



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Idebenone

Proprietary Product Name: Raxone

Sponsor: JACE Pharma Pty Ltd

February 2020

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- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
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Common abbreviations

Abbreviation	Meaning
ADD	Average daily dose
ADME	Absorption, distribution, metabolism, excretion
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the time versus concentration curve
BAE	Bronchopulmonary adverse event
BP	Blood pressure
CHMP	Committee for Medicinal Products for Human Use (EU)
CI	Confidence interval
CINRG	Cooperative International Neuromuscular Research Group
CSR	Clinical study report
CYP	Cytochrome P450
DELOS	Duchenne muscular dystrophy long-term idebenone study
DMD	Duchenne muscular dystrophy
DNA	Deoxyribonucleic acid
DNHS	Duchenne natural history study
DRESS	Drug reaction with eosinophilia and systemic symptoms
EAP	Early / expanded access program
ECG	Electrocardiogram
EMA	European Medicines Agency (EU)
EU	European Union
FEV1	Forced expiratory volume in one second

Abbreviation	Meaning
FEV1%p	Percent predicted forced expiratory volume in one second
FRDA	Friedreich's ataxia
FVC	Forced vital capacity
FVC%p	Percent predicted forced vital capacity
g	Gram(s)
GC(s)	Glucocorticoid(s)
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GLP	Good Laboratory Practice
HD	High dose
hERG-1	Human ether-a-go-go-related gene 1 (channel)
IBD	International birth date
ICARS	International Cooperative Ataxia Rating Scale
ICH	International Conference on Harmonisation
IDE	Idebenone; 2-(10-Hydroxydecyl)-5,6-dimethoxy-3-methyl-cyclohexa-2,5-diene-1,4-dione (International Nonproprietary Name)
IONIA	Idebenone effects On neurological ICARS assessments
ITT	Intent-to-Treat
IV	Intravenous
L	Litre(s)
LHON	Leber's hereditary optic neuropathy
LOCF	Last observation carried forward
MEP	Maximum expiratory pressure
mg	Milligram(s)
MICONOS	Mitochondrial protection with Idebenone in Cardiological and Neurological Outcome study

Abbreviation	Meaning
MIP	Maximum inspiratory pressure
mITT	Modified intent-to-treat
mL	Millilitre(s)
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N, n	Number of observations
NADH	Nicotinamide adenine dinucleotide
ng	Nanogram(s)
NICOSIA	National Institutes of Health Collaboration with Santhera In Ataxia
NIH	National Institutes of Health (US)
NOAEL	No observed adverse effect level
NQO1	NADH-quinone oxidoreductase 1
PASS	Post-authorisation safety study
PCF	Peak cough flow
PedsQL	Pediatric Quality of Life Inventory
PEF	Peak expiratory flow
PEF%p	Percent predicted peak expiratory flow
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PPK	Population pharmacokinetics
PPM	Prospectively planned matching
PSUR	Periodic safety update report
QS10	6-(9-carboxynonyl)-2,3-dimethoxy-5-methyl-1,4- benzoquinone
QS10-C	Conjugates of QS10
QS8	6-(7-carboxyheptyl)-2,3-dimethoxy-5-methyl-1,4- benzoquinone
QS8-C	Conjugates of QS8

Abbreviation	Meaning
QS6	6-(5-carboxypentyl)-2,3-dimethoxy-5-methyl-1,4- benzoquinone
QS6-C	Conjugates of QS6
QS4	6-(3-carboxypropyl)-2,3-dimethoxy-5-methyl-1,4- benzoquinone
QS4-C	Conjugates of QS4
QT	Interval measured from the beginning of the QRS to the end of the T wave
QTc	Interval measured from the beginning of the QRS to the end of the T wave, corrected for heart rate
QTcB	QT interval corrected according to Bazett's formula
QTcF	QT interval corrected according to Fridericia's formula
RMP	Risk management plan
ROS	Reactive oxygen species
RSI	Reference safety information request for supplementary information
SAE	Serious adverse event
SD	Standard deviation
SIDEROS	Efficacy, safety of idebenone in Duchenne muscular dystrophy patients receiving glucocorticoid steroids
SmPC	Summary of Product Characteristics (EU)
SOC	System Organ Class
t	Time
TEAE	Treatment emergent adverse event
TDS	Three times daily
WBC	White blood cells
µg	Microgram(s)
µL	Microlitre(s)

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Withdrawn
<i>Date of decision:</i>	Application withdrawn 21 August 2018
<i>Date of entry onto ARTG:</i>	Not applicable
<i>ARTG number:</i>	Not applicable
<i>Active ingredient:</i>	Idebenone
<i>Product name:</i>	Raxone
<i>Sponsor's name and address:</i>	JACE Pharma Pty Ltd 20 Clutha St West Lake QLD 4074
<i>Dose form:</i>	Film coated tablet
<i>Strength:</i>	150 mg
<i>Container:</i>	bottle
<i>Pack size:</i>	Not applicable
<i>Approved therapeutic use:</i>	Not applicable
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	Not applicable

Product background

This AusPAR describes the application by JACE Pharma Pty Ltd (the sponsor), on behalf of Santhera Pharmaceuticals (Switzerland) Ltd to register Raxone idebenone 150 mg film coated tablets for the following indication:

Raxone is for the treatment of patients with Duchenne Muscular Dystrophy (DMD) for whom the respiratory function has started to decline and who are currently not taking concomitant glucocorticoids. Raxone can be used in patients previously treated with glucocorticoids or in patients in whom glucocorticoid treatment is not desired, not tolerated or is contraindicated.

Untreated, the gradual loss of respiratory function in Duchenne muscular dystrophy (DMD) usually begins early in the second decade and progresses to restrictive pulmonary syndrome and respiratory failure and the need for assisted ventilation (nocturnal and then daytime), usually from the mid-to-late teens.¹ Aggressive respiratory management aimed at improving respiratory muscle strength and endurance has a significant impact on life expectancy;² since with progressive loss of respiratory muscle strength, patients with DMD are at increasing risk for respiratory complications.

Despite the recent improvements in the respiratory care of DMD patients, poor respiratory condition becomes critical with the progression of the disease, respiratory complications remain by far the most common cause of morbidity and mortality in DMD, being the cause of death in over 70% of patients.³ Since respiratory failure is still among the main causes of death in patients affected by DMD;⁴ it is extremely important to measure lung and respiratory muscle function in order to monitor the progression of the disease. Overall, at any time approximately 38% of DMD patients are either glucocorticoid naïve or have discontinued treatment;⁵ with this proportion increasing in the post-ambulatory phase. There is therefore an unmet medical need for the management of respiratory function deterioration in patients not taking glucocorticoids, and thus not benefiting from the respiratory effects of the glucocorticoid steroids.

Idebenone stimulates mitochondrial electron flux and cellular energy production and also functions as an antioxidant. It is proposed for the treatment of patients DMD for whom respiratory function has started to decline and who are currently not taking concomitant glucocorticoids.

The cellular pathology at the mitochondrial level in dystrophic muscle cells manifests in multiple deficiencies of various metabolic pathways to culminate in adenosine triphosphate (ATP) insufficiency and excessive reactive oxygen species (ROS) formation.

Upon entering the cell, idebenone is reduced by the cytoplasmic enzyme NADH-quinone oxidoreductase 1 (NQO1);⁶ and the resulting reduced form enters the mitochondria where it is re-oxidised by complex III, bypassing complex I-dependent ATP synthesis. Idebenone can therefore restore mitochondrial function in the presence of Complex I dysfunction.

¹ McDonald CM et al., 1995 Profiles of neuromuscular diseases. Duchenne muscular dystrophy. *Am. J. Phys. Med. Rehabil* 1995; 74: S70-S92

² Eagle M et al., 2002 Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. *Neuromuscular Disorders* 2002; 12: 926-929

³ Simonds, AK 2002 Respiratory Complications of the Muscular Dystrophies. *Seminars in respiratory and critical care medicine* 2002; 23: 231-238

⁴ LoMauro A et al., 2015 Assessment and management of respiratory function in patients with Duchenne muscular dystrophy: current and emerging options. *Therapeutics and Clinical Risk Management* 2015; 11: 1475-1488

⁵ Henricson E K et al., 2013 The cooperative international neuromuscular research group Duchenne natural history Study: glucocorticoid treatment preserves clinically meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcome measures. *Muscle Nerve* 2013; 48: 55-67

⁶ NADH = Nicotinamide adenine dinucleotide

Idebenone also inhibits mitochondrial ROS formation. It is proposed that idebenone prevents muscle deterioration in DMD via its ability to increase cellular energy production, reduce ROS formation and protect from cell-damaging oxidative stress.

Regulatory status

Orphan drug designation

This product was granted orphan drug designation on 27 February 2017 for the treatment of DMD. The proposed indication for registration is a subset of the orphan designation. The sponsor estimates the Australian prevalence of DMD to be between 4.8 and 7.2 per 100,000 individuals.

The sponsor states that idebenone was granted an Orphan Designation for the treatment of DMD in the European Union (EU) on 19 March 2007, the United States (US) Food and Drug Administration (FDA) in February 2007, and in Switzerland by Swissmedic on 6 December 2012.

At the time the TGA considered this application, a similar application was under consideration in the following countries as territories as outlined below.

United States

A New Drug Application for idebenone has not been submitted in USA.

European Union

There is no marketing authorisation for idebenone for a DMD indication. Marketing authorisation for idebenone was granted under exceptional circumstances in September 2015 for the treatment of Leber's hereditary optic neuropathy. A Type II variation to add a new therapeutic indication for DMD was submitted to European Medicines Agency (EMA) on 27 May 2016. The final opinion of the Committee for Medicinal Products for Human Use (CHMP) on 25 January 2018 recommended the refusal of the variation to the terms of the marketing authorisation. Grounds for refusal included the limited strength of the evidence for a beneficial effect, methodological concerns with the study and the lack of a scientific rationale allowing for the extrapolation of the estimated effect on measures of pulmonary functioning beyond the trial duration.

Other jurisdictions

Switzerland (Swissmedic); application submitted on 30 September 2016, withdrawn 31 January 2018.

Applications have not been submitted in Canada or Singapore.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR and Attachment 2.

Table 1: Timeline for Submission PM-2017-01423-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	30 May 2017

Description	Date
First round evaluation completed	2 January 2018
Sponsor provides responses on questions raised in first round evaluation	28 February 2018
Second round evaluation completed	21 June 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	3 July 2018
Sponsor's pre-Advisory Committee response	16 July 2019
Advisory Committee meeting	3 August 2018
Withdrawal of application	21 August 2018
Number of working days from submission dossier acceptance to withdrawal of application*	183

*Statutory timeframe for standard applications is 255 working days

Evaluations included under Quality findings and Nonclinical findings incorporate both the first and second round evaluations.

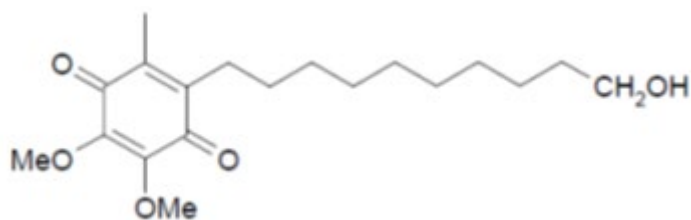
III. Quality findings

Introduction

Drug substance (active ingredient)

There is no monograph for idebenone. Figure 1 shows the structure of idebenone.

Figure 1: Structure of idebenone



The manufacture, quality control (according to in-house specifications) and stability of the active ingredient idebenone are described in the associated drug master file.

Control of the drug substance by finished product manufacturer

The proposed drug substance specifications applied by the finished product manufacturer are identical to those applied by the drug substance manufacturer except as discussed under Justification of specification.

Analytical procedures

The analytical procedures used by the drug product manufacturer are identical to those used by the drug substance manufacturer.

Batch analyses

Batch analytical data generated by both the drug substance manufacturer and the drug product manufacturer have been provided for the batches and are comparable.

Justification of specification

The drug product manufacturer applies limits of not more than (NMT) 0.05% to Impurities B and C and unspecified impurities rather than NMT 0.10% as in the drug substance manufacturer's specifications. The tighter limits are stated to be to support a different indication with a higher daily intake of the drug substance and are acceptable.

The suitability of the particle size limits is addressed.

Reference standards or materials

The reference standards for the drug substance and nominated impurities are the same as those used by the drug substance manufacturer. Certificates of analysis and characterisation data for the batch used are included in the drug master file and the data are acceptable.

Drug product

The proposed product is an orange, round, biconvex, film-coated tablet engraved with a logo on one side and '150' on the other. The tablet is approximately 10 mm in diameter.

Formulation details for the product were provided.

The excipients chosen are all commonly used in film-coated tablets. No formal compatibility studies were performed as no incompatibilities were expected.

The optimised coated tablet formulation resulting from development studies was identical to the formulation used in the Phase I to III clinical studies. Dissolution profiles for five batches used in clinical trials have been provided. The proposed formulation does not include any overages.

A wet granulation process was chosen for the manufacture of the proposed product. The process used in the formulation development studies was transferred to the site of commercial manufacture and mixing times, granulation fluid volume, drying time, and compression force were optimised to give the proposed commercial manufacturing process.

The product is manufactured by: mixing of idebenone, and excipients; wet granulation; drying; screening of the dried granules; screening and addition of additional excipients; blending; lubrication; compression; coating; and packaging.

The manufacturing process has been validated using three 100,000 tablet batches and three 1,000,000 tablet batches. All batches complied with the acceptance criteria in the validation protocol and with the proposed finished product specifications.

The test method for assay and degradation products has been validated for specificity in the presence of excipients and known synthetic impurities as shown below, accuracy, linearity, method and intermediate precision, limits of detection (0.02%) and quantitation (0.05%), solution stability, and robustness. The results reported are satisfactory.

The test method for quantitation of dissolution samples has been validated for specificity in the presence of excipients and dissolution medium, accuracy, linearity, method and intermediate precision, and solution stability. The results reported are satisfactory.

For impurities arising from the manufacture and purification of the drug substance, were assessed in the evaluation of the drug master file.

Degradation products arising from manufacture and storage of the product have not been characterised as no additional degradants were detected during the stability studies.

The specifications include tests for identification of the drug substance by high-performance liquid chromatography HPLC and by ultraviolet radiation. This is consistent with the requirements of International Conference on Harmonisation (ICH) Q6A and is acceptable.⁷

The proposed Assay limits are consistent with the requirements of TGO 78 and are acceptable.⁸

The specifications include a test for uniformity of dosage units by weight variation and are consistent with the requirements of TGO 78 and the British Pharmacopoeia/European Pharmacopoeia tablets monograph and is acceptable.

The specifications include a test for degradation products with limits for each unspecified impurity and 'Total impurities' at both release and expiry. The proposed expiry limits are consistent with the ICH Q3B;⁹ identification and qualification thresholds of 0.2% for a drug product with a maximum daily dose of 900 mg and are acceptable. The proposed release limits do not allow for any change on storage, however, this will not be pursued as no trends were observed in the stability studies.

The specifications include a test for dissolution consistent with general pharmacopoeial requirements and is acceptable, however, the results of development and stability studies indicate that the product could comply with this limit at an earlier sampling time.

The stability data provided support the proposed shelf life of 5 years for the unopened product when stored below 25°C.

Biopharmaceutics

Rate and extent of absorption

Peak plasma concentrations of idebenone occur about 1 to 4 hours after oral administration. Absolute bioavailability has not been determined.

Metabolism and distribution

Idebenone is extensively metabolised in the liver, predominantly by oxidative shortening of the side chain and by conjugation (either glucuronidation or sulphation). Approximately 56 to 78% of an oral dose is recovered as metabolites in urine compared to less than 1% as unchanged drug. Plasma concentrations of idebenone are much lower than the concentrations of its metabolites at all times after oral dosing, indicating that the first-pass effect is extensive.

⁷ ICH Topic Q6A Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances

⁸ TGO 78: Therapeutic Goods Order No. 78 Standard for tablets and capsules

⁹ ICH Topic Q3B: CPMP/ICH/2738/99; Note for guidance on impurities in new drug products

Idebenone crosses the blood-brain barrier and significant concentrations are observed in cerebral tissue.

Mode, route and rate of elimination

Idebenone is eliminated primarily by hepatic metabolism followed by renal excretion of the metabolites. The plasma elimination half-life of idebenone cannot be determined directly as measurable concentration are only obtained for approximately 6 hours after oral dosing, but is relatively short as accumulation after repeat dosing at three-times-daily intervals was minimal. The half-lives of its metabolites are approximately 4 to 7 hours.

Active entity

The active entity is idebenone.

Dose response proportionality

Pharmacokinetics of idebenone after administration of 150 mg and 750 mg doses were approximately dose-proportional.

Effects of food

Administration with food increased idebenone maximum plasma concentrations (C_{max}) and AUC;¹⁰ approximately 5 fold and 7 fold respectively when compared with the fasted state.

Absolute bioavailability

The sponsor has provided a justification for not performing an absolute bioavailability study. The main points of the justification are summarised below:

- Although idebenone is a new chemical entity in Australia, it has been marketed since 1993 in Italy, Portugal, Argentina, and Mexico for cerebral insufficiency of vascular or degenerative origin.
- Idebenone exhibits highly lipophilicity and very low solubility, making intravenous (IV) formulations difficult to develop. No reports of administration of an IV idebenone formulation to humans have been found and only one report of administration to rats in a 10% polyethoxylated castor oil solution, which is not suitable for use in humans.
- While a safe IV formulation could possibly be developed, the benefits of doing so would be minimal as idebenone has been in use for over 30 years and its pharmacokinetics and safety profile are well characterised.

Given today's technologies, it is thought that the development of an IV dose for use in an absolute bioavailability study should have been possible. However, this matter will be highlighted with the clinical Delegate for consideration.

Quality summary and conclusions

Approval is recommended in relation to the pharmaceutical chemistry and quality aspects of the submission as all matters raised during the evaluation have been satisfactorily resolved.

¹⁰ AUC = Area under the time vs. concentration curve

IV. Nonclinical findings

Introduction

The sponsor has applied to register a new chemical entity, idebenone (Raxone) for the treatment of patients with DMD for whom respiratory function has started to decline and who are currently not taking concomitant glucocorticoids. Raxone can be used in patients previously treated with glucocorticoids or in patients in whom glucocorticoid treatment is not desired, not tolerated or is contraindicated. The proposed dosing regimen involves oral administration of idebenone at 900 mg/day (300 mg, 3 times a day). The treatment duration has not been specified by the sponsor but is expected to be long-term given the chronic nature of DMD symptoms and the lack of available therapies.

General comments

The overall quality of the nonclinical dossier was satisfactory and in general accord with the ICH guideline for the nonclinical assessment of pharmaceuticals.¹¹ The nonclinical dossier included primary and secondary pharmacology studies (*in vitro* and *in vivo*); 15 repeat-dose toxicity studies in three species (up to 13 weeks duration in mice, 1 years duration in rats and 52 weeks duration in dogs); genotoxicity and carcinogenicity studies in two rodent species; a complete suite of reproductive toxicity studies in two species; and qualifying studies in support of the specifications for impurities. All pivotal safety related studies were Good Laboratory Practice (GLP) compliant. The dossier was therefore considered to be comprehensive, in accordance with relevant ICH guidelines, and adequate to evaluate the safety of idebenone.

A number of submitted studies were not evaluated. Studies C-14-339 and C-14-403 were not evaluated as these were review articles that focused on the potential of idebenone as a treatment for cerebrovascular disorders and were not considered relevant to the current application. Studies C-14-415 and C-14-416 reported on the effect of idebenone on neurological deficits following the induction of cerebrovascular lesions in stroke-prone spontaneously hypertensive rats and were also not considered relevant to the present application and not evaluated.

A deficiency in the dossier is the lack of toxicokinetic data accompanying the pivotal rat Study C-14-434 and most of the submitted reproductive and developmental toxicity studies, prohibiting a comparison of drug exposure between animals and patients on the basis of AUC (a more informative indicator of drug exposure than body surface area comparisons) and hence a correlation with toxicities.

Pharmacology

Primary pharmacology

Weakness of respiratory muscles leading to respiratory insufficiency is a key pathological feature associated with DMD. Duchenne muscular dystrophy is characterised by cell membrane fragility and intracellular Ca²⁺ dysregulation secondary to the disease-causing absence of the protein, dystrophin. This muscle cell membrane damage causes functional aberrations in mitochondrial energy transduction and increased production of cell-damaging reactive oxygen species (ROS). Mouse myoblasts from *mdx* mice (engineered to have a point mutation in the *dystrophin* gene and exhibiting a mild DMD phenotype)

¹¹ ICH M3; CPMP/ICH/286/95 Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals.

demonstrate abnormalities in several mitochondrial functions including decreased basal oxygen consumption and levels of Complex I, III and V and increased mitochondrial membrane potential and ROS production. The cellular pathology at the mitochondrial level in dystrophic muscle cells manifests in multiple deficiencies of various metabolic pathways to culminate in adenosine triphosphate (ATP) insufficiency and excessive ROS formation.

Upon entering the cell, idebenone is reduced by the cytoplasmic enzyme NADH-quinone oxidoreductase 1 (NQO1) and the resulting reduced form enters the mitochondria where it is re-oxidised by complex III, bypassing complex I-dependent ATP synthesis. Idebenone can therefore restore mitochondrial function in the presence of complex I dysfunction. Idebenone also inhibits mitochondrial ROS formation. It is proposed that idebenone prevents muscle deterioration in DMD via its ability to increase cellular energy production, reduce ROS formation and protect from cell-damaging oxidative stress.

Idebenone restored mitochondrial function in the presence of Complex I inhibition in a mouse model of Leber's hereditary optic neuropathy where it effectively prevented retinal ganglion cell death and decreased retinal thickness induced by rotenone (a complex I inhibitor). Idebenone improved cardiac parameters after induction of ischemia by mediating a more rapid recovery of pulse rate and coronary blood flow and preventing a reduction in cardiac glycogen in perfused rat hearts *ex vivo*. Idebenone also prevented ischemia induced S-T segment increases in electrocardiograms (ECG) (a hallmark of myocardial infarction) in dogs. In *mdx* mice, idebenone prevented deleterious changes in cardiac physiology (such as reductions in heart rate, end-diastolic pressure and isovolumetric relaxation during diastole) and muscular parameters (including impaired running distance and increased variability in quadriceps, but not diaphragm, striated muscle fibre diameter). Idebenone also decreased mortality in a dobutamine stress test caused by left ventricular dilatation, reduced the likelihood of cardiac fibrosis development and reduced cardiac inflammation and serum troponin levels.

Safety pharmacology

Idebenone inhibited human ether-a-go-go-related gene 1 (hERG-1) tail currents in a dose dependent manner (by 20% to 46%) *in vitro* at concentrations (3 to 10 μ M) well above the clinical C_{max} achieved in human studies.¹² However, there were no significant findings in *in vivo* cardiovascular studies on telemetered dogs at exposure levels;¹³ more than 19 fold the clinical C_{max} . Thus, no significant concerns are raised for the cardiovascular safety of idebenone.

There were no significant drug-related effects on the central nervous, respiratory or gastrointestinal systems in studies conducted in rats and mice at multiples of the clinical C_{max} of ≥ 56 x;¹⁴ and ≥ 6 x;¹⁵ respectively. Dogs received doses up to 500 mg/kg (≥ 19 fold the clinical C_{max} when compared to the C_{max} (366 ng/mL) in dogs receiving the same dose in repeat-dose Study C32393).

Overall the safety pharmacology data in animals demonstrated no overt safety concerns with respect to the clinical use of idebenone.

¹² (19.2 ng/mL; 57 nM) following repeat dosing at 750 mg TDS, Study SNT-I-003

¹³ Doses up to 500 mg/kg; C_{max} , 366 ng/mL, in dogs in repeat-dose Study C32393.

¹⁴ 1070 ng/mL; repeat-dose Study SNT-P-003

¹⁵ 106 ng/mL; Study C-14-53

Pharmacokinetics

The pharmacokinetics of idebenone were studied in mice, rats and dogs. In humans and animals, idebenone is rapidly absorbed. When idebenone was administered by the clinical (oral) route the time to maximum measure concentration (T_{max}) ranged between 0.25 hours to 8 hours post-dose in the species studied while in humans T_{max} ranged between approximately 0.5 hours to 3 hours. A high variability in pharmacokinetic values was observed between studies in all species including humans. This is attributed to variations in absorption, the effect of food, and a high first pass effect (discussed below).

Idebenone is rapidly converted to metabolites by first pass metabolism mediated by oxidative shortening (mainly by CYP1A2, CYP2C19, and CYP3A4);¹⁶ to the metabolites QS10, QS8, QS6, and QS4;¹⁷ (the number refers to the number of carbon atoms in the side-chain). Idebenone and all of these short-chain metabolites may also undergo conjugation via glucuronidation or sulfation to yield conjugated moieties yielding idebenone-C, QS10-C, QS8-C, QS6-C and QS4-C.¹⁸ Consequently, in both humans and animals, the plasma concentrations of idebenone are very low relative to its metabolites. The main metabolites are conjugates of QS10, QS6, and QS4 in rats, conjugates of idebenone and QS4 in dogs, and conjugates of idebenone and QS4 in humans. There are no metabolites unique to humans and none of the primary or secondary metabolites are pharmacologically active.

Administration of idebenone under fed conditions increased the relative bioavailability of the drug in dogs, a phenomenon that was also seen in humans, albeit to a lesser extent. In humans, the AUC and C_{max} of idebenone increased approximately 7 fold and 5 fold under fed conditions, respectively, compared to fasting conditions. In dogs the AUC and C_{max} of idebenone increased approximately 45 fold and 14 fold under fed conditions, respectively, compared to fasting conditions. As with idebenone, metabolite exposure also increased under fed conditions. In humans, the AUC and C_{max} of the conjugated metabolites increased up to 2 fold with food while in dogs the AUC and C_{max} of QS-4 (the predominant metabolite in humans) increased approximately 30 fold and 20 fold under fed conditions, respectively, compared to fasting conditions.

Oral bioavailability of idebenone is extremely low (< 1%) in all species used in the toxicology studies; thus even at very high doses only low plasma concentrations of idebenone were observed in all species.

Idebenone and metabolite pharmacokinetics were non-linear at higher doses in all species examined. There was a plateauing of idebenone plasma concentrations at higher doses in both rats and dogs, with saturation of absorption at dose levels beyond 500 mg/kg in dogs. There were generally no gender differences in pharmacokinetic parameters in any species. In humans, exposure to idebenone and its conjugated metabolites increased approximately dose proportionately: for a doubling in dose, systemic exposure increased, on average, approximately 1.7 to 2.5 fold.

Plasma protein binding of idebenone was very high and similar across all species (> 99.9%, 98.0%, and 98.5% for rat, dog, and human plasma, respectively). In rat plasma, the binding of idebenone and its metabolites to lipoproteins was weak. Less than 25% of radiolabelled idebenone and its metabolite QS-4 were bound to plasma lipoproteins, with the remainder bound to albumin and other plasma proteins. Tissue distribution studies performed in rats after oral dosing showed that ¹⁴C-idebenone uptake was rapid and widespread, with a T_{max} of 0.5 hours in both plasma and brain. The highest tissue:plasma C_{max} ratios (approximately 2) were observed in the liver and kidney and the peak brain

¹⁶ CYP = Cytochrome P450

¹⁷ QS10 = 6-(9-carboxynonyl)-2,3-dimethoxy-5-methyl-1,4- benzoquinone; QS8 = 6-(7-carboxyheptyl)-2,3-dimethoxy-5-methyl-1,4- benzoquinone; QS6 = 6-(5-carboxypentyl)-2,3-dimethoxy-5-methyl-1,4- benzoquinone; QS4 = 6-(3-carboxypropyl)-2,3-dimethoxy-5-methyl-1,4- benzoquinone

¹⁸ QS10-C = Conjugates of QS10; QS8-C = Conjugates of QS8; Conjugates of QS6; QS4-C = Conjugates of QS4

level was at least 8 fold lower than the plasma C_{max} . High concentrations of idebenone were also found in the stomach, intestine, blood, lung, spleen, skeletal muscle (the target organ), and thymus. The exposure of idebenone metabolites in the plasma and brain were 908 and 310 times greater than that of idebenone, respectively. The amount of total radioactivity in the red blood cells was less than 10% of the values in the plasma, indicating minimal penetration into the erythrocyte fraction.

Following repeated oral dosing over a 21 day period, mean levels of idebenone in vitreous or aqueous humour were approximately 6% and 28 to 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.

In dogs, the main routes of excretion were renal (approximately 50% of administered radioactivity) and faecal (approximately 30% of administered radioactivity) after oral and intravenous administration. Similarly, in humans dosed with ^{14}C -idebenone, an average of 79.8% of radioactivity was eliminated in the urine and 7.1% in the faeces.

Given the similarities in bioavailability, plasma protein binding, excretion and metabolite profiles between humans and the animal models examined, the pharmacokinetics of the animal species selected were sufficiently similar to allow them to serve as appropriate models for the assessment of idebenone toxicity in humans.

Pharmacokinetic drug interactions

Pharmacokinetic interactions of idebenone were examined *in vitro*. The ability of idebenone and one of its major metabolites, QS10, to inhibit cytochrome P450 isoforms (CYP1A, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) was assessed using human hepatic microsomes. Idebenone inhibited these P450 isoforms with half maximal inhibitory concentration (IC_{50}) values that ranged from 1.69 μM to 10.3 μM (values that exceed the clinical C_{max} by two orders of magnitude).¹⁹ QS-10 inhibited these P450 isoforms with IC_{50} values that ranged from 9.14 μM to 28.9 μM which are approximately equal to the QS-10+QS-10-C C_{max} achieved clinically;²⁰ indicating that QS-10 has the potential to inhibit these P450 enzymes. Neither idebenone nor QS-10 was predicted to inhibit systemic CYP enzymes *in vivo*. However, both idebenone and QS-10 were predicted to inhibit intestinal CYP3A4 *in vivo*, which can potentially increase absorption/exposure of co-administered drugs that are CYP3A4 substrates. Therefore, clinically relevant interactions between idebenone or QS-10 with CYP3A4 substrates are possible.

In experiments performed on primary human hepatocytes, neither idebenone nor QS-10 significantly induced CYP1A/1A2, CYP2B6 and CYP3A4 transcription or enzymatic activity.

Studies performed in *in vitro* MDR1-MDCK permeability assays;²¹ demonstrated that idebenone was not a P-glycoprotein (P-gp) substrate but inhibited transport of the model P-glycoprotein substrate loperamide with an IC_{50} value of 51.8 μM . It was predicted that idebenone could inhibit intestinal P-gp *in vivo*, potentially increasing the absorption and/or exposure of a co-administered drugs that are substrates for P-gp.

¹⁹ 19.2 ng/mL; 57 nM; 2.5 times the MRHD, Study SNT-I-003, achieved in human studies following repeat dosing at 750 mg TDS.

²⁰ 12.6 μM ; 2.5 times the MRHD, Study SNT-I-003

²¹ MDCK-MDR1: combination of Madin Darby canine kidney (MDCK) cells and MDR1 gene to encode the efflux protein, P-gp.

Toxicology

Acute toxicity

Idebenone and its QS-4 metabolite displayed a very low order of acute toxicity via the IP and PO routes in studies conducted in mice and rats. Intraperitoneal treatment caused more severe symptoms than PO including decreased locomotor activity, lowered body temperature, slightly hypotonic abdominal muscles, loss of body weight and emaciation. The direct cause of death was respiratory failure in both IP- and PO-treated animals. QS-4, given by either the intraperitoneal or PO route produced similar clinical symptoms as well as respiratory depression, and hypothermia in intraperitoneal treated animals.

Repeat-dose toxicity

Repeat dose studies were conducted in mice (up to 13 weeks), rats (up to 12 months) and dogs (up to 12 months). Durations of studies were acceptable in view of an anticipated long-term pattern of use to for providing symptomatic relief. The choice of species (rat and mouse as the rodent and dog as the non-rodent) for the pivotal studies is acceptable on the basis of pharmacokinetic considerations. Doses were administered orally, the clinical route of administration, yet were administered once daily instead of 3 split daily doses as proposed clinically. Design aspects of the studies (types of species used, group sizes, determined parameters) were appropriate and consistent with guidelines relevant to toxicity testing.²²

Relative exposure

Exposure ratios are calculated based on animal: human plasma AUC from time zero (dosing) to 6 hours post dose (AUC_{0-6h}) values. The animal AUC data shown is the mean of male and female values. Human reference values are from clinical Study SNT-I-003 where healthy human subjects (between 18 and 45 years old) received up to 2250 mg/kg/day, 2.5 times the proposed clinical dose (900 mg/day), for 14 days. High exposure ratios of up to 102 in mice, 92 in rats and 145 in dogs were achieved at the highest doses (Table 2).

Table 2: Relative exposure in repeat-dose toxicity and carcinogenicity studies

Species	Study duration (Study no.)	Dose (mg/kg/day)	AUC _{0-24 h} ^a (ng·h/mL)	Exposure ratio
Mouse (ICR)	103 weeks Study CIT-12746 (carcinogenicity)	650	1908	45.2
		1280	2658	62.5
		2000	4387	102.4
Mouse (CD-1)	13 weeks Study C-14-714	210	35	1.3
		640	172	4.0
		1280	522	12.0
		2000	1116	26.6

²² (ICH M3(R2) Step 5: ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals Step 5 (EMA/CPMP/ICH/286/1995); CPMP/SWP/1042/99 Rev 1): Guideline on repeated dose toxicity.

Species	Study duration (Study no.)	Dose (mg/kg/day)	AUC _{0-24 h} [^] (ng·h/mL)	Exposure ratio
Rat (SD)	13 weeks Study C-14-713	160	19	0.0
		500	688	16.0
		1000	1127	26.6
		2500	3575	83.8
	104 weeks Study C-14-886 (carcinogenicity)	500	1554	35.9
		1000	3222	75.8
Rat (Wistar)	26 weeks Study C-14-787	30	50	1.3
		100	141	2.7
		300	1430	33.3
		1000	3907	91.8
	4 weeks Study AA62017 (Juveniles)	20	17	0.4
		200	976	22.6
		1000	6285	147.6
Dog (beagle)	5 weeks C23325	500	2910	67.8
		750	7186	168.9
		1000	6212	145.0
	26 weeks Study C-14-800	100	181	4.0
		500	3722	87.8
	39 weeks Study C32393 (Pivotal)	500	1545	35.9
		750	2205	51.9
		1000	3471	81.1
Human (healthy volunteers)	(Study SNT-I-003)	(900 mg)	42.4	–

[^] = data are for the sexes combined at the last sampling occasion

Grouped toxicokinetic data were also obtained for idebenone plus its metabolites in rats and dogs, the species used in the pivotal toxicology studies. Exposure ratios achieved in animals were relatively low (Table 3); in neither the rat nor dog study did QS10+QS-10-C exceed clinical exposure. In rats, the maximal exposure ratios achieved for idebenone + idebenone C, QS6+QS6-C and QS4+QS4-C were 0.2, 2.7 and 6.3, respectively, while in dogs,

the maximal exposure ratios achieved for idebenone + idebenone C, QS6+QS6-C and QS4+QS4-C were 6.5, 7.2 and 4.4, respectively. These studies demonstrate that idebenone and all metabolites can be generated in the species selected for toxicological examination. While the exposures achieved for each metabolite do not exceed the clinical exposure by a wide margin, the toxicity of the metabolites are of no concern from a nonclinical perspective as they are not pharmacologically active, were present at significant levels in the species used for toxicological studies, and idebenone had a very low order of toxicity in the repeat dose studies.

Table 3: Relative exposure in repeat-dose toxicity and carcinogenicity studies

Species	Study duration (Study no.)	Dose (mg/kg/day)	Analyte	AUC _{0-24h} [^] (ng·h/mL)	Exposure ratio [#]
Rat (Wistar)	4 weeks Study B25064	20	Idebenone + Idebenone C	45	< 0.1
			QS10+QS10-C	390	< 0.1
			QS6+QS6-C	340	< 0.1
			QS4+QS4-C	8066	0.2
		100	Idebenone + Idebenone C	779	< 0.1
			QS10+QS10-C	4542	0.2
			QS6+QS6-C	4043	0.3
			QS4+QS4-C	62235	1.2
	4 weeks Study AA62017 (Juveniles)	500	Idebenone + Idebenone C	8400	0.2
			QS10+QS10-C	21493	0.9
			QS6+QS6-C	34497	2.7
			QS4+QS4-C	337951	6.3
		1000	Idebenone + Idebenone C	33104	0.7
			QS10+QS10-C	70645	3
			QS6+QS6-C	206824	16
			QS4+QS4-C	683005	13
Dog (beagle)	39 weeks	500	Idebenone + Idebenone C	150397	3.1
			QS10+QS10-C	7439	0.3

Species	Study duration (Study no.)	Dose (mg/kg/day)	Analyte	AUC _{0-24h} [^] (ng·h/mL)	Exposure ratio [#]
			QS6+QS6-C	52890	4.2
			QS4+QS4-C	177866	3.3
			Idebenone + Idebenone C	205679	4.2
			QS10+QS10-C	15034	0.6
		750	QS6+QS6-C	30154	2.4
			QS4+QS4-C	155093	2.9
			Idebenone + Idebenone C	318550	6.5
			QS10+QS10-C	24027	1.0
			QS6+QS6-C	90886	7.2
			QS4+QS4-C	236273	4.4
		1000	Idebenone + Idebenone C	318550	6.5
			QS10+QS10-C	24027	1.0
			QS6+QS6-C	90886	7.2
			QS4+QS4-C	236273	4.4
Human (healthy volunteers)	(Study SNT-I-003)	(2250 mg/day (900 mg TDS))	Idebenone + Idebenone C	49302 [#]	-
			QS10+QS10-C	25043 [#]	-
			QS6+QS6-C	12688 [#]	-
			QS4+QS4-C	53649 [#]	-

[#] = (AUC_{0-6h} × 4)/2.5 since the MRHD is 900 mg/day; [^] = data are for the sexes combined at the last sampling occasion

Major toxicities

Overall, idebenone exhibited a very low order of toxicity in the repeat dose studies in all species. The only target organ which consistently exhibited pathology in rats was the gastrointestinal system in which reversible effects were observed. This was demonstrated at necropsy in the forestomach as mucosal thickening and histopathologically as increased squamous epithelium accompanying hyperkeratosis of the forestomach, degeneration, erosion, ulceration, foci of necrosis, and oedema associated with infiltration of inflammatory cells. Effects in the glandular stomach were seen to a lesser extent, except in the 26 week oral gavage study at doses up to 1000 mg/kg, and included red spots, hyperplasia, and ulceration. Given that this pathology was not observed in dogs and that there is no anatomical equivalent of the forestomach in humans (it is anticipated that exposure to the human oesophagus will be transient whereas the rodent forestomach is a holding compartment), this toxicity is regarded as rodent-specific and of limited relevance to human toxicity.

In studies conducted in dogs up to 52 weeks in duration, dose dependent incidences of clinical signs such as vomiting of yellow fluid, mucus or feed, loose watery faeces, decreases in food consumption, and consequent body weight losses, were observed. These

effects were not considered toxicologically adverse and body weight losses tended to be reversible upon cessation of dosing. Treatment of dogs with idebenone was also associated with statistically significant changes in some haematology, clinical chemistry, and organ weight parameters. However, since no clear patterns were evident and the observed changes remained within the normal physiological limits, they were considered to be of no toxicological relevance. In a 39 week chronic toxicity study which included a supportive feeding regimen to minimize adverse body weight losses, two animals dosed at 1000 mg/kg/day showed mild liver hypertrophy and two exhibited lung fibrosis, oedema, inflammation and alveolo-bronchiolar hyperplasia, all of which were not evident in recovery animals; the only other effects in this species included dose-dependent increases in gastrointestinal disturbances (such as loose faeces, diarrhoea and emesis), body weight loss, and reductions in food intake.

Genotoxicity

The genotoxic potential of idebenone was evaluated in a battery of *in vitro* and *in vivo* assays based on endpoints for gene mutation, chromosome aberrations, and DNA damage. The methods used to assess genotoxicity were generally appropriate and utilised study designs that were consistent with ICH guidelines on genotoxicity testing;²³ and all but one bacterial reverse mutation assay were conducted under GLP conditions. Idebenone demonstrated no genotoxic potential in the *in vitro* bacterial mutagenicity assays or in the *in vivo* micronucleus tests. No genotoxic effects were induced by idebenone in an unscheduled DNA synthesis test in rat liver or in an *in vivo* chromosome aberration assay in rat bone marrow. When assayed for its ability to induce mutation at the tk locus in L5178Y TK+/- mouse lymphoma cells, idebenone produced positive mutagenic responses, however, within replicates in this study, this result was not reproducible, not statistically significant, and not dose-related. These results were therefore of limited value in predicting idebenone genotoxicity. *In vitro* chromosomal aberration studies in human peripheral lymphocytes demonstrated the induction of chromosome aberrations, however, idebenone was considered to not be potentially clastogenic as the aberrations induced were considered to be related to the redox properties of idebenone and idebenone was not carcinogenic in long term rodent studies.

Carcinogenicity

The sponsor submitted two carcinogenicity studies of 2 years in duration; one study each for mice and rats. Idebenone was administered through the diet and both males and females were used in the studies. Design aspects of the studies were generally consistent with ICH and EU guidance for carcinogenicity studies. Dose selection was based on preliminary 13 week toxicity studies that sought to determine a maximum tolerated dose for the tested species. The highest dose of idebenone used in the mouse carcinogenicity studies was based on a toxicity-based endpoint: gastric irritation manifested mainly as epithelial cell hyperplasia, and based on the histopathological findings in the forestomach and the reductions in body weight gain observed in both the 13-week dose range finding study and a previous long-term mouse carcinogenicity study. As such, 2000 mg/kg/day was considered to be the maximum tolerated dose (MTD) in the mouse and therefore to have been a suitable high dose for the subsequent long term carcinogenicity study. In an initial 104-week carcinogenicity study in rats, few toxic changes were observed. 13 week pilot toxicity studies using doses up to 2500 mg/kg/day revealed histopathological changes such as hyperplasia and hyperkeratosis of the mucosal epithelium, erosion, and oedema in the forestomach of rats at 500 mg/kg/day and above. Based on the results of

²³ ICH guidelines on genotoxicity testing 3BS6a Guidance on Specific aspects of genotoxicity tests for Pharmaceuticals

this study, a supplemental 104-week study was carried out in rats using dose levels up to 1000 mg/kg. Sufficiently high exposure ratios were achieved in both the long term mouse (102) and rat (76) studies. In both species mortality/survival rates were not significantly affected by idebenone treatment relative to untreated control groups.

In the mouse studies, idebenone treatment did not influence the incidence, time of onset, location, size, or multiplicity of palpable masses. There was no increase in incidence of forestomach tumours (given the stomach epithelial irritation observed in these and other repeat dose studies). In the mouse study in which higher doses (up to 200 mg/kg) were used, a low incidence of benign tumours (including haemangioma and leiomyoma) and malignant sarcomas (fibrosarcoma, leiomyosarcoma and endometrial sarcoma) were observed in the medium dose and high dose groups. These incidences were within the historical control range for this mouse strain in the testing facility. In the rat studies the incidence of palpable masses was not influenced by idebenone. Macroscopically there was an increase in yellow and thickened mucosa which correlated microscopically with an increased incidence of squamous cell hyperplasia/hyperkeratosis, variably accompanied by gastritis, forestomach erosions and basal cell hyperplasia. A low incidence of squamous and basal cell tumours was seen in the treated animals. These proliferative findings are considered likely to be a consequence of non-pharmacologically-related local irritation to the forestomach and, since this is a rodent-specific organ, are not considered to be relevant to the assessment of safety for human use. Other neoplastic findings in rats included lung alveolar carcinoma, adrenal carcinoma, liver and pancreas sarcoma, squamous cell papilloma, thyroid follicular cell carcinoma and thyroid C cell adenoma. The incidence of these neoplasms, which occurred only in males, lacked a dose-dependent relationship, were below the spontaneous incidence rate according to historical control data for this strain;²⁴ and were not observed in a subsequent carcinogenicity study in which doses of idebenone up to 10 times higher were used.

Reproductive toxicity

Reproductive toxicity was evaluated in fertility, embryofetal development and pre-/postnatal development studies in rats and rabbits. Animals received daily oral doses of idebenone of up to 1000 mg/kg/day in rats and up to 500 mg/kg/day in rabbits. The study designs were generally acceptable, using accepted dosing regimens appropriate for the selected test species. Toxicokinetic parameters for the reproductive toxicity studies were not determined in any of the rat studies and as such AUC values are not available for exposure comparisons. In addition, the potential placental and milk transfer of idebenone was not assessed.

No statistically significant differences were observed with regard to numbers of corpora lutea or implantations, rate of pre-implantation loss, numbers of resorptions, and dead and live embryos in fertility studies in rats. In one study there was a slight trend towards a higher rate of post-implantation losses and lower number of live embryos in the high-dose group (resulting from two dams that showed a high implantation loss). Based on body surface area comparisons, the no observed adverse effect level (NOAEL) for male fertility was determined to be 500 mg/kg/day and 1000 mg/kg/day for female fertility, which resulted in dose exposures that were 5 times and 10 times the human dose, respectively, (based on administration of the maximum recommended human dose (MRHD) of 900 mg).

In embryofetal studies in rats, reproductive parameters did not show any differences between treated and control groups, and no differences in the numbers of visceral and skeletal malformations and abnormalities or deviations were observed in the fetuses, including in studies where there were signs of maternotoxicity. The NOAEL for

²⁴ Gikin, M.L.A *et al.*, Compilation of Spontaneous Neoplastic Lesions and Survival in Crl:CD(SD) Rats F0 from Control Groups. Charles River Laboratories. March 2013.

embryofetal development in rats was 1000 mg/kg/day, equivalent to 10 times the clinical exposure at the MRHD of, 900 mg (based on body surface area). In the rabbit embryofetal studies, one abortion was observed in a high-dose group which was judged to be a spontaneous occurrence, since there were no abnormal findings at necropsy and since the spontaneous abortion rate in this strain of rabbits (Japanese White (Kbl:JW)) is of the order of 3%. No differences between idebenone-treated and control groups were observed with respect to numbers of corpora lutea and implants, rate of pre- and post-implantation losses, and to numbers, body weights, and sex ratio of live foetuses in either rabbit study. Idebenone did not induce significant differences in the frequencies of observed external, visceral and skeletal malformations, or abnormalities/deviations between treated and control group foetuses in either study. The exposure ratios achieved in the rabbit study were very low (≤ 1 , Table 4), however, maternotoxicity was evident in this study (both food consumption and body weight gain were suppressed in high dose dams).

In a peri/post-natal studies conducted in rats, the parent generation (F_0) of the 500 mg/kg/day (high) dose group displayed transient hypersalivation immediately after dosing. In the 100 mg/kg/day and 500 mg/kg/day groups red-brown urine was also evident. There were no treatment-related differences in body weight, length of gestation period and parturition, nursing, and necropsy findings in the F_0 dams. In the first filial generation (F_1) animals, no treatment-related changes were observed on litter size, pup mortality, bodyweight changes of pups, physical and functional and behavioural development. Treated females with normal delivery were not observed to exhibit differences from controls with respect to delivery, nursing, body weight, duration of pregnancy, and number of implantations and delivered pups. Their pups did not show differences between treated and control groups with respect to survival, weight gain, functional test results and developmental landmarks, nor were there any findings at necropsy. Reproductive performance was also unchanged by exposure to idebenone. At necropsy, there were no differences in the numbers and frequencies of external, visceral, and skeletal abnormalities between the dose groups. Similar results were obtained in a separate study where the maximum dose was 1000 mg/kg/day with the exception of decreased food consumption and body weight loss in the high dose group dams. The NOAEL for pup development was determined to be 500 mg/kg/day, or about 5 times the clinical exposure (at the MRHD, 900 mg, based on body surface area).

Relative exposure

Table 4: Relative exposure in reproductive toxicity studies

Species	Study (Study no.)	Dose (mg/kg/day)	Dose (mg/m ²)	Exposure ratio (BSA*)	AUC _{0-24h} (ng·h/mL)	Exposure ratio (AUC)
Rat	(C-14-332)	500	3000	5	-	-
	(C-14-749)	1000	6000	10	-	-
Rabbit (Kbl)	Embryofetal development (C-14-780)	150	1800	3	10.3	0.2
		500	6000	10	59.4	1
Human (healthy volunteers)	(Study SNT-I-003)	18 (2250 mg)	600	1	56.8 [#]	-

[#] = (AUC_{0-6h} × 4)/2.5 since the MRHD is 900 mg/day; [^] = data are from the last sampling occasion; Body Surface Area: Km = 6 (rat), 12 (rabbit), 33 (50 kg human).

Pregnancy classification

The sponsor has proposed Pregnancy Category B1.²⁵ Given the lack of adverse findings in the reproductive toxicity studies in both rats and rabbit, this category is considered appropriate.

Immunotoxicity and antigenicity

Idebenone was not immunogenic in mice; it did not yield positive passive cutaneous anaphylactic reactions, passive haemagglutination reactions or agar precipitin reactions when administered at doses up to 200 mg/kg daily for four weeks. Systemic anaphylaxis tests in guinea pigs were negative as shown by the absence of an active systemic anaphylactic reaction was elicited following an intraperitoneal challenge with idebenone after repeat oral idebenone dosing (up to 100 mg/kg) for four weeks.

Impurities

The proposed specifications for impurities in the drug substance/product are below the ICH qualification thresholds or have been adequately qualified. All identified impurities have been assessed for potential mutagenicity and are considered non-mutagenic.

Paediatric use

A repeat dose study was also conducted in juvenile animals since idebenone is intended for paediatric use. Juvenile Wistar rats were treated for 4 weeks at doses up to 1000 mg/kg/day. A slight reduction of body weight in the mid- and high-dose groups was observed and histopathological examination revealed an increased incidence and severity of hyaline droplet accumulation in the epithelial cells of the proximal renal tubules in the male rats treated at 1000 mg/kg/day. Bone densitometry investigations revealed transient lower bone content and density of the femur and lumbar vertebrae in the high dose females only, consistent with the observed treatment-related growth retardation, that were markedly reduced after the recovery period. There was no effect on the subsequent development of the animals or on reproductive function and the NOAEL was determined to be 200 mg/kg/day. The exposure ratios achieved in this study were adequate, with the exception of idebenone+idebenone-C. The exposure ratios achieved in the high dose group animals (based on AUC) on Day 28 (post-natal Day 48), compared to clinical Study SNT-I-003, were 111 for idebenone, 0.7 for idebenone+idebenone-C, 3 for QS10+QS10-C, 16 for QS6+QS6-C and 13 for QS4+QS4-C (Table 2).

Comments on the nonclinical safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for idebenone detailed in the sponsor's draft risk management plan (RMP) are in general concordance with those of the nonclinical evaluator.

Nonclinical summary and conclusions

- The submitted nonclinical dossier was in general accordance with the relevant ICH guideline.¹¹ All the pivotal safety and toxicity studies were conducted according to

²⁵ Pregnancy Category B1 is 'Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.'

GLP. The overall quality of the dossier was acceptable in view of the design and scope of the submitted studies.

- *In vitro*, idebenone prevented ATP loss in erythrocytes and inhibited mitochondrial lipid peroxidation. *In vivo*, idebenone restored mitochondrial function in a mouse model of Leber's hereditary optic neuropathy. Idebenone improved cardiomyocyte function after ischemia in perfused rat hearts and ischemia-induced S-T segment increases in ECGs in dogs. In *mdx* mice, a DMD model, idebenone prevented some deleterious changes in skeletal muscle, cardiomyocytes and cardiac physiology.
- Overall, the safety pharmacology data in animals demonstrate no overt safety concerns with respect to the clinical use of idebenone for the treatment of DMD. Safety pharmacology studies assessed effects on the cardiovascular, respiratory, renal, gastrointestinal and central nervous systems. No effects of toxicological concern were seen on central nervous system, respiratory, gastrointestinal or renal function in a variety of animal models. Idebenone significantly inhibited the tail currents of the hERG channel with an IC_{50} of 5.5 μ M, however, no adverse findings on QTc;²⁶ were evident *in vivo* as measured in a 39-week toxicology study in telemetered dogs. In the pivotal dog study, heart rate was significantly reduced, a phenotype which persisted in recovery animals.
- Overall, the pharmacokinetic profile in animals was qualitatively similar to that of humans. Idebenone was readily and rapidly absorbed with a similar T_{max} in all species. Plasma protein binding of idebenone was very high (> 98%) in all animal species and humans. In all species idebenone oral bioavailability is less than 1%. Tissue distribution of idebenone was wide but after oral administration the concentration of idebenone in the rat brain is approximately 20 fold lower than in plasma. The metabolism of idebenone by oxidation and side chain shortening (mainly by CYP1A2, CYP2C19, and CYP3A4) and subsequent conjugation is fast and extensive in humans and animals. The main human metabolites, which have high hydrophilicity and are pharmacologically inactive, were also significant metabolites in the species used in the toxicity studies. In all species, all conjugated metabolites are present at much higher concentrations than idebenone and its unconjugated metabolites. Idebenone metabolites were excreted via urine and faeces with urine as the predominant route of excretion in both humans and the animal species examined.
- Based on *in vitro* studies, idebenone is not predicted to induce CYP1A/1A2, CYP2B6 and CYP3A4. *In vitro* studies predicted that both idebenone and the metabolite QS-10 may inhibit intestinal, but not systemic, CYP3A4, potentially increasing the absorption/exposure of co-administered drugs that are CYP3A4 substrates. Idebenone may also increase the exposure of co-administered drugs that are substrates of P-glycoprotein.
- Idebenone had a low order of acute toxicity in mice and rats when administered orally (the clinical route).
- Repeat dose studies by the oral route were conducted in mice (up to 13 weeks), rats (up to 12 months) and dogs (up to 12 months) with high exposures (AUC) achieved in all species. Idebenone exhibited a low order of toxicity in repeat dose studies in all species. The major effects in rats and dogs were reductions in body weight gain in the high dose groups and gastrointestinal symptoms which manifested in the rat as forestomach changes (low clinical relevance) and in the dog as vomiting and loose faeces (local GI irritation at high doses).
- Idebenone was not mutagenic in the bacterial mutation assay, bacterial *rec* assay, *in vitro* mammalian forward mutation assay or clastogenic *in vivo* in rodent

²⁶ QTc = Interval measured from the beginning of the QRS to the end of the T wave, corrected for heart rate

micronucleus tests. Despite a positive result for clastogenicity in human lymphocytes at high concentrations (likely reflecting redox properties at high of the substance), the weight of evidence suggests no genotoxicity concerns for idebenone. No treatment related increase in tumour incidence was observed in mice or rats in 2 year oral carcinogenicity studies. High exposure ratios were achieved in both the long term mouse (77) and rat (57) carcinogenicity studies.

- Fertility was unaffected in male and female rats treated with idebenone at exposure levels ≥ 5 times the clinical dose based on body surface area comparisons. Idebenone was not teratogenic in rats or rabbits in embryofetal studies where exposure levels of 10 x and 1 x that achieved clinically were achieved, respectively. No adverse effects on pup development were observed in the rat peri/post-natal studies.

Conclusions and recommendation

- The nonclinical dossier contained no major deficiencies.
- The primary pharmacology studies suggest that idebenone can alleviate certain DMD symptoms in animal models of DMD.
- The safety pharmacology and repeat-dose toxicity studies raised no significant concerns for the clinical use of idebenone.
- Idebenone is not considered to pose a carcinogenic or mutagenic hazard in humans, and the weight of evidence suggests that it is not clastogenic.
- The proposed Pregnancy Category of B1 is considered appropriate for idebenone.²⁵
- There are no nonclinical objections to the registration of idebenone.

The nonclinical evaluator also recommended changes to the PI but these are beyond the scope of the AusPAR.

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

Idebenone is a potent antioxidant and inhibitor of lipid peroxidation which has been shown to protect cell membranes and mitochondria from oxidative damage. Idebenone also stimulates mitochondrial electron flux and cellular energy production by bypassing the complex I defect and stimulating an alternative pathway through complex III.

The sponsor's requested indication is:

Raxone is indicated for the treatment of patients with Duchenne Muscular Dystrophy (DMD) in whom respiratory function has started to decline and who are currently not taking concomitant glucocorticoids. Raxone can be used in patients previously treated with glucocorticoids or in patients in whom glucocorticoid treatment is not desired, not tolerated or is contraindicated.

Based on the wording of the indication, it appears that the sponsor is requesting both first line treatment in patients in whom glucocorticoid (GC) treatment is not considered appropriate, or is contraindicated, and second line treatment in patients previously treated with GCs. The submitted trial data supports this indication. The pivotal

DELOS study;²⁷ included patients who were both prior GC users (56.3%), and GC naïve (43.8%), however the reasons why patients ceased using GCs or were not considered for GC treatment was not discussed. This is not considered to be an important omission as it is unlikely to impact the mechanism of action or potential efficacy of idebenone.

Dosage forms and strengths

Raxone are orange, round, biconvex film-coated tablets containing 150 mg of idebenone and the excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate, colloidal anhydrous silica, and opadry II 85F23495 orange.

Raxone is presented in a high density polyethelene bottle with a polypropylene tamper evident, child resistant cap.

Dosage and administration

The recommended dose of idebenone is 900 mg/day (300 mg, three times a day (TDS)). Raxone film-coated tablets should be swallowed whole with water. The tablets should not be broken or chewed.

Raxone should be administered with food because food increases the bioavailability of idebenone.

Special populations

Elderly

No specific dose adjustment is required for the treatment in elderly patients.

Paediatric

The safety and efficacy of Raxone has not been established in children under 10 years of age.

Renal and hepatic impairment

Caution is advised in treatment of patients with hepatic or renal impairment. Based on the population pharmacokinetic (PPK) results, dose adjustment may be advisable.

Given the natural history of DMD, it is likely that children aged less than 10 years will be considered for treatment with idebenone. However, based on the natural history study it appears that respiratory decline (to a percent predicted peak expiratory flow (PEF%_p) < 80%) generally occurs from approximately age 10. It may be desirable to add '(PEF%_p < 80%)' to the wording of the indication to clarify the level of respiratory function decline where idebenone is considered beneficial.

Information on the condition being treated

Duchenne muscular dystrophy (DMD) is a severe, rapidly progressive X-linked neuromuscular disease that primarily affects young males, with an incidence of 1 in 3,600 to 6,000 live male births. DMD occurs as a result of mutations (mainly deletions) in the dystrophin gene (*DMD*; locus Xp21.2). Mutations lead to an absence of or defect in the protein dystrophin in skeletal and cardiac muscles, which results in progressive muscle degeneration and necrotising lesions. Variable phenotypic expression relates mainly to the type of mutation and its effect on the production of dystrophin. Some patients with dystrophin mutations also have an isolated cardiac phenotype. While primarily an

²⁷ Buyse G, et al; DELOS Study Group. Efficacy of idebenone on respiratory function in patients with Duchenne muscular dystrophy not using glucocorticoids (DELOS): a double-blind randomised placebo-controlled Phase 3 trial. *Lancet*. 2015 May 2;385(9979):1748-1757. doi: 10.1016/S0140-6736(15)60025-3.

X-linked condition affecting males, approximately 10% of female carriers show some disease manifestations, but usually exhibit a milder phenotype.

Clinically, affected individuals usually present by the age of 3 to 5 years with delayed motor milestones, gait disturbances, muscle pseudohypertrophy, and difficulties jumping and climbing stairs due to proximal muscle weakness. If untreated there is progressive muscle degeneration and functional decline resulting in the need for a wheelchair by 8 to 14 years, and the development of serious respiratory, orthopaedic, and cardiac complications. Death occurs at a mean age of 19 years without treatment, usually due to respiratory disease or cardiomyopathy. Life expectancy has been extended into the third or fourth decade with the introduction of GC therapy, proactive cardiac management, and nocturnal ventilator support.

Current treatment options

There are no specific treatments for DMD currently approved in Australia. Current treatment relies on medical (corticosteroids), surgical, and rehabilitative approaches to manage symptoms, maintain patient function and comfort, and improve quality of life. Glucocorticoids (prednisone and deflazacort) provide temporary improvement by slowing the rate of progression or stabilising muscle strength and function. However, corticosteroid therapy also leads to significant side effects which can limit their usefulness. Symptomatic and supportive treatment of respiratory insufficiency associated with DMD includes airway clearance, respiratory muscle training, non-invasive nocturnal ventilation, non-invasive daytime ventilation and continuous invasive ventilation. A summary of these approaches is outlined in Table 5, below.

There is thus an unmet medical need for the management of respiratory function decline in patients not taking GC.

On 31 July 2014, the EMA's CHMP granted conditional marketing authorisation for Translarna (ataluren) for the treatment of DMD resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older.

The FDA issued a Refuse to File letter for ataluren on 23 February 2016, and an appeal filed by the company was rejected by the FDA on 17 October 2016. The company resubmitted a New Drug Application during the first quarter of 2017, but in October 2017 the FDA issued a Complete Response letter stating that it is unable to approve the application in its current form.

Table 5: Summary of DMD care guidelines (reproduced from Landfeldt et al. 2015²⁸)

Care component	Frequency (minimum)	Practitioner	Aims
Neuromuscular management	Every six months	Neuromuscular specialist	Evaluation of disease status and progression (muscle strength, function, and range of movements); anticipatory planning of future developments and prevention of complications (e.g., scoliosis); ensuring immunisations schedule (e.g., varicella zoster, pneumococcal vaccine, and flu jab); planning treatment interventions (e.g., glucocorticoid therapy), efficacy and side-effect management of pharmacological treatments; evaluation of psychological issues, daily activity, and functioning
Cardiac management	At diagnosis, annually in ambulatory patients and every six months in non-ambulatory patients	Cardiac specialist	ECG and echocardiogram to evaluate dyskinesia, LV dysfunction and dilated cardiomyopathy; prompt initiation of treatment (ACE-inhibitors and/or beta blockers) with early signs of cardiac dysfunction
Respiratory management	Annually in ambulatory patients and every six months in non-ambulatory patients	Respiratory specialist	Evaluation of respiratory function (e.g., FVC and cough peak) to allow timely prevention and management of complications; ensuring immunisation schedule (e.g., pneumococcal vaccine and flu jab); trigger further respiratory investigations (e.g., overnight pulse oximetry and haemogas analysis); trigger respiratory interventions (e.g., respiratory physiotherapy, cough assist machine, NIV, and tracheostomy)
Orthopaedic management	As indicated	Orthopaedist	Evaluation of surgical options for joint contractures (e.g., Achilles tendons and hips); monitoring for scoliosis and interventions (e.g., spinal fusion)
Physiotherapy	Every six months	Physiotherapist	Assessment of disease progression and complications (e.g., joint contractures and spinal deformities); trigger interventions for management of complications (e.g., orthoses and referral to orthopaedic surgeon); advice about stretching exercises (to be done locally 4–6 times per week by parents or local physiotherapist at home or at school) and monitoring of progress
Psychosocial therapy	As indicated	Therapist and/or psychologist	Provision of family support; early evaluation and timely interventions for speech development, learning, and behavioural issues; evaluation of coping strategies; promoting independency and social development
Speech and language therapy	As indicated	Speech and language therapist	Evaluation of speech developmental delay and establishment of prompt interventions; assessment of dysphagia

ECG = Electrocardiography. LV= Left ventricle. FVC = Forced vital capacity. NIV = Non-invasive ventilation. AFO = Ankle-foot orthosis. KAFOs = Knee-ankle-foot orthosis.

Clinical rationale

In the Clinical Overview, the sponsor provides an overview of the clinical and pathophysiological symptoms and signs of DMD, noting that in the absence of treatment, weakness of respiratory muscles gradually progresses to respiratory failure and the need for assisted ventilation by the time patients reach their mid-to-late teenage years. While treatment with GCs can delay the decline in muscle strength and stabilise pulmonary function, their use is associated with recognised side effects such as growth retardation, bone demineralisation and increased fracture risk, obesity, behavioural changes, hypertension and cataracts. These side effects often lead to discontinuation of GC treatment. There is thus an unmet clinical need for an alternative effective treatment option.

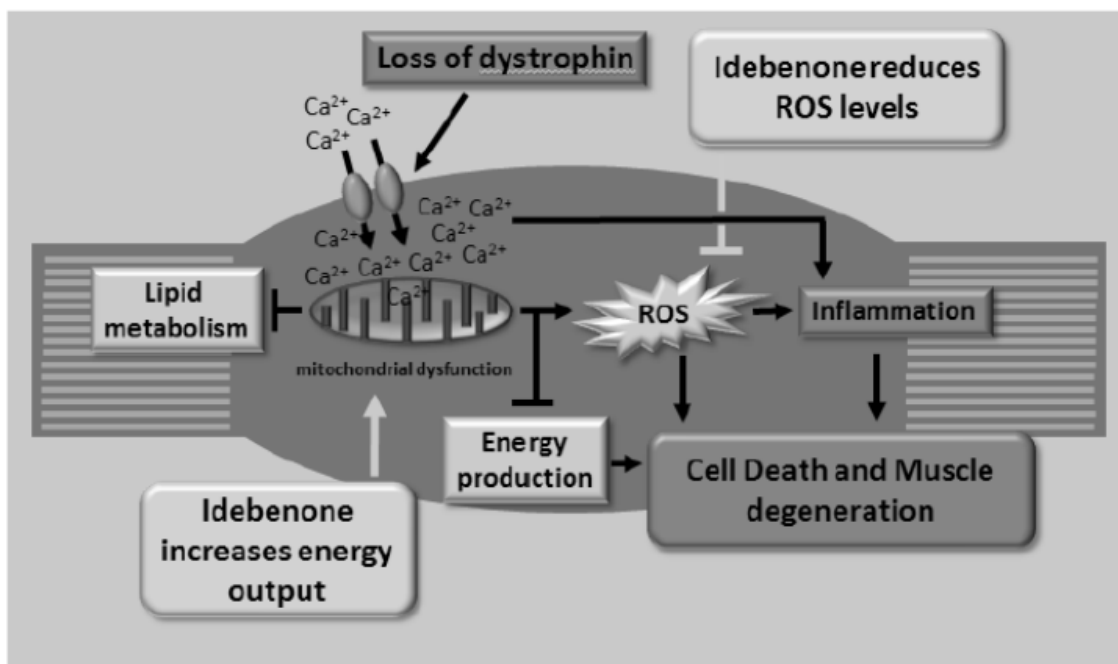
Cell membrane fragility and intracellular calcium ion (Ca^{2+}) dysregulation secondary to the disease-causing absence of the protein dystrophin is characteristic of DMD and results in functional aberrations in mitochondrial energy transduction and increased production of cell-damaging reactive oxygen species (ROS). In a well-established dystrophin-deficient *mdx* mouse disease model for DMD, one of the defective functional parameters identified was a deficiency in complex I-mediated mitochondrial ATP production rate. It is

²⁸ Landfeldt E et al 2015 Compliance to Care Guidelines for Duchenne Muscular Dystrophy. *Journal of Neuromuscular Diseases* 2015; 2: 63–72

postulated that this may contribute to pathological muscle wasting in DMD by reducing ATP availability to Ca^{2+} regulation and fibre regeneration.

Idebenone has been reported to utilise and activate complex I independent metabolic pathways enabling restoration of mitochondrial function in the presence of complex I dysfunction, and to inhibit mitochondrial ROS formation. Therefore, the anticipated mode of action of idebenone in dystrophin deficient muscle is as illustrated schematically in Figure 2.

Figure 2: Schematic presentation of the mechanism of action of idebenone in dystrophin-deficient skeletal muscle



Guidance

The TGA guidance, including EU guidelines adopted by the TGA, relevant to this submission are:

- Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy (EMA/CHMP/236981/2011)
- Guideline on clinical trials in small populations (CHMP/EWP/83561/2005)
- Points to consider on application with 1. meta-analysis 2. one pivotal study (CHMP/EWP/2330/99)
- ICH Topic E4: Note for guidance on dose response information to support drug registration (CPMP/ICH/378/95)
- Clinical investigation of medicinal products for long-term use (pp. 127 - 132 of rules 1998 (3c) - 3cc6a)
- Australian regulatory guidelines for prescription medicines (ARGPM) Guidance 8: product information; Guidance 15: biopharmaceutic studies.

The following guidance/documents were also consulted:

- Draft FDA guidance: DMD and related dystrophinopathies: developing drugs for treatment guidance for industry. US Department of Health and Human Services FDA Center for Drug Evaluation and Research (CDER) June 2015.²⁹

Contents of the clinical dossier

The dossier documented a full clinical development program of pharmacology, efficacy and safety studies, and contained the following clinical information:

- 4 Phase I studies evaluating the clinical pharmacology and bioavailability of idebenone in healthy subjects (Studies SNT-I-001, SNT-I-002, SNT-I-003 and SNT-I-004).
- 2 clinical studies (1 Phase II study (Study DELPHI SNT-II-001), 1 Phase III study (DELOS; Study SNT-III-003)) with 1 long-term extension study (Study DELPHI-E SNT-II-001-E) in DMD. In addition, there were 4 further *post-hoc* analyses in the DELPHI (Study SNT-IR-011) and DELOS studies (Studies SNT-IR-009, SNT-IR-010, and SNT-IR-012) studies.
- 2 Phase II clinical studies in Leber's hereditary optic neuropathy (Studies RHODOS SNT-II-003 and RHODOS-OFU SNT-II-003).
- 3 clinical studies (1 Phase II and 2 Phase III) in Friedreich's ataxia with 2 long-term extension studies (Studies NICOSIA SNT-II-002, IONIA SNT-III-002, MICONOS SNT-III-001, IONIA-E SNT-III-002-E and MICONOS-E SNT-III-001E).
- 1 natural history study in DMD (Study SNT-IR-013)
- 1 matching study of Duchenne muscular dystrophy long-term idebenone study (DELOS) with natural history in DMD (Study SNT-IR-014).
- 283 literature references.

In addition to the above studies developed by Santhera, the dossier included four drug-drug interaction studies, two studies in special populations (hepatic or renal impairment), and one absorption, distribution, metabolism and excretion (ADME) study, all sponsored by Takeda and performed between the mid-1980s and mid-1990s. These studies generally used much lower doses than currently proposed (Table 6, below), and used a different analytical method for the pharmacokinetic (PK) assessments which have not been cross validated with the current methods. With the exception of the studies in subjects with renal or hepatic impairment, the results are not proposed for inclusion in the Australian PI. Therefore, they have not been formally evaluated.

²⁹ Accessed via:

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM450229.pdf>

Table 6: List of Phase I studies sponsored by Takeda or Abbott/Takeda Pharmaceuticals

Study Number	Subjects completed	IDE dose	Short description
CV-2619/EC074	12	120 mg or 120 mg tds	Drug-drug interaction study: IDE & lithium
CV-2619/EC075	12	120 mg or 120 mg tds	Drug-drug interaction study: IDE & amitriptyline
CV-2619/EC076	12	120 mg or 120 mg tds	Drug-drug interaction study: IDE & fluvoxamine
CV-2619/PNFP-003	13	360 mg tds	Drug-drug interaction study: IDE & donepezil
CV-2619/EC070	12	120 mg	PK study with IDE in patients with renal impairment ($\text{CrCl} < 40 \text{ mL/min/1.73 m}^2$)
CV-2619/EC071	12	120 mg	PK study with IDE in patients with hepatic impairment
M90-441	4	30 mL of an alcoholic solution containing 90 mg ^{14}C -labelled IDE	Metabolism of ^{14}C -labelled IDE in healthy subjects

The clinical studies submitted for indications other than DMD will be evaluated for safety only.

Paediatric data

Data on children (2 to 11 years) and adolescents (12 to 17 years) have been included in this submission.

Good clinical practice

All applicant-sponsored clinical studies are stated by the sponsor to have been conducted according to Good Clinical Practice (GCP), the Declaration of Helsinki, Directive 2001/20/EC, Guideline for GCP ICH E6.³⁰ The Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS) was conducted according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site, whichever provides the greater protection of the individual.

Pharmacokinetics

Studies providing pharmacokinetic data

The pharmacokinetics (PK) of idebenone 150 mg has been evaluated in four Phase I studies (Studies SNT-I-001, SNT-I-002, SNT-I-003 and SNT-I-004) in 69 healthy volunteers, all of whom received idebenone. These studies are summarised in Table 7, below. In addition to the studies sponsored by Santhera, four drug-drug interaction studies, two studies in special populations, and one ADME study, all sponsored by Takeda, were performed. As these studies did not use the 150 mg film-coated tablet formulation of idebenone proposed for registration and with the exception of the studies in subjects with renal or hepatic impairment, have not been formally evaluated.

³⁰ ICH E6: Guideline for good clinical practice.

The PK of idebenone in the target population (DMD) was investigated to a limited degree in the DELPHI study.

A population PK (PopPK) model was developed for idebenone and its metabolite QS10 using data from Studies SNT-I-001, SNT-I-002, SNT-I-003 and SNT-I-004, the RHODOS study in Leber's hereditary optic neuropathy (LHON) patients (55 patients) and two Phase III efficacy, safety and tolerability studies in Friedreich's ataxia (FRDA) patients (MICONOS study, 173 patients and IONIA study, 46 patients). idebenone and QS10 concentration-time, dosing, demographic and covariate data from the seven clinical studies were combined.

Table 7: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	SNT-I-002	*
		SNT-I-004	*
		M90-441‡	*
	- Multi-dose	SNT-I-003	*
	Food effect	SNT-I-001	*
PK in special populations	Target population §- Multi-dose	SNT-II-001 (DELPHI)	
	Hepatic impairment	CV-2619/EC071#	*
	Renal impairment	CV-2619/EC070#	*
Population PK analyses	Healthy subjects / other patient groups (LHON and FRDA)	RA 833004	*

* Indicates the primary PK aim of the study; § Subjects who would be eligible to receive the drug if approved for the proposed indication; # sponsor: Takeda Pharmaceuticals; ‡sponsor: Abbott/Takeda.

Table 8: Pharmacokinetic results excluded from formal consideration

Study ID	Subtopics	PK results excluded
CV-2619/EC074	PK interactions - Lithium	All
CV-2619/EC075	PK interactions - Amitriptyline	All
CV-2619/EC076	PK interactions - Fluvoxamine	All
CV-2619/PNFP-003	PK interactions - Donepezil	All

Evaluator's conclusions on pharmacokinetics

The PK of idebenone 150 mg has been determined in four Phase I studies in 69 healthy volunteers, with limited data from 13 patients with DMD who participated in the

DELPHI study. On the basis of these studies the PK of idebenone can be summarised as follows:

- Idebenone is rapidly absorbed after oral administration.
- Maximum plasma levels of idebenone are reached approximately 1 hour post-administration.
- Idebenone undergoes extensive first pass metabolism.
- Idebenone is metabolised in the liver by oxidative shortening to the Phase I metabolites QS10, QS8, QS6, and QS4.
- The Phase I metabolites and idebenone are conjugated to Phase II metabolites: idebenone-C, QS10-C, QS8-C, QS6-C, and QS4-C.
- Bioavailability of idebenone and its metabolites is increased by food intake (for example approximately 7 fold increase in AUC_{0-t} and 5 fold increase in C_{max} for idebenone compared to fasting conditions).
- Systemic exposure to idebenone (AUC_{0-t}) increased slightly more than dose proportionately (approximately 2.5 fold).
- There is minimal accumulation of idebenone in plasma, consistent with a short half-life relative to the dosing interval.
- The main metabolites are eliminated primarily via the kidneys.

No absolute bioavailability study was conducted, however given the lack of an IV formulation and the safety and efficacy data presented for the proposed oral formulation, the justification provided by the sponsor was considered acceptable.

The age ranges studied in patients (9.4 to 16.4 years) and healthy volunteers (19 to 41 years) is appropriate for the indication sought, although the numbers were very limited in the DMD population ($N = 13$). While the sponsor stated that overall exposures of idebenone and its metabolites '*were comparable between the DMD patients and healthy subjects*' this comparison is limited because of the timing of the PK samples and difference in idebenone doses administered (150 to 750 mg single or three times daily (TDS) doses for up to 14 days in healthy volunteers versus 150 mg TDS for 26 and 52 weeks in the DELPHI study). However, bearing these limitations in mind, the PK data in DMD patients was not incompatible with that of healthy volunteers at the time points measured.

A PPK model was developed using data from the healthy volunteers in the four Phase I PK studies and 222 Friedrich's ataxia/Leber's hereditary optic neuropathy patients (aged 8 to 70 years). The idebenone plasma concentration-time data was adequately described by a one-compartment model with first-order absorption and elimination. Of the covariates tested, only body weight on clearance (CL) and food on absorption rate (KA) and oral clearance (CL/F) were found to be significant. Despite a reduction in apparent oral clearance of idebenone reported in the PopPK analysis for the lightest subjects (correlated with younger age) compared with a 70 kg subject (CL/F estimated to be 0.54 fold), on the basis of the safety profile of idebenone, age adjusted dosing does not appear to be required.

The PK information presented in the PI is considered satisfactory.

The sponsor has identified that there is an ongoing interaction study of Raxone with midazolam being conducted in healthy male volunteers. The results of this study should be provided as a condition of registration once it is completed.

Pharmacodynamics

Studies providing pharmacodynamic data

The primary and secondary pharmacodynamics of idebenone has been assessed in non-clinical studies and will be evaluated by the nonclinical evaluator.

The sponsor stated that no pharmacodynamic studies have been conducted with Raxone in DMD patients.³¹ However, in Study SNT-I-003, the potential enzyme inducing effect of single and repeated idebenone doses (150 mg or 5 x 150 mg TDS) on the urinary excretion of cortisone and 6- β -OH-cortisone was assessed. Based on this analysis, there was no indication of an inducing effect of idebenone on drug metabolising enzymes when given in daily doses up to 750 mg TDS for two weeks.

Evaluator's conclusions on pharmacodynamics

The sponsor has not provided a clinical pharmacodynamic program. There was only a single clinical study that provided any PD data (Study SNT-I-003), which concluded that there was no indication of an inducing effect of idebenone on drug metabolising enzymes when given in daily doses up to 750 mg for two weeks. Conclusions regarding pharmacodynamics of idebenone will rely on the evaluation of nonclinical data by the nonclinical evaluator.

Dosage selection for the pivotal studies

The sponsor submitted a justification for the absence of dose ranging studies.

Pharmacokinetics and pharmacodynamics: dose finding studies

No PK or pharmacodynamic dose ranging study has been conducted in DMD.

Phase II dose finding studies

In Friedrich's ataxia (FRDA), a 6 month Phase II safety and efficacy study with idebenone in patients aged 9 to 17 years (the NICOSIA study) was conducted using three weight adjusted dose levels. Results from this study suggested that a dose of 900 mg/day for patients > 45 kg was the optimal dose, with lower doses found to be less efficacious whilst a higher dose (2250 mg/day) did not demonstrate markedly improved clinical effect.

The majority of patients in the DELPHI study weighed \leq 45 kg and received idebenone at 450 mg/day, and this was the initial dose in the DELPHI-E study. However, this dose was increased to 900 mg/day for patients exceeding 45 kg in body weight during the 24 month study.

Patients in the DELOS study received idebenone 900 mg/day, based on the older average age and higher body weight.

Phase III pivotal studies investigating more than one dose regimen

No pivotal Phase III dose ranging study has been conducted in DMD.

³¹ page 17, Clinical Overview

Justification for the absence of dose ranging studies

The sponsor provided the following justification for the absence of dose-ranging studies:

- In the Santhera Phase I program, it was observed that idebenone is subject to a large first pass metabolism which converts > 99% of idebenone to inactive metabolites. Below dose levels of 360 mg/day idebenone, very little idebenone is detectable in plasma samples. Nanogram levels of idebenone can only be detected at dose levels of 450 mg/day or more.
- In FRDA, a dose of 900 mg/day for patients > 45 kg was determined the optimal dose for efficacy after considering 3 weight-adjusted dose levels (60 to 120 mg TDS, 150 to 300 mg TDS, and 450 to 750 mg TDS for patients 30 to ≤ 45 kg and > 45 to 80 kg, respectively). Lower doses were less efficacious whilst a higher dose (2,250 mg/day) did not markedly augment the clinical effect.
- The safety profile of idebenone was similar between FRDA patients on high doses and patients with DMD receiving 900 mg/day and in healthy subjects receiving placebo. The most commonly reported adverse events (AEs) were diarrhoea, nasopharyngitis and headache. These AEs were generally mild and short-lived, and did not lead to discontinuation of study medication.
- No new safety signals have emerged from the DMD population.

Despite differences in the pathophysiology of DMD and FRDA, they both involve mitochondrial dysfunction and it is not unreasonable to expect a similar dose-response for the two conditions. Therefore, the justification is considered acceptable.

The sponsor's justification for the absence of dose ranging studies is considered acceptable.

Efficacy

Studies providing efficacy data

Efficacy studies conducted in DMD included a single pivotal Phase III study (the DELOS study) and a supportive Phase II study (the DELPHI study) and its open-label extension (the DELPHI-E study). In addition, there were 4 further *post-hoc* or corrective analyses in the DELPHI (Study SNT-IR-011) and DELOS studies (Studies SNT-IR-009, SNT-IR-010 and SNT-IR-012). The results of these analyses will be discussed following those of the original analyses.

The evaluation was made more difficult by the lack of transparency behind the reasons for conducting the additional analyses. It was only in response to a query from the TGA about the international status of Raxone on 20 October 2017 that it became apparent that several of these additional analyses were conducted in response to issues raised by either the CHMP or FDA.

Evaluator's conclusions on efficacy

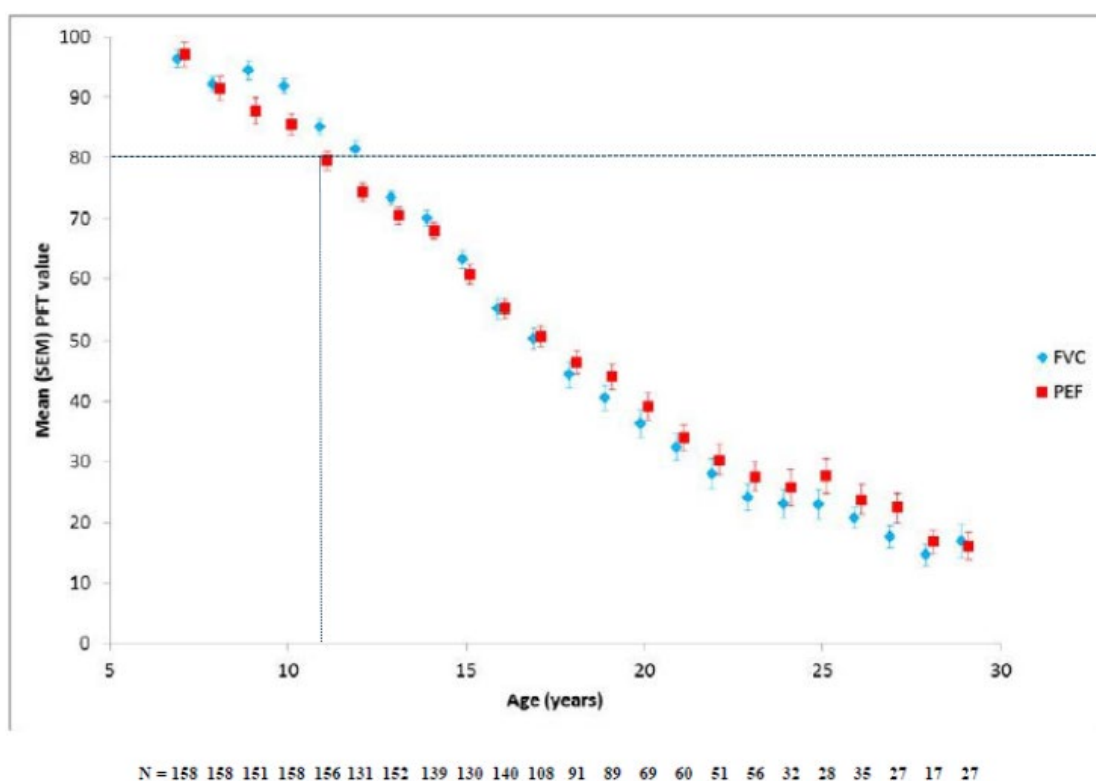
There was one Phase II plus extension study and one Phase III study providing efficacy data for idebenone in patients with DMD.

The Phase II DELPHI study was powered to determine whether treatment with idebenone improves or delays the decline in cardiac function (peak systolic radial strain of the left ventricular (LV) inferolateral wall. It failed to meet this objective, perhaps because there was an imbalance at baseline in age and peak systolic radial strain of the LV inferolateral wall. While treatment with idebenone was shown to be beneficial on both peak expiratory

flow (PEF) and PEF%p (with p values < 0.05); these were secondary endpoints and multiple other cardiac, skeletal muscle, respiratory and other endpoints were also investigated. This increases the risk of Type I errors, and that the finding of statistical significance was in fact a chance finding. However, the magnitude of the effect was clinically relevant, and PEF%p was selected as the primary efficacy variable for the Phase III DELOS study. The DELPHI-E (extension) study suffered from similar limitations, with additional variation in the dose of idebenone administered and the lack of a control group on which to compare the longer term results.

The pivotal DELOS Study was an interventional study of idebenone 300 mg TDS versus placebo in 66 patients with DMD aged 10 to 18 years who had established respiratory function decline at Baseline (PEF%p \leq 80%) and who were not using concomitant glucocorticoids. The age range enrolled is appropriate given the age at which respiratory function appears to decline in the natural history population (age approximately 10 to 11 years, see Figure 3).

Figure 3: PEF%p and FVC%p versus Age; patients with PFT data excluding patients from Indian sites (N = 334)



PEF%p = percent predicted forced expiratory volume; FVC%p = percent predicted forced vital capacity; PFT = pulmonary function testing.

It was conducted to assess the efficacy of idebenone, compared to placebo, in improving respiratory function or delaying the loss of respiratory function, in particular the change from Baseline to Week 52 in PEF%p. Although only a limited number of patients were enrolled in the study, this is an acknowledged constraint of conducting studies in rare diseases such as DMD.³² Despite this, the DELOS study was adequately powered to detect a clinically meaningful difference in PEF%p between the idebenone and placebo treatment groups.

³² Guideline on clinical trials in small populations (CHMP/EWP/83561/2005)

There is some reservation about the choice of PEF%p as the primary efficacy endpoint. While PEF%p can be considered clinically meaningful and patient relevant, the Guideline;³³ appears to prefer FVC / FVC%p;³⁴ to measure loss of lung volume in DMD, with PEF%p potentially being better in younger patients.

Minor imbalances in baseline demographics were observed (higher age at baseline and longer time since last GC use in placebo patients), but these were explored in additional analyses and found not to impact the study results.

The DELOS Study met its primary objective. Patients who received idebenone had a decline in PEF%p of 3.05% at Week 52, compared with a decline of 9.01% for patients on placebo (estimated difference 5.96%; 95% confidence interval (CI): 0.16, 11.76; $p = 0.0443$ in the modified intent-to-treat (mITT) population). A difference favouring idebenone was also found in the intent-to-treat (ITT) (estimated difference 6.27%, 95% CI: 0.61, 11.93; $p = 0.0306$) and PP populations, and in a number of sensitivity analyses suggesting that the result was robust. This result appears to be clinically relevant as well as statistically significant. However, the 95% CI is relatively wide with a lower limit approaching zero. While this could at least partly be the result of the rarity of DMD (particularly GC non-users) which limited the number of patients that could be enrolled in the study, it does raise concerns about the potential clinical relevance of this result.

Selected secondary endpoints were ranked and analysed in a hierarchical manner. The first of these endpoints (the annual rate of change in PEF%p using ASMA-1 device data;³⁵ calculated by linear regression analysis) also favoured treatment with idebenone (-2.48 versus -9.32% for idebenone and placebo, respectively; estimated difference 6.84%, 95% CI: -0.15, 13.83). However, this result was not statistically significant ($p = 0.0548$), and therefore the results for the remaining respiratory and non-respiratory endpoints can only be considered exploratory. Despite this limitation, many of the other pre-specified secondary and tertiary respiratory endpoints also suggested a treatment benefit with idebenone, including change in peak cough flow (PCF) and FVC%p. Further supportive evidence of the beneficial effect of idebenone on respiratory function was provided by the pre-specified responder analyses, which demonstrated that fewer patients on idebenone deteriorated from baseline, and fewer had their PCF drop below 160 L/min at any time point during the study. This outcome is of importance as a PCF ≥ 160 L/min is considered necessary to clear airway debris and thereby potentially decrease the risk for respiratory infection and other respiratory morbidity.³⁶

Additional evidence of the robustness of the DELOS study results was provided by the prospectively planned matching (PPM) study, which demonstrated that the rate of decline in PEF%p in the DELOS study placebo group was comparable to the rate of decline of a matched-to-DELOS placebo cohort from the CINRG DNHS, while the rate of decline in the DELOS study idebenone group was slower than both the matched-to-DELOS study placebo and matched-to-DELOS study idebenone cohorts from the CINRG DNHS.

Because only a single Phase III study for the DMD indication has been submitted, the EMA document;³⁷ is applicable. This document states that '*where the confirmatory evidence is provided by one pivotal study only, this study will have to be exceptionally compelling*'. In particular, the estimated size of the treatment benefit '*must be large enough to be clinically valuable*' and the degree of statistical significance is usually required to be '*considerably stronger than $p < 0.05$* '. It could be argued that DELOS study does not meet these

³³ EMA/CHMP/236981/2011 Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy

³⁴ FVC = Forced Vital Capacity; FVC%p = Percent predicted forced vital capacity

³⁵ AMSA-1 vitalograph.

³⁶ Bach JR, Ishikawa Y, Kim H. Prevention of pulmonary morbidity for patients with Duchenne muscular dystrophy. Chest. 1997; 112:1024-1028.

³⁷ CHMP/EWP/2330/99 Points to consider on application with 1. meta-analysis 2. one pivotal study

requirements. This document also suggests replication of scientific results in a number of circumstances including where:

- Phase II data are limited or unconvincing.
- A need to demonstrate efficacy and/or tolerability in different sub-populations.
- Any other needs to address additional questions in the Phase III program.

The limitations of the Phase II data from the DELPHI study, the lack of Phase III data in DMD patients using glucocorticoids, the preference for FVC%p to be used as the primary efficacy endpoint, and the wide 95% confidence intervals for PEF%p in the DELOS study all suggest that it would be prudent to wait for the SIDEROS study results before considering registration of Raxone.

Safety

Studies providing safety data

Pivotal studies that assessed safety as the sole primary outcome

Not applicable.

Pivotal and/or main efficacy studies in DMD

Study SNT-III-003 (the DELOS study)

Other efficacy studies in DMD

- Study SNT-II-001 (the DELPHI study)
- Study SNT-II-001-E (the DELPHI-E study (extension))

Studies with evaluable safety data: dose finding and pharmacology

- Study SNT-I-001
- Study SNT-I-002
- Study SNT-I-003
- Study SNT-I-004

In all these studies, safety was assessed by evaluation of AEs, serious adverse events (SAEs), physical examination, vital signs, ECG, and clinical laboratory evaluations (haematology, biochemistry, and urinalysis). These studies were conducted in a small number of healthy volunteers for a short duration (maximum 2 weeks) and will not be further discussed in this section.

Studies evaluable for safety only

The following studies are evaluable for safety only as they were not performed in the proposed indication of DMD.

- Leber's hereditary optic neuropathy (LHON)
 - The RHODOS study (Study SNT-II-003)
 - The RHODOS study (Study SNT-II-003 OFU)
- Friedreich's ataxia (FRDA)
 - The NICOSIA study (Study SNT-II-002):
 - The IONIA study (Study SNT-III-002)
 - The IONIA extension study (Study SNT-III-002-E)

- The MICONOS study (Study SNT-III-001)
- The MICONOS extension study (Study SNT-III-001-E).

Patient exposure

An integrated analysis was performed of the full safety population, which included all subjects who participated in Phase II and Phase III studies of idebenone who received at least 1 dose of trial medication and for whom a safety assessment was available. The number of subjects in the total safety population (including patients with DMD, LHON and FRDA) is summarised in Table 9.

Table 9: Exposure to idebenone in Phase II/III studies; population treated by idebenone in double-blind and extension studies, by dose

Population	Placebo Double-blind studies N (%)	Idebenone Dose mg/day N (%)				
		Double-blind studies Total	Double-blind and extension studies			
			180/360	450/900	1350/2250	Total
Total safety population	166 (100)	356 (100)	69 (15.7%)	200 (45.6%)	170 (38.7%)	439 (100)
DMD	42 (25.3)	45 (12.6)	-	53 (100%)	-	53 (12.1)
LHON	30 (18.1)	55 (15.4)	-	55 (100%)	-	55 (12.5)
FRDA	94 (56.6)	256 (71.9)	69 (20.8%)	92 (27.8%)	170 (51.4%)	331 (75.4)

^a Double-blind and extension studies - the dose was increased for some patients in the extension study compared to double-blind, but the dose group is defined by the double-blind dose. Each subject is counted in only one dose group.

Duration of idebenone exposure in the DMD studies is summarised in Table 10, below. In the DELOS study, the median duration (range) of treatment was similar in both the idebenone and placebo groups (362.5 (91 to 394) and 363.5 (96 to 393) days, respectively). In the DELPHI-E study, the median duration (range) of treatment was similar in both the idebenone 900 mg/day and 450 mg/day groups (729.0 (182 to 739) and 716.0 (162 to 729) days, respectively).

Table 10: Duration of exposure in DMD studies

Study Name	Cumulative overall exposure	Idebenone N (%)		Placebo N (%)	All Subjects N (%)
		900 mg/day	450 mg/day		
DELOS	3-6 months	2 (6.3)	NA	2 (5.9)	4 (6.1)
	6-12 months	10 (31.3)		11 (32.4)	21 (31.8)
	12-15 months	20 (62.5)		21 (61.8)	41 (62.1)
DELPHI	12 months	NA	13 (100)	8 (100)	21 (100)
DELPHI-E[‡]	3-6 months	0 (0.0)	1 (12.5)	NA	0 (0.0)
	6-12 months	2 (14.3)	0 (0.0)		0 (0.0)
	18-24 months	3 (21.4)	5 (62.5)		16 (31.6)
	> 24 months	9 (64.3)	2 (25.0)		13 (68.4)

Source: Tables 17 & 18, Summary of Clinical Safety. [‡] Three patients received each dose for some period of the study

In the integrated analysis, the mean (standard deviation (SD)) exposure to idebenone was:

- 340.3 (61.4) days in the DMD population enrolled in the double-blind studies
- 549.0 (315.5) days in the total DMD population enrolled in the double-blind and extension studies
- 164.0 (26.3) days in the LHON population
- 297.4 (94.4) days in the FRDA population enrolled in the double-blind studies

- 681.1 (346.4) days in the total FRDA population enrolled in the double-blind and extension studies
- 282.2 (98.7) days in the full safety population enrolled in the double-blind studies
- 600.3 (362.5) days in the full safety population enrolled in the double-blind and extension studies.

Safety issues with the potential for major regulatory impact

Liver function and liver toxicity

The DELOS study

Patients with moderate or severe hepatic impairment were excluded. No hepatobiliary AEs were reported. High values for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were observed both at Screening as well as on treatment, and were seen in both the idebenone and placebo treatment groups.

The DELPHI / DELPHI-E studies

Patients with significant impairment of hepatic function (serum gamma glutamyltransferase (GGT) > 1.5 x the upper limit for the patient's age and gender) were excluded. No hepatobiliary AEs were reported. In the DELPHI study, high values for AST and ALT were observed in the majority of patients in both the idebenone and placebo treatment groups both at Screening as well as on treatment. In the DELPHI-E study, a high proportion of patients had abnormalities in AST and ALT values, both at Baseline and all time points on treatment.

Elevated values of ALT and AST were seen in many DMD patients in both treatment groups at screening and throughout the studies. As these parameters are known to be elevated in patients with DMD, they were not considered clinically significant.

Integrated safety analyses

One subject with LHON in the RHODOS study withdrew due to severe abnormal liver function test results that occurred after 35 days of treatment with idebenone 900 mg/day. The event was considered possibly related to treatment, but occurred in the context of elevated AST and GGT levels prior to treatment and concomitant citalopram, oxazepam, carbamazepine, and omeprazole.

Abnormally high values of AST, ALT and/or bilirubin were reported in a number of patients across the indications, but were often high at baseline and occurred in patients on both idebenone and placebo.

Renal function and renal toxicity

The DELOS study

Patients with severe renal impairment were excluded from this study. No AE related to creatinine or urea was reported. Three patients on idebenone had chromaturia reported.

The DELPHI / DELPHI-E studies

Patients with significant impairment of renal function (serum creatinine > 1.5 x the upper limit for the patient's age and gender) were excluded. One patient in the DELPHI study on idebenone had haematuria reported.

Integrated safety analyses

One AE of renal failure and one of renal tubular necrosis was reported in a patient with FRDA receiving idebenone in the the MICONOS study. Three patients in the MICONOS study on idebenone had haematuria reported.

Other clinical chemistry*The DELOS study*

No clinically relevant changes in clinical chemistry were noted. While all patients had high values of creatine kinase (CK) throughout the study, this is a known marker for DMD and was therefore not considered clinically significant.

The DELPHI / DELPHI-E studies

With the exception of CK (as above), no clinically relevant changes in clinical chemistry were noted.

Integrated safety analyses

In the full safety population, with the exception of rare outliers there were only small mean changes from Baseline in the clinical chemistry values, which were generally similar in the idebenone and placebo groups in double blind studies and in extension study patients.

Haematology and haematological toxicity*The DELOS study*

No clinically relevant changes in any haematological parameter were noted. Results for the idebenone and placebo groups were generally similar.

The DELPHI / DELPHI-E studies

No clinically relevant changes in any haematological parameter were noted during the DELPHI and DELPHI-E studies.

Integrated safety analyses

In the full safety population few haematological abnormalities were noted, and these were observed in both the idebenone and placebo groups. A few cases of low white blood cell (WBC) counts occurred during the NICOSIA study but these were evenly distributed between the placebo and idebenone groups, and in all but one case were normal on rechecking at a local laboratory.

Electrocardiograph findings and cardiovascular safety*The DELOS study*

Only small mean changes from Baseline in ECG and transthoracic echocardiology parameters were observed in each treatment group. A small number of patients on both idebenone and placebo had clinically significant abnormalities in transthoracic echocardiography at baseline and at study completion.

The DELPHI / DELPHI-E studies

No clinically significant changes in ECG measurements were observed. The mean QT, QTcB and QTcF;³⁸ increased slightly during the study. The increase was greatest at Month 18 (+30.1, +30.8, and +30.3 ms, respectively) but values subsequently returned to near baseline values in the 3 patients with a QT, QTcB and/ or QTcF value above 500 ms at Month 18.

Integrated safety analyses

No clinically significant changes in ECG measurements were observed. Separate analyses of QT/QTc data were performed for patients with LHON (Study SNT-IR-004) and FRDA (Study SNT-IR-001). No difference in QT, QTcB or QTcF interval or any other ECG

³⁸ QT = Interval measured from the beginning of the QRS to the end of the T wave; QTcF = QT interval corrected according to Fridericia's formula; QTcB = QT interval corrected according to Bazett's formula

parameter was detected between the idebenone and placebo groups in LHON or FRDA patients after a 6-month treatment period.

An integrated analysis of QTcF values was also performed (Table 11, below). QTcF prolongation was generally lower in idebenone than in placebo patients in the DMD population. These results did not raise any new safety concerns, compared to the FRDA population.

Table 11: QTcF results over time by disease population

QTcF	Number (%) Subjects							
	Full safety pop		DMD		LHON		FRDA	
	Placebo	Idebenone ^a	Placebo	Idebenone	Placebo	Idebenone	Placebo	Idebenone
N	166	438	42	53	30	54	94	331
<i>Summary results</i>								
>450 msec	17 (10.2)	51 (11.6)	12 (28.6)	10 (18.9)	0	1 (1.9)	5 (5.3)	40 (12.1)
>480 msec	8 (4.8)	13 (3.0)	7 (16.7)	5 (9.4)	0	0	1 (1.1)	8 (2.4)
>500 msec	5 (3.0)	8 (1.8)	5 (11.9)	3 (5.7)	0	0	0	5 (1.5)
<i>Outlier analysis</i>								
>30 msec increase	21 (12.7)	113 (25.8)	15 (35.7)	20 (37.7)	0	9 (16.7)	6 (6.4)	84 (25.4)
>60 msec increase	9 (5.4)	35 (8.0)	9 (21.4)	8 (15.1)	0	4 (7.4)	2 (14.3)	23 (6.9)

Source: Table 127, Summary of Clinical Safety. Over time frequencies describe how many subjects had a finding at some point during the study; thus if a subject had both decreases and increases he/she is counted in both categories.

^aIncludes patients in double-blind and extension studies.

Vital signs and clinical examination findings

The DELOS study

Only small mean changes from Baseline values were observed for systolic and diastolic blood pressure (BP), heart rate, and respiratory rate, and were generally similar for the idebenone and placebo groups. Mean height increase over 52 weeks was less in the idebenone group (2.6 cm) than in the placebo group (7.0 cm), while the opposite was true for increase in weight (3.3 kg versus 1.8 kg, respectively).

The DELPHI / DELPHI-E studies

Mean height and weight increased more in the placebo group (4.6 cm, 5.06 kg) than in the idebenone group (3.4 cm, 1.62 kg) over 52 weeks in the DELPHI study. None of the differences between the treatment groups was considered medically significant. There were only small mean changes from Baseline in vital sign values during the DELPHI-E study.

The difference in height and weight changes is likely to be related to the fact that patients receiving idebenone were significantly older than patients receiving placebo at enrolment in the DELPHI study (13.4 ± 2.1 years versus 10.8 ± 1.9 years, respectively). In the DELOS study increase in height was less in the idebenone group despite these patients being younger than those on placebo. However, the range of height change was large in both groups (0 to 11 cm versus 0 to 15 cm, respectively) and may just be due to chance

Integrated safety analyses

Most systolic and diastolic BP, heart rate and respiratory rate findings were normal. With the exception of rare outliers, mean BP, heart rate and respiratory rate values and mean changes from Baseline were comparable in double-blind and extension study patients. Overall, an increase of $\geq 7\%$ in weight over time is noted; consistent with the growth of children enrolled in the studies. With the exception of rare outliers, the percentages of

patients with weight changes were comparable in idebenone and placebo patients in DB studies and comparable in extension study patients.

Immunogenicity and immunological events

The DELOS study

No AEs in the immune system disorders System Organ Class (SOC) were reported in either the idebenone or the placebo group.

The DELPHI / DELPHI-E studies

No AEs in the immune system disorders SOC were reported in either the idebenone or the placebo group during the DELPHI study, nor for patients on idebenone during the DELPHI-E study.

Integrated safety analyses

The only patient group reporting AEs in the immune system disorders SOC was the FRDA group, with 6 (2.3%) of patients on idebenone and 5 (5.3%) of patients on placebo reporting AEs in the double blind studies. A further 2 patients (2.9%) in the IONIA-E study and 3 patients (1.5%) in the MICONOS-E study also had immune system AEs. The AEs on idebenone included hypersensitivity (n = 4), allergic oedema, and seasonal allergy (n = 1 each). All but one episode of hypersensitivity were mild in severity.

Serious skin reactions

The DELOS study

No cases of photosensitivity, erythema multiforme, Stevens Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) or toxic epidermal necrolysis were reported.

The DELPHI / DELPHI-E studies

No cases of photosensitivity, erythema multiforme, Stevens Johnson syndrome, DRESS or toxic epidermal necrolysis were reported.

Integrated safety analyses

No cases of photosensitivity, erythema multiforme, Stevens Johnson syndrome, DRESS or toxic epidermal necrolysis were reported.

Other safety parameters

Results for post-hoc analysis SNT-IR-010

Because respiratory complications are the primary cause of morbidity and mortality in DMD, a post-hoc analysis of the Study SNT-III-003 (DELOS study) clinical trial was conducted to further assess the effect of idebenone versus placebo in reducing the risk of bronchopulmonary adverse events (BAEs) and to determine the use of antibiotics for the treatment of such BAEs/airway infections.

A study-independent physician who was blinded to patient treatment group reviewed and assessed treatment emergent adverse events (TEAEs) recorded in the Study SNT-III-003 (DELOS study) safety database. Those TEAEs considered likely to have involved the larynx, trachea, bronchi, smaller airways or lung they were categorised as BAEs. TEAEs were not considered BAEs if they were less precise and/or involved primarily the nose, sinuses, or throat.

The following TEAEs (preferred terms) were identified as clinically relevant BAEs:

- bronchitis
- laryngitis

- upper respiratory tract infection
- respiratory failure
- cough
- influenza
- pneumonia
- viral infection
- acute respiratory failure
- dyspnea.

The number and type of treatment-emergent BAEs are summarised in Table 12, below.

Table 12: Analysis of treatment-emergent BAEs (ITT Population)

BAE Preferred Terms	Idebenone (N=31)		Placebo (N=33)		Fisher's Exact Test ¹
	No. of Events	No. of Patients (%)	No. of Events	No. of Patients (%)	
Total BAEs	7	6 (19.4)	28	17 (51.5)	p=0.0096
Upper respiratory tract infection	2	2 (6.5)	10	6 (18.2)	
Bronchitis	5	4 (12.9)	5	5 (15.2)	
Pneumonia	0	0	3	2 (6.1)	
Cough	0	0	2	2 (6.1)	
Influenza	0	0	2	2 (6.1)	
Viral infection	0	0	2	2 (6.1)	
Acute respiratory failure	0	0	1	1 (3.0)	
Dyspnea	0	0	1	1 (3.0)	
Laryngitis	0	0	1	1 (3.0)	
Respiratory failure	0	0	1	1 (3.0)	

BAEs were reported in more patients in the placebo group (n = 17 (51.5%)) than in the idebenone group (n = 6 (19.4%)). In addition, the overall duration of BAEs was longer in the placebo group (222 days) than in the idebenone group (82 days), and there was increased use and duration of systemic antibiotics in the placebo group compared with the idebenone group (13 patients (39.4%) and 17 periods (105 days) of antibiotic use versus 7 patients (22.6%) and 8 periods (65 days)).

Other safety issues

Safety in special populations

Gender

The DELOS / DELPHI / DELPHI-E studies

DMD primarily affects young males; no females were enrolled in either the DELOS or DELPHI studies.

Integrated safety analyses

The incidence of AEs and SAEs was generally similar for male and female patients in LHON and FRDA. Treatment-related AEs appeared to be more common in female patients, but this was seen for both idebenone (male, 36.1% versus female, 61.8%) and placebo patients (male, 29.4% versus female, 59.6%).

Age

The DELOS / DELPHI / DELPHI-E studies

Patients in the DMD studies had a mean age of 9.4 to 19.0 years; AEs were not stratified by age in these studies.

Integrated safety analyses

The incidence of AEs, and treatment-related AEs was generally similar for subjects aged < 12, ≥ 12 to < 18 and ≥ 18 years. The number of SAEs or treatment-related SAEs was small, which precludes meaningful comparison.

Renal impairment

There was a single PK study in patients with moderate or severe renal impairment using a 120 mg dose of idebenone. Two AEs were reported: one SAE (cerebral bleeding) and one non-serious (headache). The investigator did not consider either AE was related to study drug.

Hepatic impairment

There was a single PK study in patients with moderate hepatic impairment (Child-Pugh-Classification A or B) using a 120 mg dose of idebenone. Only a single SAE was reported (acute episode of pancreatitis (pseudocyst)) 7 days following idebenone administration. Despite surgery the patient died. The investigator did not consider the SAE was related to study drug.

Further data on patients below 8 years of age and those with renal and/or hepatic impairment is considered Missing Information, and use of idebenone in these populations will be assessed via the Post-Authorisation Safety Study for DMD if they become available, as proposed in the EU Risk Management Plan.

Safety related to drug-drug interactions and other interactions

No clinical drug-drug interaction studies have been performed with the 150 mg film-coated tablet formulation of idebenone proposed for registration.

Four PK interaction studies were conducted in healthy adult volunteers in the 1990s with 120 mg or 120 mg TDS doses of idebenone. The drugs investigated (lithium, amitriptyline, fluvoxamine, and donepezil) were those likely to be used in adults with dementing diseases. The most common AEs reported were headache, dizziness, and tiredness. Most were mild or moderate in intensity, and resolved.

It is noted by the sponsor that in the Raxone EU-RMP for LHON that an *in vivo* Phase I study to assess the potential pharmacokinetic interaction of Raxone with midazolam in healthy male volunteers would be conducted as a post-authorisation measure. This drug-drug interaction study addresses the potential for pre-systemic inhibition of CYP3A4 and is currently on-going.

Safety data that takes into account information on stopping the drug

The sponsor provided a justification for the absence of safety data that takes into account information on stopping the drug with reference to the following TGA-adopted EMA guidelines:

Clinical Investigation of Medicinal Products for Long-Term Use. Legislative basis
Directive 75/318/EEC as amended

In summary the justification stated the following:

- specific studies on stopping the drug are not considered necessary to support the proposed dosing regimen for idebenone since long term treatment is anticipated.
- In DELOS Study, all patients attended a final follow-up 4 to 5 weeks after study medication withdrawal to perform a safety assessment where no safety alerts arose.
- the clinical experience with DMD patients demonstrated a safety profile that was consistent with that seen in previous studies in other indications, and reported in the Periodic Safety Update Reports (PSURs).

This justification is considered acceptable.

Post marketing data

Two periodic safety update reports (PSURs) were provided: one for Mnesis;³⁹ (idebenone 30 mg and 45 mg sugar-coated tablets and 150 mg film-coated tablets) covering the period 1 October 2011 to 30 September 2014, and one for Raxone (150 mg film-coated tablets) covering the period 8 September 2015 to 8 September 2016.

PSUR 1 October 2011 to 30 September 2014

Since the Mnesis (Takeda Pharmaceuticals) international birth date (IBD; 30 September 1986; Japan) to 30 September 2014 the estimated cumulative market exposure to idebenone (assuming an average daily dose (ADD) of 135 mg) is 1.46 billion ADDs corresponding to approximately 4,001,179 patient-years of treatment. The patient exposure during the period covered by this report is 11.5 million ADDs corresponding to approximately 31,480 patient-years of treatment. A further 1,422 patients received idebenone while participating in clinical trials (744 in Japan for the treatment of late effects of cerebral infarction / cerebral haemorrhage, 70 in Phase I studies, and 608 in Phase II/III trials for the treatment of FRDA or DMD).

During the reporting period, there were no safety actions taken by Takeda related to either investigational uses or marketing experience, and there were no safety related changes to the Company Core Safety Information (CCSI) during the reporting period.

Since the IBD, 719 SAEs have been reported from clinical trials with idebenone, and 586 adverse drug reactions (ADRs) (241 serious) have been received through spontaneous reporting sources including reports from regulatory authorities, and literature sources. Of the ADRs, only 9 serious and 5 non-serious were reported during the current PSUR period, with a further 3 from post-marketing surveys. No new safety signals were identified during the current reporting period. The 9 serious ADRs were: neurological decompensation (x 2), optic atrophy, sudden hearing loss (x 2), hepatitis, spontaneous abortion, condition aggravated, and exposure during pregnancy. The sponsor stated that the nature and frequency of the ADRs received from spontaneous and clinical trials sources was consistent with those described in previous PSURs.

PSUR 8 September 2015 to 8 September 2016

The commercial supply of Raxone during the period covered by this report is 566,100 tablets corresponding to approximately 258 patients (assuming 6 x 150 mg tablets/day*365 days treatment). Cumulatively since 2008, an additional 137 patients

³⁹ This PSUR covers the following tradenames of idebenone: Geniceral (Argentina), Mnesis (Italy, Switzerland), Lucebanol (Mexico), Cerestabon (Portugal), and Catena (Canada). The indications in these countries is either Cognitive Behavioural Deficit or FRDA.

received commercial supply of Catena⁴⁰, 487 received idebenone in the Santhera clinical development program (DMD 53, LHON 60, FRDA 294, and 'other' 80 patients) and 435 patients were supplied with idebenone via Early Access Programs (EAPs) and Named Patient Supply.

During the reporting period, there were no safety actions taken related to either investigational uses or marketing experience, and there were no safety related changes to the Reference Safety Information (RSI) during the reporting period.

Twenty-seven (27) cases (6 serious and 21 non-serious) were received during the reporting period. There were no cases with a fatal outcome and none of the events was life threatening. The 4 serious spontaneous AEs were: vomiting / pregnancy /abortion; hepatitis; ALT / AST increased; and epistaxis. The 3 serious solicited cases were: cataract surgery; pulmonary infection with signs of dehydration; and pneumonia.

It was stated that this PSUR 'revealed no new safety concerns.'

Evaluator's conclusions on safety

The safety of idebenone in patients with DMD is limited because of rarity of the disease. In the DELPHI, DELPHI-E and DELOS studies a total of 53 patients have been exposed to idebenone 450 / 900 mg/day for a mean (SD) of 549.0 (315.5) days. These safety data are supplemented by the use of idebenone in other therapeutic areas (LHON and FRDA) such that in the full safety analysis population (DMD, LHON, and FRDA), 439 patients have received idebenone (180 to 2,250 mg/day) for a mean (SD) of 600.3 (362.5) days. In addition, idebenone 45 mg (Mnesis) was initially developed by Takeda Pharmaceuticals Co Ltd for the treatment of cognitive disorders. Since the IBD of 30 September 1986 the estimated cumulative market exposure to idebenone is approximately 4,001,179 patient-years of treatment. Therefore, the number of overall patients treated and the duration of exposure to a variety of idebenone doses is considered adequate to allow characterisation of the safety profile of idebenone.

Duchenne muscular dystrophy

In DMD, the majority of patients experienced AEs but at a similar percentage in the idebenone (93.3%) and placebo (95.2%) treatment groups. Treatment related AEs and SAEs were reported in fewer patients on idebenone (24.4% and 6.7%) than on placebo (33.3% and 14.3%). AEs reported in $\geq 10\%$ of subjects in either treatment group (idebenone versus placebo) and higher on idebenone were diarrhoea (20.0% vs 14.3%), headache (17.8% versus 16.7%), pyrexia (13.3% versus 7.1%), gastroenteritis (13.3% versus 2.4%), and abdominal pain (11.1% versus 7.1%). The remaining AEs reported in $\geq 10\%$ of subjects in either DB treatment group were nasopharyngitis (17.8% versus 23.8%), URTI (13.3% versus 19.0%), bronchitis (11.1% versus 16.7%), constipation (6.7% versus 16.7%), and rhinitis (6.7% versus 16.7%). There were relatively few treatment-related AEs, with only diarrhoea and chromaturia being reported by 2 or more patients on idebenone. The majority of AEs and treatment-related AEs were mild to moderate in severity.

There were no deaths during the DMD studies, and none of the SAEs or discontinuations due to AEs were considered by the investigator to be treatment-related. In addition, there were no safety issues identified with possible regulatory impact.

In a post-hoc analysis of the DELOS study data, clinically relevant bronchopulmonary AEs were identified by a study-independent physician and compared between the idebenone and placebo treatment groups. Fewer patients on idebenone (19.4%) had BAEs than those

⁴⁰ Idebenone 150 mg marketed in Canada for FRDA between October 2008 and April 2013 when it was voluntarily withdrawn when additional primary efficacy studies did not meet their primary efficacy endpoint

on placebo (51.5%), and the duration of BAEs and systemic antibiotic use was shorter in the idebenone group.

Overall, the safety profile of idebenone in DMD appears relatively benign.

Integrated safety analysis population

In the integrated safety analysis, the percentage of subjects on idebenone (all doses combined) in each indication who reported at least 1 AE ranged from 89.1% (LHON) to 97.3% (FRDA), and was similar in the idebenone and placebo DB treatment groups. AEs reported in $\geq 10\%$ of subjects in either treatment group (idebenone versus placebo) and higher on idebenone were headache (29.8% versus 29.5%), nasopharyngitis (26.7% versus 21.7%), diarrhoea (17.1% versus 11.4%), and nausea (12.1% versus 10.2%). The remaining AE reported in $\geq 10\%$ of subjects in either DB treatment group was URTI (10.4% versus 13.9%). The highest proportion of treatment-related AEs occurred in the FRDA population (65.0%), but in the combined SAS was similar in idebenone (all doses combined) and placebo double blind treatment groups (idebenone 44.9% versus placebo 39.8%). The most common treatment related AEs reported in $\geq 5\%$ of subjects in either treatment group (idebenone versus placebo) were headache (12.6% versus 13.0%), diarrhoea (9.6% versus 5.4%) and nausea (9.3% versus 8.4%). While there was some variability in the incidence of individual AEs across the indications (no treatment-related AEs were reported in $\geq 5\%$ of LHON subjects), overall the safety profiles were similar.

Only a single death occurred in the SAS: one FRDA patient died of myocardial infarction during the MICONOS-extension study. The investigator assessed the death as unrelated to the study drug and attributed the event to the patient's underlying disease/pre-existing condition.

The incidences of SAEs in the overall SAS was similar in idebenone (all doses combined) and placebo DB treatment groups (idebenone 7.0% versus placebo 8.4%), but was highest in the FRDA population (21.1%). Treatment-related AEs occurred also occurred in a similar proportion of patients (idebenone 1.4% versus placebo 1.2%). The incidence of study discontinuations due to AEs was low and similar in idebenone (all doses combined) and placebo DB treatment groups (idebenone 2.0% versus placebo 3.0%).

While there was some variability in the incidence of individual AEs / SAEs across the indications, overall the safety profiles were similar in the DMD and integrated safety analysis populations.

While information on the safety of idebenone in DMD is limited, there is a long history of idebenone use in other indications. Admittedly much of this information is for idebenone use at a lower dose than is proposed for DMD and in adults rather than children, however the types and severity of AEs experienced are generally fairly benign and readily managed. No new safety signals were identified in the submitted PSURs.

First round benefit-risk assessment

First round assessment of benefits

Table 13: First round assessment of benefits

Indication: treatment of patients with DMD in whom respiratory function has started to decline and who are currently not taking concomitant glucocorticoids.	
Benefits	Strengths and uncertainties
<p>Patients who received idebenone had less decline in PEF%p at Week 52 compared with patients on placebo (-2.57% versus -8.84%; estimated difference 6.27%; 95% CI: 0.61, 11.93; p = 0.0306).</p>	<p>The efficacy of idebenone relies primarily on a single, small (n = 64 in ITT population) Phase III Study (DELOS).</p> <p>There is some reservation about the choice of PEF%p as the primary efficacy endpoint. While PEF%p can be considered clinically meaningful, it was selected on the basis of the results of the Phase II DELPHI Study in which it was only a secondary endpoint. As the DELPHI Study failed to meet its primary cardiac endpoint, the PEF%p result is not entirely convincing. In addition, while choice of PEF%p is consistent with the Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy;³³ for younger patients, FVC%p appears to be the preferred respiratory function test to measure loss of lung volume in DMD.</p> <p>While there was some supportive evidence of the efficacy of idebenone provided by secondary and tertiary respiratory endpoints in DELOS, the multiplicity of these endpoints and the post-hoc nature of some of the analyses introduce uncertainty in interpreting the results. This is further exacerbated by the lack of a consistent effect of idebenone on other, non-respiratory endpoints.</p> <p>External validation of the DELOS results was provided by the PPM Study using matched cohorts of DMD patients from the CINRG DNHS. This study demonstrated that the rate of decline in PEF%p in the DELOS Study placebo group was comparable to the rate of decline of a matched-to-DELOS placebo cohort from the CINRG DNHS, while the rate of decline in the DELOS Study idebenone group was slower than both the matched-to-DELOS placebo and matched-to-DELOS idebenone cohorts from the CINRG DNHS.</p> <p>There is limited data in patients aged < 8 years, patients with renal and/or hepatic impairment, and patients with DMD receiving GCs. This is acknowledged by the sponsor as missing information in the EU RMP, and will be collected in a Post-Authorisation Safety Study, and (for GC use) in the ongoing SIDEROS Study.</p> <p>On the basis of the limited Phase II data, the choice of, and wide confidence interval surrounding, the PEF%p endpoint, limited supportive evidence for other respiratory and non-respiratory endpoints in DELOS, and lack of data in patients receiving glucocorticoids, DELOS is not considered a sufficiently robust study to meet the requirements for a single pivotal study (Points to consider on application with 1.meta-analysis 2.one pivotal study³⁷).</p>

Indication: treatment of patients with DMD in whom respiratory function has started to decline and who are currently not taking concomitant glucocorticoids.

Benefits	Strengths and uncertainties
The safety profile of idebenone is relatively benign, with the commonly occurring AEs generally being mild to moderate in severity and easy to manage.	Although the safety profile of idebenone is long established for the lower dose of 45 mg, there is limited long term safety data with the 900 mg dose that is proposed for DMD. However the nature of the AEs and the similarities across the different indications and doses is such that this is not considered a critical issue.

First round assessment of risks

Table 14: First round assessment of risks

Risks	Strengths and uncertainties
As the wording of the proposed indication currently stands, there is potential for idebenone to be used in patients younger than aged 10 and with a PEF% _p > 80% (that is not consistent with the DELOS study patients).	It is possible that treating clinicians could prescribe idebenone to younger patients (< 10 years) or to those 'in whom respiratory function has started to decline' but who have not yet reached a PEF% _p < 80%. This could be addressed by modifying the wording of the indication to more closely reflect the entry criteria for the DELOS study.
Limited long-term safety data for the 900 mg dose of idebenone.	As stated in the assessment of benefits, there is a long established safety profile for the 45 mg dose of idebenone. In addition, the nature of the AEs and the similarities across the different indications and doses is such that this is not considered a critical issue.
In vitro data can't exclude the potential for pre-systemic inhibition of CYP3A4.	A Phase I open label study of the potential pharmacokinetic interaction of idebenone (150 mg film-coated tablet) with midazolam in healthy male volunteers is being conducted.

First round assessment of benefit-risk balance

While the DELOS study showed a reduction in the deterioration of PEF%_p with idebenone in comparison to placebo, uncertainty remains regarding the validity and clinical relevance of this outcome. As such, confirmatory Phase III data are considered desirable. While idebenone has an acceptable safety profile, the benefit-risk balance of idebenone for the treatment of DMD is considered unfavourable.

First round recommendation regarding authorisation

The evaluator is not able to recommend approval of idebenone for:

the treatment of patients with Duchenne Muscular Dystrophy (DMD) in whom respiratory function has started to decline and who are currently not taking concomitant glucocorticoids. Raxone can be used in patients previously treated with glucocorticoids or in patients in whom glucocorticoid treatment is not desired, not tolerated or is contraindicated

at this time for the following reasons:

1. while the PEF%p result in the DELOS study was statistically significant, the 95% CI was wide and therefore the clinical relevance of the result is uncertain.
2. FVC%p appears to be the preferred respiratory function test to measure loss of lung volume in DMD.
3. there was a lack of consistent supportive evidence from other respiratory and non-respiratory endpoints in the pre-specified analyses of the DELOS study.
4. while it is acknowledged that restricting the DELOS study to DMD patients not receiving GCs was the result of a planned futility analysis, it has subsequently been determined that it is not GC use *per se* that influences response to idebenone but the stage of respiratory decline. Therefore, there is a substantial sub-group of patients with DMD in whom the efficacy of idebenone has not been demonstrated.
5. the DELOS study does not provide '*statistically compelling and clinically relevant results*' as per the EMA document 'Points to consider on application with 1. meta-analysis 2. one pivotal study (CHMP/EWP/2330/99)'.

Clinical questions and second round evaluation

Pharmacokinetics

Question 1

In Study SNT-I-003 (Section 11.4.5.5), it was reported that renal clearance of 9247 to 12822 mL/hour is higher than the GFR (7500 mL/minute). Please clarify these numbers / units.

Sponsor response

The sponsor clarified there was a typographical error in the report such that the GFR should have read 7500 mL/hour.

Evaluation of response

The response is acceptable.

Question 2

In the non-clinical overview binding to human plasma proteins for idebenone was reported as 98.5% and 98.8% for idebenone (compound SNT-MC 17) and QS10 (compound SNT201343), respectively (on the basis of Study Number 862614). Please clarify whether compound SNT-MC 17 is the same formulation of idebenone as was used in the clinical trials.

Sponsor response

The sponsor confirmed that the compound code SNT-MC 17 used in the non-clinical study Nr 862614 refers to idebenone. Amendment to the PI is proposed.

Evaluation of response

The response and addition to PI are acceptable.

Efficacy

Question 3

Please comment on the change in the expected effect size in patients not using GCs between the original protocol (15%) and protocol amendment 3 (10.3%).

Sponsor response

The sponsor explained that due to the lack of natural history data at the time of the planning of DELOS, the original effect size was based on the DELPHI Study. Subsequent natural history studies indicated that the expected annual rate of decline in PEF%_p is approximately 5-6% between the age of 10 and 20 years, and that therefore the original assumptions for the sample size calculation of DELOS were not correct.

‘The sample size calculation was not changed during the DELOS Study conduct. However, as the final number of randomized patients (GC non-users) was somewhat higher than originally planned, the sponsor documented in Protocol Amendment 5 that with the final sample size, the study would have 80% power to detect a difference of 10.3% in PEF%_p between the groups. In agreement with the language in Amendment 5, the number 10.3 was not an expected effect size but rather an estimate of what kind of difference the study was powered to detect with the final sample size.’

Evaluation of response

The response is acceptable. This does not affect interpretation of the results.

Question 4

In the discussion and conclusion section of Report SNT-IR-011 it is stated that:

‘This re-analysis of the DELPHI and DELPHI-E data in the sub-group of patients in the decline phase of their disease (that is at $\leq 80\%$ PEF%_p), now suggests that the treatment effect of idebenone is similar in GC-users and non-users with no significant interaction of GC on the effect of idebenone. The difference between GC users and non-users reported in the original DELPHI Clinical Study Report (CSR) is now considered to have been an artefact of the effect of GC on delaying the onset of respiratory function decline rather than some interaction between idebenone and GC which affected the outcome in the GC-using patients. Whilst the GC non-using patients in DELPHI ($n = 8$) were all in the decline phase (that is, PEF%_p was $\leq 80\%$) at Baseline the majority of the GC-using patients (9/13 (69%)) were not in the decline phase of their disease at Baseline.’

While the evaluator accepts the lack of interaction demonstrated between GC use and the treatment effect of idebenone, it would be useful to see the data for those patients with PEF%_p > 80% presented as per the analysis of PEF%_p for the subgroup with baseline PEF%_p $\leq 80\%$ in Table 9 of the SNT-IR-011 Report.

Sponsor response

The sponsor presented the data as requested (see below). It demonstrates that even in patients not in the decline phase (PEF%_p > 80%) there is an estimated mean treatment difference favouring idebenone at month 12 of 5.1%, although this is much smaller than that seen in patients in the decline phase (18.6%), and not statistically significant.

Table 15: Data for those patients with PEF%p > 80%

	Idebenone	Placebo	Estimated Treatment Difference ¹ ± SEM (95% CI)	2-sided p-value
			Idebenone vs Placebo	
DELPHI ITT				
N	13	8		
Baseline Mean	74.1 (26.7)	74.8 (26.5)		
Month 12 Estimated Change (95% CI)	2.8 (-4.1, 9.7)	-8.4 (-17.2, 0.4)	11.2±5.3 (0.0, 22.3)	0.0497
DELPHI, Subgroup with Baseline PEF%p ≤80% (Patients in Decline Phase)				
N	8	4		
Baseline Mean	59.0 (19.6)	56.8 (24.1)		
Month 12 Estimated Change (95% CI)	8.8 (-1.0, 18.6)	-9.8 (-23.7, 4.1)	18.6±7.5 (1.6, 35.7)	0.0354
DELPHI, Subgroup with Baseline PEF%p >80%				
N	5	4		
Baseline Mean	98.2 (17.0)	92.8 (13.9)		
Month 12 Estimated Change (95% CI)	-1.8 (-16.3, 12.6)	-6.9 (-23.1, 9.4)	5.1±8.9 (-16.8, 26.9)	0.5925

¹: Estimated change and estimated difference from MMRM

Evaluation of response

The response is acceptable.

Question 5

Please provide plots of the individual PEF%p (change from baseline and progression of mean values during the study) as presented in Figure 2 of the DELOS CSR. This may help to determine variation in the timing of when patients respond, and whether lack of an early response should result in cessation of treatment.

Sponsor response

The sponsor provided the requested plots. The sponsor concluded that: 'it is difficult to assess the time of response to the treatment by viewing individual trajectories for change in PEF%p from baseline. Typically, it is challenging to draw conclusions from individual patient data on the overall outcome of a clinical trial.'

Evaluation of response

The response is acceptable. The pattern of response is quite variable, and some patients on idebenone deteriorated for a variable period of time before stabilising or improving. Therefore, it would be difficult to cease treatment purely on the basis of a lack of an early response.

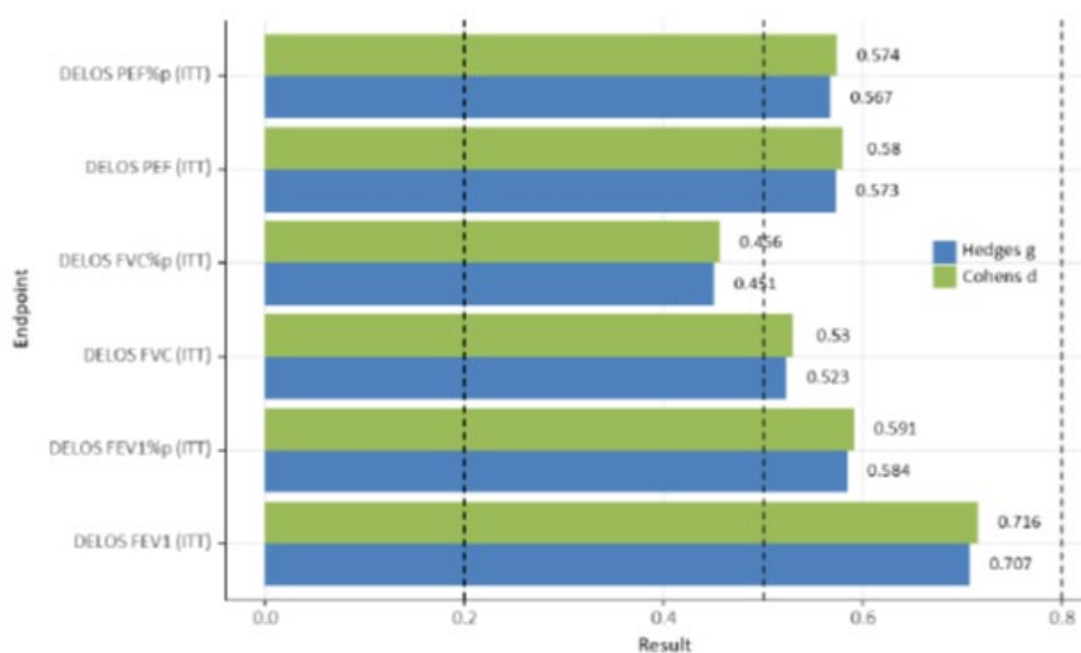
Question 6

In Q1-Table 3 of the EMA responses third RSI document, the Cohen's d statistic was calculated for respiratory function outcomes of the DELOS trial. As the Cohen's d statistic tends to over-inflate results for smaller sample sizes ($N < 50$), please confirm whether you used a correction factor in these calculations, and if not, please provide the results with and without correction.

Sponsor response

The sponsor stated that the effect sizes were calculated without correction. They provided a comparative overview of the treatment effect using the Cohen's statistic and with a Hedges g correction. This demonstrated very little difference in the effect size and hence did not alter the conclusions (see below)

Figure 4: Interpretation of the observed treatment effect from the DELOS Study by Cohen's d and Hedges' g methodology



Evaluation of response

The response is acceptable.

Question 7

Can the sponsor please indicate if there was discussion on the wording of the EAMS (unlicensed) indication and the reason for the EAMS choice?

Sponsor response

The sponsor provided a history of the discussion which occurred during the EAMS assessment to reach the final wording of the therapeutic indication. The initial indication proposed was:

'for the treatment of patients with Duchenne muscular dystrophy (DMD) in whom respiratory function has started to decline and who are currently not taking concomitant glucocorticoids. Raxone can be used in patients previously treated with glucocorticoids or in patients in whom glucocorticoid treatment is not desired, not tolerated or is contraindicated'.

The final wording approved was:

'for slowing the decline of respiratory function in patients with Duchenne Muscular Dystrophy (DMD) from the age of 10 years who are currently not taking glucocorticoids. The decline of respiratory function must be confirmed by repeated measurements of pulmonary function prior to initiation of treatment. Raxone can be used in patients previously treated with glucocorticoids or in patients in whom glucocorticoid treatment is not tolerated or is considered inadvisable.'

Changes occurred over time based on the ongoing CHMP review of the proposed wording of the summary of product characteristics (SmPC) and amendments suggested by the EMA's assessors. They were generally fairly minor in nature and reflected aspects of the data available from the DMD idebenone studies (for example absence of data in patients under the age of 10 years).

Evaluation of response

The response is acceptable.

Question 8

Only diarrhoea is listed as a common side effect, whereas there were numerous other AEs reported in the DELOS study with a percentage > 10% (very common); for example, nasopharyngitis, pyrexia, abdominal pain, bronchitis, etcetera. Please explain the basis for only including diarrhoea as a common side effect in the CMI.

Sponsor response

The sponsor considers that CMI side effects are different from AEs reported in clinical trials and post marketing experience. In particular, whether there is sufficient data available to conclude a reasonable possibility for a causal relationship to Raxone. Only diarrhoea was both a common event and had at least a reasonable possibility for a plausible causal relationship to Raxone.

Evaluation of response

The response is acceptable.

Question 9

Can the sponsor please clarify whether any additional issues were raised in the first or second RSI from the EMA that have not subsequently been raised in the third RSI? Please provide a timeline for the major interactions with the EMA.

Sponsor response

The sponsor provided the summary of the timelines.

The sponsor confirmed that there were additional questions raised in the first and second round request for supplementary information (RSI) that were resolved prior to Round 3, and provided the Round 1, Round 2 and Round 3 correspondence with their response.

Evaluation of response

The response is acceptable. The issues identified in the first and second round RSI were reviewed and the evaluator is satisfied that no additional unresolved issues have been identified that were not included in the third RSI. It is noted that there were pre-clinical

and Risk Management Plan (RMP) issues identified which may require review by the relevant evaluators.

Additional information provided by the sponsor

The sponsor's responses to the TGA evaluator recommendations and relevant information from the CHMP re-examination procedure are discussed below in relation to the first round recommendation

Issue 1

While the PEF%p result in the DELOS Study was statistically significant, the 95% CI was wide and therefore the clinical relevance of the result is uncertain.

Sponsor response

The sponsor made the following points:

- 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% in favour of Raxone.
- Natural history reference data report annual rates of respiratory function decline in PEF%p in the range between 4.1% and 6.78%.
- The observed treatment difference for the primary endpoint PEF%p in the DELOS trial represents a delay of disease progression by 1 year, which is a clinically relevant treatment effect in DMD.
- The findings observed for PEF%p from baseline to each of the post-baseline visits were supported by additional pre-specified, post-hoc and imputation analyses.
- Home-based measurement of PEF was a pre-specified secondary endpoint in the DELOS study. The treatment difference based on the weekly home-based assessments for PEF%p was consistent with the primary efficacy results using hospital spirometry measures (Estimated difference: 6.84% (95% CI: -0.154, 13.83); $p = 0.0548$). The EMA Guideline on medicinal products for the treatment of Duchenne and Becker muscular dystrophy (EMA/CHMP/236981/2011, Corr. 11), states that measurement tools from a reliable informant (for example parent or carer) should be taken into account when assessing parameters for determination of efficacy.
- The positive effect of Raxone on PEF%p was associated in a reduced number of patients reporting fewer bronchopulmonary adverse events, fewer episodes of systemic antibiotic use, and also fewer hospitalisations caused by respiratory complications, which supports the clinical relevance of PEF%p.
- A post-hoc slope analysis was included in the Information for healthcare professionals from the Early Access to Medicines Scheme (EAMS). This analysis used all available post-baseline data points to determine the 52-week trajectory of change and resulted in a tighter CI for PEF%p (Estimated difference: 5.81% (95% CI: 1.62, 10.0); $p = 0.0070$) as well as a statistically significant p value for FVC%p (estimated difference: 4.13 (95% CI: 1.72, 6.54); $p = 0.0009$). This helped to convince the MHRA to conclude on a positive benefit risk assessment for EAMS.
- Fewer patients on Raxone crossed specific clinically relevant respiratory thresholds based on FVC%p (see Table 16, below)

Table 16: Proportion of patients in whom FVC%p drops below 50%, 40% or 30% (DELOS, ITT)

Threshold	Disease status according to standard of care guideline (Bushby 2010; Birnkrant 2010)	Patients (%) falling below FVC%p category		Hazard Ratio* (95% CI)
FVC%p	Patient status	Raxone	Placebo	
< 50%	Moderate pulmonary insufficiency	20%	44%	0.34 (0.10, 1.78)
< 40%	Signs and symptoms of hypoventilation	17%	20%	0.58 (0.13, 2.60)
< 30%	High risk of hypoventilation	14%	25%	0.59 (0.17, 2.10)
< any threshold**		34%	57%	0.51 (0.23, 1.14)

*Hazard Ratios for time to first event. **each patient is only counted once. Source: 1stRSI-Q32-Table 4

- The size of the treatment effect in DELOS is comparable to treatment effect sizes for registered products in other respiratory conditions (idiopathic pulmonary fibrosis, cystic fibrosis, and chronic obstructive pulmonary disease).
- The sponsor commits to conduct an externally-controlled long-term study (Study SNT-IV-009) in patients in respiratory decline and not taking GCs to collect long term efficacy data. The study objective is to investigate the change in respiratory function and time to clinically relevant milestones, such as falling below clinically relevant thresholds for FVC%p, frequency of hospitalizations and time to assisted ventilation (see SNT-IV-009) Protocol synopsis). This study plans to enrol a minimum of 82 patients to be treated with Raxone for a minimum of 3 years.

Evaluation of response

The response is noted and it is acknowledged that the sponsor did provide additional post-hoc analyses of a number of clinically relevant respiratory endpoints to support the PEF%p endpoint. However, because the analyses were not part of the original study design (or were based on endpoints that were considered exploratory), with a number of protocol amendments occurring as understanding of the natural history, assessment and treatment of DMD emerged, they cannot fully overcome all the evaluators concerns about the validity and clinical relevance of the supportive respiratory efficacy results.

Of note, the Scientific Advisory Group⁴¹ (SAG) experts agreed:

‘that if reliable data are presented and there are no methodological issues that could influence data integrity, the observed effect could be clinically relevant, provided that it could be assumed that the effect would be maintained over several years. However, the SAG experts highlighted that it would be impossible to conclude on the question whether this effect would be maintained beyond the period of 1 year.

Additionally, the SAG experts highlighted that it is difficult to conclude whether the observed effect on the primary endpoint will definitely translate into a clinically meaningful outcome expressed in, for example, a delay of an important milestone in the disease, or improvement in daily functioning. In general, demonstrating an

⁴¹ Upon request from the CHMP, this SAG meeting was convened on 12 January 2018 in the context of a re-examination procedure of a refused variation EMEA/H/C/3834/II/0003.

effect of a single parameter of pulmonary functioning in itself should not be considered sufficient to claim clinically relevant benefit, unless in this specific population, there have been data clearly linking this parameter to objective clinically relevant outcomes.'

These concerns of the SAG formed part of the Scientific conclusions of the CHMP Final opinion document (EMA/H/C/003834/II/0003) as follows:

'In the pivotal Phase III DELOS trial, Raxone had a statistically significant effect on the primary respiratory endpoint PEF%p. However, for this difference to be considered as clinically relevant, the effect needs to be translated into effects that are directly linked to patient wellbeing such as quality of life or time to milestone events like for example time to assisted ventilation, and be confirmed that it can be maintained for longer than one year. At present, there is no scientific rationale allowing for the extrapolation of the observed effect on measures of pulmonary functioning beyond the trial duration, or for linking this effect to a clear milestone in the disease progression.'

It is acknowledged that the sponsor plans to overcome some of these concerns by collecting long-term efficacy data on the change in respiratory function and time to clinically relevant milestones. The potential to collect long-term data in the post-approval setting is consistent with the EMA DMD guideline.

It should be noted that there were members of the CHMP who did not agree with the CHMP's negative opinion recommending the refusal of the variation of the extension of indication of marketing authorisation of Raxone. The concluding paragraph of the reasons for the divergent position states:

'During the procedure, the applicant has demonstrated that the DELOS Study met its primary endpoint the results of which were consistently supported by other respiratory function endpoints. Concerns related to the robustness of the data have been resolved through numerous sensitivity analyses carried out as clinically important supportive responder analyses showed that treatment with Raxone resulted in fewer bronchopulmonary adverse events, less antibiotic use and reduced risk of hospitalisations. From a safety point of view, Raxone was safe and generally well tolerated. Taking everything together, including the planned post-authorisation measures, aimed at delivering additional efficacy and safety data in the DMD population, and considering the clear unmet medical need in the absence of any treatment alternative in this patient population, for all the reasons listed above, we consider that the Benefit-Risk ratio for Raxone in the claimed indication is positive.'

Issue 2

FVC%p appears to be the preferred respiratory function test to measure loss of lung volume in DMD

Sponsor response

The sponsor made the following points:

- It is acknowledged that the Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy (EMA/CHMP/236981/2011, Corr. 11) lists FVC%p to measure loss of lung volume in DMD, with PEF%p potentially being better in younger patients but that this guideline came into effect after the DELOS protocol was finalised.
- Choice of PEF%p as the primary endpoint was based on the advice provided by the CHMP Scientific Advice Working Party during a DELOS Protocol Assistance meeting.
- DMD experts state that PEF%p is a reliable, clinically relevant outcome measure and is used in routine clinical practice to monitor disease progression and initiate appropriate interventions.

- Decline in PEF%p is highly correlated with decline in FVC%p and FEV1%p.⁴²
- The CHMP concluded that PEF or PEF%p can in principle be accepted as the primary endpoint

Evaluation of response

The response is acknowledged. PEF%p is considered an appropriate measure of lung function in patients with DMD. However, the EMA DMD guideline considers that further data are necessary to establish how this measure correlates with quality of life, time to death and other life-changing events (for example time to wheelchair).

Of note, the SAG was split on the use of PEF%p as the primary efficacy endpoint for measuring an effect in this population. Based on the hypothesised mechanism of action of idebenone, some members considered that endurance tests could have been a better option for measuring an effect in this population.

Other SAG members stated that: 'PEF%p is indeed considered as 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 parameters, and that the fact that the decision to use it in the confirmatory trial was based on a finding from a Phase II trial, which was not considered as a problem methodologically.'

Issue 3

There was a lack of consistent supportive evidence from other respiratory and non-respiratory endpoints in the pre-specified analyses of DELOS.

Sponsor response

The sponsor stated that this issue had been resolved with the CHMP during the SAG meeting as follows:

- The DELOS trial was not designed to show an effect on non-pulmonary endpoints due to the patients being in a more advanced non-ambulant stage of the disease, and had lost most hand function.
- FVC, FEV1 and PEF demonstrate consistent results perhaps due to the strong correlation existing among those outcomes in the chosen population.
- The findings observed for PEF%p, FVC%p and FEV1%p from baseline to each of the post-baseline visits were supported by additional pre-specified, post-hoc and imputation analyses.
- The discrepancy observed with MEP/MIP and PCF⁴³ could be explained by the fact that these tests are known to be difficult to perform in this specific DMD population, and unreliable results are to be expected.
- The Phase II data from DELPHI is limited by the small sample size (Raxone: 13, Placebo: 8), BUT provides supportive PEF%p results.
- Open-label DELPHI extension data strengthen the plausibility of a long-term treatment effect of Raxone in this population.

Evaluation of response

The response is considered acceptable with regard to lack of supportive evidence from respiratory and non-respiratory endpoints. The correlation between FVC, FEV1 and PEF has previously been discussed, and the difficulties with performing the MEP/MIP and PCF

⁴² FEV1%p = Percent predicted forced expiratory volume in one second

⁴³ MEP = Maximum expiratory pressure MIP = Maximum inspiratory pressure

in DMD patients is noted. As mentioned in the earlier comments, data on quality of life, time to death and other life-changing events (for example time to wheelchair) are considered necessary by the EMA DMD guideline, and maintenance of the PEF%p response beyond one year is desirable.

The SAG considered that the inconsistency among the non-pulmonary outcome measures may be due to the fact that 'the recruited DMD population was inappropriate for most of them, as muscle strength-based outcomes are difficult to measure in late stage DMD patients. Additionally, some SAG members pointed out that the tools used for assessment were not sensitive enough in this population, due to the large number of non-ambulant patients, with a high Brooke grade, that were included'.

Issue 4

While it is acknowledged that restricting the DELOS Study to DMD patients not receiving GCs was the result of a planned futility analysis, it has subsequently been determined that it is not GC use per se that influences response to idebenone but the stage of respiratory decline. Therefore, there is a substantial sub-group of patients with DMD in whom the efficacy of idebenone has not been demonstrated.

Sponsor response

The sponsor made the following points:

- At the start of the DELOS trial, the effect of GC use on respiratory function outcomes was not sufficiently known and therefore the study was at this point only conducted in patients not using GCs
- More recently, publications have shown that GCs delay the start of respiratory function decline but not alter the rate of decline. The proposed indication is therefore specifically for patients not using GCs, which is in line with currently available data from the clinical program
- The proposed indication is therefore specifically for patients not using GCs, which is in line with currently available data from the clinical program. This population of patients not using steroids does exist in clinical practice as acknowledged by the SAG, and represents about 40% of patients in the relevant age group. The question if a similar effect can be obtained in patients using GCs is currently investigated in a separate trial (the SIDEROS trial).

Evaluation of response

The response is noted, and the evaluator accepts that the proposed indication (limiting use to patients with DMD in whom respiratory function has started to decline (PEF%p < 80%)) is in line with the available data.

Issue 5

The DELOS Study does not provide 'statistically compelling and clinically relevant results' as per the EMA document 'Points to consider on application with 1. meta-analysis 2. one pivotal study (CHMP/EWP/2330/99)'.

Sponsor response

The sponsor made the following points:

- Many aspects around the clinical science of the disease were unknown during the planning phase of this program and scientific knowledge only evolved during the conduct of the program, sometimes after the analysis of the data.
- DELOS was of moderate size for a pivotal trial (considering the constraints of conducting studies in rare diseases); however, the study was adequately powered to

detect clinically meaningful treatment differences between the treatment groups as a stand-alone Phase III study.

- It is acknowledged that the DELPHI Phase II study proceeding DELOS Study was initially designed as a cardiac study (with a positive trend favouring idebenone on the primary endpoint). The DELPHI Study did reveal a (nominally) statistically significant effect on respiratory function, PEF%p.
- The observed treatment difference for the primary endpoint PEF%p in the DELOS trial (6.27% in favour of Raxone) represents a delay of disease progression by 1 year, which is a clinically relevant treatment effect in DMD.
- Santhera considers the single pivotal study justified considering the long duration (5 years) until completion of DELOS and the urgent medical need in DMD patients not using glucocorticoids. Of note, these patients are mostly non-ambulant and in a generally very weak condition and therefore very difficult to enrol, especially in a placebo-controlled trial.
- DELOS was also the first study to be conducted in patients with DMD who are in respiratory function decline. It was based on a clear hypothesis from a Phase II phase study and is the first pivotal study in DMD that met its primary endpoint.

Evaluation of response

The response is noted, and the difficulties involved in conducting research into a rare disease in which scientific knowledge is evolving are acknowledged. However, there are several prerequisites for one pivotal study applications outlined in the EMA document.³⁷ While the evaluator is inclined to accept that the observed 6.27% treatment difference for PEF%p in favour of Raxone is clinically relevant, the EMA DMD guideline states that further data are needed to establish how respiratory function testing correlates with quality of life, time to death and other life-changing events. These data are not yet available, in part because longer follow-up than one year would be required. In addition, based on the primary pre-specified analysis of DELOS, the degree of statistical significance is not considered to be '*considerably stronger than $p < 0.05$* ' nor '*accompanied by precise estimates of treatment effects, that is narrow confidence intervals*'. The 95% CI for PEF%p of 0.61 to 11.93 is not considered narrow, and the lower limit of 0.61 indicates that it is possible that idebenone has little beneficial effect compared with placebo. Therefore, the evaluator does not believe this issue has been resolved.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to the clinical questions, the benefits of Raxone in the proposed usage are as follows (see table below).

Table 17: Second round assessment of benefits

Indication: treatment of patients with DMD in whom respiratory function has started to decline (PEF%p < 80%) and who are currently not taking concomitant glucocorticoids. <i>Raxone can be used in patients previously treated with glucocorticoids or in patients in whom glucocorticoid treatment is not desired, not tolerated or is contraindicated.</i>	
Benefits	Strengths and uncertainties
Patients who received idebenone had less decline in PEF%p at Week 52 compared with patients on placebo (-2.57% versus -8.84%; estimated difference 6.27%; 95% CI: 0.61, 11.93; p = 0.0306).	<p>The efficacy of idebenone relies primarily on a single, small (n = 64 in ITT population) Phase III study (DELOS).</p> <p>The choice of PEF%p as the primary efficacy endpoint is considered acceptable. PEF%p is consistent with the Guideline;³³ for younger patients, although FVC%p appears to be the preferred respiratory function test to measure loss of lung volume in DMD. However, the EMA DMD guideline states that further data are needed to establish how respiratory function testing correlates with quality of life, time to death and other life-changing events. It is accepted that this may require longer follow-up and that these data may not be available for inclusion in the initial application for registration.</p> <p>While there was some supportive evidence of the efficacy of idebenone provided by secondary and tertiary respiratory endpoints in DELOS, the multiplicity and exploratory nature of some of these endpoints and the post-hoc nature of some of the analyses introduce uncertainty in interpreting the results.</p> <p>External validation of the DELOS results was provided by the PPM Study using matched cohorts of DMD patients from the CINRG DNHS. This study demonstrated that the rate of decline in PEF%p in the DELOS study placebo group was comparable to the rate of decline of a matched-to-DELOS placebo cohort from the CINRG DNHS, while the rate of decline in the DELOS Study idebenone group was slower than both the matched-to-DELOS placebo and matched-to-DELOS idebenone cohorts from the CINRG DNHS.</p> <p>There is limited data in patients aged < 8 years, patients with renal and/or hepatic impairment, and patients with DMD receiving GCs. This is acknowledged by the sponsor as missing information in the EU RMP, and will be collected in a Post-Authorisation Safety Study, and (for GC use) in the ongoing SIDEROS Study.</p> <p>On the basis of the limited Phase II data and the wide confidence interval surrounding the PEF%p endpoint, DELOS is not considered a sufficiently robust study to meet the requirements for a single pivotal study.³⁷</p>
The safety profile of idebenone is relatively benign, with the commonly occurring AEs generally being mild to moderate in severity and easy to manage.	Although the safety profile of idebenone is long established for the lower dose of 45 mg, there is limited long term safety data with the 900 mg dose that is proposed for DMD. However the nature of the AEs and the similarities across the different indications and doses is such that this is not considered a critical issue.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Raxone in the proposed usage are as follows (see table below).

Table 18: Second round assessment of risks

Risks	Strengths and uncertainties
Limited long-term safety data for the 900 mg dose of idebenone.	As stated in the assessment of benefits, there is a long established safety profile for the 45 mg dose of idebenone. In addition, the nature of the AEs and the similarities across the different indications and doses is such that this is not considered a critical issue.

Second round assessment of benefit-risk balance

The benefit-risk balance of Raxone (idebenone) for the proposed usage is unfavourable.

The DELOS study showed a statistically significant reduction in the deterioration of PEF%_p with idebenone in comparison to placebo in patients with DMD who had established respiratory function decline at baseline (PEF%_p ≤ 80%) and who were not using concomitant glucocorticoids, although the confidence interval was wide. However, the multiplicity and exploratory nature of some of the supportive secondary and tertiary respiratory endpoints in the DELOS study, and the post-hoc nature of some of the analyses introduce uncertainty in interpreting these results. In addition, the EMA DMD guideline suggests that further data are needed to establish how respiratory function testing correlates with quality of life, time to death and other life-changing events. An additional concern was the limited Phase II data. Therefore the DELOS study is not considered a sufficiently robust study to meet the requirements for a single pivotal study.³⁷

Second round recommendation regarding authorisation

The evaluator is not able to recommend approval of idebenone for:

the treatment of patients with Duchenne Muscular Dystrophy (DMD) in whom respiratory function has started to decline (PEF%_p < 80%) and who are currently not taking concomitant glucocorticoids. Raxone can be used in patients previously treated with glucocorticoids or in patients in whom glucocorticoid treatment is not desired, not tolerated or is contraindicated

for the following reasons:

1. While the DELOS study shows a statistically significant reduction in the deterioration of PEF%_p with idebenone in comparison to placebo, the confidence interval is wide, and the p-value is not considerably stronger than $p < 0.05$.
2. The supportive respiratory data are difficult to interpret, and data to establish how respiratory function testing correlates with quality of life, time to death and other life-changing events are lacking.
3. There are limited Phase II data.

Therefore, the DELOS study is not considered a sufficiently robust study. This is consistent with EMA document (Points to consider on application with 1. meta-analysis 2. one pivotal study (CHMP/EWP/2330/99)).

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation⁴⁴

- The sponsor has submitted EU-RMP version 2.1 (date 21 November 2016; data lock point November 2015) and Australian specific annex (ASA) version 0.0 (date 11 April 2017) in support of this application.
- With the responses to questions the sponsor provided an updated ASA version 0.1 (date 16 January 2018).
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies for the indications of DMD and LHON (LHON; approved EU indication but not being sought in Australia) are summarised below:

Table 19: Summary of safety concerns, pharmacovigilance and risk minimisation

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None				
Important potential risks	Abnormal liver function test and hepatitis	✓	✓	✓	–
	Blood count abnormalities	✓	✓	✓	–
Missing information	Use in pregnancy and lactation	✓	✓	✓	–
	Use in children with LHON under 14 years of age	✓	✓	✓	–
	Use in children with DMD under 10 years of age	✓	✓	✓	–
	Use in elderly patients with LHON	✓	✓	✓	–
	Use in patients with hepatic impairment	✓	✓	✓	–

⁴⁴ *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Use in patients with renal impairment	✓	✓	✓	–
	Use in patients with DMD receiving GCs	✓	✓	✓	✓*
	Safety on long-term use of Raxone	✓	✓	–	–
	Potential for pre-systemic inhibition of CYP3A4	✓	✓	✓	–
	Potential for inhibition of P-gp	✓	–	✓	–

(LHON - Leber hereditary optic neuropathy. DMD - Duchenne muscular dystrophy. GCs – Glucocorticoids) *Providing physician education material is proposed for the EU, but not for Australia

- Additional pharmacovigilance activities include a Phase III study assessing the efficacy, safety and tolerability of idebenone in patients with DMD receiving glucocorticoid steroids (the SIDEROS study / Study SNT-III-012) and a post-authorisation safety study.
- Routine risk minimisation activities are proposed for all safety concerns. It is proposed to provide educational material to the physicians in the EU to prevent off-label prescription of Raxone to DMD patients receiving glucocorticoids. However, no additional risk minimisation measures are proposed for Australia. Physician education for this missing information is not considered to be a regulatory requirement in Australia, as the proposed indication excludes use in this population.

New and outstanding recommendations from second round evaluation

The recommendations (recommendations 1 to 8) made in the first round evaluation, along with consideration of the sponsor response, were provided [not included in this AusPAR].

The sponsor has satisfactorily addressed recommendations 1, 3 and 5.

With regards to recommendations 4, 6, 7 and 8, the sponsor has committed to:

- provide the details of the organisation responsible for risk management activities in Australia prior to commercialisation and launch of the product (recommendation 4);
- revise the missing information in the summary of safety concerns in the EU RMP to state '*Use in children with DMD under 10 years of age*' instead of '*under 8 years of age*' (recommendation 6);
- revise the Consumer Medicines Information (CMI) to clearly describe what Raxone is used for (recommendation 7); and
- rectify the inconsistencies between 'How much to take' and 'When to take it' sections of the CMI (recommendation 8).

It is noted that the sponsor has committed to provide the updated CMI by 28 February 2018.

There is one minor outstanding recommendation which can be addressed when the next updated ASA is submitted to the TGA:

Recommendation 2: During the next update of the ASA, the sponsor should include a section on 'Summary of the RMP', with the risk minimisation and pharmacovigilance activities summarised in a table.

There is one new recommendation (See wording for Conditions of Registration):

Recommendation 9: Raxone is a new chemical entity, and as such meets the inclusion criteria for the Black Triangle Scheme. The relevant symbol and statement should be added to the PI and CMI.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The Raxone EU-Risk Management Plan (RMP) (version 2.1 (date 21 November 2016; DLP November 2015), with Australian Specific Annex (version 0.1, dated 16 January 2018), included with submission PM-2017-01423-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

As Raxone is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

Raxone (Idebenone) is to be included in the Black Triangle Scheme. The PI and CMI for Raxone must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Background

This submission is to register a new chemical entity, idebenone (Raxone) 150 mg film coated tablet, for the proposed indication:

Raxone is indicated for the treatment of patients with DMD in whom respiratory function has started to decline ($PEF\%p < 80\%$) and who are currently not taking concomitant glucocorticoids. Raxone can be used in patients previously treated with glucocorticoids or in patients in whom glucocorticoid treatment is not desired, not tolerated or is contraindicated.

Idebenone received orphan drug designation in Australia on 27 February 2017. The incidence of DMD is 1 in 3,600 to 6,000 live male births. There is substantial unmet need for medical treatments for DMD.

TGA guidance, including EU guidelines adopted by the TGA, relevant to this submission include:

- Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy (EMA/CHMP/236981/2011)
- Points to consider on application with 1. meta-analysis 2. one pivotal study (CHMP/EWP/2330/99)
- Guideline on clinical trials in small populations (CHMP/EWP/83561/2005)
- Clinical investigation of medicinal products for long-term use (pp. 127 - 132 of Rules 1998 (3C) - 3CC6a)
- Australian regulatory guidelines for prescription medicines (ARGPM); Guidance 8: Product Information; Guidance 15: Biopharmaceutic studies.

It is noted that the initial trial protocol for the pivotal study (the DELOS study) was finalised in May 2009, prior to the publishing of the EU guideline for DMD in 2011.

Idebenone has not previously been considered by the Advisory Committee on Medicines (ACM).

Quality

All pharmaceutical chemistry and quality issues raised during the evaluation have been resolved. The quality evaluator recommends approval.

The PI is acceptable from a pharmaceutical chemistry perspective and the product labels are acceptable.

Nonclinical

There are no nonclinical objections to the registration of idebenone.

The safety pharmacology and repeat-dose toxicity studies raised no significant concerns for the clinical use of idebenone.

Idebenone is not considered to pose a carcinogenic or mutagenic hazard in humans, and the weight of evidence suggests that it is not clastogenic.

The proposed pregnancy category of B1;²⁵ is considered appropriate for idebenone.

The draft PI is acceptable from a nonclinical perspective.

Clinical

The clinical evaluator does not recommend approval of Raxone for the proposed indication because the DELOS study is not considered to be a sufficiently robust study to provide the level of evidence of efficacy required from a single pivotal study. The reasons for this recommendation include:

- While the DELOS study shows a statistically significant reduction in the deterioration of PEF%_p with idebenone in comparison to placebo, the confidence interval is wide, and the p-value is not considerably stronger than $p < 0.05$.
- The supportive respiratory data are difficult to interpret, and data to establish how respiratory function testing correlates with quality of life, time to death and other life changing events are lacking.
- There are limited Phase II data.

In response to the clinical recommendation, the sponsor provided additional analyses of previously submitted data.

The clinical dossier included:

- 4 Phase I studies evaluating the clinical pharmacology and bioavailability of idebenone in healthy subjects (Studies SNT-I-001, SNT-I-002, SNT-I-003 and SNT-I-004).
- 2 clinical studies (1 Phase II study (Study DELPHI SNT-II-001), 1 Phase III study (DELOS; Study SNT-III-003)) with 1 long-term extension study (Study DELPHI-E SNT-II-001-E) in DMD. In addition, there were 4 further *post-hoc* analyses in the DELPHI (Study SNT-IR-011) and DELOS studies (Studies SNT-IR-009, SNT-IR-010, and SNT-IR-012) studies.
- 2 Phase II clinical studies in Leber's hereditary optic neuropathy (Studies RHODOS SNT-II-003 and RHODOS-OFU SNT-II-003).
- 3 clinical studies (1 Phase II and 2 Phase III) in Friedreich's ataxia with 2 long-term extension studies (Studies NICOSIA SNT-II-002, IONIA SNT-III-002, MICONOS SNT-III-001, IONIA-E SNT-III-002-E and MICONOS-E SNT-III-001E).
- 1 natural history study in DMD (Study SNT-IR-013)
- 1 matching study of Duchenne muscular dystrophy long-term idebenone study (DELOS) with natural history in DMD (Study SNT-IR-014).
- 283 literature references.

Pharmacokinetics

The PK of idebenone has been determined in four Phase I studies in 69 healthy volunteers, with limited data from 13 DMD patients in the DELPHI study. Idebenone is rapidly absorbed when taken orally, reaching C_{\max} approximately 1 hour post-administration. Systemic exposure increased around 2.5 fold for a doubling in dose. Idebenone undergoes extensive first pass metabolism in the liver. Bioavailability is increased by food intake (around 5 fold increase in C_{\max} and around 7 fold increase in AUC_{0-t}). The main metabolites are eliminated primarily via the kidneys and there is minimal accumulation of idebenone in plasma. The justification for not performing an absolute bioavailability was considered acceptable given the very low solubility, lack of an IV formulation, and the safety and efficacy data presented for the oral formulation.

Pharmacodynamics

Primary and secondary pharmacodynamics were assessed in the nonclinical evaluation. There was limited clinical PD data, with no PD studies in DMD patients. In

Study SNT-I-003, there was no indication of an inducing effect of idebenone on drug metabolising enzymes when given in doses up to 750 mg TDS for two weeks.

No PK or PD dose ranging study has been conducted in DMD. The NICOSIA study, a 6 month Phase II safety and efficacy study of idebenone in Friedrich's ataxia, found that a dose of 900 mg/day for patients > 45kg was the optimal dose. The majority of patients in the DELPHI study weighed < 45kg and received idebenone 450 mg/day, but this was increased to 900 mg/day for patients over 45kg. Patients in the DELOS study received idebenone 900 mg/day, based on the older average age and higher body weight (idebenone group, mean weight 55.3 kg, range 28.6 kg to 91.0 kg).

Efficacy

Efficacy studies conducted in DMD include a single pivotal Phase III Study (DELOS) plus a Phase II study (the DELPHI study) and its open-label extension (DELPHI-E study). In addition, there were 4 further *post-hoc* or corrective analyses in the DELPHI (SNT-IR-011) and DELOS (SNT-IR-009, SNT-IR-010, SNT-IR-012) studies.

DELPHI study

The DELPHI study was a Phase IIa double blind, randomised, placebo-controlled, single centre study to assess the efficacy and tolerability of idebenone in 8 to 16 year old males with cardiac dysfunction associated with DMD. The primary objective was to determine whether treatment with idebenone improves or delays the decline in cardiac function (peak systolic radial strain of the LV inferolateral wall); secondary objectives were to determine whether treatment with idebenone improves or delays the decline in muscle strength and/or respiratory function, to evaluate the safety and tolerability of idebenone, and to determine whether treatment with idebenone affects the biochemical markers of cardiac overload or cardiac degeneration.

In total, 21 patients were randomised 2:1 to receive either 150 mg oral idebenone (n = 13) or placebo (n = 8), three times daily (TDS) for 12 months.

The primary efficacy outcome for the DELPHI study was not met, but a difference in PEF%p between the idebenone and placebo groups was observed. No beneficial effect was observed for other respiratory parameters, such as FVC%p and MIP%p.

Table 20: Respiratory function (ITT population), DELPHI study

Respiratory function parameter	Baseline (BL)		Week 52		Change Week 52 - BL		p value*
	Placebo	Idebenone	Placebo	Idebenone	Placebo	Idebenone	
FVC [L]	1.93 ± 0.38 (n=8)	2.19 ± 0.58 (n=13)	2.08 ± 0.59 (n=8)	2.33 ± 0.67 (n=13)	0.15 ± 0.29 (n=8)	0.14 ± 0.31 (n=13)	0.529
FVC [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
FEV1 [L]	1.70 ± 0.39 (n=8)	1.97 ± 0.59 (n=13)	1.81 ± 0.52 (n=8)	2.08 ± 0.71 (n=13)	0.10 ± 0.27 (n=8)	0.11 ± 0.37 (n=13)	0.484
FEV1 [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
PEF [L/min]	243.8 ± 73.7 (n=8)	261.5 ± 93.9 (n=13)	230.0 ± 67.8 (n=8)	292.3 ± 90.6 (n=13)	-13.8 ± 51.0 (n=8)	30.8 ± 54.4 (n=13)	0.039
PEF [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
MIP [cmH ₂ O]	-39.4 ± 16.57 (n=8)	-40.0 ± 16.58 (n=13)	-41.9 ± 15.34 (n=8)	-47.3 ± 14.09 (n=13)	-2.5 ± 6.6 (n=8)	-7.3 ± 13.0 (n=13)	0.173
MIP [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

In the DELPHI extension study (DELPHI-E), patients were treated for up to 24 months with idebenone 150 mg or 300 mg TDS (daily dose 450 mg or 900 mg). Lesser declines in

PEF%p and MIP%p than FVC%p were observed, but the lack of a control group means that it is difficult to determine the validity of these findings.

Table 21: Respiratory function outcomes (ITT population), DELPHI-E study

	Baseline Mean (SD)	Estimated Mean Change \pm SE ¹			
		Month 6	Month 12	Month 18	Month 24
PEF %p	66.13 (22.31)	2.79 \pm 2.92	-4.81 \pm 2.92	-6.65 \pm 2.92	-3.31 \pm 2.92
FVC %p	61.32 (23.52)	-2.09 \pm 1.64	-9.28 \pm 1.64	-9.48 \pm 1.64	-12.50 \pm 1.64
MIP %p	27.66 (13.57)	-1.84 \pm 2.34	2.84 \pm 2.34	1.43 \pm 2.34	0.98 \pm 2.34

The secondary respiratory findings in the DELPHI study led to the design of the DELOS study to investigate whether idebenone provides a beneficial effect on PEF%p in DMD.

DELOS study

The DELOS study was an interventional study of idebenone 300 mg TDS versus placebo in 66 patients aged 10 to 18 years with DMD who had established respiratory function decline at Baseline (PEF%p \leq 80%). The DELOS study was conducted in 23 sites in 10 countries (Belgium, Germany, the Netherlands, Switzerland, France, Sweden, Austria, United States, Italy and Spain) between July 2009 and January 2014.

The DELOS study was conducted to assess the efficacy of idebenone, compared to placebo, in improving respiratory function or delaying the loss of respiratory function, with the primary endpoint being the change from Baseline to Week 52 in PEF%p. Secondary objectives included assessment of the safety and tolerability of idebenone in patients with DMD, and assessment of 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;
- improving skeletal muscle strength/motor function or delaying the loss of skeletal muscle strength/ motor function; and
- improving quality of life or delaying the loss in quality of life.

Tertiary objectives included assessment of the effect of idebenone on biochemical markers reflecting cardiac overload or cardiac degeneration, and the efficacy of idebenone on exploratory respiratory parameters.

Inclusion criteria included age 10 to 18 years with a documented diagnosis of DMD or severe dystrophinopathy and clinical features consistent with typical DMD at diagnosis (that is, documented delayed motor skills and muscle weakness by age 5 years) who were able to provide reliable and reproducible repeat peak expiratory flow (PEF) measurements (within 15% of the first assessment, that is Baseline versus Screening). The diagnosis of DMD was to be confirmed by mutation analysis in the dystrophin gene or by substantially reduced levels of dystrophin protein (that is absent or $<$ 5% of normal) on Western blot or immunostain.

Exclusion criteria included:

- Patients with a PEF%p $>$ 80% at Baseline.
- Criteria relating to concomitant GC use
- Patients dependent on assisted ventilation at Screening and/or Baseline.
- Patients with documented DMD-related hypoventilation for which assisted ventilation was needed according to current standard of care guidelines (for example FVC%p $<$ 30%) or was required in the opinion of the investigator.

There were 67 patients (65 randomised and 2 siblings allocated to treatment) were enrolled, and 66 patients received study treatment, 32 with idebenone 900 mg/day and 34 with placebo. The most common reason for screen failure was that PEF was not reproducible (within 15% between Screening and Baseline). One patient (randomised to placebo) did not receive study treatment because he withdrew consent. The 2 siblings allocated to treatment (1 to idebenone and 1 to placebo) were excluded from the ITT population. Therefore, the ITT population included 64 patients (31 patients treated with idebenone and 33 patients treated with placebo).

There were 7 protocol amendments, all during the blinded phase of the study. They were mostly administrative, but amendment 7 (April 2014) limited the study population of the DELOS study to GC non-using patients (on the basis of the planned futility analysis) and introduced hierarchical testing of selected secondary endpoints.

There were some differences in baseline characteristics between the treatment groups (Table 22 and Table 23), particularly higher age and longer time since last GC use at Baseline in the placebo group. These differences were explored in additional analyses, including a prospectively planned matching study comparing the treatment groups with matched populations from the CINRG Duchenne Natural History Study. These exploratory analyses supported the conclusion that baseline differences were unlikely to influence the study results.

Table 22: Summary of baseline demographic characteristics (ITT population), DELOS study

	Idebenone (N=31)	Placebo (N=33)	Total (N=64)
Age, years at Baseline			
mean (SD)	13.5 (2.7)	15.0 (2.5)	14.3 (2.7)
median	13.3	15.1	14.0
min-max	10.1-19.0	10.5-18.9	10.1-19.0
Sex			
Male	31 (100%)	33 (100%)	64 (100%)
Race			
Caucasian/White	29 (93.5%)	31 (93.9%)	60 (93.8%)
Oriental	1 (3.2%)	0	1 (1.6%)
Hispanic	0	1 (3.0%)	1 (1.6%)
Other	1 (3.2%)	1 (3.0%)	2 (3.1%)
Weight (kg)			
mean (SD)	55.3 (18.3)	61.9 (18.0)	58.7 (18.3)
median	56.0	62.5	58.4
min-max	28.6-91.0	35.0-120.0	28.6-120.0
Height (cm)			
mean (SD)	157.4 (11.3)	162.4 (12.4)	160.0 (12.0)
median	156.1	166.4	160.6
min-max	138.3 – 180.7	129.4 – 181.1	129.4 – 181.1
Body Mass Index (kg/m ²)			
mean (SD)	22.0 (5.9)	23.4 (5.6)	22.7 (5.7)
median	21.2	24.4	23.6
min-max	12.1 – 35.7	12.6 – 42.2	12.1 – 42.2

Table 23: Summary of disease-relevant baseline characteristics (ITT Population), DELOS study

Disease-Relevant Baseline Characteristics	Idebenone (N=31)	Placebo (N=33)	Total (N=64)
Non-ambulatory (in wheelchair)	28 (90.3%)	31 (93.9%)	59 (92.2%)
Prior GC Use			
Yes	17 (54.8%)	19 (57.6%)	36 (56.3%)
No	14 (45.2%)	14 (42.4%)	28 (43.8%)
Time since last GC use [years]			
n	17	19	36
mean (SD)	2.9 (1.8)	4.3 (2.2)	3.7 (2.1)
median (min to max)	2.5 (0.9-6.6)	4.3 (1.3-8.9)	3.4 (0.9-8.9)
Stratification Factor			
Baseline PEF%p			
PEF%p <40%	5 (16.1%)	7 (21.2%)	12 (18.8%)
PEF%p 40% to 80%	26 (83.9%)	26 (78.8%)	52 (81.3%)
Pulmonary Function Tests, mean (SD)			
PEF%p	53.5 (10.3)	54.2 (13.2)	53.8 (11.8)
FVC%p	55.3 (15.8)	50.4 (20.0)	52.8 (18.1)
FEV1%p	53.6 (16.1)	49.5 (20.6)	51.4 (18.5)

The DELOS study met its primary endpoint, change from Baseline to Week 52 in PEF%p. In the mITT population, patients who received idebenone had a decline in PEF%p of 3.05% at Week 52, compared with a decline of 9.01% for patients on placebo (estimated difference 5.96%; 95% CI: 0.16, 11.76; $p = 0.0443$). A difference favouring idebenone was also found in the ITT and PP populations, and in a number of sensitivity analyses.

Table 24: Primary endpoint, percent predicted peak expiratory flow (mITT population), DELOS study

	Idebenone (N=30)		Placebo (N=27)		Group Difference	
Baseline mean (SD)	53.1 (10.2)		54.3 (13.5)			
Change from Baseline (MMRM)	Estimated Change (95% CI)	p-value	Estimated Change (95% CI)	p-value	Estimated Difference (95% CI)	p-value
Week 13	-1.16 (-4.48, 2.16)	0.4865	-4.33 (-7.88, -0.79)	0.0174	3.17 (-1.68, 8.03)	0.1957
Week 26	-0.98 (-4.55, 2.6)	0.5866	-8.32 (-12.13, -4.52)	<0.001	7.35 (2.13, 12.57)	0.0067
Week 39	-1.74 (-6.1, 2.62)	0.4274	-8.58 (-13.15, -4.01)	<0.001	6.84 (0.52, 13.16)	0.0344
Week 52	-3.05 (-7.08, 0.97)	0.1343	-9.01 (-13.18, -4.84)	<0.001	5.96 (0.16, 11.76)	0.0443
Week 13-52	-1.73 (-5.03, 1.57)	0.2973	-7.56 (-11.05, -4.07)	<0.001	5.83 (1.03, 10.63)	0.0183
Fixed Effect: Baseline p= 0.3816, Group p= 0.0183, Visit p= 0.1144, Group*Visit p=0.3760						

Secondary efficacy endpoints were prospectively ranked in a hierarchical manner (see Table 25). The result for the highest ranked secondary endpoint, annual rate of change of PEF%p (ASMA-1), showed a beneficial trend favouring idebenone but it did not achieve statistical significance ($p = 0.0548$), so the results for all subsequent endpoints were considered exploratory. The second ranked secondary endpoint, change in MIP%p,

showed a trend in favour of placebo. The second to fifth ranked secondary endpoints did not achieve statistical significance.

Table 25: DELOS study secondary endpoints; hierarchical testing (ITT population)

Secondary Endpoints	Idebenone (N=31)	Placebo (N=33)
Annual rate of change in PEF%p (ASMA-1). Linear regression analysis	-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 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	
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 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 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	

FVC%p = percent predicted forced vital capacity; ITT = intent-to-treat; MEP%p = percent predicted maximal expiratory pressure; MIP%p = percent predicted maximal inspiratory pressure; PCF = peak cough flow; PEF%p = percent predicted peak expiratory flow

No significant differences in muscle strength (as measured by upper limb muscle strength as the majority of patients were non-ambulatory), Pediatric Quality of Life Inventory (PedsQL) Quality of Life Inventory or Clinical Global Impression (CGI) were observed between idebenone and placebo-treated patients. It is noted that the DELOS study was not designed to show an effect on non-respiratory endpoints.

Pre-specified responder analyses were performed (Table 26) which, although exploratory, were supportive of the primary outcome. In addition, patients receiving idebenone were less likely to have their peak cough flow (PCF) drop below 160 L/sec (pre-specified), or their FVC drop below 1 litre (post-hoc) (Table 27).

Table 26: Responder rates at Week 52 for selected respiratory function variables; last observation carried forward (LOCF) approach (ITT population)

		Patients not worsening in respiratory function tests n (%)		p-value ¹
		Idebenone (N=31)	Placebo (N=33)	
Patients who did not deteriorate from Baseline	PEF%p	14 (45.2%)	8 (24.2%)	0.0806
	PEF	18 (58.1%)	9 (27.3%)	0.0134
	FVC%p	7 (22.6%)	3 (9.1%)	0.1406
	FVC	15 (48.4%)	6 (18.2%)	0.0107
	FEV ₁ %p	14 (45.2%)	4 (12.1%)	0.0036
	FEV ₁	18 (58.1%)	11 (33.3%)	0.0488

Source: Table 26, CSR

Table 27: Additional responder analyses: Results at any time point during the study; LOCF approach (ITT population)

	Idebenone (N=31) n (%)	Placebo (N=33) n (%)
PCF Patients dropping below 160L/s	1 (3.8%)	6 (18.2%)
FVC Patients dropping below 1L (all Patients)	1 (3.2%)	5 (15.6%)

Source: Table 27, CSR

A prospectively planned matching study was performed with patients enrolled in a longitudinal natural history study from the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS) to provide external validation of the results of the primary endpoint in DELOS. This matching study demonstrated that the DELOS study placebo group changes in PEF%p were reflective of the natural history of the disease, and that DELOS patients receiving treatment with idebenone had a slower decline in PEF%p than the matched natural history cohort. The difference in the decline in PEF%p over 52 weeks between the idebenone and placebo groups (5.96%) was of a similar magnitude to the annual decline in PEF%p observed in the CINRG DNHS matched-to-DELOS idebenone (-5.98%) and placebo (-6.30%) cohorts, suggesting that treatment with idebenone could delay the decline in PEF%p by approximately 1 year based on the natural history of the disease.

Additional analyses of natural history data were provided by the sponsor after the first round evaluation to support the correlation between PEF%p and FVC%p and the correlation between PEF%p and clinical outcomes (mortality and initiation of assisted ventilation).

Safety

Safety data for idebenone in DMD includes 53 patients treated with 450 or 900 mg per day for a mean (SD) of 549 (315.5) days. The full safety analysis population, comprising patients with DMD, Leber's hereditary optic neuropathy (LHON) and Friedreich's ataxia (FRDA), includes 439 patients who received idebenone 180 to 2,250 mg per day for a mean (SD) of 600.3 (362.5) days. There were differences in the age demographics and dosing regimens between the different indications. Idebenone has also been used at lower doses for the treatment of cognitive disorders since 1986.

Table 28: Summary of total safety population; exposure to idebenone in Phase II/III studies; population treated by idebenone in double-blind and extension studies, by dose

Population	Placebo Double-blind studies N (%)	Idebenone Dose mg/day N (%)				
		Double-blind studies Total	Double-blind and extension studies			
			180/360	450/900	1350/2250	Total
Total safety population	166 (100)	356 (100)	69 (15.7%)	200 (45.6%)	170 (38.7%)	439 (100)
DMD	42 (25.3)	45 (12.6)	-	53 (100%)	-	53 (12.1)
LHON	30 (18.1)	55 (15.4)	-	55 (100%)	-	55 (12.5)
FRDA	94 (56.6)	256 (71.9)	69 (20.8%)	92 (27.8%)	170 (51.4%)	331 (75.4)

^a Double-blind and extension studies - the dose was increased for some patients in the extension study compared to double-blind, but the dose group is defined by the double-blind dose. Each subject is counted in only one dose group.

In the DMD studies, the majority of patients experienced AEs but at a similar percentage in the idebenone (93.3%) and placebo (95.2%) treatment groups. Treatment-related AEs and SAEs were reported in fewer patients on idebenone (24.4% and 6.7%) than on placebo (33.3% and 14.3%). AEs reported in $\geq 10\%$ of subjects in either treatment group (idebenone versus placebo) and higher on idebenone were diarrhoea (20.0% versus 14.3%), headache (17.8% versus 16.7%), pyrexia (13.3% versus 7.1%), gastroenteritis (13.3% versus 2.4%), and abdominal pain (11.1% versus 7.1%). There were relatively few treatment-related AEs, with only diarrhoea and chromaturia being reported by 2 or more patients on idebenone. The majority of AEs and treatment-related AEs were mild to moderate in severity.

There were no deaths during the DMD studies, and none of the SAEs or discontinuations due to AEs were considered by the investigator to be treatment-related. In addition, there were no safety issues identified with possible regulatory impact.

In a post-hoc analysis of the DELOS study data, clinically relevant bronchopulmonary AEs were identified by a study-independent physician and compared between the idebenone and placebo treatment groups. Fewer patients on idebenone (19.4%) had BAEs than those on placebo (51.5%), and the duration of BAEs and systemic antibiotic use was shorter in the idebenone group.

The safety profile for the integrated safety analysis population was similar to the DMD population. The percentage of subjects on idebenone (all doses combined) in each indication who reported at least 1 AE ranged from 89.1% (LHON) to 97.3% (FRDA) and was similar in the idebenone and placebo double blind treatment groups. AEs reported in $\geq 10\%$ of subjects in either treatment group (idebenone versus placebo) and higher on idebenone were headache (29.8% versus 29.5%), nasopharyngitis (26.7% versus 21.7%), diarrhoea (17.1% versus 11.4%), and nausea (12.1% versus 10.2%). Treatment-related AEs occurred in a similar proportion of patients (idebenone 1.4% versus placebo 1.2%). The incidence of study discontinuations due to AEs was low and similar in idebenone (all

doses combined) and placebo double blind treatment groups (idebenone 2.0% versus placebo 3.0%).

In the integrated safety analysis, one death from myocardial infarction was reported in a FRDA patient during the MICONOS-extension study. This was assessed as unrelated to the study drug.

No new safety signals were identified in the two submitted PSURs which captured data from investigational uses and marketing experience.

Risk management plan

The sponsor submitted EU-RMP version 2.1 (date 21 November 2016; data lock point November 2015) and ASA version 0.0 (date 11 April 2017) with this application and provided an updated ASA version 0.1 (date 16 January 2018) with the post-first round evaluation response.

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies for the indications of DMD and Leber's hereditary optic neuropathy (approved EU indication but not being sought in Australia) are summarised in Table 19 above.

Additional pharmacovigilance activities include a Phase III study assessing the efficacy, safety and tolerability of idebenone in patients with DMD receiving glucocorticoid steroids (the SIDEROS study (Study SNT-III-012)) and a post-authorisation safety study.

Routine risk minimisation activities are proposed for all safety concerns. It is proposed to provide educational material to the physicians in the EU to prevent off-label prescription of Raxone to DMD patients receiving glucocorticoids. However, no additional risk minimisation measures are proposed for Australia. Physician education for this missing information is not considered to be a regulatory requirement in Australia, as the proposed indication excludes use in this population.

Proposed conditions of registration are recommended as above in Section VI.

Risk-benefit analysis

Efficacy

The DELPHI study was a small Phase II study which failed to meet its primary cardiac efficacy endpoint. A difference favouring idebenone was noted in PEF%p, but not other respiratory markers such as FVC%p and MIP%p. This was a hypothesis-generating finding which led to the design of the Phase III DELOS study with PEF%p as the primary endpoint. Interpretation of the findings from the DELPHI-E study is constrained by the lack of a control group.

In DELOS, the estimated decline in PEF%p in the mITT population from baseline to Week 52 was 3.05% for idebenone and 9.01% for placebo, a difference of 5.96% (95%CI 0.16 to 11.76, $p = 0.0443$), so DELOS met its primary efficacy endpoint. The findings from the DELOS study should be considered in the context of the TGA-adopted EU Guideline.³⁷ It provides guidance that, in cases where the confirmatory evidence is provided by one pivotal study only, this study will have to be exceptionally compelling. The findings from a single pivotal study should be particularly compelling with respect to statistical significance, clinical relevance and internal consistency. Statistical evidence considerably stronger than $p < 0.05$ is usually required, accompanied by precise estimates of treatment effects, that is narrow confidence intervals. The estimated size of treatment benefit must be large enough to be clinically valuable. Internal consistency should be demonstrated through all important endpoints showing similar findings.

When the DELOS study findings are considered in the context of this guideline, there is concern that the results were not sufficiently compelling and internally consistent. The confidence interval was wide, indicating a lack of precision in the primary outcome, and the p-value was not substantially stronger than 0.05. Outcomes for secondary endpoints were weak and inconsistent. There was a beneficial trend favouring idebenone for the first-ranked secondary endpoint (PEF%p, ASMA-1 device);⁴⁵ but it did not achieve statistical significance. The second ranked secondary endpoint, change in MIP%p from Baseline to Week 52, showed a trend in favour of placebo. The second to fifth ranked secondary endpoints did not achieve statistical significance. Data for non-respiratory endpoints were limited. The sponsor provided additional post-hoc analyses after milestone 5 to address the concern regarding the strength of the DELOS study results. The sponsor demonstrated that it was possible to create narrower confidence intervals by utilizing data from multiple time points in the DELOS study, but the post-hoc analyses do not overcome the fundamental issue with the strength of the DELOS study results.

There is uncertainty in correlating the change in PEF%p demonstrated over 12 months in the DELOS study to clinical outcomes in DMD. The submission provided analyses, references and a comparison with established thresholds in asthma to support the correlation of the primary endpoint with clinical outcomes. The prospectively planned matching study suggested that treatment with idebenone could delay the decline in PEF%p by approximately 1 year based on the natural history of the disease; however, the wide confidence interval for the primary endpoint and the lack of consistency in secondary respiratory endpoints introduce some uncertainty to this conclusion. After milestone 5, the sponsor provided additional analyses of natural history data to support the correlation between PEF%p and FVC%p and the correlation between PEF%p and clinical outcomes (mortality and initiation of assisted ventilation). Whilst these analyses provide some support for the correlation between PEF%p and clinical outcomes, there is residual uncertainty in correlating the primary endpoint in the DELOS study to clinical outcomes in DMD. There is uncertainty in extrapolating clinical outcomes from natural history data to the respiratory function outcomes achieved over 12 months in the DELOS study. There is also uncertainty in translating the observations regarding fast and slow progressors (defined as annual decline in PEF%p > 6.27% and ≤ 6.27%, respectively) in the natural history study to the primary outcome in the DELOS study.

Safety

As expected for a rare disease, safety data for idebenone in DMD is limited; however, there is a history of idebenone use in other indications, albeit at different doses than is proposed for DMD and involving adults as well as children/adolescents. The overall number of patients treated and duration of exposure are considered adequate for the characterisation of the safety profile of idebenone.

The safety profile in the DMD studies was consistent with that seen in studies for other indications, and reported in the PSURs. The types and severity of AEs experienced were generally mild to moderate in severity, relatively benign in nature and clinically manageable.

Data deficiencies

There are limited data in patients < 10 years of age, patients with renal and/or hepatic impairment and patients with DMD receiving glucocorticoids. Additional data is anticipated from the SIDEROS study and a post-authorisation safety study.

⁴⁵ ASMA-1 device is an electronic respiratory monitor that measures PEF and FEV1

Conclusion

There are no outstanding issues from the quality and nonclinical evaluations.

There is concern that the evidence from the DELOS study is not sufficiently robust and compelling to support the registration of idebenone for the proposed indication. The findings from a single pivotal study should be particularly compelling with respect to statistical significance, clinical relevance and internal consistency. Whilst the DELOS study met its primary endpoint, the result was not statistically compelling, in that the statistical evidence for the primary endpoint ($p = 0.0443$) was not considerably stronger than $p < 0.05$ and the confidence interval was wide (95% CI: 0.16, 11.76) indicating a lack of precision in the estimate of the treatment effect. Support from secondary efficacy outcomes was limited. The top-ranked secondary endpoint did not achieve statistical significance and there were inconsistent results across other respiratory endpoints. The lack of precision and consistency in the DELOS study results raise concern regarding the reliability and reproducibility of the findings, and suggest the need for confirmation of the findings in another Phase III study.

There are limited data correlating the primary endpoint with clinical outcomes in DMD. This leads to uncertainty in correlating the change in PEF%_p demonstrated in the DELOS study to clinical outcomes in DMD, particularly when considered in the context of the wide confidence interval for the primary endpoint and inconsistent outcomes for secondary endpoints.

Multiple *post-hoc* analyses were performed to support the primary analysis and the correlation between the primary endpoint and disease outcomes, but these analyses do not provide independent evidence of efficacy and do not address the fundamental issue that the results from the single pivotal study were not particularly compelling. There is concern that reliance on multiple post-hoc analyses in the absence of independent confirmatory data may increase the risk of false conclusions.

There are limited safety data in DMD, supported by more extensive data across other indications. The safety profile of idebenone is considered acceptable.

Further evidence is anticipated from the Phase III SIDEROS study which is in progress.

At this stage, the Delegate's view is that the results of the DELOS study are not sufficiently compelling, as a single pivotal study, to support the registration of idebenone. There is also some uncertainty in correlating the DELOS study findings with clinical outcomes in DMD. However, the Delegate remained mindful of the high level of unmet need for treatment for this group of patients and will consider expert opinion from ACM before finalising their decision.

Conditions of registration

The following are proposed as conditions of registration:

- The Raxone EU-Risk Management Plan (RMP) (version 2.1 (date 21 November 2016; data lock point November 2015), with Australian Specific Annex (version 0.1, dated 16 January 2018), included with submission PM-2017-01423-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first PSUR report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent PSUR reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted

separately as they become available. The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

- Raxone (Idebenone) is to be included in the Black Triangle Scheme. The PI and CMI for Raxone must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Indications

Proposed (initial)

Raxone is indicated for the treatment of patients with Duchenne Muscular Dystrophy (DMD) in whom respiratory function has started to decline and who are currently not taking concomitant glucocorticoids. Raxone can be used in patients previously treated with glucocorticoids or in patients in whom glucocorticoid treatment is not desired, not tolerated or is contraindicated.

Proposed (revised)

Raxone is indicated for the treatment of patients with Duchenne Muscular Dystrophy (DMD) in whom respiratory function has started to decline (PEF% p < 80%) and who are currently not taking concomitant glucocorticoids. Raxone can be used in patients previously treated with glucocorticoids or in patients in whom glucocorticoid treatment is not desired, not tolerated or is contraindicated.

Dosage

Proposed

Treatment should be initiated and supervised by a physician with experience in DMD.

The recommended dose is 900 mg/day idebenone (300 mg, 3 times a day).

No data regarding a continuous treatment with idebenone beyond 12 months is available from controlled clinical trials with DMD patients.

Raxone is not currently approved for use in DMD patients taking concomitant glucocorticoids and should not be prescribed to such patients.

Raxone film-coated tablets should be swallowed whole with water. The tablets should not be broken or chewed. Raxone should be administered with food because food increases the bioavailability of idebenone.

Summary of issues

1. The evidence for efficacy is based primarily on a single pivotal study. The DELOS study met its primary efficacy endpoint but there is concern that the findings from the single pivotal study are not sufficiently compelling and robust. The result for the primary efficacy outcome was not statistically compelling, in that the p value was 0.0443 and the confidence interval was wide. There was a beneficial trend favouring idebenone for the highest ranked secondary endpoint but it did not achieve statistical significance and there was a lack of consistency in other secondary respiratory endpoints. There were limited data for non-respiratory endpoints.

2. The DELOS study met its primary endpoint for PEF%_p but data on clinical outcomes are limited. The sponsor provided additional analyses of natural history data to support the correlation between PEF%_p and initiation of assisted ventilation and mortality. There is some uncertainty in correlating the respiratory function findings in the DELOS study with clinical outcomes in DMD, particularly when considered in the context of the wide confidence interval for the primary endpoint and weak and inconsistent outcomes for secondary endpoints.

Questions for the sponsor

1. Please outline the key timelines for the SIDEROS study. When does the sponsor anticipate that data from the SIDEROS study will be available?

Proposed action

The Delegate was not in a position to say, at this time, that the application for idebenone should be approved for registration

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

1. What is the committee's opinion on PEF%_p as the primary endpoint for the pivotal study and the correlation of this endpoint with clinical outcomes in DMD?
2. What is the committee's view on the strength and clinical relevance of the efficacy findings in the DELOS study?
3. What is the committee's view on the need for additional evidence from another Phase III study?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Response to delegate's request for advice from ACM

1. ***What is the committee's opinion on PEF%_p as the primary endpoint for the pivotal study and the correlation of this endpoint with clinical outcomes in DMD?***

Historically, FVC has been seen as the parameter that is preferred for assessing the respiratory function of DMD patients, mainly based on early work by Phillips et al., (2001);⁴⁶ which suggested that falling below FVC of 1 L is a strong marker of subsequent mortality, with a 5-year survival of 8%.

However, since then the standard of care has considerably improved and today the 5-year survival after crossing FVC of 1 L is about 85%. In order to assess the characteristics of the respiratory function parameters in DMD patients treated with the standard of care of today, analyses have recently been conducted using several contemporaneous datasets, including the most comprehensive natural history study conducted up to now, the CINRG (the Cooperative International Neuromuscular Research Group) study. The main findings from these analyses are summarised below:

⁴⁶ Phillips MF et al (2001) Changes in Spirometry Over Time as a Prognostic Marker in Patients with Duchenne Muscular Dystrophy *American journal of respiratory and critical care medicine* 2001;164: 2191-2194

- Both PEF%p and FVC%p are the most reliable longitudinal respiratory function parameter in DMD patients.⁴⁷
- Both PEF%p and FVC%p are well correlated and show a co-linear decline during the respiratory function decline phase. However, PEF%p is an earlier marker of respiratory function decline compared to FVC%p, as decline phase for PEF%p starts earlier from around 6 to 8 years. This is relevant as it makes the diagnosis of the start of respiratory dysfunction more reliable. Moreover, PEF%p declines already in ambulatory patients which is typically not seen for FVC%p.⁴⁸ This therefore makes PEF%p a more suitable endpoint in the population enrolled into the Phase III DELOS study. These patients were aged 10 to 18 years, with a subset of patients in an early stage of the respiratory function decline, representing a mix of ambulant and non-ambulant patients.
- When conducting the PEF manoeuvre, patient needs to fully engage both inspiratory (full inspiration) and expiratory muscles (maximum forced expiration). FVC also requires full engagement of the inspiratory muscles. However, for expiration, the FVC-manoeuvre is done slowly and significantly influenced by external factors such as the reduced elasticity of the chest wall and curvature of the spine inherent with progressive disease. PEF therefore is regarded as the preferred and more direct indicator of the performance of both inspiratory and expiratory respiratory muscles and hence is suitable as an endpoint in the pivotal DELOS study.
- The rate of decline of respiratory function and crossing thresholds of PEF%p and FVC%p predict equally well the time to reaching clinically relevant disease milestones, including the time to assisted ventilation and death. Crossing FVC of 1 L remains an established predictor of death, with 5 year survival of about 85%, but data now also show that crossing PEF values < 100 L/min predict the death equally well, with 5-year survival rates < 85%.

In summary, both PEF%p and FVC%p are equally relevant respiratory function parameters in DMD. As PEF%p starts to decline already in younger patients and in patients who are still ambulatory, this outcome measure offers advantages as primary endpoint in a heterogeneous study population as enrolled in the DELOS study.

Furthermore, in the second round assessment of benefits in the clinical evaluation report, the Delegate concludes that 'the choice of PEF%p as the primary endpoint is considered acceptable.'

2. *What is the committee's view on the strength and clinical relevance of the efficacy findings in the DELOS study?*

The primary endpoint of the DELOS study, change in PEF%p over the 12-month study period, showed a statistically significant between-group difference in the ITT population of 6.27% in favour of idebenone and therefore met its pre-defined objective.

The sponsor acknowledges that despite the statistically significant difference in the primary endpoint in favour of idebenone ($p = 0.0306$) at Month 12, the corresponding 95% confidence interval (0.61% to 11.93%) is wide.

The width of the confidence interval of respiratory function in DMD is driven primarily by the variability of the respiratory function measures and heterogeneity of the disease over time, not by the sample size. The sponsor has demonstrated that even a sample size of more than twice the size of the DELOS study would have led to only moderately tighter

⁴⁷ Meier T et al., 2017 Characterization of pulmonary function in 10–18 year old patients with Duchenne muscular dystrophy. *Neuromuscular Disorders* 2017; 27: 307-314

⁴⁸ Domingos Jet al., 2017 Dystrophinopathies and Limb-Girdle Muscular Dystrophies *Neuropediatrics* 2017; 48: 262-272

confidence intervals, indicating that variability of the respiratory function is inherent to the disorder being studied.

Despite the wide confidence intervals, the sponsor has provided evidence that the findings of the DELOS study are robust based on the comprehensive set of sensitivity analyses as presented in the application and summarised below:

- The DELOS study findings are consistent between the subsets of patients with different demographic and other disease relevant baseline characteristics including: age, baseline PEF%p, previous steroid use, baseline weight, baseline height, ambulatory status and age at loss of ambulation.
- The DELOS study findings are not influenced by individual patients, influential observations or outliers. Sensitivity analyses were conducted by simulations randomly removing 5% or 10% of the patients, by excluding each patient at a time and by excluding the most influential patients based on Cook's D.
- The DELOS study findings are not influenced by missing data or drop-outs. A number of sensitivity analyses were conducted by applying multiple imputation methods, assuming both that data are missing at random or missing not at random.
- The DELOS study findings are consistent between different respiratory function parameters. Statistically significant treatment differences or strong trends in favour of idebenone were seen for both percent predicted and absolute values of PEF, FVC and FEV1.
- The findings on the respiratory function parameters are consistent regardless of the methodology used to calculate predicted values. Various formulas that are used in the literature to calculate the normalized values (Godfrey, Hankinson, and Global Lung Initiative) did not influence the observed treatment difference in favour of idebenone.
- The DELOS study findings on the respiratory function parameters are supported by patient-relevant outcomes, like the incidence of bronchopulmonary adverse events, use of systemic antibiotics and hospitalisations due to respiratory causes (PPMD report); all analyses favouring the idebenone treatment group.
- The robustness of the treatment difference in favour of idebenone observed in the DELOS study can be further demonstrated by evaluating data over multiple study visits instead of a single-visit analysis (Month 12 versus Baseline). These analyses resulted in tighter confidence intervals and more robust p-values, for example for slope analysis of PEF%p ($p = 0.0070$) or analysis of weekly PEF%p assessments with handheld device ($p = 0.0018$).

Based on natural history studies, the observed treatment difference in PEF%p (6.27%) from the DELOS study is comparable to the average one-year decline of respiratory function in untreated DMD patients. This magnitude of effect thus represents maximum treatment difference that can be expected in a one-year study in a pathology that cannot currently be reversed.

In order to extrapolate the DELOS study treatment difference into clinically relevant outcomes such as initiation of assisted ventilation or death, the natural history data from the CINRG Study were classified into groups that correspond to the DELOS treatment groups. The following approach was used for this:

- In the ITT population of the the DELOS study, the estimated change from baseline to Month 12 in PEF%p was 2.6% in the idebenone group and 8.8% in the placebo group.
- The CINRG data were reviewed, in order to find thresholds that would generate two groups with rates of annual decline in PEF%p comparable to the DELOS treatment groups.

This analysis suggests that the DELOS study treatment difference in PEF%p can be linked to a prolongation of about 3.2 years in time to initiation of assisted ventilation and to a significant increase of 5-year survival.

The patient's perspective on the relevance to delay time to assisted ventilation supports the findings above, as stated by a patient representative of the 'Save our Sons Duchenne Foundation':

'Many families tell us that starting to use a ventilator was an even more difficult transition than when their child stopped being able to walk, and they would give anything to delay having to go through that difficult time of adjustment and begin a phase where participating socially is more difficult and the plethora of equipment restricts activities. Therefore, the respiratory benefits seen in clinical trials of Raxone would be greatly valued by the Duchenne community' (Klair Bayley, Executive Officer of Advocacy and Clinical Care, Save Our Sons Duchenne Foundation).

In a treatment not expected to cure a progressive degenerative muscular disease, the maximum benefit to be expected is a relative stabilisation of the rate of decline of the disease. Therefore, any treatment capable of reducing the rate of decline close to the annual rate of decline in untreated patients should be regarded as highly clinically relevant. The sponsor maintains its position on the strength and clinical relevance of the efficacy findings in the DELOS study.

3. *What is the committee's view on the need for additional evidence from another Phase III study?*

The proposed indication for Raxone is for the treatment of patients with DMD in whom respiratory function has started to decline (PEF%p < 80%) and who are currently not taking concomitant glucocorticoid steroids.

A second randomised, placebo-controlled Phase III study in patients with DMD not using glucocorticoid steroids (resembling the DELOS study) is considered not feasible both by the sponsor and the members of the World Duchenne Organisation as well as other major patient groups in the EU and US that have been solicited for their feedback on this feasibility question.

The sponsor has conducted two randomised double-blind studies each with treatment duration of 1 year which is adequate to show stabilisation of respiratory function in the active treatment arm relative to placebo. The DELOS study is the only Phase III study in DMD patients having ever achieved a positive outcome of this primary endpoint.

The sponsor is currently conducting a Phase III 18 month treatment study (the SIDEROS study) in patients taking glucocorticoid steroids. The study will not provide additional efficacy data in the proposed population, that is, patients not taking concomitant glucocorticoid steroids. While direct conclusions on the efficacy of idebenone in patients not taking glucocorticoid steroids is not possible from the SIDEROS study, evidence from this trial may be considered supportive. As of 11 July 2018, 156 of 266 patients are already randomised. The results are expected to be available in the fourth quarter of 2021 based on the current recruitment rate.

Any clinical trial targeting the DMD population have lengthy recruitment times due to the rarity of the disease. The sponsor is committed to the ongoing clinical program for idebenone in the DMD patient group as detailed in the proposed post-authorisation safety study (PASS) study described in the EU-RMP (Study SNT-IV-007; a non-interventional study of clinical experience in patients prescribed raxone for the treatment of Duchenne muscular dystrophy) that will also be conducted in Australia following positive outcome from the Delegate. The primary and one of the secondary objectives aim to further evaluate the long-term safety and effectiveness of idebenone in the treatment of patients

with DMD not using glucocorticoid steroids when used under conditions of routine clinical care.

Summary and conclusion

The sponsor acknowledges the Delegate's position to request advice from the ACM.

The sponsor reiterates as summarised by the Delegate, that:

- No outstanding issue remains on quality, nonclinical and the RMP evaluation.
- Idebenone is safe and well-tolerated. The adverse events experienced with idebenone in DMD studies are mild to moderate in severity and clinically manageable.
- There is a high unmet medical need for treatment options available to patients with DMD. Specifically, DMD patients who have progressed to the stage of respiratory function decline and who are not receiving glucocorticoid steroids represent the highest unmet need for whom no treatment options are available today.

The sponsor acknowledges the uncertainties with one pivotal Phase III study to ensure that the benefit-risk is replicable in the proposed target population. These uncertainties are addressed by analyses confirming the robustness of the data within the limitations of the study sample size. Based on these extensive analyses it can be concluded that the results seen in the DELOS study are representative of a clinically relevant benefit in the target population.

The sponsor conducted a comprehensive clinical development program in this population and demonstrated that the current clinical data are consistent with a positive benefit risk balance for DMD patients who are in respiratory function decline and not able to take concomitant glucocorticoid steroids. Moreover, the benefits of idebenone was most clearly demonstrated with a confirmed p-value for PEF%p more robust than 0.05 ($p = 0.0070$), by 'slope analyses' that measure the gradient of decline in lung function which is more able to discern benefit when there is a slow but predictable rate of decline in respiratory function, as is the case in DMD.

Of note, in the EU, despite the negative opinion from the CHMP for Raxone in this indication, the UK Commission on Human Medicines (CHM) recently renewed the Early Access Medicine Scheme (EAMS) scientific opinion on 21 June 2018 considering the very high level of unmet clinical need in this patient population, and that based on currently available data the benefits of idebenone outweigh the risks in this population.

According to data available to the DMD peak body in Australia (collected from a patient registry launched last year), there are currently at least 40 patients with DMD who could fall within the intended indication for Raxone. There are currently no treatment options available for this patient population in Australia. Therefore, the sponsor would encourage the TGA to consider the positive benefit-risk profile of idebenone in the intended population of DMD patients.

Question from the delegate

Please outline the key timelines for the SIDEROS Study. When does the sponsor anticipate that data from SIDEROS will be available?

The key timelines for the SIDEROS study as of 11 July 2018 were provided [not included in this AusPAR]. Please note the SIDEROS study is conducted in patients taking glucocorticoid steroids, which is a population clinically distinct to that proposed in the Category 1 Application of Raxone.

Advisory committee considerations⁴⁹

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACM, taking into account the submitted evidence of efficacy and safety agreed with the delegate that Raxone film-coated tablets containing 150 mg of idebenone has an overall negative benefit-risk profile for the proposed indication:

Raxone is indicated for the treatment of patients with Duchenne Muscular Dystrophy (DMD) in whom respiratory function has started to decline (PEF%p < 80%) and who are currently not taking concomitant glucocorticoids. Raxone can be used in patients previously treated with glucocorticoids or in patients in whom glucocorticoid treatment is not desired, not tolerated or is contraindicated.

The ACM concluded that the evidence provided in the sponsor's submission did not satisfactorily establish the efficacy of idebenone.

In providing this advice the ACM noted the following:

- Efficacy was based on a single Phase III study, the DELOS study, where the primary endpoint was the change in peak expiratory flow percent predicted (PEF%p) from Baseline to Week 52.
- Although the primary endpoint was met, the result was not statistically compelling, with a wide confidence interval and p-value of 0.0443.
- The correlation between the primary outcome measure of PEF%p and a clinically meaningful functional benefit in DMD is not well established.
- Results of other outcome measures in the DELOS study did not achieve statistical significance.
- The DELOS study was confined to a small proportion of the patient population with advanced disease. The natural history and outcome measures are less well established in this patient population.
- The patient population in the DELOS study was not receiving current standard of care treatment.
- A Phase III trial of idebenone in DMD, the SIDEROS study, is currently underway. The trial will measure change in forced vital capacity percent predicted (FVC%p) from Baseline to Week 78 as the primary outcome.

Specific advice

The ACM advised the following in response to the delegate's specific questions on the submission:

- 1. What is the committee's opinion on PEF%p as the primary endpoint for the pivotal study and the correlation of this endpoint with clinical outcomes in DMD?**

⁴⁹ The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

The ACM were of the view that a pulmonary function test was an appropriate outcome measure, given that respiratory function declines progressively in DMD, especially after loss of ambulation. However, the choice of PEF%_p was not considered ideal, as the clinical relevance of this outcome measure in DMD is not well established. The functional significance of the change in the primary outcome measure in the DELOS study is not clear. Further, the ACM noted that use of PEF has not been validated for non-ambulant patients. The Committee noted that more data is available on the validity of other measures of respiratory function such as FVC, maximum inspiratory and expiratory pressures, and nasal inspiratory pressure for monitoring of DMD.

2. *What is the committee's view on the strength and clinical relevance of the efficacy findings in the DELOS study?*

Noting the TGA-adopted EU Guideline;⁵⁰ on points to consider on applications with one pivotal study, the ACM did not believe the results of the DELOS study to be exceptionally compelling. The ACM considered that the strength of the findings in the DELOS study was limited given that: the primary outcome measure was only just statistically significant with a wide confidence interval; the other outcome measures in the trial were not met; and the clinical relevance of the primary outcome measure is not well established.

3. *What is the committee's view on the need for additional evidence from another Phase III study?*

The ACM considered that additional evidence from another Phase III trial was necessary to establish clinical efficacy of idebenone in DMD, ideally incorporating a glucocorticoid treated population (as in the SIDEROS study), as corticosteroid therapy is standard of care for DMD patients in Australia.

Outcome

The sponsor withdrew their submission on 21 August 2018 before a decision had been made by the TGA.

⁵⁰ CPMP/EWP/2330/99 Committee for proprietary medicinal products (CPMP). Points to consider on application with 1. Meta-analyses; 2. One pivotal Study

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