV-2619/PNFP-003). In these studies, conducted in the 1990ies by Takeda, a different tablet formulation, as compared to the film-coated to be marketed formulation has been used. Study results indicate that there is no significant effect of idebenone on the PK of fluvoxamine, lithium or donepezil. Exposure of idebenone, as measured by $AUC_{0\text{-}24h}$ and C_{max} was slightly higher after co-administration with donepezil. After administration of multiple doses 120mg idebenone, the AUC of amitriptyline increased about 30% indicating that idebenone is a weak inhibitor of CYP2D6 and CYP2C19.

3.3.3. Pharmacodynamics

No PD studies have been conducted with Puldysa in humans.

The propose mode of action supposes that idebenone improves the symptoms associated with mitochondrial dysfunction and oxidative stress in DMD, by reducing oxidative stress and improving

mitochondrial respiratory chain function and energy production. For this mechanism of action, no biomarker is currently available for testing in humans.

The PD effects of idebenone have been studied in an mdx mouse model. Idebenone, at doses of 200 mg/kg/day, given in the diet long term, was suggestive to normalise cardiac diastolic dysfunction, prevent mortality from cardiac pump failure during a dobutamine-mediated stress protocol, reduce cardiac inflammation and fibrosis, and improve voluntary running performance. For further information please refer to the section 2.3.2. (pharmacology in non-clinical aspects) of this withdrawal assessment report.

3.3.4. Discussion on clinical pharmacology

Pharmacokinetics

Information on PK has been acquired from 4 phase I clinical pharmacology studies (SNT-I-001, SNT-I-002, SNT-I-003 and SNT-I-004), three phase II and III patient studies in LHON (RHODOS) and FRDA (MICONOS and IONIA) and from a Population PK model for both idebenone and its metabolite QS10, generated from all above mentioned studies.

Validation work for the phase I studies was performed before the current guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009) was in force. Therefore, some parameters (i.e. ISR) were not tested. This was considered acceptable as the metabolites were also tested. For the new submitted validation study SBQ-16028, the analytical method for the determination of Idebenone, QS4, QS6 and QS10 in human plasma as well as respective validations are described adequately. For studies SBQ-17013 and SBQ-16085, the missing amendments have been provided with sufficient data on long term stability of idebenone, QS4, QS6 and QS10.

Idebenone was shown to be rapidly absorbed when taken orally and the maximum plasma levels were observed about 4 hours after administration. Bioavailability after oral administration of idebenone shows considerable variability after single or repeated doses. Absolute bioavailability of idebenone has not been studied as no IV administration has been investigated.

Intake of food significantly increased the absorption rate, the food-effect causes an increase in C_{max} (around 5-fold) and AUC (around 6-fold). The pivotal trials were conducted in fed conditions and the intake of idebenone is recommended with food which is endorsed.

The drug is metabolised in the liver and post-prandial administration increases its bioavailability. Experimental data have shown that idebenone passes the blood-brain barrier and is distributed at significant concentrations in cerebral tissue. The main metabolites are eliminated via the kidneys. IDE is quickly cleared from the blood by first pass metabolism and its metabolites are conjugated before excretion. IDE metabolises via oxidative shortening of the side chain to QS10, QS6, QS8 and QS4. The plasma concentrations of IDE are low relative to its metabolites. Excretion and metabolism pathways are properly characterised and understood. The metabolites behave dose-proportional like the parent compound; the increase in C_{max} and AUC values indicates linear PK profiles.

The pharmacology of idebenone has been extensively investigated within the initial MAA. In the DMD population only a limited PK data are available. In the DELPHI study plasma samples from DMD patients were taken after 26 and 52 weeks' treatment with idebenone. On Weeks 26 and 52, PK sampling was performed within a time interval of two to four hours after administration of the morning dose of idebenone. This sampling scheme allowed a limited evaluation of the PK characteristics of idebenone. A comparison with data from a study performed in healthy subjects (SNT-I-003) demonstrated that the systemic exposure of DMD patients to idebenone and its metabolites is in the same range as for healthy subjects. There were some slight differences between both populations with regards to the ratio of the

metabolites. However, this is most likely due to the blood sampling scheme rather than to a difference in the metabolism per se. These differences are not considered clinically relevant because the metabolites are not known to be pharmacologically active.

Puldysa has not been studied in elderly nor in children under 10. The safety and efficacy of Puldysa in DMD patients under 10 years of age have not yet been established. The missing of data for children < 10 years are considered in the Risk Management Plan as such.

With regards to the PK in elderly patients the usually low age of onset of DMD and the rarity of DMD in patients above 60 years of age has to be considered. Therefore, specific recommendations for the treatment of DMD in elderly patients are not required.

Effects on special populations were examined in a popPK model for idebenone and its metabolite QS10. Besides the already known food effect and a negligible effect according to body weight none of the other covariates tested (age, gender, race, dose, health status (healthy subjects, LHON patients and FRDA patients), BMI, CRCL, AST, ALT, BILI and disease status) were found to considerably affect PK parameters.

Limited data on a possible influence of renal/ hepatic impairment on the PK of idebenone were provided by two studies conducted earlier by Takeda. In these studies, a different tablet formulation, as compared to the film-coated to be marketed formulation has been used, therefore information can only be regarded as supportive. Although idebenone is not excreted unchanged, renal excretion is the main elimination route of idebenone metabolites. Exposure of idebenone and idebenone metabolites were found to be increased with AUC0-∞ values about 50% higher in renally impaired subjects compared to subjects with normal renal function (CV-2619/EC070).

In study CV-2619/EC071, 2.3-fold higher values for AUC0-∞ for IDEB+IDEB-C and 2.6-fold higher values for QS10+QS10-C were detected in hepatically impaired subjects compared with age-matched healthy subjects. No dose adjustment is recommended, but caution is required in patients with renal/hepatic impairment.

In vitro investigations to characterise idebenone's interactive potential, have been previously performed by the applicant. According to the results of these investigations (induction and inhibition studies) this potential appears to be low.

One DDI study (SNT-I-o17) investigating the effect of concomitant midazolam intake was recently performed by the applicant. Following oral administration of 300 mg idebenone t.i.d., midazolam metabolism was not considerably modified. However, after repeated administration C_{max} and AUC of midazolam were increased by 28% and 34%, respectively, when midazolam was administered in combination with 300 mg idebenone t.i.d., indicating that idebenone is a weak CYP3A4 inhibitor.

Four additional DDI studies investigating the effect of idebenone on the PK of amitriptyline, fluvoxamine, lithium and donepezil have been conducted in the 1990ies by Takeda (CV-2619/EC075, CV-2619/EC076, CV-2619/EC074, CV-2619/PNFP-003). Although the used tablet formulation is different compared to the film-coated to be marketed formulation, information obtained in these studies provide supportive data on the DDI potential of idebenone. After administration of multiple doses 120mg idebenone, the AUC of amitriptyline increased about 30% indicating that idebenone is a weak inhibitor of CYP2D6 and CYP2C19. Results from these studies further indicate that there is no significant effect of idebenone on the PK of fluvoxamine, lithium or donepezil. Exposure of idebenone, as measured by $AUC_{0\text{-}24h}$ and C_{max} was slightly higher after co-administration with donepezil, which is however not considered clinically meaningful, due to the high inter-individual variability in idebenone levels obtained in the phase I studies.

Pharmacodynamics

No PD studies have been conducted with Puldysa in humans and there is no available biomarker. The recommended dose for idebenone for the treatment of respiratory dysfunction in patients with DMD is 900 mg/day idebenone (300 mg, 3 times a day). The dose recommendation is derived from previous clinical experience of idebenone in other indications. No additional dose-response or blood-level response evaluations were performed for DMD.

The proposed mode of action for idebenone in treatment of respiratory dysfunction in patients with DMD is complex. There exist several publications investigating this mechanism *in vitro* and in preclinical *in vivo* studies using an mdx mouse model.

3.3.5. Conclusions on clinical pharmacology

Taken together, the presented data do enable a fairly conclusive description of the PK profile of idebenone in the proposed target population.

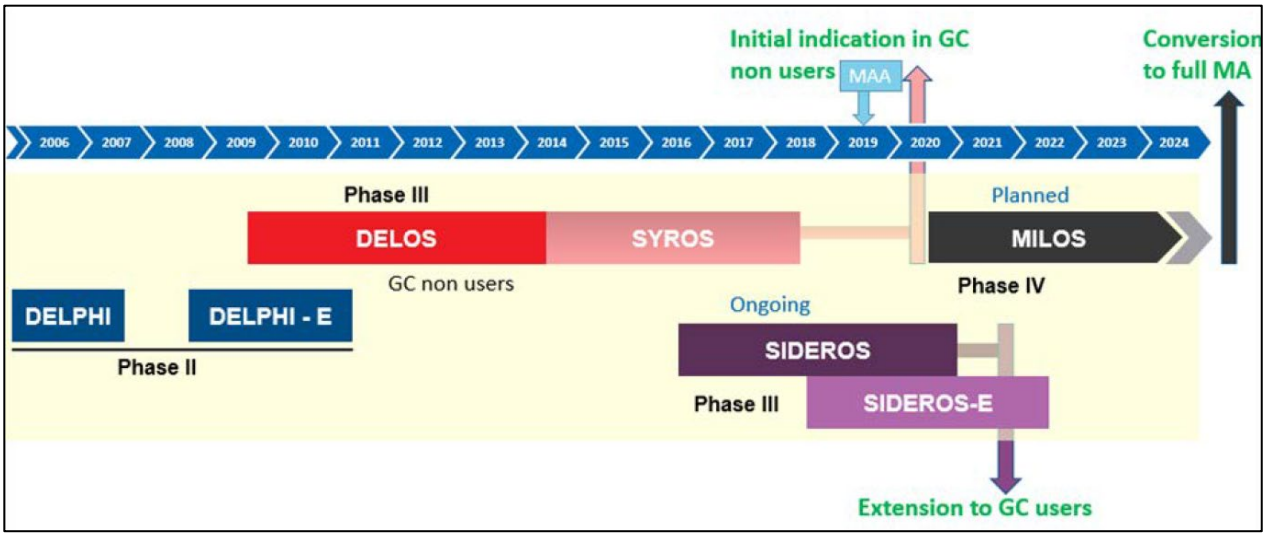
No primary or secondary PD studies in humans have been submitted. Furthermore, no dose ranging study has been carried out. There is no biomarker available. Information regarding mechanism of action is therefore mainly derived from published *in vitro* and preclinical *in vivo* study using an mdx mouse model.

3.3.6. Clinical efficacy

The Clinical efficacy section is divided into the main and the supportive clinical studies with their respective ancillary analyses reports. The main clinical studies in this report comprise the DELPHI study (with the ancillary analysis report SNT-IR-011), the DELOS study (with the ancillary analyses reports SNT-IR-009, SNT-IR-010, SNT-IR-015 and SNT-IR-017) and the SYROS study. The supportive studies comprise the DELPHI-extension study and the report SNT-IR-016.

An overview of the clinical development programme for idebenone in DMD is provided in Figure 4.

Figure 4: Overview of the idebenone Clinical development programme in DMD



DELPHI, DELPHI-E, DELOS and SYROS (new data) were the completed studies included in this MAA. DELPHI (Phase II) and DELOS (Phase III pivotal study for the CMA in GC non-users) were placebo-controlled studies, and DELPHI-E and SYROS were their respective OLE studies. The placebo-controlled Phase III SIDEROS study and its OLE SIDEROS-E study were ongoing at the time of the submission of this MAA and may be used later to extend the indication to GC users. MILOS is the planned Phase IV post-authorisation confirmatory outcome study.
GCs = glucocorticoids; MAA = Marketing Authorisation Application; OLE = Open-Label Extension

3.3.6.1. Dose-response studies

No dose response study has been conducted in DMD patients.

3.3.6.2. Main studies

The primary evidence for the efficacy of Puldysa for the treatment of respiratory dysfunction in DMD is provided by three studies:

- **Delphi Study (SNT-II-001):** A Phase IIa double blind, randomized, placebo controlled, single centre study at the University of Leuven to assess the efficacy and tolerability of idebenone in 8 – 16-year-old males with cardiac dysfunction associated with Duchenne Muscular Dystrophy
- **DELOS study (SNT-III-003):** A Phase III double-blind, randomised, placebo-controlled study of the efficacy, safety and tolerability of idebenone in 10 – 18-year-old patients with Duchenne Muscular Dystrophy
- **SYROS study (SNT-CRS-003):** Retrospective Cohort Study assessing the Long-Term Respiratory Function Evolution during Idebenone Treatment compared to Idebenone-free Periods in Patients with Duchenne Muscular Dystrophy who Completed the DELOS Study

All three studies are reported and discussed separately with their respective ancillary analyses.

3.3.6.2.1. Delphi Study (SNT-II-001)

Methods

This was a double-blind, placebo-controlled, randomized, parallel group, single center 52-week study to assess the efficacy and tolerability of idebenone in 8-16 year old patients with cardiac dysfunction associated with confirmed DMD. The original design of the study allowed for enrolment of patients from 10 - 16 years of age; however, the implementation of Amendment 1 allowed for the enrolment of patients from 8 - 16 years of age.

After written informed consent was obtained from the patient and the patient's parent/legal guardian,

patients who met the eligibility criteria were enrolled at the study centre in Leuven, Belgium and randomized to daily treatment of either idebenone (150 mg, tid) or placebo (tid). Patients underwent efficacy and/or safety assessments at the Screening visit and on Day 1 (Week 1), Week 4, Week 13, Week 26, Week 39 (telephone safety follow-up) and Week 52. A final follow-up visit was planned for Week 56, one month after the completion of study treatment.

Study participants

The study population comprised 8 – 16 year old males with cardiac dysfunction associated with DMD. The inclusion and exclusion criteria were assessed at Screening and confirmed at Visit 1, prior to the start of study treatment. Patients who did not meet these criteria were not included in the study.

Inclusion criteria (as stated in the study protocol and Amendment 1):

- Males aged 8–16 years at the time of study enrolment.
- Presence of cardiac dysfunction, as defined by abnormal peak systolic strain in the left ventricle (LV) inferolateral wall.
- Confirmed diagnosis of DMD (out-of-frame dystrophin gene deletion OR absence; <5% dystrophin protein on muscle biopsy; presence of the clinical signs and symptoms of typical DMD).
- Patients currently receiving chronic GCs treatment (i.e. deflazacort, prednisone) for DMD or any other disease must have been on a stable dosage for at least six months prior to inclusion in this study
- Those patients on chronic medication for DMD-associated cardiomyopathy (i.e. β blockers, diuretics) must have been on a stable dose three months prior to inclusion in this study.
- The quantitative muscle testing (QMT) upper limb score obtained on Visit 1/Day 1 must be within 15% of the score obtained on the Screening visit.

Exclusion criteria:

- Symptomatic cardiomyopathy or heart failure
- Asymptomatic but severe cardiac dysfunction at the Screening evaluation (fractional shortening (FS) <20% and/or ejection fraction (EF) <40%).
- Patients receiving treatment with angiotensin converting enzyme (ACE) inhibitors.
- Previous history of ventricular arrhythmias (other than isolated ventricular extrasystole); ventricular arrhythmias present at Screening.
- Previous participation in any other clinical trial for DMD, within ≤ 6 months.
- History of significant concomitant illness or significant impairment of renal or hepatic function (serum creatinine and gamma-glutamyl transpeptidase (GGT) >1.5x upper limit of normal (ULN) for age and gender).

Treatments

Both idebenone (150 mg) and matching placebo were administered as oral tablets. Patients were to take 450 mg/day as one tablet t.i.d with meals, for 12 months (52 weeks).

Objectives

Primary Objective: To determine whether treatment with idebenone improves or delays the decline in cardiac function in patients with cardiac dysfunction associated with DMD.

Secondary Objectives:

- To determine whether treatment with idebenone improves or delays the decline in muscle strength and/or respiratory function in patients with DMD

- To evaluate the safety and tolerability of idebenone in patients with DMD.

Outcomes/endpoints

Primary Endpoint: The relative change from Baseline (at Screening) to Week 52 in peak systolic radial strain of the LV inferolateral wall, assessed by Colour Doppler Myocardial Imaging (CDMI).

Secondary Endpoints:

- General and geometric cardiac and other cardiac systolic and diastolic cardiac functions
- Skeletal muscle strength (upper limb, right and left): hand grip, elbow flexors and elbow extensors (upper limb score).
- Respiratory Function: FVC, forced expiratory volume in 1 second (FEV_1), maximal inspiratory pressure (MIP) and peak expiratory flow (PEF) both as absolute and percentage predicted (%p) values.

The PEF%p was calculated using the following formula (PEF= -422.8 + 5.288 x height (in cm)) according to previous publications (Godfrey, 1970; Quanjer 1989). The formula used to calculate the MIP%p was derived from Domènech-Clar (2003): MIP= -27.020 - (4.132 x age) - ([0.003 x height x weight]).

Sample size

The primary endpoint for the sample size consideration was the change from Baseline (Screening) to Week 52 in peak systolic radial strain (LV inferolateral wall). With a total sample size of 21 patients allocated with a 2:1 ratio to idebenone and Placebo, a difference of 15 % between the two groups was assumed to be detected with 80% power and a one-sided significance level of 5%. A standard deviation (SD) of 12% was assumed for both groups. Sample size estimation was performed using the Normal approximation method.

Randomisation and blinding (masking)

Patient eligibility was planned to be established before treatment randomisation. A randomisation blocking scheme was to be used to ensure a 2:1 treatment allocation. Patients were planned to be randomised strictly sequentially, as patients were eligible for randomisation. Enrolment was planned to be closed when 21 patients have been randomised.

The treatment allocation was planned to be double blinded. The patients received either idebenone or a matching placebo.

Statistical methods

Analysis Populations

The primary efficacy analysis was planned to be performed using the intention to treat (ITT) approach defined as all subjects who were randomised to study drug analysed as randomized regardless of protocol violations and the actual treatment received (full analysis data-set).

The according-to-protocol (ATP) population was defined as all patients from the ITT population who had no major protocol violation. A major protocol violation was defined as a protocol deviation that was considered to have a major impact on the efficacy result.

The Safety population was defined as all randomised patients who received trial medication and for whom a safety assessment was available. Subjects were grouped according to the treatment they received.

Descriptive methods

All data was planned to be summarized for each treatment group. Continuous data were to be summarised by the number of patients (n), mean, SD, median, first and third quartile (Q1, Q3), minimum and maximum. Categorical data were planned to be presented by absolute and relative frequencies (n and %) or contingency tables. The percentages were to be calculated based on available observations.

Results were planned to be displayed by visit where applicable. All data collected in the case report form (CRF) was planned to be listed.

Patient demographics and physical characteristics were planned to be summarised for each treatment using descriptive statistics. Results were to be provided for both ITT and ATP populations.

Demographic information was also to be presented in a data listing sorted by patient. Previous and current diseases and medical procedures was planned to be presented in a data listing by patient.

Efficacy analyses

With the primary efficacy analysis, it was planned to compare the change from Baseline (Screening) to Week 52 in peak systolic radial strain (LV inferolateral wall), between the two treatment groups using the t-test and using the Last Observation Carried Forward (LOCF) method for missing values replacement. The underlying normal distribution assumption was planned to be assessed using the Shapiro-Wilk test. If the assumption was violated, the Wilcoxon rank sum test (Exact Test) for two sample data was planned to be used. A one-sided significance level of 5% was planned to be used.

The primary analysis was planned to be performed using the ITT population (full analysis data-set).

The mean 'change from baseline' difference between treatments was planned to be provided with its associated 90% confidence interval (Normal approximation).

In addition, the percent change from baseline to Week 52 was planned to be calculated and compared between treatment groups using the same statistical test as above for the change from baseline.

For sensitivity purpose, the analysis performed on the change from baseline (screening) to Week 52 in peak systolic radial strain (LV inferolateral wall) was planned to be repeated using the Observed Cases (OC), i.e. not imputing the missing values.

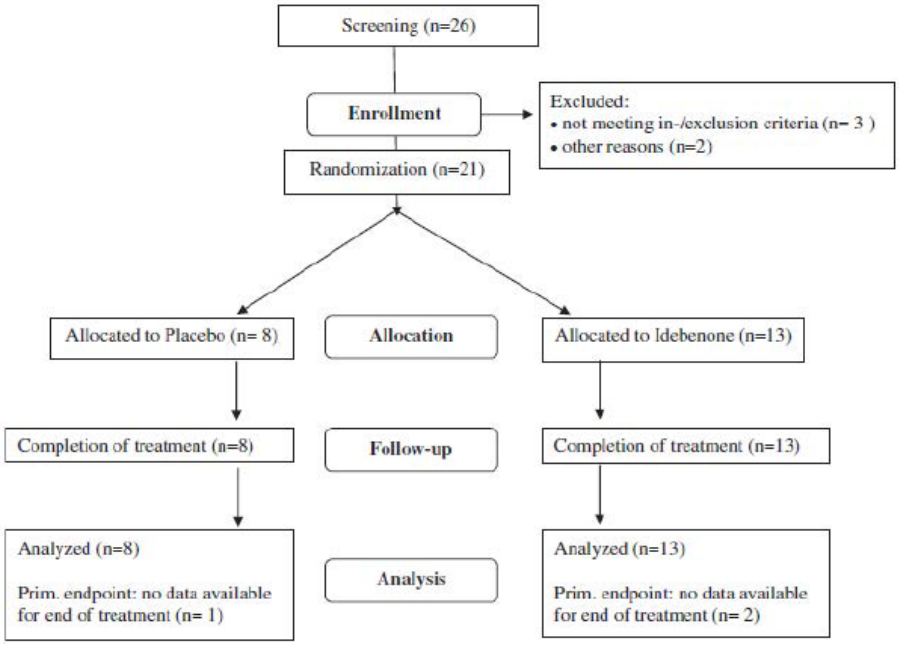
The above analyses performed on the peak systolic radial strain (LV inferolateral wall) were planned to be repeated for the ATP population.

Results

Participant flow

Twenty-one patients fulfilled all inclusion and exclusion criteria and were enrolled at a single centre. Patients were randomly allocated to treatment with idebenone or placebo. All patients completed the study; there were no patients who discontinued, and no patients were excluded from any analysis (Figure 5).

Figure 5: Study flow chart for DELPHI



Recruitment

Regarding the periods of recruitment and follow-up, the applicant reported the following dates:

- Date first subject screened: 10 October 2005
- Date last subject completed: 20 August 2007.
- Database lock date: 5 October 2007
- Final report date: 24 April 2009

This was a single-centre study at the University of Leuven, Belgium.

Conduct of the Study

Protocol amendments

There was one protocol amendment to lower the age range from 10 to 8 years of age (31 May 2006). The protocol was amended to favour recruitment (lower than anticipated) taken into account available data that suggested that the use of idebenone was safe in a population as young as 8 years.

Baseline data

There were significant differences in mean age between treatment groups. This could be expected to correlate with a different stage of disease between treatment groups (Table 2).

Six patients in each treatment group were ambulatory corresponding to 75% and 46.2% of patients in the placebo and idebenone groups, respectively. The higher proportion of wheelchair-bound patients in the idebenone group might be correlated with the older age at baseline. Use of glucocorticoids was comparable in both patient groups: eight patients (61.5%) in the idebenone group and five patients (62.5%) in the placebo group (Table 2).

Table 2: Baseline patient demographics – ITT population

Patient demographics at baseline	Placebo n=8	Idebenone n=13	p value*
Mean age ± SD [years]	10.8 ± 1.9	13.4 ± 2.1	0.01
Race			
Caucasian/white	7	13	nd
Black	1	0	
Mean height ± SD [cm]	144.6 ± 11.9	150.8 ± 20.8	0.466
Mean weight ± SD [kg]	40.5 ± 7.0	45.1 ± 18.3	0.507
Mean BMI ± SD [kg/m^2]	19.6 ± 3.9	19.3 ± 4.3	0.898
Ambulant patients; n (%)	6 (75.0%)	6 (46.2%)	nd
Glucocorticoid use; n (%)	5 (62.5%)	8 (61.5%)	nd

*two-tailed t-test; BMI = body mass index; nd = not determined; SD = standard deviation

Numbers analysed

All patients completed the study and no patients were excluded from any analysis (Table 3).

Table 3: Summary of patient disposition

	Idebenone (n=13)		Placebo (n=8)		Total (n=21)	
	n	%	n	%	n	%
Safety population	13	100	8	100	21	100
ITT* population	13	100	8	100	21	100
ATP** population	13	100	8	100	21	100
Number of patients who completed the study as per protocol	13	100	8	100	21	100
Number of premature withdrawals from the study	0	0	0	0	0	0

* ITT (intention-to-treat)
** ATP (According to protocol)

Outcomes and estimation

Cardiac endpoints: No statistically significant difference between idebenone and placebo was shown for the primary endpoint. There was a statistically significant (type-1-error controlled at 5% one-sided) difference for peak systolic longitudinal strain of the LV lateral mid region in favour of idebenone. However, none of the remaining cardiac endpoints showed any statistically significant differences between idebenone and placebo (Table 4).

Respiratory Endpoints: A statistically significant difference (type-1-error controlled at 5% one-sided) in favour of idebenone was shown for PEF (L/min) and PEF%p while no statistically significant differences where shown for any of the other respiratory endpoints (Table 5). The difference in PEF%p was greater in the subgroup of GCs-non-users than in GCs-users. However, the number of patients in these subgroups is small (idebenone: placebo GCs users:8:5 and non-GCs users 5:5), and corresponding treatment effect estimates are derived with low precision.

Other Endpoints: There were no significant differences in skeletal muscle strength or timed walking test. Assessment of the results for muscle strength/function parameters is not possible since a description of the muscle testing cannot be found in the dossier.

Table 4: Cardiac systolic function (ITT population; LOCF)

Parameters of systolic cardiac function		Baseline (BL)		Week 52		Change (Week 52 – BL)		p value*	% Change (Week 52 – BL)		p value*
		Placebo	Idebenone	Placebo	Idebenone	Placebo	Idebenone		Placebo	Idebenone	
Regional myocardial function											
peak systolic radial strain LV inferolateral wall [%]		33.71 ± 9.75 (n=8)	22.88 ± 9.10 (n=13)	41.55 ± 10.77 (n=8)	38.17 ± 11.31 (n=13)	7.8 ± 11.2 (n=8)	15.3 ± 13.0 (n=13)	0.098	30.7 ± 38.0 (n=8)	90.5 ± 90.6 (n=13)	0.047
peak systolic radial strain rate LV inferolateral wall [s^{-1}]		3.25 ± 0.93 (n=8)	2.27 ± 0.65 (n=13)	3.24 ± 0.55 (n=8)	2.64 ± 0.72 (n=13)	0.0 ± 0.9 (n=8)	0.4 ± 0.6 (n=13)	0.124	6.8 ± 34.1 (n=8)	19.8 ± 27.8 (n=13)	0.175
peak systolic longitudinal strain [%]	LV lateral mid	-18.96 ± 5.08 (n=8)	-14.67 ± 6.39 (n=12)	-17.93 ± 5.94 (n=8)	-18.85 ± 5.36 (n=12)	1.0 ± 4.4 (n=8)	-4.2 ± 6.6 (n=12)	0.033	-5.5 ± 21.5 (n=8)	41.9 ± 57.5 (n=12)	0.020
	LV lateral apex	-17.92 ± 1.94 (n=6)	-21.14 ± 7.71 (n=12)	-17.68 ± 4.89 (n=8)	-19.21 ± 4.58 (n=13)	0.1 ± 3.8 (n=6)	1.9 ± 6.8 (n=12)	0.284	-1.8 ± 22.9 (n=6)	-1.7 ± 29.2 (n=12)	0.498
	LV lateral basal	-13.21 ± 5.13 (n=8)	-15.01 ± 9.95 (n=12)	-16.15 ± 6.69 (n=8)	-16.84 ± 6.76 (n=13)	-2.9 ± 3.6 (n=8)	-1.9 ± 10.1 (n=12)	0.395	22.2 ± 29.6 (n=8)	49.8 ± 89.2 (n=12)	0.207
peak systolic longitudinal strain [%]	IVS mid	-29.54 ± 6.30 (n=8)	-25.49 ± 6.57 (n=13)	-29.06 ± 7.48 (n=8)	-23.83 ± 7.18 (n=13)	0.5 ± 8.0 (n=8)	1.7 ± 8.7 (n=13)	0.621	0.5 ± 30.2 (n=8)	-2.4 ± 32.5 (n=13)	0.581
	IVS apex	-16.22 ± 9.54 (n=8)	-19.11 ± 7.60 (n=13)	-15.02 ± 5.42 (n=8)	-18.35 ± 6.28 (n=13)	1.2 ± 11.2 (n=8)	0.8 ± 10.4 (n=13)	0.465	17.4 ± 64.5 (n=8)	24.1 ± 96.7 (n=13)	0.433
	IVS basal	-22.10 ± 3.54 (n=8)	-19.52 ± 7.47 (n=13)	-22.45 ± 5.74 (n=8)	-20.51 ± 4.67 (n=13)	-0.4 ± 4.5 (n=8)	-1.0 ± 7.3 (n=13)	0.413	1.7 ± 21.7 (n=8)	17.8 ± 49.6 (n=13)	0.201
peak systolic longitudinal strain [%]	RV apex	-32.72 ± 10.04 (n=7)	-29.51 ± 10.94 (n=13)	-35.26 ± 9.39 (n=7)	-32.23 ± 10.78 (n=13)	-2.5 ± 10.4 (n=7)	-2.7 ± 12.5 (n=13)	0.487	15.4 ± 41.4 (n=7)	22.6 ± 63.0 (n=13)	0.395
	RV basal	-39.32 ± 13.60 (n=7)	-35.64 ± 7.19 (n=13)	-41.94 ± 16.26 (n=7)	-42.11 ± 10.58 (n=13)	-2.6 ± 15.8 (n=7)	-6.5 ± 8.8 (n=13)	0.246	14.4 ± 48.6 (n=7)	19.3 ± 26.2 (n=13)	0.385
Global LV function											
fractional shortening [%]		29.32 ± 2.76 (n=8)	28.00 ± 4.29 (n=13)	30.92 ± 3.45 (n=8)	29.42 ± 5.44 (n=13)	1.6 ± 2.6 (n=8)	1.4 ± 4.1 (n=13)	0.375	5.6 ± 9.3 (n=8)	5.6 ± 18.5 (n=13)	0.323
ejection fraction modified Simpson's [%]		49.96 ± 2.18 (n=7)	50.25 ± 5.22 (n=13)	49.40 ± 5.81 (n=8)	47.41 ± 8.00 (n=13)	0.4 ± 5.5 (n=7)	-2.8 ± 10.0 (n=13)	0.783	1.0 ± 11.0 (n=7)	-4.5 ± 20.2 (n=13)	0.740
cardiac index [$l/min/m^2$]		2.99 ± 1.06 (n=7)	3.21 ± 0.79 (n=11)	2.66 ± 0.63 (n=8)	3.03 ± 1.05 (n=13)	-0.2 ± 0.9 (n=7)	-0.1 ± 0.9 (n=11)	0.415	22.4 ± 99.0 (n=7)	-0.6 ± 30.8 (n=11)	0.240
cardiac output [l/min]		4.32 ± 0.84 (n=7)	3.90 ± 0.57 (n=11)	3.63 ± 0.92 (n=8)	4.13 ± 1.32 (n=13)	-0.5 ± 0.7 (n=7)	0.1 ± 1.3 (n=11)	0.112	-11.4 ± 15.9 (n=7)	3.6 ± 31.0 (n=11)	0.129
LV function biomarker											
Brain natriuretic peptide, pro-BNP [ng/L]		52.6 ± 35.20 (n=8)	138.1 ± 262.7 (n=13)	64.3 ± 55.28 (n=8)	101.9 ± 128.26 (n=13)	11.6 ± 51.4 (n=8)	-36.2 ± 141.7 (n=13)	0.163	37.0 ± 78.2 (n=8)	18.1 ± 45.3 (n=13)	0.228
Cardiac troponin I, cTnI [ug/L]		0.10 ± 0.18 (n=8)	0.07 ± 0.07 (n=13)	0.05 ± 0.06 (n=8)	0.08 ± 0.10 (n=13)	-0.1 ± 0.1 (n=8)	0.0 ± 0.1 (n=13)	0.977	-8.5 ± 88.4 (n=8)	82.5 ± 125.8 (n=13)	0.962

Data expressed as mean ± standard deviation; * one-sided p-values.
BL: Baseline; IVS: interventricular septum; LV: left ventricle; RV: right ventricle

Table 5: Respiratory fuction (ITT population)

	Baseline (BL)		Week 52		Change Week 52 - BL		p value*	% Change Week 52 - BL		p value*
	Placebo	Idebenone	Placebo	Idebenone	Placebo	Idebenone		Placebo	Idebenone	
Respiratory function parameter										
FVC [L]	1.93 ± 0.38 (n=8)	2.19 ± 0.58 (n=13)	2.08 ± 0.59 (n=8)	2.33 ± 0.67 (n=13)	0.15 ± 0.29 (n=8)	0.14 ± 0.31 (n=13)	0.529	6.3 ± 17.8 (n=8)	6.9 ± 15.4 (n=13)	0.534
FVC [percent predicted]	80.6 ±28.87 (n=8)	76.5 ± 25.58 (n=13)	82.6 ± 37.11 (n=8)	75.3 ± 24.79 (n=13)	2.0 ± 11.0 (n=8)	-1.2 ± 6.4 (n=13)	0.793	-2.1 ± 20.5 (n=8)	-1.0 ± 10.0 (n=13)	0.561
FEV1 [L]	1.70 ± 0.39 (n=8)	1.97 ± 0.59 (n=13)	1.81 ± 0.52 (n=8)	2.08 ± 0.71 (n=13)	0.10 ± 0.27 (n=8)	0.11 ± 0.37 (n=13)	0.484	5.7 ± 19.1 (n=8)	5.8 ± 19.7 (n=13)	0.495
FEV1 [percent predicted]	81.9 ± 29.68 (n=8)	76.5 ± 23.94 (n=13)	81.5 ± 35.80 (n=8)	74.5 ± 23.88 (n=13)	-0.4 ± 9.2 (n=8)	-2.0 ± 9.2 (n=13)	0.651	-3.8 ± 18.1 (n=8)	-2.2 ± 15.0 (n=13)	0.590
PEF [L/min]	243.8 ± 73.7 (n=8)	261.5 ± 93.9 (n=13)	230.0 ± 67.8 (n=8)	292.3 ± 90.6 (n=13)	-13.8 ± 51.0 (n=8)	30.8 ± 54.4 (n=13)	0.039	-2.7 ± 20.1 (n=8)	19.8 ± 43.0 (n=13)	0.092
PEF [percent predicted]	74.8 ± 26.49 (n=8)	74.1 ± 26.75 (n=13)	66.3 ± 25.38 (n=8)	76.9 ± 20.13 (n=13)	-8.5 ± 13.8 (n=8)	2.8 ± 13.8 (n=13)	0.042	-9.1 ± 19.3 (n=8)	14.6 ± 42.9 (n=13)	0.080
MIP [cmH_2O]	-39.4 ± 16.57 (n=8)	-40.0 ± 16.58 (n=13)	-41.9 ± 15.34 (n=8)	-47.3 ± 14.09 (n=13)	-2.5 ± 6.6 (n=8)	-7.3 ± 13.0 (n=13)	0.173	9.3 ± 18.8 (n=8)	34.3 ± 54.9 (n=13)	0.116
MIP [percent predicted]	45.0 ± 18.69 (n=8)	39.2 ± 15.89 (n=13)	44.3 ± 16.66 (n=8)	44.1 ± 13.38 (n=13)	-0.8 ± 7.3 (n=8)	4.8 ± 13.0 (n=13)	0.142	0.3 ± 16.3 (n=8)	28.1 ± 54.0 (n=13)	0.088

Data expressed as mean ± standard deviation *One-sided p-values.
FVC = forced vital capacity; FEV_1 = forced expiratory volume 1 second; PEF = peak expiratory flow; MIP = maximal inspiratory pressure

3.3.6.2.2. Ancillary analyses to DELPHI

SNT-IR-011 ADDITIONAL ANALYSES OF RESPIRATORY FUNCTION MEASURES FOR DELPHI AND DELPHI-EXTENSION STUDIES

Rationale

In the original analyses, treatment effects of idebenone appeared to be greater in GCs non-users than in GCs users and it was hypothesized that there may have been some interaction between idebenone and GCs which affected the outcome in the GCs-using patients (Buyse et al., 2013). However, currently

available natural history data show that the rate of respiratory functional loss is affected by neither the age of the patient nor by GCs use once decline in respiratory function has been established. Since the DELPHI study outcomes did not appear consistent with this new information on the natural history of the rate of respiratory function loss, new analyses were performed.

Methods

The applicant´s position was that decline in PEF%p is similar to decline in FVC%p. Consequently, the applicant performed additional analyses of PEF%p. The mixed effect repeated measurement (MMRM) model was used to estimate the 12-month change from baseline in PEF%p in DELPHI and DELPHI-E studies. The model included PEF%p values from Months 6 and 12 as dependent variables and treatment group, visit and interaction between treatment group and visit as fixed factors. The baseline PEF%p value was used as a covariate. Analyses were performed for the complete DELPHI ITT population, for the subgroups of GCs users and non-users and for the subgroup of patients with a PEF%p ⩽80% at baseline. Interactions between GCs use, and treatment group were also investigated in the subgroup of patients with a PEF%p ⩽80% at baseline. In these models assessing interactions, the GCs use status and interaction terms between GCs use status and treatment group and GCs use status and visit were included as additional fixed factors. The applicant did not include any control for the family-wise error.

Results:

A decrease of 8.4% and an increase of 2.8% in mean PEF%p were observed in patients receiving placebo and idebenone, respectively (Table 6). A similar trend was observed in the subgroup of patients with a PEF%p ⩽80% at baseline (Table 7). In the subgroup of GCs users, a decrease of 5.4% and a decrease of 0.9% was observed in patients receiving placebo and idebenone, respectively. For the non-GCs users, a decrease of 12.8% and an increase of 8.3% was observed in patients receiving placebo and idebenone, respectively (Table 8). None of the p-values of the interaction terms between GC use status and treatment group and GC use status reached a value below 0.05.

Table 6: DELPHI – Reanalysis of PEF%p (ITT population)

	Idebenone	Placebo	Estimated Difference[1] ± SEM (95% CI)	p-value
			Idebenone vs. Placebo	
N	13	8		
Baseline mean (SD)	74.1 (26.7)	74.8 (26.5)	NA	NA
Month 12 Estimated Change[1] (95% CI)	2.8 (-4.1, 9.7)	-8.4 (-17.2, 0.4)	11.2 ± 5.3 (0.0, 22.3)	0.0497

[a] Estimated change and estimated difference from MMRM.
CI = confidence interval; ITT = intent-to-treat; MMRM = mixed model for repeated measures; NA = not applicable; PEF%p = peak expiratory flow expressed as percent of predicted; SD = standard deviation; SEM = standard error of the mean.

Table 7: DELPHI – Analysis of PEF%p (subgroup with PEF%p ⩽80% at baseline)

	Idebenone	Placebo	Estimated Difference[1] ± SEM (95% CI)	p-value
			Idebenone vs. Placebo	
N	8	4		
Baseline PEF%p mean (SD)	59.0 (19.6)	56.8 (24.1)	NA	NA
Month 12 Estimated Change[1] (95% CI)	8.8 (-1.0, 18.6)	-9.8 (-23.7, 4.1)	18.6 ± 7.5 (1.6, 35.7)	0.0354

[a] Estimated change and estimated difference from MMRM.
CI = confidence interval; ITT = intent-to-treat; MMRM = mixed model for repeated measures; NA = not applicable; PEF%p = peak expiratory flow expressed as percent of predicted; SD = standard deviation; SEM = standard error of the mean.

Table 8: DELPHI – Reanalysis of PEF%p (subgroups of GCs users and GCs non-users)

	Idebenone	Placebo	Estimated Difference[1] ± SEM (95% CI) Idebenone vs. Placebo	p-value
GC-users	8	5		
Baseline mean (SD)	86.0 (21.4)	88.4 (15.5)	NA	NA
Month 12 Estimated Change[1] (95% CI)	-0.9 (-8.1, 6.4)	-5.4 (-14.6, 3.8)	4.6 ± 5.3 (-7.1, 16.3)	0.4044
GC non-users	5	3		
Baseline mean (SD)	55.0 (24.6)	52.0 (27.1)	NA	NA
Month 12 Estimated Change[1] (95% CI)	8.3 (-6.8, 23.4)	-12.8 (-32.3, 6.7)	21.1 ± 9.6 (-3.6, 45.7)	0.0794

[1] Estimated change and estimated difference from MMRM.
CI = confidence interval; ITT = intent-to-treat; MMRM = mixed model for repeated measures; NA = not applicable; PEF%p = peak expiratory flow expressed as percent of predicted; SD = standard deviation; SEM = standard error of the mean: GCs = Glucocorticosteroids.

3.3.6.2.3. DELOS study (SNT-III-003)

Methods

The study was a Phase III double-blind, randomized, placebo-controlled, parallel group, multicentre study of the efficacy, safety and tolerability of idebenone in patients with DMD.

This trial was initially set up to enrol two separate and independent patient populations, namely GCs non-users and GCs users. As such, a group sequential design was initially proposed for the study whereby GCs non-users were to be enrolled prior to enrolment of GCs users. Both groups were independently powered und would have been analysed independently. However, the study was amended (see protocol amendments in section conduct of the study) and only patients not using GCs were enrolled.

Patients' participation lasted up to 15 months (or up to 17 months if washout from acute systemic glucocorticoid burst therapy prior to Visit 6/Week 52 was required): up to 2 months' Screening, 12 months' treatment period (or up to 14 months) and 1-month Follow-up. Patients were treated as out-patients.

Efficacy assessments (see outcomes/endpoints section) were made at Baseline and at weeks 13, 26, 39 and 52. Safety assessments were performed after enrolment at weeks 4, 13, 26, 39, 52 and at the Follow-up Visit.

Study participants

The eligibility criteria were assessed at Screening and confirmed at Visit 1, prior to the start of study treatment.

Inclusion Criteria:

- Patients 10-18 years of age at baseline.
- Documented diagnosis of DMD or severe dystrophinopathy and clinical features consistent of typical DMD at diagnosis. DMD was to 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.
- Ability to provide reliable and reproducible repeat PEF within 15% of the first assessment (i.e. baseline vs. screening).

- Patients assessed by the Investigator as willing and able to comply with the requirements of the study, possessing the required cognitive abilities and able to swallow study medication.

Exclusion Criteria

- Patients dependent on assisted ventilation at Screening and/or Baseline (defined as non-invasive nocturnal ventilation, daytime non-invasive ventilation or continuous invasive ventilation).
- Patients with documented DMD-related hypoventilation for which assisted ventilation was needed according to current standard of care guidelines (e.g. FVC%p <30%) or was required in the opinion of the investigator.
- Patients with a PEF%p >80% at baseline.
- Patients unable to form a mouth seal to allow precise respiratory flow measurements and mouth pressures.
- Symptomatic heart failure (high probability of death within one year of baseline) and/or symptomatic ventricular arrhythmias.
- Participation in DELPHI or DELPHI-E of idebenone.
- Moderate or severe hepatic impairment or severe renal impairment.
- Asthma, bronchitis/chronic obstructive pulmonary disease, bronchiectasis, emphysema, pneumonia or presence of any other non-DMD respiratory illness that affects PEF.
- Chronic (daily intake>14 days) use of beta2-agonists or any use of other bronchodilating medication.
- The following additional exclusion criteria were applied with respect to concomitant GCs use:
    - Chronic use of systemic GCs therapy for DMD related conditions within 12 months of baseline (the "12-month non-use period").
    - More than 2 rounds of acute systemic GCs burst therapy (of >2 week duration) for non-DMD related conditions within the 12 month non-use period.
    - Use of any round of systemic GCs burst therapy of longer than 2 weeks duration within the 12-month non-use period.
    - Use of systemic GCs burst therapy less than 8 weeks prior to baseline.

Treatments

Patients were treated with one of the following treatments:

- Idebenone 150 mg film-coated tablets, 2 tablets t.i.d with meals (total daily dose 6 tablets, 900 mg).
- Matched placebo tablets, 2 tablets t.i.d with meals (total daily dose 6 tablets).

Objectives

Primary Objective: To assess the efficacy of idebenone, compared to placebo, in improving respiratory function or delaying the loss of respiratory function in patients with DMD.

Secondary Objectives (relevant to this MAA):

- To assess the efficacy of idebenone, compared to placebo, in improving respiratory function or delaying the loss of respiratory function using measures other than those used for the primary endpoint.
- To assess the efficacy of idebenone, compared to placebo, in improving skeletal muscle strength / motor function or delaying the loss of skeletal muscle strength / motor function.
- To assess the efficacy of idebenone, compared to placebo, in improving quality of life or delaying the loss of quality of life.
- To assess the safety and tolerability of idebenone in patients with DMD.

Tertiary objectives

- To assess the efficacy of idebenone, compared to placebo, in improving respiratory function or delaying the loss of respiratory function using measures other than those used for the primary and secondary endpoints.
- To assess the effect of idebenone on biochemical markers reflecting cardiac overload or cardiac degeneration.

Outcomes/endpoints

Primary endpoint: The change from baseline to Week 52 in PEF%p) measured by spirometry at hospital visits.

Secondary endpoints (relevant to this MAA):

- Respiratory function:
    - The change in PEF%p assessed by weekly home based measurement by ASMA-1 device.
    - The change from baseline to Week 52 in FVC%p) as measured by spirometry.
    - The change from baseline to Week 52 in Peak Cough Flow (PCF) as measured by spirometry
    - The change from baseline to Week 52 in percent predicted Maximal Expiratory Pressure (MEP%p) as measured using the MicroRPM (Micro Respiratory Pressure Meter)
    - The change from baseline to Week 52 in MIP%p as measured using the MicroRPM.
- Muscle strength I motor function:
    - The change from baseline to Week 52 in muscle strength as measured by hand-held myometry (HHM).
    - The change from baseline to Week 52 in motor function as assessed using the Brooke and Vignos scales.
- Quality of life, clinical global impression of efficacy, tolerability and satisfaction:
    - The change from baseline to Week 52 in Quality of Life assessed by PedsQL TM Quality of Life Inventory (PedsQL™) (child and teen report forms)
    - The change from baseline to Week 52 in the PedsQL™ Multidimensional Fatigue scale (child and teen report forms).
    - Differences in the Clinical Global Impression of efficacy and tolerability at Week 52 between the two study arms.
    - Differences between patient responses to the "satisfaction with treatment" question at Week 52 between the two study arms.
    - Number of patients in each study arm that during the study period require:
        - Acute hospitalization for treatment of a respiratory or other complication associated with disease progression (no elective hospitalization for diagnostic testing and no surgery).
        - The initiation of the use of a brace or spinal jacket.
        - Initiation or change in systemic GCs treatment.
        - Need for assisted ventilation.
- Measures of safety and tolerability of idebenone:
    - Nature and frequency of adverse events (AEs).
    - Laboratory parameters (haematology, biochemistry, and urinalysis).
    - Physical examinations and vital signs.

- ECG.
- Transthoracic echocardiography.

Tertiary Endpoints (relevant to this MAA):

- The change from baseline to week 52 in Inspiratory Flow Reserve (IFR) as measured by spirometry.
- The change from baseline to week 52 in PEF%p as measured with the ASMA-1 device at hospital visits.
- The change from baseline to week 52 FEV1%p as measured with the ASMA-1 device at hospital visits.

Respiratory function assessment

For PEF, FVC, PCF, MEP and MIP the highest value from a minimum of 3 and up to 5 consecutive manoeuvres was used for each assessment. For PEF, FVC, PCF, MEP and MIP the conversion from measured values to percent predicted values was done using published equations that include the parameters height in cm, weight in kg and age in years (Table 9). In all patients, height (for calculation of the predicted respiratory values) was planned to be estimated from standardized ulna length measurement following Gauld (2004): Height = ((4.605* ulna length [cm]) + (1.308 * age [years]) + 28.003. No "shortening" of the ulna length was permitted. If an ulna length was reported that was shorter than at a previous visit, it was replaced by the value measured at this previous visit.

Table 9: Formulae for Calculation of Percent Predicted Respiratory Function Variables

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))
FEV_1%p (Hankinson et al., 1999)	FEV_1*100 / ((-0.7453 - (0.04106 * age)) + (0.004477 * (age^2)) + ((0.00014098 * (height^2))*1))

PEP%p = Peak Expiratory Flow Percentage Predicted; PEP = Peak Expiratory Flow; FVC%p = Forced Vital Capacity Percentage Predicted; FVC = Forced Vital Capacity; MEP%p= Maximum Expiratory Pressure Percentage Predicted; MEP = Maximum Expiratory Pressure; MIP%p= Maximum Inspiratory Pressure Percentage Predicted; MIP = Maximum Inspiratory Pressure ; FEV_1%p = Forced Expiratory Volume in 1 Second Percentage Predicted; FEV_1 = Forced Expiratory Volume in 1 Second

Using a child-compatible, light-weight hand-held respiratory function device (type ASMA-1 from Vitalograph®) allowed frequent home-based collection of PEF and FEV_1 data. The patient and parent/caregiver were trained in using this device during the Screening visit. The patient, assisted by the parent/caregiver, was requested to measure PEF and FEV_1 values with this device once per week throughout the study duration. The patient was called once per month by the study coordinator and reminded to conduct the home-based respiratory function test. The patient was to be discouraged from performing the test more than once per week as this might have resulted in unwanted training effects. Data readout and maintenance (e.g. battery check) of the ASMA-1 device was performed by the physiotherapist/investigator during each site visit. The patient repeated the respiratory function test with the ASMA-1 device at every site protocol visit (except at Visit 7/week 56) under the supervision of the physiotherapist as the last assessment of the respiratory function tests.

The IFR is the ratio between the largest inspiratory flow during tidal breathing and the largest inspiratory flow during an inspiratory forced vital capacity manoeuvre (De Bruin et al., 2001). For the IFR only 3 tests were required but measurements from all 3 tests were to be recorded in the CRF.

Muscle force/motor function assessment

The maximum isometric muscle force using HHM was evaluated for each of the following muscle groups: elbow flexors, elbow extensors, hip flexors (right, left), knee flexors, and knee extensors. Moreover, the following three summed scores were also to be evaluated: HHM lower limb score (sum of right and left hip flexors, knee flexors and knee extensors), HHM upper limb score (sum of right and left elbow flexors and elbow extensors), and HHM total score (sum of right and left elbow flexors, elbow extensors, hip flexors, knee flexors and knee extensors).

Motor function was evaluated by using the Brooke Upper Extremity Scale (1-6) (Brooke et al., 1981) for upper limbs and the Vignos Lower Extremity Scale (1-10) (Vignos et al., 1963) for lower limbs. In both scales a higher score indicates a more severe functional impairment. Loss of ambulation was defined by a Vignos score >5.

Quality of Life, clinical global impression of efficacy, tolerability and satisfaction

The 23-item PedsQL™ Paediatric Quality of Life Inventory encompasses 4 essential core domains for pediatric HRQOL measurement: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), and 4) School Functioning (5 items). There are five response alternatives to each item: 0=Never, 1=Almost never, 2=Sometimes, 3=Often, 4=Almost always. For ease of interpretability, items are reversed scored and linearly transformed to a 0-100 scale, so that higher scores indicate better quality of life. Additionally, three summary scores can be computed: Total Scale Score, Physical Health Summary Score, and Psychosocial Health Summary Score. To create Scale summary scores, the mean is computed as the sum of the items over the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the summary score should not be computed. A higher score indicates better quality of life. The 18-item PedsQL™ Multidimensional Fatigue Scale was designed to measure three dimensions of fatigue: 1) general fatigue (6 items), 2) sleep/rest fatigue (6 items) and 3) cognitive fatigue (6 items). A higher score means less fatigue.

A clinical global impression of efficacy was to be rated by the investigator. The patient's condition compared to that at Baseline was to be rated on a 7-point scale from much better (1) to much worse (7), with 4 representing no change. A higher score indicates better quality of life. A clinical global impression of tolerability was to be rated by the investigator using the following 5-point scale: 1 = very good; 2 = good; 3 = moderate; 4 = poor and 5 = very poor. The investigator was to ask the patient and caregiver about their general satisfaction with the treatment as compared to the previous visit using a 5-point Likert scale ranging from "very dissatisfied" (scale score 1) to "very satisfied" (scale score 5) with 3 representing a neutral position.

Sample size

Before the final decision was made to restrict the trial population to GCs non-using patients, it was initially planned to randomise 240 DMD patients (34 GCs non-users and 206 GCs-users), to ensure 30 and 186 respectively provide Month 12 data. The description of sample size considerations in this assessment report is restricted to GCs non-users group.

The sample size calculation was based on the results of the Phase II DELPHI trial. Based on those data, a conservative expected treatment effect of 15% (SD=14%) was used for the calculation of the sample size for the subgroup of GCs non-users in the DELOS trial. This resulted in 15 patients per treatment

group to complete the trial to obtain 80% power for the comparison in PEF%p based on the assumptions made.

The PEF testing scheme was changed by Amendment 3 (18 August 2020) to allow for multiple respiratory tests/day to reduce variability due to fatigue. Since fatigue was expected to influence the outcome of PEF testing, it was not expected that pre- and post-Amendment 3 data would be comparable (in terms of variability) and the total sample size was increased to allow for the randomization of 40 post-Amendment 3 GCs non-users patients. This was to ensure that, allowing for drop-outs, Month 12 data is available from a minimum of 30 post-Amendment 3 GCs non-user patients i.e. 15 patients per treatment group. However, after 29 post-amendment 3 GCs non-users had been randomized, based on a blinded assessment of variability, pre- and post-Amendment 3 data was found to be comparable and therefore could be combined to form a population of GCs non-users. Based on variability information from this interim look (including Week 24 and Week 52 data from 34 patients randomised pre-Amendment 3 and Week 24 data from 11 patients randomised post-Amendment 3), the study was assumed to have 80% power to detect a difference of 10.3% in the subset of GCs non-users.

Randomisation and blinding

Central randomization was used to ensure a 1:1 treatment allocation (idebenone: placebo) using an Interactive Web Response System (IWRS). The randomization list was generated by the IWRS system. It was stratified by GCs use (non-users and users) and baseline PEF (<40% vs. 40-80%). Within each stratum, treatments were randomly allocated in blocks of 4 (2 idebenone and 2 placebo). A total of 100 blocks were assigned to each stratification factor.

Treatment allocation was double-blinded. The patient and any persons involved in the conduct of the study (investigators and their site staff, monitors and sponsor) were blinded to the treatment.

Statistical methods

Analysis Populations

Four populations were defined for this study: the safety population, the ITT population, the modified ITT population (mITT), and the Per Protocol (PP) population.

ITT population was used for analyses of efficacy variables. This population included all randomized patients who received at least one dose of the study medication and provided at least one post-baseline assessment. It excluded siblings who had been allocated to the same study treatment as a randomized sibling. Patients were analysed as randomized regardless of protocol violations.

mITT population was also used for analyses of efficacy variables. The mITT population was the same as the ITT population but excluded 7 randomized patients who had more than 20% difference between the change in PEF%p (as measured by spirometry at hospital) between baseline and end of study and the assessment of the annual rate of change in PEF%p by home-based weekly ASMA-1 device. The mITT population was specified prior to database lock and data unblinding with the intention of identifying and prospectively eliminating from the analysis patients with potentially unreliable data which would inappropriately influence the outcome for the primary efficacy variable. Briefly, the two assessment methods for PEF%p used in the study were compared: prior to database lock the change from baseline to week 52 in PEF%p (primary endpoint) was compared in a blinded manner for every patient with the annual rate of changes in PEF%p over the study period using ASMA-1 device data, calculated by linear regression analysis (secondary endpoint). For each patient, the absolute difference in these two measurements was calculated and used to identify patients with inconsistent results. By applying a cut-off of 20% for the difference between these methods, 7 randomized patients were identified and based on this blinded data review these patients were prospectively excluded from the mITT population.

PP population was also used for analyses of efficacy variables. All patients from the ITT population who completed the study and who had no major protocol deviation were included in the PP population. In this context, a major protocol deviation was defined as a protocol deviation that was considered to have a major impact on the efficacy results based on clinical judgment.

The safety population was used for analysis of all safety variables. It included all patients who received at least one dose of the study medication. Patients were analysed according to the treatment actually received.

Primary efficacy endpoint

The primary aim of the present analysis is to show the superiority of idebenone versus placebo in the change from baseline to Week 52 in PEF%p for the GCs non-users. The primary analysis for PEF%p was on data obtained by spirometry during hospital visits. Prior to Amendment 3, PEF was measured once per each assessment visit, after amendment 3, PEF was measured twice at the beginning and at the end of each assessment visit.

The null and alternative hypotheses were designed to establish superiority of idebenone over placebo:

- H_0: No difference in change from Baseline to Week 52 in PEF%p between Puldysa and placebo.
- H_A: Difference in change from Baseline to Week 52 in PEF%p between Puldysa and placebo.

The estimated treatment difference between Puldysa and placebo for the change from baseline to Week 52 in PEF%p was calculated using a MMRM. All available PEF data from all post-baseline visits were to be used as response variables in the model. The treatment group, visit and the interaction between the treatment group and visit were to be used as fixed factors in the model and the Baseline assessment as a covariate. The difference between Puldysa and placebo at Week 52 was planned to be estimated based on the MMRM model using contrasts. The unstructured covariance structure (UN) was planned to be used for the estimation. In case the UN did not converge, compound symmetry (CS) was planned to be used instead. In case the PEF%p data turned out to be considerably skewed or other assumptions of the MMRM were not met, sensitivity analysis were planned to be performed using a suitable data transformation.

Other respiratory efficacy endpoints

The change from baseline to week 52 in FVC%p, PCF, MEP%p and MIP%p endpoints were analysed using the same statistical method as for the primary efficacy endpoint.

The PEF%p data obtained using the ASMA-1 device were used to derived two endpoints as follows:

1. *The annual rate of change in PEF%p, assessed by home-based pulmonary function test using the ASMA-1 device and calculated by linear regression analysis (secondary endpoint).*

The annual rate of change in PEF%p was calculated by fitting an individual linear regression line for each patient for the time of the study, i.e. an intercept and slope were estimated for each patient. The slopes were then analysed using the analysis of covariance (ANCOVA) method with treatment as factor and the calculated intercept value as a covariate. For each day with available ASMA-1 data, the highest PEF%p value was used in this analysis. Patients who did not submit home based ASMA-1 data for at least the first 6 months (up to Visit 4) were excluded from this analysis.

2. *Change from Baseline to week 52 in PEF%p with data obtained by home-based pulmonary function assessments using ASMA-1 device (tertiary endpoint)*

The change from baseline to week 52 in PEF%p as measured by the ASMA-1 device was analysed using the same method described for the primary endpoint. To minimize data variability, the average of home-based results during a time-window was computed to represent the PEF%p from ASMA-1 for that

particular visit. The window included results from 3 weeks before the hospital visit and 3 weeks after the hospital visit and the result from the hospital visit itself. For each day with available ASMA-1 data, the highest value was used to calculate an average PEF%p for the time window. Baseline and week 52 values were calculated in the same fashion, by using the average of the home-based results from 3 weeks after entering the study (baseline) and 3 weeks before ending treatment at Week 52 of the study and the result of the hospital visit.

Muscle strength/motor function endpoints

The change from baseline to week 52 in the strength as measured by HHM of each of the muscle groups and the three summed scores was to be calculated and analysed using the same statistical method as for the primary efficacy variable.

In addition, Brooke Upper Extremity Scale were to be also compared between treatments at each post baseline visit using the Cochran-Mantel-Haenszel Test (CMHT). Moreover, the change from baseline to each of the follow-up visits in Vignos Lower Extremity Scale was to be calculated and the patient classified as improved/unchanged/worsened relative to the baseline visit. This classification was based on 1 grade of change on the scale being counted as an event. For each post-baseline visit, this ordered categorical variable was then to be compared between the treatment groups using the CMHT. For each visit, the proportion of patients with a Vignos score > 5 was to be compared between the treatment groups using the CMHT.

Quality of life endpoints

Analysis of four core domains and three summary scores of 23-item PedsQL™ Paediatric Quality of Life Inventory and the total score and the scores for the three dimensions of 18-item PedsQL™ Multidimensional Fatigue Scale were conducted using the same statistical method as for the primary efficacy variable. The analysis was done for both the child/teen evaluations (combined) and for the parent evaluations.

The Clinical Global Impression of efficacy was categorized into three classes: improvement/no change/deterioration, where "improvement" represented 1-3, "no change" represented 4, and "deterioration" represented 5-7 on the original scale. The Clinical Global Impression of tolerability was categorized into three classes: good/moderate/poor, where "good" represented 1-2, "moderate" represented 3, and "poor" represented 4-5 on the original scale. The ordinal scale assessing satisfaction with treatment was categorized into three classes: dissatisfied/neutral/satisfied, where "dissatisfied" represented 1-2, "neutral" represented 3, and "satisfied" represented 4-5 on the original scale. The values at week 52 for these categorized variables were compared between treatments using the CMHT.

Interim and Final Analysis strategy, Type-1-error control

In order to confirm the assumptions used in the sample size calculation and not to under- or overpower the study, a blinded or unblinded sample size reassessment was planned to be performed. This reassessment was planned to be performed by the data and safety monitoring board (DSMB) after the pre-planned number of randomised patients in the "GCs non-user" subgroup has been followed up for 6 months (#1 Table 10). The study team or the Sponsor was not to be involved and the DSMB would not disclose any results or data. The DSMB was planned to provide a recommendation of the updated sample size, if needed, i.e. the approximate number of randomised patients needed compared to the original sample size. Furthermore, it was planned that DSMB should perform a futility analysis to potentially recommend terminating the study in case of futility. A separate plan was to be prepared describing the responsibilities of the DSMB and the processes used to maintain the confidentiality of the data. Furthermore, the method to control the type I error of the final analysis was planned to be defined in

the plan (#1 Table 10). The plan was supposed to be completed before the start of any activities related to the sample size reassessment /futility analysis.

The SAP of the study was planned to be updated after the plan for the sample size reassessment has been completed, taking into account the method to control the type I error rate. In the final analysis, the baseline and outcome data collected before and after the sample size reassessment were planned to be compared for consistency.

Safety data was planned to be reviewed regularly by the DSMB. If any safety issues should arise, the independent DSMB should make an appropriate recommendation to the Sponsor.

DELOS trial was initially set up to enrol two separate and independent patient populations, namely GCs non-users and GCs users. Both groups were independently powered and would have been analysed independently. Moreover, , it was initially planned to conduct the final analysis of the DELOS study on the total cohort of randomized patients of "GCs users" and "GCs non-users" (#1 Table 10).

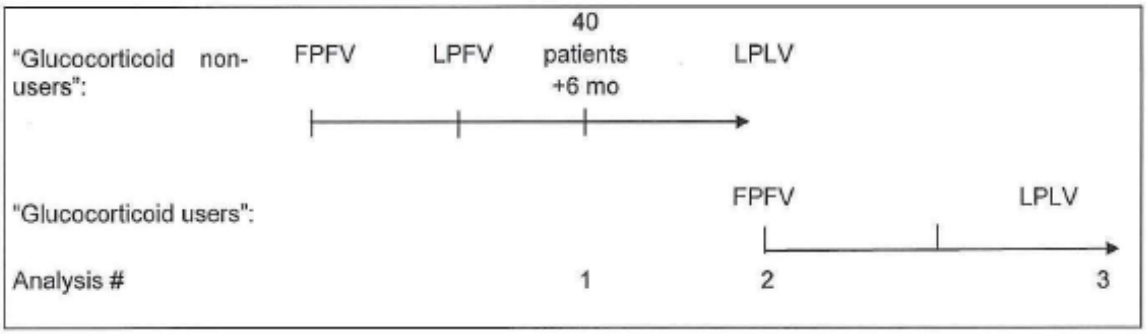
A group sequential design was initially proposed for the study whereby GCs non-users were to be enrolled prior to enrolment of GC users. The time point for starting recruitment of the GCs users was changed in amendment 6 (19 June 2013) so instead of starting the recruitment of GCs users after the futility analysis (#1 Table 10), the recruitment was delayed until the final analysis of the GCs non-user subgroup was done (#2 Table 10).However, prior to final analysis of the GCs non-user subgroup (#2 Table 10), there was a new amendment of the protocol (amendment 7 (24 April 2014)) and the decision was taken to terminate the study and to conduct the final analysis of the DELOS study based on "GCs non-users" only. Interim analysis number 2 (final analysis of the glucocorticoid non-user subgroup) became the final analysis of the study. The final analysis (#2 Table 10) of the "GCs non-user'' subgroup, constituting the total population of the DELOS study was planned to be performed after all randomised patients have completed the whole study period and the database had been locked. As there was no subsequent analyses, multiple testing was no longer planned to be undertaken and methods to control type I error rates were no longer considered required. Consequently, data analysis was performed on the 5% significance level without any adjustments due to multiple testing.

The processes related to the interim and final analyses and the timing of the interim and final analyses are displayed in Table 10.

Table 10: Interim and final analyses (processes and timing)

#	Analysis	Time point	Actions	Method of blinding	Method to control type I error rate
1	Sample size re-calculation/futility analysis	When Month 6 data from the first 45 glucocorticoid non-users is available	(1) No actions or (2) adjustment of randomised sample size in both "glucocorticoid non-users" and "glucocorticoid users" or (3) stop the study for futility	Data is unblinded for the DSMB. All other study personnel will remain blinded to the data and rationale behind the decisions	According to the suggestion by the DSMB
2	Final analysis of the DELOS study, analysing only randomised "glucocorticoid non-users"	After all randomised patients in the "glucocorticoid non-user" subgroup have completed the study	Final analysis	Study will be unblinded after the database has been locked	No adjustments for multiplicity
Following Amendment 7, Analysis 3 is obsolete and will not be conducted.					
3	Final analysis of the "glucocorticoid user" subgroup and a final analysis of the total randomised cohort	After all randomised patients have completed the study	Final analysis of the "glucocorticoid user" subgroup and a final analysis of the total randomised cohort	Study will be completely unblinded	O'Brien-Fleming criteria will be used, considering this as final analysis following one interim analysis, in case an interim analysis was performed

Timing of the interim and final analyses



FPFV = First randomised patient, first visit; LPFV = Last patient first, visit; LPLV = Last patient, last visit. Analysis #: see table above for details.

Subgroup analyses

Analyses of the primary endpoint and other respiratory endpoints based on the following subgroups were to be performed:

- PEF%p at Baseline (<40% or 40-80%), a pre-defined stratification factor.
- Age (above/below median age at Baseline).
- Ambulatory status at baseline.

The following *post hoc* analyses were also performed:

- In addition, *post hoc* analyses were performed in subgroups based on previous GCs use (patients who had never used GCs/patients who had used GCs).

- For all pulmonary function endpoints additional responder analyses were performed using the number of patients who did not decline and did not decline by 10% or more in the respective parameter (two definitions).

Moreover, analyses were to be performed to compare the number of patients in whom the PCF fell below 160 L/s (pre-specified analysis), and the number of patients in whom the FVC fell below 1 L (*post hoc* analysis).

Sensitivity analyses

Analysis of the primary and secondary respiratory function endpoints were to be analysed in the mITT and ITT populations. Sensitivity analyses using the PP population were also to be performed.

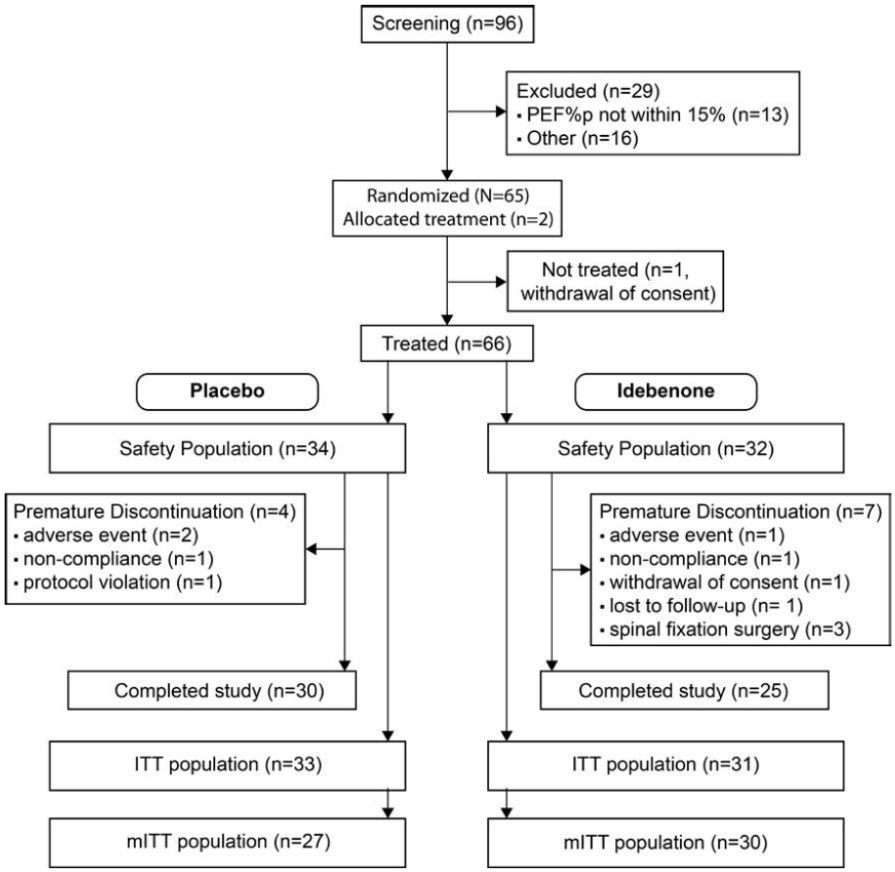
For the primary efficacy endpoint, a sensitivity analysis was performed using an ANCOVA model, with treatment as factor and the baseline value as covariate, with LOCF imputation. A *post hoc* sensitivity analysis was performed for the primary endpoint using the primary analysis model but excluding two patients who had been identified as outliers in a Cook's D analysis.

Results

Participant flow

Sixty-seven patients fulfilled eligibility criteria and were enrolled into the study (Figure 6)

Figure 6: DELOS Participant Flow



Recruitment

Regarding the periods of recruitment and follow-up, the applicant reported the following dates:

- Date first subject screened: 27 July 2009

- Date last subject completed: 14 January 2014.
- Database lock date: 5 May 2014
- Final report date: 24 April 2015

A total of 23 centres participated in the study. Patients were treated in 17 study sites in 10 countries (Belgium, Germany, The Netherlands, Switzerland, France, Sweden, Austria, United States, Italy, and Spain).

Conduct of the study

Protocol amendments The original protocol was dated 04 May 2009. There were 7 amendments to the protocol. The changes made in each of these amendments are described below (only the changes relevant for this assessment report considering the indication pursed by the applicant were presented):

Amendment 1 (24 September 2009)

- Introduction of Group Sequential Design to allow an interim assessment of efficacy in glucocorticoid non-using patients before glucocorticoid using patients were enrolled into the study.
- Glucocorticoid non-user definition and new glucocorticoid use-related exclusion criteria introduced.
- Introduction of regular assessments of PEF by the patient at home using a hand-held device.
- Removal of Cough Frequency assessment as a study endpoint.
- Introduction of muscle strength and motor function testing at the Screening Visit.

Amendment 2 (22 February 2010)

- Introduction of strategies to allow siblings to be enrolled into the study.
- Introduction of strategies to avoid systematic variability in the conduct of assessments in patients with concomitant respiratory infections or receiving medication for same.
- Clarification of the dual role for the DSMB in monitoring the safety aspects of the study and in conducting the interim analyses.

Amendment 3 (18 August 2010)

- Introduction of a second PEF assessment at Screening Visit, Baseline/Visit 1 and every efficacy visit to minimize the effect of fatigue, improve Baseline assessment variability and unnecessary exclusions or additional patient visit burden
- Introduction of use of ASMA-1 device at Screening to allow provision of reliable ASMA-1 assessment at Baseline

Amendment 4 (05 July 2011)

- Increase of sample size for glucocorticoid non-users from 40 to 80 patients.

Amendment 5 (05 December 2012)

- Amendment of sample size required for the planned futility analysis.
- Clarification of height prediction from ulna length and arm span.

Amendment 6 (19 June 2013)

- Amendment of the time point for starting recruitment of the glucocorticoid using patients (decision to be made after study analysis number 2, the final analysis of the glucocorticoid non-user subgroup rather than after the study analysis number 1, the futility analysis) and removal of study analysis number 3, interim analysis of the total cohort which was to be performed at the time of the final analysis of the glucocorticoid non-user subgroup.
- Amendment of the time point for initiating the open-label extension study for patients who have completed the DELOS study.

- Clarification of the duration of subject participation and conditions under which DELOS subjects could gain access to idebenone treatment after study completion.

Amendment 7 (24 April 2014)

- Termination of the study following the planned final analysis of the randomized glucocorticoid non-user subgroup. Interim analysis number 2 (final analysis of the glucocorticoid non-user subgroup) became the final analysis of the study.
- Adaptation of the final statistical analysis. Amendment of the Type I error rate in study analysis number 2. Bonferroni adjustment to the statistical testing was no longer required.
- Amendment of the method for the statistical analysis of primary efficacy variable from ANCOVA to MMRM
- Introduction of an adjudication procedure to identify patients with potentially unreliable data for the primary efficacy endpoint
- Amendment of the statistical analysis strategy for secondary endpoints
- Clarification of the PCF analysis
- Introduction of a new secondary endpoint: The annual rate of change in PEF%p assessed by home-based pulmonary function test using the ASMA-1 device

Changes in the Planned Analyses

A futility analysis was performed on 10 April 2013. Details of this analysis were documented in SAP Version 1.0, dated 1 March 2013. The SAP which detailed the final analyses to be performed for the study was dated 30 April 2014. No changes to the analyses in the study protocol (incorporating Amendment 7) were described in the SAP.

The following changes from the analyses described in the SAP were made:

- The primary population for analysis of the primary efficacy endpoint and all other pulmonary function endpoints was to be the mITT population. The full ITT population was to be used for sensitivity analyses of these endpoints. *The results for the primary endpoint were very similar for both the mITT and ITT population. Thus, it was decided that all pulmonary function parameters would be analysed using the full ITT population as the primary analysis population. Results for the mITT population were also reported.*
- The results from the primary efficacy variable were to be presented descriptively by center, pooled by country (countries with less than 5 patients were to be pooled into a single category). *This analysis by pooled by country was not performed.*
- An additional sensitivity analysis of the primary endpoint was performed excluding the two most influential patients on the MMRM model. These patients were identified using two Cook's D patient influence models. *These analyses were performed using the previously specified MMRM and using MMRM without group included as a factor.*
- In the SAP, the 'number of patients in each treatment group that began assisted ventilation during the study period (due to documented development of DMD related hypoventilation)' was included as a pulmonary function secondary endpoint as well as in event secondary endpoints. *This endpoint has only been included with the event endpoints in this document*.
- A *post hoc* analysis was performed to compare the number of patients in whom the FVC fell below 1 L.
- Additional *post hoc* responder analyses were performed for all pulmonary function endpoints. These analyses were based on the number of patients who did not decline by 10% or more in the respective parameter.

- The numbers of patients in each treatment group reporting a respiratory tract infection (defined as preferred terms (PT) of nasopharyngitis, upper respiratory tract infection, rhinitis, pharyngitis, viral infection, laryngitis, bronchitis or pneumonia) an infection of the upper respiratory tract (defined as PT of nasopharyngitis, upper respiratory tract infection, rhinitis, pharyngitis, viral infection or laryngitis) and an infection of the lower respiratory tract (defined as PT of bronchitis or pneumonia) were compared statistically using Fisher's Exact Test. The time to these events was analysed using Kaplan Meier plots and Cox proportional Hazard models (CPHM).
- As the majority of patients (92%) were non-ambulatory only analyses of upper limb parameters for muscle strength/motor function were performed. Therefore, hip flexors, knee flexors and knee extensors measured by HHM were not analysed and the HHM lower limb score and HHM total score were not evaluated. For the same reason, there were no analyses of the Vignos scale.
- The sensitivity analysis of the Brooke Upper Extremity Scale in which patients were to be classified as improved/unchanged/worsened relative to the baseline visit was not performed.
- Additional subgroups based on previous GCs use were defined (patients who had never used GCs/patients who had previously used GCs but who stopped treatment and went through a wash-out period in accordance with study entry criteria prior to enrolment). The primary efficacy endpoint and other respiratory variables were analysed in these subgroups.
- The influence of age at baseline on the treatment effect on PEF%p and FVC%p was evaluated by looking at the interaction terms of the treatment group and dichotomized age (included as fixed factor in the respective MMRM models).

Baseline data

In the ITT population, patients allocated to idebenone were younger (13.5 vs. 15 years) and had lower BMI (22.0 vs. 23.4 kg/m^2) and height (157.4 cm vs. 164.4cm) than those assigned to placebo (Table 11). In both groups, most of the patients were non-ambulant at baseline, had PEF 40-80% (stratification factor) and more than a half had previously used GCs during the disease course (Table 11).

Table 11: Summary of Demographic and disease-relevant baseline characteristics (ITT population)

Disease-Relevant Baseline Characteristics	Idebenone (N=31)	Placebo (N=33)
Age, years at Baseline		
mean (SD)	13.5 (2.7)	15.0 (2.5)
median (min-max)	13.3 (10.1-19.0)	15.1 (10.5-18.9)
Height, cm[a]		
mean (SD)	157.4 (11.3)	162.4 (12.4)
median (min-max)	156.1 (138.3 – 180.7)	166.4 (129.4 – 181.1)
Ambulatory Status, n (%)		
Ambulatory	3 (9.7%)	2 (6.1%)
Non-ambulatory	28 (90.3%)	31 (93.9%)
Age at Loss of Ambulation, n (%)		
< 8 years	2 (6.5%)	5 (15.2%)
≥8 years to <11 years	20 (64.5%)	21 (63.6%)
≥11 years to <16 years	6 (19.4%)	5 (15.2%)
Ambulatory	3 (9.7)	2 (6.1%)

Disease-Relevant Baseline Characteristics	Idebenone (N=31)	Placebo (N=33)
Prior GC Use, n (%)		
Yes	17 (54.8)	19 (57.6)
No	14 (45.2)	14 (42.4)
Time Since Last GC Use, years		
n	17	19
mean (SD)	2.9 (1.8)	4.3 (2.2)
median (min-max)	2.5 (0.9-6.6)	4.3 (1.3-8.9)
Stratification Factor, n (%)		
Baseline PEF%p:		
PEF <40%	5 (16.1)	7 (21.2)
PEF 40% to 80%	26 (83.9)	26 (78.8)
Pulmonary Function Tests, mean (SD)		
PEF%p	53.5 (10.3)	54.2 (13.2)
FVC%p	55.3 (15.8)	50.4 (20.0)
FEV1%p	53.6 (16.1)	49.5 (20.6)

[a] Height derived from ulna length FEV1%p = forced expiratory volume in 1 second expressed as percent of predicted; FVC%p = forced vital capacity expressed as percent of predicted; GCs = glucocorticoids; ITT = intent-to-treat; max = maximum; min = minimum; PEF = peak expiratory flow; PEF%p = peak expiratory flow expressed as percent of predicted; SD = standard deviation

Numbers analysed

Table 12: Numbers analysed in DELOS trial

	Idebenone N=32		Placebo N=34		Total N=66	
	n	%	n	%	n	%
Safety Population	32	100	34	100	66	100
ITT Population[1]	31	97	33	97	64	97
mITT Population	30	94	27	79	57	86
PP Population	21	66	27	79	48	73
Premature Withdrawals[2]	7	22	4	12	12	18
Reasons for Withdrawal						
- AE	1	3	2	6	3	5
- Protocol violation	0	0	1	3	1	2
- Non Compliance	1	3	1	3	2	3
- Withdrew Consent	1	3	0	0	1	2
- Lost to Follow Up	1	3	0	0	1	2
- Spinal Fixation Surgery[3]	3	9	0	0	3	5

[1]Two sibling patients were allocated to treatment and were not randomized and therefore were not included in the ITT Population
[2]One patient (randomized to idebenone) was not included in this table as a premature withdrawal. This patient completed the study treatment period but experienced an AE for which the action taken was "treatment discontinued".
[3]Shown as "other" in other sections of submitted documents in this MAA

Outcomes and estimation

Primary Endpoint

The primary endpoint of the study was the change from Baseline to Week 52 in PEF%p, as assessed by spirometry during hospital visit using the mITT. At baseline, the mean PEF%p was similar for idebenone and placebo. In the placebo group PEF%p declined between baseline and week 52 by 9.01% compared to a decline in the idebenone group of 3.05%. The estimated difference between treatments of 5.96% 95%CI (0.16, 11.76) was in favour of idebenone at Week 52.

The primary endpoint was also analysed using the ITT population and results were very similar with an estimated difference between treatments of 6.27% instead of 5.96% (Table 13). Since the results for the mITT and ITT population for the effects on PEF%p were similar, it was decided that the ITT population rather than the mITT would be used for the main analysis of other respiratory endpoints since this population included all randomized and treated patients. A sensitivity analysis of PEF%p analysed using the PP population (21 idebenone-treated patients and 27 placebo-treated patients) with consistent results (estimated difference between treatments of 6.28% 95%CI (-0.48, 13.04). An additional sensitivity analysis using ANCOVA found an estimated difference between treatments of 6.39% 95%CI (0.99, 11.79). The *post hoc* sensitivity analysis excluding the two most influential patients using two Cook's D patient influence models showed similar results.

The PEF change (L/min) was also reported and results were consistent with those for PEF%p (Table 14).

Table 13: Percent Predicted Peak Expiratory Flow (ITT Population)

	Idebenone (N=31)		**Placebo (N=33)**		**Group Difference**	
Baseline mean (SD)	53.5 (10.3)		54.2 (13.2)			
Change from Baseline (MMRM)	Estimated Change (95% CI)	p-value	Estimated Change (95% CI)	p-value	Estimated Difference (95% CI)	p-value
Week 13	-0.69 (-4.07, 2.68)	0.6825	-4.59 (-7.9, -1.29)	0.0073	3.90 (-0.83, 8.63)	0.1044
Week 26	-0.71 (-4.14, 2.72)	0.6792	-9.04 (-12.38, -5.69)	<0.001	8.32 (3.53, 13.11)	<0.001
Week 39	-1.31 (-5.73, 3.12)	0.5565	-8.91 (-13.14, -4.68)	<0.001	7.60 (1.48, 13.72)	0.0158
Week 52	**-2.57 (-6.68, 1.54)**	**0.2154**	**-8.84 (-12.73, -4.95)**	**<0.001**	**6.27 (0.61, 11.93)**	**0.0306**
Week 13-52	-1.32 (-4.59, 1.94)	0.4213	-7.84 (-11.00, -4.69)	<0.001	6.52 (1.98, 11.06)	0.0056
Fixed Effects: Baseline p=0.4239, Group p=0.0056, Visit p=0.1439, Group*Visit p=0.1856						

ITT = Intention to Treat; SD = Standard Deviation; CI = Confidence Intervals ; MMRM = Mixed Effect Repeated Measurement

Table 14: Peak Expiratory Flow (L/min) (ITT population)

	Idebenone (N=31)		Placebo (N=33)		Group Difference	
Baseline mean (SD)	217.7 (48.6)		233.8 (59.6)			
Change from Baseline (MMRM)	Estimated Change (95% CI)	p-value	Estimated Change (95% CI)	p-value	Estimated Difference (95% CI)	p-value
Week 13	-1.78 (-16.62, 13.06)	0.8109	-15.92 (-30.46, -1.38)	0.0324	14.14 (-6.73, 35.00)	0.1805
Week 26	1.87 (-13.09, 16.83)	0.8034	-31.7 (-46.27, -17.13)	<0.001	33.57 (12.63, 54.51)	0.0021
Week 39	4.14 (-15.1, 23.37)	0.6687	-28.58 (-46.98, -10.18)	0.0029	32.72 (6.06, 59.37)	0.0170
Week 52	**1.72 (-16.71, 20.14)**	**0.8529**	**-26.38 (-43.81, -8.95)**	**0.0036**	**28.09 (2.69, 53.50)**	**0.0308**
Week 13-52	1.48 (-12.96, 15.93)	0.8379	-25.65 (-39.62, -11.67)	0.0005	27.13 (6.97, 47.29)	0.0092
Fixed Effects: Baseline p=0.1625, Group p=0.0092, Visit p=0.5297, Group*Visit p=0.2332						

ITT = Intention to Treat; SD = Standard Deviation; CI = Confidence Intervals ; MMRM = Mixed Effect Repeated Measurement

Secondary Endpoints

The change in PEF%p using home-based assessments with ASMA-1 (calculated by linear regression analysis) showed an estimated difference between treatments of 6.84% 95%CI (-0.15, 13.83) (Table 15). The estimated difference between treatment was 3.27% 95%CI (-0.43, 6.97) for FVC%p (Table 15). Other secondary respiratory endpoints are shown in Table 15.

Table 15: DELOS – Outcomes for the secondary respiratory endpoints

Secondary Endpoints	Idebenone (N=31)	Placebo (N=33)
	Estimated Change (95% CI)	Estimated Change (95% CI)
Annual rate of change in PEP%p (ASMA-1) Linear Regression analysis[1]	-2.48 (-7.39, 2.44) p=0.317	-9.32 (-14.2, -4.40) p=0.004
	Estimated difference: 6.84 (-0.15, 13.83); p=0.0548	
Change in FVC%p	-5.67 (-8.36, -2.99) p<0.001	-8.95 (-11.47, -6.42) p<0.001
	Estimated difference: 3.27 (-0.43, 6.97); p=0.0819	
Change in PCF (L/s)	0.14 (-0.15, 0.43) p=0.3455	-0.02 (-0.29, 0.25) p=0.881
	Estimated difference: 0.16 (-0.24, 0.56); p=0.4287	
Change in MEP%p	-1.79 (-4.44, 0.85) p=0.1802	-3.01 (-5.48, -0.55) p=0.0175
	Estimated difference: 1.22 (-2.41, 4.85); p=0.5047	
Change in MIP%p	-7.17 (-11, -3.35) p<0.001	-5.28 (-8.87, -1.69) p=0.0046
	Estimated difference: -1.89 (-7.16, 3.37); p=0.4754	

Analysis according to MMRM for change from baseline to week 52; data are estimated mean (95% CI).
[1] Four patients were excluded due to not providing data for at least the first 6 months of the study (n = 30:30)
ITT = Intention to Treat; PEP%p = Peak Expiratory Flow Percentage Predicted; FVC%p = Forced Vital Capacity Percentage Predicted; PCF = Peak Cough Flow; MEP%p= Maximum Expiratory Pressure Percentage Predicted; MIP%p= Maximum Inspiratory Pressure Percentage Predicted.

Muscle Strength and Motor Function

As almost all patients were non-ambulatory, only analyses of upper limb muscle strength were performed. No nominally statically differences between treatments for the change from Baseline in either

elbow flexor (Table 16) or elbow extensor (Table 17) force were seen at week 52. Baseline upper limb score was 50.2 in the idebenone group and 41.8 in the placebo group. At Week 52, the estimated mean difference was -3.82 95%CI (-16.2, 8.52). No differences seen between idebenone and placebo at Week 52 or any other time point either using CMHT on rank scores or using an MMRM analysis of changes from baseline were found in the Brooke Upper Extremity Scale.

Table 16: Muscle Strength Measured by Hand Held Myometry (Newtons): Elbow Flexors (ITT Population)

	Idebenone (N=25)		Placebo (N=27)		Group Difference	
Baseline mean (SD)	25.2 (21.8)		19.8 (13.6)			
Change from Baseline (MMRM)	Estimated Change (95% CI)	p-value	Estimated Change (95% CI)	p-value	Estimated Difference (95% CI)	p-value
Week 52	-2.32 (-6.73, 2.09)	0.2949	0.13 (-4.16, 4.41)	0.9534	-2.45 (-8.62, 3.72)	0.4290
Fixed Effects: Baseline p=0.8550, Group p=0.1792, Visit p=0.1868, Group*Visit p=0.4220						

The number of patients (N) in each treatment group is the number of patients with Baseline assessments.
ITT = Intention to Treat; SD = Standard Deviation; CI = Confidence Intervals ; MMRM = Mixed Effect Repeated Measurement

Table 17: Muscle Strength Measured by Hand Held Myometry (Newtons): Elbow Extensors (ITT Population)

Hand Held Myometry [N]	Idebenone (N=27)		Placebo (N=31)		Group Difference	
Baseline mean (SD)	23.5 (21.7)		21.5 (15.8)			
Change from Baseline (MMRM)	Estimated Change (95% CI)	p-value	Estimated Change (95% CI)	p-value	Estimated Difference (95% CI)	p-value
Week 52	0.26 (-3.95, 4.46)	0.9021	1.32 (-2.53, 5.18)	0.4941	-1.07 (-6.78, 4.65)	0.7100
Fixed Effects: Baseline p=0.3900, Group p=0.1318, Visit p=0.6531, Group*Visit p=0.2371						

The number of patients (N) in each treatment group is the number of patients with Baseline assessments.
ITT = Intention to Treat; SD = Standard Deviation; CI = Confidence Intervals ; MMRM = Mixed Effect Repeated Measurement

Quality of Life

Health-related quality of life assessed by PedsQL™ Quality of Life Inventory is shown in Table 18. Fatigue assessed by PedsQL™ Multidimensional Fatigue scale is shown in Table 19. At week 52, results showed a deterioration in the idebenone group compared with an improvement in the placebo group in total score in the quality of life inventory and in the fatigue scale. Results for each of the individual domain scores in the PedsQL™ Quality of Life Inventory (physical functioning, emotional functioning, social functioning, school functioning) and in the PedsQL™ Multidimensional Fatigue scale (general fatigue, sleep/rest fatigue, and cognitive fatigue) were consistent and in favour of placebo.

Table 18: PedsQL Quality of Life Inventory, Total Scale Score (ITT Population)

Total Scale Score: Child/Teen Report						
	Idebenone (N=30)		**Placebo (N=33)**		**Group Difference**	
Baseline mean (SD)	61.3 (15.2)		58.1 (12.7)			
Change from Baseline (MMRM)	Estimated Change (95% CI)	p-value	Estimated Change (95% CI)	p-value	Estimated Difference (95% CI)	p-value
Week 52	-1.34 (-5.99, 3.31)	0.5655	2.46 (-1.77, 6.69)	0.2488	-3.80 (-10.1, 2.50)	0.2318
Fixed Effects: Baseline p<0.0001, Group p=0.2293, Visit p=0.7163, Group*Visit p=0.6329						
Total Scale Score: Parent Report						
	Idebenone (N=30)		**Placebo (N=33)**		**Group Difference**	
Baseline mean (SD)	55.7 (17.5)		51.6 (14.8)			
Change from Baseline (MMRM)	Estimated Change (95% CI)	p-value	Estimated Change (95% CI)	p-value	Estimated Difference (95% CI)	p-value
Week 52	-2.82 (-8.60, 2.97)	0.3338	4.25 (-0.79, 9.28)	0.0968	-7.06 (-14.8, 0.63)	0.0712
Fixed Effects: Baseline p<0.0001, Group p=0.4072, Visit p=0.3790, Group*Visit p=0.1909						

The number of patients (N) in each treatment group is the number of patients with Baseline assessments.
ITT = Intention to Treat; SD = Standard Deviation; CI = Confidence Intervals ; MMRM = Mixed Effect Repeated Measurement

Table 19: PedsQL™ Multidimensional Fatigue, Total Scale Score (ITT Population)

Total Scale Score: Child/Teen Report						
	Idebenone (N=30)		**Placebo (N=32)**		**Group Difference**	
Baseline mean (SD)	73.8 (14.2)		78.2 (12.3)			
Change from Baseline (MMRM)	Estimated Change (95% CI)	p-value	Estimated Change (95% CI)	p-value	Estimated Difference (95% CI)	p-value
Week 52	-2.71 (-6.44, 1.01)	0.1498	4.05 (0.63, 7.46)	0.0210	-6.76 (-11.8, -1.70)	0.0097
Fixed Effects: Baseline p=0.0061, Group p=0.0823, Visit p=0.9137, Group*Visit p=0.1716						
Total Scale Score: Parent Report						
	Idebenone (N=30)		**Placebo (N=33)**		**Group Difference**	
Baseline mean (SD)	72.9 (16.7)		73.9 (13.1)			
Change from Baseline (MMRM)	Estimated Change (95% CI)	p-value	Estimated Change (95% CI)	p-value	Estimated Difference (95% CI)	p-value
Week 52	-2.82 (-7.87, 2.23)	0.2685	3.32 (-1.09, 7.72)	0.1370	-6.14 (-12.8, 0.56)	0.0719
Fixed Effects: Baseline p=0.0106, Group p=0.1459, Visit p=0.8156, Group*Visit p=0.4753						

The number of patients (N) in each treatment group is the number of patients with Baseline assessments.
ITT = Intention to Treat; SD = Standard Deviation; CI = Confidence Intervals ; MMRM = Mixed Effect Repeated Measurement

Secondary endpoints on Clinical Global Impression of Efficacy and Tolerability and Satisfaction with Treatment

At Week 52, the majority of patients in each treatment group reported no change in the Clinical Global Impression of Efficacy, tolerability was reported as good in almost all patients and most of the patients were satisfied with the treatment in both groups (Table 20).

Table 20: Clinical Global Impression of Efficacy and Tolerability and Satisfaction with Treatment (ITT Population)

Results at Week 52	Idebenone n (%)	Placebo n (%)	Total n (%)	Cochran-Mantel-Haenszel Test p-value
Clinical Global Impression of Efficacy				
Deterioration	2 (8.0)	5 (16.7)	7 (12.7)	
No change	17 (68.0)	19 (63.3)	36 (65.5)	0.4391
Improvement	6 (24.0)	6 (20.0)	12 (21.8)	
Clinical Global Impression of Tolerability				
Poor	0	0 (0.0)	0 (0.0)	
Moderate	1 (4.0)	2 (6.7)	3 (5.5)	0.6674
Good	24 (96.0)	28 (93.3)	52 (94.5)	
Satisfaction with Treatment				
Satisfied	17 (68.0)	17 (56.7%)	34 (61.8)	
Neutral	7 (28.0)	12 (40.0%)	19 (34.5)	0.4264
Dissatisfied	1 (4.0%)	1 (3.3%)	2 (3.6)	

ITT = Intention to Treat

Tertiary end-points

Home-based assessment of PEF%p with the ASMA-1 device were also analysed using values obtained during a ± 3-week window around each hospital visit to derive values. Using this approach, the estimated difference between treatments was 7.24% 95%CI (0.82, 13.66) in favour of idebenone. The estimated differences between treatments were 7.24 95%CI (0.82, 13.66) and -0.06 95%CI (-0.16, 0.05) for FEV_1%p as measured with the ASMA-1 device at hospital visits and for IFR as measured by Spirometry, respectively.

Post hoc analyses: respiratory tract infection

There were 23 patients in the placebo group and 14 patients in the idebenone group and who reported respiratory tract infections. More patients reported infections of the upper respiratory tract in the placebo group (20 patients) than in the idebenone group (11 patients). The hazard ratio for AEs reported during treatment and classified as "upper respiratory tract infection" calculated using a CPHM favoured idebenone over placebo (HR=0.41; 95% CI (0.19, 0.91)).

Examination of Subgroups

PEF%p at Baseline (<40% or 40-80%), a pre-defined stratification factor

For the primary efficacy endpoint, change from baseline in PEP%p, there was an estimated mean treatment difference of -7.82% 95% CI (-13.2, -2.45) in the subgroup of patients with baseline PEF%p <40% while the difference found in the subgroup of patients with baseline PEF%p 40-80% was of 8.22% 95% CI (1.75, 14.69), similar to the one reported for the ITT population (6.52% 95%CI (1.98, 11.06)) (Table 21). For FVC%p, for the subgroup of patients with Baseline PEF%p <40%, the estimated mean treatment difference was -1.72% 95% CI (-10.5, 7.08) while this difference was 3.88% 95% CI (-0.21,

7.97) in favour of idebenone and consistent with the one reported for the ITT population (3.27% 95%CI (-0.43, 6.97)). However, there were only 12 patients with baseline PEF <40% predicted so these results for this subgroup should be interpreted with caution.

Table 21: Percent Predicted PEF by Subgroups Based on Baseline Percent Predicted PEF (ITT Population)

Subgroup: Baseline PEF%p <40%						
	Idebenone (N=5)		Placebo (N=7)		Group Difference	
Baseline mean (SD)	36.2 (4.1)		35.7 (4.2)			
Change from Baseline (MMRM)	Estimated Change (95% CI)	p-value	Estimated Change (95% CI)	p-value	Estimated Difference (95% CI)	p-value
Week 52	-15.52 (-19.80, -11.25)	<0.0001	-7.70 (-10.90, -4.51)	0.0004	-7.82 (-13.2, -2.45)	0.0093
Fixed Effects: Baseline p=0.0357, Group p=0.5106, Visit p=0.0016, Group*Visit p=0.0616						

Subgroup: Baseline PEF%p 40 to 80%						
	Idebenone (N=26)		Placebo (N=26)		Group Difference	
Baseline mean (SD)	56.8 (7.3)		59.1 (9.8)			
Change from Baseline (MMRM)	Estimated Change (95% CI)	p-value	Estimated Change (95% CI)	p-value	Estimated Difference (95% CI)	p-value
Week 52	-0.92 (-5.49, 3.64)	0.6854	-9.14 (-13.72, -4.56)	0.0002	8.22 (1.75, 14.69)	0.0139
Fixed Effects: Baseline p=0.5143, Group p= 0.0040, Visit p= 0.3927, Group*Visit p=0.0839						

ITT = Intention to Treat; SD = Standard Deviation; CI = Confidence Intervals ; MMRM = Mixed Effect Repeated Measurement

Other subgroups

The median age of the ITT population was 14 years and 2 subgroups based on age were defined: patients aged ≤14 years and patients aged >14 years. At Week 52, changes in PEF%p and in FVC%p were generally consistent with main results the in the 2 subgroups.

As the majority of patients (92%) were non-ambulatory at Baseline, the subgroup analyses based on ambulatory status were not performed.

At Week 52, changes in PEF%p and in FVC%p were generally consistent with main results in the group (n=28) who never used GCs [estimated difference PEF%p=6.19 95%CI (-3.39, 15.77) and FVC%p=3.34 95%CI (-3.48, 10.17)] and in the group (n=36) who had previously used GCs [estimated difference PEF%p=6.73 95%CI (-0.66, 14.13) and FVC%p=3.22 95%CI (-1.05, 7.49)]

Due the low number of patients [idebenone: placebo PCF<160L/s (6:1) and FVC<1L (5:1)] statistical analyses were not performed.

3.3.6.2.4. Ancillary analyses to DELOS

SNT-IR-009 REPORT ON ADDITIONAL ANALYSES OF INSPIRATORY FUNCTION FOR PATIENTS PARTICIPATING IN THE PHASE III DELOS CLINICAL TRIAL

Rationale

There were errors in the original analyses of inspiratory function. First, IFR was mistakenly understood to be equivalent to the ratio between the largest inspiratory flow during tidal breathing (V'I,max(t)) and

the largest inspiratory flow during an inspiratory forced vital capacity manoeuvre (V'I,max(FVC). This is the definition of the inspiratory flow ratio (i.e. V'I,max(t) / V'I,max(FVC)) and the IFR is equal to 1 minus this ratio. Second, it was noted during the data analysis that some Investigators had incorrectly transcribed the highest inspiratory flow ratio value (i.e. the "worst" value) onto the CRF rather than the lowest value (i.e. the "best"/ "most favourable" value). Thirdly, it was noted that at some visits more than three inspiratory flow manoeuvres were performed (up to five manoeuvres), but only three data sets were transferred to the CRF. In most of these cases, the data transcribed to the CRF from the three manoeuvres did not represent the "best" value (i.e. the lowest inspiratory flow ratio). Thus, in order to allow correct data analysis of the inspiratory component of the pulmonary function tests conducted during DELOS clinical trial, a separate database (the Inspiratory Flow Source Database) was constructed with ALL available inspiratory function data (three to five manoeuvres per visit for each patient) collected during the trial.

Methods

The change from baseline to week 52 in IFR as measured by spirometry, with IFR values at each study visit calculated as:

$$\text{Highest IFR [\%] achieved in a series of consecutive tests} = \left(1 - \frac{\text{The lowest V'I,max(t) reported in a series of consecutive tests}}{\text{The highest V'I,max(FVC) reported in a series of consecutive tests}}\right) \times 100\%$$

As a sensitivity analysis, the highest reported IFR value achieved during one individual test manoeuvre at each study visit was calculated as:

$$\text{Highest IFR [\%] achieved in one individual maneuver} = \left(1 - \frac{\text{V'I,max(t) in the Nth maneuver}}{\text{V'I,max(FVC) in the Nth maneuver}}\right) \times 100\%$$

In this current report IFR values have been multiplied by 100% in order to express the IFR values in terms of a percentage. The applicant presented other definitions as sensitivity analyses.

In this report the change from baseline to week 52 in V'I,max(FVC), as measured by spirometry, was included as an additional *post hoc* efficacy analysis. The largest V'I,max(FVC) value achieved in three and up to five manoeuvres per patient per visit was used in this analysis.

Basically, continuous data were summarized using the mean, SD, standard error of the mean (SEM), median, minimum (min) and maximum (max). Categorical data were presented in contingency tables with frequencies and percentages. All hypotheses tests and CI were two-sided and nominal statistical significance was declared for p-values below 5%. Other than for the primary analyses, all other statistical analyses were of an exploratory nature with no formal hypothesis testing, with p-values intended to aid interpretation only. There was no adjustment of the significance level for multiple testing. Graphical representations were used as appropriate.

These additional analyses of change from Baseline to Week 52 for IFR and for V'I,max(FVC) were performed on the ITT population, using the same statistical methods used for the primary endpoint (change from Baseline to Week 52 in PEF%p) of the SNT-III-003 (DELOS) clinical trial. Specifically, the estimated treatment difference between idebenone and placebo for the change from Baseline to Week 52 was calculated using a Mixed Model for Repeated Measurements (MMRM) using SAS 9.3, as described in the SNT-III-003 (DELOS) Clinical Study Report. For both the IFR and the V'I,max(FVC) analyses, all available data from all post-Baseline visits were used as response variables in the model. The treatment group, visit and the interaction between the treatment group and visit were used as fixed factors in the

model and the Baseline assessment used as a covariate.

The difference between idebenone and placebo at Week 52 was estimated based on the MMRM model using contrasts. The unstructured covariance structure was used for the estimation. If the unstructured covariance structure did not converge, compound symmetry was to be used instead.

Within subject coefficients of variation and correlations between inspiratory function data at Baseline and other Baseline respiratory function parameters (Spearman's rho) were calculated using R (R Core Team, 2015).

Results

At Baseline, the mean IFR was comparable in the idebenone and placebo treatment groups. The IFR increased during the study period by 2.8% among patients receiving idebenone and decreased by -3.0% among patients on placebo. The between-group difference at Week 52 was 5.8% 95% CI (0.3, 11.3). The between-group difference for the change from baseline to week 52 was 5.0% 95% CI (-1.2, 11.2) in favour of idebenone treatment in the sensitivity analyses.

At Baseline, the mean V'I,max(FVC) was similar in the idebenone and placebo treatment. During the study period, V'I,max(FVC) continued to decline in patients on placebo, with a change from baseline to Week 52 of -0.29 L/s 95% CI(-0.51, -0.08). Conversely, among patients in the idebenone group the V'I,max(FVC) remained stable throughout the study period with a change from baseline to Week 52 of 0.01 L/s 95% CI: (-0.22, 0.24) resulting in a between-group difference of 0.30 L/s 95% CI (-0.01, 0.62).

SNT-IR-010 ADDITIONAL ANALYSES OF THE EFFECT OF IDEBENONE IN REDUCING RESPIRATORY COMPLICATIONS IN PATIENTS PARTICIPATING IN THE PHASE III DELOS CLINICAL TRIAL

Rationale

Following the lower appearance of respiratory tract infections in patients allocated to idebenone compared to placebo in a *post hoc* analyses on the frequencies of in DELOS, this *post hoc* analysis of the SNT-III-003 (DELOS) clinical trial determined "bronchopulmonary adverse events" (BAEs) as medically important treatment-emergent adverse events (TEAEs) recorded in the SNT-III-003 (DELOS) safety database.

Methods

The duration of the BAEs was calculated from the starting date to end date recorded in the DELOS clinical trial safety database. If an event extended the period of study medication intake, the duration was only calculated until the last day of study medication intake. For events with unknown end date, the median length of events with identical preferred term was imputed. A study-independent pulmonologist determined the use of antibiotics listed as concomitant medications.

The numbers of patients in each treatment group reporting BAEs were compared statistically using the Fisher's Exact Test. The proportion of patients reporting BAEs at least once during the 52-week treatment period was analysed using the CPHM. The hazard ratios (HR) were calculated for idebenone over placebo using the day of the first event of a subject or the last day of study medication intake as censoring time if a patient had no events. Similarly, for all events, the mean cumulative frequency of BAEs versus time were analysed using a Proportional Means Regression analysis (Nelson, 2003; Lin et al., 2000). The Proportional Means Regression Model (PMRM) for recurrence data was used which allowed for multiple events per patient.

To elucidate the impact of baseline age, PEF%p and FVC%p and prior GCs use on the time to first BAE

as well as time to BAE, all factors were included in multivariate CPHM and PMRM, respectively.

The proportion of patients using antibiotics at least once during the 52-week treatment period was analysed using the CPHM. The mean cumulative frequency of systemic antibiotic use versus time was analysed using a Proportional Means Regression analysis (Nelson, 2003; Lin et al., 2000). HR were calculated for both models.

Results

The Proportion of Patients Reporting Treatment-Emergent BAEs, Number of Treatment-Emergent BAEs Reported and Duration of Treatment-Emergent BAEs

A total of six patients (19.4%) in the idebenone group reported seven BAEs compared to 17 patients (51.5%) reporting 28 BAEs in the placebo group (p=0.0096 for difference in patients experiencing BAEs). The resulting HR from the CPHM for the number of patients experiencing at least one BAE was 0.327 (95% CI: 0.129, 0.830; p=0.0187;) in favour of idebenone treatment. Likewise, PMRM resulted in a HR of 0.281 (95% CI: 0.123, 0.642; p=0.0026) also in favour of idebenone treatment (Figure 7). The mean duration of BAEs was slightly longer in the idebenone group compared to placebo; the median durations were comparable in the two treatment groups. The total number of days for which BAEs were reported in the idebenone group was 82 days and 222 days reported for the placebo group (Table 22).

Figure 7: Cumulative frequency for BAEs from baseline to week 52 (ITT population)

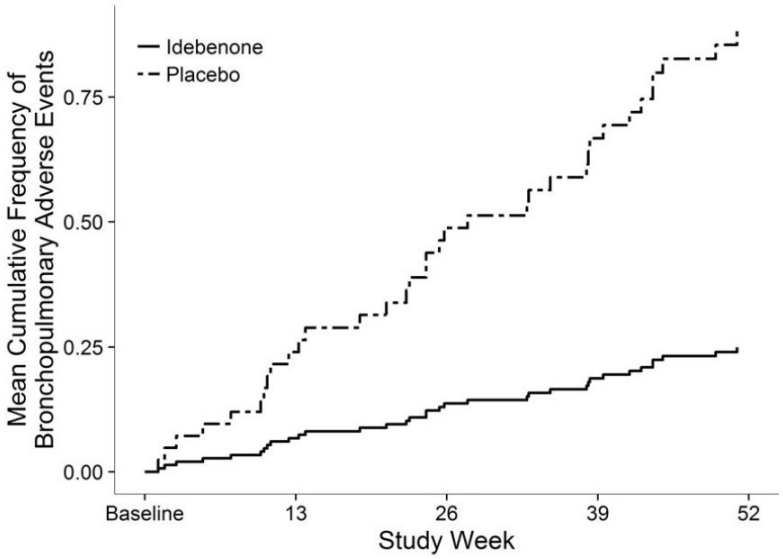


Table 22: Duration of BAEs (ITT population)

Treatment Group	Total Number of BAEs	Number of Patients	Duration [Days] of BAEs[1] Mean (SD); Median; Range	Total Duration [Days] per Group
Idebenone	7	6	11.7 (8.3); 9; 5-28	82
Placebo	28	17	7.9 (5.4); 8; 1-26	222

[1]Count of days for the period the patient has study medication
ITT = Intention to Treat; BAEs = Bronchopulmonary Adverse Events

Effect of Age, Baseline Respiratory Function and Previous Steroid use on BAEs

Patients in the placebo group who experienced BAEs were older than those in the idebenone group with BAEs (15.1 vs. 12.3 years old). PEF%p was comparable and largely overlapping between all groups. For

FVC%p at baseline patients in the placebo group who experienced BAEs had lower Baseline FVC%p compared to patients in the idebenone group with BAEs (Table 23).

None of the factors showed statistically significant influence on the model in in CPHM and PMRM.

Table 23: Influence of Age, Baseline PEF%p and baseline FVC%p on occurrence of BAEs (ITT population)

BAEs reported	Treatment	N	Baseline Age [years]	Baseline PEF%p	Baseline FVC%p
Yes	Idebenone	6	12.3 (1.5)	57.4 (8.3)	69.8 (12.4)
	Placebo	17	15.1 (2.2)	53.7 (12.9)	47.8 (18.0)
No	Idebenone	25	13.8 (2.9)	52.5 (10.6)	51.9 (14.7)
	Placebo	16	14.9 (2.8)	54.7 (13.8)	53.2 (22.1)

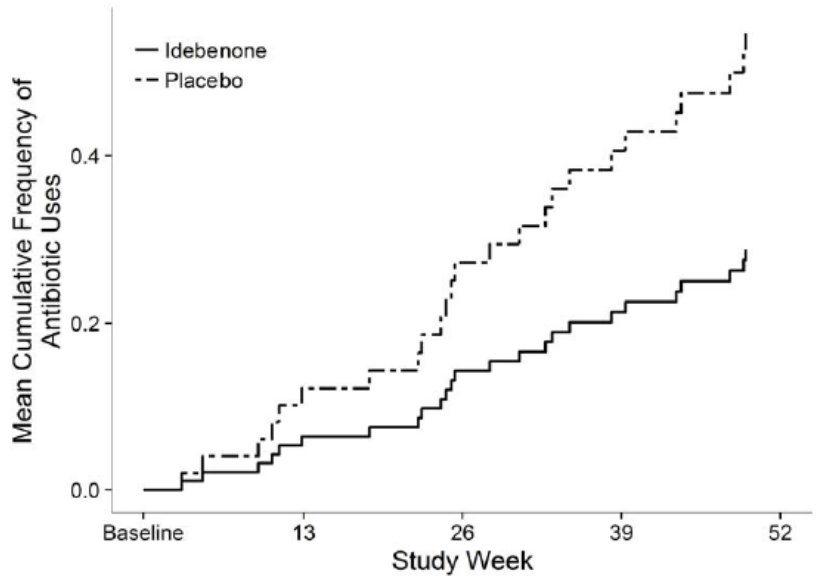
Data are mean (SD)
ITT = Intention to Treat; BAEs = Bronchopulmonary Adverse Events; Peak Expiratory Flow Percentage Predicted; FVC%p = Forced Vital Capacity Percentage Predicted.

Effect of Idebenone on Systemic Antibiotic Use

Regarding the number of patients using systemic antibiotics, as well as the duration of antibiotic use, seven patients (22.6%) reported eight periods of antibiotic use for the treatment of BAEs/respiratory tract infections in the idebenone group compared to 13 patients (39.4%) reporting 17 periods of antibiotic use in the placebo group. The mean and median duration of antibiotic use of approximately one week (6-8 days) was comparable between treatment groups. The cumulative duration of antibiotic use was 105 days among patients on placebo, compared to patients receiving idebenone (65 days).

The resulting HR from the CPHM for time to first use of antibiotics was 0.52 (95% CI: 0.207, 1.304; p=0.1631), favouring idebenone Investigating the cumulative frequency of use of antibiotics (allowing for multiple use per patient) by the PMRM, resulted in a HR of 0.52 (95% CI: 0.226, 1.217; p=0.1330) also in favour of idebenone treatment (Figure 8).

Figure 8: Cumulative use of systemic antibiotics for treatment of BAEs from baseline to week 52 (ITT population)



SNT-IR-015 INTEGRITY, CONSISTENCY AND ROBUSTNESS OF OUTCOMES OBTAINED IN THE PHASE III DELOS (SNT-III-003) STUDY

Rationale

PEF%p as Primary Endpoint

According to the applicant, PEF%p is one of the recommended respiratory function outcomes in the EMA DMD Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy (EMA/CHMP/236981/2011, Corr. 11) (Section 6.2). The applicant has extensively collaborated with clinical experts to further validate PEF%p as a clinically relevant respiratory function measure in DMD. The following summarises the main findings of this work as described in detail in various scientific publications.

The PEF-manoeuvre depends on efficient inspiration to allow efficient expiration, and as such is a measure of expiration directly assessing respiratory muscle strength. Several groups have now shown that PEF%p is a sensitive, reproducible and robust measure of total respiratory muscle force and function (e.g. Mayer et al., 2015; McDonald et al., 2018b; LoMauro et al., 2018; Ricotti et al., 2019). According to the applicant, these publications have shown that the rate of decline of PEF%p follows closely that of FVC%p.

Predictable (linear) decline is a pre-requisite for the use of PEF%p as a suitable endpoint, as, in order to show a treatment difference, placebo group has to decline predictably within the 1-year observation period. Inclusion criteria of the DELOS trial were set to ensure that the patients were in the respiratory function decline stage, i.e. PEF%p had to be abnormal (≤80%) at baseline. As claimed by the applicant, PEF%p can be measured reliably in the respiratory function decline phase in patients with DMD at age 10 to 18 years, as documented by the low within-subject variability (Table 24).

Table 24: Within-subject variability of respiratory function endpoints in the DELOS study

Respiratory function parameter	Within-subject coefficient of variation (%) (variability between screening and baseline)
PEF%p	6.97
FVC%p	6.69
FEV1%p	11.11
MIP%p[1]	18.00
MEP%p[1]	15.73

PEP%p = Peak Expiratory Flow Percentage Predicted; FVC%p = Forced Vital Capacity Percentage Predicted; FEV_1%p = Forced Expiratory Volume in 1 Second Percentage Predicted; MIP%p = percent of predicted maximal inspiratory pressure; MEP%p = percent of predicted maximal expiratory pressure
Source: Meier et al., 2017

Publications have shown that PEF%p declines earlier than FVC%p (LoMauro et al., 2018; McDonald et al., 2018b; Ricotti et al., 2019) and Ricotti et al., 2019 also showed specifically that PEF%p declined prior to the loss of ambulation. According to the applicant, this could indicate that PEF%p may be a more sensitive respiratory function measure across the continuum of ambulatory and non-ambulatory patients. This is particularly relevant to the patient population enrolled in DELOS (with a mix of ambulant and non-ambulant patients). However, it should be noted that according to baseline DELOS characteristics, 92% of the population was non-ambulatory as reported by the applicant.

Primary Objective and Primary Endpoint

Of note, PEF%p had not been used previously as a primary endpoint in an interventional trial in DMD. In fact, there had been no previous randomised placebo-controlled study in DMD with the objective of

investigating the respiratory function. All three respiratory function outcomes assessed in this study (PEF%p, FVC%p, FEV1%p) are listed on the EMA DMD Guideline as potential endpoint in DMD studies.

As claimed by the applicant, several studies have now shown PEF%p to be a sensitive, reproducible and robust measure of respiratory function, and that the rate of decline in PEF%p follows closely that of FVC%p and FEV1%p.The collinearity was also evidenced in DELOS, where the PEF%p results were supported by concordant results of FVC%p and FEV1%p, the other two respiratory function endpoints listed in the EMA DMD Guideline (see above). As described above, emerging evidence also indicated that PEF%p declines prior to the loss of ambulation whereas FVC%p declines later. For this reason, the applicant position is that PEF%p may be the most sensitive measure for the patient population (a mix of ambulant and non-ambulant patients) enrolled in DELOS. However, it should be noted that according to baseline DELOS characteristics, 92% of the population was non-ambulatory as reported by the applicant. As claimed by the applicant, PEF%p is now an established clinical measure routinely used in clinical practice to monitor respiratory function status of patients with DMD.

During the re-examination of the extension of indication of Raxone for DMD, there was a Scientific Advisory Group (SAG) meeting that was invited to discuss the external and the internal support (i.e. previous experience as well as results from the pivotal study and the mechanism of action of idebenone) for the relevance of the use of PEF%p as the primary efficacy endpoint in the studied population. The role of PEF%p as primary respiratory outcome measure for this trial was also discussed in the EMA Scientific Advisory Group meeting (SAG Meeting, 2018). The SAG was split on the use of PEF%p as the primary efficacy endpoint. Some experts stated that PEF%p was chosen based on the findings of the Phase II DELPHI study rather than on a scientific rationale. Other SAG members stated that PEF%p was indeed considered clinically meaningful and relevant to measure effects in the studied population. This position was based on the fact that PEF is currently used in clinical practice to monitor respiratory function, it correlates with other respiratory function parameters, and the decision to use it in the confirmatory trial was based on a finding from a phase II trial, which was not considered a problem methodologically.

The position of the applicant is that the design of the DELOS study took full account of the relevant regulatory guidelines and scientific knowledge available at the time of planning and adopted the CHMP/SAWP scientific advice. Therefore, the choice of the primary endpoint (PEF%p) was well-grounded both from regulatory and clinical perspective in the view of the applicant.

The rationale of the present report is to recapitulate the accumulated evidence on the consistency, robustness and clinical relevance of the DELOS clinical trial results. During a previous MAA (type II variation for extension of indication of Raxone) several issues arising from DELPHI and DELOS trials resulted in a negative opinion. The report SNT-IR-015 addresses the most relevant issues and is interpreted as a compilation of the responses from the previous procedure.

Methodological considerations

Study Integrity

DELOS was the first ever randomized study in DMD with respiratory function as the primary endpoint. The natural history of DMD, especially with respect to respiratory function evolution, was not well documented at the time of planning the study.

Concurrently emerging natural history data, as well as experiences encountered during the study conduct triggered decisions to amend the study protocol. In this context and compared to many other studies, DELOS did not incorporate an unusual number of amendments. The DELOS protocol underwent 7 protocol amendments during the 5 years course of the study that are displayed in the DELOS results section above.

Superiority: Statistical and Clinical Significance

Assessment of clinical relevance in a superiority study is a two-step process (EMA Guideline EMEA/CPMP/EWP/2158/99). In the first step, statistical significance is confirmed by using the $p<0.05$ criterion, and then, in the second step, clinical relevance is confirmed by showing the point estimate of the observed treatment difference exceeds the threshold of clinical relevance.

The primary endpoint of the DELOS trial, change in PEF%p over the 52-week study period, showed a between-group difference of 6.27% (95% CI: 0.61 to 11.93; p=0.0306) in favour of idebenone for the ITT population. Notably, the result was consistent across all analysis populations (ITT mITT and PP) and sensitivity analyses as presented before.

Results

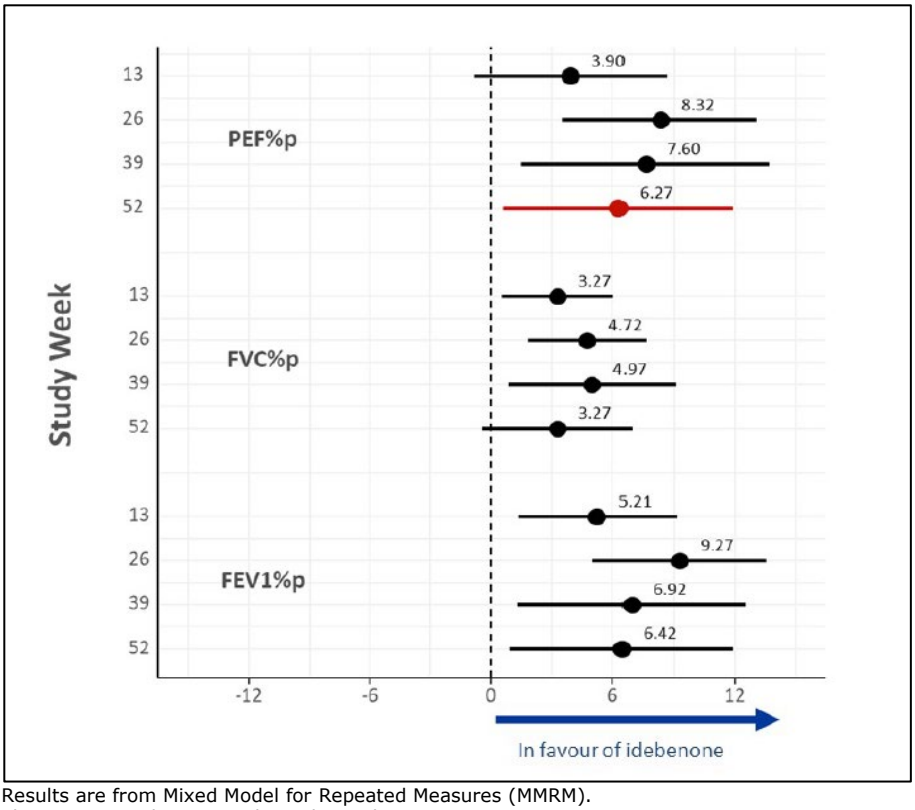
Consistency Across Other Respiratory Function tests

The treatment difference shown for the primary endpoint, change from baseline to Week 52 in PEF%p, was further supported by the results of other respiratory function endpoints (FVC%p and FEV1%p) (see previous results in above section).

The non-normalized results of PEF, FVC and FEV1 were consistent with the normalized results, a finding that has been interpreted by the applicant as that nominal statistically significant treatment differences (or strong trends) seen for all parameters and the treatment effects observed in DELOS were not biased/influenced by the normalisation to %p.

DELOS findings were consistent among the respiratory function parameters over the course of the study, as formally or nominally statistically significant treatment differences (or strong trends) were seen for PEF%p, FVC%p and FEV1%p at all study visits (Figure 9).

Figure 9: Treatment difference in change from baseline to all post-baseline study time points of the DELOS study for PEP%p, FVC%p and FEV_1%p



Results are from Mixed Model for Repeated Measures (MMRM).
The primary endpoint is indicated in red.
A lower limit of the 95% CI >0 indicates statistical significance.

PEP%p = Peak Expiratory Flow Percentage Predicted; FVC%p = Forced Vital Capacity Percentage Predicted; FEV_1%p = Forced Expiratory Volume in 1 Second Percentage Predicted

Supportive DELPHI Study

Clinical evidence for the proposed indication is not limited to the Phase III DELOS trial, but supported by outcomes from the Phase II DELPHI program. The limitations of interpretation attributable to the small sample size of the DELPHI study is acknowledged. However, DELPHI data on respiratory function outcomes are in line with the observations of the DELOS trial. Therefore, the applicant's position is that positive results for PEF%p were observed in two independent, randomised, placebo-controlled studies each with a follow-up period of 1 year (Table 25).

Table 25: Overview of DELPHI and DELOS study results

Study	Phase II DELPHI [1]		Phase III DELOS [2]	
Treatment	Idebenone	Placebo	Idebenone	Placebo
PEF%p change from Baseline at Month 12 (95% CI)				
Within-group	8.79 (-1.04, 18.62)	-9.83 (-23.74, 4.07)	-2.57 (-6.68, 1.54)	-8.84 (-12.73, -4.95)
Between-group	18.63 (1.59, 35.67) p=0.0354		6.27 (0.61, 11.93) p=0.0306	
FVC%p change from Baseline at Month 12 (95% CI)				
Within-group	-0.30 (-6.27, 5.68)	-7.87 (-17.73, 1.99)	-5.67 (-8.36, -2.99)	-8.95 (-11.47, -6.42)
Between-group	7.57 (-4.06, 19.20) p=0.1717		3.27 (-0.43, 6.97) p=0.0819	
FEV1%p change from Baseline at Month 12 (95% CI)				
Within-group	1.36 (-8.70, 11.41)	-5.10 (-17.02, 6.83)	-4.23 (-8.21, -0.25)	-10.65 (-14.43, -6.87)
Between-group	6.45 (-9.25, 22.16) p=0.3770		6.42 (0.92, 11.92) p=0.0230	

Data are estimate (95% CI) p-value
Results are from MMRM
ITT= Intention to Treat; SD = Standard Deviation; CI = Confidence Intervals; MMRM = Mixed Model for Repeated Measures; PEP%p = Peak Expiratory Flow Percentage Predicted; FVC%p = Forced Vital Capacity Percentage Predicted; FEV_1%p = Forced Expiratory Volume in 1 Second Percentage Predicted.
1 Analyses were done for the following subgroups ITT population, respectively:
- PEF%p ≤80% (n=8 in idebenone group and n=4 in placebo group),
- FVC%p ≤80% (n=8 in idebenone group and n=3 in placebo group),
- FEV1%p ≤80% (n=7 in idebenone group and n=5 in placebo group),

2 Analyses were done for the full ITT population - PEF%p ≤80% (n=31 in idebenone group and n=33 in placebo group).

Robustness of DELOS trial Primary efficacy result

Robustness of the Methodology Used to Calculate PEF%p

In DELOS, the formula of Godfrey (Godfrey et al, 1970) was used to calculate the percent of predicted for PEF (PEF%p) (Table 26). The Hankinson formula (Hankinson et al, 1999) was used to calculate the FVC%p and FEV1%p (Table 26). The use of these equations was defined in the SAP which was finalized prior to database lock. As a sensitivity analysis, PEF%p was calculated using the Hankinson equation and similar results were obtained (Table 27). The calculations were performed using height derived from ulna length and age obtained at clinic visits.

Table 26: Equations to calculate percent of predicted values (PEF%p) for PEF

PEF%p reference	Equation
Godfrey et al., 1970	PEF*100 / (- 422·8 + 5·288 x height)
Hankinson et al., 1999	PEF*100 / ((-0·5962 - (0·12357 * age)) + (0·013135 * (age^2)) + ((0·00024962 * (height^2))*1))

Note: Height was derived from ulna length.
Source: Godfrey: Godfrey et al., 1970; Quanjer et al., 1989 Hankinson: Hankinson et al., 1999
PEP%p = Peak Expiratory Flow Percentage Predicted

Table 27: Mixed model results for two normalization methods of PEF (ITT population)

Parameter	Idebenone Change at Week 52 (N = 31)	Placebo Change at Week 52 (N = 33)	Treatment Difference
PEF%p [1] Godfrey et al., 1970	-2.57 (-6.68, 1.54) 0.2154	-8.84 (-12.73, -4.95) <0.0001	6.27 (0.61, 11.93) 0.0306
PEF%p Hankinson et al., 1999	-4.22 (-8.45, 0.01) 0.0504	-10.80 (-14.82, -6.79) <0.0001	6.58 (0.74, 12.43) 0.0279

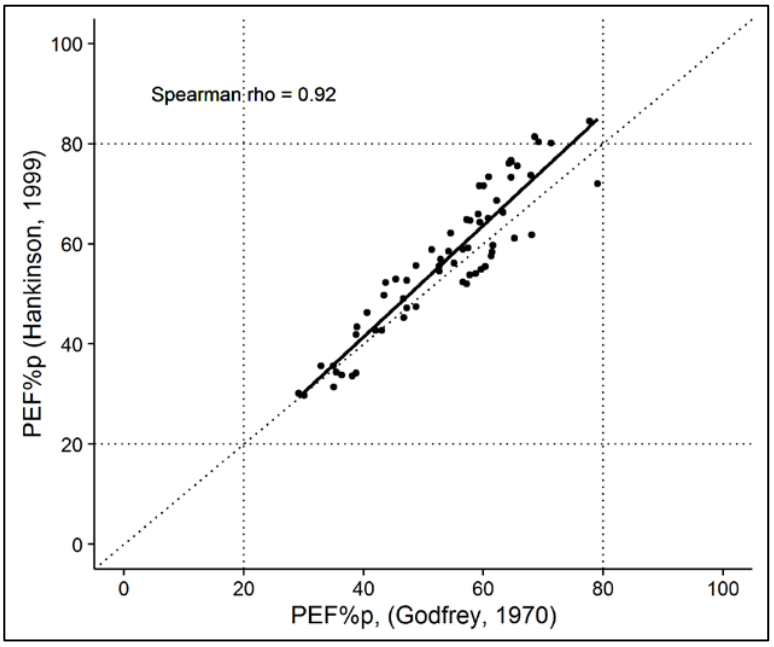
Data are estimate (95% CI) p-value
Results are from MMRM.
[1]Pre-specified primary analysis in DELOS
ITT= Intention to Treat; CI = Confidence Intervals; MMRM = Mixed Model for Repeated Measures; PEP%p = Peak Expiratory Flow Percentage Predicted

The two methods were well correlated as depicted in Figure 10 (Baseline). Of note, 4 patients (1 with idebenone and 3 with placebo) had PEF%p >80% at baseline with the Hankinson formula (Figure 10). These patients would have been excluded from enrolment if the Hankinson equation (instead of the Godfrey equation) had been used for the calculation of PEF%p at baseline (patients had to be ≤80% in PEF%p to fulfil the inclusion criterion).

A sensitivity analysis showed that even after excluding these 4 patients from the ITT population strong trends were observed for the between group difference in PEF%p at week 52: p=0.0735 (Godfrey) and p=0.0835 (Hankinson).

In addition, Week 52 changes went in opposite direction for 4 patients. In other words, a positive change observed with one formula resulted in a negative change with the other formula; in general, however such cases were few (6.3%) and the resulting differences were small.

Figure 10: Correlation of PEF%p at baseline by Godfrey and Hankinson formulas (ITT population)



PEF%p = percentage predicted peak expiratory flow. ITT = intention to treat.

The applicant position is that the use of the Godfrey equation to calculate PEF%p and Hankinson equation to calculate FVC%p and FEV1%p did not introduce undue bias to the study outcome, as analyses with alternative normalization equations resulted in comparable outcomes.

Robustness of Methodology Used to Estimate Height

The age range of patients in DELOS resulted in a high proportion of non-ambulant patients. Thus, measures of ulna length and arm span were pre-specified in the protocol along with that of standing height (when allowed by patient's condition) to obtain height measures for the calculation of %p values of respiratory function endpoints. As shown in Table 28, ulna length and arm span were recorded for essentially all patients at Screening/Baseline, while standing height was available in only 44% of DELOS patients.

Table 28: Available height parameters as recorded in CRFs (ITT population)

Height parameter	Screening or Baseline		
	Placebo	Idebenone	All
Ulna length	33 (100%)	31 (100%)	64 (100%)
Arm span	32 (97%)	31 (100%)	63 (98%)
Standing height	13 (39%)	15 (48%)	28 (44%)

Data are N (%)
ITT= Intention to Treat; CSF = Case report forms.

According to the applicant, the use of ulna length to determine patient's height is appropriate, did not introduce bias and reflects current clinical practice (Finder at al., 2017). Particularly as the patients with DMD are getting older, ulna length has become a standard methodology in routine clinical care to estimate patient height in the non-ambulatory phase of the disease.

SNT-IR-017 NORMALIZED RESPIRATORY FUNCTION VALUES IN THE PHASE III DELOS STUDY (SNT-III-003) OBTAINED USING EXPLORATORY PREDICTION EQUATIONS DEVELOPED FROM PATIENTS WITH DMD

Rationale

In this report, new exploratory prediction equations developed from patients with DMD were utilised in the calculation of %p values for PEF and FVC and results of the DELOS study were re-calculated with these new DMD patient-derived prediction equations.

The objective of this analysis was to demonstrate that the results for PEF%p and FVC%p were consistent for the DELOS study regardless of the prediction equation used to calculate the predicted values (i.e., equations based on the general population vs equations derived from DMD patients).

Methods

Exploratory prediction equations were generated using non-linear models. The evolution of PEF and FVC was estimated in patients with DMD as a function of age, using data from the Italian natural history study (LoMauro et al., 2018). The most recent data cut of this natural history study (from 2019) was used for the modelling. Separate models were fitted for relevant subgroups, based on the following factors that were expected to influence the evolution of respiratory function:

- GCs use (current user vs. previous user/GCs-naive),
- Age at loss of ambulation (<11 years vs ≥11 years).

In total, 103 DMD patients aged 9 to 21 years with 558 visits were included in the modelling. Mean values for normal PEF and FVC (in age steps of approximately 0.03 years) along with lower and upper confidence bands were to be obtained from the models for each subgroup.

For each subgroup, the mean values for normal PEF and FVC depend on age of the patient. The normal PEF and FVC values were intrapolated with linear methods to match the exact age at the time of the assessment for each subgroup with the following formula:

$$(1)\ m = m_0 + (m_1 - m_0)\ x\ (age - age_{bound})\ /\ age_{step},$$

where m0 and m1 are the mean values below and above the exact age, age is the exact age at the time of the assessment, agebound is the age category below the exact age and agestep is the interval between the age categories below and above the exact age.

Percent of predicted values (PEF%p and FVC%p) were then derived from the normal PEF and FVC values at the exact age, by dividing the observed PEF/FVC value by the corresponding predicted value, multiplied by 100%. Finally, treatment difference between idebenone and placebo for the PEF%p and FVC%p changes from baseline to week 52 were estimated using a MMRM as previously described.

Results

The patient disposition of the DELOS study is described in above in the assessment of the main study DELOS. The ITT population comprised 64 patients (31 treated with idebenone and 33 treated with placebo).

At Baseline, the mean (SD) PEF%p and FVC%p calculated with the exploratory prediction equations derived from DMD patients were 143.56% (40.73%) and 122.64% (32.02%), respectively.

According to the applicant, the results of the new analyses were comparable with those described in the DELOS CSR. A consistent separation between the idebenone and placebo groups was seen in PEF%p. The 1-year treatment difference for the change from baseline in PEF%p was 14.10% (95% CI: -2.38%, 30.57%) in favour of idebenone (Table 29). Comparable results were seen for FVC%p. The 1-year

treatment difference for the change from baseline in FVC%p was 5.18% (95% CI: -3.45%, 13.81%) in favour of idebenone (Table 29).

Table 29: MMRM results for PEF%p and FVC%p with two normalization methods (ITT population)

Estimate (95% CI)	Idebenone Change at Week 52 (N = 31)	Placebo Change at Week 52 (N = 33)	Treatment Difference
PEF%p (%)[1] Godfrey et al., 1970	-2.57 (-6.68, 1.54)	-8.84 (-12.73, -4.95)	6.27 (0.61, 11.93)
PEF%p (%)[2] Aliverti and LoMauro (Appendix 1)	0.14 (-11.79, 12.07)	-13.96 (-25.21, -2.70)	14.10 (-2.38, 30.57)
FVC%p (%)[1] Hankinson et al., 1999	-5.67 (-8.36, -2.99)	-8.95 (-11.47, -6.42)	3.27 (-0.43, 6.97)
FVC%p (%)[2] Aliverti and LoMauro (Appendix 1)	-1.64 (-7.93, 4.64)	-6.82 (-12.72, -0.92)	5.18 (-3.45, 13.81)

Data are estimate (95% CI)
Results are from MMRM
1Pre-specified analyses in DELOS CSR using general population-based normalisation
2New analyses using DMD population-based normalisation (Appendix 1)
ITT= Intention to Treat; CI = Confidence Intervals; MMRM = Mixed Model for Repeated Measures; PEP%p = Peak Expiratory Flow Percentage Predicted; FVC%p = Forced Vital Capacity Percentage Predicted

3.3.6.2.5. SYROS

Methods

This was a prospectively planned, retrospective cohort study conducted in patients who had completed the randomized, placebo-controlled DELOS study and were enrolled in the DELOS Expanded Access Programs (EAPs) [Named Patient Programs (DELOS-NPP) or Compassionate Use Programs (DELOS-CUP] in countries where such programs are feasible according to national laws and regulations.

The retrospective data collection started once patients and investigators had signed the data release agreement form. Available medical data recorded after the subject had completed Visit 6 (Month 12) of the DELOS study, until data from the most recent hospital visit available at the time of this data collection were retrieved from the patients' medical records and entered in the CRF by the principal investigator. Coded data, using the former DELOS patient number as patient identifier for the present study, were collected from the periods of time when the patients were treated in the EAPs, from periods preceding the enrolment into the EAPs and from periods after the EAPs, when available.

Study participants

Inclusion Criteria

- Patients who completed the DELOS study and are currently under the medical care of a study site in Belgium, Germany, the Netherlands and Switzerland.
- Patients who took idebenone as part of the EAPs (DELOS-NPP or DELOS-CUP) available in their country, following their participation to DELOS.
- Patients that have provided a signed Data Release Agreement (mandatory before any data can be collected by sites or the applicant).

Exclusion Criteria

There were no exclusion criteria defined for this study.

Treatments

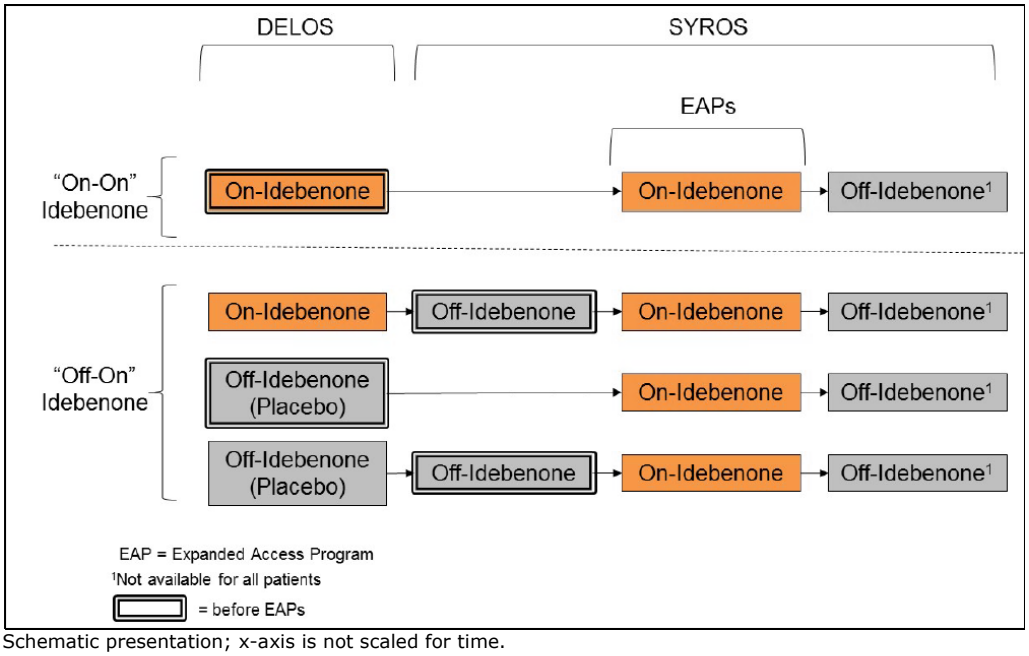
The SYROS protocol was set up to only define the data collection and analysis. Treatment with idebenone was given prior the SYROS data collection: according to the DELOS protocol during the DELOS study, and under the discretion of the treating physician during the EAP period. During their participation in the EAPs (DELOS-NPP or DELOS CUP), all patients were administered idebenone 150 mg film-coated tablets (2 x 150 mg tablets t.i.d with meals, total daily dose 900 mg).

The decision to participate in the EAP, and the initiation or discontinuation of idebenone treatment was under the sole discretion of the patient and his caregiver(s)/family and treating physician.

Idebenone treatment periods, referred to in this document as On-Idebenone periods were defined as any periods of time when patients received idebenone either during the randomized DELOS study (i.e. the idebenone treatment group of DELOS) or during the EAPs collected in the present SYROS study (Figure 11).

Idebenone free periods, referred to in this document as Off-Idebenone periods were defined as any periods of time when patients did not receive idebenone, either during the randomized DELOS study (i.e. the placebo group of DELOS) or after the completion of DELOS and collected in the present SYROS study (Figure 11).

Figure 11: Illustration of terminology used in this report



Schematic presentation; x-axis is not scaled for time.
"Off-On" Idebenone = On-Idebenone in the EAPs and Off-Idebenone before the EAPs
"On-On" Idebenone = On-Idebenone both in the EAPs and before the EAPs
EAP Expanded Access Program.

Objectives

Primary objective: to evaluate the long-term evolution of the respiratory function during idebenone treatment, compared to the evolution during idebenone-free periods in DMD patients who after completing the DELOS trial received idebenone treatment as part of Expanded Access Programs, DELOS-NPP and/or DELOS-CUP in their respective countries.

Secondary objective: to evaluate the effect of idebenone on clinically relevant disease milestones, medical events, treatment interventions and other relevant medications.

Outcomes/endpoints

SYROS original protocol

In the study protocol, the primary efficacy endpoint was planned to be the PEF assessed with the hospital spirometry, expressed as PEF%p. Predicted values were planned to be calculated in accordance with the DELOS study. FVC%p and FEV1%p were planned to be evaluated as secondary endpoints according to the protocol.

SYROS protocol included the following secondary endpoints:

Annual decline of (PEF%p, FEV_1%p and FVC%p) and time when PEF%p or FVC%p falls below different thresholds (50%, 40, 30%) for the first time (confirmed by a subsequent assessment below same threshold) for the subset of patients with values above that threshold at baseline (six secondary endpoints: three per each respiratory parameter) during three periods: DELOS study (idebenone-on or idebenone-free depending on randomization); idebenone-free periods after completing the DELOS study and before participating to the EAP in SYROS (all idebenone-free) and idebenone-on periods while participating to the EAPs in SYROS (all idebenone-on).

Time of treatment interventions using the time when the patient started assisted ventilation (non-invasive nocturnal, non-invasive daytime or continuous invasive); any other treatment intervention to treat the DMD-related respiratory dysfunction and any other treatment intervention to treat DMD.

Time to and frequency of clinically relevant medical events including BAE after a centralized and blinded review conducted after data collection, hospitalizations due to respiratory causes and hospitalizations for any reason

Time to and duration of use of other relevant medications including antibiotics, GCs, other medications to treat the respiratory function or DMD.

Changes from SYROS protocol to SAP

Because SYROS was considered a real-world data collection and availability of the data was not known at the time of the finalization of the SAP, the general approach to define the primary objective was specified with the following hierarchy depending on the availability of the data as follows:

1. Primary comparison based on SYROS data only:

    • In case the majority (>90%) of patients have evaluable On-Idebenone and Off-Idebenone periods in the SYROS study (i.e., after the completion of the DELOS study), the evolution of respiratory function will be compared between these two periods from the SYROS study.

2. Primary comparison based on On-Idebenone periods from SYROS compared with On-Idebenone or Off-Idebenone periods from SYROS or DELOS:

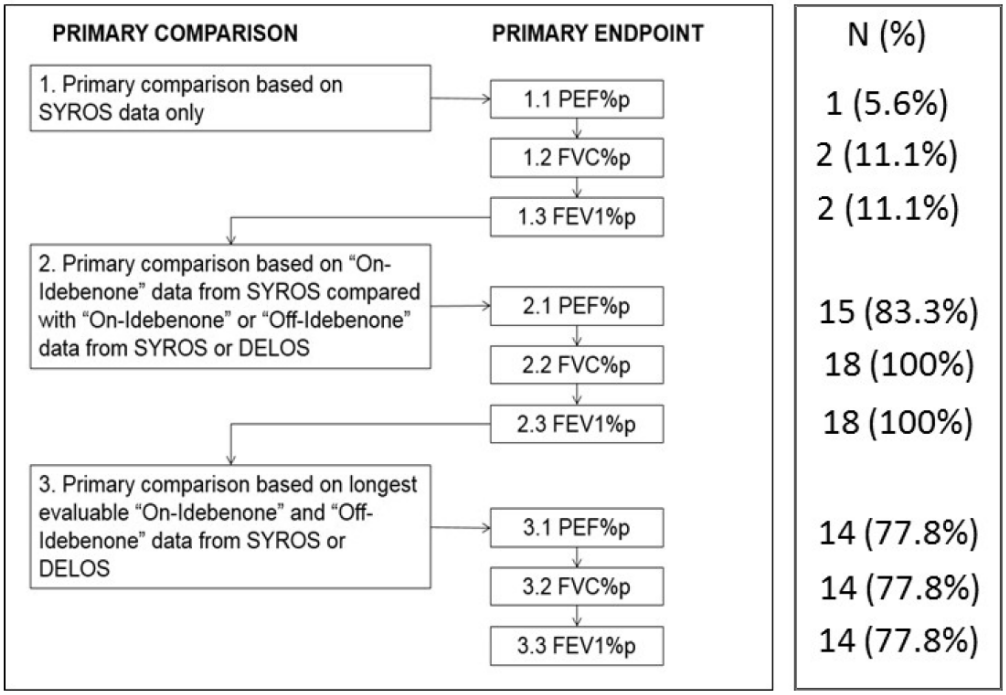
    • In case the majority (>90%) of patients have evaluable On-Idebenone periods but no evaluable Off-Idebenone periods in the SYROS study, the primary objective is to evaluate the evolution of respiratory function between the On-Idebenone period in SYROS and the preceding evaluable period from either SYROS or DELOS study (control period). This control period can be either an On-Idebenone or an Off-Idebenone period, depending on which preceded the On-Idebenone period in SYROS. The evolution of the respiratory function will be compared for "On-On" Idebenone periods and "Off-On" Idebenone periods, as further illustrated in Figure 12.

3. Primary comparison based on longest evaluable On-Idebenone and Off-Idebenone periods from SYROS or DELOS:

• In case the majority (>90%) of the patients do not have evaluable On-Idebenone periods in the SYROS study, the evolution of the respiratory function will be evaluated between the longest evaluable On-Idebenone period (either DELOS or SYROS) and the longest evaluable Off-Idebenone period (either DELOS or SYROS).A period was considered evaluable if there was a baseline and at least two post-baseline assessments of respiratory function outcomes (FVC%p, PEF%p or FEV1%p). Each of these three assessments had to be at least 6 months apart from each other during the period.

With the SAP the approach for the primary comparison of change in respiratory function was amended and the primary endpoint was planned to be specified following a hierarchy depending on the availability of the data. The first combination of comparison and endpoint that can be evaluated for at least 90% of the patients was planned be used as the primary analysis of this study. According to Figure 12, analysis scenario 2.2. fulfilled this prespecified criterion, defining FVC%p as the primary variable. PEF%p, FEV1%p were analysed as secondary efficacy variables.

Figure 12: Decision algorithm for the primary comparison and primary endpoint



PEP%p = Peak Expiratory Flow Percentage Predicted; FVC%p = Forced Vital Capacity Percentage Predicted; FEV_1%p = Forced Expiratory Volume in 1 Second Percentage Predicted

Primary efficacy endpoint:

Annual Change in FVC%p using a comparison of On-Idebenone periods from SYROS (i.e., during EAPs) to preceding evaluable periods (either On-Idebenone or Off-Idebenone) from SYROS or DELOS (i.e. before EAPs) (primary analysis).

Secondary endpoints:

- Annual Change in FVC%p using a comparison based on On-Idebenone periods from EAPs or DELOS compared with Off-Idebenone periods from DELOS, after DELOS but before EAPs or after EAPs (secondary analysis).
- Annual change in PEF%p, FEV1%p using primary and secondary comparison analyses defined for the primary efficacy endpoint.
- Time to clinically relevant worsening defined as the time from baseline to first relative decline of at least 10% in FVC%p confirmed by the next consecutive assessment which also had to show at least

10% relative decline from baseline. The endpoints assessing the time to FVC%p or PEF%p thresholds of 30%, 40% or 50% were removed from SAP.
- Time to clinically relevant treatment interventions (as previously defined).
- Time to and frequency of BAEs (as previously defined)
- Time to and frequency of hospitalizations due to respiratory causes or hospitalization for any reason
- Time to use of other relevant medications (as previously defined).

Sample size

No formal sample size calculation was done. All patients who received idebenone in the EAPs and consented to the SYROS study by signing the data release agreement form were included in the analyses.

Randomisation and blinding

Not applicable for this retrospective study

Statistical methods

Analysis Populations

Three analysis populations were defined for this study:

- All Available Analysis Set: all patients who were enrolled to the DELOS study, of which only a subset of patients were treated with idebenone under the EAPs. This data was used to describe the disposition of the patients.
- ITT Analysis Set: all patients who were included in the ITT population of the DELOS study and were enrolled to the present SYROS study. The ITT analysis set was used for the primary efficacy analyses.
- Safety analysis set: the safety analysis set included all patients enrolled in the present study.

Primary efficacy endpoint: definition of periods for comparisons

The primary comparison was determined to be for FVC%p using a comparison of On-Idebenone periods from SYROS (i.e., during EAPs) to preceding evaluable periods (either On-Idebenone or Off-Idebenone) from SYROS or DELOS (i.e. before EAPs).

- On-Idebenone period during EAPs: annual rate of change in the respiratory function was estimated for the longest consecutive On-Idebenone period during the EAP.
- Preceding On-Idebenone period: annual rate of change in the respiratory function was estimated for the last evaluable On-Idebenone period before EAPs, i.e. during the idebenone treatment period of DELOS.
- Preceding Off-Idebenone period: annual rate of change in the respiratory function was estimated for the last evaluable Off-Idebenone period before EAPs. This Off-Idebenone period could be the placebo treatment period of DELOS or Off-Idebenone period after DELOS but before EAPs. If the placebo treatment period of DELOS was followed by an Off-Idebenone period before EAPs, these two periods were combined.

For the secondary comparison, based on On-Idebenone periods from EAPs or DELOS compared with Off-Idebenone periods from DELOS, after DELOS but before EAPs or after EAPs:

- On-Idebenone period: annual rate of change in the respiratory function was estimated for the longest consecutive On-Idebenone period in DELOS or in the EAPs. If the idebenone treatment period of DELOS was followed by an On-Idebenone period in the EAPs, these two periods were combined.

- Off-Idebenone period: annual rate of change in the respiratory function was estimated for the longest consecutive Off-Idebenone period in DELOS, after DELOS but before the EAPs or after the EAPs. This Off-Idebenone period could be the placebo treatment period of DELOS, Off-Idebenone period before EAPs or Off-Idebenone period after EAPs. If the placebo treatment period of DELOS was followed by an Off-Idebenone period before EAPs, these two periods were combined.

A patient may have had temporary interruptions during the idebenone treatment while participating in the EAPs. Interruptions less than 10% of the total duration of the On-Idebenone periods around the interruption were not considered as interruptions.

Primary efficacy endpoint

Primary analysis of the primary efficacy endpoint

The annual rate of change in FVC%p within each period was estimated using random coefficient regression models. The random coefficient regression models included the respiratory function values from each period as response data, age at the time of the assessment as a factor and the baseline value at the beginning of the first period as a covariate. The models included random slopes and intercepts and autoregressive covariance structure (AR(1)) was used within subjects. Four separate models were fitted: two separate models for "On-On" Idebenone analysis (a separate model for On-Idebenone period during the EAPs and a separate model for On-Idebenone period before the EAPs) and two separate models for "Off-On" Idebenone analysis (a separate model for On-Idebenone period during the EAPs and a separate model for Off-Idebenone period before the EAPs). The annual changes in the FVC%p were estimated from the models along with 95% CIs. Baseline values used in the statistical analyses were estimated with linear regression models based on data from preceding or subsequent periods regardless the baseline value was available or not (baseline real values were replaced by predicted ones with sole exception of DELOS baseline values which were never replaced).

Furthermore, sensitivity analyses were conducted: analysis using random coefficient regression models similar to above, but without the baseline covariate; analysis using a single random coefficient regression without baseline covariate, with indicator variables for the period (before EAPs versus during EAPs) and analysis with the primary model, excluding patients one at a time to evaluate the influence of individual patients on the primary analysis.

Secondary analysis of the primary efficacy endpoint

Further secondary analysis of the respiratory function endpoints was conducted using the longest consecutive On-Idebenone and Off-Idebenone periods (scenario #3 Figure 12).

Because the On-Idebenone periods were considerably longer than the Off-Idebenone periods, the changes in On-Idebenone periods were additionally compared to external data from untreated patients enrolled in the CINRG-DNHS. This external comparison was not included in the SAP and was considered a *post hoc* analysis.

The annual rates of changes as a function of time since baseline were calculated for both the longest consecutive On-Idebenone period and longest consecutive Off-Idebenone period with random coefficient regression models similar as described above. However, the baseline value was not used as a covariate in these analyses and the covariance structure was set as unstructured, in agreement with analyses conducted earlier on the CINRG-DNHS.

The changes were estimated separately for each two-year bin (years 1-2, 2-3, 3-4, 4-5, 5-6), in order to evaluate the long-term evolution in the respiratory function outcomes. The bin had to include at least 2 assessments, at least 6 months apart from each other.

Secondary efficacy endpoints:

Primary and secondary analysis for PEF%p and FEV_1%p were done using same method described for the primary efficacy endpoint.

In the SYROS protocol, it was originally planned to evaluate the time when PEF%p or FVC%p falls below different thresholds (50%, 40, 30%) for the first time during the three described periods (during DELOS, before EAP and during EAP). These analyses were planned to use the longest consecutive idebenone treatment period and idebenone-free period from SYROS or DELOS (comparison strategy #3 Figure 12). HR between the patients randomized to idebenone or placebo in DELOS were planned to be estimated for each period using a CPHM.

For the analyses of other secondary endpoints:

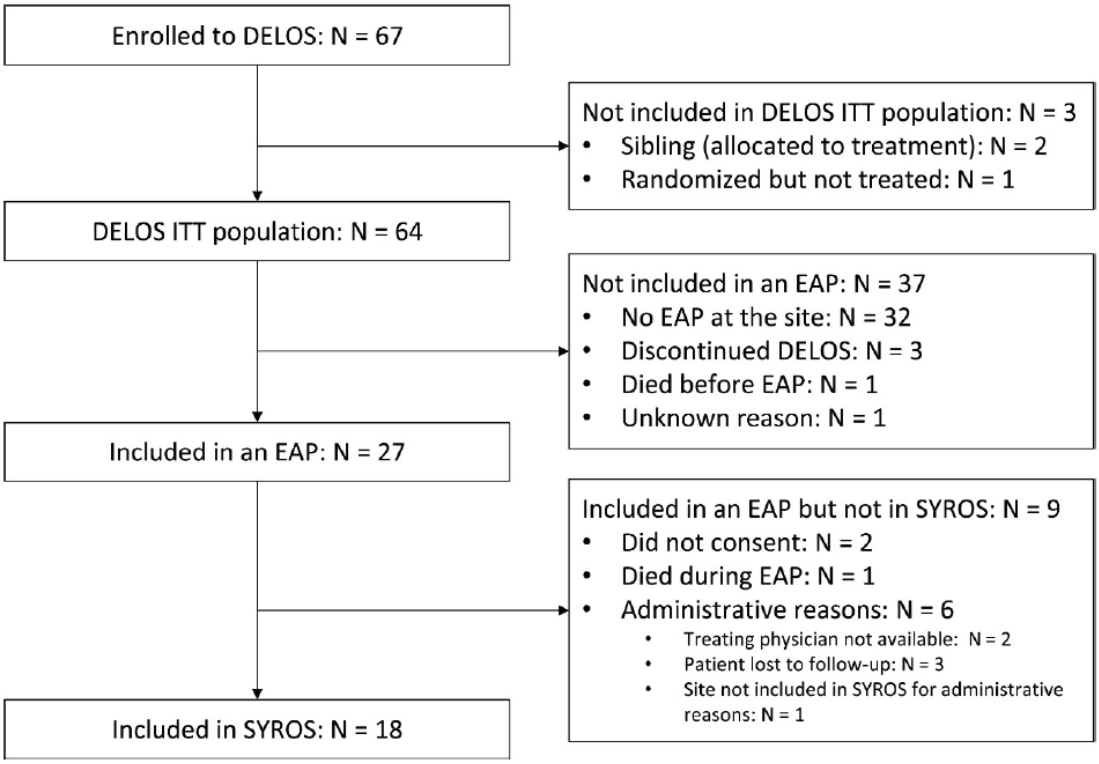
- The time-to-event endpoints were planned to be evaluated using the Kaplan-Meier methodology. For this analysis, the longest consecutive on-idebenone and off-idebenone periods from SYROS or DELOS were used (comparison strategy #3 Figure 12). HR between these periods were planned to be estimated for each period using CPHM. Time to clinically relevant worsening in FVC%p was evaluated using this approach.
- The mean cumulative frequency of recurrent events were to be estimated using a PMRM for recurrence data using the longest consecutive On-idebenone and Off-idebenone periods. Time to appearance of BAES was to be estimated using this model.

Results

Participant flow

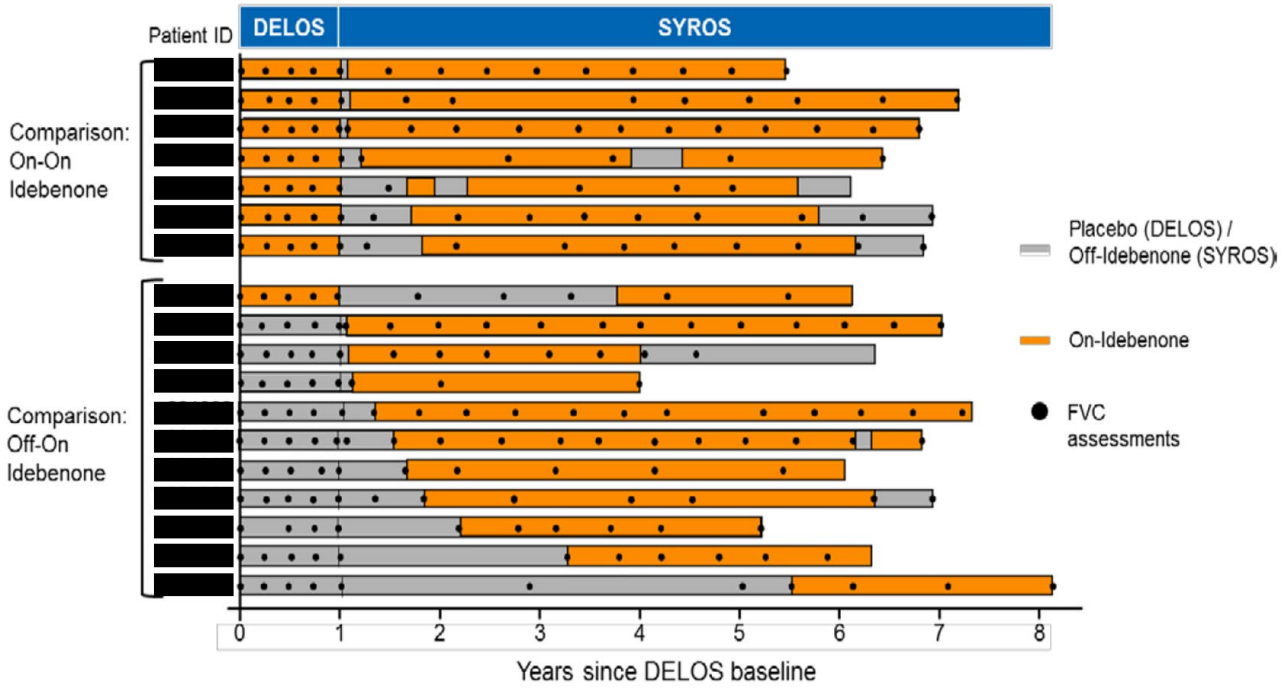
The disposition of patients in the DELOS study and EAPs contributing to the SYROS study is summarized in Figure 13. All 18 patients were included in the safety analysis set and in the ITT analysis set. Altogether 11 of the 18 patients were not treated with idebenone before the EAP (i.e., the last evaluable period before the EAP was Off-Idebenone) while the remaining 7 patients were On-Idebenone prior to starting the EAP (i.e., the last evaluable period before the EAP was On-Idebenone).

Figure 13: Patient disposition in DELOS, Expanded Access Programs and SYROS



EAP = Expanded Access Program, ITT = Intent-to-Treat
32/37 patients were not included in an EAP due to lack of availability of an EAP in the country (two EAP requested by treating physician but not implemented and two EAPs were not requested by treating physician).

Figure 14: Summary of treatment, follow-up and respiratory function (FVC) assessments in DELOS and SYROS



Treatment assignment, On-Idebenone or Off-Idebenone, is colour coded by orange and grey bars, respectively. Patients are grouped into comparison "On-On" Idebenone and "Off-On" Idebenone according the procedure described before. In addition to the FVC assessments shown in the figure, baseline values for FVC%p in SYROS were estimated with linear regression models as described before
FVC = Forced Vital Capacity.

Recruitment

Regarding the periods of recruitment and follow-up, the applicant reported the following dates:

- First subject signed Data Release agreement: 29 August 2017
- Period covered by this data collection: 30 August 2010 (first hospital visit included in this data collection) to 13 March 2018 (last hospital visit included in this data collection)
- Database lock date: 01 June 2018
- Final report date: 14 May 2009

Participants were recruited 5 centres in 4 countries (Germany, The Netherlands, Belgium, and Switzerland).

Conduct of the study

GCP Statement

According to the applicant, the study was conducted according to the protocol, the latest version of the Declaration of Helsinki, with the current requirements for Good Pharmacoepidemiology Practices (GPP Guideline 2015), Good Pharmacovigilance Practices (GVP-Module VI) and with local laws and regulations.

Protocol amendments

The original protocol dated 21 July 2017 was finalized prior to any data collection in SYROS. There were no amendments to the protocol.

Changes from Protocol to SAP

The SAP (dated 30 May 2018) detailed the analyses to be performed for the SYROS study and was completed prior to data base lock and before the author or reviewers of the SAP had access to the study data. The following key changes to the analyses described in the study protocol were outlined in the SAP:

- Due to the real world data collection approach and upon consultation with the independent DSMB statistician, a decision algorithm based on data availability was developed for the selection of the primary endpoint and primary comparison. Based on the algorithm, FVC%p was selected as the primary endpoint (see Outcomes/endpoints section).
- The secondary endpoints assessing the time to FVC%p or PEF%p thresholds of 30%, 40% or 50% were removed, as time to these endpoints depends on the length of the assessment period, i.e. they were more likely to occur later in the study and would be difficult to evaluate with the present study design (see Outcomes/endpoints section). Instead, the time to 10% relative decline, another well accepted, and clinically relevant threshold of respiratory function decline was added as an endpoint.
- Deaths were not analysed, because data from patients who die cannot be collected in a retrospective setting (the patients who died cannot provide informed consent).

Changes from SAP

Based on the actual data that could be retrieved from patients' medical records for this retrospective study, a number of analyses that were detailed in the SAP were not performed due to insufficient amount of data or were done with a methodology different from SAP:

- The analyses comparing annual rates of changes between the On-Idebenone periods and the Off-Idebenone periods in SYROS (i.e., not using data from the DELOS study) were not performed, as such data from evaluable periods were available from only two patients.

- Separate random coefficient regression models were fitted for each evaluable period instead of a single model using indicator variables for the periods. The reason for this was that the models using indicator variables did not converge. However, in case the models using indicator variables converged by simplifying the model (i.e., by excluding baseline covariates), these analyses are presented in this report as sensitivity analyses.
- The analysis of the longest consecutive On-Idebenone and Off-Idebenone period was analysed as overlapping 2-year bins, in order to evaluate the temporal changes.
- In addition, because the On-Idebenone periods were considerably longer than the Off-Idebenone periods, data from untreated patients from the CINRG-DNHS were used as external comparator groups to compare the annualized rate of change in respiratory function outcomes to the annualized change for the On-Idebenone periods of this study (see statistical analysis section).
- Time-to-event analyses were not conducted for endpoints with small numbers of events. Instead, the number of patients with these events were tabulated for each period (longest consecutive On-Idebenone and Off-Idebenone period). In addition, the rate of events (number of events divided by the duration of the period) and cumulative durations of events were tabulated.

Baseline data

Participants enrolled in SYROS were on averaged one year younger than those in DELOS, less frequently in a non-ambulatory status (Table 30) and had higher average FVC%p and PEF%p values at DELOS baseline than patients in the DELOS ITT population (Table 31).

The longest consecutive On-Idebenone periods (n=18) and Off-Idebenone periods (n=14) were compared in the secondary analysis. Patients contributing to On-Idebenone periods had a median age of 14.9 years while median age of the patients contributing to the Off-Idebenone periods was 14 years (Table 32) and had lower baseline FVC%p and PEF%p values than those contributing to Off-Idebenone periods (Table 31).

Table 30: Summary of key demographic characteristics in DELOS and SYROS at DELOS baseline (primary analyses)

	DELOS ITT population N=64	DELOS ITT patients not included in SYROS N=46	SYROS ITT Analysis Set N=18
Age, years			
mean (SD)	14.3 (2.7)	14.7 (2.6)	13.3 (2.7)
median	14.0	14.7	12.9
minimum-maximum	10.1, 19.0	10.3, 19.0	10.1, 18.5
Estimated Height (cm) [a]			
mean (SD)	160.0 (12.0)	161.4 (9.8)	156.4 (16.3)
median	160.6	161.5	156.0
minimum-maximum	129.4, 181.2	141.5, 179.6	129.4, 181.2
Prior glucocorticoid use, n (%)			
Non-user	28 (43.8)	21 (45.7)	7 (38.9)
Previous user	36 (56.3)	25 (54.3)	11 (61.1)
Time since last glucocorticoid use, years			
n	36	25	11
mean (SD)	3.7 (2.1)	3.5 (2.2)	4.1 (1.9)
median	3.5	2.8	4.2
minimum, maximum	0.9, 8.9	0.9, 8.9	1.3, 6.9
Ambulatory Status, n (%)			
Ambulatory	5 (7.8)	2 (4.3)	3 (16.7)
Non-ambulatory	59 (92.2)	44 (95.7)	15 (83.3)
Age at loss of ambulation, years			
n	59	44	15
mean (SD)	9.7 (1.5)	9.6 (1.4)	10.0 (1.7)
median	9.5	9.3	9.8
minimum, maximum	7.2, 14.3	7.2, 14.3	7.8, 12.8

Results shown reflect results at the baseline of the DELOS study.
[a]Height was derived from ulna length

Table 31: Baseline respiratory function (ITT Analysis Set) (primary and secondary analyses)

	FVC%p	PEF%p
DELOS Baseline (Figure 6, panel A)		
DELOS ITT population (n=64)		
mean (SD)	52.8 (18.1)	53.8 (11.8)
median	53.0	56.9
minimum-maximum	22.6, 96.4	29.1, 79.1
SYROS ITT Analysis Set (n=18)		
mean (SD)	58.7 (17.6)	58.5 (10.2)
median	61.5	59.1
minimum-maximum	22.6, 96.4	30.1, 77.7
Baseline of the primary analysis (Figure 6, panel B)		
SYROS, Off-Idebenone before EAP (n=11)		
mean (SD)	54.3 (21.3)	56.9 (12.4)
median	56.0	57.2
minimum-maximum	22.6, 96.4	30.1, 77.7
SYROS, On-Idebenone before EAP (n=7)		
mean (SD)	65.0 (9.2)	61.0 (5.1)
median	65.7	60.9
minimum-maximum	50.2, 81.5	52.7, 68.6
Baseline of the secondary analysis (Figure 6, panels C, D)		
SYROS, longest Off-Idebenone period (n=14) [a]		
mean (SD)	53.9 (21.0)	56.1 (16.8)
median	56.9	58.6
minimum-maximum	12.6, 96.4	7.3, 77.7
SYROS, longest On-Idebenone period (n=18) [b]		
mean (SD)	47.0 (19.8)	43.8 (15.6)
median	49.0	44.8
minimum-maximum	13.6, 81.5	15.4, 68.6

[a]FVC%p and PEF%p values missing from one patient (n=13)
[b]PEF%p value missing from one patient (n=17)
EAP = Expanded Access Program; ITT= Intention to Treat; SD = Standard Deviation; PEP%p = Peak Expiratory Flow Percentage Predicted; FVC%p = Forced Vital Capacity Percentage Predicted

Table 32: Summary of key demographic characteristics at the baseline of the secondary analysis (ITT Analysis Set)

	Longest Off-Idebenone period, N=14	Longest On-Idebenone period, N=18
Age, years		
mean (SD)	14.7 (3.4)	14.9 (3.3)
median	14.0	14.9
minimum-maximum	10.5, 20.1	10.1, 22.0
Estimated Height (cm) [a]		
mean (SD)	160.2 (17.4)	164.0 (16.2)
median	158.3	169.1
minimum-maximum	129.4, 181.2	138.3, 186.5
Prior glucocorticoid use, n (%)		
Non-user	5 (35.7)	7 (38.9)
Previous user	8 (57.1)	11 (61.1)
Current user	1 (7.1)	0 (0)
Time since last glucocorticoid use, years		
n	8	11
mean (SD)	4.8 (2.9)	5.9 (2.1)
median	4.6	5.9
minimum, maximum	1.3, 10.0	3.5, 10.4
Ambulatory Status, n (%)		
Ambulatory	1 (7.1)	3 (16.7)
Non-ambulatory	13 (92.9)	15 (83.3)
Age at loss of ambulation, years		
n	13	15
mean (SD)	9.9 (1.6)	10.0 (1.7)
median	9.8	9.8
minimum, maximum	7.8, 12.8	7.8, 12.8

[a]Height was derived from ulna length; data missing from one patient in the Off-Idebenone column (n=13).
ITT= Intention to Treat

Numbers analysed

The primary efficacy analysis included 18 participants (11 in OFF-ON Idebenone group and 7 in the ON-ON Idebenone group). The secondary efficacy analysis included 18 On-Idebenone periods and 14 Off-Idebenone periods as 4 patients did not have a valuable Off-Idebenone periods.

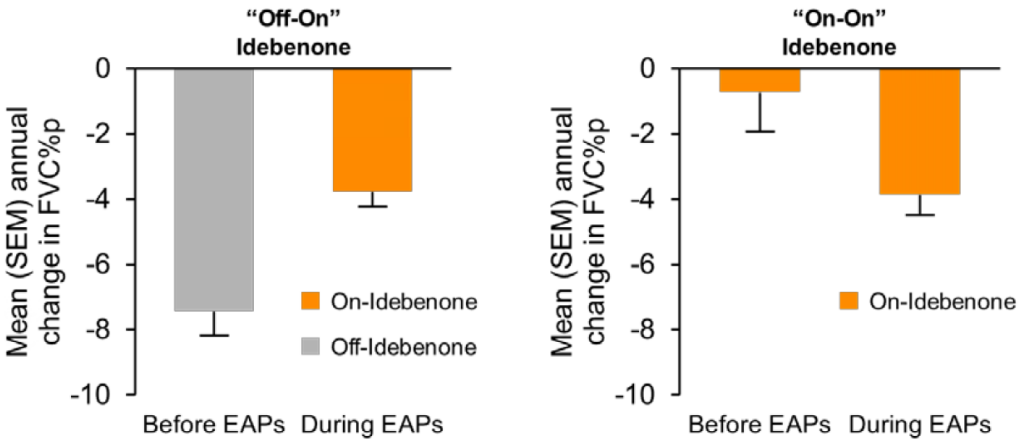
Outcomes and estimation

Primary Efficacy Endpoint

Primary Analysis of the Primary Efficacy Endpoint

In the subset of 11 patients who were in the OFF-ON group, the annual rate of change in FVC%p was reduced from an estimated rate of -7.4% (95% CI -9.1, -5.8) while Off-Idebenone to -3.8% (95% CI -4.8, -2.8) while On-Idebenone (comparison "Off-On" Idebenone) (Figure 15). In the remaining 7 patients in the ON-ON group, the annual rate of decline in FVC%p was reduced from an estimated rate of -0.7 (95% CI -3.7, 2.2) during the On-Idebenone period before the EAPs and further reduced during the On-Idebenone period in the EAPs, with an estimated rate of and -3.9 (95% CI -5.4, -2.3). Similar results were obtained in the three planned sensitivity analyses.

Figure 15: Annual rate of change in FVC%p (ITT Analysis Set, random coefficient regression model) – primary analysis of the primary endpoint



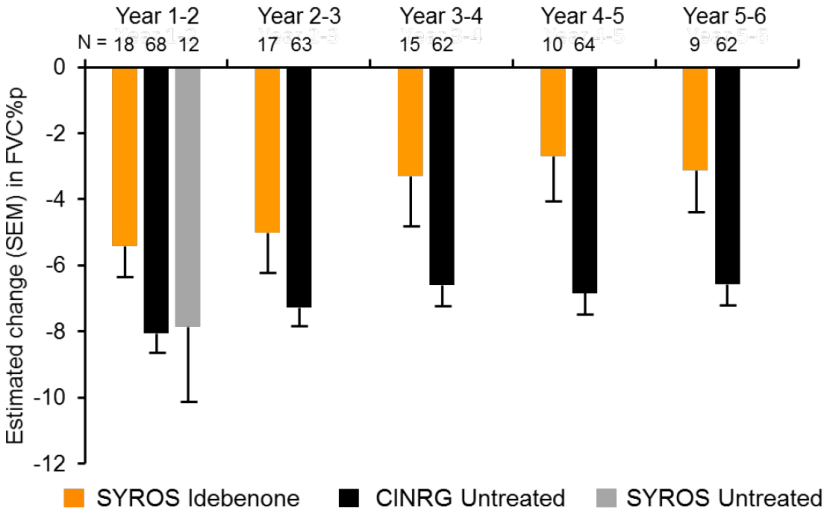
EAP = Expanded Access Program
SEM = standard error of the mean; FVC%p = forced vital capacity expressed as percent of predicted; ITT = Intention to Treat.
"Off-On" Idebenone = On-Idebenone in the EAPs and Off-Idebenone before the EAPs (n = 11)
"On-On" Idebenone = On-Idebenone both in the EAPs and before the EAPs (n = 7)

Secondary Analysis of the Primary Efficacy Endpoint

All 18 patients had evaluable data during the first bin (years 1-2), while 9 patients provided data at years 5-6. During the first two years of the longest consecutive On-Idebenone period, the average annual rate of change in FVC%p was -5.4% (n=18/18). Comparable rate of change was seen during years 2-3 (n=17/18). During years 3-4 (n=15/18), 4-5 (n=10/18) and 5-6 (n=9/18), the average annual rates of changes ranged between -3.3% and -2.7 (Figure 16).

In the untreated patients extracted from the external comparator dataset (n=62-68), the rate of decline was stable regardless of the baseline FVC%p, with average annual rate of change in FVC%p ranging between -8.1% and -6.6%, i.e. showing numerically greater decline in each bin compared to the On-Idebenone periods in DELOS/SYROS (Figure 16).

Figure 16: Annual rate of change in FVC%p by time during the longest consecutive On-Idebenone period (ITT Analysis Set, random coefficient regression model) and in the external comparator dataset (random coefficient regression model) – secondary analysis



CINRG = Cooperative International Neuromuscular Research Group Duchenne Natural History Study; SEM = standard error of the mean; FVC%p = forced vital capacity expressed as percent of predicted; ITT = Intention to Treat.

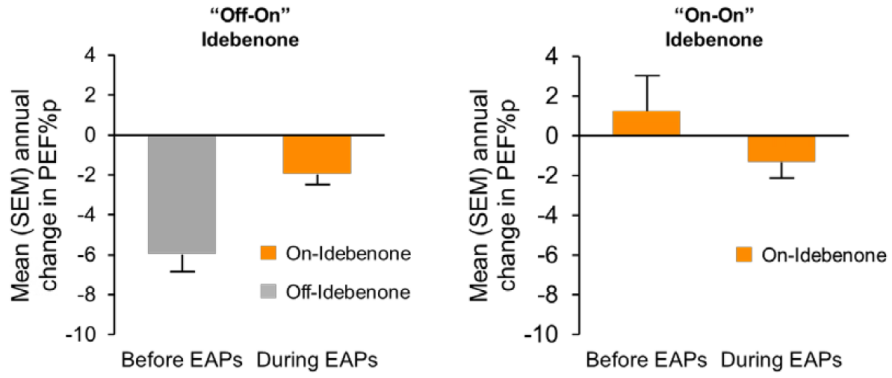
Secondary Efficacy Endpoints

1. Change in PEF%p

Primary analysis of the secondary efficacy endpoint

In the subset of 9 (9/11) patients included in the OFF-ON group, the estimated annual rate of change in PEF%p was reduced from -5.9% (95% CI -8.0%, -3.9%) during the Off-Idebenone period to -1.9% (95% CI -3.2%, -0.7%) during the On-Idebenone period (Figure 17). In the remaining 6 (6/7) patients included in the ON-ON group, the estimated annual rate of change in PEF%p was increased to 1.3 (95% CI -3.3, 5.8) before the EAPs and decreased from 1.3 (95% CI -3.4, 0.8) during the EAPs (Figure 17).

Figure 17: Annual rate of change in PEF%p (ITT Analysis Set, random coefficient regression model) – primary analysis of a secondary endpoint



EAP = Expanded Access Program; data shown as mean (SEM)
SEM = standard error of the mean; PEF%p = peak expiratory flow expressed as percent of predicted; ITT = Intention to Treat.
"Off-On" Idebenone = On-Idebenone in the EAPs and Off-Idebenone before the EAPs (n = 9)
"On-On" Idebenone = On-Idebenone both in the EAPs and before the EAPs (n = 6)

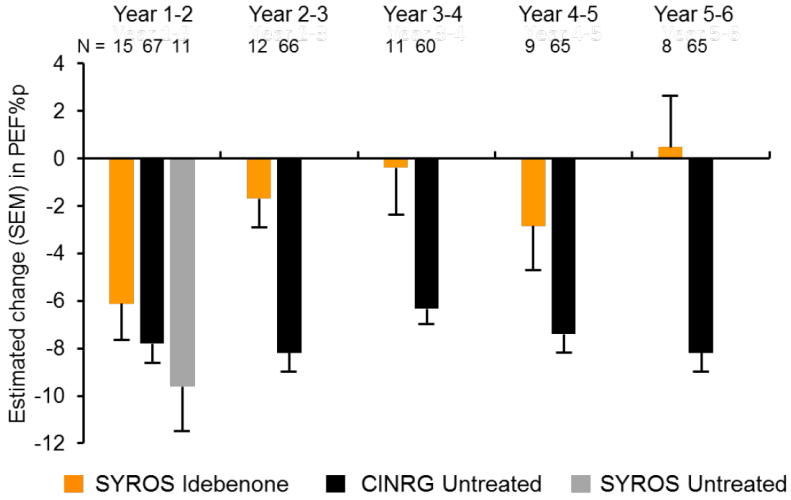
Secondary analysis of the secondary efficacy endpoint

15 patients had evaluable data during the first bin (years 1-2), while 8 patients provided data at years 5-6. During the first two years of the longest consecutive On-Idebenone period, the average annual rate

of change in PEF%p was -6.1% (n=15/15). During the subsequent years, up to years 5-6, the average annual rates of changes ranged between -2.9% and -0.5% (n=8-12 out of 15) (Figure 18).

In the untreated patients extracted from the external comparator dataset (n=60-67), the average annual rate of change in PEF%p ranged between -8.2% and -6.3% (Figure 18).

Figure 18: Annual rate of change in PEF%p by time during the longest consecutive On-Idebenone period (ITT Analysis Set, random coefficient regression model) and in the external comparator dataset (random coefficient regression model) – secondary analysis



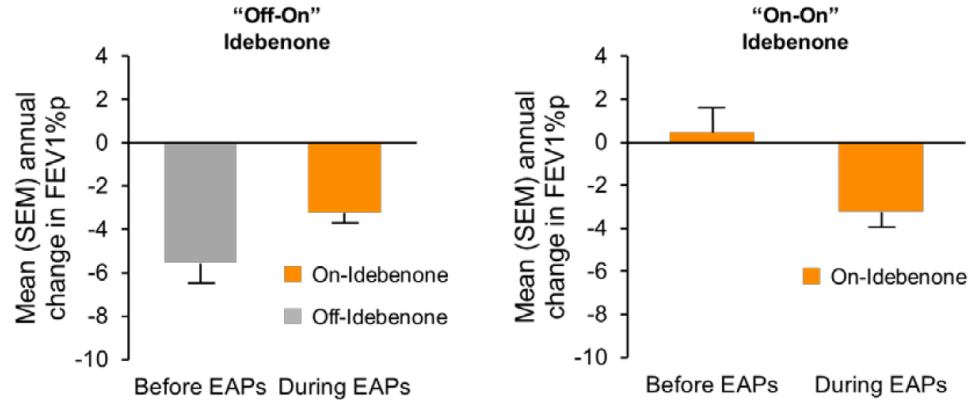
CINRG = Cooperative International Neuromuscular Research Group Duchenne Natural History Study; SEM = standard error of the mean; PEF%p = peak expiratory flow expressed as percent of predicted; ITT = Intention to Treat.

2. Change in FEV1%p

Primary analysis of the secondary efficacy endpoint

In the subset of 11 patients in the OFF-ON group, the estimated annual rate of change in FEV1%p was reduced from -5.5% (95% CI -7.6%, -3.5%) during the Off-Idebenone period to -3.2% (95% CI -4.3%, -2.1%) during the On-Idebenone period (Figure 19). In the remaining 7 patients in the ON-ON group, the estimated annual rate of change in FEV1%p was increased to 0.5% (95% CI -2.4%, 3.3%) before the EAPs and decreased from -3.2 (95% CI -4.9, -1.5) during the EAPs (Figure 19).

Figure 19: Annual rate of change in FEV1%p (ITT Analysis Set, random coefficient regression model) – primary analysis of a secondary endpoint



EAP = Expanded Access Program; data shown as mean (SEM)
SEM = standard error of the mean; FEV_1%p = forced expiratory volume in 1 second percentage predicted; ITT = Intention to Treat.
"Off-On" Idebenone = On-Idebenone in the EAPs and Off-Idebenone before the EAPs (n = 11)
"On-On" Idebenone = On-Idebenone both in the EAPs and before the EAPs (n = 7)

Secondary analysis of the secondary efficacy endpoint

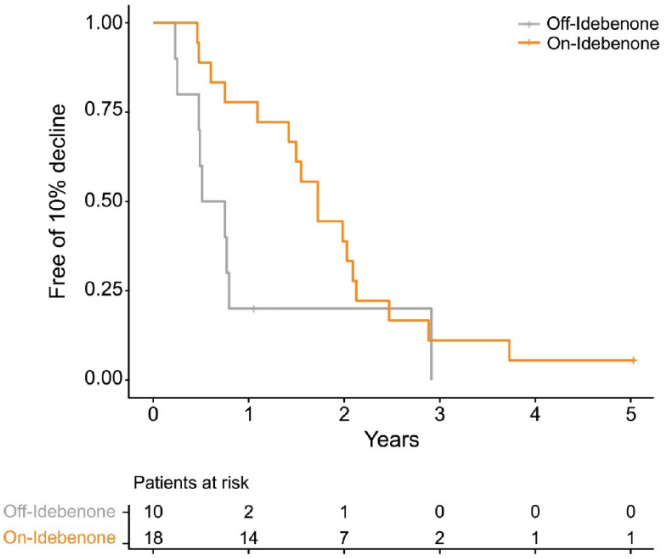
Annual decline in FEV_1 was consistently smaller at each year of treatment during the On-Idebenone periods than in the untreated patients in the external comparator dataset from the CINRG-DNHS.

3. Clinically relevant worsening

Altogether 10 out of 14 patients had a baseline assessment at the beginning of the longest consecutive Off-Idebenone period, while all 18 patients had a baseline assessment at the beginning of the longest consecutive On-Idebenone period. The 4 patients who did not have a baseline assessment at the beginning of the Off-Idebenone period were excluded from this analysis.

Most patients (9 out of 10 during the Off-Idebenone period and 17 out of 18 during the On-Idebenone period) had a decline of at least 10%. 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 (Figure 20). This difference is equal to a HR estimate of 0.44 95% CI (0.19, 1.02).

Figure 20: Time to first decline of at least 10% (relative) in FVC%p (ITT Analysis Set)



FVC%p = forced vital capacity percentage predicted; ITT = Intention to Treat.

4. Clinically Relevant Treatment Interventions

The use of assisted ventilation was evaluated for the longest consecutive Off-Idebenone and On-Idebenone periods. Altogether 12 out of the 18 patients started assisted ventilation. Ten patients started nocturnal ventilation only, while 2 patients started also day time ventilation after starting nocturnal ventilation.

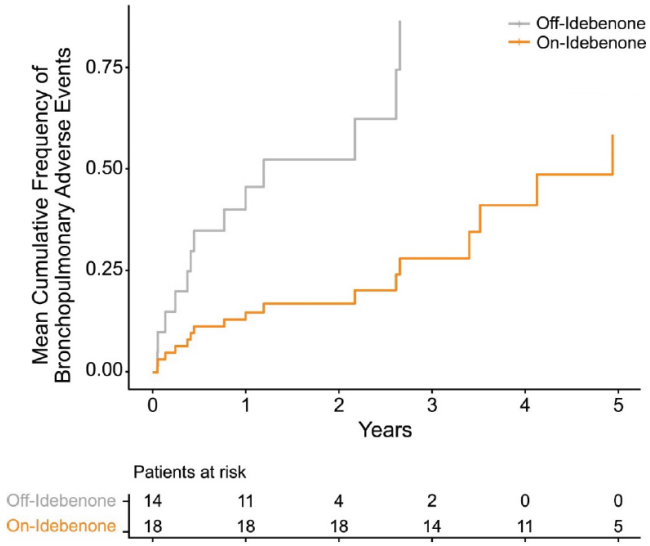
During the Off-Idebenone period, 1 patient started nocturnal ventilation and 1 day-time ventilation, while 10 patients started nocturnal ventilation and 1 patient both nocturnal and day-time ventilation during the On-Idebenone period. Due to the long duration of the On-Idebenone periods, it was expected that eventually the patients start using assisted ventilation during this period.

5. Bronchopulmonary Adverse Events (BAEs)

During the Off-Idebenone period, 5 patients (35.7%) reported 9 BAEs, i.e. 0.33 events per person-year of follow-up. During the On-Idebenone period, 6 patients (33.3%) reported 8 BAEs, i.e. 0.10 events per person year of follow-up. The cumulative duration of the BAEs was 48 days (0.6 days per person year of follow-up) during the On-Idebenone period and 105 days (3.8 days per person year of follow-up) during the Off-Idebenone period. Durations of BAEs with incomplete start and/or stop dates during the On-Idebenone period (4 BAEs) and Off-Idebenone period (1 BAE) were derived from the mean duration of BAEs within the same period.

The cumulative frequency of the BAEs as a function of time was evaluated using a PMRM. This analysis showed that the BAEs were more frequent during the Off-Idebenone period, compared with the On-Idebenone period (Figure 21). The difference in the cumulative frequencies is equal to a HR of 0.32 95% CI (0.11, 0.92).

Figure 21: Cumulative frequency of BAEs as function of time (ITT Analysis Set)



Data are shown up to a point when at least 3 patients were at risk. ITT = Intention to Treat.

6. Hospitalizations due to Respiratory Causes or Hospitalizations for Any Reason

During the Off-Idebenone period, there were 4 and 13 hospitalizations for respiratory infection or related disorder and for any reason, respectively. The corresponding event rates were 0.15 and 0.48 events / person-year. During the On-Idebenone period, there were 5 and 24 hospitalizations for respiratory infection or related disorder and for any reason, respectively. The corresponding event rates were 0.06 and 0.29 events / person-year.

7. Use of other relevant medications

During the Off-Idebenone period, 3 patients reported 4 events of antibiotics use, i.e. 0.15 events per person year. During the On-Idebenone period, 3 patients reported 3 events of antibiotics use, i.e. 0.04 events per person year.

Summary of main efficacy results

The following tables summarise the efficacy results from the studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the

benefit risk assessment (see later sections).

Table 33: Summary of efficacy for the DELPHI trial

Title: A Phase IIa double blind, randomized, placebo controlled, single centre study to assess the efficacy and tolerability of idebenone in 8–16-year-old males with cardiac dysfunction associated with Duchenne Muscular Dystrophy				
Study identifier	Protocol SNT-II-001 EudraCT Number: 2005-002520-33			
Design	Double blind, randomised, placebo controlled, single centre			
	Duration of main phase:		52 weeks (12 months)	
Hypothesis	Superiority: to determine if idebenone treatment, compared to placebo, delays the decline in cardiac function, muscle strength and/or respiratory function.			
Treatments groups	Idebenone		Oral administration with meals 150 mg t.i.d. (450 mg /day) 12 months 13 patients	
	Placebo		Oral administration with meals t.i.d. 12 months 8 patients	
Endpoints and definitions	Primary endpoint	Cardiac function	Change from baseline to Week 52 in peak systolic radial strain of the LV inferolateral wall, assessed by CDMI	
	Other endpoints	Respiratory function	Change from baseline to week 52 in PEF%p, FVC%p, FEV1%p	
Database lock	5 October 2007			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (ITT) All subjects who were randomized to study drug treatment, using both the LOCF and OC data sets (full analysis dataset). Time point: 52 weeks			
Descriptive statistics and estimate variability	Treatment group		idebenone	placebo
	Number of subjects		13	8
	Cardiac function: peak systolic radial strain of the LV inferolateral wall [%] (Mean ± SD)		Absolute change: LOCF 15.3 ± 13.0 OC 17.3 ± 13.1 (n=11)	Absolute change: LOCF 7.8 ± 11.20 OC 7.5 ± 12.0 (n=7)
	Respiratory function: (Mean ± SD) PEF%p FVC%p FEV1%p		Absolute change (LOCF/OC): 2.8 ± 13.8 -1.2 ± 6.4 -2.0 ± 9.2	Absolute change (LOCF/OC): -8.5 ± 13.8 2.0 ± 11.0 -0.4 ± 9.2
Effect estimate per comparison	Primary endpoint Cardiac function; absolute change		Comparison groups	Idebenone vs. placebo
			difference in means between groups (LOCF)	7.45
			90% CI	-2.16; 17.06

		P-value (2-sample t-test)	1-sided: 0.098 2-sided: 0.196
	Other endpoints Respiratory function PEF%p	Comparison groups	Idebenone vs. placebo
		difference in means between groups (LOCF)	11.3
		90% CI	0.6, 22.1
		P-value (2-sample t-test)	1-sided: 0.042 2-sided: 0.083
	Other endpoints Respiratory function FVC%p	Comparison groups	Idebenone vs. placebo
		difference in means between groups (LOCF)	-3.2
		90% CI	-9.7, 3.4
		P-value (2-sample t-test)	1-sided: 0.793 2-sided: 0.414
	Other endpoints Respiratory function FEV_1%p	Comparison groups	Idebenone vs. placebo
		difference in means between groups (LOCF)	-1.6
		90% CI	-8.8, 5.5
		P-value (2-sample t-test)	1-sided: 0.651 2-sided: 0.698
Notes	The DELPHI patient population was a mix of GCs users and GCs non-users. The study included both ambulatory and non-ambulatory patients, and only a fraction of patients (12 out of 21) had abnormal respiratory function (i.e. PEF%p ≤80%) at baseline.		

%p = percent of predicted; CI = confidence interval; FEV_1 = forced expiratory volume 1 second; FVC = forced vital capacity; GCs: glucocorticoid; ITT = intent-to-treat; LOCF = last observation carried forward; LV = left ventricular; MMRM = mixed model for repeated measures; N = number of subjects; OC = Observed cases; PEF = peak expiratory flow; SEM = standard error of the mean; SD = standard deviation; t.i.d = three times per day
[a] Estimated change and estimated difference from MMRM

Table 34: Summary of efficacy for the DELOS trial

Title: A Phase III double-blind, randomised, placebo-controlled study of the efficacy, safety and tolerability of idebenone in 10–18-year-old patients with Duchenne Muscular Dystrophy			
Study identifier	Protocol SNT-III-003 Eudract No.:2009-012037-30 ClinicalTrials.gov Identifier: NCT01027884		
Design	Phase III double-blind, randomized, placebo-controlled, parallel-group, multicenter study in patients with DMD		
	Duration of main phase:	52 weeks (12 months)	
Hypothesis	Superiority: To assess the efficacy of idebenone, compared to placebo, in delaying the loss of respiratory function		
Treatments groups	Idebenone		Oral administration with meals 300 mg t.i.d. (900 mg/day) 12 months (52 weeks) 31 patients (ITT)
	Placebo		Oral administration with meals t.i.d 12 months (52 weeks) 33 patients (ITT)
Endpoints and	Primary endpoint	PEF%p	Change from baseline to week 52 in PEF%p assessed by hospital-based spirometry

definitions	Secondary respiratory function endpoints	PEF%p, by home-based assessment FVC%p PCF (L/s) MIP%p MEP%p	Change from baseline to week 52
Database lock	5 May 2014		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) ITT population included all randomised patients (excluded 2 siblings who were allocated to treatment assignment rather than randomised) who received at least 1 dose of study drug and had at least 1 post-baseline assessment of PEF. Time point: 52 weeks (12 months)		
Descriptive statistics and estimate variability Estimate (95% CI) from MMRM	Treatment group	idebenone	placebo
	Number of subject	31	33
	PEF%p using hospital spirometry	-2.57 (-6.68, 1.54)	-8.84 (-12.73, -4.95)
	PEF%p by home-based Assessment	-2.48 (-7.39, 2.44)	-9.32 (-14.2, -4.40)
	FVC%p using hospital spirometry	-5.67 (-8.36, -2.99)	-8.95 (-11.47, -6.42)
	PCF (L/s) as measured by spirometry	0.14 (-0.15, 0.43)	-0.02 (-0.29, 0.25)
	MIP%p using the MicroRPM	-7.17 (-11, -3.35)	-5.28 (-8.87, -1.69)
	MEP%p using the MicroRPM	-1.79 (-4.44, 0.85)	-3.01 (-5.48, -0.55)
Effect estimate per comparison		Comparison groups	Idebenone vs placebo
	Primary endpoint		
	PEF%p, using hospital spirometry	Estimated difference 95% CI P-value	6.27 0.61, 11.93 0.0306
	Secondary respiratory endpoints		
	PEF%p, by Home-based Assessment	Estimated difference 95% CI P-value	6.84 -0.15, 13.83 0.0548
	FVC%p using hospital spirometry	Estimated difference 95% CI P-value	3.27 -0.43, 6.97 0.0819
	PCF (L/s) using hospital spirometry	Estimated difference 95% CI P-value	0.16 -0.24, 0.56 0.4287

	MIP%p using the MicroRPM	Estimated difference 95% CI P-value	-1.89 -7.16, 3.37 0.4754
	MEP%p using the MicroRPM	Estimated difference 95% CI P-value	1.22 -2.41 4.85 0.5047
Notes	Only the secondary respiratory parameters for DELOS were listed here. No relevant difference was seen in any other secondary endpoint.		

%p = percent of predicted; CI = confidence interval; PCF = Peak Cough Flow; FVC = forced vital capacity; ITT = intent-to-treat; MMRM = mixed model for repeated measures; PEF = peak expiratory flow;
[a]estimated with a proportional means regression model

Table 35: Summary of efficacy for the SYROS trial

Title: Retrospective cohort study assessing the long-term respiratory function evolution during idebenone treatment compared to idebenone-free periods in patients with Duchenne Muscular Dystrophy who completed the DELOS study			
Study identifier	Protocol SNT-CRS-003		
Design	Retrospective cohort study conducted in patients who had completed the randomized, placebo-controlled DELOS study and were enrolled in the DELOS EAPs (DELOS-NPP or DELOS-CUP) Patients acted as their own controls, with data from periods when they were treated with idebenone (On-Idebenone) in the present study planned to be compared to periods when they were not treated with idebenone (Off-Idebenone).		
	Period covered by this data collection:	30 August 2010 (first hospital visit included in this data collection) to 13 March 2018 (last hospital visit included in this data collection)	
Hypothesis	Superiority: To evaluate the long-term evolution of the respiratory function during idebenone treatment ("On-Idebenone"), compared to the evolution during idebenone-free periods ("Off-Idebenone").		
Treatments groups	On-Idebenone	Idebenone treatment	
	Off-Idebenone	Placebo or untreated	
Endpoints and definitions	Primary endpoint	FVC%p	Annual rate of change; comparison between "Off-Idebenone" periods and "On-Idebenone periods"
	Secondary endpoint	PEF%p	
		FEV1%p	
Database lock	1 June 2018		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT The ITT analysis set included all patients who were included in the ITT population of the DELOS study and who were enrolled to the present study. The ITT analysis set included 18 patients.		

Statistical Analysis			"Off-On" Idebenone	"On-On" Idebenone	Total
	Number of subjects		N=11	N=7	N=18
	Annual Rate of Change[a] in FVC%p	**Before EAPs** Estimate (95% CI)	-7.4 (-9.1, -5.8)	-0.7 (-3.7, 2.2)	Not applicable
		During EAPs Estimate (95% CI)	-3.8 (-4.8, -2.8)	-3.9 (-5.4, -2.3)	Not applicable
	Number of subjects		N=9	N=6	N=15
	Annual Rate of Change[a] in PEF%p	**Before EAPs** Estimate (95% CI)	-5.9 (-8.0, -3.9)	1.3 (-3.3, 5.8)	Not applicable
		During EAPs Estimate (95% CI)	-1.9 (-3.2, -0.7)	-1.3 (-3.4, 0.8)	Not applicable
	Number of subjects		N=11	N=7	N=18
	Annual Rate of Change[a] in FEV_1%p	**Before EAPs** Estimate (95% CI)	-5.5 (-7.6, -3.5)	0.5 (-2.4, 3.3)	Not applicable
		During EAPs Estimate (95% CI)	-3.2 (-4.3, -2.1)	-3.2 (-4.9,-1.5)	Not applicable

%p = percent of predicted; CI = confidence interval; FEV_1 = forced expiratory volume 1 second; FVC = forced vital capacity; ITT = intent-to-treat; N = number of patients; PEF = peak expiratory flow; EAP = Expanded Access Program.
[a:] random coefficient regression model
"Off-On" Idebenone = On-Idebenone in the EAPs and Off-Idebenone before the EAPs
"On-On" Idebenone = On-Idebenone both in the EAPs and before the EAPs

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

3.3.6.3. Supportive studies

3.3.6.3.1. DELPHI Extension Study (SNT-II-001-E)

Design

This was a Phase II OLE study to a phase IIa double blind, randomized, placebo-controlled study in Idebenone (SNT-II-001; DELPHI) to obtain long-term safety, tolerability and efficacy data of idebenone in the treatment of DMD.

The study lasted approximately 27 months: up to 2 months for the screening phase, 24 months for the treatment phase and a 1-month follow-up phase.

Study Participants

19 out of the 21 patients who participated in study SNT-II-001 were enrolled in the DELPHI-E study.

Inclusion criteria

- Completion of DELPHI study (SNT-II-001)
- Body weight ≥25 kg
- GCs and ACE-inhibitors were allowed, if on stable dosage within 2 months prior to inclusion
- Eligibility to participate in the extension study as confirmed by the investigator

Exclusion criteria

- Safety or tolerability issues arising during the course of the DELPHI study (SNT-II-001) which in the opinion of the investigator precluded further treatment with idebenone
- Clinically significant abnormalities of haematology or biochemistry
- Abuse of drugs or alcohol
- Use of coenzyme Q10 or idebenone within 30 days prior to inclusion
- Intake of any investigational drug within 30 days prior to inclusion
- Symptomatic heart failure
- Previous history of ventricular arrhythmias (other than isolated ventricular extrasystole); ventricular arrhythmias present at Baseline

Treatment

All patients were treated with idebenone. Patients ≤45 kg in weight took 1 x 150 mg tablets orally t.i.d with meals (total daily dose 450 mg daily). Patients >45 kg in weight took 2 x 150 mg tablets orally t.i.d with meals (total dose 900 mg daily).

Objectives

- To gather long-term data on the safety and tolerability of idebenone in DMD patients.
- To explore the effect of idebenone after longer term administration on respiratory, cardiac and motor functions, and skeletal muscle strength/function.

Outcomes/endpoints

- Measures of safety and tolerability of idebenone: Nature and frequency of AEs; Laboratory parameters (haematology, biochemistry and urinalysis); Physical examinations and vital signs; ECGs
- Measures of efficacy of idebenone determined primarily as changes from DELPHI-E baseline to last available observation.
    - Cardiac: FS, EF (M-mode), peak systolic radial strain of LV inferolateral wall, LV end-diastolic diameter, LV end-systolic diameter, heart rate. In addition, LV end diastolic diameter z-score and LV posterior wall thickness z-score were included
    - Respiratory: PEF, PEF%p , MIP, MIP%p, FVC, and FVC%p.
    - Motor function and muscle strength: Motor Function Measure (MFM) scale, QMT, HHM (amendment 1).

Sample Size

According to the nature of the study no sample size estimations were done.

Randomization and blinding

Not applicable

Statistical Methods

Analysis Populations

The primary efficacy analysis was planned to be performed using the ITT approach defined as all subjects who received at least one dose of the study medication and for whom an efficacy assessment was available in DELPHI-E.

The safety population was used for analysis of all safety variables. It was to include all patients who received at least one dose of the study medication and for whom a safety assessment was available in the DELPHI-E study.

The PP population was defined as all patients from the ITT population who had no major protocol deviation.

Efficacy analyses

The changes from baseline MFM, QMT, HHM and cardiac biomarker data were analysed using a repeated measures analysis of covariance (RMANCOVA) model including visit as a fixed factor and baseline value and age at Baseline as covariates.

The change rate between the off-medication period (period between the end on DELPHI and start of the DELPHI-E study) and on-medication period (duration of DELPHI-E study) for certain cardiac parameters and respiratory parameters were analysed using a random regression coefficient model. Age was not included in the models.

Results

Participant flow

All 19 patients were included in the Safety and ITT Populations. Of those, 11 patients had received idebenone treatment and 7 patients had received placebo in the DELPHI study and 1 patient who had not participated in the DELPHI study was included in the DELPHI-E study (brother form another patient in the study).

Recruitment

Regarding the periods of recruitment and follow-up, the applicant reported the following dates:

- Date first subject in the study: 15 September 2008
- Date last subject completed: 10 January 2011
- Final report date: 15 November 2013

All participants were recruited at a single centre at the University of Leuven, Belgium.

Conduct of the study

Protocol amendments

There was three protocol amendments. The amendment 1 (12 June 2008) added HHM as a secondary outcome measure. The second amendment (22 August 2008) included an updated drug safety reporting requirements. The third one (21 October 2009) included administrative changes.

Protocol compliance and reasons for protocol violations

One patient did not complete the study in accordance with the protocol as he was non-compliant with study treatment between Month 18 and Month 24.

Baseline data

The mean age of the 19 patients recruited was 15.1 years. All patients were male, and all were Caucasian/white. Of the 19 patients, 7 patients were ≤45 kg in weight. All 19 patients had a history of DMD, with 15 (78.9%) being wheelchair-bound. The mean time off medication from the end of the DELPHI study to the start of the DELPHI-E study was 619.1 days (range 447 to 769 days).

Numbers analysed

All 19 patients were included in the Safety and ITT Populations. One patient was non-compliant with study treatment between Month 18 and Month 24. Due to this non-compliance, efficacy data for this visit and this patient should not have been used in the PP data set. However, since this was the only major violation and as the expected impact of this data exclusion was minimal, no PP analyses were performed.

Outcomes and estimation

Cardiac function

During the 24-month study treatment period, the different cardiac parameters remained stable with no clinically important changes. No clinically important changes were observed in cardiac remodelling. No significant decline was observed in global cardiac function in patients on treatment. Due to the lack of a control group, it is uncertain whether this stability in global function is due to drug treatment. No significant changes were observed in regional myocardial function and cardiac biomarkers were unchanged during the study period.

Respiratory function

- During the 24 months of idebenone treatment, there was a significant decline in FVC and FEV_1. Most of this decline was apparent in the first 12 months and less so in the second year of the treatment period.
- MIP remained stable and PEF did not show a significant deterioration during the 24 months of idebenone treatment. For MIP, the stability during this study was significantly different from its decline during the off-idebenone period preceding the study.
- Use of concomitant GCs did not have any apparent influence on changes in PEF%p, FVC%p and MIP%p as idebenone treated patients with or without concomitant GCs use showed comparable stabilization in respiratory strength measures (PEF%p, MIP%p) or decline in lung volume (FVC%p) over the 24 months study period.

Motor Function and Muscle Strength:

- During the study, there was a significant decline in the total MFM score as well as in the D1 (standing and transfers) and D2 (axial and proximal motor capacity) subscores. In contrast, the D3 (distal motor capacity) subscore remained stable over the 24-month period.
- With HHM, the arm score increased significantly over the 24-month treatment period. There was a significant improvement for elbow extensor strength and a similar trend for elbow flexor strength. Although the increase in arm score as measured with HHM contrasts the expected natural history evolution, this finding was not replicated in the strength assessments by QMT. There was also a trend to improvement in knee extensor strength.
- With QMT, the total upper limb score decreased over the 24-month treatment period. The decline in the total upper limb score seemed to be caused predominantly by a decline in hand grip strength.

3.3.6.3.2. SNT-IR-016 NATURAL HISTORY OF RESPIRATORY FUNCTION DECLINE IN DUCHENNE MUSCULAR DYSTROPHY

Rationale

This report was aimed to summarize the current understanding of respiratory function evolution in DMD (part 1) and to provide new data to further sustain this CMA (part 2).

Part 1: Survey of the Published Literature

- Methods of assessment of respiratory function in patients with DMD.
- Disease factors affecting the rate of respiratory function decline.
- Clinical outcome of progressive respiratory dysfunction.
- Disease burden and patient and caregiver preference for treatment.

Part 2: New Data

- Introduce new equations developed with data from patients with DMD for the calculation of "%p" from PEF and FVC.
- Validate changes in FVC%p and PEF%p as predictors of life-changing events.
- Provide information on current attempts to determine a "minimal clinically relevant difference" for respiratory function measure PEF%p.

Part1

Methods of assessment of respiratory function in patients with DMD

Several measures can be used to assess respiratory function in patients with DMD, including measures for pressure (MIP, MEP), flow (PEF, inspiratory flow, inspiratory flow reserve, PCF), and volume (FVC, FEV_1) (Mayer 2018).

In the absence of obstructive pulmonary disease, FVC (liters), PEF (liters/minute), and FEV_1 (liters) are well-established dynamic spirometry measures useful in the assessment of restrictive pulmonary function changes due to neuromuscular weakness. Both PEF and FVC represent global measures of respiratory muscles requiring full inspiration followed by full expiration. With disease progression, inspiration and expiration become dysfunctional due to progressive weakness of diaphragm and chest wall muscles, reduced chest wall compliance, and scoliosis together resulting in the disease-typical restrictive pulmonary disease (LoMauro et al., 2018).

A recent expert consensus statement recommends FVC as the preferred outcome measure but acknowledges the value of PEF as a supportive measure (Finder et al., 2017).

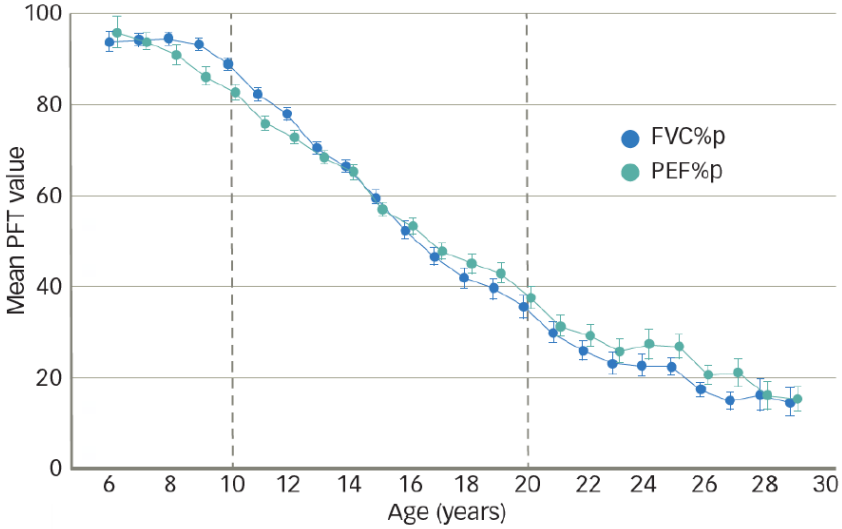
To account for maturational changes (i.e., body growth), normalization to "%p" is routinely performed during clinical monitoring of patients with DMD and recommended by expert statements and standard of care guidelines (Finder et al., 2017; Birnkrant et al., 2018; Mayer 2018).

Normalization equations typically include height and/or age to account for the influence of patient growth on respiratory function and to derive FVC%p, PEF%p and FEV_1%p data.

All currently used normalization equations are derived from the general population. However, efforts are currently ongoing to develop normalization equations from natural history data of patients with DMD to account for disease-specific aspects that can influence respiratory function, as discussed in a later section.

Both PEF%p and FVC%p follow a linear and parallel decline from approximately 10 years when respiratory function becomes abnormal (i.e., falling below the recognized threshold of <80%; Finder et al., 2017) to adulthood (Figure 22). Floor PEF%p and FVC%p of ~20% are reached by the time patients reach their mid-20's. Considering currently available natural history studies, the average rate of decline of PEF%p and FVC%p is around 4–6% per year (McDonald et al., 2013; Connolly et al., 2016; Mayer et al., 2015; LoMauro et al., 2018; Mayer et al., 2018; McDonald et al., 2018b; Ricotti et al., 2019).

Figure 22: Evolution of PEF%p and FVC%p by age (CINRG-DNHS study)



Data are mean ± SEM of pulmonary function tests from 334 patients of the CINRG-DNHS data.
Dotted lines at ages 10 and 20 years represent the period of approximately linear decline in PEF%p and FVC%p.
FVC%p: Percent predicted forced vital capacity; PEF%p: Percent predicted peak expiratory flow; PFT: Pulmonary function test; SEM: Standard error of the mean. CINRG-DNHS: Cooperative International Neuromuscular Research Group Duchenne Natural History Study.
Source: Mayer et al., 2017; McDonald et al., 2018b.

Disease factors affecting the rate of respiratory function decline

Respiratory function decline is influenced by general disease aspects. Earlier age at loss of ambulation and progressively more severe upper limb dysfunction and scoliosis is associated with a faster rate of decline of respiratory function. GCs treatment delays the start of respiratory function decline by 2–3 years, but once decline has started, GCs use does not influence the annual rate of decline.

Clinical consequences of progressive respiratory dysfunction

Inspiratory and expiratory muscle weakness progresses in parallel as measured by linearly declining spirometry measures (e.g., PEF, FVC or FEV_1). With time, patients lose the ability to fully inhale and forcefully exhale preventing an effective cough, which is monitored by reduced PEF and low PCF, respectively. Inability to cough forcefully prevents patients from mobilizing and clearing mucus secretions from airways. Mucus retention in turn increases the risk of benign upper respiratory tract infections progressing to lower respiratory tract infections/pneumonia and further reduces the amount of lung tissue available for gas exchange (atelectasis) (e.g. Dohna-Schwake et al., 2006, LoMauro et al., 2015). Airway infections frequently require antibiotic treatment and the requirement of aggressive inpatient respiratory care including assisted ventilation to prevent respiratory failure.

Disease burden and patient and caregiver preference for treatment

Early death occurs in patients with DMD, even in centers that provide state-of-the-art care. This is illustrated by data from the CINRG-DNHS, which prospectively followed 340 children and young adults with DMD for eight years (2007-2015) at centers in the US and Europe. During this time, 40 patients died (11.8%) at a mean age of 20 years (median ~18 years). The majority of deaths (55%) were from respiratory failure with another 32% from cardiac failure. The high rate of deaths caused by respiratory failure was recently confirmed by Van Ruiten et al., 2016. Moreover, a direct link between loss of respiratory function and increased risk of death has been established (McDonald et al., 2018a).

The importance of maintaining effective cough and reducing the risk of airway infections has recently been quantitatively assessed by a patient and caregiver survey. In a community engaged approach (Peay et al., 2014) conducted by Parent Project Muscular Dystrophy in the US, 155 individuals, the majority of which represented patients with DMD, rated effective cough and reduced airway infections as important treatment objectives for their disease (Hollin et al., 2017; Hollin et al., 2018).

Part2

Exploratory equations to calculate %p values for FVC and PEF developed from patients with DMD

This approach is described in detail in report SNT-IR17.

Change in PEF%p and FVC%p are predictive of life-changing events

Methods

Data from the CINRG-DNHS were analysed to determine whether PEF%p and FVC%p, and crossing of clinically-relevant threshold values, are predictive of clinically-relevant milestones in respiratory function decline. The analyses were also used to investigate how changes in rates of decline of PEF%p and FVC%p would be expected to impact the natural history and progression of DMD, and time to occurrence of life-changing events.

For each patient in the CINRG-DNHS, the annual rates of decline in PEF%p and FVC%p during the respiratory function decline phase (i.e. between 80% to 30%) were estimated, and patients were classified as 'fast' or 'slow' progressors using a cut-off rate of 5% annual decline, which represents an average rate of decline in respiratory function observed in natural history studies. The time when PEF%p (or FVC%p) crossed 50% for the first time was used as baseline for the time-to-event analysis. The time from baseline to (i) date of death or (ii) start of assisted ventilation were used as endpoints. The groups of fast and slow progressors were compared with Kaplan-Maier methods. Statistical analyses were calculated with the log-rank test and HRs were estimated by the CPHM, with the grouping factor only in the model.

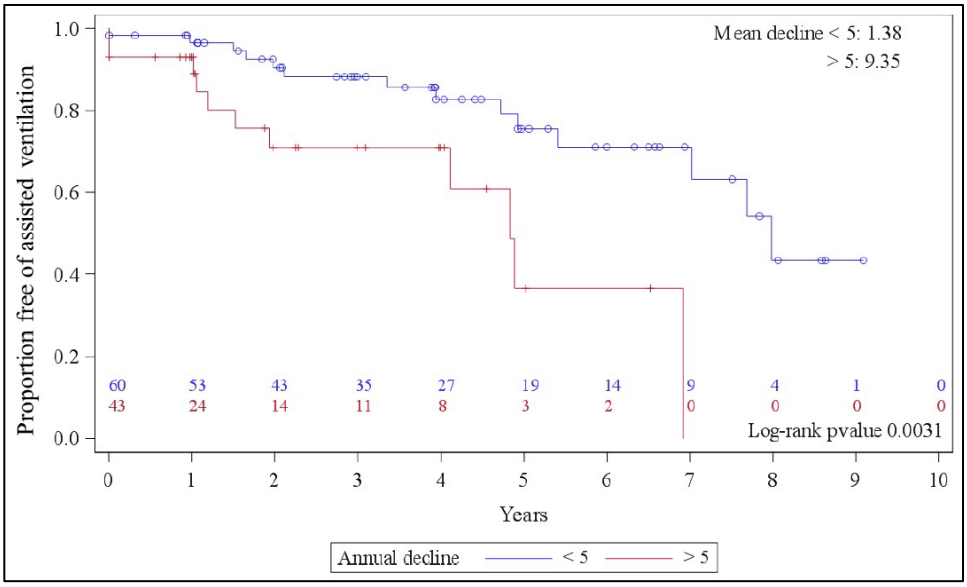
Results

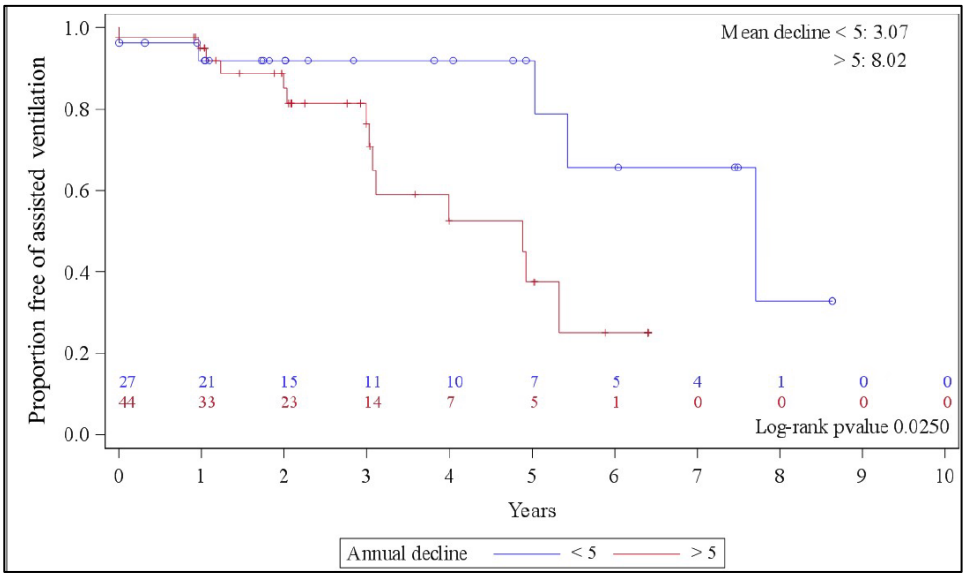
Using a cut-off of 5% for PEF%p, 61 patients were grouped as patients with a slower rate of decline with annual declines of <5% and 45 patients were classed as patients with a faster rate of decline with annual declines ≥5%. Using a cut-off of 5% for FVC%p, there were 29 and 45 patients classified into the slower and faster groups. At time crossing 50% PEF%p or FVC%p, slower DMD patients were more frequently ambulant and GCs users than faster DMD patients. The mean rate of annual decline in PEF%p was 1.4% for patients with a slower rate of decline and 9.4% for patients with a faster rate of decline. For FVC%p, mean rates were 3.1% and 8.0%, respectively.

When stratifying patients using a cut-off of 5% annual decline in PEF%p, the median time from crossing 50% PEF%p to initiation of assisted ventilation was around 8 years for patients with a slower rate of decline versus around 5 years for patients with a faster rate of decline, with the difference between groups being an approximate a 3-year delay in the time to assisted ventilation (HR=0.30, 95% CI 0.13

to 0.70, p=0.0031) (Figure 23). A similar result was seen when stratifying patients using a cut-off of 5% annual decline in FVC%p (Figure 23).

Figure 23: Estimated benefit of being a slow versus fast progressor, by rate of decline of PEF%p (top) and FVC%p (bottom), in terms of delayed need for assisted ventilation in the CINRG-DNHS





There was also a significant difference in 5-year survival after crossing 50% respiratory function decline between slow and fast progressors when stratified by 5% annual decline in PEF%p, which was 70% for fast progressors versus 93% for slow progressors (HR=0.16, 95% CI 0.04 to 0.66, p=0.0045). The results followed a similar trend when patients were stratified by 5% annual decline in FVC%p.

Current attempts to determine a "minimal clinically relevant difference" for respiratory function measures

PEF%p

Methods

Step 1: Selection of patients for the analysis

For each patient in the CINRG-DNHS, the annual rates of decline in PEF%p during the respiratory function decline phase (i.e., PEF%p between 80% and 30%) were estimated, provided that sufficient data were available for the estimation. A minimum of two data points were required for a patient to be included in this analysis. Out of all patients, a subset was selected with patients who crossed the threshold of 50% PEF%p during the study (i.e., had PEF%p values >50% at the start of observation period and declined to PEF%p <50% during the observation period). This analysis set represents the same set of patients (N= 103) that was used for the analyses presented in the section above.

Step 2: Random allocation of patients into two groups

Patients in the analysis set were then repeatedly randomized to two different groups to generate multiple samples with different separations in the annual rate of decline for PEF%p. As described below, the targeted between-group separation in annual rate of decline in PEF%p were set to be between 2% and 6%. For each target separation, a range was allowed; i.e., to achieve a target separation in annual rate of decline in PEF%p of 2%, actual allowed differences ranged between 1.75% and 2.25%. Similar margins were allowed to generate groups with a difference in annual rate of decline in PEF%p of 2.5%, 3%, 4%, 5% and 6%.

It was estimated that for each target separation in PEF%p, 400 pairs of groups would be needed for this analysis. Consequently, the randomization procedure was repeated several tens of thousands of times until 400 samples with each target separation had been generated.

Step 3: Data analysis

Once the 400 samples had been generated, the time from crossing the PEF%p threshold of 50% to initiation of assisted ventilation as recorded in the CINRG-DNHS data base was evaluated for each sample. Because in many samples less than 50% of the patients started using assisted ventilation during the study in at least one of the groups, it was not possible to estimate the median time to assisted ventilation in each group. Due to this, the difference between the groups in time to assisted ventilation was quantified by a HR and the associated CI. Once the 400 HR were available for each sample, an average estimate over the samples was calculated as a geometric mean of the HRs.

Results

The difference between the two groups is increasing as a function of separation, from 0.888 with a separation of 2% in the annual rate of change in PEF%p to 0.528 with a separation of 6% (Table 36).

Table 36: Time from crossing PEF%p of 50% to initiation of assisted ventilation calculated as hazard ratios between groups

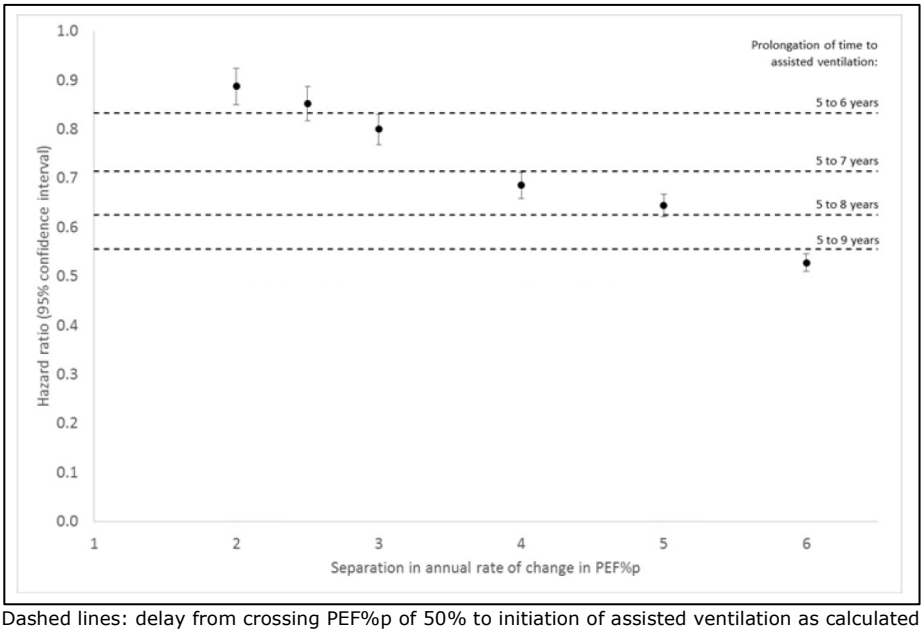
Target separation in PEF%p between Group 1 and Group 2	N	Geometric mean of hazard ratios between Group 1 and Group 2	95% CI for the hazard ratios
2%	400	0.888	0.852, 0.925
2.5%	400	0.853	0.819, 0.888
3%	400	0.801	0.771, 0.833
4%	400	0.686	0.659, 0.713
5%	400	0.645	0.622, 0.668
6%	400	0.528	0.510, 0.546

PEF%p: percentage predicted peak expiratory flow; HR: hazard ratio; CI: confidence interval.

Based on previously reported natural history data from the CINRG-DNHS, the median time from crossing PEF%p of 50% to initiation of assisted ventilation is about 5 years. This information can be used to put the results summarized in Table 36 into clinical context. As shown in

Figure 24, a prolongation of one year in time to assisted ventilation (from 5 years to 6 years) is equal to a HR of 0.833, while prolongations of 2, 3, or 4 years would result in HRs of 0.714, 0.625, or 0.556, respectively.

Figure 24: Time from crossing PEF%p of 50% to initiation of assisted ventilation, hazard ratios between the groups in samples extracted from the CINRG-DNHS



Dashed lines: delay from crossing PEF%p of 50% to initiation of assisted ventilation as calculated from HR.
Data of observed mean HR (95% CIs) by separation in PEF%p.
PEF%p: Percent predicted peak expiratory flow; HR: hazard ratio; CI: confidence interval.

According to the applicant, this analysis provides an estimate of what magnitude of treatment difference in the annual rate of change in PEF%p can be extrapolated to a clinically meaningful prolongation in time to assisted ventilation. From the data reported in Table 36 and shown in

Figure 24, a separation in PEF%p by 3% falls below the minimum threshold required to conclude a 1 year delay in time to assisted ventilation.

Based on the analyses presented above, the difference of about 2.7% in the annual rate of decline in PEF%p would result in prolongation of about 1 year (from 5-6 years in

Figure 24) from crossing 50% of PEF%p to initiation of assisted ventilation. In conjunction with the statement by the Community Advisory Board that a 1-year delay is considered relevant for patients and families, this could be considered a first approximation of a minimal clinically relevant difference.

3.3.7. Discussion on clinical efficacy

Aspects of design and conduct of clinical studies were discussed in this section together with those relative to efficacy data and additional analyses for each of the main and supportive studies and reports.

The main evidence for the efficacy of Puldysa for the treatment of respiratory dysfunction in DMD is derived from three sources: a phase II trial (DELPHI, SNT-II-001), a phase III trial (DELOS, SNT-III-003) and the retrospective cohort study SYROS (SNT-CRS-003). DELPHI and DELOS were prospective, double-blind, randomized, placebo-controlled trials in DMD patients.

Furthermore, an uncontrolled OLE trial to DELPHI was submitted (DELPHI-E). Additionally, several *post hoc* analyses and supportive reports were submitted: SNT-IR-011 (additional analyses of respiratory function measures for DELPHI and DELPHI-E); SNT-IR-009 (additional analyses of inspiratory function in the DELOS trial); SNT-IR-010 (additional analyses on the effect of idebenone in reducing respiratory complications in the DELOS trial); SNT-IR-015 (report on the integrity, consistency and robustness of the DELOS trial); SNT-IR-017 (re-calculation of DELOS study results with new DMD patient-derived prediction equations); SNT-IR-016 (report on the current understanding of respiratory function evolution in patients with DMD).

In the **DELPHI** trial 21 DMD patients from 8 to 16 years of age were included irrespective of the use of GCs. The primary endpoint in DELPHI was a cardiac parameter: the relative change from baseline (at screening) to week 52 in peak systolic radial strain of the LV inferolateral wall, assessed by CDMI. This primary endpoint was not met. Secondary endpoints comprised additional cardiac parameters, respiratory function tests, skeletal muscle strength, timed walking test (ambulatory patients only) and clinical global assessment of efficacy and tolerability. No endpoints such as activities of daily living or health-related quality of life were planned. This is considered a drawback of this phase II trial. The applicant decided to control the type-1-error at 5% one-sided for this phase II trial. Whilst it can generally be acceptable in an exploratory phase II setting to pre-specify the type-1-error more liberal than the conventional 5% two-sided, no justification was provided for this choice. Against this background, it needs to be pointed out that DELPHI-results reported as "significant" (at 5% one-sided) contribute as separate and stand-alone source of evidence of a treatment effect in the applicant's overall line of argumentation to describe idebenone's benefit. Hence, for the interpretation of all efficacy results which are reported as "statistical significant", the liberal choice of the type-1-error as well as the lack of any measures to handle the multiplicity issue (arising from many additional tests carried out for secondary parameters) need to be kept in mind and therefore, DELPHI results cannot be seen as main evidence to support idebenone's benefit. During the procedure, the applicant also confirmed that the statistical procedure originally applied for the DELPHI study is not appropriate for stand-alone evidence of efficacy arising from this exploratory phase 2 trial. From the assessment perspective, this is important to be kept in mind when eventually the totality of evidence of an idebenone treatment effect shall inform the benefit-risk (B/R) assessment. It is concluded that the outcome of DELPHI study cannot be considered as stand-alone evidence of efficacy arising from this exploratory phase 2 trial.

A statistically significant difference (type-1-error controlled at 5% one-sided) in favour of idebenone was shown for PEF and PEF%p, while no statistically significant differences where shown for any of the other respiratory endpoints. Stratified analyses of PEF%p data suggested a larger treatment effect size in GCs non-users. This influenced the planning and conduct of the DELOS trial, in which a plan for population restriction to GCs-non-users was implemented through a protocol amendment (initially both GCs users and non-users were planned to be enrolled). However, based on emerging data from the natural history of respiratory function decline in DMD patients, DELPHI data were re-analysed by the applicant (SNT-IR-011) and it was concluded that GCs use does not influence the outcome for change in PEF%p. According to the applicant, GCs use rather delays the onset of respiratory decline. Specifically, all GCs non-users in DELPHI were in the decline phase whereas the majority of the GCs-users were not in the decline phase of their respiratory function at baseline. At the time of publication of this withdrawal AR, there is only limited data of use of Puldysa in GCs users and the applicant is currently carrying out a phase III trial specifically investigating the efficacy and safety of Puldysa on respiratory function outcomes in DMD patients using concomitant GCs (i.e. SIDEROS trial).

Whilst it can be agreed that DELPHI data for respiratory function deliver a signal for an idebenone treatment effect, the applicant's view concerning the consistency of the treatment effect cannot be shared, as derived estimates might indicate effect sizes of different magnitude between DELOS (estimated difference for PEF%p: 6.27; 95%CI: 0.61, 11.93) and DELPHI (estimated difference for PEF%p: 18.63; 95%CI: 1.59, 35.67). For planning DELOS, this led to over-optimistic assumptions concerning expected effect on PEF%p and FEV1%p, which by itself triggered the need to revise planning assumptions in relation to effect size during DELOS-trial conduct. Hence, after in-depth regulatory review, a claim for consistency in terms of magnitude of treatment effect size in respiratory function parameters between the various sources of evidence (DELPHI, DELOS, SYROS) cannot be supported. It appears that a divergent view to the applicant remains in that matter.

In the **DELOS** trial, 64 DMD patients from 10 to 18 years of age were included without concomitant use of GCs. Furthermore, in the DELOS trial, patients were included in whom respiratory function "started to decline (PEF%p ≤80% at baseline)". In this regard, it also has to be kept in mind that the fulfilment of the criterion PEF%p≤80 can also depend on the formula used for calculation of PEF%p values. If the Hankinson equation had been used instead of the Godfrey equation to estimate PEF%p, 4 patients would have had PEF%p >80% at baseline, and therefore they would have not been included in the trial as it was shown in **SNT-IR-015**. There is no further issue raised to the inclusion criteria to this study, but the applicant is asked to further discuss how an adequate target population can be defined. In this context, a proper definition of a patient being in the respiratory decline phase should be provided (decline based on which parameter; formula; how often measured). The applicant is also asked to specify the age group for which the product is indicated.

No justification for the selected dose (daily dose of 900mg idebenone) was provided. It is understood that options for dose-finding trials might indeed be limited due to the orphan setting. Nevertheless, it needs to be kept in mind that keeping at 900 mg daily follows pragmatic decision making rather than scientific exploration. Furthermore, no gain in efficacy could be discerned from doubling of idebenone dose in DELOS compared to DELPHI. Whereas the question of optimal dosing is not pursued, the lack of a signal for dose response needs to be accounted for in the assessment.

For the assessment of the DELOS trial, the report **SNT-IR-015**, in which the applicant justified the integrity, consistency and robustness of the DELOS trial, was also taken into consideration and assessed in detail.

There were several amendments to the protocol of DELOS and changes in the planned analyses, with some of them giving rise to concern regarding trial conduct. Based on the fact that DELOS was the first ever randomized study in DMD with respiratory function as the primary efficacy endpoint, one has to

realise and acknowledge that a trial carried out under such circumstances faces a lot of uncertainties in the beginning. These uncertainties pertained to the actually targeted patient population (GCs use), data distributional aspects (variability) of the primary endpoint, as well as the expected effect (size) between treatment arms in the primary endpoint. These uncertainties were reflected in trial plan and trial conduct by foreseeing a broad flexibility involving interim analyses, blinded data review, futility analysis, plans to adapt the trial population, as well as sample size reassessment. Whilst most of the implemented trial amendments can be tracked based on the documentation provided, it seems important to mention that the DELOS study substantially deviates from what is commonly understood as 'confirmatory phase III trial'. Especially with regard to concomitant GCs use, this trial needs to be seen rather exploratory in its nature. Methodological concern regarding trial conduct is mostly related to the sequence of decisions made (based on trial-internal and trial-external information retrieved) to finally end up deciding to restrict the study population to GCs non-users. As a consequence, bias in the estimation of treatment effects cannot be excluded in such a situation, and the extent of this potential bias can hardly be quantified. This adds to the uncertainty of beneficial effects in the benefit risk assessment. From an assessment perspective, the consequence is that DELOS should be seen as the single pivotal trial, with hardly any potential to serve for the purpose to deliver confirmatory evidence.

The primary endpoint in the DELOS trial was a respiratory parameter: The change from baseline to Week 52 in PEF%p. Secondary endpoints comprised additional respiratory function tests, muscle strength, motor function and quality of life.

The adequacy of the selected primary endpoint, PEF%p, is considered questionable. The applicant refers to the "Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy" (EMA/CHMP/236981/2011, Corr. 11) to justify PEF%p as primary endpoint. The mentioned guideline specifies in section 6.2 "*All trials should include measurement of respiratory function as appropriate, especially in non-ambulant patients. As the main impact of the illness is the loss of lung volume, suitable parameters should be volume-related parameters. Measurement of forced vital capacity (FVC), vital capacity (VC), as restriction- related parameters may be suitable efficacy parameters to show an effect on pulmonary function and should be performed in accordance to current standards. As properties might change with patient`s age and disease stage, for younger patients expiratory flow (PEFR (peak expiratory flow rate)/FEV1 (forced expiratory volume in 1 second)) would be better while for older patients it might be lung volume. It is acknowledged that pulmonary function tests are difficult to perform in non-ambulant patients and have poor reproducibility. Therefore, only a small number of the most sensitive tests should be selected to provide relevant information without extreme burden for the patients participating in the study*". It is agreed that the guideline mentions PEF as one out of three respiratory endpoints. However, this endpoint is only recommended in younger patients while for older patients volume-related parameters such as FVC or VC are recommended. Moreover, the above-mentioned guideline states that pulmonary function tests are difficult to perform in non-ambulant patients (the majority of DELOS patients was non-ambulatory) and have poor reproducibility. Additionally, the guideline states in section 6.1 that "*the objectives of each study should be well defined according to the expected stage and functional status-related improvement in certain symptom domains, e.g. walking, daily functioning, maintaining ambulant stage, use of upper limb in non-ambulant subjects, time to assisted ventilation or survival*".

Furthermore, selection of the primary endpoint in the DELOS trial was mainly driven by results from the preceding DELPHI trial rather than by a scientifically sound justification.

During the scientific advice (EMEA/H/SA/561/2/2008/PA/PED/SME/II) it was recommended that "*the lung function parameter which is a) best validated and b) most sensitive to change should be the primary variable. (…) If PEF% predicted is chosen as the primary efficacy variable, every effort should be taken to collect all material related to the validation of the chosen endpoint. Moreover, the applicant should be aware that the evaluation of a possible dossier and approval of an indication would not solely rely on the*

results for the primary parameter (and the significance and relevance of the effect) but on the consistency of all lung-function related parameters and the effects on other secondary endpoints."

Indeed, there are important methodological issues identified related to the calculation of the PEF%p, and hence the validity of this endpoint was questioned in the former extension of indication Type II variation procedure for Raxone (EMEA/H/C/003834/II/0003).

One issue is the choice of the prediction formula to compute individual PEF%p values. The applicant states that the use of the Godfrey equation to calculate PEF%p in DELOS did not introduce bias as the use of an alternative equation (Hankinson) resulted in consistent results. However, the impact on the interpretation of PEF%p results seems to be difficult to estimate. From the presented results, it can be seen that substantial over- as well as underestimation of PEF%p occurs depending on the formula used. Furthermore, there were four patients for which the changes from baseline at week 52 were either positive or negative, depending on the formula used. Against this background, profound interpretation of PEF%p outcome is not possible. In addition, the use of the Hankinson equation instead of the Godfrey equation would have excluded four patients as their PEF%p would have been >80% at baseline. Excluding these four patients in the primary efficacy analysis resulted in non-significant differences in PEF%p between the placebo and the Idebenone group at week 52. Therefore, the primary endpoint would not have been met if the alternative equation formula would have been used. Thus, any general view that trial outcome would be robust and insensitive to the actual choice of the prediction equation formula cannot be shared. On the contrary, profound interpretation of PEF%p outcome is not possible and this adds uncertainty relating to the validity of the endpoint.

The second issue in relation to PEF%p computation was the use of ulna-length based estimation of body height in DMD patients. Both prediction formulas mentioned above require 'body height' as input variable. Therefore, PEF%p is based on a clear-cut understanding of standing height as measurable as in healthy children and adolescents. However, the majority of DELOS patients were wheelchair bound and measurement of standing height was actually not possible in most of the cases. The transfer of PEF%p concept to a disease where patients are frequently non-ambulant and/or suffer from advanced muscle weakness, scoliosis and joint contractures is considered difficult. It is acknowledged that for lack of more suitable alternatives, the method of ulna-length-based height estimation is also used in the DMD patient setting in practice ("state of the art") to derive PEF%p. However, it has been observed that for some patients in DELOS there are considerable differences between real body height and body height estimated from ulna-length, which leads to substantial over- as well as underestimation of PEF%p. Therefore, assessment of Puldysa' s B/R ratio needs to include a judgement of the adequacy of the primary efficacy endpoint used and the concern regarding height estimation based on ulna-length adds uncertainty to the interpretation and validity of the primary endpoint.

The validity issue has been discussed extensively in the former Type II variation procedure (EMEA/H/C/003834/II/0003). Although PEF%p is still not considered fully valid in the DMD setting, it has been decided that this issue will not be further pursued. Therefore, no further questions regarding the validity and the adequacy of this endpoint are raised, but uncertainties on the results remain.

In order to circumvent the issue of validity of %p, the applicant provided an additional analysis approach in report **SNT-IR-017** using new exploratory prediction equations developed from patients with DMD for the re-calculation of %p values for PEF and FVC of the DELOS study. The underlying idea and expectation was that patients under placebo control would approximately follow the mean progressive time-course of untreated patients, whereas the %p time courses of idebenone treated patients were expected to separate from natural disease data patterns, eventually (on average) lying above the mean time course of natural disease standard. Unfortunately, additional analyses carried out did not meet those expectations. Hence, the report did not provide additional insight enabling a solid interpretation of

the DELOS PEF%p effect based on natural disease progression standardisation and therefore cannot contribute to the B/R assessment.

During the clinical development, the anticipated effect (difference in PEF%p between idebenone and placebo) was downsized from 20%-points (one-year change difference to placebo in GCs non-user population in DELPHI trial) to 15%-points (sample size calculation for DELOS) to 10%-points (based on a futility analysis of DELOS) to 6%-points (criterion for superiority of idebenone over placebo according to the latest protocol synopsis). Although nominal statistical significance was achieved for PEF%p in DELOS (difference between idebenone and placebo: 6.27%; 95% CI: 0.61, 11.93), the clinical relevance of this difference is considered questionable in light of the above described proceeding and due to the large uncertainty of the derived estimate in the primary analysis. Concerning the assessment of clinical relevance of a potential treatment effect, the applicant correctly quotes Guideline EMEA/CPMP/EWP/2158/99 to justify superiority of idebenone over placebo. According to the EMA Guideline EMEA/CPMP/EWP/2158/99 "*When data from trials designed to show superiority of a test product over placebo are being interpreted, an informal two-stage procedure is employed involving the consideration of both statistical significance and clinical relevance" · It would first be expected that the test product demonstrated a statistically significant advantage over placebo. Statistical significance is generally assessed using the two-sided 0.05 level of significance (or one-sided 0.025)."* The primary endpoint of the DELOS trial, change in PEF%p over the 52-week study period, showed a between-group difference of 6.27% 95% CI (0.61 to 11.93) in favour of idebenone for the ITT population. Therefore, statistical significance was confirmed by using the $p<0.05$ criterion. The Guideline EMEA/CPMP/EWP/2158/99 described the second stage as following: *"the next step in interpreting a superiority trial is to consider whether the difference from placebo is clinically relevant. Establishing a clinically relevant benefit over placebo is accomplished by considering the point estimate of the difference between the test product and placebo and assessing its clinical relevance. A judgement must be made regarding whether the difference seen is clinically useful*." According to the applicant clinical relevance was confirmed by showing the point estimate of the observed treatment difference (6.27%) exceeds the threshold of clinical relevance (4-6% the estimate of the annual rate of PEF%p decline in non-treated patients). However, aside the judgment of the most reasonable point estimate for clinical relevance, a benefit/risk assessment needs also to include consideration of the "*range of values of the true difference that are plausible in light of the results of the trial*" (Guideline CPMP/EWP/482/99), i.e. the CI. Hence, the discussion around persuasiveness of the effect seen also needs to account for the lower limit of the CI estimated. In this regard, it has to be considered that there is a large uncertainty of the derived estimate in the primary analysis (95% CI: 0.61; 11.93). This level of precision achieved needs to be accounted for when judging robustness of the effect estimate and for the clinical interpretation of the effect. The applicant´s argumentation that the observed difference for the primary endpoint PEF%p is equivalent to the 1-year decline expected in untreated patients is based on the PEF%p- difference point estimate. For the still likely case where the true difference would be closer to zero, the claimed correspondence to a 1-year decline in untreated patients would not hold true. During the procedure, the applicant investigated the potential of the true treatment difference being lower than the assumed minimum clinically relevant effect. The probabilities for the DELOS study treatment difference at Month 12 being below different PEF%p-group-difference thresholds (2.7% and 1.3%) were computed. With the answer provided, no description of the actual method how these probabilities had been derived were included. Hence, the adequacy of the estimation technique to derive the desired cumulative probabilities cannot be fully assessed. Under the circumstances described above, the applicant's conclusion "that based on the DELOS study data, the probability of the true treatment difference in PEF%p not being clinically relevant is small (about 5-10%)" can be taken forward to B/R assessment as best-case scenario from the assessment perspective at the moment.

The applicant performed a number of *post hoc* analyses in order to translate the observed effect in respiratory parameters into a patient benefit. However, the interpretation of anticipated milestone events

that are based on the parameters PEF%p, FVC%p and FEV1%p is severely hampered by the methodological issues concerning these parameters. Furthermore, the applicant made an attempt to define a minimal clinically relevant difference for PEF%p measures. Based on the presented analyses, the applicant states that the difference of 2.7% in the annual rate of decline in PEF%p would result in prolongation of about 1 year from crossing 50% of PEF%p to initiation of assisted ventilation. For this analysis, the applicant selected patients from the CINRG-DNHS data base. However, beside the *post hoc* nature of the analysis, there were several issues regarding patient selection, data generation, construction of the analysis sets and underestimation of the variance due to resampling. Given the descriptions provided, there remains concern that the 95% CIs derived are associated with a pseudo precision, which strongly and directly depends on the choice of N (number of "pairs of groups"). Furthermore, it needs to be assumed that due to resampling the variance is systematically underestimated, if data from one and the same patient is used repeatedly for estimation purposes. Implications of this potential underestimation of variance remain unclear. In addition, the magnitude of uncertainty in relation to the estimation of time point where an individual PEF%p-curve would cross an (arbitrary) 50% threshold also remains unclear. Therefore, the chosen approach to determine a minimal clinically relevant difference for PEF%p measures is not supported and considerable uncertainty remains whether the effect shown on decline of PEF%p translates into clinical benefit, namely prolongation of the time to initiation of assisted ventilation of one year as claimed by the applicant. Currently, this argumentation is considered hypothetical and lacks clinical confirmation.

The **SYROS** study was a prospectively planned, retrospective cohort study in patients who had completed the DELOS study and were enrolled in idebenone EAPs. In order to participate and allow data collection from their medical records, the subjects and investigators had to sign a data release agreement form. The primary objective of the study was to evaluate the long-term evolution of the respiratory function. In the SYROS protocol, the primary endpoint was defined to be PEF%p. With the preparation of the SAP the choice of the primary outcome variable was made dependent on actual data availability of respiratory function read-outs, leading to a set of rather different analysis scenarios to eventually address the general study objective. Finally, FVC%p was selected as primary endpoint. From a formal GCP perspective, changing the primary endpoint of a study would principally require a substantial amendment. As acknowledged by the applicant during the procedure, this amendment has not been prepared and submitted by the applicant, which is regarded a shortcoming. The applicant's position was that SYROS was conducted following GCP principles as it was described in the prospectively defined SAP which was finalised prior to database lock and PEF%p, FVC%p and FEV_1%p were analysed in the same way according to the prospectively defined SAP. However, as a maintenance of the effect could not be shown anyway and the applicant will not be able to change the GCP compliance issue retrospectively, there are no further questions posed regarding GCP compliance. However, from an assessment perspective, the fact that respiratory function parameters (PEF, FVC etc.) were obviously not routinely measured during off-treatment phases after DELOS participation needs to be taken into consideration in the discussion of the relevance/importance of these endpoints for B/R assessment.

There are also several issues regarding the patient selection in SYROS. On general grounds, it is interesting to note that only 7 out of 31 patients from the DELOS idebenone arm continued treatment in SYROS after ending treatment under the DELOS protocol. The fact that this number of continued patients in the ON-ON group is lower than the resulting number of 11 patients in the OFF-ON group needs further consideration in the assessment. Furthermore, it is generally well acknowledged that SYROS patient numbers strongly depend on enabled access to idebenone treatment via NPP and/or CUP. During the procedure, the applicant provided comprehensive information why only such a limited number of patients were included in the SYROS study. For the four countries in which the EAP was not started (approximately half of the DELOS patients), it seems as if the expected benefit for the patients did not outweigh the administrative effort to initiate such a programme. Although it is understood that all sites were provided with the equal possibility to participate in the EAP, the limited number of patients in SYROS limit the

interpretability and generalizability of the SYROS outcome data. Furthermore, the fact that not all DELOS investigators/treating physicians requested the option to initiate an EAP for their patients under NPP/CUP is informative to some extent and cannot be ignored in the current assessment.

For the interpretation of SYROS main outcome, it is key to have best possible understanding in how far the two patient sets in the two defined groups (OFF-ON, ON-ON) can indeed represent the former idebenone and placebo groups from DELOS. Patients included in idebenone arm in DELOS (n=31) had 13.5 years old as mean age at baseline, 90.5% were in a non-ambulatory status at baseline and had mean values of FVC%p and PEF%p of 55.3% and 53.5%, respectively. Out of these 31, 7 patients were enrolled in SYROS (ON-ON group). These 7 patients had 11.8 years old as mean age at baseline, only 57% were in a non-ambulatory status at baseline and had mean values of FVC%p and PEF%p of 65.0% and 61.0%, respectively. Therefore, set of 7 patients from DELOS who were enrolled into SYROS were on average younger and had better baseline respiratory function than patients in the DELOS idebenone group. In order to explore that question, it also seems relevant to use outcome data aside baseline characteristics. Taking a closer look at the ON-ON patient set, there are several strong signals in the material provided to assume that all those patients showed a rather favourable course of respiratory function over the 52-weeks DELOS study period. E.g., the derived estimate for the annual rate of change in FVC%p (i.e. -0.7) during the DELOS (on-treatment) period is much larger than the upper limit of the 95% CI reported for the FVC%p one-year change in the (total) idebenone treatment group (i.e. -2.99). Similar observations can be made for PEF%p and FEV1%p. This gives reason to believe that this set of 7 patients cannot be considered representative of the DELOS idebenone treatment group with respect to respiratory function changes over DELOS study time. During the procedure, the applicant argues that the slow rate of decline in FVC%p during DELOS for the ON-ON group was mainly driven by one patient. Indeed, the exclusion of this patient who had a favourable evolution during DELOS, decreases this imbalance. However, the contribution of this patient to the overall result needs to be seen as data from a patient representing a fraction of the total patient population of interest. Aside analysis investigating this patient's data particular influence, interpretation of an analysis excluding the data would be misleading. The argumentation provided by the applicant is not regarded sufficient and therefore the 7 patients in the ON-ON group selected for SYROS cannot be regarded representative for the patients in DELOS. Hence, generalisability of the SYROS results remains questionable.

During the procedure, the applicant is requested to justify why 100% of the patients provided data for FVC%p, while only 83.3% of the patients provided data for PEF%p. The applicant state that data collection was performed according to routine clinical monitoring of the patients in SYROS study. However, the applicant cannot provide information on the question if separate manoeuvres were used to derive these data from. As the availability of the data is also influencing the primary endpoint selection in SYROS (i.e. the first combination of comparison and endpoint that could be evaluated for at least 90% of the patients was used as the primary analysis of this study), a non-recording of data for some patients without being able to provide reasons for the missing of these data is regarded as a shortcoming for the integrity of the SYROS data.

In addition, the start dates of idebenone treatment after completion of the DELOS period are quite different among the patients. This raises the concern to which extent these patients are comparable to each other. A patient being at an age of 10 is in a completely different disease state concerning respiratory function decline as compared to a patient at the age of 18. Therefore, it was questioned if this selection brings the necessary comparability concerning baseline respiratory parameters at the start of idebenone treatment and this will also have to be taken into account in the interpretation of the results. From the CINRG-DNHS study results, it is obvious that patients who reach the 30% PEF%p threshold have an annual decline of PEF%p that is lower compared to patients being in the phase between 80% and 30% PEF%p. Therefore, it might be difficult to interpret annual decline rates obtained from these different disease phases. During the procedure, the applicant investigated the influence of a

possible floor effect on the rate of change in FVC%p by providing sensitivity analyses excluding data from patients if they have reached certain thresholds (<20%, <25% or <30%). Although there does not seem to be a marked effect on the annual rate of decline in FVC%p when excluding these data, there is still a slight increase of the FVC%p decline if excluding data from patients <30% for the On-Idebenone group during the EAP. Therefore, there seem to be a slight effect when excluding data after a floor is reached and baseline respiratory function would to some extent affect the annual rate of decline. In the sensitivity analyses, the applicant only focused on FVC%p, while there were no data presented for PEF%p and FEV1%p. Therefore, a general statement that the floor effect does not influence the overall results reported for SYROS cannot be made. However, further sensitivity analyses were not requested as they are not considered to impact the B/R assessment substantially.

In addition, apart from the issues mentioned above, it seems as if there is a consistent trend that the 'stable' respiratory function seen during the DELOS period could not be maintained in the second ON treatment phase for PEF%p, FVC%p and FEV1%p. In the set of 7 patients included in the ON-ON group, most of the patients had a faster decline during SYROS compared to DELOS. Therefore, the results of SYROS do not support a positive effect of idebenone on the long-term respiratory function evolution in patients with DMD.

The **DELPHI-E** study and most of the additional *post hoc* analyses provided from the reports **SNT-IR-009**, **SNT-IR-010**, **SNT-IR-011** and **SNT-IR-016** are regarded as supplementary information but do not have an impact on the overall efficacy conclusions.

Additional efficacy data needed in the context of a CMA

The applicant requested a CMA for Puldysa. As Puldysa is intended to treat a "seriously debilitating disease or life-threatening disease" and it is designated as an orphan medicinal product it is eligible for consideration for a CMA.

The applicant argues that comprehensive data will be available in a timely manner as data from the ongoing SIDEROS/SIDEROS-E study, as well as data from the phase IV confirmatory clinical trial **MILOS** will be provided. While **SIDEROS** study results are expected to be available in 2022 and would be submitted to extend the indication of idebenone to all DMD patients irrespective of GCs use, MILOS would be a post-authorization study and would last about 5 years.

In principal, the confirmatory phase IV MILOS study is regarded as a good opportunity to investigate the time to a milestone event (primary objective: reaching the criteria for assisted ventilation) and this is also in line with the EMA DMD guideline (EMA/CHMP/236981/2011), which allows the post approval performance of studies investigating such endpoints, as such studies might be of very long duration. However, also after the responses received during the procedure, there are still aspects regarding the design and the feasibility of the MILOS study which the applicant will have to elaborate on. In addition, the applicant should provide a clear strategy how the knowledge gained with SIDEROS is integrated in the overall licensing strategy.

In order to show that it is likely to be able to provide comprehensive data after conditional marketing approval, the applicant clarified during the procedure, why from their point of view, a marketing authorization for Puldysa might not have consequences on the recruitment for MILOS and CINRG 2.0. Furthermore, the protocol of the proposed confirmatory MILOS study was revised with regard to important methodological design elements.

The applicant conducted a feasibility study for MILOS across the globe. From the 122 feasibility questionnaires that were sent to sites, 52 questionnaires were received back (51 with sites interested), 34 sites did not provide feedback and 37 sites declined study participation. In addition, the applicant argues that a large number of proposed sites are outside Europe in countries in which market

authorization is not planned or commercial availability will take more than five years. The applicant further states that even after a MAA in the EU, the commercial availability may take several years in some European countries. Therefore, the applicant concludes that a sufficient number of patients will be available for enrolment in MILOS. Similarly, the applicant argues that most of the CINRG 2.0 sites are located in countries in which the commercial availability of Puldysa is not foreseen in the near future and therefore patient availability will not be affected. This argumentation cannot entirely be followed. On the one hand, idebenone could be used off-label by using Raxone or Mnesis and on the other hand, importation through international pharmacies is possible within Europe in case a licensed product is not marketed in the country. Nevertheless, it can be agreed that there will indeed be countries and or regions where idebenone will not be available and more importantly not immediately implemented in DMD treatment guidelines and in consequence not be used as standard of care. Therefore, it might be regarded acceptable that patient availability will not be affected in the near future.

Regarding the external controlled study design, the applicant argues that a long-term placebo part is not feasible, as the maximum duration of placebo that patients and physicians are willing to accept is one year. Therefore, part 1 of the study (randomization to idebenone or placebo) lasts one year. Afterwards, all patients will be treated with idebenone in addition to standard of care and CINRG 2.0 will serve as the matched external control group. According to the CINRG 2.0 support letter, a strong motivating factor for participation is the ability to receive standard of care during the participation and being monitored by clinical experts with state-of-the-art outcome measures. In this regard, the argumentation of the applicant is still not understood, as this might also be applicable for a placebo-controlled study (in addition to standard of care). Therefore, the applicant is still asked to provide a clear explanation why it is not regarded feasible to foresee a placebo-phase (in addition to standard of care) within MILOS being substantially longer than 1 year in countries where marketing authorization/commercial availability is not expected within the next 5 years.

Regarding the design of the MILOS study, the applicant proposed to conduct a **non-inferiority analysis** of the placebo group to the natural history external control group after the completion of the placebo part of the MILOS study. The annual rate of decline in FVC%p will be evaluated between the MILOS placebo group and matched untreated patients from the CINRG 2.0 natural history study, as collected during the first year of each study. The estimated difference between these two groups will be compared to a pre-defined non-inferiority margin. In case the patients in the MILOS placebo group decline similarly or more than the matched untreated patients, i.e. the patients in the MILOS placebo group are at a similar or higher risk of reaching the criteria for assisted ventilation, the primary endpoint of the study, no actions will be undertaken. In case the patients in the MILOS placebo group decline less than the matched untreated patients, i.e. the patients in the MILOS placebo group are at a smaller risk of reaching the criteria for assisted ventilation, the result of the non-inferiority analysis will be used to adjust the primary analysis (i.e., the time-to-event analysis). This adjusted time-to-event analysis is referred to as "natural history adjusted analysis" during the remainder of this response. Three scenarios are foreseen for the outcome of the non-inferiority analysis:

- Scenario 1: non-inferiority is shown and the point estimate of the difference is above zero. There will be no adjustment on the primary analysis;
- Scenario 2: non-inferiority is shown, but the point estimate of the difference is below zero, i.e. despite of the non-inferiority the respiratory function of patients in the MILOS placebo group declines slightly less than in the matched untreated patients from the CINRG 2.0 natural history study. The primary analysis will not be adjusted, but a natural history adjusted key sensitivity analysis will be considered when interpreting the results.
- Scenario 3: non-inferiority is not shown, i.e. the respiratory function of patients in the MILOS placebo group declines less than the matched untreated patients from the CINRG 2.0 natural

history study. The natural history adjusted analysis will be used as the primary analysis of the study.

This strategy was seen as an attempt to safeguard against undesired differences in respiratory function decline between patients in the MILOS placebo group and patients from the CINRG 2.0 natural history study.

However, the suggested 3-scenarios approach mixes elements from inferential and descriptive statistical methodology. On the one hand, eventually demonstrated non-inferiority would need to be interpreted as an inferential outcome going beyond the sampled patients groups. On the other hand, any additional condition to define analysis scenarios involving the position of derived point estimates for the group difference in respiratory function decline would be descriptive in nature with clear relation to the patients actually sampled. This mix of inferential and descriptive elements in defining conditions for the data analysis strategy for MILOS makes a methodological assessment of the current plans difficult. Justification of the suggested '3-scenarios'-approach seems to be based on pragmatic reasoning rather than on explicit explanations that the common standards required for a statistical analysis in a confirmatory trial setting can be guaranteed. Those standards would, on the one hand, involve undisputable protection of the experiment-wise type-1-error, accounting for measures to correct for multiple testing of (different) hypotheses/endpoints during trial conduct. On the other hand, unbiased and interpretable effect estimates would be required for the primary endpoint evaluated with the final analysis. Guaranteeing those standards is of particular importance in the context of the MILOS trial, which is expected to deliver persuasive confirmation of the assumed idebenone effects on respiratory function in DMD patients.

The applicant's answer to questions posed during the procedure does not provide sufficient elaboration from the general methodological perspective that the standards mentioned above can be achieved with the plans described. Primarily, three aspects require further elaboration/explanation: (i) implications of the conduct of the non-inferiority test ad interim to a full nominal level of 5% for the protection of overall experiment-wise type-1-error, (ii) interpretability of eventually derived treatment estimates for the group difference in time to assisted ventilation, given the plans to implement a penalty in estimation in presence of inferior respiratory function decline in the external control group ad interim (scenario 3), (iii) Overall, safeguarding against the potential phenomenon that any effect seen in the time-to-ventilation endpoint is caused by differences between trial patients and external controls which are not associated with the test drug .

Finally, the applicant is made aware that any concomitant use of GCs in MILOS would need to be conceptually aligned with the applicant's general approach to identify the population eventually targeted. According to the MILOS protocol, patients included in the MILOS study will be treated with idebenone in addition to standard of care. These patients will be compared to the matched external controls treated with standard of care. During a clarification meeting held during the procedure, the applicant explained that GCs users and GCs non-users are distinct populations and that an effect of idebenone in GCs-uses has not been proven yet (this is investigated in the SIDEROS study). Therefore, it is unclear how a study primarily performed in GCs users (MILOS: idebenone in addition to standard of care) might be able to serve as a confirmatory study for an effect seen in GCs non-users. In addition, from the provided MILOS feasibility report it is apparent that the great majority of sites administer GCs to patients with DMD (globally 73% of patients ≥10 years are GCs users). It also remains unclear how change in GCs use in both MILOS patients and in matched controls will be handled with. It can be expected that the study duration/observation period will be several years, and GCs use, or non-use might not be stable over several years. From that it is considered unrealistic to conduct a long-term study in strict GCs-non-users only or to identify matched controls (especially if matching is based on baseline characteristics). In CINRG, GCs use cannot be controlled at all. That means that matched controls could change the GCs use during the course of the natural history study.

The applicant was also asked to discuss the potential of a positive/negative outcome in SIDEROS for the chances of conversion to full MA. In case of a positive outcome, the applicant plans to submit the results as a Type II variation to extend the indication to include GCs users into the CMA, while the MILOS study would continue in GCs users and GCs non-users. In the case that SIDEROS would not support an extension to GCs users, the applicant proposes that the results of SIDEROS will be submitted and discussed with the CHMP. However, according to the applicant, MILOS would still be able to provide comprehensive data in GCs non-users. Following the applicant's line of argumentation, the applicant believes that the outcome of SIDEROS does not necessarily impact the regulatory decision on Puldysa in GCs non-users. This view is currently not shared. In a scenario where SIDEROS would be able to reproduce effects seen in DELOS (GCs non-user), the situation emerging would be that confirmation of an idebenone treatment effect on respiratory function decline would require re-assessment of B/R with a focus on a combined GCs-user + non-user patient population. As, at the moment, no clear hypotheses exist to support an assumption of idebenone being less efficacious in GCs-users, such a proceeding would be seen as a logical consequence. In this context, it is reiterated that confirmation of the effect on respiratory function in a (DELOS independent) DMD patient study population would by itself be one of the most valuable sources of evidence within the whole development program. Vice versa, if SIDEROS would show negative outcome, the lack of a clear-cut reasoning that/how GCs-use lessens idebenone efficacy would have negative impact on the continued attempts to convert the conditional approval to a full approval in GCs-non-users only. On top of that, the implications for continuation of the conduct of the (then ongoing) MILOS trial remain unclear. In particular, it remains open in how far a restriction to GCs-non-users could be realistically implemented, without introducing again methodological difficulties, e.g. in matching of external control patients etc.

Hence, given current knowledge, the size of SIDEROS as well as the expected potential to confirm earlier idebenone efficacy findings in DMD patients makes it very difficult to agree to specific obligations that would ignore the outcome of SIDEROS in the regulatory decision on Puldysa in GCs non-users. At the moment, the separation of the patient population according to GCs use is primarily motivated by early signals in clinical development of idebenone but could not further be substantiated scientifically. On top of that, the definition of "GCs-use" for a single patient might remain blurred in practice, e.g. it might become difficult to categorise patients with former or intermittent GCs use. This categorisation issue introduces one further source of uncertainty to the task of supporting a label claim within the DMD-patient population.

Another aspect to be considered is the timeframe until confirmatory data can be expected. Due to the study design as well as the milestone event of interest (time to need of assisted ventilation), results of the MILOS study will only be available several years after granting CMA. However, the SIDEROS trial is ongoing and a final study report is expected in Q2 2022. Hence, results from that study would be available within a more appropriate timeframe than MILOS results and could serve as first confirmatory evidence of the effect on respiratory function decline. The extent of clinical benefit will then in a next step be confirmed by MILOS results.

Thus, the applicant is asked to provide a clear post approval strategy that:

- addresses the potential to keep GCs-users separated from non-users, in particular with regard to conduct of MILOS but also in general clinical practice,
- respects and integrates the knowledge gained with SIDEROS into the overall licensing strategy

Although not considered crucial for the decision if it is likely that the applicant will be able to provide comprehensive data or not, there are further aspects concerning MILOS-trial design that would have to be addressed in more detail in separate interaction with the applicant, among those aspects are:

- The schedule of assessment: the half-year intervals might be too long for the assessment of the primary endpoint. This might primarily be a risk on the applicant's side, i.e. the assessment schedule might not be tight enough in order to be able to detect relevant differences.
- Patients randomised to placebo will start idebenone treatment 1 year later than patients randomised to active arm. Regarding this aspect, the baseline criteria in these groups at the start of idebenone treatment might not be comparable. Furthermore, it is unclear how events happening in the first year during placebo treatment will be handled in the part 2-analysis.
- Handling of patients in the primary analysis in whom assisted ventilation would be initiated without fulfilling the protocol criteria.

3.3.8. Conclusions on clinical efficacy

In the phase II DELPHI trial, the primary endpoint was not met, and secondary endpoints indicated a trend in favour of idebenone. However, due to liberal choice of the type-1-error as well as the lack of any measures to handle the multiplicity issue, the DELPHI study cannot be considered as stand-alone evidence of efficacy and results of this study can only be seen as supportive evidence to support idebenone's benefit. In the phase III DELOS trial, the primary endpoint was met, but there are concerns regarding trial integrity, validity of the primary endpoint, effect size and clinical relevance, which hampered a proper assessment of the results of the primary endpoint. From an assessment perspective, the consequence is that DELOS should be seen as the single pivotal trial, with hardly any potential to serve for the purpose to deliver confirmatory evidence. The retrospective SYROS study suffers from several issues regarding GCP aspects, methodological issues and patient selection. Therefore, the interpretability and generalizability of the SYROS outcome data is limited and no convincing conclusion on the long-term positive effect of idebenone on the respiratory function evolution can be drawn. Furthermore, a claim for consistency in terms of magnitude of treatment effect size in respiratory function parameters between the various sources of evidence (DELPHI, DELOS, SYROS) cannot be supported.

It can be agreed to the applicant that idebenone has showed the ability to slow the rate of respiratory function decline in the targeted patient population to a certain extent. In DELOS, the point estimate of the treatment difference observed for PEF%p was above 2.7%, which was postulated by the applicant to be associated with a delay in time to assisted ventilation of 1 year. However, as extensively discussed above, there remains considerable uncertainty in relation to this association between the respiratory function decline and ventilation delay, namely the clinical benefit of idebenone. Furthermore, the effect seen in DELOS lacks confirmation so far.

3.3.9. Clinical safety

The clinical safety experience of Santhera's completed clinical studies of idebenone includes data from

- 3 studies in patients with DMD,
- 1 study in patients with LHON,
- 5 studies in patients with FRDA, and
- 6 Phase I studies in healthy volunteers.
- In addition, 7 legacy studies conducted by Takeda have been included, mainly to support clinical pharmacology review.

In addition, serious adverse events (SAEs) are summarised from the ongoing study in DMD (SNT-III-012 [SIDEROS]) based on data reported up to 15 December 2018, additionally a blinded summary table with preliminary adverse event data has been generated using a data cut of 14 February 2019.

Additionally, SAEs are summarised from 2 ongoing Post Authorisation Safety Studies in LHON (open label study SNT-IV-005 [LEROS], and non-interventional study SNT-IV-003 [PAROS]) based on data reported in up to 15 December 2018.

Pooled Safety Data:

The clinical safety experience of idebenone was evaluated by pooling data from the Phase II and Phase III studies conducted in DMD patients, the study in LHON patients, as well as from all except 1 of the studies conducted in FRDA. The pooled data only include patients who participated in Phase II or Phase III studies. Any patient who received ≥1 dose of study drug and had a safety assessment available was included in the safety analysis. Data pools were generated for double-blind placebo-controlled studies, repeat-dose open-label studies, and for double-blind and extension studies combined as shown in Table 37

Table 37: Data pools in the integrated analysis

Data pool	Population			
	DMD	LHON	FRDA	Full Safety
Double-blind placebo-controlled	SNT-II-001 (DELPHI) SNT-III-003 (DELOS)	SNT-II-003 (RHODOS)	SNT-II-002 (NICOSIA) SNT-III-001 (MICONOS) SNT-III-002 (IONIA)	SNT-II-001 (DELPHI) SNT-III-003 (DELOS) SNT-II-003 (RHODOS) SNT-II-002 (NICOSIA) SNT-III-001 (MICONOS) SNT-III-002 (IONIA)
Repeat dose open-label study	SNT-II-001-E (DELPHI-E)	None	SNT-III-001-E (MICONOS-E) SNT III 002-E (IONIA-E)	SNT-II-001-E (DELPHI-E) SNT-III-001-E (MICONOS-E) SNT-III-002-E (IONIA-E)
Double-blind placebo-controlled and repeat dose open-label studies combined	SNT-II-001 (DELPHI) SNT-III-003 (DELOS) SNT-II-001-E (DELPHI-E)	SNT-II-003 (RHODOS)	SNT-II-002 (NICOSIA) SNT-III-001 (MICONOS) SNT-III-002 (IONIA) SNT-III-001-E (MICONOS-E) SNT III 002-E (IONIA-E)	SNT-II-001 (DELPHI) SNT-III-003 (DELOS) SNT-II-001-E (DELPHI-E) SNT-II-003 (RHODOS) SNT-II-002 (NICOSIA) SNT-III-001 (MICONOS) SNT-III-002 (IONIA) SNT-III-001-E (MICONOS-E) SNT-III-002-E (IONIA-E)

Patient exposure

In total, 53 DMD patients received idebenone in the double-blind and extension studies combined (34 of whom received idebenone only in a double-blind study, 11 of whom received idebenone both in a double-blind and extension study, 7 of whom received placebo in a double-blind study then switched to idebenone in the extension study, and 1 of whom was a new patient who entered directly in an extension study).

Upon request, the applicant clarified the dosage of idebenone over sponsored clinical studies in patients with DMD. In the DELPHI study (SNT-II-001), all patients received idebenone at a dose of 450 mg/day. In the DELPHI-extension study (SNT-II-001-E), the dose was either 450 mg/day or 900 mg/day, depending on the weight of the patient. In the DELOS study (SNT-III-003), a dose of 900 mg/day was used. Altogether 46 out of the 53 idebenone-treated patients (86.8%) have received idebenone at a dose of 900 mg/day including 32 out of the 45 patients included in the double blind studies and 14 out the 19 patients in the extension studies. The total duration of treatment in the DMD population is described in Table 38.

Table 38: Total Duration of Treatment (DMD Population)

	Double-blind		Double-blind and extension
	Placebo	Idebenone	Idebenone
	n=42	n=45	n=53
Duration of exposure (days)			
Mean	348.6	341.0	549.5
Standard deviation	59.0	61.8	315.1
Exposure >0.5 years	40 (95.2)	43 (95.6)	51 (96.2)
Exposure >1 year	14 (33.3)	11 (24.4)	29 (54.7)
Exposure >1.5 years			19 (35.8)
Exposure >2 years			11 (20.8)
Exposure >2.5 years			11 (20.8)
Exposure >3 years			1 (1.9)

DMD = Duchenne Muscular Dystrophy

In addition, as of 31 January 2020 there are 243 patients who were randomised and received blinded treatment (900 mg/day idebenone or placebo) in the ongoing SIDEROS study. Of those, 112 are enrolled in the ongoing SIDEROS-extension study and receive idebenone at 900 mg/day.

In the United Kingdom, an Early Access to Medicines registry was initiated for DMD patients. From the start of this program in September 2017 until the last data lock point (Early Access to Medicines Report #9), a cumulative number of 79 patients with DMD received idebenone at 900 mg/day.

Additionally, in the US the applicant provides idebenone via an EAP to allow the treatment of DMD patients. From the start of this program in December 2017 a cumulative number of 35 patients received idebenone at 900 mg/day.

Full Safety Population

Patients in the full safety population by study type and duration are displayed in Table 39 and Table 40.

Table 39: Enumeration of Patients by Dose and Study Type (Full Safety Population)

	Number (%) patients[a]				
	Placebo	Idebenone	Baseline dose (mg/day)		
		All doses	180/360	450/900	1350/2250
Double-blind	166	356	69 (19.4)	192 (53.9)	95 (26.7)
Extension		287[b]	0	19 (6.6)	268 (93.4)
Double-blind and extension		439[b]	69 (15.7)	200 (45.6)	170 (38.7)

For patients in the idebenone group participating in several studies, the dosage from the first study is used to define the subgroups for the Double-bind and Extension
[a]% shown are for the row
[b] includes 82 patients who had received placebo in a double-blind study.

Table 40: Total Duration of Treatment (Full Safety Population)

	Double-blind		Double-blind and extension
	Placebo	Idebenone	Idebenone
	n=166	n=356	n=439
Duration of exposure (days)	n=166	n=355	n=438
Mean	279.3	282.2	600.3
Standard deviation	101.1	98.7	362.5
Exposure >0.5 years	100 (60.2)	220 (61.8)	344 (78.4)
Exposure >1 year	39 (23.5)	91 (25.6)	276 (62.9)
Exposure >1.5 years			205 (46.7)
Exposure >2 years			148 (33.7)
Exposure >2.5 years			127 (28.9)
Exposure >3 years			47 (10.7)
Exposure >3.5 years			2 (0.5)

Adverse events

Overview of TEAEs

In the DMD population, the incidence of TEAEs and discontinuations of study drug due to TEAEs were similar for the idebenone and placebo groups in the double-blind studies (Table 41).

In the full safety population, incidence of TEAEs was also similar, a higher percentage of discontinuations of study drug due to TEAEs was found for the idebenone group but still numbers were very low (Table 42).

Table 41: Overview of TEAEs (DMD Population)

	Number (%) patients		
	DMD Population		
	Double-blind		Double-blind and extension
	Placebo	Idebenone	Idebenone
	n=42	n=45	n=53
Patients with at least 1 TEAE	40 (95.2)	42 (93.3)	49 (92.5)
Treatment-related TEAE[a]	14 (33.3)	11 (24.4)	17 (32.1)
Severe TEAE	4 (9.5)	1 (2.2)	3 (5.7)
SAE	6 (14.3)	3 (6.7)	11 (20.8)
Deaths	0	0	0
TEAE leading to discontinuation of study	2 (4.8)	1 (2.2)	1 (1.9)
TEAE leading to discontinuation of treatment	2 (4.8)	2 (4.4)	2 (3.8)

[a] Causality unknown, unlikely, possible, probable or related
DMD=Duchenne muscular dystrophy, SAE=serious adverse event, TEAE=treatment-emergent adverse event

Table 42: Overview of TEAEs (Full Safety Populations)

	Number (%) patients		
	Full Safety Population		
	Double-blind		Double-blind and extension
	Placebo	Idebenone	Idebenone
	n=166	n=356	n=439
Patients with at least 1 TEAE	153 (92.2)	329 (92.4)	420 (95.7)
Treatment-related TEAE[a]	66 (39.8)	160 (44.9)	236 (53.8)
Severe TEAE	12 (7.2)	26 (7.3)	54 (12.3)
SAE	14 (8.4)	25 (7.0)	82 (18.7)
Deaths	0	0	1 (0.2)
TEAE leading to discontinuation of study	5 (3.0)	7 (2.0)	15 (3.4)
TEAE leading to discontinuation of treatment	4 (2.4)	17 (4.8)	43 (9.8)

[a] Causality unknown, unlikely, possible, probable or related
DMD=Duchenne muscular dystrophy, SAE=serious adverse event, TEAE=treatment-emergent adverse event

Common AEs

DMD Population

During the double-blind studies, the following were the most common TEAEs in the idebenone group: diarrhoea, headache, nasopharyngitis, upper respiratory tract infection, pyrexia, bronchitis, abdominal pain and gastroenteritis. The most common TEAEs in the placebo group were: nasopharyngitis, upper respiratory tract infection, headache, bronchitis, constipation, rhinitis and diarrhoea were the most common TEAEs.

The TEAEs that were most frequent (≥5.0% of patients) in the idebenone group and that were ≥2.0% units more frequent than in the placebo group in the double-blind studies were diarrhoea (20.0% vs 14.3%), pyrexia (13.3% vs 7.1%), abdominal pain (11.1% vs 7.1%), gastroenteritis (11.1% vs 2.4%), left ventricular failure (6.7% vs 2.4%), otitis media (6.7% vs 0%), and chromaturia (6.7% vs 0%). All other TEAEs were reported at an incidence below 5.0% (i.e., 2 patients or fewer) in the idebenone group in the double-blind studies (Table 43).

When considering TEAE data from the double-blind and extension studies combined, no new safety signal was identified compared with the double-blind studies.

Table 43: TEAEs Reported by > 1 Patient in any Treatment Group (DMD Population)

System organ class Preferred term	Double-blind		Double-blind and extension
	Placebo n=42	Idebenone n=45	Idebenone n=53
Cardiac disorders			
Cardiomyopathy	1 (2.4)	1 (2.2)	3 (5.7)
Left ventricular failure	1 (2.4)	3 (6.7)	3 (5.7)
Gastrointestinal Disorders			
Diarrhoea	6 (14.3)	9 (20.0)	10 (18.9)
Abdominal pain	3 (7.1)	5 (11.1)	6 (11.3)
Constipation	7 (16.7)	3 (6.7)	4 (7.5)
Nausea	2 (4.8)	1 (2.2)	3 (5.7)
Dyspepsia	0	1 (2.2)	2 (3.8)
Gastrointestinal disorder	0	2 (4.4)	2 (3.8)
Vomiting	3 (7.1)	2 (4.4)	2 (3.8)
Toothache	0	0	2 (3.8)
Abdominal discomfort	2 (4.8)	0	1 (1.9)
Abdominal pain upper	2 (4.8)	0	0
Haemorrhoids	2 (4.8)	0	0
General disorders and administration site conditions			
Pyrexia	3 (7.1)	6 (13.3)	6 (11.3)
Influenza-like illness	1 (2.4)	2 (4.4)	3 (5.7)
Infections and Infestations			
Upper respiratory tract infection	8 (19.0)	6 (13.3)	13 (24.5)
Nasopharyngitis	10 (23.8)	8 (17.8)	9 (17.0)
Bronchitis	7 (16.7)	5 (11.1)	8 (15.1)
Gastrointestinal infection	1 (2.4)	2 (4.4)	6 (11.3)
Respiratory tract infection	0	2 (4.4)	6 (11.3)
Gastroenteritis	1 (2.4)	5 (11.1)	5 (9.4)
Pharyngitis	3 (7.1)	1 (2.2)	4 (7.5)
Viral infection	3 (7.1)	2 (4.4)	4 (7.5)
Otitis media	0	3 (6.7)	3 (5.7)
Rhinitis	7 (16.7)	3 (6.7)	3 (5.7)
Ear infection	0	1 (2.2)	2 (3.8)
Pneumonia	3 (7.1)	0	2 (3.8)
Influenza	2 (4.8)	0	1 (1.9)
Injury, poisoning, and procedural complications			
Femur fracture	2 (4.8)	2 (4.4)	2 (3.8)
Joint dislocation	2 (4.8)	0	0

System organ class Preferred term	Double-blind		Double-blind and extension
	Placebo n=42	Idebenone n=45	Idebenone n=53
Investigations			
Electrocardiogram abnormal	1 (2.4)	2 (4.4)	2 (3.8)
Weight decreased	0	1 (2.2)	2 (3.8)
Blood cholesterol increased	2 (4.8)	1 (2.2)	1 (1.9)
Blood phosphorous increased	3 (7.1)	1 (2.2)	1 (1.9)
Breath sounds abnormal	2 (4.8)	1 (2.2)	1 (1.9)
Metabolism and nutrition disorders			
Hypocalcemia	0	2 (4.4)	2 (3.8)
Musculoskeletal and connective tissue disorders			
Scoliosis	1 (2.4)	2 (4.4)	4 (7.5)
Back pain	4 (4.9)	3 (6.7)	3 (5.7)
Muscle contracture	0	2 (4.4)	2 (3.8)
Arthralgia	2 (4.8)	0	1 (1.9)
Pain in extremity	2 (4.8)	0	0
Osteoporosis	2 (4.8)	0	0
Nervous system disorders			
Headache	7 (16.7)	8 (17.8)	10 (8.9)
Migraine	2 (4.8)	1 (2.2)	4 (7.5)
Renal and urinary disorders			
Chromaturia	0	3 (6.7)	3 (5.7)
Respiratory, thoracic, and mediastinal disorders			
Cough	2 (4.8)	1 (2.2)	4 (7.5)
Nasal congestion	1 (2.4)	2 (4.4)	3 (5.7)
Oropharyngeal pain	1 (2.4)	2 (4.4)	3 (5.7)
Rhinorrhea	2 (4.8)	3 (6.7)	3 (5.7)
Epistaxis	0	2 (4.4)	2 (3.8)
Restrictive pulmonary disease	0	1 (2.2)	2 (3.8)
Skin and subcutaneous tissue disorders			
Rash	0	2 (4.4)	2 (3.8)
Seborrhoeic dermatitis	2 (4.8)	1 (2.2)	1 (1.9)
Surgical and medical procedures			
Tooth extraction	0	1 (2.2)	2 (3.8)

DMD=Duchenne muscular dystrophy, F= Number of events, TEAE=treatment-emergent adverse event

The profile of common TEAEs is consistent with that from the completed clinical studies. It should be noted that these data are preliminary and as the study is still blinded include events on idebenone and placebo (Table 44).

Table 44: Adverse Events Reported by ≥ 2% of Total SIDEROS Population (Blinded Data) as of 14 Feb 2019 (Safety Population)

	Number (%) patients N=216	
Any AE	146	(67.6)
Nasopharyngitis	41	(19.0)
Headache	29	(13.4)
Oropharyngeal pain	20	(9.3)
Cough	19	(8.8)
Upper respiratory tract infection	19	(8.8)
Diarrhoea	17	(7.9)
Back pain	14	(6.5)
Vomiting	11	(5.1)
Abdominal pain	8	(3.7)
Abdominal pain upper	8	(3.7)
Arthralgia	8	(3.7)
Constipation	7	(3.2)
Epistaxis	7	(3.2)
Chromaturia	6	(2.8)
Fall	6	(2.8)
Nausea	6	(2.8)
Pharyngitis	6	(2.8)
Contusion	5	(2.3)
Ear infection	5	(2.3)
Pneumonia	5	(2.3)

TEAE=treatment-emergent adverse event

Full Safety Population

During the double-blind studies, the following TEAEs were the most common in the idebenone group and in the placebo group: headache, nasopharyngitis, diarrhoea, nausea, and upper respiratory tract infection.

The TEAEs that were most frequent (≥5.0% of patients) in the idebenone group and that were ≥2.0% more frequent than in the placebo group in the double-blind studies were nasopharyngitis (26.7% vs 21.7%), diarrhoea (17.1% vs 11.4%), cough (8.4% vs 5.4%), vomiting (9.3% vs 6.6%) and gastroenteritis (6.5% vs 4.2%). All other TEAEs were reported at an incidence below 5.0% in the idebenone group in the double-blind studies (Table 45).

When considering TEAE data from the double-blind and extension studies combined, no new safety signal was identified compared with the double-blind studies

Table 45: TEAEs Reported by ≥2.0% Patients in any Treatment Group (Full Safety Population)

System organ class Preferred term	Double-blind studies		Double-blind and extension
	Placebo n=166	Idebenone n=356	Idebenone n=439
Cardiac disorders			
Tachycardia	5 (3.0)	6 (1.7)	13 (3.0)
Ear and labyrinth disorders			
Vertigo	3 (1.8)	5 (1.4)	9 (2.1)
Gastrointestinal disorders			
Diarrhoea	19(11.4)	61 17.1( )	94 (21.4)
Nausea	17 (10.2)	43 (12.1)	73 (16.6)
Abdominal pain upper	12 (7.2)	27 (7.6)	51 (11.6)
Vomiting	11 (6.6)	33 (9.3)	51 (11.6)
Abdominal pain	13 (7.8)	20 (5.6)	27 (6.2)
Toothache	3 (1.8)	14 (3.9)	24 (5.5)
Dyspepsia	4 (2.4)	15 (4.2)	23 (5.2)
Constipation	12 (7.2)	11 (3.1)	21 (4.8)
Gastroesophageal reflux disease	1 (0.6)	4 (1.1)	12 (2.7)
Abdominal discomfort	4 (2.4)	2 (0.6)	6 (1.4)
Flatulence	5 (3.0)	3 (0.8)	4 (0.9)
General disorders and administration site conditions			
Pyrexia	9 (5.4)	21 (5.9)	44 (10.0)
Fatigue	10 (6.0)	21 (5.9)	38 (8.7)
Pain	0	3 (0.8)	19 (4.3)
Asthenia	0	3 (0.8)	11 (2.5)
Chest pain	3 (1.8)	7 (2.0)	11 (2.5)
Influenza-like illness	1 (0.6)	6 (1.7)	10 (2.3)
Oedema peripheral	1 (0.6)	3 (0.8)	9 (2.1)
Infections and Infestations			
Nasopharyngitis	36 (21.7)	95 (26.7)	148 (33.7)
Upper respiratory tract infection	23 (13.9)	37 (10.4)	64 (14.6)
Influenza	12 (7.2)	29 (8.1)	58 (13.2)
Gastroenteritis	7 (4.2)	23 (6.5)	32 (7.3)
Bronchitis	8 (4.8)	15 (4.2)	28 (6.4)
Sinusitis	6 (3.6)	10 (2.8)	23 (5.2)
Rhinitis	12 (7.2)	9 (2.5)	20 (4.6)
Cystitis	1 (0.6)	7 (2.0)	19 (4.3)
Ear infection	2 (1.2)	7 (2.0)	15 (3.4)
Pharyngitis	4 (2.4)	7 (2.0)	14 (3.2)

System organ class Preferred term	Double-blind studies		Double-blind and extension
	Placebo n=166	Idebenone n=356	Idebenone n=439
Urinary tract infection	1 (0.6)	7 (2.0)	14 (3.2)
Gastroenteritis viral	4 (2.4)	3 (0.8)	13 (3.0)
Viral infection	3 (1.8)	4 (1.1)	13 (3.0)
Pneumonia	3 (1.8)	2 (0.6)	11 (2.5)
Respiratory tract infection	0	5 (1.4)	10 (2.3)
Gastrointestinal infection	2 (1.2)	4 (1.1)	9 (2.1)
Injury, poisoning, and procedural complications			
Fall	9 (5.4)	24 (6.7)	47 (10.7)
Ligament sprain	3 (1.8)	12 (3.4)	27 (6.2)
Contusion	1 (0.6)	5 (1.4)	15 (3.4)
Procedural pain	1 (0.6)	6 (1.7)	11 (2.5)
Laceration	3 (1.8)	6 (1.7)	11 (2.5)
Limb injury	3 (1.8)	6 (1.7)	10 (2.3)
Investigations			
Blood creatine phosphokinase increased	4 (2.4)	3 (0.8)	11 (2.5)
Blood triglycerides increased	4 (2.4)	7 (2.0)	7 (1.6)
Gamma glutamyl transferase increased	6 (3.6)	3 (0.8)	5 (1.1)
Blood cholesterol increased	4 (2.4)	1 (0.3)	1 (0.2)
Musculoskeletal and connective tissue disorders			
Back pain	13 (7.8)	34 (9.6)	54 (12.3)
Pain in extremity	8 (4.8)	23 (6.5)	46 (10.5)
Arthralgia	8 (4.8)	13 (3.7)	28 (6.4)
Muscle spasms	6 (3.6)	12 (3.4)	25 (5.7)
Myalgia	5 (3.0)	14 (3.9)	20 (4.6)
Musculoskeletal pain	0	8 (2.2)	16 (3.6)
Scoliosis	4 (2.4)	2 (0.6)	15 (3.4)
Neck pain	3 (1.8)	3 (0.8)	11 (2.5)
Bursitis	2 (1.2)	4 (1.1)	9 (2.1)
Nervous system disorders			
Headache	49 (29.5)	106 (29.8)	151 (34.4)
Dizziness	6 (3.6)	18 (5.1)	36 (8.2)
Migraine	3 (1.8)	9 (2.5)	14 (3.2)

TEAE=treatment-emergent adverse event

TEAE Incidence Rates

DMD Population

The following events (PT) were reported at an incidence rate ≥5.0 units higher with idebenone compared with placebo: headache, diarrhoea, epistaxis, pyrexia, gastroenteritis, chromaturia, and otitis media. All other TEAEs were reported at a similar, or at a lower incidence, in the idebenone group versus placebo (Table 46).

Table 46: TEAEs with Incidence Rates ≥5.0 per 100 Patient-Years in Either Treatment Group During the Double-Blind Studies (DMD Population)

	F (Incidence rate)		
	Double-blind		Double-blind and extension
	Placebo	Idebenone	Idebenone
	Patient-years 40.1	Patient-years 42.0	Patient-years 79.7
Headache	15 (37.4)	22 (52.4)	38 (47.7)
Upper respiratory tract infection	12 (29.9)	7 (16.7)	20 (25.1)
Nasopharyngitis	12 (29.9)	12 (28.6)	13 (16.3)
Diarrhoea	8 (20.0)	11 (26.2)	12 (15.0)
Abdominal pain	5 (12.5)	6 (14.3)	11 (13.8)
Bronchitis	8 (20.0)	6 (14.3)	10 (12.5)
Migraine	7 (17.5)	4 (9.5)	9 (11.3)
Epistaxis	0	3 (7.1)	8 (10.0)
Pharyngitis	3 (7.5)	2 (4.8)	8 (10.0)
Constipation	7 (17.5)	4 (9.5)	7 (8.8)
Pyrexia	4 (10.0)	7 (16.7)	7 (8.8)
Cough	2 (5.0)	1 (2.4)	6 (7.5)
Gastroenteritis	1 (2.5)	6 (14.3)	6 (7.5)
Nausea	2 (5.0)	2 (4.8)	5 (6.3)
Rhinitis	9 (22.5)	4 (9.5)	4 (5.0)
Viral infection	3 (7.5)	2 (4.8)	4 (5.0)
Back pain	6 (15.0)	3 (7.1)	3 (3.8)
Chromaturia	0	3 (7.1)	3 (3.8)
Electrocardiogram abnormal	1 (2.5)	3 (7.1)	3 (3.8)
Influenza like illness	2 (5.0)	2 (4.8)	3 (3.8)
Left ventricular failure	1 (2.5)	3 (7.1)	3 (3.8)
Otitis media	0	3 (7.1)	3 (3.8)
Rhinorrhoea	2 (5.0)	3 (7.1)	3 (3.8)
Femur fracture	2 (5.0)	2 (4.8)	3 (3.8)
Penumonia	4 (10.0)	0	2 (2.5)
Vomiting	4 (10.0)	2 (2.8)	2 (2.5)
Abdominal discomfort	2 (5.0)	0	1 (1.3)
Arthralgia	9 (22.5)	0	1 (1.3)
Blood cholersterol increased	2 (5.0)	1 (2.4)	1 (1.3)
Blood phosphorus increased	4 (10.0)	1 (2.4)	1 (1.3)
Breath sounds abnormal	2 (5.0)	1 (2.4)	1 (1.3)
Influenza	2 (5.0)	0	1 (1.3)
Seborrhoeic dermatitis	2 (5.0)	1 (2.4)	1 (1.3)
Abdominal pian upper	2 (5.0)	0	0
Haemorrhoids	3 (7.5)	0	0
Joint dislocation	2 (5.0)	0	0
Osteoporosis	2 (5.0)	0	0
Pain in extremity	2 (5.0)	0	0
Tendinous contracture	2 (5.0)	0	0

Incidence rate is number of events/ treatment exposure (in patient-years)* 100
DMD=Duchenne muscular dystrophy, F= Number of events, TEAE=treatment-emergent adverse event

Full Safety Population

In the full safety population, the following events (PT) were reported at an incidence rate ≥5.0 units higher in the idebenone group compared with placebo: nasopharyngitis, diarrhoea, abdominal pain

upper, cough, dyspepsia and chromaturia. All other preferred terms in the double-blind studies were reported at a similar, or at a lower incidence, in the idebenone group versus placebo (Table 47).

Table 47: TEAEs with Incidence Rates ≥5.0 per 100 Patient-Years in Either Treatment Group During the Double-Blind Studies (Full Safety Population)

	F (Incidence rate)		
	Double-blind		Double-blind and extension
	Placebo	Idebenone	Idebenone
Preferred term	Patient-years 126.9	Patient-years 274.3	Patient-years 719.8
Headache	143 (112.7)	203 (74.0)	359 (49.9)
Nasopharyngitis	51 (40.2)	127 (46.3)	245 (34.0)
Diarrhoea	29 (22.8)	83 (30.3)	159 (22.1)
Nausea	28 (22.1)	65 (23.7)	117 (16.3)
Upper respiratory tract infection	30 (23.6)	59 (21.5)	103 (14.3)
Abdominal pain upper	12 (9.5)	41 (14.9)	82 (11.4)
Influenza	15 (11.8)	40 (14.6)	80 (11.1)
Vomiting	18 (14.2)	45 (16.4)	75 (10.4)
Back pain	16 (12.6)	40 (14.6)	74 (10.3)
Cough	9 (7.1)	38 (13.9)	74 (10.3)
Pain in extremity	9 (7.1)	31 (11.3)	71 (9.9)
Oropharyngeal pain	16 (12.6)	35 (12.8)	64 (8.9)
Fall	11 (8.7)	30 (10.9)	59 (8.2)
Pyrexia	12 (9.5)	23 (8.4)	51 (7.1)
Dizziness	10 (7.9)	20 (7.3)	48 (6.7)
Dyspepsia	4 (3.2)	32 (11.7)	45 (6.3)
Fatigue	12 (9.5)	23 (8.4)	43 (6.0)
Abdominal pain	16 (12.6)	29 (10.6)	41 (5.7)
Gastroenteritis	9 (7.1)	29 (10.6)	38 (5.3)
Bronchitis	9 (7.1)	17 (6.2)	34 (4.7)
Arthralgia	15 (11.8)	15 (5.5)	32 (4.4)
Myalgia	5 (3.9)	23 (8.4)	31 (4.3)
Dysmenorrhoea	12 (9.5)	6 (2.2)	28 (3.9)
Chromaturia	0	14 (5.1)	27 (3.8)
Constipation	12 (9.5)	12 (4.4)	27 (3.8)
Toothache	4 (3.2)	15 (5.5)	26 (3.6)
Epistaxis	8 (6.3)	10 (3.6)	22 (3.1)
Migraine	8 (6.3)	14 (5.1)	22 (3.1)
Rhinitis	15 (11.8)	10 (3.6)	15 (2.1)
Insomnia	12 (9.5)	5 (1.8)	15 (2.1)

Incidence rate is number of events/ treatment exposure (in patient-years)* 100
F= Number of events, TEAE=treatment-emergent adverse event

TEAEs by Severity

DMD Population

In the double-blind DMD studies, the incidences of mild and moderate TEAEs were similar in the idebenone and placebo groups (Table 48).The severe TEAE in the idebenone group in the double-blind DMD studies was sleep apnoea syndrome reported for 1 patient (2.2%). Severe TEAEs reported in the placebo group were pneumonia reported for 2 patients (4.8%), and femur fracture, osteoporosis, post-traumatic pain, respiratory failure, and scoliosis reported for 1 patient each (2.4%) in the placebo group. During the extension study, severe TEAEs reported were cardiopulmonary failure and pneumonia in 1 patient, and scoliosis in 1 patient.

Table 48: TEAEs by Severity (DMD Population)

	Number (%) patients		
	Double-blind		Double-blind and extension
	Placebo	Idebenone	Idebenone
	n=42	n=45	n=53
Mild	39 (92.9)	40 (88.9)	47 (88.7)
Moderate	15 (35.7)	16 (35.6)	23 (43.4)
Severe	4 (9.5)	1 (2.2)	3 (5.7)

DMD=Duchenne muscular dystrophy, TEAE=treatment-emergent adverse event

Full Safety Population

In the double-blind DMD studies, the incidences of mild, moderate and severe TEAEs were similar in the idebenone and placebo groups (Table 49). The severe TEAEs by more than 1 patient receiving idebenone are as follows: During the double-blind studies, severe diarrhoea, back pain, and pain in extremity were each reported for 3 patients (0.8%) in the idebenone group vs 0 in the placebo group. Severe migraine, nausea, vomiting, toothache, chest pain, procedural pain, and atrial fibrillation were each reported for 2 patients (0.6%) in the idebenone group vs 0 in the placebo group, and severe headache was reported for 2 patients (0.6%) vs 1 (0.6%)

Table 49: TEAEs by Severity (Full Safety Population)

	Number (%) patients		
	Double-blind		Double-blind and extension
	Placebo	Idebenone	Idebenone
	n=166	n=356	n=439
Mild	136 (81.9)	301 (84.6)	394 (89.7)
Moderate	59 (35.5)	121 (34.0)	214 (48.7)
Severe	12 (7.2)	26 (7.3)	54 (12.3)
Unknown	11 (6.6)	19 (5.3)	34 (7.7)

TEAE=treatment-emergent adverse event

TEAEs by Causality

DMD Population

The TEAEs assessed as related to study drug for ≥2 patients in the double-blind DMD studies (regardless of treatment group) were chromaturia reported for 3 patients (6.7%) in the idebenone group and 0 in the placebo group, blood phosphorus increased reported for 1 patient in the idebenone group (2.2%) and 3 (7.1%) in the placebo group, diarrhoea reported for 2 patients in each group (4.4% and 4.8%, in the idebenone and placebo groups, respectively), and constipation reported for 1 patient in each group (2.2% and 2.4%, respectively). Additionally, abdominal discomfort was reported for 2 patients (4.8%) in the placebo group and 0 in the idebenone group (Table 50).

No TEAEs were assessed as related to study drug in the extension studies.

Table 50: TEAEs with Related, Possible or Unlikely Relationship to Study Drug (DMD Population)

Preferred term	Causality	Double-blind		Double-blind and extension
		Placebo n=42	Idebenone n=45	Idebenone n=53
Chromaturia	Related	0	3 (6.7)	3 (5.7)
Diarrhoea	Related	2 (4.8)	2 (4.4)	2 (3.8)
Headache	Related	0	1 (2.2)	1 (1.9)
Constipation	Related	1 (2.4)	1 (2.2)	1 (1.9)
Nausea	Related	0	1 (2.2)	1 (1.9)
Rhinitis	Related	1 (2.4)	0	0
Ear infection	Related	0	1 (2.2)	1 (1.9)
Electrocardiogram abnormal	Related	0	1 (2.2)	1 (1.9)
Abdominal discomfort	Related	2 (4.8)	0	0
Rash	Related	0	1 (2.2)	1 (1.9)
Blood phosphorus increased	Related	3 (7.1)	1 (2.2)	1 (1.9)
Blood triglycerides increased	Related	1 (2.4)	0	0
Decreased appetite	Related	0	1 (2.2)	1 (1.9)
Fatigue	Related	1 (2.4)	0	0
Fluid intake reduced	Related	0	1 (2.2)	1 (1.9)
Gastritis	Related	0	1 (2.2)	1 (1.9)
Gastrooesophageal reflux disease	Related	0	1 (2.2)	1 (1.9)
Pruritus	Related	0	1 (2.2)	1 (1.9)
Sciatica	Related	0	1 (2.2)	1 (1.9)
Troponin i increased	Related	1 (2.4)	0	0
Urticaria	Related	1 (2.4)	0	0
Arrhythmia supraventricular	Related	1 (2.4)	0	0
Back disorder	Related	1 (2.4)	0	0
Fatigue	Possible	0	1 (2.2)	1 (1.9)
Nausea	Possible	0	0	1 (1.9)
Blood cholesterol increased	Possible	1 (2.4)	0	0
Diarrhoea	Unlikely	1 (2.4)	0	0
Headache	Unlikely	0	1 (2.2)	1 (1.9)
Abdominal pain	Unlikely	0	1 (2.2)	2 (3.8)
Cough	Unlikely	0	0	1 (1.9)
Migraine	Unlikely	0	0	1 (1.9)
Cardiomyopathy	Unlikely	0	0	1 (1.9)
Dyspepsia	Unlikely	0	0	1 (1.9)
Epistaxis	Unlikely	0	1 (2.2)	1 (1.9)
Gastrointestinal disorder	Unlikely	0	1 (2.2)	1 (1.9)
Vomiting	Unlikely	1 (2.4)	1 (2.2)	1 (1.9)
Blood cholesterol increased	Unlikely	1 (2.4)	1 (2.2)	1 (1.9)
Cystitis	Unlikely	0	0	1 (1.9)
Fungal infection	Unlikely	0	0	1 (1.9)
Fungal skin infection	Unlikely	1 (2.4)	1 (2.2)	1 (1.9)
Haematuria	Unlikely	0	1 (2.2)	1 (1.9)
Pruritus	Unlikely	1 (2.4)	0	0
Abdominal pain upper	Unlikely	2 (4.8)	0	0

TEAE=treatment-emergent adverse event

Full Safety Population

During the double-blind studies, the study drug related TEAEs reported by ≥2 patients in the Full Safety Population receiving idebenone were chromaturia reported for 7 patients (2.0%) in the idebenone group and 0 in the placebo group, abdominal pain upper reported for 6 patients (1.7%) in the idebenone group and 1 (0.6%) in the placebo group, headache, nausea, diarrhoea each reported for 6 patients (1.7%) in the idebenone group and 3 (1.8%) in the placebo group, fatigue reported for 5 patients (1.4%) in the idebenone group and 3 (1.8%) in the placebo group, abdominal pain, dizziness, and constipation each reported for 2 patients (0.6%) in the idebenone group and 1 (0.6%) in the placebo group, and decreased appetite and pollakiuria each reported for 2 patients (0.6%) in the idebenone group and 0 in the placebo group.

In the extension studies, 28 patients (9.8%) experienced study drug related TEAEs. The related TEAEs reported by 2 or more patients were nausea reported for 9 patients (3.1%), chromaturia 7 patients (2.4%), abdominal pain upper 6 patients (2.1%), headache 5 patients (1.7%), and abdominal pain and muscle spasms each reported for 2 patients (0.7%).

TEAEs of abnormal liver function or hepatitis, and TEAEs related to blood count abnormalities

No DMD patients experienced a TEAE related to abnormal liver function or hepatitis. Only 1 DMD patient receiving placebo in the double-blind studies (2.4%) experienced a TEAE related to blood count abnormalities (anaemia).

In the full-safety population, the incidence of TEAEs related to abnormal liver function or hepatitis was lower in the idebenone group (2.8%) vs placebo (4.8%) in the double-blind studies (Table 51).The incidence of TEAEs related to blood count abnormalities was similar in the idebenone group (2.8%) vs placebo (3.0%) in the double-blind studies (Table 52).

Table 51: TEAEs Related to Abnormal Liver Function or Hepatitis (Full Safety Population)

	Number (%) patients		
	Double-blind		Double-blind and extension
	Placebo n=166	Idebenone n=356	Idebenone n=439
Total with adverse events	8 (4.8)	10 (2.8)	21 (4.8)
Hepatobiliary disorders	0	1 (0.3)	3 (0.7)
Liver injury	0	0	1 (0.2)
Hepatic function abnormal	0	1 (0.3)	1 (0.2)
Hyperbilirubinaemia	0	0	1 (0.2)
Investigations	8 (4.8)	10 (2.8)	19 (4.3)
Alanine aminotransferase increased	3 (1.8)	3 (0.8)	8 (1.8)
Gamma-glutamyltransferase increased	6 (3.6)	3 (0.8)	5 (1.1)
Blood bilirubin increased	1 (0.6)	3 (0.8)	4 (0.9)
Aspartate aminotransferase increased	1 (0.6)	1 (0.3)	4 (0.9)
Liver function test abnormal	0	1 (0.3)	2 (0.5)
Hepatic enzyme increased	0	0	1 (0.2)
Blood alkaline phosphatase increased	1 (0.6)	0	0

TEAE=treatment-emergent adverse event

Table 52: TEAEs Related to Blood Count Abnormalities (Full Safety Population)

	Number (%) patients		
	Double-blind		Double-blind and extension
	Placebo n=166	Idebenone n=356	Idebenone n=439
Total with adverse events	5 (3.0)	10 (2.8)	22 (5.0)
Blood and lymphatic system disorders	1 (0.6)	1 (0.3)	9 (2.1)
Anaemia	1 (0.6)	0	5 (1.1)
Microcytic anaemia	0	0	2 (0.5)
Neutropenia	0	1 (0.3)	1 (0.2)
Thrombocytopenia	0	0	1 (0.2)
Investigations	4 (2.4)	9 (2.5)	14 (3.2)
White blood cell count decreased	3 (1.8)	4 (1.1)	7 (1.6)
Haemoglobin decreased	1 (0.6)	1 (0.3)	3 (0.7)
Haematocrit decreased	1 (0.6)	1 (0.3)	2 (0.5)
Neutrophil count decreased	0	2 (0.6)	2 (0.5)
Lymphocyte count decreased	0	1 (0.3)	1 (0.2)
Monocyte count decreased	0	1 (0.3)	1 (0.2)
Red blood cell count decreased	0	1 (0.3)	1 (0.2)

TEAE=treatment-emergent adverse event

Safety Profile as described in the SmPC of Raxone (current version taken from EMA Homepage on 2019-07-15)

Summary of the safety profile

The most commonly reported adverse reactions to idebenone are mild to moderate diarrhoea (usually not requiring the discontinuation of the treatment), nasopharyngitis, cough and back pain.

Tabulated list of adverse reactions

The following adverse reactions emerging from clinical trials in LHON patients or reported post-marketing in other indications are tabulated below. Frequency groupings are defined to the following convention: very common (≥1/10), common (≥1/100 to <1/10), not known (cannot be estimated from the available data).

Table 53

System Organ Class	Preferred Term	Frequency
Infections and Infestations	Nasopharyngitis	Very common
	Bronchitis	Not known
Blood and lymphatic system disorders	Agranulocytosis, anaemia, leukocytopenia, thrombocytopenia, neutropenia	Not known
Metabolism and nutrition disorders	Blood cholesterol increased, blood triglycerides increased	Not known
Nervous system disorders	Seizure, delirium, hallucinations, agitation, dyskinesia, hyperkinesia, poriomania, dizziness, headache, restlessness, stupor	Not known
Respiratory, thoracic and mediastinal disorders	Cough	Very common
Gastrointestinal disorders	Diarrhoea	Common
	Nausea, vomiting, anorexia, dyspepsia	Not known

Hepatobiliary disorders	Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, gamma-lutamyltransferase increased, blood bilirubin increased, hepatitis	Not known
Skin and subcutaneous tissue disorders	Rash, pruritus	Not known
Musculoskeletal and connective tissue disorders	Back pain	Common
	Pain in extremity	Not known
Renal and urinary disorders	Azotaemia, chromaturia	Not known
General disorders and administration site conditions	Malaise	Not known

Serious adverse events and deaths

Deaths

DMD Population

No DMD patients died during the clinical programme.

Full Safety Population

In the Full Safety Population, there was 1 fatal SAE in a non-ambulatory patient receiving idebenone in an extension study (SNT-III-001-E). The death was determined to be unrelated to study drug.

Serious AEs

DMD Population

The incidence of SAEs was lower in the idebenone group vs placebo in the double-blind studies (6.7% vs 14.3%), with no TEAE preferred term reported by >1 patient in the idebenone group.

Considering the double-blind and extension studies combined, 11 patients (20.8%) receiving idebenone experienced an SAE. Pneumonia and scoliosis were each reported in 2 patients (3.8%). All other SAEs were reported in individual patients (1.9%) (Table 54). None of the SAEs were considered related to study drug.

Table 54: Incidence of Serious Adverse Events (DMD Population)

	Number (%) patients		
	Double-blind		Double-blind and extension
	Placebo	Idebenone	Idebenone
Preferred term	n=42	n=45	n=53
Patients with ≥1 SAE	6 (14.3)	3 (6.7)	11 (20.8)
Pneumonia	2 (4.8)	0	2 (3.8)
Scoliosis	0	0	2 (3.8)
Ankle fracture	0	1 (2.2)	1 (1.9)
Appendicitis	0	0	1 (1.9)
Cardiopulmonary failure	0	0	1 (1.9)
Muscle spasms	0	0	1 (1.9)
Sleep apnoea syndrome	0	1 (2.2)	1 (1.9)
Somnolence	0	0	1 (1.9)
Supraventricular tachycardia	0	0	1 (1.9)
Urticaria	0	1 (2.2)	1 (1.9)
Acute respiratory failure	1 (2.4)	0	0

Preferred term	Number (%) patients		
	Double-blind		Double-blind and extension
	Placebo	Idebenone	Idebenone
	n=42	n=45	n=53
Dehydration	1 (2.4)	0	0
Femur fracture	2 (4.8)	0	0
Nasopharyngitis	1 (2.4)	0	0
Pulmonary microemboli	1 (2.4)	0	0
Pyrexia	1 (2.4)	0	0
Respiratory failure	1 (2.4)	0	0
Tendinous contracture	1 (2.4)	0	0
Vomiting	1 (2.4)	0	0

DMD=Duchenne muscular dystrophy, SAE=serious adverse event

Twenty-six SAEs reported in 16 cases were collected from the ongoing double-blinded SIDEROS study. The most frequently reported SAEs included femur fracture (n=3), and acute respiratory failure (n=2). These 26 SAEs are presented in Table 59. Among these 16 cases, 1 concerned a patient who had not been exposed to study drug yet at the time of the events. Thirteen cases were assessed as not related to the administration of blinded treatment by both Santhera and the investigator, but rather to the underlying patient's condition, accidental origin or the patient's concomitant medications (nephrolithiasis) (Table 55). Three patients had SAEs considered related to the investigational medicinal product by the investigator: two cases of a cardiac event and fracture and another case of cardiac-related SAE. The investigators assessed these event as related to the blinded study medication, since a causal relationship could not be ruled out. The applicant position was that there is no sufficient evidence to conclude a causal relation between the blinded study medication and the events.

Table 55: Serious Adverse Events in the SIDEROS Study (15 Dec 2018)

	Blinded treatment (N=189)
	N (%)
Total number of serious adverse events	16 (8.5)
Injury, poisoning and procedural complications	
Femur fracture	3 (1.6)
Lower limb fracture	1 (0.5)
Lumbar vertebral fracture	1 (0.5)
Thoracic vertebral fracture	1 (0.5)
Tibia fracture	1 (0.5)
Cardiac disorders	
Atrioventricular block	1 (0.5)
Cardiac failure	1 (0.5)
Cardiogenic shock	1 (0.5)
Myocardial infarction	1 (0.5)
Infections and infestations	
Gastroenteritis viral	1 (0.5)
Influenza	1 (0.5)
Pneumonia	1 (0.5)
Sepsis	1 (0.5)
General disorders and administration site conditions	
Chest pain	1 (0.5)
Condition aggravated	1 (0.5)

	Blinded treatment (N=189)
	N (%)
Investigations	
Ejection fraction decreased	1 (0.5)
Troponin T increased	1 (0.5)
Renal and urinary disorders	
Nephrolithiasis	1 (0.5)
Calculus urinary	1 (0.5)
Respiratory, thoracic and mediastinal disorders	
Acute respiratory failure	2 (1.1)
Nervous system disorders	
Idiopathic intracranial hypertension	1 (0.5)
Psychiatric disorders	
Delirium	1 (0.5)
Vascular disorders	
Deep vein thrombosis	1 (0.5)

No AEs or SAEs were reported from the SIDEROS-E study.

Full Safety Population

The incidence of SAEs was slightly lower in the idebenone group (7.0%) vs the placebo group (8.4%) in the double-blind studies.

In the double-blind studies, atrial fibrillation was the most frequent SAE, reported for 3 patients (0.8%) in the idebenone group and 1 (0.6%) in the placebo group in the Full Safety Population. Chest pain and exposure during pregnancy were each reported for 2 patients (0.6%) in the idebenone group vs 0 in the placebo group, and pneumonia was reported for 2 patients (1.2%) in the placebo group vs none in the idebenone group (Table 56).

Considering the double-blind and extension studies combined in the idebenone group of the Full Safety Population, atrial fibrillation was reported for 5 patients (1.1%), pneumonia, scoliosis, and tachycardia were each reported for 4 patients (0.9%), and atrial flutter, cardiac failure and diarrhoea were each reported for 3 patients (0.7%). All other SAEs were reported for 2 (0.5%) or fewer patients in the double-blind and extension studies combined (Table 56).

The majority of SAEs in the full safety population were assessed as unrelated to study drug. Table 26 details the 8 patients who received idebenone and 2 patients who received placebo who experienced an SAE that was not judged to have a causality of unrelated to study drug. All of these patients were from studies in FRDA.

Table 56: Serious Adverse Events Reported by ≥2 Patients in the Double-Blind and Extension Studies Combined (Full Safety Population)

	Number (%) patients		
	Double-blind		Double-blind and extension
	Placebo	Idebenone	Idebenone
Preferred term	n=166	n=356	n=439
Total with SAEs	14 (8.4)	25 (7.0)	82 (18.7)
Atrial fibrillation	1 (0.6)	3 (0.8)	5 (1.1)
Pneumonia	2 (1.2)	0	4 (0.9)
Scoliosis	0	0	4 (0.9)
Tachycardia	0	1 (0.3)	4 (0.9)
Atrial flutter	0	1 (0.3)	3 (0.7)
Cardiac failure	0	1 (0.3)	3 (0.7)
Diarrhoea	0	1 (0.3)	3 (0.7)
Abortion spontaneous	0	1 (0.3)	2 (0.5)
Ankle fracture	0	1 (0.3)	2 (0.5)
Back pain	0	0	2 (0.5)
Chest pain	0	2 (0.6)	2 (0.5)
Deep vein thrombosis	0	0	2 (0.5)
Dehydration	1 (0.6)	0	2 (0.5)
Exposure during pregnancy	0	2 (0.6)	2 (0.5)
Fibula fracture	0	0	2 (0.5)
Gastroenteritis	1 (0.6)	0	2 (0.5)
Hand fracture	0	1 (0.3)	2 (0.5)
Pelvic fracture	0	0	2 (0.5)
Pneumonia aspiration	0	1 (0.3)	2 (0.5)
Supraventricular tachycardia	2 (1.2)	1 (0.3)	2 (0.5)
Thermal burn	0	0	2 (0.5)
Vomiting	1 (0.6)	1 (0.3)	2 (0.5)

SAE = Serious Adverse Event

Laboratory findings

Haematology Clinical Laboratory Values

For the DMD and the full safety population, there were no relevant differences in the percentages of patients with shifts in haematology values for the idebenone and placebo groups in the double-blind studies. Mean haematology laboratory values and mean changes from screening/baseline were generally comparable for placebo and idebenone in the double-blind studies and no clinically concerning results were observed when considering data from the double-blind and extension studies combined.

Clinical Chemistry Laboratory Values

DMD Population

For the DMP and the full safety population, there were no relevant differences in the percentages of patients with shifts in clinical chemistry values for the idebenone and placebo groups in the double-blind studies. Mean clinical chemistry laboratory values and mean changes from screening/baseline were comparable in idebenone and placebo patients in double-blind studies and no clinically concerning results were observed when considering data from the double-blind and extension studies combined.

Urinalysis Laboratory Values

There were no relevant differences between the idebenone and placebo groups in the double-blind studies for either the DMD or the full safety population.

In the SIDEROS and SIDEROS-E There was no evidence observed for a clinically relevant effect of idebenone on any haematological or clinical chemistry parameter. The review of other safety data such as vital signs, ECG parameters (including QTc) and physical examinations did not detect any noteworthy findings.

Safety in special populations

The applicant provided several analyses in the summary of clinical safety for safety in special groups and situations. Those considered most relevant for the indication are presented here in the AR.

Age

The number of patients with severe TEAEs, TEAEs that lead to discontinuation of study or study drug appeared to increase with increasing age group (Table 57 and Table 58).

Table 57: Overview of TEAEs by Age Subgroup in the Double-Blind and Extension Studies Combined (Full Safety Population)

Patients with at least 1:	Number (%) patients		
	<12 years n=50	≥12 to <18 years n=147	≥18 years n=242
TEAE	47 (94.0)	141 (95.9)	232 (95.9)
Treatment-related TEAE[a]	27 (54.0)	78 (53.1)	131 (54.1)
Severe TEAE	2 (4.0)	12 (8.2)	40 (16.5)
SAE	8 (16.0)	17 (11.6)	57 (23.6)
Deaths	0	0	1 (0.4)
TEAE leading to discontinuation of study	0	3 (2.0)	12 (5.0)
TEAE leading to discontinuation of treatment	0	8 (5.4)	35 (14.5)

[a] Causality unknown, unlikely, possible, probable or related
Age groups are defined based on the baseline age at the start of the first study with idebenone exposure.
SAE=serious adverse event, TEAE=treatment-emergent adverse event

Table 58: Incidence by Age of the Most Frequent TEAEs in the Double-Blind and Extension Studies Combined (Full Safety Population)

Preferred term	Number (%) patients		
	<12 years n=50	≥12 to <18 years n=147	≥18 years n=242
Headache	16 (32.0)	61 (41.5)	74 (30.6)
Nasopharyngitis	6 (12.0)	38 (25.9)	104 (43.0)
Diarrhoea	10 (20.0)	27 (18.4)	57 (23.6)
Nausea	11 (22.0)	31 (21.1)	31 (12.8)
Upper respiratory tract infection	17 (34.0)	37 (25.2)	10 (4.1)
Influenza	8 (16.0)	20 (13.6)	30 (12.4)
Back pain	3 (6.0)	17 (11.6)	34 (14.0)
Cough	8 (16.0)	14 (9.5)	32 (13.2)
Abdominal pain upper	10 (20.0)	18 (12.2)	23 (9.5)
Vomiting	9 (18.0)	18 (12.2)	24 (9.9)
Oropharyngeal pain	5 (10.0)	17 (11.6)	26 (10.7)
Fall	5 (10.0)	22 (15.0)	20 (8.3)
Pain in extremity	8 (16.0)	15 (10.2)	23 (9.5)

Preferred term	Number (%) patients		
	<12 years n=50	≥12 to <18 years n=147	≥18 years n=242
Pyrexia	14 (28.0)	21 (14.3)	9 (3.7)
Fatigue	6 (12.0)	17 (11.6)	15 (6.2)
Dizziness	8 (16.0)	16 (10.9)	12 (5.0)
Gastroenteritis	9 (18.0)	12 (8.2)	11 (4.5)
Arthralgia	6 (12.0)	8 (5.4)	14 (5.8)
Bronchitis	2 (4.0)	8 (5.4)	18 (7.4)
Abdominal pain	7 (14.0)	9 (6.1)	11 (4.5)
Ligament sprain	2 (4.0)	14 (9.5)	11 (4.5)
Muscle spasms	4 (8.0)	11 (7.5)	10 (4.1)
Toothache	2 (4.0)	4 (2.7)	18 (7.4)
Dyspepsia	5 (10.0)	6 (4.1)	12 (5.0)
Sinusitis	3 (6.0)	10 (6.8)	10 (4.1)

Most frequent TEAEs are those reported by ≥5.0% of patients in the double-blind and extension studies combined.
Age groups are defined based on the baseline age at the start of the first study with idebenone exposure.
TEAE=treatment-emergent adverse event

Ambulatory Status

The general incidence of TEAEs was similar in the 2 subgroups, but the nonambulatory subgroup had higher incidences of severe and serious TEAEs, and discontinuations of study and treatment compared with the ambulatory group (Table 59 and

Table 60).

Table 59: Overview of TEAEs by Ambulatory Status in the Double-Blind and Extension Studies Combined (Full Safety Population)

Patients with at least 1:	Number (%) patients	
	Ambulatory n=285	Nonambulatory n=154
TEAE	275 (96.5)	145 (94.2)
Treatment-related TEAE[a]	146 (51.2)	90 (58.4)
Severe TEAE	23 (8.1)	31 (20.1)
SAE	32 (11.2)	50 (32.5)
Deaths	0	1 (0.6)
TEAE leading to discontinuation of study	4 (1.4)	11 (7.1)
TEAE leading to discontinuation of treatment	11 (3.9)	32 (20.8)

a Causality unknown, unlikely, possible, probable or related
Ambulatory status groups for the double-blind and extension results are defined based on the ambulatory status at the start of the first study with idebenone exposure.
SAE=serious adverse event, TEAE=treatment-emergent adverse event

Table 60: Incidence by Ambulatory Status of the Most Frequent TEAEs in the Double-Blind and Extension Studies Combined (Full Safety Population)

Preferred term	Number (%) patients	
	Ambulatory n=285	Nonambulatory n=154
Headache	111 (38.9)	40 (26.0)
Nasopharyngitis	91 (31.9)	57 (37.0)
Diarrhoea	53 (18.6)	41 (26.6)
Nausea	48 (16.8)	25 (16.2)
Upper respiratory tract infection	51 (17.9)	13 (8.4)
Influenza	45 (15.8)	13 (8.4)
Back pain	32 (11.2)	22 (14.3)
Cough	36 (12.6)	18 (11.7)
Abdominal pain upper	34 (11.9)	17 (11.0)
Vomiting	33 (11.6)	18 (11.7)
Oropharyngeal pain	36 (12.6)	12 (7.8)
Fall	38 (13.3)	9 (5.8)
Pain in extremity	32 (11.2)	14 (9.1)
Pyrexia	34 (11.9)	10 (6.5)
Fatigue	30 (10.5)	8 (5.2)
Dizziness	32 (11.2)	4 (2.6)
Gastroenteritis	23 (8.1)	9 (5.8)
Arthralgia	24 (8.4)	4 (2.6)
Bronchitis	10 (3.5)	18 (11.7)
Abdominal pain	14 (4.9)	13 (8.4)
Ligament sprain	24 (8.4)	3 (1.9)
Muscle spasms	17 (6.0)	8 (5.2)
Toothache	15 (5.3)	9 (5.8)
Dyspepsia	15 (5.3)	8 (5.2)
Sinusitis	18 (6.3)	5 (3.2)

Most frequent TEAEs are those reported by ≥5.0% of patients for the double-blind and extension studies combined.
TEAE=treatment-emergent adverse event

Respiratory Status in DMD

The overall incidence of TEAEs was similar in patients with PEF%p <50%p and PEF%p ≥50% but results should be interpreted with caution due to the small number of patients and events (Table 61 and Table 62).

Table 61: Overview of TEAEs by Respiratory Status in the Double-Blind and Extension Studies Combined (DMD Population)

Patients with at least 1:	Number (%) patients	
	PEF%p <50%p n=15	PEF%p ≥50%p n=38
TEAE	14 (93.3)	35 (92.1)
Treatment-related TEAE[a]	4 (26.7)	13 (34.2)
Severe TEAE	2 (13.3)	1 (2.6)
SAE	3 (20.0)	8 (21.1)
Deaths	0	0
TEAE leading to discontinuation of study	1 (6.7)	0
TEAE leading to discontinuation of treatment	2 (13.3)	0

a Causality unknown, unlikely, possible, probable or related
Respiratory status groups for the combined double-blind and extension results are defined based on the status at the start of the first study with idebenone exposure.
DMD=Duchenne muscular dystrophy, PEF%P=percent predicted peak expiratory flow, SAE=serious adverse event, TEAE=treatment-emergent adverse event

Table 62: Incidence by Respiratory Status of the Most Frequent TEAEs in the Double-Blind and Extension Studies Combined (DMD Population)

Preferred term	Number (%) patients	
	PEF%p <50%p n=15	PEF%p ≥50%p n=38
Headache	2 (13.3)	8 (21.1)
Nasopharyngitis	4 (26.7)	5 (13.2)
Diarrhoea	3 (20.0)	7 (18.4)
Nausea	0	3 (7.9)
Upper respiratory tract infection	3 (20.0)	10 (26.3)
Influenza	0	1 (2.6)
Back pain	0	3 (7.9)
Cough	0	4 (10.5)
Abdominal pain upper	0	0
Vomiting	0	2 (5.3)
Oropharyngeal pain	1 (6.7)	2 (5.3)
Fall	0	1 (2.6)
Pain in extremity	0	0
Pyrexia	1 (6.7)	5 (13.2)
Fatigue	0	1 (2.6)
Dizziness	0	0
Gastroenteritis	2 (13.3)	3 (7.9)
Arthralgia	0	1 (2.6)
Bronchitis	2 (13.3)	6 (15.8)
Abdominal pain	2 (13.3)	4 (10.5)
Ligament sprain	1 (2.6)	1 (2.6)
Muscle spasms	0	1 (2.6)
Toothache	1 (6.7)	1 (2.6)
Dyspepsia	0	2 (5.3)
Sinusitis	0	0

Most frequent TEAEs are those reported by ≥5.0% of patients for the double-blind and extension studies combined.
DMD=Duchenne muscular dystrophy, PEF%P=percent predicted peak expiratory flow, TEAE=treatment-emergent adverse event.

Renal Impairment

Study CV-2619/EC070 was Phase I, single-centre, open-label, nonrandomised parallel-group study to determine the PK characteristics of idebenone and the evaluation of rate and extent of bioavailability of idebenone after single dose administration to patients with renal impairment. No clinically relevant changes in the clinical status of patients were reported after administration of study drug.

Hepatic Impairment

Study CV-2619/EC071 was Phase I, single-centre, open-label, nonrandomised parallel-group study to determine the PK characteristics of idebenone and the evaluation of rate and extent of bioavailability of idebenone after single dose administration to patients with hepatic impairment. One SAE of fatal septic multi-organ failure after surgery for an underlying pancreatitis, which resulted in the patient's death. The SAE was classified as unexpected and not related to the study drug. No other TEAEs were reported.

Steroid-Emergent TEAEs

The overall incidence of SAE seemed to be higher in GCs users. However, the data in GCs users were limited precluding any meaningful conclusions (Table 63 and Table 64).

Table 63: Overview of TEAEs by Steroid Use in the Double-Blind and Extension Studies Combined (Full Safety Population)

	Number (%) patients	
Patients with at least 1:	Steroid-use* n=37	Non-steroid use* n=424
TEAE	31 (83.8)	409 (96.5)
Treatment-related TEAE[a]	14 (37.8)	226 (53.3)
Severe TEAE	4 (10.8)	52 (12.3)
SAE	10 (27.0)	74 (17.5)
Deaths	0	1 (0.2)
TEAE leading to discontinuation of study	2 (5.4)	14 (3.3)
TEAE leading to discontinuation of treatment	2 (5.4)	41 (9.7)

a Causality unknown, unlikely, possible, probable or related
* Steroid use (systemic steroids) during the study, defined based on on-study concomitant medication information
SAE=serious adverse event, TEAE=treatment-emergent adverse event

Table 64: Incidence by Steroid Use of the Most Frequent TEAEs in the Double-Blind and Extension Studies Combined (Full Safety Population)

Preferred term	Number (%) patients	
	Steroid-use* n=37	Non-steroid use* n=424
Headache	10 (27.0)	144 (34.0)
Nasopharyngitis	1 (2.7)	147 (34.7)
Diarrhoea	3 (8.1)	92 (21.7)
Nausea	3 (8.1)	71 (16.7)
Upper respiratory tract infection	7 (18.9)	57 (13.4)
Influenza	2 (5.4)	57 (13.4)
Back pain	2 (5.4)	52 (12.3)
Cough	4 (10.8)	50 (11.8)
Abdominal pain upper	0	51 (12.0)
Vomiting	1 (2.7)	50 (11.8)
Oropharyngeal pain	1 (2.7)	48 (11.3)
Fall	0	47 (11.1)
Pain in extremity	1 (2.7)	45 (10.6)
Pyrexia	3 (8.1)	41 (9.7)
Fatigue	1 (2.7)	37 (8.7)
Dizziness	0	36 (8.5)
Gastroenteritis	1 (2.7)	31 (7.3)
Arthralgia	2 (5.4)	26 (6.1)
Bronchitis	3 (8.1)	25 (5.9)
Abdominal pain	3 (8.1)	24 (5.7)
Ligament sprain	0	27 (6.4)
Muscle spasms	2 (5.4)	23 (5.4)
Toothache	2 (5.4)	22 (5.2)
Dyspepsia	1 (2.7)	22 (5.2)
Sinusitis	0	23 (5.4)

Most frequent TEAEs are those reported by ≥5.0% of patients in the double-blind and extension studies combined.
* Steroid use (systemic steroids) during the study, defined based on on-study concomitant medication information
TEAE=treatment-emergent adverse event

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

Please refer to the pharmacology part of this report.

Discontinuation due to AEs

DMD Population

The incidence of TEAEs leading to study drug discontinuation was similar in the idebenone and placebo groups in the double-blind studies (4.4% vs 4.8%). One patient discontinued idebenone treatment due to sleep apnoea and another due to diarrhoea in the double-blind studies.

Two patients have been withdrawn from the SIDEROS study. One was withdrawn prior to the occurrence of the SAE as he was unable to cope with multiple visits. Another patient dropped out of the study due to the occurrence of a non-serious AE.

Full Safety Population

The incidence of TEAEs leading to study drug discontinuation was slightly higher in the idebenone group vs placebo in the double-blind studies (4.8% vs 2.4%) in the Full Safety Population (Table 65).

Table 65: TEAEs Leading to Study Drug Discontinuation of ≥2 Patients (Full Safety Population)

	Number (%) patients		
	Double-blind		Extension
	Placebo	Idebenone	Idebenone
	n=166	n=356	n=287
Patients with ≥1 TEAE leading to study drug discontinuation	4 (2.4)	17 (4.8)	27 (9.4)
Diarrhoea	0	4 (1.1)	3 (1.0)
Nausea	0	3 (0.8)	1 (0.3)
Abdominal pain upper	0	1 (0.3)	1 (0.3)
Atrial fibrillation	0	1 (0.3)	1 (0.3)
Cardiac failure	0	1 (0.3)	1 (0.3)
Chest pain	0	2 (0.6)	0
Exposure during pregnancy	0	2 (0.6)	0
Influenza like illness	0	2 (0.6)	0
Scoliosis	0	0	2 (0.5)
Vomiting	0	2 (0.6)	0

TEAE=treatment-emergent adverse event

Post marketing experience

In the European Union, Santhera received on 08 September 2015, a MA under exceptional circumstances for Raxone® (idebenone 150 mg film-coated tablets); and on 22 August 2017, a MA was granted in Israel. Raxone® is indicated for the treatment of visual impairment in adolescent and adult patients with LHON. The recommended dose is 900 mg/day (300 mg, 3 t.i.d.). Santhera marketed idebenone in Canada in the symptomatic management of patients with FRDA between October 2008 and April 2013 under the trade name Catena®. Santhera agreed to the voluntary withdrawal of Catena® from the Canadian market after additional confirmatory efficacy studies failed to meet their primary efficacy endpoint. No specific safety issues prompted this action. A total of 137 patients received therapy with Catena® between October 2008 and April 2013.

Cumulatively, an estimated total of 515 patients were supplied with commercial idebenone via EAP and Named Patient Supply since 2008.

A total of 1,175,940 tablets of Raxone® had been sold during the most recent PSUR reporting period (Idebenone PSUR#3). Therefore, it was estimated that 537 patients were exposed to Raxone® through commercial supply during the reporting period. Cumulatively, an estimated total of 1216 patients (cumulative exposure to Catena® between 2008 and 2013 + cumulative patient exposure to Raxone® since 2015) have been exposed to idebenone via commercial supply.

Takeda markets idebenone for the treatment of cognitive and behavioural deficit due to cerebral pathologies of vascular or degenerative origin in 4 countries. The 30-mg dose is available in Argentina, Mexico, and Portugal and the 45-mg dose is available in Argentina and Italy. Worldwide exposure was estimated at 1467.5 average daily doses (average daily dose estimated as 135 mg) and cumulatively since launch/International Birth date to 30 September 2017, the total exposure globally was approximately 4,021,709 patient-years (Takeda PSUR 2017).

No safety concerns have been raised in the post-marketing setting.

Post Authorisation Studies in LHON

The PAROS study is an ongoing Phase IV open-label non-interventional study in patients with LHON receiving idebenone 900 mg/daily.

As of 15 December 2018, 156 patients had been enrolled and 8 serious individual case safety reports (ICSRs) have been received; 6 of which were considered unrelated to idebenone by both Santhera and

the investigator, and for the remaining 2 cases was not applicable due to the occurrence of the events preceding idebenone administration.

The LEROS study is an ongoing Phase IV open-label interventional study in patients with LHON. The study treatment (idebenone 900 mg/daily) is planned for a period of 24 months.

As of 08 September 2018, 165 patients had been enrolled and a total of 11 serious ICSRs have been received, 8 were assessed as not related to idebenone by both Santhera and the investigator, and 2 (one case of drug reaction with eosinophilia and systemic symptoms and another case of an increase liver enzymes) were assessed as related to idebenone by the applicant and/or the investigator. The causality in the remaining serious case was not applicable due to the occurrence of the events preceding idebenone administration.

3.3.10. Discussion on clinical safety

Main safety data are derived from 3 studies in DMD patients. Supportive safety data were submitted from patients with LHON (1 study) and patients with FRDA (5 studies). In addition, SAEs from the ongoing study in DMD and two ongoing studies in LHON patients as well as a summary of safety findings from the compassionate use programmes were submitted. Safety data were presented for the DMD population and for the Full Safety population consisting of pooled safety data from DMD, LHON and FRDA patients (phase II and III studies).

A total of 53 DMD patients received idebenone during clinical trials and 54.7% of patients received idebenone for more than 1 year. The very limited number of DMD patients is considered acceptable due to the orphan setting. Besides, additional safety data in DMD patients could be expected from the currently ongoing SIDEROS/SIDEROS-E study as well as from the planned MILOS study. Furthermore, there are supportive data available from other indications. The full safety population comprises a total of 439 patients who received idebenone either during the DMD, the FRDA or the LHON clinical development programme. 62.9% of these patients had an exposure for more than 1 year. Overall, extent of safety data from clinical trials is considered sufficient for assessment.

In DMD patients, the most frequently reported TEAEs for idebenone treated patients were diarrhoea, headache, nasopharyngitis, upper respiratory tract infection, pyrexia, bronchitis, abdominal pain and gastroenteritis. In placebo patients the most frequently reported TEAEs were nasopharyngitis, upper respiratory tract infection, headache, bronchitis, constipation, rhinitis and diarrhoea. Of note, the following of the most common TEAEs (incidence of ≥5%) were reported more frequently for idebenone than for placebo: diarrhoea (20% vs. 14.3%), pyrexia (13.3% vs. 7.1%), abdominal pain (11.1% vs 7.1%), gastroenteritis (11.1% vs 2.4%), left ventricular failure (6.7% vs 2.4%), otitis media (6.7% vs 0%), and chromaturia (6.7% vs 0%). Preliminary and still blinded data from ongoing DMD studies are comparable with that from completed studies, although oropharyngeal pain and cough seem to be reported more frequently.

In the full safety population, the most commonly reported TEAEs in idebenone and placebo patients were headache, nasopharyngitis, diarrhoea, nausea, and upper respiratory tract infection. Those reported most frequently (≥5.0% of patients) in the idebenone group and that were ≥2.0% more frequent than in the placebo group in the double-blind studies were nasopharyngitis (26.7% vs 21.7%), diarrhoea (17.1% vs 11.4%), cough (8.4% vs 5.4%), vomiting (9.3% vs 6.6%) and gastroenteritis (6.5% vs 4.2%).

Data regarding most frequently reported TEAEs in the full safety population are in general comparable with that from the DMD population. In both the DMD patients and the full safety population the majority of TEAEs were of mild or moderate severity.

TEAEs evaluated as related, possibly related or unlikely related to idebenone were reported in a low number of DMD patients. Most frequent adverse reactions according to the current SmPC of Raxone/proposed SmPC of Puldysa comprise: nasopharyngitis (very common), cough (very common), diarrhoea (common) and back pain (common). Due to the nature of the disease, these AEs are considered challenging in a DMD population, especially in more advanced patients who are wheelchair-bound and suffer from respiratory dysfunction. This needs to be taken into account for B/R assessment.

According to the SmPC Guideline, all adverse reactions for which a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility should be included in section 4.8 of the SmPC. However, this guideline requirement is not fulfilled, and the applicant was therefore asked to include all adverse reactions with their respective frequency in section 4.8 of the SmPC according to GL. The applicant´s argumentation submitted during the procedure against including any additional adverse drug reactions (ADRs) observed during DMD studies is not endorsed for several reasons. Raxone was also authorized through a hybrid application and the SmPC indeed contains ADRs from the reference medicinal product (Mnesis) and from LHON studies (indication for Raxone only and not for the reference medicinal product). Furthermore, the SmPC Guideline requests that section 4.8 "*should include all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility*". Taken together, it is not considered self-evident that the following TEAEs reported in the DMD population and evaluated as related or possibly related to idebenone are not proposed to be included in the SmPC: constipation, ear infection, electrocardiogram abnormal, blood phosphorus increased, fluid intake reduced, gastritis, gastrooesophageal reflux disease, sciatica and fatigue. Therefore, the applicant is asked to include these ADRs accordingly with their respective frequency. In case of a different evaluation of relationship between the sponsor and the investigator, a sound justification needs to be provided. Moreover, the following ADRs reported during DMD studies and evaluated as related or possibly related to idebenone are in fact proposed to be included in the SmPC, however, with the frequency "unknown": chromaturia, headache, nausea, rash, decreased appetite/anorexia and pruritus. As frequencies can be calculated for ADRs occurring during clinical studies, the applicant is asked to update section 4.8 accordingly.

During completed studies, there were no deaths in the DMD population and one death in the full safety population. This death was not considered related to idebenone. Of note, during the ongoing SIDEROS trial three patients experienced SAEs with a fatal outcome as further discussed below.

There was a lower incidence of SAEs in idebenone treated patients as compared to placebo in both the DMD (6.7% vs. 14.3%) and the full safety population (7.0% vs. 8.7%). In the DMD population none of the SAEs was considered related to idebenone.

In total, 3 patients in the idebenone group and 6 patients in the placebo group experienced a SAE in the double-blind studies in DMD population. In the DELOS study, one patient experienced sleep apnoea syndrome, which was assessed as unrelated to idebenone and attributed the event to the patient' s underlying disease and one patient had an urticaria, which was considered as moderate and unrelated to idebenone and attributed to the event of intercurrent disease. In the DELPHI study, one patient in the idebenone group had an ankle fracture, which was moderate in severity and deemed as unrelated to study drug. No safety concerns related to the treatment with idebenone are raised based on the collected SAE data. Considering the extension study, in total 8 patients receiving idebenone had a SAE. Except pneumonia and scoliosis observed in two cases, all other reported SAEs were reported only in one subject. None of these events were considered related to idebenone and none led to permanent premature study discontinuation. All cases were resolved without sequalae except for one subject with pneumonia and cardiopulmonary failure which were reported as resolved with sequelae (left ventricular dysfunction). The case narratives of all reported events were provided and no causal relationship to the idebenone treatment was detected.

However, during the ongoing DMD studies, there were a total of 26 SAEs in 16 patients of whom 3 patients experienced SAEs considered related to investigational medicinal product (data are still blinded).In 2 patients, the SAEs had a fatal outcome. Due to the nature of the disease, including cardiac failure, it is considered difficult to draw any conclusions whether these events constitute a new safety signal and the impact on the B/R cannot be reliably judged based on available data. The applicant was asked to discuss these events in more detail and to clarify whether data are still blinded. Upon request, the applicant clarified that only two serious cases were reported from the SIDEROS study that were evaluated by the investigator as possibly related to idebenone. Both of these cases had a fatal outcome. For the third case the final evaluation by the investigator was "likely not related to the study treatment". Furthermore, the applicant clarified that these cases were unblinded by assigned staff of the applicant´s pharmacovigilance department in order to report these cases as Suspected Unexpected Serious Adverse Reaction whereas the study team and investigator were kept blinded. In a patient population with an advanced stage of disease and where cardiac failure is part of the clinical picture of the disease, any cardiac events are considered difficult to judge in terms of relationship . The same applies to the event of fracture in both patients since both of the concerned patients received GCs treatment for several years. While the applicant´s argumentation that the cause of the events is unassessable or that there is no sufficient evidence to conclude a causal relation between the study medication and the events can in general be followed, no final conclusion can be made regarding causal relationship for these two fatal cases. Some reassurance on the begnin safety profile of idebenone derives from the completed DMD studies and the full safety populations: no deaths and no related SAEs were reported in the DMD population. In the full safety population only one fatal event occurred and this death was determined to be unrelated to idebenone. Furthermore, the rate of SAEs with a causality other than unrelated/not related was low (8/439 idebenone treated patients). Overall, there remains some degree of uncertainty regarding relationship of the two fatal cases to blinded study medication (placebo or idebenone) in the ongoing SIDEROS study. However, available safety data from the DMD population and full safety population are in general supporting the benign safety profile of idebenone.

The most frequently reported SAE in the full safety population was atrial fibrillation. This was evaluated as a signal during the last PSUR period and it was concluded to close this signal and not being classified as risk (EMEA/H/C/PSUSA/00010412/201809).

The incidence of severe TEAEs as well as the number of patients discontinuing due to AEs seems to increase with age. The same can be seen for non-ambulatory patients and patients with PEF%p<50%, i.e. a higher incidence of severe TEAEs in those patients compared to ambulatory patients and patients with PEF%p>50%. These observations are most probably due to natural course of the disease. There are no apparent safety issues arising from TEAEs in patients with renal or hepatic impairment. The presentation of TEAEs by steroid use do not reveal any unexpected safety concerns. However, the data in steroid users are limited precluding any meaningful conclusions.

In the DMD population the discontinuation due to AEs was similar between idebenone and placebo groups. In the ongoing trials 2 patients are withdrawn. No concerns arise from these data.

In the full safety population, the number of patients discontinuing due to AEs was higher in the idebenone group with the most common AE of diarrhoea. However, the overall number of patients discontinuing due to AEs is considered low. Of note, the AE of diarrhoea is considered more challenging in the DMD population, especially in non-ambulatory boys, as compared to the other indications.

Postmarketing data were recently assessed through a PSUSA (EMEA/H/C/PSUSA/00010412/201809; period covered by the PSUR: from 08/09/2017 to 08/09/2018) concluding on a positive B/R balance and recommending the maintenance of the MA in the authorised indication LHON.

3.3.11. Conclusions on clinical safety

Due to the orphan nature of the disease, safety data in the target population are limited. However, supportive data from other indications are available. Moreover, additional safety data from DMD patients could be expected from the ongoing SIDEROS/SIDEROS-E study as well as the planned MILOS study. While idebenone is well-tolerated and AEs seem to be manageable in general, the most common AEs known from other indications need to be evaluated in light of the target population (advanced, non-ambulatory DMD boys who suffer from respiratory dysfunction): nasopharyngitis, cough, diarrhoea and back pain.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant identified the following safety concerns in the RMP:

Table 66: Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Abnormal liver function test and hepatitis Blood count abnormalities
Missing information	Safety in children with DMD under 10 years of age and with LHON under 14 years of age Safety in patients with hepatic impairment Safety in patients with renal impairment Safety in elderly patients with LHON Safety in pregnancy and in breastfeeding Safety in patients with DMD receiving GCs Safety of long-term use

Inclusion of *abnormal liver function test and hepatitis* as important potential risk is endorsed since a PASS is currently ongoing in LHON indication to elucidate this safety concern.

No significant blood count abnormalities were observed in the studies with DMD patients and no SAEs of blood disorders have been received from the post authorisation experience in the FRDA and LHON indications. However, in the PASS protocol (a Non-interventional Study of Clinical Experience in Patients Prescribed Raxone® for the Treatment of Leber's Hereditary Optic Neuropathy (LHON)) *blood count abnormalities* is an AESI to be monitored.

In the course of this MAA new data on PK of idebenone in subjects with renal / or hepatic impairment were submitted. Increased values for IDEB+IDEB-C were observed in renally-impaired and hepatically-impaired subjects compared with age-matched healthy subjects. Since presented data are limited and no data are available for DMD patients it is accepted that *use in patients with renal and hepatic impairment* is included as missing information.

The risk profile *in children with DMD under 10 years of age and with LHON under 14 years of age, in patients with hepatic and renal impairment, in elderly patients with LHON* and *in pregnancy and in breastfeeding patients with LHON* will be defined in the PAROS study in LHON indication. *In patients with DMD receiving GCs* safety data will be evaluated in the ongoing SIDEROS and SIDEROS-E studies.

The safety of idebenone in long-term use in patients with DMD will be evaluated as secondary objective in a planned PAES: *Phase IV, two-part, randomized, placebo and externally controlled study assessing the long-term efficacy of idebenone in patients with Duchenne Muscular Dystrophy who have abnormal respiratory function (MILOS, SNT-IV-009)*.

The missing information is agreed. The applicant also included safety in pregnancy and breastfeeding as missing information, as requested, since females are also affected in rare instances.

The safety concerns included as missing information have been specified by rewording to "Safety in children/elderly/etc ..." as requested.

Having considered the data in the safety specification

The Rapporteur agrees that the safety concerns listed by the applicant are appropriate.

3.4.2. Pharmacovigilance Plan

Routine pharmacovigilance activities

The post-authorisation safety profile of idebenone will be evaluated through routine pharmacovigilance activities described in the Pharmacovigilance System Master File. However additional pharmacovigilance activities are needed to better characterize the safety profile in DMD indication, including the long-term safety profile of Puldysa in the treatment of respiratory dysfunction in patients with DMD, when used under conditions of usual clinical care, the potential risk of abnormal liver function tests and hepatitis and the use in populations not studied in clinical trials such as pregnancy and lactation, children under 10 years of age, hepatic impairment, renal impairment.

Summary of additional PhV activities

Table III.1: On-going and planned additional PV activities

Study Status	Objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
A non-interventional study of clinical experience in patients prescribed Raxone for the treatment of LHON (PAROS, SNT-IV-003) Ongoing	Primary • To further evaluate the long-term safety profile of Raxone in the treatment of patients with LHON when used under conditions of routine clinical care Secondary • To further evaluate the long-term effectiveness of Raxone in the treatment of patients with LHON when used under conditions of routine clinical care • To quantify discontinuation of treatment due to adverse events or due to lack of or loss of therapeutic response • To further elucidate the risk of abnormal liver function tests and hepatitis	Long term safety, Use in populations not studied in clinical trials: pregnancy and lactation, elderly, children under 14 years of age, hepatic impairment, renal impairment	Annual interim reports Final report	Reports to be submitted with annual re-assessments
A non-interventional study of clinical experience in patients prescribed Puldysa in DMD (SNT-IV-007) Planned	Primary • To further evaluate the long-term safety profile of Puldysa in the treatment of respiratory dysfunction in patients with DMD, when used under conditions of usual clinical care Secondary • To monitor the rate of discontinuation from treatment due to AEs or due to lack of or loss of therapeutic response • To further monitor the potential risk of abnormal liver function tests and hepatitis • To evaluate the long-term effectiveness of Puldysa in the treatment of respiratory dysfunction in patients with DMD when used under conditions of usual clinical care, by routine monitoring of clinically relevant milestones	Use in populations not studied in clinical trials: pregnancy and lactation, children under 10 years of age, hepatic impairment, renal impairment	Annual interim reports Final report	Reports to be submitted annually Q2 2024
Category 3 – Required additional pharmacovigilance activities				
None				

The additional pharmacovigilance activities include the PASS (SNT-IV-007) in DMD indication that has as primary objective "long term safety" and as secondary objectives the long term effectiveness and the rates of discontinuation and of lack of efficacy. The safety concerns addressed will include the use in populations not studied in clinical trials: children under 10 years of age, hepatic impairment, renal

impairment use in use in pregnancy and breastfeeding that are missing information in the RMP. Furthermore, the important potential risk of "abnormal liver function test and hepatitis" will be a secondary objective and the important potential risk "Blood count abnormalities" will be monitored in this PASS as AESI. The additional Pharmacovigilance activities included in proposed RMP are appropriate and proportionate to the importance of the risks and concerns to be investigated , although Section III.2 "Additional pharmacovigilance activities and table of additional Pharmacovigilance activities – Table III.1 needs minor amendments.

Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures. Several information provided in this part of the proposed RMP needs amendment for purpose of consistency with the other parts of the documents and updated with administrative details.

3.4.3. Plans for post-authorisation efficacy studies

Summary of Post authorisation efficacy development plan

Table IV.1 Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific requirements

Study (Status)	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorisation				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
External Natural History Controlled, open-Label Intervention Study to Assess the Efficacy and Safety of Long-Term Treatment with Raxone in LHON (LEROS, SNT-IV-005) Ongoing	Primary: • To assess efficacy of Raxone in the promotion of recovery or stabilization of VA in patients treated with Raxone ⩽1 year after the onset of symptoms, compared to an external natural history control group Secondary: • To assess efficacy of Raxone in the promotion of recovery or stabilization of vision in LHON patients treated with Raxone >1 year after the onset of symptoms, compared to an external natural history control group • To compare the promotion of recovery or stabilization of VA in LHON patients treated with Raxone ⩽1 and >1 year after the onset of symptoms • To assess the influence of mutation on the promotion of recovery or stabilization of VA in LHON patients treated with Raxone • To assess the influence of time since onset of symptoms prior to the initiation of treatment with Raxone on the promotion of recovery or stabilization of VA in LHON patients • To assess the influence of duration of treatment with Raxone on changes in VA in LHON patients • To assess safety of long-term treatment of LHON patients with Raxone	Long term safety and efficacy	Annual interim reports Final report	Interim reports: To be provided at the time of annual re-assessments Final study report: 31 August 2021
Historical Case Record Survey (CRS) of Visual Acuity Data from Patients with LHON	• To establish the clinical course (natural history) and visual acuity (VA) outcomes in	To provide control group to the open label study	Final report	Final study report: 31 July 2019 (completed)

(SNT-CRS-002) (Completed)	patients with a genetically confirmed diagnosis of LHON. • To combine data from this CRS with CRS data collected previously (as reported in SNT-IR-006, NCT01892943) to be used to generate the comparator group for the open-label study SNT-IV-005			
Follow up of patients in the existing LHON Expanded Access Programme (SNT-EAP-001) (completed)	• To collect further long-term real-world efficacy and safety data	Long term safety and efficacy	Final report	Final report: 31 August 2019 (completed)
A Phase III, Double-blind, Randomized, Placebo-Controlled Study assessing the Efficacy, Safety and Tolerability of Idebenone in Patients with DMD Receiving Glucocorticoid Steroids (SIDEROS, SNT-III-012) Ongoing	Primary: • To assess the efficacy of idebenone compared to placebo, in delaying the loss of respiratory function in patients with DMD receiving glucocorticoid steroids as measured by changes in FVC %p using clinic based spirometry. Secondary: • To assess the efficacy of idebenone compared to placebo in delaying the loss of respiratory function in patients with DMD receiving glucocorticoid steroids as measured by: • Changes PEF %p using clinic-based spirometry • Time to loss of 10% of FVC using clinic-based spirometry • To assess the efficacy of idebenone compared to placebo in delaying the loss of inspiratory muscle function as measured by changes in Inspiratory Flow Reserve (IFR) using clinic-based spirometry.	Efficacy and safety	Final report	H2 2022
A Phase IV, two-part, randomized, placebo and externally controlled study assessing the long-term efficacy of idebenone in patients with Duchenne Muscular Dystrophy who have abnormal respiratory function	Primary: • To assess the effect of idebenone, in comparison to standard of care, in reducing the risk of reaching the criteria for initiating assisted ventilation in patients with DMD who have abnormal respiratory function.	Long term efficacy and safety	Annual interim reports Final report	Annual reports Q4 2025

(MILOS, SNT-IV-009) Planned	Secondary: • To assess the effect of idebenone, in comparison to standard of care, in patients with DMD who have abnormal respiratory function: ○ In slowing the rate of respiratory function decline ○ In extending the time to clinically relevant worsening of the respiratory function ○ In reducing hospitalizations due to respiratory events ○ In extending the time to death ○ In slowing the decline of upper limb function (using PUL 2.0) ○ In patient-reported outcomes assessing functional ability and upper limb function ○ In extending the time to clinically relevant worsening of the upper limb strength • To assess the safety of idebenone in long-term use in patients with DMD.			

3.4.4. Risk minimisation measures

Routine Risk Minimisation Measures

For most safety concerns, routine risk minimization measures include routine risk communication such as PI text; other routine risk minimisation measures beyond the Product Information will include the legal status of prescription only medicine, and furthermore the recommendation that treatment should be initiated and supervised by a physician with experience in DMD or in LHON.

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

Summary of additional risk minimisation measures

V.3 Summary of risk minimisation measures

V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important potential risk 1: Abnormal liver function test and hepatitis	**Routine risk minimisation measures:** SmPC Prescription only medicine Treatment should be initiated and supervised by a physician with experience in DMD or in LHON **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PAROS study (PASS) in LHON indication PASS in DMD indication
Important potential risk 2: Blood count abnormalities	**Routine risk minimisation measures:** SmPC Prescription only medicine Treatment should be initiated and supervised by a physician with experience in DMD or in LHON **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PAROS study (PASS) in LHON indication PASS in DMD indication
Missing information 1: Use in children with DMD under 10 years of age and with LHON under 14 years of age	**Routine risk minimisation measures:** SmPC Prescription only medicine Treatment should be initiated and supervised by a physician with experience in DMD or in LHON **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PAROS study (PASS) in LHON indication PASS in DMD indication
Missing information 2: Use in patients with hepatic impairment	**Routine risk minimisation measures:** SmPC Prescription only medicine Treatment should be initiated and supervised by a physician with experience in DMD or in LHON **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PAROS study (PASS) in LHON indication PASS in DMD indication
Missing information 3: Use in patients with renal impairment	**Routine risk minimisation measures:** SmPC Prescription only medicine Treatment should be initiated and supervised by a physician with experience in DMD or in LHON **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PAROS study (PASS) in LHON indication PASS in DMD indication
Missing information 4: Use in elderly patients with LHON	**Routine risk minimisation measures:** SmPC Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PAROS study (PASS) in LHON indication

V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Missing information 5: Use in pregnancy and in breastfeeding patients	**Routine risk minimisation measures:** SmPC Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PAROS study (PASS) in LHON indication PASS in DMD indication
Missing information 6: Use in patients with DMD receiving GCs	**Routine risk minimisation measures:** SmPC Prescription only medicine Treatment should be initiated and supervised by a physician with experience in DMD **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PASS in DMD indication
Missing information 7: Safety of long term use	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PAROS study (PASS) in LHON indication PASS in DMD indication

Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Several information provided in this part of the proposed RMP needs amendment for purpose of consistency with the other parts of the documents and updated with administrative details.

3.4.5. Summary of the risk management plan

The public summary of the RMP requires revision.

Changes to Annexes 2, 3, 5 and 7 are also needed.

PRAC Outcome

During the plenary meeting held on 14-17 April 2020, the PRAC fully supported the assessment of the pharmacovigilance plan and risk minimisation measures as detailed in the assessment report and agreed that the RMP for Puldysa (idebenone) in the proposed indication could be acceptable provided that an update to RMP version 2.5 (dated 10 February 2020) and satisfactory responses to the questions detailed in the list of outstanding issues are submitted.

3.4.6. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 2.5 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report.

3.5. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

4. Benefit risk assessment

4.1. Therapeutic Context

4.1.1. Disease or condition

The targeted indication applied for by the applicant is for the treatment of respiratory dysfunction in patients with DMD not using GCs.

In DMD, the progressive respiratory insufficiency requires the use of non-invasive and, in some circumstances, invasive ventilation which, following the loss of ambulation, is the second irreversible disease milestone in DMD greatly impacting the patients' quality of life. The aim of the therapy is to prolong the time to assisted ventilation.

4.1.2. Available therapies and unmet medical need

DMD is a seriously debilitating and life-threatening disease. At present, there is one product approved for DMD in the EU: Translarna™ (ataluren). It primarily focuses on restoring dystrophin levels in early childhood with the aim to prevent or delay the loss of ambulation and preserve upper and lower limb function. GCs are not approved for the treatment of DMD in the EU but are part of the current standard of care for the treatment of DMD (Matthews et al., 2016, Henricson et al., 2013; McDonald et al., 2018b; Birnkrant et al., 2018a; 2018b). Early and continued use of GCs treatment has been shown to prolong the time to loss of ambulation and delays the onset of respiratory function decline (e.g. McDonald et al., 2018b).

4.1.3. Main clinical studies

The primary evidence for the efficacy of Puldysa for the treatment of respiratory dysfunction in DMD is provided by three studies:

- **Delphi Study (SNT-II-001):** A Phase IIa double blind, randomized, placebo controlled, single centre study at the University of Leuven to assess the efficacy and tolerability of idebenone in 8 – 16 year old males with cardiac dysfunction associated with Duchenne Muscular Dystrophy. DMD patients were included irrespective of the use of GCs. The primary endpoint in DELPHI was a cardiac parameter: the relative change from baseline (at screening) to Week 52 in peak systolic

radial strain of the LV inferolateral wall, assessed by CDMI. Main secondary endpoints comprised respiratory function tests.

- **DELOS study (SNT-III-003):** A Phase III double-blind, randomised, placebo-controlled study of the efficacy, safety and tolerability of idebenone in patients with Duchenne Muscular Dystrophy. DMD patients from 10 to 18 years of age without concomitant use of GCs and in whom respiratory function 'started to decline (PEF%p ≤80% at baseline)' were included. The primary endpoint in the DELOS trial was a respiratory parameter: the change from baseline to Week 52 in PEF%p. Secondary endpoints comprised additional respiratory function tests, muscle strength, motor function and quality of life.
- **SYROS study (SNT-CRS-003):** A retrospective Cohort Study assessing the Long-Term Respiratory Function Evolution during Idebenone Treatment compared to Idebenone-free Periods in Patients with Duchenne Muscular Dystrophy. In the SYROS study, data from patients who had completed the DELOS study, were enrolled in idebenone EAPs and had signed a data release agreement form, were collected. The primary objective of the study was to evaluate the long-term evolution of the respiratory function.

Supportive evidence from an open-label, uncontrolled extension-trial to DELPHI was submitted (DELPHI-E). Additionally, several *post hoc* analyses and supportive reports were submitted: SNT-IR-011 (additional analyses of respiratory function measures for DELPHI and DELPHI-E); SNT-IR-009 (additional analyses of inspiratory function in the DELOS trial); SNT-IR-010 (additional analyses on the effect of idebenone in reducing respiratory complications in the DELOS trial); SNT-IR-015 (report on the integrity, consistency and robustness of the DELOS trial); SNT-IR-017 (re-calculation of DELOS study results with new DMD patient-derived prediction equations); SNT-IR-016 (report on the current understanding of respiratory function evolution in patients with DMD).

4.2. Favourable effects

In DELPHI the primary endpoint (relative change from baseline (at screening) to Week 52 in peak systolic radial strain of the LV inferolateral wall) was not met. The secondary endpoint "change from baseline to Week 52 in PEF%p" revealed a difference of 11.3% in favour of idebenone and further triggered the evaluation of respiratory benefit.

In DELOS the primary endpoint (change from baseline to Week 52 in PEF%p) revealed a statistically significant difference in favour of idebenone (difference between idebenone and placebo: 6.27%; 95% CI: 0.61, 11.93). Furthermore, a weak trend was seen in favour of idebenone from most of the other respiratory endpoints although lacking statistically significant difference. In addition, *post hoc* analyses seemingly showed a treatment benefit in the patient-relevant outcomes BAEs, use of antibiotics and hospitalisations.

In SYROS, the annual rate of decline in FVC%p for the 7 patients in the "ON-ON" treatment group was -3.9 (95% CI -5.4, -2.3) during the EAP, while it was -0.7 (95% CI -3.7, 2.2) before the EAP.

The DELPHI-E study and most of the additional *post hoc* analyses provided from the reports SNT-IR-009, SNT-IR-010, SNT-IR-011 and SNT-IR-016 are regarded as supplementary information only and do not have a substantial impact on the B/R of idebenone.

4.3. Uncertainties and limitations about favourable effects

The primary endpoint of the DELPHI trial was not met. The secondary endpoint "change from baseline to Week 52 in PEF%p" showed a "statistically significant" effect, but the type-1-error was controlled at 5% one-sided for this trial. Furthermore, no statistically significant differences where shown for any of

the other respiratory endpoints and no endpoints such as activities of daily living or health-related quality of life were planned in this study.

In the DELOS trial several methodological issues were identified in relation to calculation of PEF%p, which question the validity of the study's primary endpoint.

The first issue is the choice of the prediction formula to compute individual PEF%p values. In DELOS, the Godfrey equation was used to calculate PEF%p. The applicant states that the use of an alternative equation (Hankinson) results in consistent results. However, the impact on the interpretation of PEF%p results seems to be difficult to estimate. From the presented results it is obvious that substantial over- as well as underestimation of PEF%p occurs depending on the formula used. Furthermore, there were four patients who would have been excluded from the trial as their baseline PEF%p would have been >80% with the use of the alternative equation. Excluding these four patients would have resulted in non-significant differences between the placebo and the idebenone group.

The second issue in relation to PEF%p computation is the use of ulna-length based estimation of body height in DMD patients. Both prediction formulas mentioned above require 'body height' as input variable. The majority of the included patients were wheelchair-bound, and measurement of standing height was not possible. Therefore, formulas were used for prediction of body height estimated from ulna length. However, for some subjects with available standing height and ulna length it can be seen that ulna-based estimation of height differs substantially from standing height. In consequence, this has marked impact on PEF%p values which differ substantially depending on the use of ulna-based height or standing height for the prediction formula. In this regard, profound interpretation of the PEF%p outcome is not possible.

Further uncertainty is derived from the observed effect size and the confidence interval (PEF%p difference between idebenone and placebo: 6.27%; 95% CI: 0.61, 11.93). The anticipated effect was downsized during the clinical development which questions the clinical relevance of an effect of 6.27%-points. In addition, considering the lower limit of the CI, it is obvious that there is a large uncertainty of the derived estimate in the primary analysis which affects the clinical interpretation of the effect, i.e. that effect sizes close to zero are not unrealistic.

Given the descriptions provided for resampling methods applied for derivation of a minimal clinically relevant difference, there remains concern that the 95% CI derived are associated with a pseudo precision, which strongly and directly depends on the choice of N (number of "pairs of groups"). Furthermore, there is concern that due to resampling the variance is systematically underestimated, if data from one and the same patient is used repeatedly for estimation purposes. Implications of this potential underestimation of variance remain unclear. In addition, the magnitude of uncertainty in relation to the estimation of time point where an individual PEF%p-curve would cross an (arbitrary) 50% threshold also remains unclear in the context of these calculations.

As a consequence, the mapping of the difference of about 2.7% in the annual rate of decline in PEF%p to the time scale from crossing 50% of PEF%p to initiation of assisted ventilation is associated with a considerable magnitude of (unavoidable) uncertainty.

Without addressing this caveat, there is the risk that certain claims (e.g. "2.7% in the annual rate of decline in PEF%p would result in prolongation of about 1 year from crossing 50% of PEF%p to initiation of assisted ventilation") are carried forward for further argumentation with the intention to support an idebenone effect, omitting the uncertainties attached to the methodological approach of mapping/estimation.

Additionally, the applicant investigated the potential of the true treatment difference being lower than the assumed minimum clinically relevant effect. The applicant concluded that based on the DELOS study data, the probability of the true treatment difference in PEF%p not being clinically relevant is small

(about 5-10%). However, as no detailed description of the actual method how the probabilities had been derived were included, the provided estimate of 10% is taken a lower bound for B/R.

There is also a concern regarding the exploratory nature of DELOS, as there were several amendments to the protocol of DELOS and changes in the planned analyses. This led to an enriched population of GCs non-users and as a consequence, bias in the estimation of treatment effects cannot be excluded.

In SYROS the primary endpoint of the study was changed without a protocol amendment during trial conduct. Furthermore, the fact that the data collection for the respiratory function parameter PEF was less complete than for FVC during off-treatment phases after DELOS participation questions the relevance/importance of this endpoint. In addition, the ON-ON treatment group for this study is not representative for the DELOS idebenone treatment group regarding the baseline features and their annual rate of change in respiratory parameters. It also needs to be stressed that not all DELOS investigators/treating physicians requested the option to initiate an EAP for their patients under NPP/CUP which resulted in only 18 patients being in the SYROS study (compared to 67 patients being enrolled in DELOS). Although all sites were provided with the equal possibility to participate in the EAP, it seems as if for nearly half of the treating physicians the expected benefit for the patients did not outweigh the administrative effort to initiate such a programme. Due to the above described issues, the generalisability of the SYROS results remains questionable.

Further uncertainty is derived from the comparability of annual decline rates obtained from patients being in different disease states. From the CINRG study results, it is obvious that patients who reach the 30% PEF%p threshold have an annual decline of PEF%p that is lower compared to patients being in the phase between 80% and 30% PEF%p. In SYROS, there were several patients starting idebenone treatment at a low baseline level and several patients starting at a high baseline level of PEF%p. Although sensitivity analyses were provided to investigate the influence of a possible floor effect on the rate of change in FVC%p, the general statement that the floor effect does not influence the overall results reported for SYROS is not supported. Therefore, the effect of idebenone treatment on respiratory evolution is hard to quantify when having such a heterogeneous population. In addition, the presented results do not suggest a positive effect of idebenone on long-term respiratory function evolution, as the 'stable' respiratory function seen during the DELOS period could not be maintained in the second ON treatment phase for PEF%p, FVC%p and FEV1%p.

Furthermore, a claim for consistency in terms of magnitude of treatment effect size in respiratory function parameters between the various sources of evidence (DELPHI, DELOS, SYROS) cannot be supported.

Further uncertainty is derived from the proposed indication. With the wording "treatment of respiratory dysfunction", it is unclear when treatment should be started.

In addition, there are major objections raised in the quality part of the assessment report. One is pertaining to potential nitrosamine impurities. Thus, the applicant is requested to provide a risk evaluation concerning the presence of nitrosamine impurities. The other issue is concerning the site of physical importation of the product. According to the submitted GMP documents, currently there is no company authorised for importation of the product in the primary packaging in the manufacturing chain. Unless other EU company provably authorised for importation of the product in primary packaging (code 2.3.2 in the scope) is selected as a site for importation of the product in primary packaging, the company Excella GmbH& Co. KG, as secondary packaging site should be removed from all related documents.

4.4. Unfavourable effects

In DMD patients, the most frequently reported TEAEs for idebenone treated patients were diarrhoea, headache, nasopharyngitis, upper respiratory tract infection, pyrexia, bronchitis, abdominal pain and

gastroenteritis. In placebo patients the most frequently reported TEAEs were nasopharyngitis, upper respiratory tract infection, headache, bronchitis, constipation, rhinitis and diarrhoea. Of note, the following of the most common TEAEs (incidence of ≥5%) were reported more frequently for idebenone than for placebo: diarrhoea, pyrexia, abdominal pain, gastroenteritis, left ventricular failure, otitis media, and chromaturia. Preliminary and still blinded data from ongoing DMD studies are comparable with that from completed studies, although oropharyngeal pain and cough seem to be reported more frequently.

In the full safety population (comprising pooled safety data from DMD, LHON and FRDA) the most commonly reported TEAEs in idebenone and placebo patients were headache, nasopharyngitis, diarrhoea, nausea, and upper respiratory tract infection. Those reported most frequent (≥5.0% of patients) in the idebenone group and that were ≥2.0% more frequent than in the placebo group in the double-blind studies were nasopharyngitis, diarrhoea, cough, vomiting and gastroenteritis.

In both the DMD patients and the full safety population the majority of TEAEs were of mild or moderate severity.

TEAEs evaluated as related, possibly related or unlikely related to idebenone were reported in a low number of DMD patients. Most frequent adverse reactions according to the current SmPC of Raxone/proposed SmPC of Puldysa comprise: nasopharyngitis, cough, diarrhoea and back pain.

During completed clinical studies, there were no deaths in the DMD population and one death in the full safety population that was not considered related to idebenone.

There was a lower incidence of SAEs in idebenone treated patients in both the DMD (6.7% vs. 14.3%) and the full safety population (7.0% vs. 8.7%). In the DMD population none of the SAEs was considered related to idebenone. The most frequently reported SAE in the full safety population was atrial fibrillation.

In the DMD population the discontinuation due to AEs was similar between idebenone (4.4%) and placebo (4.8%) groups. In the full safety population, the number of patients discontinuing due to AEs in the double blind studies was higher in the idebenone group (4.8% vs. 2.4%) with the most common AE of diarrhoea (1.1%).

Postmarketing data were recently assessed through a PSUSA (EMEA/H/C/PSUSA/00010412/201809; period covered by the PSUR: from 08/09/2017 to 08/09/2018) concluding on a positive B/R balance and recommending the maintenance of the MA in the authorised indication LHON.

4.5. Uncertainties and limitations about unfavourable effects

A total of 53 DMD patients received idebenone during clinical trials and 54.7% of patients received idebenone for more than 1 year. The full safety population comprises a total of 439 patients who received idebenone either during the DMD, the FRDA or the LHON clinical development programme. Overall, only a very limited number of DMD patients contribute to the safety database. Additional safety data from DMD patients could be expected from the ongoing SIDEROS/SIDEROS-E study as well as the planned MILOS study.

During the ongoing DMD studies, there were a total of 26 SAEs in 16 patients of whom 3 patients experienced SAEs considered related to investigational medicinal product (data are still blinded). In 2 patients, the SAEs had a fatal outcome. During the procedure the applicant clarified that only two serious cases were reported from the SIDEROS study that were evaluated by the investigator as possibly related to idebenone. Both of these cases had a fatal outcome. For the third case the final evaluation by the investigator was "likely not related to the study treatment". Furthermore, the applicant clarified that these cases were unblinded by assigned staff of the applicant´s pharmacovigilance department in order to report these cases as Suspected Unexpected Serious Adverse Reaction whereas the study team and investigator were kept blinded.

4.6. Effects Table

Table 67: Effects Table for Puldysa.

Effect	Short Description	Unit	Idebenone	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
PEF%p	Change from baseline to Week 52 (hospital-based spirometry)	%	-2.57 (-6.68, 1.54)	-8.84 (-12.73, -4.95)	Uncertainty regarding validity of the endpoint	DELOS
FVC%p	Change from baseline to Week 52	%	-5.67 (-8.36, -2.99)	-8.95 (-11.47, -6.42)	Uncertainty regarding validity of the endpoint	DELOS
PCF	Change from baseline to Week 52	L/s	0.14 (-0.15, 0.43)	-0.02 (-0.29, 0.25)	Uncertainty regarding validity of the endpoint	DELOS
PEF%p	Change from baseline to Week 52	%	2.8 ± 13.8	-8.5 ± 13.8	Uncertainty regarding validity of the endpoint	DELPHI
Unfavourable Effects						
Most common TEAEs (incidence of ⩾5%) reported more frequently for idebenone than for placebo, DMD safety population						
Diarrhoea	TEAE	%	20	14.3	Limited number of patients	DMD safety population
Pyrexia	TEAE	%	13.3	7.1	Limited number of patients	DMD safety population
Abdominal pain	TEAE	%	11.1	7.1	Limited number of patients	DMD safety population
Gastroenteritis	TEAE	%	11.1	2.4	Limited number of patients	DMD safety population
Left ventricular failure	TEAE	%	6.7	2.4	Limited number of patients	DMD safety population
Otitis media	TEAE	%	6.7	0	Limited number of patients	DMD safety population
Chromaturia	TEAE	%	6.7	0	Limited number of patients	DMD safety population
Most frequent adverse drug reactions						
Nasopharyngitis	Frequency according to SmPC	ADR	Very common		Not comprehensive as not all AEs with causal relationship from DMD studies are included in 4.8	SmPC Raxone/ SmPC Puldysa
Cough	Frequency according to SmPC	ADR	Very common		Not comprehensive as not all AEs with causal relationship from DMD studies are included in 4.8	SmPC Raxone/ SmPC Puldysa
Diarrhoea	Frequency according to SmPC	ADR	Common		Not comprehensive as not all AEs with causal relationship from DMD studies are included in 4.8	SmPC Raxone/ SmPC Puldysa
Back pain	Frequency according to SmPC	ADR	Common		Not comprehensive as not all AEs with causal relationship from DMD studies are included in 4.8	SmPC Raxone/ SmPC Puldysa

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

Results of the phase II trial DELPHI only show a weak trend of an effect of idebenone, but the type-1-error was controlled at 5% one-sided for this trial. Although this could generally be acceptable in the setting of an exploratory phase II study, it is not regarded acceptable that the results of the DELPHI trial

are seen as a separate and stand-alone source of evidence of a treatment effect of idebenone. Therefore, DELPHI results cannot be seen as pivotal evidence to support idebenone's benefit.

In the DELOS trial the primary endpoint was met, but several methodological concerns regarding the calculation of the primary endpoint were identified which question the validity of the endpoint. These concerns could also apply for the other respiratory endpoints. The validity issue has been discussed extensively in the former Type II variation extension of indication procedure and also in the present MAA. Although PEF%p is still not considered fully valid in the DMD setting, it has been decided that this issue will not be further pursued. Nevertheless, the lack of reliable confirmation of effects on respiratory function within the idebenone development program constitutes a major uncertainty.

Besides the validity issue and based on the statistically significant difference between idebenone and placebo for PEF%p and positive trends for FVC%p and FEV_1%p, it can be agreed to the applicant that idebenone has showed the ability to slow the rate of respiratory function decline in the targeted patient population to a certain extent. In DELOS, the point estimate of the treatment difference observed for PEF%p was above 2.7%, which was postulated by the applicant to be associated with a delay in time to assisted ventilation of 1 year. However, the chosen approach to determine a minimal clinically relevant difference for PEF%p measures is not supported and considerable uncertainty remains whether the effect shown on decline of PEF%p translates into clinical benefit, namely prolongation of the time to initiation of assisted ventilation of one year as claimed by the applicant. Currently, this argumentation is considered hypothetical and lacks clinical confirmation.

In addition, DELOS should be seen as the single pivotal trial, with hardly any potential to serve for the purpose to deliver confirmatory evidence.

The SYROS trial suffers from several design and methodological issues that limit the interpretability and generalizability of the observed long-term effects.

Overall, although there are some issues in the clinical efficacy that might call for additional clarification, pursuing those details further is not expected to significantly improve the basis for overall B/R assessment of idebenone in the targeted indication.

In conclusion, the available efficacy data lack confirmation of the effects seen so far as well as information on the clinical benefit in terms of time to relevant clinical milestone events.

Due to the orphan nature of the disease, safety data in the target population are limited. However, supportive data from other indications are available. Additional safety data from DMD patients could be expected from the SIDEROS/SIDEROS-E study as well as the planned MILOS study. While idebenone is well-tolerated and adverse reactions seem to be manageable in general, the most common adverse reactions known from other indications need to be evaluated in light of the target population (advanced, non-ambulatory DMD boys who suffer from respiratory dysfunction): nasopharyngitis, cough, diarrhoea and back pain. Moreover, there remains some degree of uncertainty regarding relationship of the two fatal cases to blinded study medication (placebo or idebenone) in the SIDEROS study: 2 patients experienced SAEs evaluated as related to blinded study medication by the investigator with a fatal outcome in both patients. In a patient population with an advanced stage of disease and where cardiac failure is part of the clinical picture of the disease, any cardiac events are considered difficult to judge in terms of relationship. The same applies to the event of fracture in both patients since both of the concerned patients received GCs treatment for several years. While the applicant´s argumentation that the cause of the events is unassessable for one of the patients or that there is no sufficient evidence to conclude a causal relation between the study medication and the events for the other patient, can in general be followed, no final conclusion can be made regarding causal relationship for these two fatal cases. However, reassurance on the begnin safety profile of idebenone derives from the completed DMD studies and the full safety populations: no deaths and no related SAEs were reported in the DMD

population. In the full safety population only one fatal event occurred and this death was determined to be unrelated to idebenone. Furthermore, the rate of SAEs with a causality other than unrelated/not related was low (8/439 idebenone treated patients).

4.7.2. Balance of benefits and risks

There are currently two major objections in the quality, pertaining to potential nitrosamine impurities and the site of physical importation of the product.

The clinical considerations on the B/R-balance at the current stage are primarily influenced by the evidence generated in DELPHI, DELOS and SYROS.

While DELPHI and SYROS results do not deliver substantial evidence on efficacy, an effect on pulmonary function parameters was shown in the pivotal study DELOS. However, there remains considerable uncertainty regarding reliability and validity of the available evidence. Furthermore, the effects seen in DELOS lack confirmation so far and the clinical relevance of the observed effects remain unclear.

The safety profile derived from completed studies in DMD patients did not reveal any new signals compared to what is already known for idebenone. Available safety data from the DMD population and full safety population are in general supporting the benign safety profile of idebenone.

Weighing available evidence for potential benefits and risks, from a clinical point of view, the B/R balance of idebenone is negative.

4.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation (CMA)

As comprehensive data on the product are not available, a CMA was requested by the applicant in the initial submission.

The product falls within the scope of Regulation (EC) No 507/2006 concerning CMAs, as it aims at the treatment of a seriously debilitating and life-threatening disease and is designated as an orphan medicinal product.

The following list provides judgements concerning the fulfilment of the requirements for a CMA: :

- The benefit-risk balance is negative, as discussed.
- It might be possible that the applicant will be able to provide comprehensive data. In principle, the proposed confirmatory phase IV MILOS study could be regarded as a good opportunity to investigate the time to a milestone event (primary objective: reaching the criteria for assisted ventilation) and this is also in line with the EMA DMD guideline (EMA/CHMP/236981/2011), which allows the post approval performance of studies investigating such endpoints, as such studies might be of very long duration. However, there are aspects regarding the design and the feasibility of the MILOS study which the applicant will have to elaborate on in order to make sure that comprehensive data could potentially be provided. In addition, the applicant should provide a clear strategy how the knowledge gained with SIDEROS could potentially be integrated in the overall licensing strategy. Another aspect to be considered is the timeframe until confirmatory data can be expected. Due to the study design as well as the milestone event of interest (time to need of assisted ventilation), results of the MILOS study will only be available several years after granting CMA. However, the SIDEROS trial was ongoing at the time of the submission of this MAA and a final study report was expected in Q2 2022. Hence, results from that study would be available within a more appropriate timeframe than MILOS results.

- Unmet medical needs could be addressed, as there is at present only one product approved for DMD in the EU: Translarna. It is indicated for the treatment of DMD resulting from a nonsense mutation in the dystrophin gene in ambulatory patients aged 2 years and older. Only 10 - 15% of DMD patients have a confirmed nonsense mutation (Dent et al., 2005) and are thus eligible for treatment with Translarna. In conclusion, Translarna is available for a restricted population only. However, in case of a CMA the legislation provides only the possibility to grant a MA based on less comprehensive data in response to unmet medical needs and therefore the indications based on less comprehensive data need to be restricted to those where there is a major therapeutic advantage versus an existing therapy. Therefore, as the currently applied for indication of Puldysa seems to overlap with that of Translarna, the applicant should justify that Puldysa provides major therapeutic advantage compared to Translarna or modify the currently applied for indication accordingly.
- As the B/R is negative, the benefits do not outweigh the risks inherent in the fact that additional data are still required.

4.8. Conclusions

The overall B/R of Puldysa is currently negative.